



Emerging Low-Calorie Sweeteners in Diabetes Management: A comprehensive review of Rare Sugars, Polyols and Natural Compounds including Stevioside, Rebaudiosides, Mogrosides and Tagatose

Sant Kumar*, Alfya Gazna Padath, Nithya Sri Dasam, R. Siri Varshini, Keya Jigneshbhai Patel, Zanje Shrushti Arun, Sourav Lahiri

Department of Pharmaceutical Sciences, Gurugram University, Kankrola Haryana- 122505

Padath House, Kuttippiram, Malappuram Kerela

B.Pharm, Vigan Institute of Pharmaceutical Technology, Andhra Pradesh

M.Pharmacy, Department of Pharmaceutics, Gitam University, Prahaladapuram Simhachalam

Parul Institute of Pharmacy & Research, Vadodara Gujrat, India

Intern, Doctor of Pharmacy, Manjalpur Vadodara, Gujrat, India

Intern, Doctor of Pharmacy, Uma Chaar Rasta, Vadodara, Gujrat

*Corresponding author's E-mail : team@clinivancelabs.com

ABSTRACT

In recent decades, the world prevalence of diabetes mellitus and other metabolic disorders has shown a sharp rise, mainly attributed to improper dietary habits, a lack of physical activity, and increased intake of sugars in food products. Excessive consumption of sugars, like sucrose and high-fructose corn syrup, is strongly linked with metabolic disorders, like obesity, insulin resistance, and poor glycemic control, leading to an increased risk of type 2 diabetes and cardiovascular diseases. This has prompted a strong interest in finding safe and effective low-calorie sweeteners that can satisfy human taste without compromising their adverse metabolic impact on health. Rare sugars, polyols, and plant-derived sweeteners are some of the emerging alternatives that have shown promise in diabetic nutrition and functional food development. Rare sugars such as tagatose and allulose have low caloric value along with a low glycemic response. Polyols such as erythritol, xylitol, sorbitol, and mannitol have low energy values. These have a good dental and metabolic profile compared to other sugars. Additionally, plant-derived sweeteners such as stevioside, rebaudiosides, and mogrosides are high-potency sweeteners. These have low caloric values along with low blood glucose response. Experimental and clinical studies have shown that the blood glucose response of these sweeteners can be improved by reducing the caloric content along with weight management. Aside from nutritional aspects, these sweeteners also have a significant use in pharmaceutical and nutraceutical formulations such as in sugar-free syrups and chewable tablets. In conclusion, these newly identified low-calorie sweeteners have shown great potential as alternatives to conventional sugars. However, more clinical studies need to be conducted to assess their metabolic safety and therapeutic potential in managing diabetes.

Keywords: Rare sugars; Polyols; Steviol glycosides; Mogrosides; Glycemic index; Diabetes management; Low-calorie sweeteners.

INTRODUCTION

Diabetes mellitus has been recognized as one of the major global health challenges of the 21st century. The prevalence of diabetes, particularly type 2 diabetes mellitus (T2DM), has increased rapidly due to factors such as urbanization, sedentary lifestyles, and unhealthy dietary patterns [1]. According to global health statistics, the number of individuals living with diabetes continues to rise each year, posing a significant public health concern worldwide. Among all cases of diabetes, type 2 diabetes mellitus accounts for approximately 90–95% of the total disease burden [2]. This metabolic disorder is characterized by impaired insulin secretion, insulin resistance, and persistent hyperglycemia. Longterm hyperglycemia contributes to several chronic complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, which significantly reduce the quality of life of affected individuals [3]. The growing burden of diabetes not only threatens public health but also imposes a substantial economic burden on healthcare systems due to the high costs associated with long-term treatment and management [4].

Dietary patterns play an essential role in both the development and management of diabetes mellitus. High consumption of refined sugars and energy-dense foods has been identified as a major risk factor for

metabolic disorders such as obesity, insulin resistance, and impaired glucose tolerance [5]. Sugars such as sucrose and high-fructose corn syrup are widely used in processed foods, beverages, and confectionery products. These sugars contribute significantly to increased caloric intake and rapid postprandial elevations in blood glucose levels [6]. Frequent consumption of such high-sugar foods may disrupt metabolic homeostasis and increase the risk of developing type 2 diabetes and other metabolic complications, including obesity and cardiovascular diseases [7].

Conventional sugars, particularly sucrose, possess a relatively high glycemic index (GI), meaning they are rapidly digested and absorbed in the gastrointestinal tract, leading to sharp increases in blood glucose concentrations [8]. This rapid glycemic response represents a major limitation for individuals with diabetes or those at risk of developing the disease. Elevated postprandial glucose levels contribute to poor glycemic control and may accelerate the progression of diabetes-related complications [9]. Therefore, reducing the intake of high glycemic sugars is considered an important strategy in the dietary management of diabetes. In addition to their effects on glycemic control, excessive consumption of conventional sugars has been linked to several health concerns, including obesity, metabolic syndrome, and insulin resistance [10]. High sugar intake increases total caloric consumption without providing significant nutritional value, thereby promoting weight gain and adiposity. Furthermore, sugars play a significant role in the development of dental caries, as oral bacteria ferment sugars to produce acids that damage tooth enamel [11]. These adverse health effects highlight the importance of identifying healthier alternatives that can provide sweetness without producing undesirable metabolic consequences.

The rising prevalence of diabetes and other metabolic disorders has intensified the search for low-calorie and low-glycemic sweeteners that can serve as alternatives to conventional sugars in food and beverage products. Such alternatives are particularly beneficial for individuals who require strict regulation of blood glucose levels, including patients with diabetes and prediabetes [12]. Low-calorie sweeteners help reduce overall caloric intake while maintaining desirable sweetness and sensory properties in food products. In recent years, considerable research has focused on the development of natural and functional sweeteners derived from plant sources or produced using advanced biotechnological processes. These sweeteners may offer additional health benefits beyond sweetness, including improved glycemic control and potential metabolic advantages [13]. Advances in food science and biotechnology have enabled the identification and large-scale production of promising sugar substitutes, including rare sugars, polyols, and plant-derived glycosides such as steviol glycosides and mogrosides. These compounds exhibit favorable metabolic properties, including reduced caloric value, minimal glycemic impact, and improved safety profiles, making them attractive alternatives for use in diabetic nutrition and functional food development [14].

Scope and Objectives of the Review

In view of the growing interest in alternative sweeteners for diabetes control, the present review article aims to present a comprehensive overview of emerging low-calorie sweeteners and their potential applications in diabetic nutrition and pharmaceutical formulations. The present review article is based on three major categories of alternative sweeteners, namely, rare sugars, polyols, and plant-derived sweeteners. Special emphasis is given to emerging low-calorie sweeteners, such as tagatose, stevioside, rebaudiosides, and mogrosides, which have gained attention in recent times in view of their high sweetness intensity and minimal effect on blood glucose levels [15-20].

In addition to their source, chemical characteristics, and other relevant aspects, the present review article aims to present an overview of their metabolic effects, glycemic response, and safety aspects in view of emerging scientific evidence. In addition, the present review article aims to highlight their potential applications in food technology, nutraceuticals, and pharmaceutical formulations, especially in the development of sugar-free and diabetic nutrition products [21]. In view of emerging scientific evidence, the present article aims to present a comprehensive overview of the benefits, limitations, and prospects of emerging low-calorie sweeteners in diabetes control, based on a comprehensive collection of relevant literature on emerging low-calorie sweeteners.

CLASSIFICATION OF EMERGING LOW-CALORIE SWEETENERS

Low-calorie sweeteners have attracted significant interest as substitutes for traditional sugars owing to their lower-calorie composition and insignificant effect on blood glucose levels. Low-calorie sweeteners are commonly used in food products, drinks, and pharmaceutical products, especially for people suffering from diabetes or who want to minimize their caloric consumption. Low-calorie sweeteners that are emerging can be classified into three main categories: rare sugars, polyols or sugar alcohols, and plant-derived sweeteners.

