Chapter 5
Natural Sweeteners

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5.1 Introduction

Natural sweeteners are substitutes for sucrose also known as "table sugar", commonly obtained from sugar cane (*Saccharum officinarum*) [1] and sugar beet (*Beta vulgaris*) [2], also substitutes for honey and maple syrup. These sweeteners are food additives (FAs) that provide or mimic a sweet flavor similar to sugar (sucrose) but with less caloric energy, then their impact on the diet is remarkably considered. Since the eighteenth century, the use of sugar in the form of sucrose extracted from sugar cane was widespread in the food industry and population [3, 4]. Over the years, metabolic disorders, obesity, and diabetes mellitus were increasing worldwide, becoming a health problem, since those conditions can trigger other diseases, thus, a non-caloric, non-nutritive alternative was necessary to sweeten beverages and foods. The first sweetener discovered was saccharine in 1879, a synthetic sweetener developed apparently as a suitable option for diabetic people [3]. Although sweeteners play an essential role in health and being safe for human diet, they are also important for the food industry since sweeteners are FAs that can provide specific characteristics to food products [5].

Water solubility, low rate of dissolution, temperature stability, colorless, odorless, length shelf life, non-toxic, non-after taste, low-cost and availability to produce it, among others [1, 6] are characteristics should be remarkably considered to choose a determine sweetener to food applications, beyond to sweeten foods, sweeteners are additives which also can provide properties of texture, moisture, bulk, flavor,

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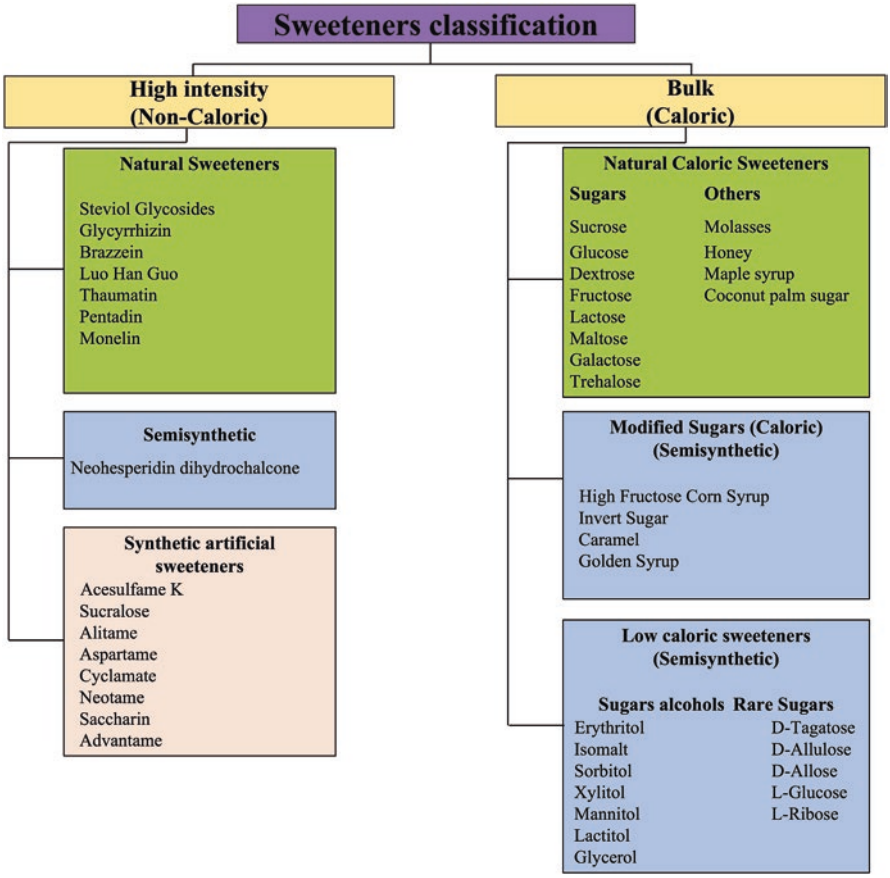

Fig. 5.1 Types of sweeteners and their classification according to calorie intake. (Adapted from García-Almeida et al. [7])

and color. In general, sweeteners can be categorized along two lines as high intensity (Non-caloric) or bulk (Caloric) (Fig. 5.1). Consequently, those two categories can be further divided into natural, semisynthetic, and artificial sweeteners (synthetic), depending on origin and production [8]. Categories as non-nutritive and nutritive, high, and low potency are usually used in the food industry, but still, the primary vantage of sweeteners is related to their low calories.

Natural (caloric) sweeteners are understood as minimally processed products extracted from plants or natural resources, these include sugars (sucrose, fructose, glucose, maltose, lactose, maltose, galactose, among others), honey, maple syrup, molasses, and coconut palm sugar, nonetheless with a high caloric level. In contrast, natural sweeteners (Non-caloric) have been also extracted from naturals sources (plants) or have undergone physicochemical processes, but all low calories, in this group may include Steviol glycosides (SGs), Glycyrrhizin, Thaumatin, Pentadin, Brazzein and Monellin [9]. Next are artificial sweeteners (synthetic), made strictly

from chemical substances through different reactions, which have high intensity sweetness power, such as acesulfame K, aspartame, alitame, cyclamate, neotame, saccharin, and sucralose. All of them have been applied in several foods and beverages such as desserts, canned foods, dairy products, baked goods, carbonated beverages, powdered drink mixes, soups, among others. However, artificial sweeteners consumption is regulated by the U.S. Food and Drug Administration by means of the acceptable daily intake (ADI) value, in view of some controversial safety health effects and instability of these sweeteners when applied in foods [10]. Low caloric sweeteners (semisynthetic) include sugars alcohols (erythritol, maltitol, lactitol, mannitol, glycerol, xylitol, isomalt) [11] and rare sugars (D-Tagatose, D-Allulose, D-Allose, L-Glucose, L-Ribose) [12], they are known also as semi-naturals because can be often found in foods or plants, however, are industrially treated through enzymes, yeasts or fungi to produce them [13]. As well as natural sweeteners can be applied in different preparations such as beverages, yogurts, cookies, cakes, and even in the cosmetic industry such as toothpaste, dental rinses, and so on [14]. According to Scoot et al. [15], people are becoming more conscious about their quality of life in terms of controlling weight and keeping it at acceptable levels. Thus, consumers in recent decades have focused on making choices for food products that do not directly affect health. On the other hand, the food industry has designed the development of lines of research into healthier foods for this market niche.

5.2 Main Natural Sweeteners: Properties and Applications

5.2.1 Erythritol

Erythritol is a natural sweetener found in fruits like grapes (0–42 mg/kg), melons (22–47 mg/kg), pears (0–40 mg/kg), mushrooms, seaweeds, wines (130–300 mg/l), beers, soy sauce (910 mg/l), sake (1550 mg/l), miso bean paste (1310 mg/l) [16, 17]. It was discovered in 1948 by the Scottish chemist John Stenhouse, isolated in 1952, and finally introduced to the Japanese market in 1990 as a sugar substitute for soft drinks, chewing gum, jams, and candies, and nowadays it is used as a growing ingredient [18–21]. For large-scale industrial production, erythritol can be obtained through several chemical methods, also extraction, however, fermentation is a more cost-effective process to produce it [17, 19]. Nowadays, glucose fermentation with yeast-like fungi such as Moniliella pollinis, Trichosporonoides megachiliensis, and Yarrowia lipolytica are commonly employed due to their high production. After the separation and purification process, erythritol results as a white-crystalline granular substance apparently similar to table sugar with a percent relative sweetness between 60% and 70% when compared to sucrose [17], but with a glycemic index of 0 [5], being its most valuable property.

