

Artificial Sweeteners: Current Discoveries, Healthy Effects and Future Developments

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Abstract:

Saccharin, aspartame and sucralose are the most common artificial sweeteners. They are widely used in food and beverages to provide sweetness without adding calories or affecting blood glucose levels. This paper investigated the application of three artificial sweeteners, saccharin, aspartame and sucralose, on glucose metabolism. There is no conclusive evidence of the effects of saccharin, aspartame and sucralose on glucose metabolism. Because saccharin cannot be metabolized by the body, it does not raise blood glucose levels. Aspartame is metabolized by the body to phenylalanine, aspartic acid and methanol, but is not involved in the body's metabolic processes and does not raise blood glucose levels. Sucralose may affect the expression of sweet taste receptors and glucose transporter proteins, thus affecting the metabolic process of glucose. However, saccharin may affect the intestinal microbiota, and sucralose may negatively affect intestinal health by decreasing the number of colonies of probiotic bacteria in the intestines and increasing the number of colonies of pathogenic bacteria. Regular consumption of beverages containing artificial sweeteners may also lead to metabolic disorders. Data from human trials are lacking at present, and more research data are needed to support it.

Keywords: Artificial sweeteners; Glucose Metabolism; Non-nutritive sweeteners.

1. Introduction

As people's health concepts change and develop, sugar-free foods are sought after because of their low-calorie content. Since purely unadulterated sugar destroys the flavor of the food, the food industry often chooses to add a variety of non-nutritive sweeteners in place of sucrose. Such products may be particularly helpful in managing obesity or diabetes. High-intensity sweeteners currently approved for use in the United States include aspartame, potassium vinyl sulfonate, neotame, saccharin, sucralose, cyclohexanones and allulose [1]. However, with more in-depth research in nutrition, questions have arisen about the breakdown products and metabolic effects of these artificial sweeteners. Typically, it has been assumed that non-nutritive sweeteners are not involved in the process of glucose metabolism in humans, but a growing body of research suggests that sweeteners affect glucose metabolism in other ways. Specific variations piqued the interest of the researcher on the mechanism by which sweeteners affect glucose metabolism and whether this effect could lead to new applications of sweeteners in places other than the food sector. This paper summarized the discovery, synthesis, and application of several common non-nutri-

tive sweeteners and their effects on glucose metabolism, with a focus on three representative sweeteners: saccharin, aspartame, and sucralose. The applications of these three sweeteners in new areas and the mechanisms affecting glucose metabolism are explored.

2. Saccharin

2.1 Discovery, Synthesis, and Applications

According to CAS. Saccharin was discovered in 1878 by Constantine Fahlberg. It is the first widely commercialized non-nutritive sweetener. It is a white crystal, water solubility is 3.45 g/L. The Empirical formula of Saccharin is $C_7H_5NO_3S$, the molar mass of Saccharin is 183.18 g/mol, the melting point is 229-230°C.

The synthesis of Saccharin by Constantine Fahlberg is to oxidize toluene sulfonamides. In the Remsen-Fahlberg procedure, toluene is nitrated to form ortho-toluene sulfonamide. The sulfonamide is then oxidized using chlorine or nitric acid to produce saccharin (Fig. 1). In the early 20th century, Adolf von Heyden procedure introduced another way of synthesis of Saccharin. Phthalic anhydride (an aromatic compound) reacts with ammonia to form o-sulfobenzoic acid amide and this amide is then cyclized

to yield saccharin. (Fig. 2). A commercial way of synthesizing saccharin is the Maumee-Synthesis for saccharin manufacture (Fig. 3) [2].

