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Review Article

Food sweeteners: Angels or clowns for human health?

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ABSTRACT

With the global prevalence of obesity and diabetes continuing to rise, metabolic diseases caused by excessive sugar intake have become a significant public health issue. In this context, various sweeteners as sugar substitutes have been widely used in the food industry. Sweeteners are highly favored for their good safety profile, cost-effectiveness, low-calorie properties, and potential blood sugar regulation effects, and their applications have extended to fields such as pharmaceuticals and daily chemicals. However, recent studies indicate that the impact mechanisms of sweeteners on human health are more complex than previously understood, and the long-term safety of their use has sparked widespread concern in both academia and the public. This review systematically examines relevant literature from the past three decades, employing evidence-based medicine methods for screening and meta-analysis, aiming to comprehensively assess the potential effects of sweeteners on human metabolic indicators (including blood glucose homeostasis and body fat composition) and cancer risk. The discussion will unfold in the following four sections: (1) Definition and classification of sweeteners; (2) Application areas of various sweeteners; (3) Beneficial effects of sweetener use on human health; (4) Adverse effects of sweetener use on health issues in different population groups. Current evidence suggests that the rational use of specific types of sweeteners within recommended dosage ranges can effectively improve blood glucose control, promote weight management, and play a positive role in maintaining oral health. However, excessive or long-term use of certain sweeteners may disrupt gut microbiota balance, affect glucose and lipid metabolism homeostasis, increase cardiovascular disease risk, and potentially be associated with the occurrence of certain malignant tumors. Notably, sweetener exposure during pregnancy may affect the fetus through mechanisms such as epigenetic modifications, necessitating special caution in sweetener selection for pregnant women. This review aims to provide clinicians, nutritionists, and food science professionals with the latest evidence-based medical evidence, guiding consumers to make informed sweetener choices by weighing health benefits against potential risks. It also offers scientific basis for formula optimization and product development in the food industry, thereby promoting public health.

1. Introduction

A high-sugar diet is associated with the development of dental caries, obesity, type 2 diabetes (T2D) and other common diseases, among which T2D and obesity are the most prevalent. T2D is among the most prevalent metabolic disorders worldwide, with a continuous upward trend in patient numbers over recent decades. Obesity is also one of the prevalent public problems in today's society, which is caused by the interaction of various host factors and external environmental factors (Pearlman et al., 2017). Sugar-sweetened beverages (SSBs) constitute a significant source of dietary sugar and excessive energy intake. Multiple studies have demonstrated that consumption of sugar-sweetened beverages is associated with weight gain, obesity, and an elevated risk of diabetes (Huang et al., 2017). Following the steady improvement of living standards, individuals seek to attain a "sweet" lifestyle while maintaining good health and happiness. Sweeteners, also known as

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sugar substitutes, have emerged as a preferred option due to their high safety profile, excellent stability, cheap price, low calorie content and ability to regulate blood glucose levels. Consequently, they have replaced sugar in numerous food and beverage products (Chattopadhyay et al., 2014). Artificial sweeteners are associated with weight loss compared to sucrose (Raben et al., 2002; Sørensen et al., 2014). The American Diabetes Association recommends the use of NNS as a substitute for added sugar in structured diets, which can promote health, maintain weight stability and mitigate the risk of hypertension, diabetes and other diseases (Huang et al., 2017). As a consequence, products that substitute sugar with artificial sweeteners have emerged as the primary preference for young individuals and are also favored by other age groups. Nevertheless, after a period of usage, even well-regarded sweeteners begin to exhibit drawbacks. Several studies have demonstrated that their utilization poses certain risks to intestinal microorganisms, blood glucose levels and the circulatory system. A recent study published in the British journal Nature Medicine has cautioned that erythritol, an artificial sweetener, may accelerate thrombosis and increase the risk of stroke and heart attack (Witkowski et al., 2023). Researchers in Israel have also discovered that artificial sweeteners can impact the body's glucose metabolism, leading to fluctuations in blood glucose levels (Suez et al., 2022). In conclusion, sweeteners possess both advantages and disadvantages. This article aims to provide a comprehensive introduction of sweeteners from various perspectives, enabling individuals to better comprehend their effects on human health.

2. Definition and classification of sweeteners

2.1. What are sweeteners?

Sweeteners are additives that provide food with sweetness, and belongs to a flavor agent with higher safety, better stability and cheaper price. When added to foods and beverages, sweeteners can enhance flavor and other functional properties of the products (Gallagher and Logue, 2019). In the past, excessive consumption of sweeteners has been led to a range of health issues, including obesity, T2D, cardiovascular disease, non-alcoholic fatty liver disease, as well as dental caries, neurological disorders, chronic inflammatory conditions (Moriconi et al., 2020).

2.2. Classification of sweeteners

2.2.1. Classification based on source

The classification of sweeteners can be based on their origin, which includes natural sweeteners and artificial sweeteners (see Fig. 1).

Natural sweetener is a sweet chemical component directly extracted from nature and obtained after proper treatment, most of which are secondary metabolites of microorganisms or plants. Natural sweeteners including a wide range of compounds such as sucrose, sugar alcohols, terpenoid glycosides and some polyphenols (Saraiva et al., 2020). Although natural sweeteners may be slightly less sweet than artificial ones, they are generally considered safer for consumption (Saraiva et al., 2020).

The term "artificial sweeteners" refers to sugar substitutes or non-sugar sweeteners (Castro-Muñoz et al., 2022). These synthetic substances are used to replace sugar in the production of various products (Castro-Muñoz et al., 2022). Most artificial sweeteners are low in calories and high in sweetness, which makes them appealing to both consumers and food manufacturers (Castro-Muñoz et al., 2022). Six of these artificial sweeteners have been approved by the U.S. Food and Drug Administration (FDA) as food additives, including aspartame, neotame, saccharin, acesulfame-potassium (Ace-K), sucralose and advantame (Castro-Muñoz et al., 2022).

2.2.2. Classification by sweetness

The sweetener of sweeteners also has a big difference. Based on the sweetness of sucrose, there are two types of sweeteners, namely low-sweetness sweeteners and high-sweetness sweeteners (see Fig. 1) (Saraiva et al., 2020).

Low-sweetness sweeteners have a sweetness similar to or lower than sucrose (Saraiva et al., 2020). These sweeteners are commonly utilized to enhance the volume, flavor and preservation properties of foods. For instance, sugar alcohols (such as maltitol, sorbitol, lactitol, xylitol, erythritol, mannitol) are frequently incorporated into baked goods, breakfast cereals and pickled foods to better cater to consumer preferences (Saraiva et al., 2020).

High-sweetness sweeteners are much sweeter than sucrose and have different effects (Saraiva et al., 2020). Due to their high sweetness, only a minute is required to achieve the desired level of sweetness (Saraiva et al., 2020). These sweeteners are widely used in food processing

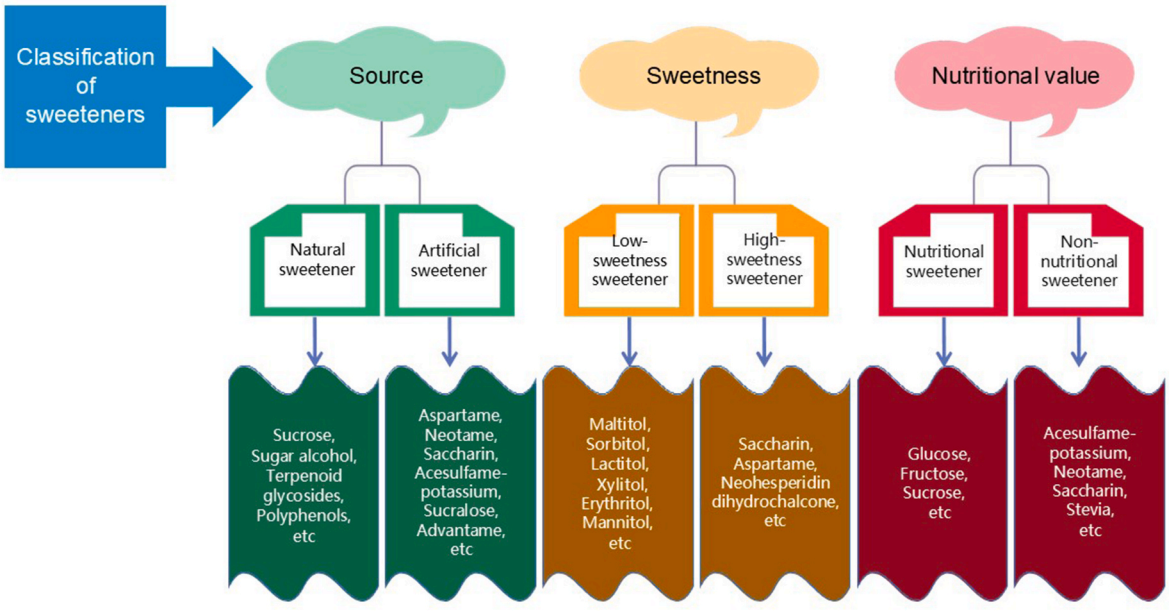

Fig. 1. Classification of sweeteners.

because their low contribution towards the energy value of the product (Saraiva et al., 2020). Saccharin, aspartame and other high-sweetness sweeteners are frequently added to sugar-free carbonated and non-carbonated beverages (Saraiva et al., 2020).

2.2.3. Classification by nutritional value

Sweeteners can be divided into nutritional sweeteners (NS) and non-nutritional sweeteners (NNS) based on their nutritional composition (see Fig. 1).

NS can provide the body with a certain amount of energy and participate in the body's metabolic processes. Due to urbanization and the accessibility of beverages, the global demand for NS has increased sharply (Pham et al., 2019). NS used in foods and beverages include glucose, fructose and sucrose (Pham et al., 2019). The harmful effects of sucrose, glucose, and fructose on health have long been discussed, particularly on excessive consumption of sugar (Pham et al., 2019).

NNS, also known as very low-calorie sweeteners (LCS) or non-calorie sweeteners (Romo-Romo et al., 2017). NNS provide sweetness with seldom caloric impact (negligible in typical human doses), and some also enhance the sensory experience of food. These sugar substitutes are typically hundreds to thousands of times sweeter than traditional sugar. At present, the common NNS on the market include Ace-K, neotame, saccharin and stevia, which are widely used in the field of "sugar-free" products (Romo-Romo et al., 2017).

3. The use of sweeteners (see Figs. 2 and 3)

3.1. Used in sugar-free beverages

3.1.1. Aspartame

Aspartame is a synthetic sweetener commonly used in carbonated and powdered soft drinks and is about 200–300 times sweeter than sucrose (Choudhary and Pretorius, 2017). Aspartame has a relatively pure sugar taste and does not have an unpleasant metallic taste or bitter taste, which is especially suitable for adding to drinks to enhance the flavor of drinks (Choudhary and Pretorius, 2017). In addition to carbonated and soft drinks, aspartame is also used in mixed desserts, frozen desserts, yogurt, chewable multivitamins and breakfast cereals (Choudhary and Pretorius, 2017).

The FDA has established the acceptable daily intake (ADI) for aspartame as 50 mg per kilogram of body weight per day (50 mg/kg bw/d). Aspartame is broken down in the gastrointestinal tract by esterases and peptidases, which are then absorbed into the bloodstream (Magnuson et al., 2016).

3.1.2. Erythritol

Erythritol is a low-power sweetener widely found in nature, with a sweetness of about 70 % that of sucrose and negligible calories (Mazi and Stanhope, 2023). Erythritol can be mixed with stronger sugars to increase the sweetness and rich taste of the drink, which can mask some unwanted aftertastes, such as astringency and the stimulating effects of strong sweeteners, and improve the flavor of the drink (Regnat et al., 2018). Furthermore, when erythritol dissolves, because of its relatively high negative heat of dissolution, it exhibits a strong cooling effect (Regnat et al., 2018).