Table 1. Comparison of Selected Emerging Low-Calorie Sweeteners Used in Diabetes Management

| Sweetener | Category | Relative Sweetness (Sucrose = 1) | Glycemic Index (GI) | Caloric Value (kcal/g) | Key Characteristics | Applications |
|--------------------------------|-------------------------|----------------------------------|---------------------|------------------------|--|---|
| Tagatose | Rare sugar | 0.8–0.9 | 3 | 1.5 | Low glycemic response, prebiotic effects, sucrose-like taste | Diabetic foods, beverages, functional foods |
| Allulose (D-Psicose) | Rare sugar | 0.6–0.7 | 0–1 | 0.2–0.4 | Minimal metabolic impact, anti-hyperglycemic effects | Low-calorie foods, baked products |
| Allose | Rare sugar | 0.7–0.8 | 0–5 | 0.2 | Antioxidant and potential anti-inflammatory effects | Functional foods, nutraceuticals |
| Xylitol | Polyol | 1.0 | 7–13 | 2.4 | Dental benefits, cooling sensation | Chewing gums, dental products, sugar-free foods |
| Sorbitol | Polyol | 0.5–0.6 | 9 | 2.6 | Humectant, widely used in pharmaceuticals | Syrups, confectionery, sugar-free products |
| Mannitol | Polyol | 0.5–0.7 | 0–2 | 1.6 | Non-hygroscopic, cooling effect, stable | Tablets, chewables, pharmaceutical formulations |
| Erythritol | Polyol | 0.6–0.7 | 0 | 0–0.2 | Nearly zero calories, high tolerance, minimal GI effects | Beverages, baked goods, diabetic foods |
| Stevioside | Plant derived sweetener | 200–300 | 0 | 0 | Natural steviol glycoside, may influence glucose metabolism | Beverages, sugar-free foods |
| Rebaudioside A / M | Plant derived sweetener | 250–350 | 0 | 0 | Improved taste, less bitterness than stevioside | Beverages, tabletop sweeteners |
| Mogrosides (Monk fruit) | Plant derived sweetener | 150–250 | 0 | 0 | High sweetness, antioxidant properties, no glycemic effect | Functional foods, beverages |

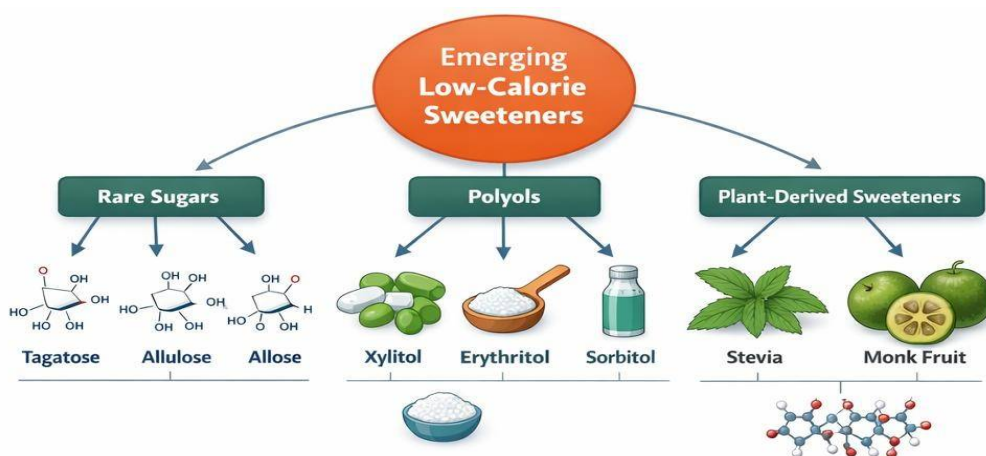


Figure 1: Classification of Emerging Low-Calorie Sweeteners

Rare Sugars

Rare sugars are a group of monosaccharides and their derivatives that occur in very small quantities in natural sources. These sugars differ from common dietary sugars such as glucose and fructose because they possess unique stereochemical configurations that influence their metabolic behavior in the human body [15]. Due to these structural differences, rare sugars are often metabolized differently and typically provide fewer calories and a lower glycemic response compared with conventional carbohydrates [16]. Because of their reduced caloric value and low glycemic index, rare sugars have attracted significant attention as potential alternatives to traditional sugars in diabetic and low-calorie food formulations. Recent advances in enzymatic conversion and microbial biotechnology have enabled the efficient production of rare sugars from abundant carbohydrate sources, making their large-scale commercial production increasingly feasible [17].

Important examples of rare sugars include tagatose, allulose, allose, and psicose. Tagatose is a naturally occurring monosaccharide derived from lactose and has been extensively studied due to its low glycemic index and reduced caloric content [18]. Allulose (also known as D-psicose) is another rare sugar structurally similar to fructose but metabolized differently, resulting in minimal impact on blood glucose levels [19]. Allose is a rare aldohexose that has been reported to exhibit antioxidant and potential anti-inflammatory properties [20]. Similarly, psicose has demonstrated beneficial metabolic effects, including reduced postprandial glucose levels and potential anti-obesity properties [21]. Due to these favorable metabolic characteristics, rare sugars are increasingly being explored as functional ingredients in diabetic diets and health-oriented food products [22].

Polyols (Sugar Alcohols)

Polyols, also known as sugar alcohols, are hydrogenated carbohydrates in which the carbonyl group of sugars is chemically reduced to a hydroxyl group. These compounds are widely used as sugar substitutes because they provide sweetness with fewer calories than conventional sugars and exhibit a lower glycemic index [23]. Polyols are absorbed slowly and incompletely in the small intestine and are metabolized at a slower rate compared with traditional sugars such as glucose and sucrose. As a result, their consumption produces a smaller increase in blood glucose and insulin levels, making them suitable sweetening agents for individuals with diabetes [24].

Commonly used polyols include xylitol, sorbitol, mannitol, and erythritol. Xylitol is widely used in chewing gums and oral health products due to its ability to reduce dental caries and inhibit the growth of cariogenic bacteria such as *Streptococcus mutans* [25]. Sorbitol and mannitol are frequently used in pharmaceutical formulations, including syrups, chewable tablets, and sugar-free medicinal preparations, because of their stability and sweetness [26]. Erythritol is another widely used polyol that has gained popularity due to its extremely low caloric value and better gastrointestinal tolerance compared with other sugar alcohols [27]. Although polyols provide several metabolic and dental benefits, excessive consumption may lead to gastrointestinal discomfort such as bloating and laxative effects because they undergo fermentation by intestinal microbiota in the large intestine [28].

Natural Plant-Derived Sweeteners

Natural plant-derived sweeteners are sweetening agents obtained from botanical sources and are increasingly used as alternatives to conventional sugars in foods and beverages. These compounds are considered high-intensity sweeteners because they provide significantly greater sweetness compared with sucrose while contributing little or no calories [29]. Due to their negligible caloric contribution and minimal effects on blood glucose levels, plant-derived sweeteners are widely used in diabetic diets and low-calorie food products [18]. Some of the most important plant-derived sweeteners include stevioside, rebaudioside A, rebaudioside M, and mogrosides. Stevioside and rebaudioside A are steviol glycosides extracted from the leaves of *Stevia rebaudiana*. These compounds are approximately 200–300 times sweeter than sucrose and have minimal effects on blood glucose and insulin levels [30]. Rebaudioside A and rebaudioside M are particularly valued for their improved taste profiles and reduced bitterness compared with stevioside [31]. Another important class of natural sweeteners is mogrosides, which are derived from the fruit of *Siraitia grosvenorii*, commonly known as monk fruit. Mogrosides possess strong sweetness intensity and have been reported to exhibit antioxidant and potential antidiabetic properties [32]. Due to their safety profile, natural origin, and negligible glycemic impact, plant derived sweeteners are increasingly used as substitutes for sucrose in both the pharmaceutical and food industries [33].

RARE SUGARS AND THEIR ROLE IN DIABETES MANAGEMENT

Rare sugars are monosaccharides that occur naturally in very small quantities in nature and differ structurally from common dietary sugars such as glucose, fructose, and sucrose. In recent years, rare sugars have attracted considerable attention in nutritional science and diabetes research because of their low caloric value and minimal effects on blood glucose levels. These sugars exhibit unique metabolic

pathways that distinguish them from conventional carbohydrates and make them promising candidates for diabetic nutrition and functional food formulations [34].

Chemical Structure and Production

The chemical structures of rare sugars differ slightly from common monosaccharides due to variations in the spatial orientation of hydroxyl groups around the carbon atoms. These stereochemical differences significantly influence their absorption, metabolism, and physiological effects. For example, rare sugars such as D-tagatose, D-allulose (also known as D-psicose), and D-allose are structural isomers of common hexoses but are metabolized differently by the human body.

Because rare sugars occur only in trace amounts in natural sources, large-scale production relies primarily on enzymatic and biotechnological methods. Modern production techniques involve enzymatic epimerization, isomerization, and microbial fermentation processes that convert abundant sugars such as fructose or lactose into rare sugar derivatives. Enzymes such as L-arabinose isomerase and D-tagatose 3-epimerase are commonly used in industrial processes to synthesize tagatose and allulose from lactose or fructose. These technologies have enabled cost-effective production and expanded the potential application of rare sugars in functional foods and pharmaceutical formulations [35].

D-Tagatose

D-Tagatose is one of the most extensively studied rare sugars and has been recognized as a promising low-calorie sweetener for diabetes management. Structurally, D-tagatose is a ketohexose that is an epimer of fructose and belongs to the class of rare sugars with unique stereochemical properties [36]. It occurs naturally in small quantities in dairy products and certain fruits and is commonly produced through enzymatic conversion of lactose using microbial or enzymatic technologies [36]. Tagatose exhibits approximately 90% of the sweetness of sucrose while providing significantly fewer calories, typically around 1.5 kcal/g, making it a suitable ingredient for sugar-reduced and diabetic food formulations [37]. One of the most important characteristics of D-tagatose is its very low glycemic index. Following ingestion, only a small proportion of tagatose is absorbed in the small intestine, whereas a considerable fraction reaches the large intestine where it undergoes fermentation by intestinal microbiota [38]. Due to this limited absorption and slower metabolism, tagatose produces only minimal increases in blood glucose and insulin levels compared with conventional sugars such as sucrose and glucose [46]. Several experimental and clinical studies have demonstrated that tagatose can reduce postprandial glucose spikes and may contribute to improved glycemic control in individuals with type 2 diabetes [39]. These metabolic properties have encouraged the incorporation of tagatose into functional foods and diabetic dietary products designed to improve glucose regulation.