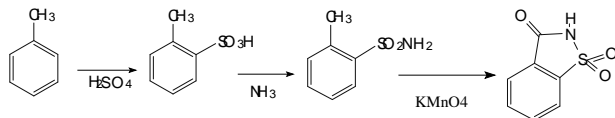


Fig. 1 Remsen-Fahlberg Procedure

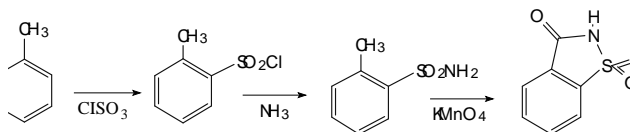


Fig. 2 Von Heyden Procedure

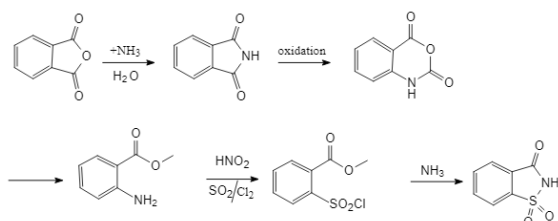


Fig. 3 Maumee-Synthesis for saccharin manufacture

Saccharin is widely used. In the industrial production of food, it is commonly used as a substitute for sucrose as a non-nutritive sweetener and is widely used in sugary products that require reduced calorie content, especially baked goods, soft drinks, confectionery, and sauces. Due to its stability, saccharin can be used in cooking, baking and canning. Acceptable levels of use range from 100 to 500 mg/kg, depending on the food category and local food industry laws and regulations. In addition to the food industry, saccharin can also be used in the medical field due to its stability, and even in tobacco products. It is often used as an artificial sweetener in medicines and oral care products. In addition, saccharin is suspected to be carcinogenic and has been shown to be a potential antidote for metal poisoning. In general, saccharin is widely used as a substitute for sugar in the food industry, pharmaceutical and tobacco products due to its sweet taste, stability and calorie-free properties. But the bitter and metallic taste of saccharin is inevitable [2]. Nowadays, due to the development of people's health concept and the disadvantage of taste, the use of saccharin in food products is also less and less, and more applications need more research to expand.

2.2 Effects of saccharin on glucose metabolism

One study showed that the effects of saccharin depend on an individual's physical fitness and intake. Saccharin is a non-nutritive artificial sweetener that is often used as a

substitute for sucrose. It can help reduce calorie intake and help with weight control by providing sweetness without adding extra calories. Saccharin does not raise blood sugar levels because it is not metabolized by the body. This makes it promising as a suitable option for people with diabetes or those looking to control their blood sugar levels. Saccharin has a sweet taste, and while it may not provide the same satisfaction as natural sugar, it can still improve the palatability of some foods. There is some research suggesting that consuming artificial sweeteners such as saccharin may increase cravings for sweets, leading to overeating or a preference for high-calorie foods. Current studies on the effects of saccharin on gut health are limited and contradictory. Some studies suggest that saccharin may alter gut microbiota composition, possibly negatively affecting gut health. Saccharin may also cause allergic reactions, and some people may be allergic to saccharin, with symptoms including rashes, itching, or gastrointestinal discomfort [3].

But there are some studies that show that saccharin can raise fasting blood sugar levels in rats in rat models. However, it had no negative effect on Homeostasis Model Assessment (HOMA) indices of other metabolic parameters such as triglycerides, insulin and insulin resistance. A high-fructose diet is associated with changes in liver fat. It can lead to the accumulation of fat in liver cells, which leads to non-alcoholic fatty liver disease (NAFLD) and may further progress to non-alcoholic steatohepatitis (NASH) and liver damage. In contrast, saccharin has no adverse effects on the liver. It does not cause fatty liver changes like a high-fructose diet does. These findings highlight the different effects of saccharin and high-fructose diets on blood sugar levels and liver health. While saccharin may affect fasting blood sugar, it does not cause liver insulin resistance or fat accumulation [4]. In a recent human blood sugar test, saccharin was also shown to be similar to a rat model, and the intake of saccharin also raised blood sugar levels in people, leading to insulin secretion [5].

In conclusion, saccharin may cause abnormal glucose metabolism resulting in elevated blood sugar levels [6]. Some studies have also suggested that the rise in blood sugar after ingestion of saccharin is due to the fact that saccharin may alter the composition of the gut microbiome, which affects glucose metabolism [2]. More effects on health of saccharin depend on further studies.

3. Aspartame

3.1 Discovery, Synthesis, and Applications

According to CAS. Aspartame was discovered by James M. Schlatter in 1965. Aspartame's sweetness is about 200

times greater than that of sucrose which is a white crystalline powder or colorless needles. The empirical formula of aspartame is $C_{14}H_{18}N_2O_5$ and the molar mass is 294.31 g/mol. The melting point is 246-250°C, water solubility is 10 g/L.