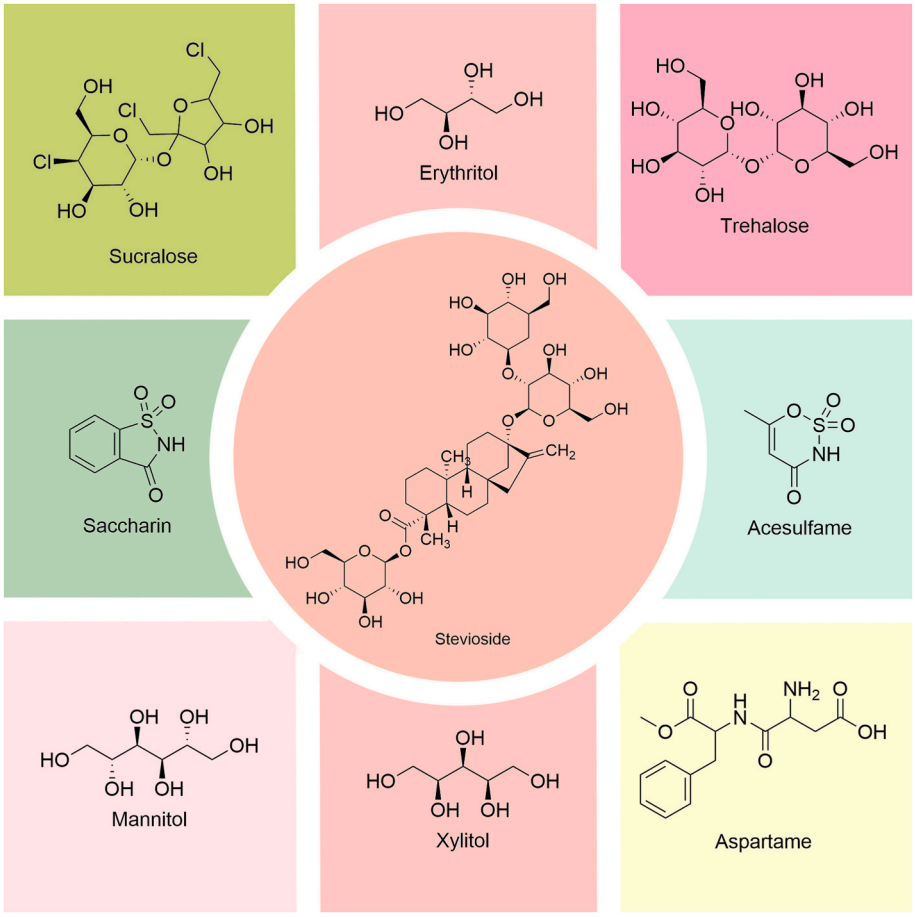

Fig. 2. Structural formula of sweeteners.

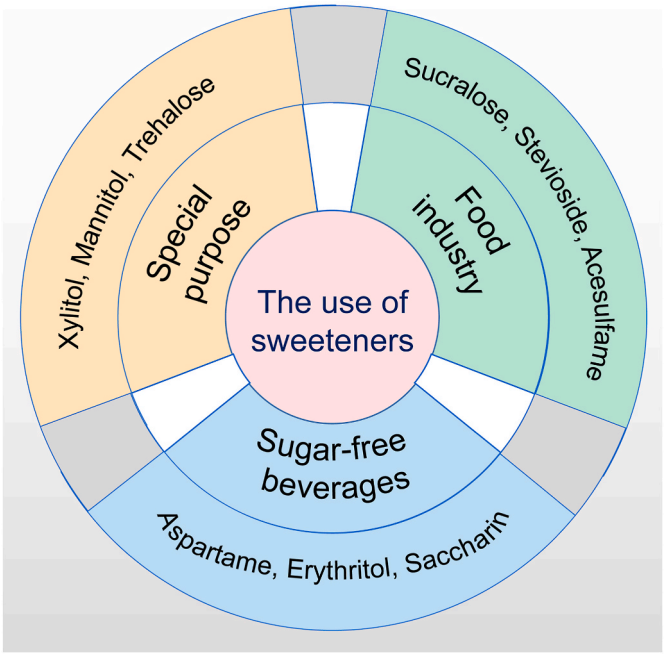

Fig. 3. Use of sweeteners (main).

Erythritol is mostly absorbed in the small intestine and then excreted in urine unmetabolized (Mazi and Stanhope, 2023).

3.1.3. Saccharin

Saccharin has been used for a long time and is about 300 times sweeter than sucrose (Chattopadhyay et al., 2014). It has a disagreeable bitter or metallic odor (Chattopadhyay et al., 2014). Since the parent compound is only slightly soluble in water, sweeteners are often used in the form of sodium or calcium salts (Chattopadhyay et al., 2014). It is often used in sugar-free beverages, and because it does not provide energy, does not participate in human metabolism, it is also used to produce sweet foods for diabetics (Romo-Romo et al., 2017).

The FDA has established the ADI for saccharin as 15 mg/kg bw/d. Most of the saccharin are excreted in the urine (Magnuson et al., 2016).

3.2. Used in the food industry

3.2.1. Sucralose

Sucralose is a non-caloric sweetener that is widely approved for food and beverage use worldwide (Magnuson et al., 2017). It is extracted from sucrose by selective substitution of three hydroxyl groups by chlorine atoms (Magnuson et al., 2017). Sucralose is about 600 times sweeter than sucrose, so adding very small amounts of sucralose can sweeten foods and drinks (Magnuson et al., 2017). It has good water solubility, chemical stability and thermal stability, and is often used in baking and frying foods (AlDeeb et al., 2013).

The FDA has established the ADI for sucralose as 5 mg/kg bw/d. Sucralose is poorly absorbed, undergoes little metabolism (Del Pozo, Gómez-Martínez, Díaz, Nova, Urrialde and Marcos, 2022).

3.2.2. Stevioside

Stevioside is a natural sweetener extracted from the plant stevia, which tastes similar to sucrose and is about 200–300 times sweeter than sucrose (Peteliuk et al., 2021). It is often used in candy, yogurt, baked goods. In addition, because stevioside has very low calories and does not participate in human metabolism, it can be eaten by diabetes, cardiovascular disease and obesity patients (Chattopadhyay et al., 2014).

The FDA has established the ADI for steviol as 4 mg/kg bw/d. Stevioside are hydrolyzed by intestinal flora in the colon and then excreted in the urine after gluconaldehyde acidification by the liver (Geuns et al., 2007).

3.2.3. Acesulfame

Acesulfame is a non-caloric sweetener that is about 120 times sweeter than sucrose (Chattopadhyay et al., 2014). It is thermally stable and can be used in cooking and baking, but when used alone to sweeten a food or drink, it can have a bitter taste, so it is often mixed with other sweeteners (usually sucralose or aspartame), showing a synergistic effect to make the mixture sweeter than its ingredients, and is often used in various dry grain products and alcoholic beverages (Chattopadhyay et al., 2014).

The FDA has established the ADI for Ace-K as 15 mg/kg bw/d. Acesulfame is excreted by the kidney without metabolites (Magnuson et al., 2016).

3.3. Special purposes (see Table 1)

3.3.1. Xylitol

Xylitol, as the representative sweetener of the polysugar alcohols group, has been shown to have dental health benefits and reduce the risk of dental caries (Salli et al., 2019). And because it is indigestible but fermentable, it also helps relieve constipation and improve bone mineral density (Salli et al., 2019). It can also regulate the immune system, which together with its antibacterial activity greatly reduces the risk of respiratory infections, sinusitis and otitis media (Salli et al., 2019), and NADPH produced during xylitol metabolism helps treat hemolytic anemia associated with Glucose-6-phosphate deficiency (Ahuja et al., 2020).

About half of xylitol is absorbed through passive diffusion in the intestine, and the rest is broken down in the intestine by intestinal flora (Salli et al., 2019).

3.3.2. Mannitol

Mannitol is a natural sweetener. Its osmotic diuretic properties allow it to be used as an intravenous solution for the treatment of intracranial pressure increase and brain edema after brain injury (Moriconi et al., 2020), and it is the main drug for the treatment of cerebral hemorrhage (Huang et al., 2020). However, attention should be paid to the side effects such as intracranial pressure (ICP) rebound and acute kidney failure after repeated administration (Huang et al., 2020).

3.3.3. Trehalose

Trehalose is a naturally occurring non-reducing disaccharide with a small molecular weight and easy absorption by the skin (Vinciguerra et al., 2022). Trehalose enters the cell to play its unique role of water replacement stress factor and protection of cell membrane (Vinciguerra et al., 2022). It is widely used in the cosmetics and skin care industry due to its stability and freezing protection properties (Vinciguerra et al., 2022).

Table 1
Special uses of sweeteners.

Name	Broad categories of use	Specific use
Xylitol	Oral products	Mouthwash (Krupa et al., 2022), toothpaste (Riley et al., 2015)
	Medicines	Anti-respiratory infection, treatment of hemolytic anemia and osteoporosis, anti-cancer and anti-inflammatory, etc (Ahuja et al., 2020)
Mannitol	Medicines	Treatment of cerebral hemorrhage (Huang et al., 2020), intracranial pressure increased and brain edema after brain injury (Moriconi et al., 2020), etc
Trehalose	Cosmetics and skincare products	Bath oils, hair growth tonics, and moisturizers (Ohtake and Wang, 2011)

Trehalose is enzymatically hydrolyzed in the small intestine by a trehalose-specific disaccharidase into two d-glucose molecules, which are subsequently absorbed and metabolized (Richards et al., 2002).

4. The benefits of food sweeteners

4.1. Food sweeteners are beneficial for weight control

4.1.1. Sweeteners can effectively reduce the consumption of sugars and fats

Raben et al. conducted a 10-week controlled study on overweight subjects, comparing the effects of daily consumption of sucrose and artificial sweeteners (54 % aspartame, 23 % cyclamate, 22 % acesulfame, and 1 % saccharin). The results showed that those who consumed sucrose had increased energy and fat intake, body weight gain and elevated blood pressure (Raben et al., 2002). In contrast, no such effects were observed in subjects who consumed artificial sweeteners. The findings indicate that artificial sweeteners, when compared to sucrose, result in a reduction of sugar and fat intake, leading to a slight decrease in body weight (Raben et al., 2002; Sørensen et al., 2014).

4.1.2. Aspartame helps obese people lose weight

To investigate the potential of artificial sweeteners in long-term food intake and body weight management, Tordoff and Alleva conducted a study where free-living normal weight participants were given 1150 g of aspartame soda or high fructose corn syrup (HFCS) daily. The results showed that consuming aspartame-sweetened soda reduced calorie intake and weight loss in men, while consuming high fructose corn syrup soda increased calorie intake and gained weight (Tordoff and Alleva, 1990).

Blackburn et al. conducted a long-term investigation and study on 163 obese women to assess the potential impact of incorporating aspartame into the weight control regimen. Data analysis revealed a positive correlation between aspartame intake and percentage weight loss during active weight loss among women in the aspartame-treated group (Blackburn et al., 1997). Participants in the aspartame group exhibited a slower rate of initial weight regain during maintenance and follow-up compared to those in the non-aspartame group (Blackburn et al., 1997). The findings indicated that women who received aspartame-based intervention exhibited more significant weight loss and less weight regain compared to the control group (Blackburn et al., 1997). Therefore, the weight management program incorporating aspartame was deemed more effective in facilitating weight reduction among obese individuals (Blackburn et al., 1997).