BIOLOGICAL EFFECTS OF RARE SUGARS

Rare sugars exert several beneficial metabolic effects that support their potential application in diabetes management. One of the most important advantages of rare sugars is their reduced glycemic response compared with conventional carbohydrates. Unlike glucose and sucrose, many rare sugars are absorbed slowly or incompletely in the gastrointestinal tract, resulting in a gradual and limited rise in blood glucose concentrations [48]. This property is particularly beneficial for individuals with diabetes who require strict control of postprandial glycemia to prevent metabolic complications [49].

In addition to their glycemic effects, rare sugars may also influence lipid metabolism and energy homeostasis. Experimental studies suggest that certain rare sugars, particularly D-psicose and Dtagatose, can reduce hepatic lipid accumulation and improve lipid metabolism by decreasing triglyceride synthesis and enhancing fatty acid oxidation [50]. These metabolic actions may contribute to a reduced risk of metabolic syndrome, obesity, and cardiovascular diseases associated with insulin resistance [51].

Another emerging area of research focuses on the interaction between rare sugars and gut microbiota. Because a proportion of these sugars' escapes digestion in the upper gastrointestinal tract, they can serve as fermentable substrates for beneficial intestinal microorganisms [52]. The fermentation of rare sugars in the colon may stimulate the growth of probiotic bacteria and promote a healthier gut microbial balance [53]. Improved gut microbiota composition has been associated with better metabolic regulation, reduced inflammation, and enhanced intestinal health.

HEALTH BENEFITS OF RARE SUGARS

Rare sugars offer several additional health benefits beyond their direct role in glycemic control. Some rare sugars have been reported to exhibit antioxidant properties that may help reduce oxidative stress, which plays a crucial role in the progression of diabetes and its complications [54]. By reducing oxidative damage to cells and tissues, these compounds may contribute to improved metabolic stability and protection against chronic disease development.

Another important benefit of rare sugars is their potential prebiotic activity. The fermentation of rare sugars in the colon may stimulate the growth of beneficial gut bacteria such as *Bifidobacterium* and *Lactobacillus* species [55]. This prebiotic effect may enhance intestinal health, improve nutrient absorption, and support immune function. A healthy gut microbiota is increasingly recognized as an important factor in metabolic regulation and the prevention of metabolic diseases [56].

Rare sugars may also contribute to weight management due to their lower caloric content and reduced glycemic impact. Because these sugars provide fewer calories than conventional sugars and cause a slower rise in blood glucose levels, their use may help reduce total energy intake and prevent excessive fat accumulation [57]. Replacing traditional sugars with rare sugars in foods and beverages may therefore support improved metabolic health and reduce the risk of obesity-related disorders.

Overall, rare sugars represent an innovative class of carbohydrate sweeteners with promising applications in diabetic nutrition, functional foods, and pharmaceutical formulations. Their unique metabolic characteristics, low glycemic impact, and potential health benefits make them valuable alternatives to conventional sugars and attractive candidates for the development of healthier dietary products [58].

Polyols in Diabetic Diets

Polyols, also referred to as sugar alcohols, are a group of low-calorie sweeteners commonly used as alternatives to conventional sugars, particularly for individuals with diabetes or those requiring sugar-free dietary products. These compounds are derived from carbohydrate sources through the hydrogenation of their carbonyl groups to hydroxyl groups, resulting in the formation of polyhydric alcohols [40, 46]. This structural modification alters their metabolic pathways compared with traditional sugars such as glucose and sucrose. As a result, polyols are digested and absorbed more slowly in the gastrointestinal tract, leading to a lower glycemic response and reduced impact on blood glucose levels [41-44]. Due to their moderate sweetness, lower caloric value, and desirable physicochemical properties, polyols have become important functional ingredients in the development of sugar-free and reduced-calorie products.

Sugar alcohols are widely used in the formulation of sugar-free confectionery products, chewing gums, beverages, baked goods, and pharmaceutical syrups. These compounds can provide both bulk and sweetness similar to sucrose while delivering fewer calories and producing a smaller increase in blood glucose levels [60]. Because of these characteristics, polyols serve as valuable alternatives to traditional sugars for individuals with diabetes and for consumers seeking reduced-calorie diets. Their widespread use in functional foods, dietary products, and pharmaceutical formulations highlights their importance as a versatile class of sweeteners in modern food technology and diabetic nutrition [61].

Structure and Classification

Polyols can be chemically defined as sugar alcohols because their molecular structure contains multiple hydroxyl groups (-OH) attached to carbon atoms. These compounds are typically synthesized through the catalytic hydrogenation of monosaccharides or disaccharides, during which the carbonyl group present in the sugar molecule is reduced to a hydroxyl group [62]. This conversion results in the formation of stable polyhydric alcohols with altered physicochemical and metabolic characteristics. Compared with conventional sugars such as glucose and fructose, polyols exhibit different stereochemical configurations and metabolic pathways. While glucose and fructose are rapidly absorbed and metabolized in the body, polyols are absorbed slowly and incompletely in the small intestine, which leads to a reduced glycemic response and lower caloric availability [63]. Based on the number of carbon atoms present in their molecular structure, polyols can be classified into different groups including tetritols, pentitols, and hexitols [61].

Major Polyols Used in Food and Pharmaceuticals

Several polyols are widely used as sugar substitutes in both the food and pharmaceutical industries. Among these compounds, xylitol, sorbitol, mannitol, and erythritol are the most commonly utilized due to their favorable sweetness profile and functional properties [53].

Xylitol is a five-carbon sugar alcohol that occurs naturally in small amounts in fruits and vegetables. It possesses a sweetness level comparable to that of sucrose and provides a lower caloric value of approximately 2.4 kcal/g [64]. Xylitol is extensively used in chewing gums, toothpaste, and diabetic food products because of its low glycemic impact and its ability to inhibit the growth of cariogenic bacteria associated with dental caries [62].

Sorbitol is another widely used polyol that is produced by the hydrogenation of glucose. It provides approximately 60% of the sweetness of sucrose and is commonly used as both a sweetener and a humectant in sugar-free confectionery products and pharmaceutical syrups [55]. Due to its stability and moisture-retaining properties, sorbitol is also frequently incorporated into tablets, syrups, and processed food products [57].

Mannitol is a hexitol polyol derived primarily from fructose. Compared with sorbitol, mannitol is less hygroscopic and exhibits greater chemical stability. Because of these characteristics, it is widely used in

pharmaceutical formulations such as tablets, chewable tablets, and powdered dosage forms [59]. Mannitol is also valued for its cooling sensation when dissolved in the mouth, which enhances the sensory properties of food and pharmaceutical products.

Erythritol is a four-carbon sugar alcohol that has gained increasing popularity in recent years as a low-calorie sweetener. Unlike many other polyols, erythritol is almost completely absorbed in the small intestine and is excreted unchanged in the urine [45]. As a result, erythritol provides nearly zero calories and produces minimal gastrointestinal effects compared with other sugar alcohols. These properties have made erythritol a preferred sweetener in sugar-free beverages, confectionery products, and diabetic dietary formulations [46].

Metabolic Pathways

Polyols, also known as sugar alcohols, have different metabolic pathways compared to other carbohydrates such as glucose and sucrose. This is mainly attributed to their different chemical structure and absorption pattern in the gastrointestinal tract. After ingestion, polyols are only partially absorbed in the small intestine through a passive mechanism of diffusion and not through an active transport mechanism as seen in monosaccharides such as glucose [47]. The rate and degree of absorption depend on the type of polyol consumed. For instance, erythritol is fully and rapidly absorbed from the small intestine and then excreted in the urine in an unchanged form, while sorbitol, mannitol, and xylitol are only partially and slowly absorbed [48].

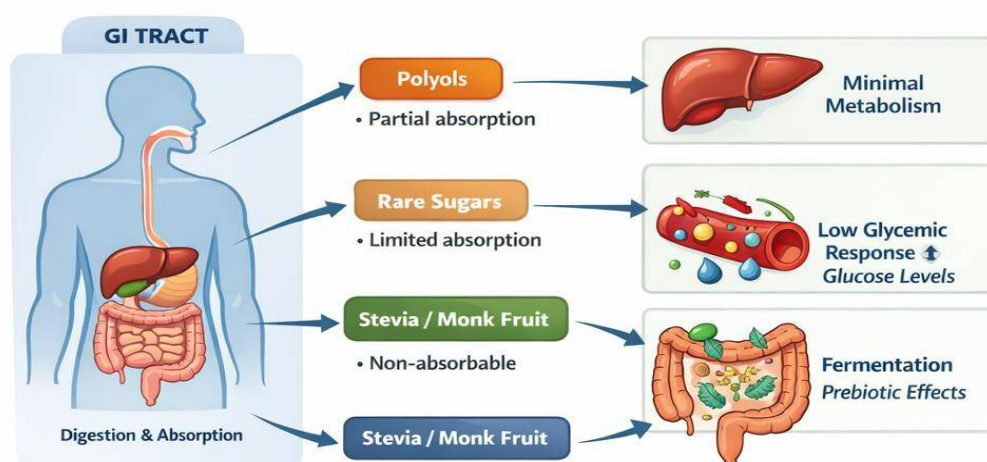


Figure 2: Metabolic Fate of Low-Calorie Sweeteners

The amount of polyol that is absorbed is then metabolized in the liver to various intermediates of carbohydrate metabolism such as fructose and glucose derivatives. Because this metabolic conversion occurs slowly and incompletely, polyols produce a significantly lower glycemic response than sucrose, making them particularly useful in diabetic diets for maintaining stable postprandial blood glucose levels [46]. Furthermore, their reduced caloric contribution—typically ranging from 0.2 to 2.6 kcal/g depending on the compound—also supports energy-controlled diets and weight management in individuals with diabetes.