It belongs to the carbohydrate family known as a sugar alcohol, or polyol or polyhydric alcohol because of its hydroxyl groups (HO^- radical) on the formula (Fig. 5.2). The polyols family is a class of low molecular weight compounds with a

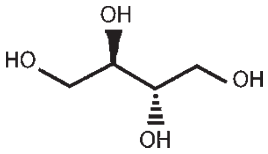

Fig. 5.2 Chemical structure of erythritol

general formula of (CHOH)n H_2 where n = 4–6. Erythritol is a 4-carbon sugar alcohol, its formula is $C_4H_{10}O_4$, whose properties are: molar weight of 122.120 g/mol, density of 1.45 g/cm^3, melting point at 126 °C, a boiling point between 329 and 331 °C, solubility of 38% at 25 °C (61 g/100 g water), heat of solution of −43.9 cal/g [17, 21–23]. In spite of the name sugar alcohol, erythritol is a noncaloric organic, non-glycemic sweetener, then is safe for diabetic patients because there is no influence on blood insulin levels due to its chemical structure [17] and is secreted by urine [22].

Erythritol was approved as safe for consumption by FDA (Food and drug Administration) in the United States and also in the European Union (EU) under the code of E968 [18, 24, 25]. Because of its small molecular size, erythritol has a high digestive tolerance being absorbed into the small intestine and is no fermented in the large intestine as other polyols do, exhibiting a vantage among other sweeteners to use in food formulation. Although, doses should be regulated, due to excess larger than 50 g of intake can lead to borborygmus and nausea [26], according to Oku and Okazaki [27], the highest safe dose of erythritol is 0.80 g/kg BW for females and 0.66 g/kg body weight (BW) for males to avoid laxative effect on the body. Tetzloff et al. [28] observed that even daily doses of 1 g/kg BW were safe for humans without gastrointestinal effects and urinary electrolytes excretion was not affected.

Erythritol has been extensively used in foods due to its sweetness profile (60–70%) and texture (small crystals), similar to sucrose. The most common is the table-top use, but also it is a flavor enhancer in foods because of its large cooling effect when dissolved in water, an endothermic reaction caused for its high negative heat of solution of −43.9 cal/g. Although this is a normal characteristic of polyols, erythritol has the highest value when compared to the others and even sucrose. Perko et al. [23] studied the drop in temperature (cooling effect) of different polyols, dissolving 30 g of each sweetener in 100 g of water; authors observed that sorbitol, xylitol and erythritol temperature dropped from 37 °C to 31, 29, and 27 °C, respectively, and for maltitol, isomalt, and sucrose, temperature decrease only close to 35 °C for 13 s of time. The cooling effect might be potentially an advantage in enhancing consumer enjoyment of such mint-flavored products. Therefore, erythritol is commonly combined with a mint flavor creating a feeling of freshness on chewing gums, hard candies, frostings, ice creams and low-calorie beverages [6, 29–31]. Also, one of the advantages to used erythritol in food formulations is the no contribution to the formation of tooth decay caused by dental plaque turning sugars into acid. Some of erythritol properties are summarized in Table 5.1. Erythritol is stable to acid and alkaline pH conditions, also to high temperatures even until 180 °C without decomposition. It is a bulk sweetener providing volume which makes it a good ingredient

Table 5.1 Applications of erythritol in food products

Properties	Industrial use	Product	References
Sweetener, flavor enhancer and cooling sensation	Food	Frostings, chewing gum, hard candy, glazed goods, and chocolate	[6, 23, 29, 32]
Sweetener and texture	Bakery products	Cookies, muffins, and cakes	[33–36]

to use in baked products such as cookies [33, 34], cakes [18, 35] and muffins [36], with good hedonic acceptance from consumers when compared to sugar products.

Akesowan [35] evaluated chiffon cakes containing 0, 25, 50, 75 and 100% of erythritol as a blend with sucralose as sugar (sucrose) replacer. Cakes made with 50% of erythritol-sucralose had better scores an acceptable sensory quality similar when compared with control cake. Cake moistness and water activity increased as the level of erythritol-sucralose rise, while tenderness decreased. At 100% level, cake batter had a lower ability to retain air resulting in a compacted cake. These results were attributed to lower sweetener solubility in water compared to sucrose, leaving more available water to the process. But also, because sugar (sucrose) plays a role in wheat flour, used to produce cakes, delaying starch gelatinization affecting its temperature. Sucrose binds the amylose and amylopectin chains of starch in the amorphous zones of the granules, stabilizing them. These bridges increase energy requirements, which results in higher gelatinization temperatures [37]. Sweeteners are no able to create these bridges then sometimes it is necessary to use stabilizers such as inulin (a polysaccharide) and soluble fiber, mainly extracted from chicory root with a slightly sweet flavor with zero glycemic index, non-caloric and safe for diabetic people [20], but with properties of high swelling, then inulin bonds with water and can be used as a thickening agent.

Laguna et al. [34] produced cookies with 25% and 50% of erythritol and inulin as a sucrose replacement, obtaining a suitable dough from a processing point of view, and cookies color, but cookies with 50% erythritol were scored negatively for all sensory attributes being texture main. Cookies with 25% of erythritol obtained better scores from consumers' acceptance also were harder than cookies made with inulin which were softer.

Erythritol used in chewing gum provides high flexibility and a soft texture, these properties increase chewing gum shelf life avoiding dryness and hard gums texture, undesirable characteristics for consumers [23].

5.2.2 Other Polyols

Other polyols are recognized as sugar substitutes, some examples are glycerol, xylitol, sorbitol, and mannitol which are derived from monosaccharides, whereas maltitol, isomalt, and lactitol are disaccharide derivatives [1]. Although some are nearly 50% as sweet as sucrose and their glycemic index is lower than sucrose, their consumption is limited once those polyols may cause gastrointestinal discomfort to

human body, then their amount intake is regulated. Maximum bolus doses not causing laxation for sorbitol are 0.17 (males) and 0.80 (females) g/kg body weight, whereas maltitol, isomalt, and xylitol is 0.3 g/kg body weight (both males and female), and for erythritol is 0.66 and 0.80 g/kg body weight for males and females, respectively [23]. The industrial production of these polyols mostly involves the chemical hydrogenation of sugars, but low-cost alternatives such as biotechnological production have been considered during the past years due to the high market demand for low-calorie sweeteners by fermentation through microbial routes [38]. The chemical and physiological characteristics of polyols are summarized in Table 5.2.

Besides erythritol, polyols also have a corresponding number from the European Union such as (E420) sorbitol, (E421) mannitol, (E953) isomalt, (E965) maltitol, (E966) lactitol, xylitol (E967) and erythritol (E968) [40]. Some polyols have been studied as sweeteners for chewing gum production because of their humectant, plasticizing and cooling properties, but also because sugar-free chewing gum has proven to decrease caries incidence, these include xylitol, sorbitol [41] and erythritol [21]. Those sweeteners have gained interest because they are not metabolized by most oral bacteria, then they do not produce acid and the saliva pH does not decrease, a common factor after eating, in contrast, they increase or stimulate saliva production, a positive factor to prevent plaque and caries [41–43]. Jeon et al. [44] observed xylitol affect negatively texture quality on moisture content and hardness of hard candy used in their formulation, because its high hygroscopicity, however blending isomalt, maltitol, and xylitol in different percentages as 90.21%, 8.63%, and 1.16% respectively produced high acceptability from consumers, in hard candies formulated without sugar.