LABS continue to explore new laboratory methods for making aspartame, bypassing the 1965 patent. The synthesis of aspartame by thermolysin is one of them (Fig. 4) The pyrolytic synthesis of aspartame involves protease-mediated peptide synthesis (PMPS). The process utilizes the properties of thermolysin to synthesize aspartame precursors, thereby synthesizing aspartame. Thermolysin is a heat-stable extracellular zinc plus metalloproteinase, a reaction that is enantioselective to the desired L-phenylalanine methyl ester (PM) substrate, initiated in particular by binding to the amino donor side of the enzyme's active site. PM binds to enzymes, and both substrates effectively bind to thermolysin. Enzymes catalyze the formation of tetrahedral intermediates, which then collapse to form the product aspartame precursor ZAPM. As an apparent salt insoluble in water, the precipitation of ZAPM drives the entire reaction toward peptide synthesis [7].

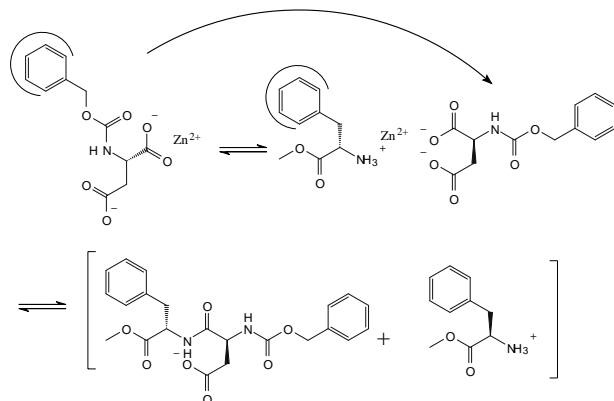


Fig. 4 Synthesis of Aspartame by Thermolysin

Also, a new industrial use of aspartame production is by combining enzymatic and chemical reactions which are introduced by Japanese researchers. In this method. First, L-aspartic acid dimethyl ester and L-phenylalanine are reacted enzymatically using α -amino acid ester acyl transferase to produce α -L-aspartyl-L-phenylalanine, β -methyl ester. This intermediate product is then chemically transformed into α -L-aspartyl-L-phenylalanine methyl ester hydrochloride (aspartame hydrochloride) in an aqueous solution with methanol and HCl. The HCl is then removed to form aspartame (Fig. 5) [8]. Compared with the traditional method, this new route has the advantages of simplifying the production process, increasing the total output, efficient enzyme reaction and industrial application. In general, the ultimate goal of such research is to explore more convenient and efficient synthesis methods.

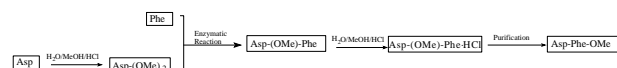


Fig. 5 Synthesis of Aspartame in Industrial Use

Aspartame has always been sold under trade names such as Equal or NutraSweet. It was originally intended as a substitute for sucrose and does not have the slightly bitter and metallic taste of saccharin. Recent studies have shown that in addition to adding food, it also has potential research value in medicine. One study suggests that high concentrations of aspartame may have an inhibitory effect on the development of colorectal cancer [8]. Other studies show aspartame has been shown to affect the enrichment of cancer stem cells in PANC-1 cells [9]. In general, further research is needed to expand aspartame's applications.

3.2 Effects of aspartame on glucose metabolism

In the small intestine, digestive enzymes break down aspartame into methanol, phenylalanine and aspartic acid. These metabolites are further broken down into formaldehyde and formic acid. Unlike other NNS, aspartame has a certain nutritional value when metabolized in the body :1g of aspartame provides about 4kcal of energy. The FDA and Health Canada have determined the acceptable daily intake (ADI) respectively to be 50mg/kg body weight per day and 40mg/kg body weight per day. The ADI is an estimate of the maximum intake (expressed in body weight) of a food additive in a food or drink that is safe to consume every day of a person's life without any health risk to the consumer, including a factor of 100 safety [10].

Many studies have shown that aspartame does not affect glucose metabolism in a study evaluating the effects of people consuming beverages containing aspartame on glucose metabolism. Results showed that in a healthy population, consumption of artificially sweetened beverages for two weeks did not change fasting glucose and fasting insulin concentrations, area under the curve of glucose and insulin on oral glucose tolerance tests, area under the curve of glucose and insulin increment, HOMA of insulin resistance (HOMA-IR), and Matsuda index [11]. In addition, there was no significant difference in blood sugar concentrations after two weeks of artificially sweetened beverages versus two weeks of mineral water. Another study in which subjects were given aspartame directly in its pure form showed the same. The total area under the glucose, insulin, active GLP-1, and leptin curves of the subjects taking aspartame was similar to the baseline values for healthy participants. Insulin sensitivity did not change after NNS treatment compared to baseline values. These findings suggest that repeated daily consumption of pure aspartame for two weeks had no effect on glucose metabolism in adults with normal blood sugar [12].