The proportion of polyol not absorbed in the small intestine is transferred to the large intestine, where it is made available for fermentation by microbiota. Bacteria in the large intestine ferment polyol to produce short-chain fatty acids and gases such as hydrogen and carbon dioxide [34]. The fermentation products may be linked to health benefits such as improvement of gut microbiota composition and intestinal health, as well as the modulation of lipid and glucose metabolism. However, an excessive intake of polyol is known to induce gastrointestinal discomfort such as bloating and laxative effects due to its osmotic effect and fermentation in the large intestine [45]. Despite such negative health effects, moderate polyol intake is regarded as safe and beneficial to individuals suffering from diabetes due to its sweetness and minimal impact on blood glucose and insulin levels. Its distinct metabolic pathway and minimal glycemic index and caloric value make polyol a valuable ingredient in diabetic nutrition and pharmaceutical formulations used to manage diabetes and related metabolic disorders.

Glycemic Effects

One of the significant benefits of polyols in diabetic nutrition is that they cause a minimum increase in blood glucose levels. Unlike traditional carbohydrates such as glucose and sucrose, polyols are not easily or rapidly absorbed by the small intestine because of their unique chemical structure. This implies that the metabolism of polyols is slower compared to traditional carbohydrates. Consequently, polyols cause a

minimum increase in blood glucose levels. Most polyols have a low glycemic index, which is much lower than that of traditional carbohydrates. For example, erythritol and mannitol have a glycemic index close to zero. Xylitol and sorbitol have a low glycemic index. Therefore, polyols are considered good alternatives to traditional carbohydrates used to manage blood glucose levels in diabetic nutrition. The glycemic index is a measure of how much a particular carbohydrate increases blood glucose levels. The glycemic index ranges from 0 to 100. The closer a carbohydrate is to zero, the less it increases blood glucose levels. The closer a carbohydrate is to 100, the more it increases blood glucose levels. Therefore, polyols are good alternatives to traditional carbohydrates because they have a low glycemic index.

The low glycemic index of polyols makes them more suitable for use in diabetic food products. The replacement of regular sugars with polyols has been seen to greatly decrease the glycemic index of food products while retaining their sweetness, volume, and texture [46]. This is particularly advantageous to diabetic patients because they need to closely monitor blood glucose levels after meals. Apart from helping to manage glycemic levels, the addition of polyols to sugar-free food products has also been seen to lead to a decrease in calorie consumption and an improvement in metabolic management [54]. Therefore, polyols are used to make a variety of sugar-free food products, including candies, beverages, chewing gum, and pharmaceuticals intended for diabetic patients or for healthy individuals seeking to manage blood glucose levels [55].

Dental Benefits

The low glycemic response of polyol compounds makes them particularly useful in the development of diabetic foods and beverages. The ability of polyol compounds to replace conventional sugars in food and beverage formulations can result in a considerable decrease in the glycemic load of the product while preserving its sweetness, bulk, and texture [59]. This makes polyol compounds particularly useful in the development of food and beverage formulations for individuals with diabetes who need to closely monitor and manage their blood glucose levels after meals. In addition to the beneficial effect on glycemic control, the addition of polyol compounds to sugar-free formulations can result in a decrease in caloric intake and contribute to the management of blood glucose levels [60]. As a result, polyol compounds are commonly used in various sugar-free formulations, including confectionery, beverages, chewing gums, and pharmaceutical formulations for individuals with diabetes and those desiring to maintain stable blood glucose levels [61].

Aside from the beneficial effect of polyols on glycemic control, the use of polyols in sugar-free and reduced-calorie foods may also play an important role in the reduction of overall energy intake and metabolic control of patients with diabetes or obesity [62]. The beneficial metabolic effect of polyols has made it widely used as an important component of various sugarfree foods such as confectionery, baked goods, beverages, chewing gums, and pharmaceuticals such as syrups and chewable tablets [63]. The beneficial effect of polyols on blood glucose control has made it an important component of the formulation of functional foods and sugar-free foods for the dietary management of metabolic diseases by maintaining stable blood glucose levels [64].

Safety Considerations

Although polyols are generally regarded as safe and have been approved for use in food products and pharmaceuticals, overconsumption may lead to side effects such as gastrointestinal problems. As the polyols are only partially absorbed in the intestine, there is an osmotic effect which leads to the absorption of water into the gastrointestinal tract [50-52].

Consumption of high amounts of polyols may lead to side effects such as bloating, discomfort, flatulence, and laxation. However, the regulatory authorities have recommended the moderate consumption of polyols. In addition, there are advisory statements on the sugar-free products containing polyols, which state that overconsumption may lead to a laxative effect.

Although there are limitations associated with the use of polyols, they are important sugar substitutes because of their metabolic profile, low glycemic effect, and functional attributes in food products and pharmaceutical products. The future use of polyols is likely to have a major impact on the dietary options available to diabetics and others seeking sugar-free products with low-calorie sweeteners [53-56].

Plant-Derived Sweeteners

Plant-derived sweeteners are natural compounds obtained from botanical sources that provide intense sweetness with little or no caloric contribution. These sweeteners have gained considerable attention in recent years due to the increasing prevalence of diabetes, obesity, and other metabolic disorders associated with excessive sugar consumption [54]. Unlike conventional sugars such as sucrose and glucose, plant-derived sweeteners typically have a negligible glycemic index and minimal effect on blood glucose levels. Because of these properties, they are increasingly incorporated into functional foods, beverages, and nutraceutical formulations designed for diabetic individuals and consumers seeking healthier dietary alternatives [33, 55].

Stevia (Stevioside and Rebaudiosides)

The plant *Stevia rebaudiana*, commonly referred to as stevia, is a perennial shrub belonging to the Asteraceae family and is native to South America. The leaves of the plant contain a number of sweet-tasting molecules known as steviol glycosides, which are responsible for the extreme sweetness of stevia extracts [58]. The major steviol glycosides identified as having extreme sweetness properties include stevioside, rebaudioside A, and rebaudioside M, which have been widely studied and analyzed for their sweetness and health benefits [59]. The molecules have been identified as having a sweetness level 50 to 300 times greater than that of sugar [53].

The chemical composition of steviol glycosides is a steviol molecule linked to a glucose molecule through a glycosidic bond. The chemical structure of steviol glycosides is responsible for their extreme sweetness and zero-calorie content when consumed in moderate amounts (Samreen & Dhaneshwar, 2022). Once ingested, steviol glycosides are not significantly absorbed in the gastrointestinal tract but are instead metabolized to steviol by intestinal microbiota and then absorbed and excreted mainly through the urine after conjugation in the liver [59].

Several studies have indicated the potential metabolic benefits of steviol glycosides, especially in the management of diabetes. Research has indicated the potential of stevia to enhance the tolerance of the body to sugar, thus helping to manage diabetes. The research indicates that stevia can stimulate the pancreas to secrete insulin into the blood, thus helping to manage diabetes. Stevia has been studied to have the potential to manage high blood sugar levels, high blood pressure, and to have antioxidant activity, thus helping to manage diabetes. In terms of the safety of stevia, the Joint FAO/WHO Expert Committee on Food Additives has established the acceptable daily intake of steviol glycosides to be 4 mg/kg body weight/day, which is a steviol equivalent. This indicates the safety of steviol glycosides for consumption.

Mogrosides (Monk Fruit)

The mogrosides are natural sweet substances extracted from the fruit of *Siraitia grosvenorii*, also known as monk fruit or Luohanguo. The plant is native to southern China and is used in traditional Chinese medicine for its medicinal and sweetening properties [1]. Monk fruit extracts contain a mixture of triterpenoid glycosides called mogrosides, which are known to produce intense sweetness in the fruit. Among the mogrosides, mogroside V is known to be the major and most bioactive component that is responsible for the intense sweetness of the monk fruit extracts [3].

The mogrosides are known to be high-intensity natural sweeteners since they are 150 to 250 times sweeter than sugar and have almost zero-calorie content [7]. Unlike other natural and artificial sweeteners, the mogrosides do not raise blood glucose levels since they are not metabolized by the body as carbohydrates are [8]. Instead, the mogrosides pass through the gastrointestinal tract without significant absorption into the bloodstream. As a result, the blood glucose levels do not increase when the monk fruit extracts are consumed, making them a preferred choice for people living with diabetes and those seeking to use sugar-free and low-calorie foods.

In addition to their sweetening properties, mogrosides are said to have several potential health benefits. Some research has indicated that mogrosides are rich in antioxidants, which are believed to reduce oxidative stress and protect the body from free radicals [12]. Some research has indicated that mogroside compounds are effective in improving glucose metabolism and inflammation in people with metabolic disorders, thus preventing diabetes [61]. As a result of these beneficial properties, sweeteners from the monk fruit are used to make functional foods and beverages with health benefits.