Erythritol is often used in chewing gum coatings, however rough surfaces are obtained due to the fast crystallization of this sweetener, consequently, sorbitol, maltitol, and xylitol represent an alternative to avoid this problem. Analysis of crunchiness and stability against moisture parameters, for chewing gum coatings using sorbitol, xylitol, isomalt, maltitol, and mixtures at a ratio of 40:60 of erythritol/sorbitol and erythritol/maltitol were evaluated (Fig. 5.3). Chewing gum coating with xylitol showed similar results on all parameters, although the erythritol/sorbitol 40:60 represented a suitable alternative to produce a chewing gum low calorie and with consumer acceptance [23]. These findings suggest that polyols combinations may help the desirable characteristics to develop a product.

5.2.3 Tagatose

D-tagatose is a hexose monosaccharide classified as a “rare sugar” according to the ISRS (International Society of Rare Sugars) because minimal quantities are available in nature. In rare sugars group are also found low caloric monosaccharides as the L-glucose a L isomer of glucose synthesized artificially in a laboratory, the D-allulose and L-ribose, among others [12]. Lately, this natural sweetener has

Table 5.2 Chemical and physiological characteristics of sweeteners: chemical formula, systematic (IUPAC) name, percent (%) relative sweetness compared to sucrose[a], glycemic index[b], caloric value (kcal/g), solubility at 25 °C (g/100 ml), heat of solution (cal/g), source, taste, and food application

Sweetener	Chemical formula[a]	Systematic (IUPAC) name[a]	% Relative sweetness vs. sucrose[a]	Glycemic index[b]	Caloric value (kcal/g)[c]	Solubility at 25 °C (g/100 ml)[c]	Heat of solution (cal/g)[c]	Source[d]	Taste[e]	Applications[e]
Sucrose	$C_{12}H_{22}O_{11}$	(2R,3R,4S,5S,6R)-2-{[(2S,3S,4S,5R)-3,4-Dihydroxy-2,5-bis(hydroxymethyl) oxolan-2-yl]oxy}-6-(hydroxymethyl) oxane-3,4,5-triol	100	65	4.0	185	−4.5	Sugarcane, sugar beet (Extraction process)	Na	Sweetener[d] Humectant[d] Flavor enhancer Color enhancer: Caramelization[d] Preservative[d] (Confectionery, candies, jams, beverages, table-top, etc)
Maltitol	$C_{12}H_{24}O_{11}$	4-O- α-d-Glucopyranosyl-d-glucitol	87	35	3.0	175	−5.5	High Maltose, Corn Syrup	Lower cooling effect	Sweetener Emulsifier Humectant Stabilizer Thickener Bulking agent
Lactitol	$C_{12}H_{24}O_{11}$	4-O-ß-1Galactopyranosyl-1glucitol	35	3	2.0	140	−13.9	Lactose	Slightly cooling effect	Sweetener Emulsifier Thickener
Isomalt	$C_{12}H_{24}O_{11}$	(2R,3R,4R,5R)-6-[[(2S,3R,4S,5S,6R)-3,4,5-Trihydroxy-6-(hydroxymethyl)-2-tetrahydropyranyl]oxy] hexane-1,2,3,4,5-pentol	54	2	0.45–0.65	39	−9.4	Sucrose	No cooling effects. Off-taste: bitter metallic	Sweetener Stabilizer Thickener Bulking agent Anti-caking agent Glazing agent

(continued)

Table 5.2 (continued)

Sweetener	Chemical formula[a]	Systematic (IUPAC) name[a]	% Relative sweetness vs. sucrose[a]	Glycemic index[b]	Caloric value (kcal/g)[c]	Solubility at 25 °C (g/100 ml)[c]	Heat of solution (cal/g)[c]	Source[d]	Taste[e]	Applications[e]
Sorbitol	$C_6H_{14}O_6$	D-Glucitol	58	4	2.6	235	−26.5	Glucose (Zymomonas mobilis)	Cooling effect	Sweetener Humectant Stabilizer Thickener Bulking agent Sequestrant
Mannitol	$C_6H_{14}O_6$	D-Mannitol	50	2	1.6	22	−28.9	Fructose (Fermentation: Leuconostoc *spp,* Lactobacilus spp	Cooling effect	Sweetener Humectant Stabilizer Thickener Bulking agent Anti-caking agent
Xylitol	$C_5H_{12}O_5$	D-erythro-pentitol	97	12	2.4	200	36.6	D-xylose (Yeast, Candida spp. Debaromyces spp.	Intense cooling sensation	Sweetener Emulsifier Humectant Stabilizer Thickener
Erythritol	$C_4H_{10}O_4$	1,2,3,4 butanetetrol, meso-erythritol	63	0	0.2	61	−43.9	Glucose (Fermentation, Moniella spp. Penicillium spp Pseudozyma tsukubaensis)	Cooling sensation	Sweetener Humectant Flavor enhancer

IUPAC International Union of Pure and Applied Chemistry, *Na* not applicable
[a]Chéron et al. [1]
[b]Livesey [5]
[c]Hartel et al. [4]
[d]Canada G [39]
[e]Grembecka [11]

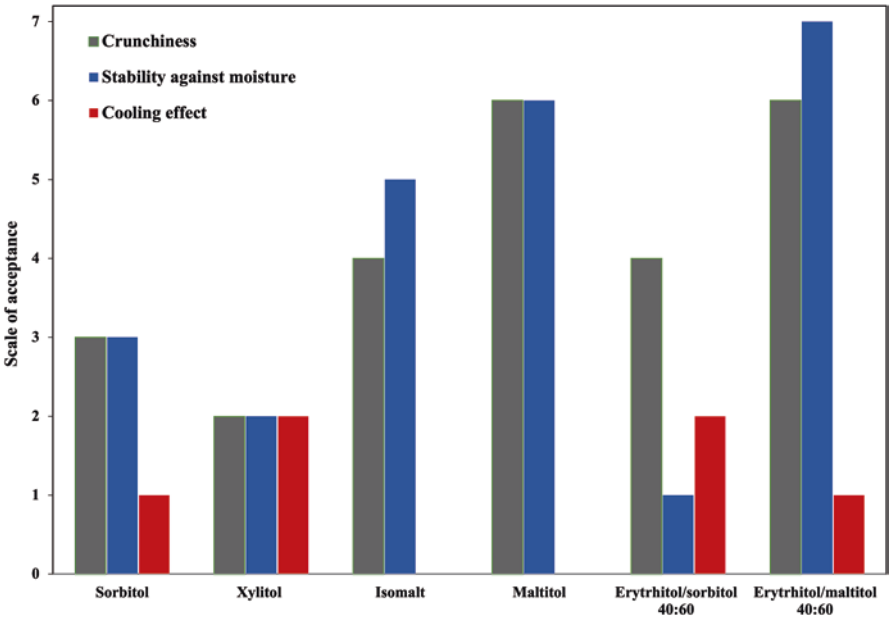

Fig. 5.3 Chewing gum coating parameters (crunchiness, stability against moisture, cooling effect) compared to sorbitol, xylitol, isomalt, maltitol, and mixtures of erythritol/sorbitol 40:60 and erythritol/maltitol 40:60. Scale level (high = 7, low = 0). (Adapted from Perko and Decock [23])

attracted attention because beyond providing sweetness, it is an additive with many vantages and potential applications in food as a stabilizer, moisturizer, texturizer, and flavor enhancer. It is suitable for dental products It is suitable for dental products due to D-tagatose does not cause tooth decay, which happens with sugar, once this rare sugar is not converted to acids by bacteria in the mouth, this acid slowly dissolves the enamel creating holes and cavities in the teeth. D-tagatose is a health promoter since D-tagatose is partially absorbed, only 15–20% is metabolized on small intestine [45], therefore has a minimal effect on blood glucose and insulin levels, being fermented on large intestine where are produced short-chain fatty acids (SCFA) which improve the gut health [14, 46].