4.1.3. Sucralose helps with weight control

Ruyter and colleagues carried out an 18-month experimental investigation into the effects of NNS. In this study, a total of 203 children were randomly assigned to two groups: one group received a beverage containing NNS (specifically sucralose and acesulfame), while the other group consumed a sugar-sweetened beverage without any added NNS (Wilk et al., 2022). After 18 months, the satiation effects of NNS and SSBs on subjects were comparable, resulting in a decreased desire to consume both types of beverages (Wilk et al., 2022). A subsequent investigation revealed that NNS exhibited superior efficacy in reducing daily energy intake compared to SSBs (Wilk et al., 2022). Consequently, the utilization of NNS as a substitute for sugar may contribute significantly to weight management (Wilk et al., 2022).

4.1.4. Erythritol reduces obesity and impaired glucose tolerance induced by high-fat diet

Kawano's team investigated the impact of erythritol on metabolic disorders induced by a high-fat diet (HFD) in mice, revealing potential therapeutic benefits (Kawano et al., 2021). The mice in the experimental group received an additional injection of erythritol, while those in the control group were solely administered a high-fat diet. It was demonstrated that starting from 11 weeks of age, mice in the experimental group supplemented with an additional 5 % erythritol exhibited significant weight reduction, enhanced glucose tolerance and increased energy expenditure (Kawano et al., 2021).

4.1.5. The effect of artificial sweeteners on appetite

The effect of artificial sweeteners on hunger, satiety, and long-term dietary patterns is a complex and controversial area of research. Compared to caloric sweeteners, although NNS appears to elicit different brain responses in appetite and reward regions, the finding is unclear whether these different brain responses can predict subsequent metabolic consequences (Yunker et al., 2020). There is some consensus on the potential benefits of artificial sweeteners in reducing net energy intake and aiding weight management, the mechanisms by which they affect eating behavior, glucose homeostasis and weight control remain complex and not fully understood (Wilk et al., 2022). This is associated with multiple factors, including food intake, reward depend insulin secretion, energy expenditure and glucose homeostasis (O'Connor et al., 2021).

4.2. Sweeteners are beneficial for controlling blood glucose levels

4.2.1. Effects of SSBs on individuals with a healthy status

In a meta-analysis of prospective cohort studies examining the relationship between SSBs consumption and diabetes risk, daily intake of such beverages (1–2 servings of sugar-sweetened beverages per day) was found to be associated with a 26 % higher risk of T2D compared to no or infrequent consumption (less than one serving per month) (Evert et al., 2019; Pan et al., 2012).

However, in another meta-analysis report, drinking the same amount of water instead of SSBs reduced the risk of T2D by 7–8 %, drinking diet soda increased the risk of T2D by 8 % and drinking regular soda increased the risk of T2D by 13 % (Evert et al., 2019; Imamura et al., 2015).

These analyses indicate that substituting regular soda with diet soda may lower the risk of developing T2D. However, both diet soda and SSBs increase the risk of T2D.

4.2.2. Erythritol helps control blood glucose in patients with T2D

The Omiya Research Laboratory conducted a study to investigate the impact of oral erythritol on blood glucose and insulin levels in healthy individuals, as well as estimating its energy availability in humans (Noda et al., 1994). The experimental results demonstrated that erythritol did not elicit an increase in serum glucose or insulin levels, whereas the identical dose of glucose provoked a rapid elevation of blood glucose and insulin levels within 30 min (Noda et al., 1994).

In a clinical trial conducted by M Ishikawa, 11 diabetic patients were administered oral erythritol at a dosage of 20 g per day for a period of 14 days (Ishikawa et al., 1996). Over the course of this period, there was a gradual decrease in both mean blood glucose and glycosylated hemoglobin levels among the patients. The study's findings indicate that twice-daily administration of erythritol did not have any significant impact on diabetic patients' metabolism or their ability to control blood glucose (Ishikawa et al., 1996).

A study on the anti-postprandial hyperglycemic effect of erythritol in alloxan induced diabetic mice models found that erythritol likely exerts its activity through competitive inhibition of α-glucosidase (Wen et al., 2018). This suggests that erythritol can be used as a glucose substitute to control postprandial blood glucose levels and as a treatment for T2D (Wen et al., 2018).

According to the above studies, erythritol has been shown to elicit the secretion of intestinal hormones, resulting in delayed gastric emptying and reduced intestinal glucose absorption (Ishikawa et al., 1996). The administration of acute doses of erythritol (20–75 g) had no or little effect on blood glucose or insulin levels. Consequently, erythritol exhibits considerable potential as a favorable substitute for saccharides in both individuals with good health and those suffering from

diabetes (Mazi and Stanhope, 2023).

4.2.3. Stevioside have dual positive effects as anti-hyperglycemic and a blood pressure-lowering substance

Jeppesen's team conducted a long-term study on Goto Kakizaki (GK) rats with T2D to evaluate the potential antihyperglycemic and antihypertensive effects of their intervention (Jeppesen et al., 2003). The rats were administered a daily dose of 0.025 g/kg stevioside (purity >99.6 %) for six weeks, and at the end of this period, arterial glucose tolerance tests were conducted on the conscious rats. The results showed that stevioside enhanced the first-phase insulin response and suppressed glucagon levels, which may partly be related to the induction of genes involved in glycolysis (Jeppesen et al., 2003). It also improves nutrient sensing mechanisms, increases cytosolic long-chain fatty acyl-coenzyme A (CoA) and regulates phosphodiesterase 1 (PDE1) downregulation (Jeppesen et al., 2003). In addition, stevioside can significantly inhibit systolic and diastolic blood pressure (Jeppesen et al., 2003). In conclusion, stevioside exhibits dual positive effects on both anti-hyperglycemia and a blood pressure-lowering substance, indicating its therapeutic potential in the treatment of T2D and metabolic syndrome (Dyrskog et al., 2005; Jeppesen et al., 2003).

4.3. Sweeteners are beneficial for decreasing the incidence of dental caries

4.3.1. Pathogenesis of dental caries

The role of sugars in the development of dental caries is widely acknowledged as paramount among dietary factors. The majority of studies have demonstrated a significant correlation between sugar consumption and the pathogenesis of dental caries. After the fermentation of sucrose by oral bacteria, sucrose molecules are converted into energy and a significant amount of acidic substances (Ferrazzano et al., 2015). These substances increase the concentration of hydrogen ions, leading to a reduction in pH, and dissolve enamel, cementum and dentin (Ferrazzano et al., 2015). Frequent exposure to carbohydrates creates favorable conditions for the development of dental caries (Ferrazzano et al., 2015). The consumption of sweeteners instead of sucrose alters the metabolic process by decreasing lactic acid production in the oral cavity. Consequently, aspartame, saccharin, cyclamate, xylitol and mannitol are commonly utilized as sugar substitutes for patients with active dental caries (Ferrazzano et al., 2015; Gupta et al., 2013).

4.3.2. Erythritol reduces the risk of dental caries

Early studies have shown that erythritol inhibits growth, lactate production, and plaque formation in a variety of associated bacteria like *S. mutans* (deCock et al., 2016*)*. Furthermore, erythritol does not act as a substrate for *S. mutans* cell aggregation and is not involved in cell adhesion (deCock et al., 2016). A 6-month human study was conducted to investigate the impact of sweets containing erythritol, xylitol and sorbitol on premonitory symptoms of dental caries. The present study demonstrated that erythritol, xylitol and sorbitol exhibited reductions in the weight of fresh plaques, with erythritol demonstrating superior efficacy compared to xylitol and sorbitol (deCock et al., 2016).

4.3.3. Stevia glycosides as noncariogenic sweeteners

Brambilla et al. conducted an assessment of the impact of stevia extract on Streptococcus mutans biofilm formation in vitro and plaque pH in vivo (Brambilla et al., 2014). Three solutions containing 10 % stevioside, rebaudioside A, and sucrose were prepared (Brambilla et al., 2014). Each solution was used to rinse the mouths of 20 volunteers for 1 min, and plaque pH was measured at seven time points after each rinse (Brambilla et al., 2014). The experiment revealed a statistically significant reduction in pH value resulting from sucrose rinsing solution compared to stevia extract, indicating that stevia extract is non-acidic and does not cause substantial acidification leading to enamel dissolution, thus exhibiting certain anti-caries properties (Brambilla et al., 2014).

4.4. The therapeutic value of sweeteners for certain diseases

4.4.1. Various medical values of stevia glycosides

Multiple experimental studies have shown that steviol glycosides and their related compounds may have broad medical value (Ferrazzano et al., 2015; Orellana-Paucar, 2023), including anti-hyperglycemia, anti-hypertension, antioxidant (Dyrskog et al., 2005), anti-tumor (Chen et al., 2018; Mizushina et al., 2005; Velesiotis et al., 2022), antiviral (Takahashi et al., 2001), immunomodulatory actions (Boonkaewwan et al., 2006; Sehar et al., 2008), gastric, protective activity (Shiozaki et al., 2006), kidney protection, diuresis (Melis, 1995) and anti-diarrhea.

4.4.2. Mannitol is widely used in pharmaceutical and medical fields

Mannitol is chemically inert (Martínez-Miranda et al., 2022) and can be incorporated into pharmaceutical formulations of chewable tablets and pellet powders to prevent moisture absorption from the air (Akinterinwa et al., 2008). It also serves as a medication for diabetic patients (Ohrem et al., 2014). In sugar-free gum, mannitol is non-cariogenic and imparts a sweet taste (Ortiz et al., 2013). In the nano-confinement of acetaminophen, mannitol increases the dissolution rate of the drug (Saffari et al., 2016). Mannitol is utilized in the treatment of ischemia-reperfusion injury during renal transplantation and partial nephrectomy (Lugo-Baruqui et al., 2019). In products that contain hyaluronic acid, mannitol serves as a protective agent against reactive oxygen species in vivo (André and Villain, 2017). Additionally, mannitol can be employed to evaluate bronchial hyper-responsiveness, which aids in the diagnosis of asthma (Backer, 2019).

5. The disadvantages of food sweeteners (see Table 2)

5.1. Effects on gut microbes

5.1.1. Mechanisms by which artificial sweeteners affect the gut microbiota

The mechanisms by which artificial sweeteners influence the gut microbiota may encompass two primary aspects. Firstly, artificial sweeteners can alter the composition and abundance of gut microbiota by modulating their metabolic pathways or modifying their living environment (Di Rienzi and Britton, 2020). Secondly, gut microbiota alter their genetic information to enhance their competitiveness for growth and reproduction (Di Rienzi and Britton, 2020).

Aspartame mainly resulted in an increase in *Enterobacteriaceae* and a decrease in *Clostridium cluster XI* (Feng et al., 2024). *Clostridium cluster XI* is a probiotic, and the reduction of *Clostridium cluster XI* may affect the number of pathogenic bacteria in other gut microbiota (Feng et al., 2024). The increase in *Enterobacteriaceae* may produce more harmful proteins, gases, and short-chain fatty acids, which in turn affect the intestinal microbial population (Feng et al., 2024).

Sucralose led to an increase in the abundance of *Firmicutes* while causing a decrease in *Lactobacillus acidophilus* (Méndez-García et al., 2022). These microbial alterations are correlated with changes in insulin levels, insulin homeostasis, as well as inflammation in both the gut and liver (Méndez-García et al., 2022).

Administration of Ace-K significantly enhances lymphocyte migration to intestinal microvessels, elevates the levels of pro-inflammatory cytokines, and suppresses the expression of both GLP-1R and GLP-2R receptors (Hanawa et al., 2021). As a result, Ace-K affected multiple gut microbial populations including *Actinobacteria*, *Bacteroidetes*, *Deferribacteres*, *Proteobacteria* and *Verrucomicrobia* (Hanawa et al., 2021).