Sensory Characteristics

Table 2: Sensory Characteristics of Natural Sweeteners Compared with Sucrose

| Sensory Parameter | Description | Examples of Sweeteners | Impact on Food Products |
|----------------------------|--|--|--|
| Sweetness Intensity | Degree of perceived sweetness compared with sucrose (reference = 1). Many natural sweeteners are significantly sweeter than sucrose. | Stevioside, Rebaudioside A/M, Mogrosides | Allows use of smaller quantities of sweetener, reducing calorie content in foods and beverages. |
| Aftertaste | Lingering taste sensation that remains after consumption. Some natural sweeteners produce bitter or licorice-like aftertastes. | Stevioside, Steviol glycosides | May affect consumer acceptance; often improved through blending with other sweeteners. |
| Flavor Modulation | Ability of sweeteners to modify or enhance overall flavor perception in food products. | Mogrosides, Stevia blends | Can improve flavor balance and mask undesirable tastes in functional foods or pharmaceutical formulations. |

| | | | |
|------------------------------|--|-------------------|--|
| Texture and Mouthfeel | Influence of sweeteners on the physical and sensory properties of foods, including viscosity and bulk. | Polyols, Tagatose | Helps maintain structural properties in reduced-sugar foods. |
|------------------------------|--|-------------------|--|

The sensory properties of natural sweeteners are also significant in the selection of the sweeteners to be used in the formulation of sugar-free and low-calorie foods. The sweetness intensity of the sweeteners is one of the most significant sensory properties of sweeteners. Most of the sweeteners are found to have sweetness intensities many times higher than that of sugar, thus enabling the formulation of foods with less sugar and fewer calories [63]. However, the aftertaste of some sweeteners, which is bitter and somewhat similar to licorice, is not desirable in most foods and thus affects the acceptance of the product by consumers. The flavor modulation property of sweeteners is another significant sensory property of sweeteners. The interaction of sweeteners with other ingredients in foods enhances the flavor of the product [64]. In addition to the taste properties of sweeteners, the texture and mouthfeel of the product are also affected by the addition of sweeteners in the formulation of sugar-free and low-calorie foods [64]. Therefore, the sensory properties of sweeteners are significant in the formulation of functional foods and pharmaceutical formulations for diabetic and health-conscious consumers.

GLYCEMIC INDEX AND METABOLIC EFFECTS

Glycemic Index Concept

The glycemic index is a nutritional measure that has been frequently employed to assess the rate at which the level of blood glucose increases following the consumption of a given food item. It has been established through a comparative analysis of the effect of a given food item on the level of blood glucose with the effect of a reference food item, such as glucose or bread, which has a glycemic index of 100 [65]. Food items with high glycemic indices are readily digested and absorbed, thus causing a rapid increase in the level of blood glucose. Conversely, food items with low glycemic indices are digested and absorbed slowly, thus causing a moderate increase in the level of blood glucose [56]. The glycemic index has emerged as a major nutritional measure in the dietary management of diabetes, as low glycemic index food items help in the regulation of the level of blood glucose. Sweeteners such as rare sugars, polyols, and plant glycosides have low glycemic indices compared to other sweeteners, thus offering a better alternative to the general population, especially to diabetics.

Glycemic Response of Different Sweeteners

The glycemic response varies among sweeteners according to their chemical composition, digestion, and metabolism. Common sugars like sucrose have a glycemic index of about 65 and offer 4 kcal/g of energy, which can substantially elevate blood glucose concentrations when taken in large quantities [57]. On the other hand, less common sugars like tagatose offer fewer calories, about 1.5 kcal/g, and result in a very low glycemic response because of their low absorption in the small intestine and slow rate of metabolism [55]. Polyol sweeteners such as sorbitol, xylitol, mannitol, and erythritol also display low glycemic indices because of their slow absorption and metabolism in the gastrointestinal tract, thus raising blood glucose concentrations to a lesser extent [56]. High-intensity sweeteners from plants like stevia are known to display zero glycemic indices and offer fewer calories while possessing 200 to 300 times more sweetness compared to common sugar [57]. These characteristics of alternative sweeteners are beneficial in the development of diabetic foods and low-calorie dietary supplements.

Table 3: Comparison of Glycemic Index, Caloric Value, and Sweetness of Selected Sweeteners

| Sweetener | Glycemic Index (GI) | Calories (kcal/g) | Relative Sweetness (Sucrose =1) |
|-----------------------------|---------------------|-------------------|---------------------------------|
| Sucrose | 60-65 | 4.0 | 1.0 |
| Tagatose | 3 | 1.5 | 0.8-0.9 |
| Polyols (average range) | 0-13 | 0-2.6 | 0.5-1.0 |
| Stevia (steviol glycosides) | 0 | 0 | 200-300 |

Effects on Insulin Sensitivity

Low-calorie sweeteners and rare sugars have been suggested to play a role in insulin sensitivity via their low glycemic index. This is because, unlike regular sugars that increase blood glucose levels rapidly, leading to a corresponding increase in insulin levels, low-calorie sweeteners increase blood glucose levels more slowly. This slower increase is a controlled metabolic response to low-calorie sweeteners, as suggested by Sakon et al. [53]. Rare sugars such as D-tagatose and D-psicose have been suggested to enhance insulin sensitivity. Steviol glycosides, which are found in *Stevia rebaudiana*, increase insulin secretion by pancreatic β -cells. This increase is observed in patients with type 2 diabetes, as suggested by Sevenpiper et al., [55]. This increase in insulin secretion indicates that alternative sweeteners can support the dietary management of diabetes.

Impact on Gut Microbiota

Recent studies have identified the interaction of alternative sweeteners with the gut microbiota, which is a vital factor in the regulation of the metabolic state. Some sweeteners, such as rare sugars and polyols, are not completely digested in the upper part of the gastrointestinal tract and therefore reach the large intestine, where they are fermented by the intestinal microorganisms [16]. The fermented products include short-chain fatty acids such as acetate, propionate, and butyrate, which are known to have beneficial effects on the intestines. In addition, the short-chain fatty acids may have prebiotic activity, which increases the growth of beneficial microorganisms such as *Bifidobacterium* and *Lactobacillus* species [11]. However, excessive consumption of alternative sweeteners may have adverse effects on the balance of the gut microbiota or may cause gastrointestinal disorders such as bloating or diarrhea because of increased levels of fermentation products [18]. In conclusion, although alternative sweeteners have beneficial effects on the metabolic state, their consumption should be done in moderation within the limits of the dietary allowance.

SAFETY AND TOXICOLOGICAL EVALUATION

Regulatory Approvals

The safety of low-calorie sweeteners, such as rare sugars, polyols, and plant-derived sweeteners, has been thoroughly evaluated and approved by various international regulatory authorities before their approval and acceptance for food and pharmaceutical applications. The major regulatory organizations that have approved and accepted low-calorie sweeteners are the Food and Drug Administration (FDA), the European Food Safety Authority (EFSA), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). These organizations have thoroughly evaluated and scientifically studied various toxicological parameters to assess the safety of low-calorie sweeteners before their approval and acceptance for human consumption [15]. For instance, steviol glycosides derived from *Stevia rebaudiana* and mogrosides derived from monk fruit have been scientifically evaluated and approved by these organizations and are considered safe for food applications when ingested in recommended amounts [14]. Similarly, polyols such as xylitol, sorbitol, erythritol, and mannitol have been classified as generally recognized as safe (GRAS) by the FDA due to their long history of safe use in foods and pharmaceutical formulations [23]. The rigorous safety evaluations conducted by these regulatory bodies ensure that approved sweeteners meet strict safety standards before being introduced into the global food supply.

Acceptable Daily Intake (ADI)

The acceptable daily intake is an important parameter on which the regulatory authorities make judgments to ensure the safe consumption of food additives, like sweeteners. The acceptable daily intake is defined as the amount of a substance that can be safely consumed on a daily basis over an entire lifetime without posing significant health hazards. The acceptable daily intake is expressed as milligrams of the substance per kilogram of body weight. The determination of the acceptable daily intake values is based on the results of toxicological tests, like animal studies and human clinical trials. The values are also supported by large safety margins to cover the differences between the responses of different individuals. For instance, the acceptable daily intake values of steviol glycosides have been established at 4 mg/kg body weight per day expressed as steviol equivalent by JECFA and EFSA. The ADI values of polyol sweeteners like sorbitol, xylitol, and erythritol are not strictly defined because of the low toxicity of these compounds. The large intake of polyol sweeteners may cause gastrointestinal discomfort by inducing osmotic effects in the intestine. The determination of ADI values is important to ensure the safe consumption of sweeteners by the general public.

Long-Term Safety Evidence

Long-term safety tests are critical in assessing the possible health hazards linked to the chronic intake of alternative sweeteners. Several toxicological and epidemiological studies have been carried out to investigate the long-term metabolic effects of low-calorie sweeteners and have confirmed their safety when used within recommended levels [34]. Steviol glycosides have been thoroughly tested using both animal and human models and have not been found to induce cancer, genetic toxicity, or reproductive toxicity [31]. Polyol sweeteners such as erythritol and xylitol have been found to have excellent safety profiles when tested using long-term tests because of their minimal impact on the metabolic system and quick excretion from the body [23]. Rare sugars such as tagatose and allulose have been tested for their metabolic safety and have been found to be promising in clinical studies on glycemic control and weight loss [44]. Although some of the alternative sweeteners may induce minor gastrointestinal side effects when consumed in large quantities, the current scientific consensus is that approved low-calorie sweeteners are safe for chronic use when consumed within recommended levels [49].