D-tagatose was discovered in 1987 by Lobry de Bruyn and Van Ekenstein who were experimentally studying the transformations of reducing sugars in aqueous alkaline solutions [47]. Although just until 2001 D-tagatose was considered as a GRAS (Generally Recognized as Safe) additive by the U.S FDA (Food and Drug Administration), and the FAO (Food and Agriculture Organization) has suggested its use in food products after several clinical studies regarding D-tagatose effects and tolerance in humans [48–55]. As well the European Union, South Africa, New Zealand, and Australia also approved its consumption as a new ingredient [56]. D-tagatose can be found naturally in limited amounts in pineapples, apples, oranges [57], in gum exudate of the cacao tree (*Sterculia setigera*) [58], as a component of an oligosaccharide in lichens of the *Rocella* species [59] and also in dairy products

when milk is heated as UHT, pasteurized milk [60–62]. Industrially D-tagatose could be synthesized from lactose, a disaccharide formed by D-glucose and D-galactose present in milk or whey with both by the chemical and biological (enzymatic) processes. Firstly, the lactose is hydrolyzed, and D-glucose is eliminated, leaving only the D-galactose to be isomerized.

Under the chemical process, D-galactose is isomerized reacting with metal hydroxide (alkaline conditions) and neutralized with acid, after being filtered and purified, although this method involves the use of complex purification steps leading to the formation of unsafe chemical residues and a reduction in their sweetening properties representing high costs and disadvantages to producers. Then, several biological processes have been studied for years [63–65], since 1984, Izumori et al. [66] carried out the first enzymatic synthesis through the oxidation of D-galactitol using the enzyme sorbitol dehydrogenase from different microorganisms such as *Arthrobacter globiformis* ST48. Nowadays, the biological process more used is the isomerization of D-galactose using enzymes such as β-galactosidase and L-arabinose isomerase (L-AI) as biocatalysts, respectively, which is considered the greatest potential in use for the production of tagatose [67].

This sweetener is a 6-carbon monosaccharide with a chemical formula of $C_6H_{12}O_6$, it is known as an epimer of D-fructose due to both chemical structures are similar, only D-tagatose differs from D-fructose at the 4-carbon atom (Fig. 5.4). It is highly similar to sweet sucrose with 92% of its content in an aqueous solution of 10%, with a lower caloric value of 1.5 kcal/g, without after taste as other sweeteners, and prebiotic, antidiabetic, and obesity control properties. It is stable in a pH range between 2 and 7, very soluble in water (58% w/w at 21 °C) [14]. In Table 5.3 are shown the chemical and general properties of D-tagatose.

D-tagatose has a wide variety of uses in foods. As a low-calorie bulk sweetener make it a suitable ingredient for beverages (soft drinks) and dietary supplements. The flavor-enhancing properties of D-tagatose makes it a perfect and probable agent to mask the unpleasant taste of medicines or health products. Acu et al. [69]

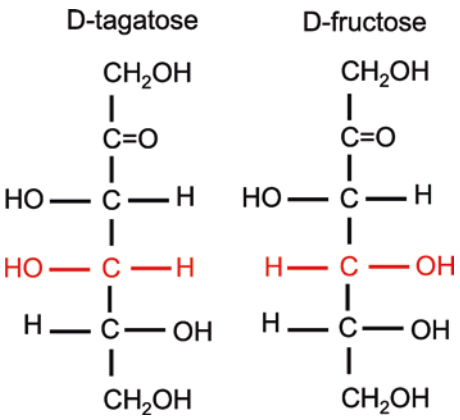

Fig. 5.4 Chemical structure of D-tagatose and the D-fructose epimer with fourth carbon as mirror image of D-tagatose in red color

Table 5.3 Chemical and general properties of D-tagatose [56, 68]

Properties	Value
Systematic (IUPAC) name	(3S,4S,5R)-1,3,4,5,6-Pentahydroxy-hexan-2-one
Chemical formula	$C_6H_{12}O_6$
Molecular weight	180.16 g/mol
Melting temperature	134 °C
pH	2–7
Solubility	160 g/100 mL at 20 °C
Relative sweetness	92% of sucrose
Odor	None
Color	White
Form	Crystalline solid
Caloric value	1.5 kcal/g
After taste	None
Maillard reaction and caramelization	Yes

IUPAC International Union of Pure and Applied Chemistry

evaluated the probiotic viability of ice cream made with frozen raspberry fruits, commercial raspberry and blackberry fruit purees, and tagatose as prebiotics. The authors observed that the ice cream samples maintained their probiotic properties during 120 days of storage and were generally well appreciated in terms of sensory properties by panelists.

In another research, Taylor et al. [70] used both partial and 100% sucrose replacer in cookies with tagatose. Rheological properties such as spread, hardness, and overall texture were similar when compared with control sweetened cookies (sucrose cookies), however, the authors compared the cookies having tagatose with cookies made with fructose which showed a softener dough cookie. Those results depend on sweetener solubility. D-tagatose solubility is slightly lower than sucrose at 20 °C (61% and 65%, respectively) while fructose is 88% at the same temperature. According to Manley [71], there are two types of cookies, hard and soft cookies, the difference is the existence or not of long chains of gluten that give the dough extensibility. The gluten development in the dough is directly related to water availability in the process. More water available allows wheat flour proteins hydration, consequently enabling the formation of the gluten chains. The dough will exhibit viscoelastic properties giving rise to hard cookies without spreading the dough too far; therefore, cookies preserve their round shape on the baking sheet; however, when sugar amount is high and consequently highly soluble in water, water availability decreases, and gluten is not able to be developing resulting in softer cookies, due to the dough does not achieve elasticity, and it spreads during baking creating irregular sizes. Fat excess also interferes with gluten development, coating proteins in flour responsible for forming the gluten, making an impermeable layer on the dough. Low-fat content results in strong doughs. Thus gluten, water, sugar, and fat play an essential role in the dough [71].

Tagatose also improved the color of the cookies, based on high scores data from panelists who liked the brown color of cookies with 100% tagatose cookies better than the control [70], this is due to tagatose participation in Maillard reaction and caramelization. Although the sweetness of 100% of tagatose was perceived, the overall likeness was acceptable for panelists. D-Tagatose is also useful as a texturizer and stabilizer enhancing storage stability by anti-blooming effects on chocolate when compared to sucrose and maltitol added to chocolate. Also, the acceptance of chocolates produced with tagatose was superior to stevia added chocolate, according to consumers responses (n = 219). Tagatose was scored positively as more similar to sucrose added chocolate rather than stevia, also overall liking was better on texture, bitterness, duration of aftertaste and intensity of aftertaste [72]. In summary, Table 5.4 showed some applications of tagatose in different food and non-food products.

5.2.4 Steviol Glycosides

Among all-natural sweeteners, steviol glycosides SGs (stevioside and rebaudioside-A) are popularly known as zero-caloric intense sweetening compounds of natural origin [80]. Stevia rebaudiana Bertoni (Stevia) is a perennial herb of the Arteraceae family, native to South America. Stevia leaves contain steviol glycosides that have been used as a sweetener in South America for centuries and today their consumption has spread throughout the world [81].