Short-term consumption of saccharin did not significantly alter the composition of the gut microbiota (Serrano et al., 2021). However, the effects of saccharin remain controversial among scholars, necessitating additional experimental investigations to clarify its biological and physiological impacts.

Table 2
Recent findings of sweeteners.

Sweeteners and related products	Research population or experimental subjects	Conclusions	References
Sweetened beverages	Pancreatic cancer patients and patients without cancer diagnosis	A positive correlation between consumption of beverages containing sweeteners and the development of pancreatic cancer.	Davis et al. (2023)
Aspartame	Aspartame and the target of gastric cancer	Aspartame may promote the progression of gastric cancer by affecting multiple keys signaling proteins and regulatory factors.	Chen and Hou (2024)
Aspartame, Ace-K	Adults aged ≥18 years with Internet access	Aspartame and Ace-K are associated with cancer risks, especially breast cancer and obesity-related cancers.	Debras et al. (2022)
Ace-K	C57BL/6 J mice (8 weeks old)	Ace-K affected multiple gut microbial populations including *Actinobacteria*, *Bacteroidetes*, *Deferribacteres*, *Proteobacteria* and *Verrucomicrobia*	Hanawa et al. (2021)
Erythritol	Patients and healthy volunteers	Elevated levels of erythritol directly enhance platelet reactivity and increase the risk of thrombosis by promoting calcium release and aggregation within platelet cells, thereby augmenting platelet responsiveness to various agonists.	Witkowski et al. (2023)
Sucralose	Male C57BL/6 mice (8 weeks old)	Sucralose may promote ROS production via taste receptor T1R3, thereby facilitating hepatic lipogenesis.	Wu et al. (2022)

5.1.2. Non-caloric artificial sweeteners (NAS) supplements cause dysbiosis of gut microbes

To investigate the effects of artificial sweeteners on gut microbiota, Suez and colleagues performed a series of experiments with NAS supplements consisting of saccharin, sucralose or aspartame, which were added to the daily diet of 10-week-old C57Bl/6 mice (Suez et al., 2014). The results showed that the intake of NAS supplements could induce intestinal microbiota dysbiosis and glucose intolerance by inducing changes in the composition and function of intestinal microbiota in mice (Suez et al., 2014).

On the basis of this experiment, Suez et al. collected data from 172 randomly selected healthy subjects for analysis (Suez et al., 2014). The findings indicate that the human gut microbiota changes after consumption of sweeteners, particularly non-caloric artificial sweeteners, and the consumption of NAS may be positively correlated with the *Enterobacteriaceae family*, the *Deltaproteobacteria class*, and the *Actinobacteria phylum* (Suez et al., 2014*)*. In addition, in a week-long follow-up study of seven healthy subjects, they obtained results similar to those in the mouse experiment (Ruiz-Ojeda et al., 2019; Suez et al., 2014).

The results of these three experiments suggest that the consumption of NAS supplements (especially large doses of saccharin) may induce alterations the gut microbiota, which can have harmful effects on glucose tolerance. Notably, some of the bacterial taxa that changed after NAS supplements consumption were associated with T2D in humans (Ruiz-Ojeda et al., 2019; Suez et al., 2014).

5.1.3. Ace-K alters intestinal microbial diversity

To investigate the effects of high-intensity Ace-K on the gut microbiota, Frankenfeld et al. conducted a 4-day food record study in 31 adults, collected stool samples on day 5, and compared bacterial diversity in the samples using UniFrac analysis (Frankenfeld et al., 2015). The results show that the overall bacterial diversity of Ace-K consumers and non-consumers is different (Frankenfeld et al., 2015). Following Ace-K consumption, the number of bacterial species in the human gut decreased from 24 to 7, and the diversity of intestinal microbes decreased (Frankenfeld et al., 2015; Ruiz-Ojeda et al., 2019).

In another study, Bian et al. treated CD-1 mice (approximately 8 weeks of age) with Ace-K by gavage (Bian, Chi, Gao, Tu, Ru and Lu, 2017a). After a 4-week treatment, it was found that Ace-K disrupted the gut microbiome of mice, and the changes were highly sex-specific (Bian, Chi, Gao, Tu, Ru and Lu, 2017a). The abundance of *Bacteroides* and *Sutterella* in the gut of male mice was significantly increased, and ingestion of Ace-K may disrupt intestinal bacterial composition and activate bacterial energy harvesting pathways, resulting in a significant increase in male mouse body weight (Bian, Chi, Gao, Tu, Ru and Lu, 2017a). However, several intestinal bacteria genera, such as *Lactobacillus* and *Clostridium*, were also significantly reduced in the gut of female mice, and the consumption of Ace-K impairs the polysaccharide digestion and fermentation ability of the gut microbiome in female mice, possibly further affecting the host's energy collection (Bian, Chi, Gao, Tu, Ru and Lu, 2017a; Ruiz-Ojeda et al., 2019).

5.1.4. Sucralose perturbs the gut microbiota and increases the risk of inflammation

In a recent experiment aimed at investigating the structural and functional effects of sucralose on the host gut microbiota and associated inflammation, C57BL/6 male mice were given drinking water containing sucralose (0.1 mg/ml) for 6 months to detect differences in the composition and metabolites of the mice's gut microbiota, as well as the expression of inflammatory genes (Bian, Chi, Gao, Tu, Ru and Lu, 2017b).

The results showed that the consumption of sucralose for six months changed the composition of the gut microbiome, fecal metabolites, and the expression of pro-inflammatory genes in the liver of the mice (Bian, Chi, Gao, Tu, Ru and Lu, 2017b). At the same time, the enrichment of bacterial pro-inflammatory genes and the destruction of fecal metabolites suggest that 6 months of sucralose ingested at an ADI for humans may disrupt the gut microbiota, release more pro-inflammatory mediators and alter functional metabolites, thereby increasing the risk of developing tissue inflammation and further affecting other physiological functions in the body (Bian, Chi, Gao, Tu, Ru and Lu, 2017b).

5.2. Effects on glycemic levels

5.2.1. Sweeteners increase the risk of T2D

Most people believe that sweeteners do not pose a risk of raising blood sugar levels, hence sweeteners are often used as substitutes for sugar. However, in an 18-year follow-up study conducted by Fagherazzi et al. involving 61,440 women, it was found that frequent and prolonged consumption of artificial sweeteners in sachet or tablet form was associated with an increased risk of T2D (Fagherazzi et al., 2017). This indicates that artificial sweeteners may have a cumulative effect on the development of T2D (Fagherazzi et al., 2017). A large-scale cohort study (with a median follow-up period of 9.1 years) also indicated that individuals who consumed higher amounts of artificial sweeteners had a greater risk of developing T2D compared to those who did not consume artificial sweeteners (Debras et al., 2023).

The consumption of artificial sweeteners may lead to overeating, reduced secretion of hormones such as GLP-1, and impaired blood glucose regulation, which could ultimately contribute to the development of diabetes (Fagherazzi et al., 2017). Additionally, the high consumption of artificial sweeteners can also activate sweet taste receptors

T1R2 and T1R3, which may participate in metabolic regulation processes such as sugar perception, glucose homeostasis, and the release of satiety hormones (Fagherazzi et al., 2017). This could potentially promote intestinal glucose absorption and energy intake, thereby contributing to an increased risk of obesity and diabetes (Fagherazzi et al., 2017).

5.2.2. Sucralose may induce insulin resistance

In a randomized, double-blind crossover study, daily intake of 200 mg sucralose for four consecutive weeks was found to reduce systemic and hepatic insulin sensitivity in healthy volunteers (Lertrit et al., 2018). Prolonged use of sucralose may induce insulin resistance and reduce the acute insulin response, which could potentially serve as the earliest indicators for the development of T2D (Lertrit et al., 2018).

However, the clinical significance of these findings remains to be further elucidated (Lertrit et al., 2018). These observations indicate that artificial sweeteners may not be entirely beneficial for human health.

5.2.3. Sweetened beverages increase the risk of diabetes

An observational study by Nicolì et al. assessed the association between consumption of non-nutritious sweetened soft drinks and the risk of gestational diabetes in 376 pregnant women who were continuously screened for gestational diabetes at the Diabetes Clinic of the University Hospital of Pisa and found that consumption of non-nutritive-sweetened soft drinks was associated with an increased risk of gestational diabetes (Nicolì et al., 2021).

Additionally, in another study to assess the association between artificially sweetened beverages (ASBs) and SSBs consumption and the risk of developing diabetes, analysis of data from 64,850 postmenopausal women revealed that 4675 women developed diabetes during an average follow-up of 8.4 years (M. Huang et al., 2017). Both the intake of ASBs and SSBs was associated with an increased risk of diabetes. Furthermore, a dose-dependent relationship was observed between higher ASB consumption and an increased risk of developing diabetes in postmenopausal women (M. Huang et al., 2017). Therefore, the impact of sweeteners on blood glucose should be considered, and they should be used with caution.

5.3. Damage on circulatory system

5.3.1. Higher intake of ASBs increase the incidence of stroke

A multicenter longitudinal study of postmenopausal women in the United States (mean follow-up: 11.9 years) found that increased intake of ASBs was associated with a higher risk of stroke, particularly the small artery occlusion subtype, as well as an increased risk of coronary heart disease and all-cause mortality (Mossavar-Rahmani et al., 2019). However, due to the observational nature of this study, the underlying biological mechanisms remain to be explored.

5.3.2. Artificial sweeteners lead to the loss of anti-atherosclerotic activity

A study demonstrated that high-dosage treatment with artificial sweeteners (including aspartame, Ace-K, and saccharin) on human high-density lipoprotein (HDL) may impair the beneficial functions of HDL, resulting in the loss of antioxidant and anti-atherosclerotic activities (Kim et al., 2015). Aspartame and saccharin may cause toxicity to the human circulatory system by damaging the function of lipoproteins (Kim et al., 2015). Furthermore, Long-term consumption of artificial sweeteners, even though in lower dose, may accelerate atherosclerosis progression and promote cellular senescence via impairment of the function and structure of apolipoprotein A-I (apoA-I) and HDL (Jang et al., 2011).

5.3.3. Artificial sweeteners are associated with the risk of cardiovascular diseases

Furthermore, a study spanning over a decade revealed that substituting sugar with artificial sweeteners conferred no benefit for cardiovascular diseases outcomes (Debras et al., 2022). Specifically, aspartame consumption was linked to an increased incidence of cerebrovascular events, while Ace-K and sucralose were correlated with a higher risk of coronary heart disease (Debras et al., 2022).

In a large-scale cohort study, researchers identified a significant correlation between erythritol and the risk of major adverse cardiovascular events (MACE; includes death or nonfatal myocardial infarction or stroke) and thrombosis (Witkowski et al., 2023). Mechanistic studies have demonstrated that elevated levels of erythritol directly enhance platelet reactivity and increase the risk of thrombosis by promoting calcium release and aggregation within platelet cells, thereby augmenting platelet responsiveness to various agonists (Witkowski et al., 2023).

5.4. Damage on the embryonic development

5.4.1. Artificially sweetened soft drinks increase the risk of preterm delivery

Many people believe that the consumption of sweeteners can satisfy pregnant women's cravings for sweetness while simultaneously mitigating the risks of weight gain and gestational diabetes (Concha et al., 2023). However, a Danish prospective cohort study suggests that daily consumption of artificially sweetened soft drinks may be associated with an elevated risk of preterm delivery (<37 weeks) (Halldorsson et al., 2010). Additionally, The Norwegian Pregnant Cohort Study has also demonstrated that daily consumption of artificially sweetened beverages may increase the risk of preterm delivery in pregnant women (Englund-Ögge et al., 2012). However, due to the limitations of observational studies, the mechanisms underlying the increased risk of preterm birth remain to be elucidated.