PHARMACEUTICAL AND NUTRACEUTICAL APPLICATIONS

Role in Drug Formulation

Low-calorie sweeteners are also essential ingredients used in pharmaceutical formulations, especially as sweetening agents for liquid oral dosage forms, including syrups, suspensions, and elixirs. Most pharmaceutical ingredients have an inherent bitter or unpleasant taste, which can lead to a decrease in patient compliance, especially among pediatric or elderly populations [58]. The use of sweeteners such as polyols, rare sugars, and plant-based sweeteners is common in pharmaceutical formulations to mask unpleasant tastes while keeping the calorie content low [59]. The sweetening agents used have a pleasant taste while providing a sweet experience without a rapid increase in blood glucose levels, making them suitable for sugar-free medicinal formulations for diabetic patients. The sweetening agents used also have good physicochemical properties, including solubility and stability, which makes them suitable for pharmaceutical formulations.

Another significant role that low-calorie sweeteners play in the field of pharmacy is their application in the taste masking of bitter-tasting drugs. Many drugs, particularly antibiotics, antihistaminics, and analgesics, possess a bitter taste that may influence a patient's compliance to a specific treatment regimen [59]. Low-calorie sweeteners, such as stevia extracts and polyols, and other natural sweetening agents are used in combination with flavor enhancers to effectively mask the bitter taste of drugs and improve their sensory acceptability [60]. Low-calorie sweeteners are also used in pediatric formulations, including chewable tablets, lozenges, and oral dispersible tablets, which are very important to ensure patient compliance, particularly in pediatric cases. The use of low-calorie sweeteners in pediatric and diabetic formulations is particularly beneficial because it allows the formulation of drugs that are not only sugar-free but also ensure that patients do not suffer from dental caries and excessive caloric intake [61].

Functional Foods and Nutraceutical

Low-calorie sweeteners are being used in functional foods and nutraceuticals to support various metabolic functions and prevent diet-associated diseases. In the field of diabetic nutrition, low-calorie sweeteners like steviol glycosides, rare sugars, and polyols are often used in the development of diabetic-friendly foods, including sugar-free confectionery, bakery goods, dairy alternatives, and dietary supplements [57]. Due to their low effect on blood glucose levels and low caloric value compared to sugar, low-calorie sweeteners are often regarded as good alternatives to sugar in the diet of individuals who need to monitor their blood glucose levels. The addition of low-calorie sweeteners to diabetic foods enables the manufacturer to achieve good taste and sweetness while minimizing the glycemic properties of the product [59]. In addition to diabetic foods, low-calorie sweeteners are widely used in energy-reduced beverages and diet drinks aimed at consumers seeking weight management and healthier lifestyles. Beverages sweetened with stevia extracts, monk fruit compounds, or erythritol have gained significant popularity due to their natural origin and reduced caloric content [63]. These sweeteners enable manufacturers to develop beverages with desirable sweetness profiles without contributing excessive calories or causing rapid increases in blood glucose levels. As a result, they are commonly used in diet soft drinks, flavored waters, sports drinks, and nutritional beverages designed for individuals with diabetes or obesity.

Furthermore, low-calorie sweeteners are increasingly incorporated into functional nutrition products, including protein bars, dietary supplements, and nutraceutical formulations aimed at improving metabolic health and overall well-being. In many cases, these sweeteners are combined with bioactive ingredients such as dietary fiber, probiotics, vitamins, and plant extracts to create multifunctional products that provide both nutritional and health benefits [65]. The growing demand for natural, low-calorie, and diabetic-friendly ingredients has accelerated the development of innovative functional foods and nutraceutical products that incorporate alternative sweeteners as key components. Consequently, low-calorie sweeteners play a significant role in modern food technology and nutraceutical science by enabling the production of healthier dietary products that support metabolic health and disease prevention.

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

The development and use of alternative sweeteners are expected to continue to improve with the advancement of science and technology. The most promising areas of future research include the production of rare sugars by biotechnological means, such as the use of enzymatic conversion and microbial fermentation. This may provide an effective means of large-scale production of the rare sugar's tagatose, allulose, and allose on a large scale by microbial fermentation of the most abundant carbohydrates. Another important area of future research is the development of combination sweetener systems. In combination sweetener systems, different sweeteners such as rare sugars, polyols, and plant-derived glycosides may be mixed to provide the optimal sweetness response with the least amount of

unwanted aftertastes. The concept of personalized nutrition is also expected to play an important role in future dietary guidelines. With the development of nutritional science and the study of metabolism, it is possible to develop personalized dietary plans that take into account genetic factors, metabolic responses, and the composition of the human microbiome when selecting the most appropriate sweeteners to manage cases of diabetes and other forms of metabolism. In addition, while most of the sweeteners available in the market are promising in terms of their effect on human metabolism, there is a need to conduct long-term studies among diabetic patients to determine the safety and effectiveness of these sweeteners on human health in the long term. In addition, further research in these areas is likely to contribute to the development of safer and more effective sweetener alternatives to those in common use among the population with cases of diabetes and other individuals who are looking for healthier sweeteners in the long term.

CONCLUSION

In conclusion, the increased incidence of diabetes mellitus and associated metabolic disorders worldwide has stimulated interest in developing alternatives to conventional sugars. The excessive consumption of conventional sugars, including sucrose and high-fructose corn syrup, has been strongly implicated as a causative factor for obesity, insulin resistance, and poor glycemic control. These risk factors increase the risk of developing type 2 diabetes and cardiovascular complications. Consequently, the development and use of low-calorie sweeteners with low glycemic potential have become an essential strategy for dietary management and formulation of diabetic food products and pharmaceuticals.

The emerging sweeteners, including rare sugars, polyols, and plant glycosides, have been recognized as potential alternatives to conventional sugars because of their beneficial metabolic properties. Rare sugars, including tagatose, allulose, etc., offer a reduced caloric content with minimal glycemic potential while retaining a comparable sweetness level to conventional sugars. The polyols, including xylitol, sorbitol, mannitol, and erythritol, are used extensively in food and pharmaceutical formulations because of their low glycemic index, reduced caloric content, and additional benefits such as protection against dental caries. Similarly, plant glycosides, including stevioside, rebaudiosides, mogrosides, etc., have been recognized for their high sweetness potential with negligible caloric content and minimal effect on blood glucose levels.

Apart from contributing to sweetness, these new sweeteners also display promising health advantages, including glycemic control, antioxidant activities, and even the modulation of intestinal microbiota. The scope of application of these new sweeteners is not limited to diabetic foods but also includes energy-decreased beverages, functional nutrition supplements, and sugar-free pharmaceutical formulations to enhance patient compliance. The FDA, EFSA, and JECFA have already assessed most of these sweeteners and provided guidelines on their safe usage. New low-calorie sweeteners are promising solutions to overcome the difficulties and adverse health consequences of excessive sugar intake and associated diseases. Long-term studies and new biotechnology are expected to further expand the scope of application of these sweeteners to promote healthy lifestyles and combat diseases.

REFERENCES

1. Abhirama Rada Asasta, Dechen Wangmo Armando, Janice Clarisa Tissadharmma, Kimberly Alecia Theo, & Natasya Nobelta. (2024). Sugar Alcohol: A Comparison of Xylitol and Sorbitol in Food Application. *Deleted Journal*, 1(4), 231–239. <https://doi.org/10.55324/jgi.v1i4.39>
2. An, J.-P., Wang, Y., Munger, S. D., & Tang, X. (2024). A review on natural sweeteners, sweet taste modulators and bitter masking compounds: structure-activity strategies for the discovery of novel taste molecules. *Critical Reviews in Food Science and Nutrition*, 1–24. <https://doi.org/10.1080/10408398.2024.2326012>
3. Anie, Y., Hazeena, V. N., Hariha, V. H., & Binchu, V. S. (2019). Aldose Reductase Inhibitors for Multi-Faceted Anti-Diabetic Actions. *Plant Secondary Metabolites for Human Health*, 183–238. <https://doi.org/10.1201/9780429425325-7>
4. Ayoub, A. (2026). The Sweetener Innovation 4.0 Manifesto: How AI Is Architecting the Future of Functional Sweetness. *Sustainability*, 18(5), 2488. <https://doi.org/10.3390/su18052488>
5. Barrea, L., Vetrani, C., Verde, L., Frias-Toral, E., Ceriani, F., Cernea, S., Docimo, A., Chiara Graziadio, Tripathy, D., Savastano, S., Colao, A., & Muscogiuri, G. (2023). Comprehensive Approach to Medical Nutrition Therapy in Patients with Type 2 Diabetes Mellitus: From Diet to Bioactive Compounds. *Antioxidants*, 12(4), 904–904. <https://doi.org/10.3390/antiox12040904>
6. Dragomir, N., Grigore, D.-M., & Pogurschi, E. N. (2025). Beyond Sugar: A Holistic Review of Sweeteners and Their Role in Modern Nutrition. *Foods*, 14(18), 3182. <https://doi.org/10.3390/foods14183182>
7. Eissa, M. E. (2025). The Role of Allulose and Sugar Alcohols in Gut Microbiota Modulation and Metabolic Health: A Review. *Universal Journal of Pharmaceutical Research*. <https://doi.org/10.22270/ujpr.v9i6.1238>
8. Erickson, S., & Carr, J. (2020). The technological challenges of reducing the sugar content of foods. *Nutrition Bulletin*, 45(3), 309–314. <https://doi.org/10.1111/nbu.12454>