Table 5.4 Applications of tagatose in food and non-food products

Properties	Industrial use	Product	References
Sweetener	Food	Frostings	[56]
Probiotic and sweetener	Food	Ice cream	[69]
Probiotic and sweetener	Food	Yogurt	[73]
Sweetener and flavor enhancer	Food	Beverages	[74, 75]
Sweetener and flavor enhancer	Food	Hard candies, soft candies and jelly	[56, 76]
Texturizer, stabilizer, and sweetener	Food	Chocolates	[72, 77, 78]
Sweetener, color enhancer, texturizer	Food	Baked food, cookies, cake	[70]
Sweetener and texturizer	Food	Chewing gum	[56]
Sweetener	Food	Breakfast cereals	[79]
Sweetener and flavor enhancer	Cosmetic, personal hygiene	Toothpaste, mouthwash, cosmetics	[67]
Sweetener	Drug	Oral antibiotics, Chewable flavored antibiotic tablets	[14]
Flavor enhancer	Cosmetic	Flavored lipstick	[46]

According to Singh et al. [82], stevia rebaudiana (Bertoni) is a plant widely known in the Amambay region of Paraguay and used as a natural sweetener and in traditional local medicine. In addition to the sweetening power of stevia, it has bioactive compounds with anti-inflammatory, immunomodulatory, antimicrobial, cardiovascular, anticancer and antidiabetic properties [80]. Stevia extracts have been widely used to elevate sweetness levels in foods and the sweet taste of stevia is mainly attributed to various glycosides such as stevioside, rebaudioside-A, -B, -C, -D, -E and dulcoside-A. Among them, stevioside, and rebaudioside-A can be extracted with hot water [80, 83, 84].

In the last two decades, stevia rebaudiana bertoni leaves have attracted much interest not only as a non-caloric sweetener known as steviol glycosides, but also as a valuable by-product [85]. In fact, the use of stevia rebaudiana bertoni leaf extracts as a low-calorie sweetener is trending upward for beverages, and these extracts are sources of bioactive compounds (e.g., polyphenols, chlorophylls, carotenoids, and ascorbic acid) with antimicrobial properties and antioxidants [86]. In this correlation of interest and properties, stevia rebaudiana bertoni leaves have attracted much interest from researchers and the food industry not only as a non-caloric sweetener, but also as a valuable by-product [85].

Stevia rebaudiana is a perennial shrub, being a member of the 950 genera of the Asteraceae family. To date, more than 150 species of stevia are known, with stevia rebaudiana (Bertoni) being the one that differs from other species due to its high degree of sweetness [87]. Stevia rebaudiana is a short-day plant that grows up to 1 m tall. Its leaves have an elliptical shape and a length between 2 and 3 cm with an alternating arrangement. The stem of the plant is fragile and allows a condition to be broken easily. In addition, its root system is extensive. The flowers have a white coloration and a pale purple color in the throat of the same. The flowers are smaller than the leaves and are arranged in the form of small corymbs [82].

Stevia can be found naturally in subtropical regions of semi-humid conditions at a height between 200 and 400 m above sea level. For its natural growth, rainfall of around 1500–1800 mm and a wide temperature range between −6 and 43 °C are required [8]. According to Yadav et al. [8], the first stevia crops were domesticated in 1968 in Japan, allowing in the 1970s stevioside, from the Stevia leaf, to become a commercially important sweetener and food supplement. Currently, Stevia has been adopted and commercialized by several countries such as Brazil, Korea, United Kingdom, China, and Malaysia.

From the leaves of the evergreen stevia rebaudiana Bertoni shrub, indigenous people obtained extracts that were used as a sweetener for various foods and beverages and in medicines [88]. Steviol glycoside extracts of high purity (≥95%) after several studies have been approved for use as a food sweetener in several countries and regions, including the European Union and the United States. the sweetening property is a result of the presence of natural plant constituents known as steviol glycosides (SGs) [89, 90].

The SGs obtained from the plant are four-ring diterpenes composed of an aglycone backbone called steviol to which various numbers and types of sugars are attached (Fig. 5.5a). Currently, >40 SGs have been identified, stevioside (CAS No.

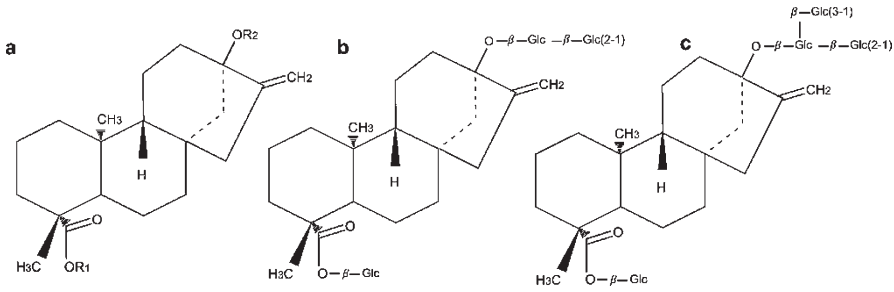

Fig. 5.5 Backbone structure of SGs (**a**), Stevioside (**b**), and Rebaudioside A (**c**). (Adapted from Anker et al. [81])

57817-89-7, 4–13% wt:wt, Fig. 5.5b) and rebaudioside A (CAS No. 58543-16, Reb A—2–4% wt:wt, Fig. 5.5c) being the most abundant glycosides in stevia rebaudiana leaves. Stevioside and Reb A are non-caloric compounds with a sweetening capacity of around ~200–300 times more than 0.4 M sucrose and are chemically very similar, differing only by an additional glucose fraction in Reb A. In general, SGs differ only in the number and type of monosaccharides attached to the aglycone [81].

According to Puri et al. [91], steviol is a chemically and thermally stable compound, which does not lose its sweetness index of 300, thus allowing its wide use in various industries with possible application with greater use in the food industry. Consequently, Brahmachari et al. [88] cited that steviol has a wide acceptance of use worldwide, considered the "third" glycogen in the world; in addition, they report that there is no evidence of side effects related to its use in humans. On the other hand, Azarpazhood et al. [92] informed that stevioside and rebaudioside A have economic advantages when compared to other glycosides derived from this plant.

In addition to the known facts of its sweetening power, there is scientific evidence that stevia has medicinal benefits, including nematicide, antioxidant, wound healing activity, antiviral, anti-inflammatory, antidiabetic, and kidney protection [93–96]. Stevioside is non-toxic and its therapeutic value consists of the possibility of replacing sugar and the ability of this compound to stimulate insulin secretion in the pancreas in the treatment of diabetes and other disorders of carbohydrate metabolism [97].

Interestingly, stevia-derived glycosides are non-carcinogenic, non-mutagenic, non-teratogenic, and do not induce acute or subacute toxicity [98]. It is important to highlight that those studies show an improvement in cholesterol regulation with the frequent use of stevia, in addition to presenting antiviral properties and producing a positive therapeutic effect in neuralgia treatments [99]. Researchers have associated the benefits of Stevia mainly to its nutritional composition, since it has a good source of carbohydrates, protein, and crude fiber, thus promoting well-being and consequently reducing the risk of certain diseases. In Table 5.5 it is possible to find the nutritional information of stevia reported by several authors.