5.4.2. Artificial sweeteners increase offspring's sweet food preference

Research indicates that children's taste preferences may be influenced in utero by maternal dietary exposure (Goran et al., 2019; Ventura and Worobey, 2013). The capacity for taste perception originates from the development and initial functioning of gustatory and olfactory systems in the utero (Ventura and Worobey, 2013).

An animal study demonstrated that maternal intake of Ace-K during pregnancy or lactation alters sweet preference in adult offspring (Goran et al., 2019; Zhang et al., 2011). Ace-K may be transferred to amniotic fluid or breast milk after absorption by the digestive tract epithelium, and mice can ingest sweeteners through maternal amniotic fluid (prenatal) or breast milk (postnatal), thus affecting the sweet taste preference of adult mice (Goran et al., 2019; Zhang et al., 2011). Additionally, in another study, prenatal exposure to aspartame was found to increase the consumption of sweet foods in adulthood (Goran et al., 2019; von Poser Toigo, Huffell, Mota, Bertolini, Pettenuzzo and Dalmaz, 2015). Therefore, the use of sweeteners should be approached with caution during pregnancy and lactation.

5.5. Promoting on the weight gain and hepatic lipogenesis

5.5.1. ASBs are associated with childhood obesity

A longitudinal study involving 13,170 children aged 7–11 years revealed that the consumption of ASBs was associated with body mass index (BMI) and body fat percentage in prepubertal children (Laverty et al., 2015). Moreover, a regional study involving 1200 children in England found that the intake of ASBs was positively correlated with changes in obesity among children aged 5–9 years (Laverty et al., 2015).

Sweeteners may increase appetite or train the palate to enjoy similar sweet foods, and may also lead individuals to consciously overcompensate for these low calorie choices and overindulge in other intake (Laverty et al., 2015). However, these mechanisms require further investigation.

5.5.2. Saccharin induces weight gain and obesity

In a 14-week experiment involving 16 male Wistar rats, it was shown

that despite similar total caloric intake, the weight gain induced by saccharin was more significant compared to the non-sugar control group (Foletto et al., 2016). Similarly, in the study on Sprague-Dawley rats, Swithers and Davidson also demonstrated that rats consuming saccharin-sweetened yogurt exhibited greater increases in body weight and body fat compared to those consuming glucose-sweetened yogurt (Swithers and Davidson, 2008). These results may suggest that consuming artificial sweeteners could lead to weight gain and obesity by disrupting fundamental homeostatic and physiological processes (Swithers and Davidson, 2008).

5.5.3. Sucralose facilitates hepatic lipogenesis

Among artificial sweeteners, sucralose is considered safe and widely used due to its pH and thermal stability (Wu et al., 2022). However, some studies have suggested that sucralose may promote the upregulation of pro-inflammatory gene expression in the liver, induced hepatic lymphocytic infiltration, and increase the levels of hepatic lipogenesis-related gene in rats (Wu et al., 2022).

In order to investigate the impact of sucralose on hepatic steatosis associated with obesity, Wu et al. conducted a 12-week experiment on male C57BL/6 mice to assess the effects of sucralose on hepatic lipid accumulation (Wu et al., 2022). The experimental results at 12 weeks demonstrated that both the HFD group (fed a high-fat diet) and the HFSUC group (HFD supplemented with sucralose) exhibited significant body weight gain compared to the Chow group (fed with a chow diet) (Wu et al., 2022). Notably, the HFSUC group showed significantly higher liver weight than the HFD group (Wu et al., 2022). These data suggested that sucralose supplementation exacerbated high-fat diet-induced hepatic steatosis (Wu et al., 2022). Sucralose may promote ROS production via taste receptor T1R3, thereby facilitating hepatic lipogenesis (Wu et al., 2022).

5.5.4. Aspartame and sucralose induce cytoplasmic fatty change of liver

To investigate the effects of aspartame and sucralose on the cytoplasmic fatty change of liver, Haq et al. conducted a study using Wistar albino rats (Haq et al., 2019). The experimental results demonstrated that both aspartame and sucralose caused fatty changes in liver cells (Haq et al., 2019). Notably, the effect was most obvious in the high-dose aspartame group, and the least obvious in the low-dose sucralose group (Haq et al., 2019). The fatty change observed in this study may be attributed to oxidative stress (Haq et al., 2019). However, further research is required to elucidate the effects of prolonged sweetener exposure.

5.6. Promoting on cancer development

5.6.1. Aspartame may promote the progression of gastric cancer

In a new study, Chen et al. combined network toxicology with molecular docking strategies to explore the potential carcinogenicity of aspartame and its molecular mechanism of action, and conducted preliminary validation through microarray data analysis and survival analysis (Chen and Hou, 2024).The findings suggest that aspartame has the potential to affect various cancer-related proteins, interfere with biomolecular function, and increase the likelihood that cells will cause cancer (Chen and Hou, 2024).

So that, aspartame may promote the progression of gastric cancer by affecting multiple keys signaling proteins and regulatory factors (Chen and Hou, 2024). Key proteins like AKT1, IL1B, SRC, EGFR, MMP9, CCND1, GSK3B, CASP3, NFKBIA, and MMP2 play roles in various biological functions such as cell growth, cell death, immune response, cell attachment, and restructuring of the extracellular matrix (Chen and Hou, 2024).

5.6.2. Sweeteners increase the risk of pancreatic cancer

Pancreatic cancer is a highly lethal malignancy. A report by Davis et al. mentions numerous studies showing a positive correlation between consumption of beverages containing sweeteners and the development of pancreatic cancer (Davis et al., 2023).

Increased sweetener intake is more likely to cause weight gain and T2D. These unhealthy factors further contribute to insulin resistance, oxidative stress, and chronic inflammation, a range of diseases associated with the development and progression of cancer. Insulin resistance increases the production of insulin-like growth factor. Insulin-like growth factor is associated with increased cell proliferation and survival, which can be carcinogenic and increase the risk of pancreatic cancer (Davis et al., 2023).

5.6.3. Artificial sweeteners increase the risk of breast cancer and obesity-related cancers

The NutriNet-Sante study began in 2009 with 102,865 French volunteers (78.5 % female) followed for a median of 7.8 years (Debras et al., 2022). This large-scale population-based cohort study suggests associations between artificial sweeteners, especially aspartame and Ace-K, and cancer risk, more specifically breast cancer and obesity-related cancers (Debras et al., 2022).

Multiple in vitro studies have also demonstrated that aspartame significantly increases the risk of cancer through mechanisms related to inflammation, angiogenesis, promotion of DNA damage, and inhibition of apoptosis (Czarnecka et al., 2021).

5.6.4. Aspartame increases the risk of thyroid cancer

Navdeep Singh et al. completed a retrospective observational study. This retrospective observational study enrolled 50 patients with proven diagnosis of well-differentiated thyroid cancer and 50 control subjects diagnosed as having benign thyroid nodule by fine-needle aspiration (Singh et al., 2020). They found an increased risk of thyroid cancer with artificial sweetener consumption (Singh et al., 2020).

One study mentioned that aspartame is further metabolized into formaldehyde in the body. Formaldehyde causes degeneration of thyroid follicular epithelial cells (Sachmechi et al., 2018). It is also possible that formaldehyde increases stimulation of the thyroid follicles, which rapidly worsens the gland's capacity (Sachmechi et al., 2018).And according to another research, artificial sweeteners significantly reduce the number of beneficial bacteria in the gut, which leads to an increase in pH (Sachmechi et al., 2018). As the massive reduce of gut microbes, which suppresses the immune system and then the thyroid gland (Sachmechi et al., 2018).

6. Discussion

Embarking on a journey through the lens of scientific scrutiny, a burgeoning body of evidence, initially rooted in experimental endeavors, sheds light on the multifaceted implications of artificial sweetener consumption. These sweet substitutes, pitted against their caloric counterparts, have unfurled a tapestry of benefits, notably for individuals embroiled in the battle against obesity. The nexus between artificial sweeteners and weight mitigation unfurls a promising narrative, heralding not only a decline in adiposity for those with excessive weight but also a maintenance of a healthful weight continuum for individuals within the normal weight spectrum.

The physiological nuances tethered to artificial sweetener consumption extend to the glycemic realm, where a modulation of blood glucose levels takes center stage. The mechanistic underpinning of this glucose modulation hinges on the interaction between artificial sweeteners and GPS-1 cells nestled within the gastrointestinal tract. This interaction orchestrates a modulatory dance, influencing the secretion of these cells, thereby painting a picture of glycemic regulation. Moreover, the narrative of short-term supplementation with artificial sweeteners unveils a potential boon for patients grappling with digestive disorders, especially those with residual GPS-2 isolated cells (Iizuka, 2022). Moreover, artificial sweeteners may act as deterrents against dental caries by altering the proliferation of oral bacteria and the

resultant production of acidic substances, thus, they are perceived as an advantageous choice for fostering oral health (Ferrazzano et al., 2015). The interplay between artificial sweeteners, oral bacteria proliferation, and the genesis of acidic substances sketches a scenario of reduced dental caries risk (Ferrazzano et al., 2015). This, in turn, propels artificial sweeteners to the forefront as a harbinger of oral health promotion (Ferrazzano et al., 2015).

With the expanding user base and escalating popularity of artificial sweeteners, a burgeoning contingent of researchers have embarked on investigations into their supplementary effects on human physiology, and the underlying mechanistic pathways, propelling further scrutiny into the potential risks linked to their consumption. A substantial body of research conducted over the preceding decade has elucidated that the employment of artificial sweeteners can perturb the stability and biodiversity of intestinal microbiota, alongside inducing a decrement in intestinal enzyme activity and fostering glucose intolerance within consumers (Suez et al., 2014). Furthermore, it may augment the likelihood of gastrointestinal inflammation.

In an extended perspective, the prolonged and habitual ingestion of sweeteners might culminate in blood glucose level aberrations, heightened fat accumulation and steatosis, alongside an amplified risk of diabetes. Recent scholarly inquiries have underscored a possible correlation between the intake of erythritol and the onset of adverse cardiovascular events (Witkowski et al., 2023), while aspartame has been purported to harbor carcinogenic attributes (Chen and Hou, 2024). These empirical revelations accentuate the profound implications of sweeteners on the predisposition towards cardiovascular ailments and cancer, rendering a comprehensive understanding of artificial sweeteners' physiological impacts imperative for public health policy and individual dietary choices.

In summary, while artificial sweeteners present a promising alternative to sugar with regards to weight management and blood sugar regulation, the burgeoning body of evidence pointing towards potential adverse effects, particularly in the realms of gastrointestinal health, metabolic disorders, cardiovascular diseases, and oncogenesis, necessitates a judicious approach in their endorsement and utilization. The ongoing research endeavors aimed at unraveling the intricate interplay between artificial sweeteners, human physiology, and disease susceptibility will indubitably contribute to a more nuanced understanding and consequently, more informed dietary recommendations. As the pendulum of scientific inquiry swings, the comprehensive elucidation of the benefits and potential pitfalls of artificial sweeteners continues to be an academic and public health priority. Through the lens of rigorous scientific inquiry, the journey towards unraveling the full spectrum of artificial sweetener implications continues unabated.