9. Franchi, F., Yaranov, D. M., Rollini, F., Rivas, A., Rios, J. R., Been, L., Tani, Y., Tokuda, M., Iida, T., Hayashi, N., Angiolillo, D. J., & Mooradian, A. D. (2021). Effects of D-allulose on glucose tolerance and insulin response to a standard oral sucrose load: results of a prospective, randomized, crossover study. *BMJ Open Diabetes Research and Care*, 9(1), e001939. <https://doi.org/10.1136/bmjdr-2020-001939>
10. Garrido-Romero, M., Montilla, A., & Moreno, F. J. (2023). Dietary carbohydrates: a trade-off between appealing organoleptic and physicochemical properties and ability to control glucose release and weight management. *Current Opinion in Food Science*, 49, 100976. <https://doi.org/10.1016/j.cofs.2022.100976>
11. Gasmí Benahmed, A., Gasmí, A., Arshad, M., Shanaida, M., Lysiuk, R., Peana, M., PshykTitko, I., Adamiv, S., Shanaida, Y., & Björklund, G. (2020). Health benefits of xylitol. *Applied Microbiology and Biotechnology*, 104(17), 7225–7237. <https://doi.org/10.1007/s00253-02010708-7>
12. Girigosavi, K. B., Eтта, I., Saisravika Kambham, & Panjiyar, B. K. (2024). Sweet Surprises: An In-depth Systematic Review of Artificial Sweeteners and Their Association with Cerebrovascular Accidents. *Current Nutrition Reports*. <https://doi.org/10.1007/s13668-02400537-9>
13. Gogoi, R. (2025). Sugar Polyols: Functional Characteristics, Production Pathways, Health Effects, and Contemporary Applications. <https://doi.org/10.2139/ssrn.5775083>
14. Gomes, A., Bourbon, A. I., Peixoto, A. R., Silva, A. S., Tasso, A., Almeida, C., Nobre, C., Nunes, C., Sánchez, C., Gonçalves, D. A., Castelo-Branco, D., Figueira, D., Coelho, E., Gonçalves, J., Teixeira, J. A., Pastrana Castro, L. M., Coimbra, M. A., Pintado, M., Ribeiro Cerqueira, M. Á. P., & Fuciños, P. (2023, January 1). *Chapter 9 - Strategies for the reduction of sugar in food products* (M. Á. P. R. Cerqueira & L. M. Pastrana Castro, Eds.). ScienceDirect; Academic Press. <https://www.sciencedirect.com/science/article/pii/B9780323855136000086>
15. Gómez-Fernández, A. R., Santacruz, A., & Jacobo-Velázquez, D. A. (2021). The complex relationship between metabolic syndrome and sweeteners. *Journal of Food Science*, 86(5), 1511–1531. <https://doi.org/10.1111/1750-3841.15709>
16. Gupta, P., & Kumar, M. (2023). Low Calorie Artificial Sweeteners as An Alternative in Pharmaceutical Dosage Form Design. *Indian Drugs*, 60(09), 7–21. <https://doi.org/10.53879/id.60.09.12662>
17. Han, H., Kim, Y., Gim, M., Shin, H., Jang, H., Yoon, W. J., Lee, G.-H., & Park, Y. K. (2024). Effect of Sugar-Free Jelly on Glycemic Metabolism and Its Potential Health Benefits in Non-Diabetic Adults. *Foods*, 13(6), 920. <https://doi.org/10.3390/foods13060920>
18. Hernandez-Hernandez, O., Sabater, C., Calvete-Torre, I., Doyagüez, E. G., Muñoz-Labrador, M., Julio-Gonzalez, C., de las Rivas, B., Muñoz, R., Ruiz, L., Margolles, A., Mancheño, J. M., & Moreno, F. J. (2024). Tailoring the natural rare sugars D-tagatose and L-sorbose to produce novel functional carbohydrates. *Npj Science of Food*, 8(1). <https://doi.org/10.1038/s41538-024-00320-8>
19. Ilaria Benucci, Lombardelli, C., & Esti, M. (2024). A comprehensive review on natural sweeteners: impact on sensory properties, food structure, and new frontiers for their application. *Critical Reviews in Food Science and Nutrition*, 1–19. <https://doi.org/10.1080/10408398.2024.2393204>
20. Kabore, I., Diao, M., Guenne, S., Metuor-Dabire, A., Sama, H., Ciobica, A., Hilou, A., Kiendrebeogo, M., & Dicko, M. H. (2022). Phytochemistry and Alternative use of Sweeteners in Metabolic Diseases. *Annals of the Academy of Romanian Scientists Series on Biological Sciences*, 11(1), 109–119. <https://doi.org/10.56082/annalsarscibio.2022.1.109>
21. Kakleas, K., Christodouli, F., & Karavanaki, K. (2020). Nonalcoholic fatty liver disease, insulin resistance, and sweeteners: a literature review. *Expert Review of Endocrinology & Metabolism*, 15(2), 83–93. <https://doi.org/10.1080/17446651.2020.1740588>
22. Kim, E. (2023). Effects of Natural Alternative Sweeteners on Metabolic Diseases. *Clinical Nutrition Research*, 12(3), 229–229. <https://doi.org/10.7762/cnr.2023.12.3.229>
23. Kodumayil, S., Gebril, A., Nair, S., Saifudeen, I., Alhermi, A., Shamsi, N., Alamuddin, N., & Kumar, N. (2025). Association of sucralose consumption with insulin response and sensitivity. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 19(12), 103343. <https://doi.org/10.1016/j.dsx.2025.103343>
24. Kołodziejczyk, A., & Nowak, J. (2025). A Comparative Analysis of the Use of Low-Calorie and No-Calorie Sweeteners in Food Products Without and With Added Sugar on the Polish Market. *Nutrients*, 17(11), 1899. <https://doi.org/10.3390/nu17111899>
25. Kossiva, L., Kakleas, K., Christodouli, F., Soldatou, A., Karanasios, S., & Karavanaki, K. (2024). Chronic Use of Artificial Sweeteners: Pros and Cons. *Nutrients*, 16(18), 3162. <https://doi.org/10.3390/nu16183162>
26. Laribi, A., Bartłomiej Zieniuk, Bouchedja, D. N., Kahina Hafid, Lamia Elmechta, & Becila, S. (2025). Valorization of Olive Mill Wastewater via *Yarrowia lipolytica*: Sustainable Production of High-Value Metabolites and Biocompounds—A Review. *Fermentation*, 11(6), 326–326. <https://doi.org/10.3390/fermentation11060326>
27. Lei, P., Chen, H., Ma, J., Fang, Y., Qu, L., Yang, Q., Peng, B., Zhang, X., Jin, L., & Sun, D. (2022). Research progress on extraction technology and biomedical function of natural sugar substitutes. *Frontiers in Nutrition*, 9. <https://doi.org/10.3389/fnut.2022.952147>
28. Leone, A., De Amicis, R., Lessa, C., Tagliabue, A., Trentani, C., Ferraris, C., Battezzati, A., Veggiotti, P., Foppiani, A., Ravella, S., & Bertoli, S. (2019). Food and Food Products on the
29. Italian Market for Ketogenic Dietary Treatment of Neurological Diseases. *Nutrients*, 11(5), 1104. <https://doi.org/10.3390/nu11051104>
30. Li, J., Chen, T., Zeng, Y., Yang, J., Men, Y., & Sun, Y. (2022). Review of natural sugar substitutes and comparing their potential impacts on obesity issue. *CABI Reviews*. <https://doi.org/10.1079/cabireviews202217034>