Table 5.5 Approximate analysis of dried stevia leaves

Components	Comment on					
	Jyoti et al. [100]	Goyal et al. [101]	Serio [102]	Abou-Arab et al. [103]	Lemus-Mondaca et al. [104]	Kaushik et al. [105]
Moisture	7	4.65	Nd	5.37	Nd	7.7
Carbohydrates	52	Nd	53	61.9	35.2	Nd
Protein	10	11.2	11.2	11.40	20.4	12
Fat	3	1.9	5.6	3.73	4.34	2.7
Crude Fiber	18	15.2	15	15.5	Nd	Nd
Ash	11	6.3	Nd	7.41	13.1	8.4

Nd not determined

Consequently, it is possible to observe that there are no significant changes in the composition reported by the researchers, thus allowing the possible application of the extracts as dietary supplements.

In relation to the numerous results found in the literature that report the benefits of stevia, it has a potential for use as a source of natural antioxidants in the cosmetic and food industries. It should be noted that even though stevia did not present levels of toxicity and was accepted as a GRAS food, several authors still recommended caution regarding the use of extracts before further toxicological studies are carried out due to the cytotoxicity of ethanolic and aqueous glycol extracts [106]. Table 5.6 shows the wide use of stevia at an industrial level, focusing on the use of elements of natural origin to reduce the impacts that synthetics can bring. It is clear that this natural sweetener has been widely used in the food and beverage industry as well as the pharmaceutical industry. Its use and acceptance at the medicinal level is due to studies that have shown promising benefits against diabetes, obesity, hypertension, cancer, tooth decay, oxidative and antimicrobial stress.

5.2.5 Glycyrrhizin

The glycyrrhizin (18 β-glycyrrhetinic-acid-3-O-[β-d-glucuronopyranosyl-(1 → 2)-β-d-glucuronopyranoside], GL), which is more correctly called glycyrrhizinic acid [117], is a kind of natural edulcorant as well as one component in Oriental medicine. The hydrophobic backbone is built by a triterpene called glycyrrhetinic acid [118]. GL is the main component of licorice extract (*Glycyrrhiza glabra*), being commonly used as a sweetener. GL is until 150 times sweeter than sucrose [119]. Moreover, it exhibits low toxicity and is therefore used as a sweetener. However, the recommended daily consumption is less than 0.229 mg glycyrrhizin/kg body weight/day [120].

According to Zhang et al. [120], licorice extract is extensively used worldwide as a natural sweetener, pharmaceutical agent, and dietary supplement. Besides that, glycyrrhizin is generally regarded as safe (GRAS) in the USA, European, and other

Table 5.6 Principal industrial applications of stevia

Properties	Industrial use	Product	References
Antioxidant	Food	Wheat bread	[107]
Improve concentration of phenolic compounds and antioxidant	Food	Juice	[108]
Antioxidant	Food	Yogurts	[109]
Organoleptic properties	Food	Oatmeal raisin cookies	[110]
Sensory acceptability	Food	Dairy dessert	[111]
Biosurfactant	Food	Small micelles with size of around 4.70 nm	[112]
Anti-tumor property	Medical	Na	[113]
Anticancer activity (gastrointestinal cancer cells)	Medical	Na	[114]
Colon cancer cell lines	Medical	Na	[115]
Reducing glycemic index	Medical/ Food	Bakery (Muffins)	[116]

Na not applicable

countries [121]. On the other hand, in the literature it is possible to find evidence indicating that glycyrrhizin has other differentiated biological activities when compared to other sweeteners, thus, it is possible to cite its anti-inflammatory [122], antioxidant [123], antiviral [124], antitumor [125] and hepatoprotective [126] activity.

Native to Asia and the Mediterranean region, licorice (*Glycyrrhiza glabra*) is a tall shrub in the family Leguminosae, thus the genus Glycyrrhiza Linn. (Fabaceae) is composed of approximately 20 species [127]. Although most commercial licorice is extracted from varieties of G. glabra grown in southern and central Europe (var. *typica*), central and southern Russia (var. *glandulifera*) and Iran and Iraq (var. *violacea*). Licorice also grows in the United States (var. *lepidota*) and England (var. *typica*), but neither represents a significant contribution to world production [128]. According to Isbrucker et al. [128] the fresh root contains about 20% of water-soluble extractives, and around 3–5% of the root is composed of glycyrrhizin, present as a mixture of potassium and calcium salts. Licorice root extract contains between 10% and 25% glycyrrhizin as the primary active ingredient. Minor constituents which may also confer some pharmacological activities include liquiritigenin, isoliquiritigenin, and their corresponding aglycones [129].

Chemically, glycyrrhizin is composed of hydrophobic aglycone 18β-glycyrrhetinic acid ($C_{30}H_{46}O_4$, 470.68 g/mol) bound at position C-3 via an ether bond to a sugar chain composed of two glucuronic acid units, making the molecule amphiphilic (Fig. 5.6) [118]. The acidic group at the C-20 position of glycyrrhetinic acid significantly influences the amphiphilicity of the whole molecule depending on the pH value. The polyvalent weak acid group also determines the solubilizing properties of the molecule. According to Matsuoka et al. [118], glycyrrhizin is insoluble at low and native pH ($pH \leq 4.5$). In contrast, at pH 4.5–5.0,

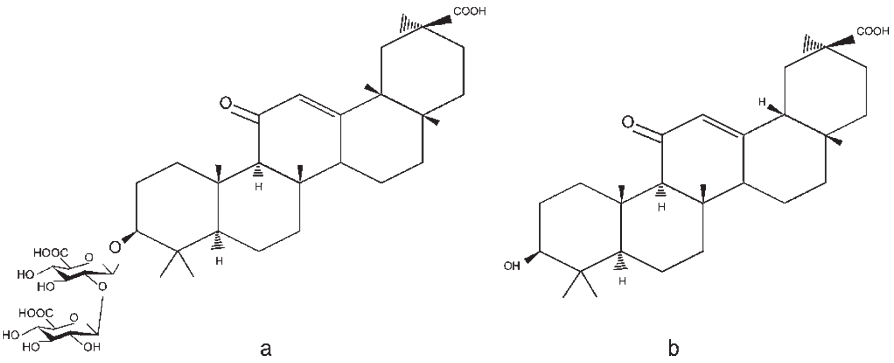

Fig. 5.6 Chemical structures of Glycyrrhizinic (**a**) and Glycyrrhizinic acid (**b**). (Adapted from Graebin [117])

the anisotropic structure of glycyrrhizin led to the formation of rod-like micelles and fibrils with a height of 2.5 nm and periodicity of 9 nm that self-assembled either at the interface or within the continuous phase into a fibrillary network at concentrations of 5.3–10 mmol/L [130]. Upon increasing concentrations, this is most probably due to the deprotonated acidic bound groups to the backbone at opposite sites, which causes the loss of the clear amphiphilic structure and moreover induces repulsion effects between different glycyrrhizin molecules [131, 132].

According to Hosseini et al. [133], the sweetening power of glycyrrhizin allows it to be commonly used in the agro-food industries and due to its versatility, saponite has its scope in traditional Chinese, Tibetan and Indian medicinal preparations, while glycyrrhetinic acid is used in the treatment of chronic liver diseases, being marketed in Japan, China, Korea, Taiwan, Indonesia, India and Mongolia [117].