7. Outlook

While the advantages and disadvantages are contradictory, it is imperative to conduct more extensive large-scale experiments in order to further investigate the effects and mechanisms of sweetener usage on glucose metabolism and fat metabolism under insulin influence. Additionally, it is crucial to evaluate both the advantages and disadvantages of sweeteners on blood glucose levels and body weight. In order to control diabetes, obesity and other common long-term public problems worldwide that need to be controlled and solved. Some animal experiments on the effect of sweetener use on digestive tract diseases can also be developed to study the good or bad of sweetener for common and special types of digestive tract diseases and whether there is a remission effect. For dental caries, a variety of different sweeteners can be used in combination with other drugs to see whether the treatment effect is improved, has no effect, or decreases the effect. Studies should also take into account individual differences in physical fitness. Through a comprehensive introduction to sweeteners, our goal is to assist individuals in accurately comprehending the impact of sweeteners on the human body, so that healthy individuals to use sweetener-containing products appropriately according to their own needs, patients with gastrointestinal diseases, hyperglycemia, diabetes, cardiovascular diseases, pregnant women and other individuals should regulate the intake of sweeteners based on their physical conditions in order to prevent or alleviate disease progression, so as to achieve today's social needs for the goal of healthy life.

CRediT authorship contribution statement

Qiao-Yun Hong: Writing – original draft, Conceptualization, Methodology, Supervision, Investigation. **Yan Huang:** Writing – original draft, Investigation. **Jie Yang:** Writing – original draft, Writing – review & editing. **Long-Teng Su:** Writing – original draft, Writing – review & editing. **Zhao-Ri Dai:** Writing – original draft, Supervision. **Cheng-Fei Zhao:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No data was used for the research described in the article.

References

Ahuja, V., Macho, M., Ewe, D., Singh, M., Saha, S., Saurav, K., 2020. Biological and pharmacological potential of xylitol: a molecular insight of unique metabolism. Foods 9 (11). https://doi.org/10.3390/foods9111592.

Akinterinwa, O., Khankal, R., Cirino, P.C., 2008. Metabolic engineering for bioproduction of sugar alcohols. Curr. Opin. Biotechnol. 19 (5), 461–467. https://doi.org/10.1016/j.copbio.2008.08.002.

AlDeeb, O.A., Mahgoub, H., Foda, N.H., 2013. Sucralose. Profiles Drug Subst. Excipients Relat. Methodol. 38, 423–462. https://doi.org/10.1016/b978-0-12-407691-4.00010-1.

André, P., Villain, F., 2017. Free radical scavenging properties of mannitol and its role as a constituent of hyaluronic acid fillers: a literature review. Int. J. Cosmet. Sci. 39 (4), 355–360. https://doi.org/10.1111/ics.12386.

Backer, V., 2019. Mannitol and the mechanisms behind bronchoconstriction. J. Allergy Clin. Immunol. 144 (4), 931–932. https://doi.org/10.1016/j.jaci.2019.06.048.

Bian, X., Chi, L., Gao, B., Tu, P., Ru, H., Lu, K., 2017a. The artificial sweetener acesulfame potassium affects the gut microbiome and body weight gain in CD-1 mice. PLoS One 12 (6), e0178426. https://doi.org/10.1371/journal.pone.0178426.

Bian, X., Chi, L., Gao, B., Tu, P., Ru, H., Lu, K., 2017b. Gut microbiome response to sucralose and its potential role in inducing liver inflammation in mice. Front. Physiol. 8, 487. https://doi.org/10.3389/fphys.2017.00487.

Blackburn, G.L., Kanders, B.S., Lavin, P.T., Keller, S.D., Whatley, J., 1997. The effect of aspartame as part of a multidisciplinary weight-control program on short- and long-term control of body weight. Am. J. Clin. Nutr. 65 (2), 409–418. https://doi.org/10.1093/ajcn/65.2.409.

Boonkaewwan, C., Toskulkao, C., Vongsakul, M., 2006. Anti-inflammatory and immunomodulatory activities of stevioside and its metabolite steviol on THP-1 cells. J. Agric. Food Chem. 54 (3), 785–789. https://doi.org/10.1021/jf0523465.

Brambilla, E., Cagetti, M.G., Ionescu, A., Campus, G., Lingström, P., 2014. An in vitro and in vivo comparison of the effect of Stevia rebaudiana extracts on different caries-related variables: a randomized controlled trial pilot study. Caries Res. 48 (1), 19–23. https://doi.org/10.1159/000351650.

Castro-Muñoz, R., Correa-Delgado, M., Córdova-Almeida, R., Lara-Nava, D., Chávez-Muñoz, M., Velásquez-Chávez, V.F., Hernández-Torres, C.E., Gontarek-Castro, E., Ahmad, M.Z., 2022. Natural sweeteners: sources, extraction and current uses in foods and food industries. Food Chem. 370, 130991. https://doi.org/10.1016/j.foodchem.2021.130991.

Chattopadhyay, S., Raychaudhuri, U., Chakraborty, R., 2014. Artificial sweeteners - a review. J. Food Sci. Technol. 51 (4), 611–621. https://doi.org/10.1007/s13197-011-0571-1.

Chen, D., Hou, X., 2024. Aspartame carcinogenic potential revealed through network toxicology and molecular docking insights. Sci. Rep. 14 (1), 11492. https://doi.org/10.1038/s41598-024-62461-w.

Chen, J., Xia, Y., Sui, X., Peng, Q., Zhang, T., Li, J., Zhang, J., 2018. Steviol, a natural product inhibits proliferation of the gastrointestinal cancer cells intensively. Oncotarget 9 (41), 26299–26308. https://doi.org/10.18632/oncotarget.25233.

Choudhary, A.K., Pretorius, E., 2017. Revisiting the safety of aspartame. Nutr. Rev. 75 (9), 718–730. https://doi.org/10.1093/nutrit/nux035.

Concha, F., Sambra, V., Cáceres, P., López-Arana, S., Carvajal, B., Gotteland, M., 2023. Maternal consumption and perinatal exposure to non-nutritive sweeteners: should we be concerned? Front Pediatr 11, 1200990. https://doi.org/10.3389/fped.2023.1200990.

Czarnecka, K., Pilarz, A., Rogut, A., Maj, P., Szymańska, J., Olejnik, Ł., Szymański, P., 2021. Aspartame-true or false? Narrative review of safety analysis of general use in products. Nutrients 13 (6). https://doi.org/10.3390/nu13061957.

Davis, E.W., McCann, S.E., Joseph, J.M., Yeary, K.H.K., Fountzilas, C., Moysich, K.B., 2023. Sugar sweetened and artificially sweetened beverage consumption and pancreatic cancer: a retrospective study. Nutrients 15 (2). https://doi.org/10.3390/nu15020275.

deCock, P., Mäkinen, K., Honkala, E., Saag, M., Kennepohl, E., Eapen, A., 2016. Erythritol is more effective than xylitol and sorbitol in managing oral health endpoints. Int J Dent 2016, 9868421. https://doi.org/10.1155/2016/9868421.

Debras, C., Chazelas, E., Sellem, L., Porcher, R., Druesne-Pecollo, N., Esseddik, Y., de Edelenyi, F.S., Agaësse, C., De Sa, A., Lutchia, R., Fezeu, L.K., Julia, C., Kesse-Guyot, E., Allès, B., Galan, P., Hercberg, S., Deschasaux-Tanguy, M., Huybrechts, I., Srour, B., Touvier, M., 2022a. Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort. Bmj 378, e071204. https://doi.org/10.1136/bmj-2022-071204.

Debras, C., Chazelas, E., Srour, B., Druesne-Pecollo, N., Esseddik, Y., Szabo de Edelenyi, F., Agaësse, C., De Sa, A., Lutchia, R., Gigandet, S., Huybrechts, I., Julia, C., Kesse-Guyot, E., Allès, B., Andreeva, V.A., Galan, P., Hercberg, S., Deschasaux-Tanguy, M., Touvier, M., 2022b. Artificial sweeteners and cancer risk: results from the NutriNet-Santé population-based cohort study. PLoS Med. 19 (3), e1003950. https://doi.org/10.1371/journal.pmed.1003950.

Debras, C., Deschasaux-Tanguy, M., Chazelas, E., Sellem, L., Druesne-Pecollo, N., Esseddik, Y., Szabo de Edelenyi, F., Agaësse, C., De Sa, A., Lutchia, R., Julia, C., Kesse-Guyot, E., Allès, B., Galan, P., Hercberg, S., Huybrechts, I., Cosson, E., Tatulashvili, S., Srour, B., Touvier, M., 2023. Artificial sweeteners and risk of type 2 diabetes in the prospective NutriNet-santé cohort. Diabetes Care 46 (9), 1681–1690. https://doi.org/10.2337/dc23-0206.

Del Pozo, S., Gómez-Martínez, S., Díaz, L.E., Nova, E., Urrialde, R., Marcos, A., 2022. Potential effects of sucralose and saccharin on gut microbiota: a review. Nutrients 14 (8). https://doi.org/10.3390/nu14081682.

Di Rienzi, S.C., Britton, R.A., 2020. Adaptation of the gut microbiota to modern dietary sugars and sweeteners. Adv. Nutr. 11 (3), 616–629. https://doi.org/10.1093/advances/nmz118.

Dyrskog, S.E., Jeppesen, P.B., Colombo, M., Abudula, R., Hermansen, K., 2005. Preventive effects of a soy-based diet supplemented with stevioside on the development of the metabolic syndrome and type 2 diabetes in Zucker diabetic fatty rats. Metabolism 54 (9), 1181–1188. https://doi.org/10.1016/j.metabol.2005.03.026.

Englund-Ögge, L., Brantsæter, A.L., Haugen, M., Sengpiel, V., Khatibi, A., Myhre, R., Myking, S., Meltzer, H.M., Kacerovsky, M., Nilsen, R.M., Jacobsson, B., 2012. Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study. Am. J. Clin. Nutr. 96 (3), 552–559. https://doi.org/10.3945/ajcn.111.031567.

Evert, A.B., Dennison, M., Gardner, C.D., Garvey, W.T., Lau, K.H.K., MacLeod, J., Mitri, J., Pereira, R.F., Rawlings, K., Robinson, S., Saslow, L., Uelmen, S., Urbanski, P.B., Yancy Jr., W.S., 2019. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 42 (5), 731–754. https://doi.org/10.2337/dci19-0014.

Fagherazzi, G., Gusto, G., Affret, A., Mancini, F.R., Dow, C., Balkau, B., Clavel-Chapelon, F., Bonnet, F., Boutron-Ruault, M.C., 2017. Chronic consumption of artificial sweetener in packets or tablets and type 2 diabetes risk: evidence from the E3N-European prospective investigation into cancer and nutrition study. Ann. Nutr. Metab. 70 (1), 51–58. https://doi.org/10.1159/000458769.

Feng, J., Peng, J., Hsiao, Y.C., Liu, C.W., Yang, Y., Zhao, H., Teitelbaum, T., Wang, X., Lu, K., 2024. Non/low-caloric artificial sweeteners and gut microbiome: from perturbed species to mechanisms. Metabolites 14 (10). https://doi.org/10.3390/metabo14100544.

Ferrazzano, G.F., Cantile, T., Alcidi, B., Coda, M., Ingenito, A., Zarrelli, A., Di Fabio, G., Pollio, A., 2015. Is Stevia rebaudiana bertoni a non cariogenic sweetener? A review. Molecules 21 (1), E38. https://doi.org/10.3390/molecules21010038.

Foletto, K.C., Melo Batista, B.A., Neves, A.M., de Matos Feijó, F., Ballard, C.R., Marques Ribeiro, M.F., Bertoluci, M.C., 2016. Sweet taste of saccharin induces weight gain without increasing caloric intake, not related to insulin-resistance in Wistar rats. Appetite 96, 604–610. https://doi.org/10.1016/j.appet.2015.11.003.