In another study on the effects of aspartame on glucose tolerance, only people who consumed aspartame had a stronger positive association between body mass index (BMI) and glucose tolerance compared to multiple sweeteners. This means that the association between increased BMI and worsening glucose tolerance is more pronounced in people who consume aspartame. It may be that aspartame is associated with insulin resistance in obese people [13].

In general. Some studies have shown that aspartame intake does not lead to changes in blood sugar and glycosylated hemoglobin levels. However, other studies have shown that aspartame intake may have some effect on blood sugar and the secretion of gut hormones such as glucagon. At present, the evidence of aspartame on glucose metabolism is still contradictory. Further studies are needed to determine the specific mechanisms and effects [10].

4. Sucralose

4.1 Discovery, Synthesis, and Applications

According to CAS. Sucralose is a sweetener developed in collaboration with Queen Elizabeth College, University of London, and patented in 1976. It is the only artificial sweetener based on sucrose. Usually white crystalline or crystalline powder, odorless, sweet taste. Soluble in water. It has excellent stability under acidic conditions. The molecular formula of sucralose is $C_{12}H_{19}Cl_3O_8$ and the molecular weight is 397.63. The melting point is 130 °C. Its sweetness can reach 320-1000 times that of sucrose. There are two main methods to synthesize sucralose: mono-group protection and omni-group protection. omni-group protection is limited in its application because of its low yield and complex operation. This method proposed by Chinese scholars obtained sucralose by synthesizing sucrose-6-acetate and then chlorinating and deacetylating it (Fig. 6) [14].

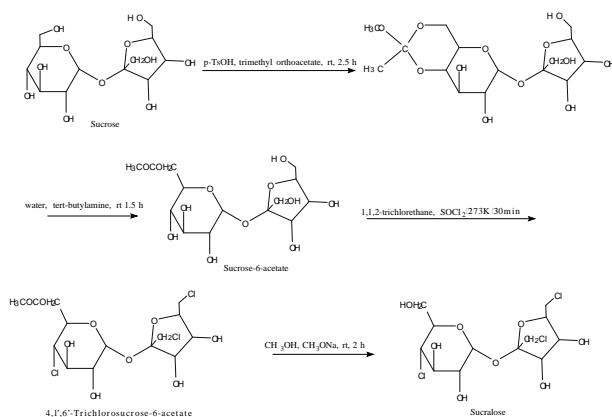


Fig. 6 Single Base Method Synthesis of Sucralose

In another US patent, another reaction of sucrose with a chlorinated reagent in an aprotic polar solution is described, followed by a reaction with a carboxylate in the dissolution solution, and finally decarboxylated in a sodium methoxy/methanol solution to sucralose (Fig. 7). Due to the advantages of mild reaction conditions, high yield and simple operation, this method is generally used in the industrial production of sucralose [14].

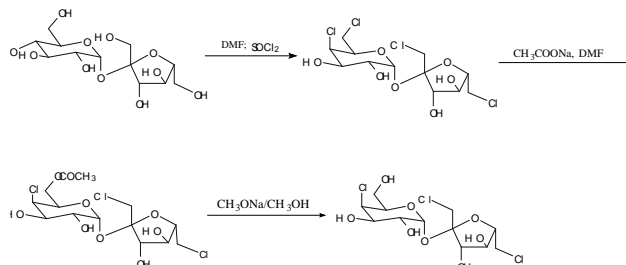


Fig. 7 US patent's Synthesis of Sucralose

In the reaction of azo reagent as catalyst and acetic acid as acylating agent, the conversion rate of chlorination is more than 80%, and the final yield can reach 50% (Fig. 8). But there is a disadvantage that the reaction is not sufficient under the condition of using sodium methylated sodium methoxide as the catalyst for the alcoholysis of sucralose ester. However, if potassium hydroxide is used as the catalyst, the advantage of the former is that the reaction in methanol solution can make the reaction complete without producing other products at the appropriate temperature. Studies have also shown that sucralose can be synthesized by microbial methods, which are more productive and the synthesis route is simpler [14].