The extracts collected or the powder prepared predominantly from the roots and rhizomes usually hold pharmacological importance. Thus, Wang and Nixon [134] evaluated the potential anticancer effects of licorice extract and glycyrrhizable compounds by establishing that licorice polyphenols induce apoptosis in cancer cells. Thus, these and other activities of licorice infer a suggested justification for combinations of agents in preventive clinical trials. On the other hand, Ruschitzka et al. [135] evaluated the effects of glycyrrhizin (50 mg/kg, i.p., twice a day for 7 days) on nitric oxide production and vascular endothelin response were monitored in male Wistar rats. The aortic endothelial nitric oxide response was significantly inhibited by glycyrrhizin treatment, as indicated by reduced aortic tissue nitrate concentrations and decreased endothelial nitric oxide synthase protein levels.

Recently, Gomaa and Abdel-Wadood [129] reported scientific evidence on the use of glycyrrhizin and licorice extract as a fighting agent against COVID-19. Thus, the researchers conclude that in relation to the literature, licorice extract has capacity against COVID-19, but that randomized clinical trials are needed to reach an accurate conclusion [136]. The sweet-tasting yellow licorice root extract, which is considered a blend with various bioactive constituents (flavonoids and various phenolic acids), has a variety of benefits and applications [137, 138]. For example,

polyphenolic compounds like tannins and flavonoids, which are found in abundance in licorice extract, are radical scavengers. In general, naturally occurring phytochemical substances with antioxidant/free radical scavenging characteristics based on their existing structure in plant extracts are reported to have corrosion inhibitory capacity [139]. Licorice being a traditional Chinese medicinal herb began to be used in industrial applications with wide impact in the food and cosmetics industries [140].

Licorice and licorice derivatives are generally recognized as safe (GRAS) for use in food by the US FDA (21 CFR 184.1408 [141]). In Table 5.7, the maximum authorized concentrations for the use of licorice (glycyrrhizin) and its derivatives for use in food are established.

Regarding the limitations established by the FDA, it is possible to find in the literature several applications of GL in the food industry, as can be seen in Table 5.8, which presents the wide use of the sweetener at an industrial level.

However, as licorice application scenarios continue to be discovered, the worldwide demand for licorice is also increasing and the problem of supply of licorice resources has arisen [136]. China is a major producer of licorice and its products and is extensively involved in the international licorice trade. However, at the same time, China faces depletion of licorice resources and related international trade competitive problems. Thus, Han et al. [152] conclude that still, the main focus is on the use of licorice extracts, while there is little attention given to licorice residues. Further inferring that it is necessary to pay attention to the transformation of licorice waste into by-products and increase the added value to promote a circular economy in addition to promoting cooperation and exchange between the main producers to improve the industrial chain and achieve the sustainable use of resources.

GL has wide acceptance and industrial use around the world. Therefore, given the properties of licorice and its active constituents, it is suggested that their potential roles be evaluated by their effects on both food and medicine. However, further studies are needed to confirm these effects.

Table 5.7 Maximum authorized concentrations of glycyrrhizin in foods regulated by Food and Drug Administrations (FDA) [141]

Food category	Maximum allowable levels of glycyrrhizin	Functional use
Baked goods	0.05	FE, FA
Alcoholic beverages	0.1	FE, FA, SA
Non – alcoholic beverages	0,15	FE, FA, SA
Chewing gum	1.1	FE, FA
Hard candy	16.0	FE, FA
Soft candy	3.1	FE, FA
Herbs and seasonings	0.15	FE, FA
Plant protein products	0.15	FE, FA
Vitamins or mineral dietary supplements	0.5	FE, FA

FE flavor enhancer, *FA* flavoring agent, *SA* surface-active agent

Table 5.8 Main activities of glycyrrhizin and the action mechanisms

Properties	Industrial use	Product	References
Antioxidant capacity	Food	Preserved the quality of Japanese sea bass fillets	[142]
Antioxidant activity	Food	Precooked pork patties	[143]
Antimicrobial activity	Food	Meat products (fresh pork and ham products)	[144]
Antibacterial effects	Food	Milk and labneh	[145]
Sensorial and rheological properties	Food	Probiotic product (ROSALACT®)	[146]
Bioavailability	Food	Nano-emulsions containing Glycyrrhizin	[147]
Low-sugar flavored drinks	Food	Milk products	[148]
Anti-inflammatory and anti-ulcer	Medical	Na	[149]
Preventing and treating dental caries, periodontitis, gingivitis, candidiasis, recurrent aphthous ulcer, and oral cancer.	Medical	Na	[150]
Probiotic and prebiotic activities	Medical	Na	[151]

Na Not applicable

5.2.6 Thaumatin

Thaumatin is it a mixture of sweet proteins (thaumatin I and II) extracted from the arils of the fruit of *Thaumatococcus daniellii* (Benth) a West African rainforest shrub. It has a high intense sweetener about 2000 times sweeter than sugar, a potent flavor/aroma enhancer, and has the ability to mask unwanted aftertaste from numerous substances, including artificial sweeteners. It was first documented in 1855 by scientist W.F. Daniell, who described it as a powerful sweetener and flavor and aroma enhancer in local foods and beverages [9, 153, 154].

While there are others sweet proteins which have been identified and isolated from tropical plants such as brazzein [155], pentadin [156], curculin [157], and monellin [158], thaumatin has been most studied [159], however, a large-scale production, cost, quality, and acknowledged applications are currently some limitations to commercialize this sweet protein [160, 161].

Thaumatin is composed of a sequence of 207 amino acids, and it is digested by the human body and animals following the normal metabolism of other natural proteins, for that reason thaumatin is considered GRAS by the U.S FDA and by the European Union under the code E957. Its properties include, odorless, flavor enhancer, flavor masker (bitter or unpleasant taste), stable at 120 °C and both acid and alkaline pH environments (from 2.0 to 10 at room temperature), water soluble, slow onset sweetness but sweet aftertaste, and 4 kcal. g^{-1} [159].

In spite its high-intensity sweetness and flavor enhancer and masking effect, not several data were found in the literature on the use of thaumatin in food applications. Until now the applications found of thaumatin added were to Skyr yogurt with

mango pulp by Pereira et al. [162] which observed the sweetener had better acceptance on the sensory profile above stevia from consumers panelists results, also stevia/thaumatin blend (ratio 1:1). Thaumatin did not affect the texture and syneresis of natural skyr yogurt when compared to sucrose formulation of yogurt. Firsov et al. [163] used thaumatin in salted, pickled tomatoes stored through 6 months, and processed tomatoes. Thaumatin showed high stability during salting, acidic (at a pH = 3.1) and storage. Its amount was similar to the content added to fresh tomatoes before processing. Therefore, both salt and acid environments do not influence on thaumatin sweetener properties. Although both salted and pickled tomatoes had a common thaumatin after taste, the overall likeness of pickled tomatoes was scored by panelists as better compared to fresh and salted tomatoes after 6 months of storage, which means thaumatin was a flavor enhancer in acid conditions.

A reducing sugar concentration from 17% of sucrose in strawberry petit Suisse cheese was achieved using a combination of thaumatin/sucralose (at ratio 2:1) at 0.018% with a potency 157.40 reaching the same sweetness sensation as sucrose evaluated by Sousa et al. [164] reducing calories. Authors evaluated four formulations as sucralose, sucralose/acesulfame-K (4:1), thaumatin/sucralose (2:1) and cyclamate/saccharin (1:1). Even results showed cyclamate/saccharin (at ratio 1:1) were the sweeteners with the highest concentration 0.349%, thaumatin and sucralose (at ratio 2:1) might reach the same sweetness sensation.

5.3 Conclusions

Food applications of sweeteners require reformulation in manufacturing and food production to address crucial and technical challenges.