Frankenfeld, C.L., Sikaroodi, M., Lamb, E., Shoemaker, S., Gillevet, P.M., 2015. High-intensity sweetener consumption and gut microbiome content and predicted gene function in a cross-sectional study of adults in the United States. Ann. Epidemiol. 25 (10), 736–742.e734. https://doi.org/10.1016/j.annepidem.2015.06.083.

Gallagher, A.M., Logue, C., 2019. Biomarker approaches to assessing intakes and health impacts of sweeteners: challenges and opportunities. Proc. Nutr. Soc. 78 (3), 463–472. https://doi.org/10.1017/s0029665119000594.

Geuns, J.M., Buyse, J., Vankeirsbilck, A., Temme, E.H., 2007. Metabolism of stevioside by healthy subjects. Exp Biol Med (Maywood) 232 (1), 164–173.

Goran, M.I., Plows, J.F., Ventura, E.E., 2019. Effects of consuming sugars and alternative sweeteners during pregnancy on maternal and child health: evidence for a secondhand sugar effect. Proc. Nutr. Soc. 78 (3), 262–271. https://doi.org/10.1017/s002966511800263x.

Gupta, P., Gupta, N., Pawar, A.P., Birajdar, S.S., Natt, A.S., Singh, H.P., 2013. Role of sugar and sugar substitutes in dental caries: a review. ISRN Dent 2013, 519421. https://doi.org/10.1155/2013/519421.

Halldorsson, T.I., Strøm, M., Petersen, S.B., Olsen, S.F., 2010. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women. Am. J. Clin. Nutr. 92 (3), 626–633. https://doi.org/10.3945/ajcn.2009.28968.

Hanawa, Y., Higashiyama, M., Kurihara, C., Tanemoto, R., Ito, S., Mizoguchi, A., Nishii, S., Wada, A., Inaba, K., Sugihara, N., Horiuchi, K., Okada, Y., Narimatsu, K., Komoto, S., Tomita, K., Hokari, R., 2021. Acesulfame potassium induces dysbiosis and intestinal injury with enhanced lymphocyte migration to intestinal mucosa. J. Gastroenterol. Hepatol. 36 (11), 3140–3148. https://doi.org/10.1111/jgh.15654.

Haq, N., Tafweez, R., Saqib, S., Bokhari, Z.H., Ali, I., Syami, A.F., 2019. Aspartame and sucralose-induced fatty changes in rat liver. J Coll Physicians Surg Pak 29 (9), 848–851. https://doi.org/10.29271/jcpsp.2019.09.848.

Huang, M., Quddus, A., Stinson, L., Shikany, J.M., Howard, B.V., Kutob, R.M., Lu, B., Manson, J.E., Eaton, C.B., 2017. Artificially sweetened beverages, sugar-sweetened beverages, plain water, and incident diabetes mellitus in postmenopausal women: the prospective Women's Health Initiative observational study. Am. J. Clin. Nutr. 106 (2), 614–622. https://doi.org/10.3945/ajcn.116.145391.

Huang, X., Yang, L., Ye, J., He, S., Wang, B., 2020. Equimolar doses of hypertonic agents (saline or mannitol) in the treatment of intracranial hypertension after severe traumatic brain injury. Medicine (Baltim.) 99 (38), e22004. https://doi.org/10.1097/md.0000000000022004.

Iizuka, K., 2022. Is the use of artificial sweeteners beneficial for patients with diabetes mellitus? The advantages and disadvantages of artificial sweeteners. Nutrients 14 (21). https://doi.org/10.3390/nu14214446.

Imamura, F., O'Connor, L., Ye, Z., Mursu, J., Hayashino, Y., Bhupathiraju, S.N., Forouhi, N.G., 2015. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. Bmj 351, h3576. https://doi.org/10.1136/bmj.h3576.

Ishikawa, M., Miyashita, M., Kawashima, Y., Nakamura, T., Saitou, N., Modderman, J., 1996. Effects of oral administration of erythritol on patients with diabetes. Regul. Toxicol. Pharmacol. 24 (2 Pt 2), S303–S308. https://doi.org/10.1006/rtph.1996.0112.

Jang, W., Jeoung, N.H., Cho, K.H., 2011. Modified apolipoprotein (apo) A-I by artificial sweetener causes severe premature cellular senescence and atherosclerosis with impairment of functional and structural properties of apoA-I in lipid-free and lipid-bound state. Mol. Cells 31 (5), 461–470. https://doi.org/10.1007/s10059-011-1009-3.

Jeppesen, P.B., Gregersen, S., Rolfsen, S.E., Jepsen, M., Colombo, M., Agger, A., Xiao, J., Kruhøffer, M., Orntoft, T., Hermansen, K., 2003. Antihyperglycemic and blood pressure-reducing effects of stevioside in the diabetic Goto-Kakizaki rat. Metabolism 52 (3), 372–378. https://doi.org/10.1053/meta.2003.50058.

Kawano, R., Okamura, T., Hashimoto, Y., Majima, S., Senmaru, T., Ushigome, E., Asano, M., Yamazaki, M., Takakuwa, H., Sasano, R., Nakanishi, N., Hamaguchi, M., Fukui, M., 2021. Erythritol ameliorates small intestinal inflammation induced by high-fat diets and improves glucose tolerance. Int. J. Mol. Sci. 22 (11). https://doi.org/10.3390/ijms22115558.

Kim, J.Y., Park, K.H., Kim, J., Choi, I., Cho, K.H., 2015. Modified high-density lipoproteins by artificial sweetener, aspartame, and saccharin, showed loss of anti-atherosclerotic activity and toxicity in zebrafish. Cardiovasc. Toxicol. 15 (1), 79–89. https://doi.org/10.1007/s12012-014-9273-z.

Laverty, A.A., Magee, L., Monteiro, C.A., Saxena, S., Millett, C., 2015. Sugar and artificially sweetened beverage consumption and adiposity changes: national longitudinal study. Int. J. Behav. Nutr. Phys. Activ. 12, 137. https://doi.org/10.1186/s12966-015-0297-y.

Lertrit, A., Srimachai, S., Saetung, S., Chanprasertyothin, S., Chailurkit, L.O., Areevut, C., Katekao, P., Ongphiphadhanakul, B., Sriphrapradang, C., 2018. Effects of sucralose on insulin and glucagon-like peptide-1 secretion in healthy subjects: a randomized, double-blind, placebo-controlled trial. Nutrition 55-56, 125–130. https://doi.org/10.1016/j.nut.2018.04.001.

Lugo-Baruqui, J.A., Ayyathurai, R., Sriram, A., Pragatheeshwar, K.D., 2019. Use of mannitol for ischemia reperfusion injury in kidney transplant and partial nephrectomies-review of literature. Curr. Urol. Rep. 20 (1), 6. https://doi.org/10.1007/s11934-019-0868-6.

Magnuson, B.A., Carakostas, M.C., Moore, N.H., Poulos, S.P., Renwick, A.G., 2016. Biological fate of low-calorie sweeteners. Nutr. Rev. 74 (11), 670–689. https://doi.org/10.1093/nutrit/nuw032.

Magnuson, B.A., Roberts, A., Nestmann, E.R., 2017. Critical review of the current literature on the safety of sucralose. Food Chem. Toxicol. 106 (Pt A), 324–355. https://doi.org/10.1016/j.fct.2017.05.047.

Martínez-Miranda, J.G., Chairez, I., Durán-Páramo, E., 2022. Mannitol production by heterofermentative lactic acid bacteria: a review. Appl. Biochem. Biotechnol. 194 (6), 2762–2795. https://doi.org/10.1007/s12010-022-03836-5.

Mazi, T.A., Stanhope, K.L., 2023. Erythritol: an in-depth discussion of its potential to Be a beneficial dietary component. Nutrients 15 (1). https://doi.org/10.3390/nu15010204.

Melis, M.S., 1995. Chronic administration of aqueous extract of Stevia rebaudiana in rats: renal effects. J. Ethnopharmacol. 47 (3), 129–134. https://doi.org/10.1016/0378-8741(95)01271-e.

Méndez-García, L.A., Bueno-Hernández, N., Cid-Soto, M.A., De León, K.L., Mendoza-Martínez, V.M., Espinosa-Flores, A.J., Carrero-Aguirre, M., Esquivel-Velázquez, M., León-Hernández, M., Viurcos-Sanabria, R., Ruíz-Barranco, A., Cota-Arce, J.M., Álvarez-Lee, A., De León-Nava, M.A., Meléndez, G., Escobedo, G., 2022. Ten-week sucralose consumption induces gut dysbiosis and altered glucose and insulin levels in healthy young adults. Microorganisms 10 (2). https://doi.org/10.3390/microorganisms10020434.

Mizushina, Y., Akihisa, T., Ukiya, M., Hamasaki, Y., Murakami-Nakai, C., Kuriyama, I., Takeuchi, T., Sugawara, F., Yoshida, H., 2005. Structural analysis of isosteviol and related compounds as DNA polymerase and DNA topoisomerase inhibitors. Life Sci. 77 (17), 2127–2140. https://doi.org/10.1016/j.lfs.2005.03.022.

Moriconi, E., Feraco, A., Marzolla, V., Infante, M., Lombardo, M., Fabbri, A., Caprio, M., 2020. Neuroendocrine and metabolic effects of low-calorie and non-calorie sweeteners. Front. Endocrinol. 11, 444. https://doi.org/10.3389/fendo.2020.00444.

Mossavar-Rahmani, Y., Kamensky, V., Manson, J.E., Silver, B., Rapp, S.R., Haring, B., Beresford, S.A.A., Snetselaar, L., Wassertheil-Smoller, S., 2019. Artificially sweetened beverages and stroke, coronary heart disease, and all-cause mortality in the women's health initiative. Stroke 50 (3), 555–562. https://doi.org/10.1161/strokeaha.118.023100.

Nicolì, F., Prete, A., Citro, F., Bertolotto, A., Aragona, M., de Gennaro, G., Del Prato, S., Bianchi, C., 2021. Use of non-nutritive-sweetened soft drink and risk of gestational diabetes. Diabetes Res. Clin. Pract. 178, 108943. https://doi.org/10.1016/j.diabres.2021.108943.

Noda, K., Nakayama, K., Oku, T., 1994. Serum glucose and insulin levels and erythritol balance after oral administration of erythritol in healthy subjects. Eur. J. Clin. Nutr. 48 (4), 286–292.

O'Connor, D., Pang, M., Castelnuovo, G., Finlayson, G., Blaak, E., Gibbons, C., Navas-Carretero, S., Almiron-Roig, E., Harrold, J., Raben, A., Martinez, J.A., 2021. A rational review on the effects of sweeteners and sweetness enhancers on appetite, food reward and metabolic/adiposity outcomes in adults. Food Funct. 12 (2), 442–465. https://doi.org/10.1039/d0fo02424d.

Ohrem, H.L., Schornick, E., Kalivoda, A., Ognibene, R., 2014. Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? Pharmaceut. Dev. Technol. 19 (3), 257–262. https://doi.org/10.3109/10837450.2013.775154.

Orellana-Paucar, A.M., 2023. Steviol glycosides from Stevia rebaudiana: an updated overview of their sweetening activity, pharmacological properties, and safety aspects. Molecules 28 (3). https://doi.org/10.3390/molecules28031258.

Ortiz, M.E., Bleckwedel, J., Raya, R.R., Mozzi, F., 2013. Biotechnological and in situ food production of polyols by lactic acid bacteria. Appl. Microbiol. Biotechnol. 97 (11), 4713–4726. https://doi.org/10.1007/s00253-013-4884-z.