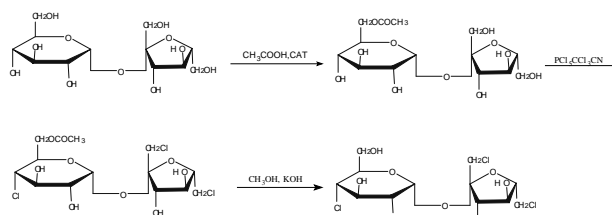


Fig. 8 Synthesis of Sucralose using azo reagent and acetic acid

In terms of application, it is worth mentioning that sucralose will decompose at high temperatures to produce toxic substances, so it is not suitable for products requiring high temperature processing [15]. In addition to its use as a non-nutritive sweetener in processed foods, sucralose has been suggested for use in urine tests to assess intestinal permeability. The principle is roughly that sucralose, unlike lactose, cannot be metabolized by gut bacteria. By measuring the concentration of sucralose in the urine, it is possible to assess the permeability of the entire intestine. The higher the concentration of sucralose, the higher the

intestinal permeability. The advantages of this method are that it is simple, convenient, non-hazardous, and can be analyzed using a smaller urine sample [16]. Overall, more research is needed to discover the role of sucralose in other areas.

4.2 Effects of sucralose on glucose metabolism

Although it is generally believed that non-nutritive sweeteners are not involved in glucose metabolism, one study showed that sucralose intake significantly altered the gut microbiota of mice in a mouse model. In the study, giving mice a low dose of sucralose significantly altered the gut microbiota of the mice, including increasing the number of *Tenacibaculum*, *Ruegeria*, *Staphylococcus* and *Allobaculum* in the mice's jejunum, ileum and colon. In the cecum, the amounts of *Lachnospiraceae* and *Lachnospiraceae* were reduced in mice that ingested sucralose [17]. At the same time, another study suggests that sucralose may influence glucose metabolism by regulating the sweetness signaling pathway. In a rat model, sucralose intake had a positive effect on glucose tolerance in obese rats. The study also found that consuming 0.78 mM of sucralose for four weeks improved glucose tolerance in obese rats. In addition, sucralose intake increased the expression of sweet taste receptors and glucose transporters in obese rats [18].

The above studies are limited to mouse models, and the metabolic diseases caused by sucralose in the population require more research. Most studies have shown that sucralose and aspartame do not affect a person's glucose metabolism [10]. However, some studies have shown that when sucralose is consumed with carbohydrates, it can lead to decreased insulin sensitivity in healthy people. In addition, the study found that participants who consumed sucralose and maltodextrin showed a reduced response to sweetness in the midbrain, insula, and cingulate regions of the brain. However, no change in insulin sensitivity was observed when participants consumed maltodextrin alone. Thus, this study suggests that the combination of sucralose with carbohydrates may lead to metabolic dysfunction [19]. In general, the effects of sucralose on human metabolism and health need further research.

5. Conclusion

Non-nutritive sweeteners have both positive and negative effects on glucose metabolism. The negative effects of artificial sweeteners on human glucose metabolism focus on the potential for metabolic disruption. It has been shown that saccharin and sucralose may alter the composition of the intestinal flora; saccharin does not have a clear mode of effect, but if sucralose is ingested, the results of its effects are shown by an increase in the number of patho-

genic bacteria and a decrease in the number of probiotic bacteria in the intestinal tract. Sucralose can also affect sweet taste receptors and glucose transporter proteins, leading to disturbances in glucose metabolism. There is insufficient evidence to suggest that aspartame can raise blood glucose levels in humans, but it can cause insulin levels to rise. There is a lack of research on the effects of sweeteners on human metabolism, and more research is needed on the negative effects on human metabolism.

The positive effects of artificial sweeteners on the human body focus on not having to take on the extra calories of nutritive sweeteners such as sucrose. One application of non-nutritive sweeteners is to replace sucrose when added to foods to provide sweetness, and these foods are commonly believed to help consumers manage their weight and risk of diabetes. At the same time, non-nutritive sweeteners can provide a sweetening experience for those who cannot consume nutritive sweeteners such as sucrose, such as diabetics. Also, these sweeteners have medical applications. For example, saccharin may be used as an antidote for metal poisoning, and high concentrations of aspartame may have an inhibitory effect on the development of colorectal cancer. Sucralose may be used to assess intestinal permeability. More research is needed to discover the benefits of artificial sweeteners in people's lives.

In conclusion, non-nutritive sweeteners such as saccharin, aspartame and sucralose help reduce caloric intake, but their effects on glucose metabolism and human health need further study. The current study is limited to mouse models, and the metabolic diseases caused in the population require more research. Future research should focus on the long-term effects of these sweeteners, individual differences in response to these sweeteners, and their effects and applications on other aspects of human health.

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