31. Li, J., Dai, Q., Zhu, Y., Xu, W., Zhang, W., Chen, Y., & Mu, W. (2023). Low-calorie bulk sweeteners: Recent advances in physical benefits, applications, and bioproduction. *Critical Reviews in Food Science and Nutrition*, 1–15. <https://doi.org/10.1080/10408398.2023.2171362>
32. Li, J., Li, H., Liu, H., & Luo, Y. (2023). Recent Advances in the Biosynthesis of Natural Sugar Substitutes in Yeast. *Journal of Fungi*, 9(9), 907. <https://doi.org/10.3390/jof9090907>
33. Li, Q., Xu, S., Li, T., Ji, L., & Cheng, H. (2025). Threitol, a Novel Functional Sugar Alcohol Biosynthesized by Engineered *Yarrowia lipolytica*, Has the Potential as a Low-Calorie Sugar-
34. Reducing Sweetener. *Foods*, 14(14), 2539–2539. <https://doi.org/10.3390/foods14142539>
33. Lina Maria Rayo-Mendez, & Jaiber Humberto Rodriguez-Llanos. (2022). Natural Sweeteners. *Springer EBooks*, 123–150. https://doi.org/10.1007/978-3-031-17346-2_5
35. Lu, F., Xu, W., Zhang, W., Guang, C., & Mu, W. (2019). Polyol dehydrogenases: intermediate role in the bioconversion of rare sugars and alcohols. *Applied Microbiology and Biotechnology*, 103(16), 6473–6481. <https://doi.org/10.1007/s00253-019-09980-z>
36. Majewski, M., Chruścicka, I., Buchta, J., Egierska, D., Burzyńska, P., Pietruszka, P., Perszke, M., & Całkosiński, A. (2020). What do we know about sugar substitutes? *Journal of Education, Health and Sport*, 10(4), 90. <https://doi.org/10.12775/jehs.2020.10.04.011>
37. Manish Sachan, & Pushpraj Singh. (2025). Artificial Sweeteners: Chemistry, Health Impacts and Regulatory Perspectives. *Asian Journal of Pharmaceutical Research and Development*, 13(5), 39–43. <https://doi.org/10.22270/ajprd.v13i5.1624>
38. Martínez-Miranda, J. G., Chairez, I., & Durán-Páramo, E. (2022). Mannitol Production by Heterofermentative Lactic Acid Bacteria: a Review. *Applied Biochemistry and Biotechnology*, 194(6), 2762–2795. <https://doi.org/10.1007/s12010-022-03836-5>
39. Mattes, R. D., Rivera, B. N., Giorgia Rutigliani, Rogers, S., Mendoza, I. D., Wang, L., Beckemeier, K., & Wikoff, D. (2024). A Review of Low- and No-Calorie Sweetener Safety and Weight Management Efficacy. *Nutrition Today*, 59(6), 261–288. <https://doi.org/10.1097/nt.0000000000000723>
40. McKenzie, E., & Lee, S.-Y. (2022). Sugar reduction methods and their application in confections: a review. *Food Science and Biotechnology*, 31(4), 387–398. <https://doi.org/10.1007/s10068-022-01046-7>
41. Mijailovic, N., Nesler, A., Perazzolli, M., Ait Barka, E., & Aziz, A. (2021). Rare Sugars: Recent Advances and Their Potential Role in Sustainable Crop Protection. *Molecules*, 26(6), 1720. <https://doi.org/10.3390/molecules26061720>
42. Mora, M. R., & Dando, R. (2021). The sensory properties and metabolic impact of natural and synthetic sweeteners. *Comprehensive Reviews in Food Science and Food Safety*, 20(2). <https://doi.org/10.1111/1541-4337.12703>
43. More, T. A., Shaikh, Z., & Ali, A. (2021). Artificial Sweeteners and their Health Implications: A Review. *Biosciences Biotechnology Research Asia*, 18(2), 227–237. <https://doi.org/10.13005/bbra/2910>
44. 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. *Frontiers in Endocrinology*, 11. <https://doi.org/10.3389/fendo.2020.00444>
45. Muñoz-Labrador, A., Hernandez-Hernandez, O., & F. Javier Moreno. (2023). A review of the state of sweeteners science: the natural versus artificial non-caloric sweeteners debate. *Stevia rebaudiana and Siraitia grosvenorii* into the spotlight. *Critical Reviews in Biotechnology*, 1–23. <https://doi.org/10.1080/07388551.2023.2254929>
46. Niranjana Karukayil Gopalakrishnan, Balasubramanian, B., Rohan Kundapur, Chaudhary, A., Arun Meyyazhagan, & Manikantan Pappuswamy. (2024). Unraveling connections with artificial sweeteners and their impact on human health: A comprehensive review. *EFood*, 5(5). <https://doi.org/10.1002/efd2.184>
47. Park, E., & Kwon, K. H. (2025). Metabolic characteristics and health effects of low-calorie sweeteners focusing on the prevention of obesity and metabolic diseases. *Journal of Food and Nutrition Research*, 64(2), 104. <https://doi.org/10.64122/aubp7404>
48. Piekara, A., Krzywonos, M., & Szymańska, A. (2020). Sweetening Agents and Sweeteners in Dietary Supplements for Children-Analysis of the Polish Market. *Nutrients*, 12(8), 2387. <https://doi.org/10.3390/nu12082387>
49. Plaza-Diaz, J., Pastor-Villaescusa, B., Rueda-Robles, A., Abadia-Molina, F., & Ruiz-Ojeda, F. J. (2020). Plausible Biological Interactions of Low- and Non-Calorie Sweeteners with the Intestinal Microbiota: An Update of Recent Studies. *Nutrients*, 12(4), 1153. <https://doi.org/10.3390/nu12041153>
50. Ram Snehi Dwivedi. (2022). *Saccharide Sweet (SS) Principles, Classification and Structural and Functional Details of SS Sweeteners and Plants*. 113–223. https://doi.org/10.1007/978981-33-6350-2_4
51. Ramsey, I., Liu, J., Swiegers, J. H., & Olayide Oladokun. (2025). From Sweetness to Mouthfeel: A Review on Overcoming Sensory Barriers in Sugar-Free Beverages. *International Journal of Food Science*, 2025(1). <https://doi.org/10.1155/ijfo/2345722>
52. Sakon, NA, Montakan Aimkaew, Saynamphung Tongchai, & Wannarat Leesuksawat. (2023). Low-sugar egg-based dessert (sweet egg yolk drops): Characterization, consumer acceptance and driver of liking. *Heliyon*, 9(11), e21937–e21937. <https://doi.org/10.1016/j.heliyon.2023.e21937>
53. Samreen, H., & Dhaneshwar, S. (2022). Artificial Sweeteners: Perceptions and Realities. *Current Diabetes Reviews*, 18. <https://doi.org/10.2174/1573399818666220429083052>
54. Shariffar, F., Ashrafzadeh, A., & Kavirimanesh Khanaman, M. (2022). A Review of Natural Peptide Sweeteners. *International Journal of Peptide Research and Therapeutics*, 28(6). <https://doi.org/10.1007/s10989-022-10464-4>

55. Sievenpiper, J. L., Sidd Purkayastha, Grotz, V. L., Mora, M., Zhou, J., Hennings, K., Goody, C. M., & Germana, K. (2025). Dietary Guidance, Sensory, Health and Safety Considerations When Choosing Low and No-Calorie Sweeteners. *Nutrients*, 17(5), 793–793. <https://doi.org/10.3390/nu17050793>
56. Smith, A., Avery, A., Ford, R., Yang, Q., Goux, A., Mukherjee, I., Neville, D. C. A., & Jethwa, P. (2022). Rare sugars: metabolic impacts and mechanisms of action: a scoping review. *British Journal of Nutrition*, 128(3), 389–406. <https://doi.org/10.1017/S0007114521003524>
57. Sokołowska, E., Sadowska, A., Sawicka, D., Kotulska-Bąblińska, I., & Car, H. (2021). A head-to-head comparison review of biological and toxicological studies of isomaltulose, d-tagatose, and trehalose on glycemic control. *Critical Reviews in Food Science and Nutrition*, 1–26. <https://doi.org/10.1080/10408398.2021.1895057>
58. Stanner, S. A., & Spiro, A. (2020). Public health rationale for reducing sugar: Strategies and challenges. *Nutrition Bulletin*, 45(3), 253–270. <https://doi.org/10.1111/nbu.12460>
59. Tahmouzi, S., Marand, S. A., Tarahi, M., Almasi, H., Reza Morakian, Elham Khalili Sadrabad, & Mollakhalili-Meybodi, N. (2025). Application of FDA-Approved Artificial Sweeteners in Food Science: Technological and Nutritional Challenges. *Comprehensive Reviews in Food Science and Food Safety*, 24(4). <https://doi.org/10.1111/1541-4337.70208>
60. Teyseire, F., Bordier, V., Beglinger, C., Wölnerhanssen, B. K., & Meyer-Gerspach, A. C. (2024). Metabolic Effects of Selected Conventional and Alternative Sweeteners: A Narrative Review. *Nutrients*, 16(5), 622. <https://doi.org/10.3390/nu16050622>
61. Tuseef Asghar, M., Yusof, Y., Noriznan Mokhtar, M., Yaacob, M., Ghazali, H., & Chang, L. (n.d.). *Journal of Nutrition and Food Sciences A Review of Nutritional Facts, Production, Availability and Future Aspects of Coconut Palm Sugar*. <https://dicasdadraanamaria.com/artigos/acucar-de-coco01.pdf>
62. Vaclavik, V. A., Christian, E. W., & Campbell, T. (2020). Sugars, Sweeteners, and Confections. *Food Science Text Series*, 281–299. https://doi.org/10.1007/978-3-030-468149_14
63. Van Laar, A. D. E., Grootaert, C., & Van Camp, J. (2020). Rare mono- and disaccharides as healthy alternative for traditional sugars and sweeteners? *Critical Reviews in Food Science and Nutrition*, 1–29. <https://doi.org/10.1080/10408398.2020.1743966>
64. Van, Poppe, J., Stef Deyaert, Laurie, I., Gravert, O., Abrahamsson, A., Aurélien Baudot, Karnik, K., & Risso, D. (2023). Low-no-calorie sweeteners exert marked compound-specific impact on the human gut microbiota *ex vivo*. *International Journal of Food Sciences and Nutrition*, 74(5), 630–644. <https://doi.org/10.1080/09637486.2023.2240037>
65. Witkowski, M., Nemet, I., Li, X. S., Wilcox, J., Ferrell, M., Alamri, H., Gupta, N., Wang, Z., Tang, W. H. W., & Hazen, S. L. (2024). Xylitol is prothrombotic and associated with cardiovascular risk. *European Heart Journal*, 45(27), ehae244. <https://doi.org/10.1093/eurheartj/ehae244>

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