Pan, A., Malik, V.S., Schulze, M.B., Manson, J.E., Willett, W.C., Hu, F.B., 2012. Plain-water intake and risk of type 2 diabetes in young and middle-aged women. Am. J. Clin. Nutr. 95 (6), 1454–1460. https://doi.org/10.3945/ajcn.111.032698.

Pearlman, M., Obert, J., Casey, L., 2017. The association between artificial sweeteners and obesity. Curr. Gastroenterol. Rep. 19 (12), 64. https://doi.org/10.1007/s11894-017-0602-9.

Peteliuk, V., Rybchuk, L., Bayliak, M., Storey, K.B., Lushchak, O., 2021. Natural sweetener Stevia rebaudiana: functionalities, health benefits and potential risks. Excli j 20, 1412–1430. https://doi.org/10.17179/excli2021-4211.

Pham, H., Phillips, L.K., Jones, K.L., 2019. Acute effects of nutritive and non-nutritive sweeteners on postprandial blood pressure. Nutrients 11 (8). https://doi.org/10.3390/nu11081717.

Raben, A., Vasilaras, T.H., Møller, A.C., Astrup, A., 2002. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. Am. J. Clin. Nutr. 76 (4), 721–729. https://doi.org/10.1093/ajcn/76.4.721.

Regnat, K., Mach, R.L., Mach-Aigner, A.R., 2018. Erythritol as sweetener-wherefrom and whereto? Appl. Microbiol. Biotechnol. 102 (2), 587–595. https://doi.org/10.1007/s00253-017-8654-1.

Richards, A.B., Krakowka, S., Dexter, L.B., Schmid, H., Wolterbeek, A.P., Waalkens-Berendsen, D.H., Shigoyuki, A., Kurimoto, M., 2002. Trehalose: a review of properties, history of use and human tolerance, and results of multiple safety studies. Food Chem. Toxicol. 40 (7), 871–898. https://doi.org/10.1016/s0278-6915(02)00011-x.

Romo-Romo, A., Aguilar-Salinas, C.A., Gómez-Díaz, R.A., Brito-Córdova, G.X., Gómez-Velasco, D.V., López-Rocha, M.J., Almeda-Valdés, P., 2017. Non-nutritive sweeteners: evidence on their association with metabolic diseases and potential effects on glucose metabolism and appetite. Rev. Invest. Clin. 69 (3), 129–138. https://doi.org/10.24875/ric.17002141.

Ruiz-Ojeda, F.J., Plaza-Díaz, J., Sáez-Lara, M.J., Gil, A., 2019. Effects of sweeteners on the gut microbiota: a review of experimental studies and clinical trials. Adv. Nutr. 10 (Suppl. l_1), S31–s48. https://doi.org/10.1093/advances/nmy037.

Sachmechi, I., Khalid, A., Awan, S.I., Malik, Z.R., Sharifzadeh, M., 2018. Autoimmune thyroiditis with hypothyroidism induced by sugar substitutes. Cureus 10 (9), e3268. https://doi.org/10.7759/cureus.3268.

Saffari, M., Ebrahimi, A., Langrish, T., 2016. A novel formulation for solubility and content uniformity enhancement of poorly water-soluble drugs using highly-porous mannitol. Eur. J. Pharmaceut. Sci. 83, 52–61. https://doi.org/10.1016/j.ejps.2015.12.016.

Salli, K., Lehtinen, M.J., Tiihonen, K., Ouwehand, A.C., 2019. Xylitol's health benefits beyond dental health: a comprehensive review. Nutrients 11 (8). https://doi.org/10.3390/nu11081813.

Saraiva, A., Carrascosa, C., Raheem, D., Ramos, F., Raposo, A., 2020. Natural sweeteners: the relevance of food naturalness for consumers, food security aspects, sustainability and health impacts. Int. J. Environ. Res. Publ. Health 17 (17). https://doi.org/10.3390/ijerph17176285.

Sehar, I., Kaul, A., Bani, S., Pal, H.C., Saxena, A.K., 2008. Immune up regulatory response of a non-caloric natural sweetener, stevioside. Chem. Biol. Interact. 173 (2), 115–121. https://doi.org/10.1016/j.cbi.2008.01.008.

Serrano, J., Smith, K.R., Crouch, A.L., Sharma, V., Yi, F., Vargova, V., LaMoia, T.E., Dupont, L.M., Serna, V., Tang, F., Gomes-Dias, L., Blakeslee, J.J., Hatzakis, E., Peterson, S.N., Anderson, M., Pratley, R.E., Kyriazis, G.A., 2021. High-dose saccharin supplementation does not induce gut microbiota changes or glucose intolerance in healthy humans and mice. Microbiome 9 (1), 11. https://doi.org/10.1186/s40168-020-00976-w.

Shiozaki, K., Fujii, A., Nakano, T., Yamaguchi, T., Sato, M., 2006. Inhibitory effects of hot water extract of the Stevia stem on the contractile response of the smooth muscle of the Guinea pig ileum. Biosci. Biotechnol. Biochem. 70 (2), 489–494. https://doi.org/10.1271/bbb.70.489.

Singh, N., Singh Lubana, S., Arora, S., Sachmechi, I., 2020. A study of artificial sweeteners and thyroid cancer risk. J. Clin. Med. Res. 12 (8), 492–498. https://doi.org/10.14740/jocmr4258.

Sørensen, L.B., Vasilaras, T.H., Astrup, A., Raben, A., 2014. Sucrose compared with artificial sweeteners: a clinical intervention study of effects on energy intake, appetite, and energy expenditure after 10 wk of supplementation in overweight subjects. Am. J. Clin. Nutr. 100 (1), 36–45. https://doi.org/10.3945/ajcn.113.081554.

Suez, J., Cohen, Y., Valdés-Mas, R., Mor, U., Dori-Bachash, M., Federici, S., Zmora, N., Leshem, A., Heinemann, M., Linevsky, R., Zur, M., Ben-Zeev Brik, R., Bukimer, A., Eliyahu-Miller, S., Metz, A., Fischbein, R., Sharov, O., Malitsky, S., Itkin, M., Stettner, N., Harmelin, A., Shapiro, H., Stein-Thoeringer, C.K., Segal, E., Elinav, E., 2022. Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. Cell 185 (18), 3307–3328.e3319. https://doi.org/10.1016/j.cell.2022.07.016.

Suez, J., Korem, T., Zeevi, D., Zilberman-Schapira, G., Thaiss, C.A., Maza, O., Israeli, D., Zmora, N., Gilad, S., Weinberger, A., Kuperman, Y., Harmelin, A., Kolodkin-Gal, I., Shapiro, H., Halpern, Z., Segal, E., Elinav, E., 2014. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514 (7521), 181–186. https://doi.org/10.1038/nature13793.

Swithers, S.E., Davidson, T.L., 2008. A role for sweet taste: calorie predictive relations in energy regulation by rats. Behav. Neurosci. 122 (1), 161–173. https://doi.org/10.1037/0735-7044.122.1.161.

Takahashi, K., Matsuda, M., Ohashi, K., Taniguchi, K., Nakagomi, O., Abe, Y., Mori, S., Sato, N., Okutani, K., Shigeta, S., 2001. Analysis of anti-rotavirus activity of extract from Stevia rebaudiana. Antivir. Res. 49 (1), 15–24. https://doi.org/10.1016/s0166-3542(00)00134-0.

Tordoff, M.G., Alleva, A.M., 1990. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. Am. J. Clin. Nutr. 51 (6), 963–969. https://doi.org/10.1093/ajcn/51.6.963.

Velesiotis, C., Kanellakis, M., Vynios, D.H., 2022. Steviol glycosides affect functional properties and macromolecular expression of breast cancer cells. IUBMB Life 74 (10), 1012–1028. https://doi.org/10.1002/iub.2669.

Ventura, A.K., Worobey, J., 2013. Early influences on the development of food preferences. Curr. Biol. 23 (9), R401–R408. https://doi.org/10.1016/j.cub.2013.02.037.

Vinciguerra, D., Gelb, M.B., Maynard, H.D., 2022. Synthesis and application of trehalose materials. JACS Au 2 (7), 1561–1587. https://doi.org/10.1021/jacsau.2c00309.

von Poser Toigo, E., Huffell, A.P., Mota, C.S., Bertolini, D., Pettenuzzo, L.F., Dalmaz, C., 2015. Metabolic and feeding behavior alterations provoked by prenatal exposure to aspartame. Appetite 87, 168–174. https://doi.org/10.1016/j.appet.2014.12.213.

Wen, H., Tang, B., Stewart, A.J., Tao, Y., Shao, Y., Cui, Y., Yue, H., Pei, J., Liu, Z., Mei, L., Yu, R., Jiang, L., 2018. Erythritol attenuates postprandial blood glucose by inhibiting α-glucosidase. J. Agric. Food Chem. 66 (6), 1401–1407. https://doi.org/10.1021/acs.jafc.7b05033.

Wilk, K., Korytek, W., Pelczyńska, M., Moszak, M., Bogdański, P., 2022. The effect of artificial sweeteners use on sweet taste perception and weight loss efficacy: a review. Nutrients 14 (6). https://doi.org/10.3390/nu14061261.

Witkowski, M., Nemet, I., Alamri, H., Wilcox, J., Gupta, N., Nimer, N., Haghikia, A., Li, X. S., Wu, Y., Saha, P.P., Demuth, I., König, M., Steinhagen-Thiessen, E., Cajka, T., Fiehn, O., Landmesser, U., Tang, W.H.W., Hazen, S.L., 2023. The artificial sweetener erythritol and cardiovascular event risk. Nat. Med. 29 (3), 710–718. https://doi.org/10.1038/s41591-023-02223-9.

Wu, H.T., Lin, C.H., Pai, H.L., Chen, Y.C., Cheng, K.P., Kuo, H.Y., Li, C.H., Ou, H.Y., 2022. Sucralose, a non-nutritive artificial sweetener exacerbates high fat diet-induced hepatic steatosis through taste receptor type 1 member 3. Front. Nutr. 9, 823723. https://doi.org/10.3389/fnut.2022.823723.

Yunker, A.G., Patel, R., Page, K.A., 2020. Effects of non-nutritive sweeteners on sweet taste processing and neuroendocrine regulation of eating behavior. Curr Nutr Rep 9 (3), 278–289. https://doi.org/10.1007/s13668-020-00323-3.

Zhang, G.H., Chen, M.L., Liu, S.S., Zhan, Y.H., Quan, Y., Qin, Y.M., Deng, S.P., 2011. Effects of mother's dietary exposure to acesulfame-K in Pregnancy or lactation on the adult offspring's sweet preference. Chem. Senses 36 (9), 763–770. https://doi.org/10.1093/chemse/bjr050.

Krupa, N.C., Thippeswamy, H.M., Chandrashekar, B.R., 2022. Antimicrobial efficacy of Xylitol, Probiotic and Chlorhexidine mouth rinses among children and elderly

population at high risk for dental caries - A Randomized Controlled Trial. J Prev Med Hyg 63 (2), e282–e287. https://doi.org/10.15167/2421-4248/jpmh2022.63.2.1772.

Riley, P., Moore, D., Ahmed, F., Sharif, M.O., Worthington, H.V., 2015. Xylitol-containing products for preventing dental caries in children and adults. Cochrane Database Syst Rev 2015 (3), Cd010743. https://doi.org/10.1002/14651858.CD010743.pub2.

Ohtake, S., Wang, Y.J., 2011. Trehalose: current use and future applications. J Pharm Sci 100 (6), 2020–2053. https://doi.org/10.1002/jps.22458.