Despite sugar reduction or total replacement, its impact is not only on sweetness but also overall texture, color, taste, and flavor of products; however, several sweeteners can also act as a bulking and stabilizer agent and have culinary properties that can affect positively baked goods, candies, glazes, dairy products, and others.

Characteristics such as after taste are mainly associated with the natural plants extracted sweeteners such as steviol glycosides, glycyrrhizin, and thaumatin; however, the advantage to providing zero calories and zero glycemic indexes without impact on the human body is desirable for low caloric food applications. Sugar alcohols and rare sugars are low caloric with potential uses; however, their doses should be regulated. Water solubility is a concern that affects specially baked products to choose the sweetener, however blends or mixtures of them improve product characteristics with better sensorial acceptance. Nevertheless, sugar alcohols provide a cooling effect to products specially mixed with other flavors.

In general, the introduction of food additives such as sweeteners to the market has provided new opportunities to study the chemical interactions of different ingredients and their impact on human health. More studies need to be done to reach other food products.

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Conflicts of Interest The authors declare no conflict of i**nterest.**

References

1. Chéron JB, Marchal A, Fiorucci S. Natural sweeteners. Encyclopedia of food chemistry. Amesterdam: Elsevier; 2018. p. 189–95.
2. Biancardi EJ, Mitchell M, Panella LW, Lewellen RT, Stevanato P. Chapter 6. Sugar beet. In: Bradshaw J, editor. Root and tuber crops. New York: Springer; 2015. p. 173–219.
3. Inglett GE. A history of sweeteners-natural and synthetic. J Toxicol Environ Health. 1976;2(1):189–206.
4. Hartel RW, Von Elbe JH, Hofberger R. Confectionery science and technology. In: Hartel RW, Von Elbe JH, Hofberger R, editors. Confectionery science and technology. 1st ed. Cham: Springer Nature Switzerland; 2018. p. 1–517.
5. Livesey G. Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. Nutr Res Rev. 2003;16(2):163–91.
6. O'Brien NL. In: O'Brien Nabors L, editor. Alternative sweeteners. 4th ed. Boca Raton: CRC Press; 2012. p. 1–587.
7. García-Almeida JM, Fdez GMC, Alemán JG. Una visión global y actual de los edulcorantes. Aspectos de regulación. Nutr Hosp. 2013;28(4):17–31.
8. Yadav SK, Guleria P. Steviol glycosides from stevia: biosynthesis pathway review and their application in foods and medicine. Crit Rev Food Sci Nutr. 2012;52(11):988–98.
9. Lindley MG. Natural high-potency sweeteners. In: O'Donnell K, Kearsley MW, editors. Sweeteners and sugar alternatives in food technology. 2nd ed. Oxford: John Wiley & Sons, Ltd.; 2012. p. 185–212.
10. Chattopadhyay S, Raychaudhuri U, Chakraborty R. Artificial sweeteners – a review. J Food Sci Technol. 2014;51(4):611–21.
11. Grembecka M. Sugar alcohols—their role in the modern world of sweeteners: a review. Eur Food Res Technol. 2015;241(1):1–14.
12. Kagawa, University, Miki J. International Society of Rare Sugars. 2019. Available from: https://www.isrs.kagawa-u.ac.jp/society.html.
13. Mijailovic N, Nesler A, Perazzolli M, Aït Barka E, Aziz A. Rare sugars: recent advances and their potential role in sustainable crop protection. Molecules. 2021;26(6):1720.
14. Levin GV. Tagatose, the new GRAS sweetener and health product. J Med Food. 2002;5(1):23–36.
15. Scott SK, Rabito FA, Price PD, Butler NN, Schwartzbaum JA, Jackson BM, et al. Comorbidity among the morbidly obese: a comparative study of 2002 U.S. hospital patient discharges. Surg Obes Relat Dis. 2006;2(2):105–11.
16. Yoshida H, Hayashi J, Sugahara T. Studies on free sugars, free sugar alcohols and organic acids of wild mushrooms. J Jpn Soc Food Sci Technol. 1987;33(6):426–33.
17. Rzechonek DA, Dobrowolski A, Rymowicz W, Mirończuk AM. Recent advances in biological production of erythritol. Crit Rev Biotechnol. 2018;38(4):620–33.
18. Bernt WO, Borzelleca JF, Flamm G, Munro IC. Erythritol: a review of biological and toxicological studies. Regul Toxicol Pharmacol. 1996;24(2 II):191–7.
19. Moon HJ, Jeya M, Kim IW, Lee JK. Biotechnological production of erythritol and its applications. Appl Microbiol Biotechnol. 2010;86(4):1017–25.

20. Kumar S, Tyagi PK, Gola D, Mishra AK, Arya A. Plant-based sweeteners and their applications in modern lifestyle. In: Husen A, Bachheti KR, Archana B, editors. Non-timber forest products. Cham: Springer Nature Switzerland; 2021. p. 75–103.
21. Regnat K, Mach RL, Mach-Aigner AR. Erythritol as sweetener—wherefrom and whereto? Appl Microbiol Biotechnol. 2018;102(2):587–95.
22. Röper HV, Goossens JB. Erythritol, a new raw material for food and non-food applications. Starch – Stärke. 1993;45(11):400–5.
23. Perko R, Decock P. Part three reduced-calorie bulk sweeteners erythritol. In: Helen M, editor. Sweeteners and sugar alternatives in food technology. Iowa: Blackwell Publishing Ltd.; 2006. p. 151–76.
24. Boesten DMPHJ, den Hartog GJM, de Cock P, Bosscher D, Bonnema A, Bast A. Health effects of erythritol. Forum Nutr. 2015;14(1):3–9.
25. Carocho M, Morales P, Ferreira ICFR. Natural food additives: quo vadis? Trends Food Sci Technol. 2015;45(2):284–95.
26. Storey D, Lee A, Bornet F, Brouns F. Gastrointestinal tolerance of erythritol and xylitol ingested in a liquid. Eur J Clin Nutr. 2007;61(3):349–54.
27. Oku T, Okazaki M. Laxative threshold of sugar alcohol erythritol in human subjects. Nutr Res. 1996;16(4):577–89.
28. Tetzloff W, Dauchy F, Medimagh S, Carr D, Bär A. Tolerance to subchronic, high-dose ingestion of erythritol in human volunteers. Regul Toxicol Pharmacol. 1996;24(2 II):286–95.
29. Carocho M, Morales P, Ferreira ICFR. Sweeteners as food additives in the XXI century: a review of what is known, and what is to come. Food Chem Toxicol. 2017;107:302–17.
30. De Cock P, Bechert CL. Erythritol. Functionality in noncaloric functional beverages. Pure Appl Chem. 2002;74(7):1281–9.
31. O'Donnell K, Kearsley M. Sweeteners and sugar alternatives. In: O'Donnell K, Kearsley M, editors. Sweeteners and sugar alternatives in food technology. 2nd ed. Oxford: Wiley-Blackwell; 2012. p. 1–471.
32. Fry J. Natural low-calorie sweeteners. In: Baines D, Seal R, editors. Natural food additives, ingredients and flavourings. 1st ed. Cambridge: Woodhead Publishing; 2012. p. 41–5.
33. Lin SD, Lee CC, Mau JL, Lin LY, Chiou SY. Effect of erythritol on quality characteristics of reduced-calorie danish cookies. J Food Qual. 2010;33(Suppl. 1):14–26.
34. Laguna L, Primo-Martín C, Salvador A, Sanz T. Inulin and erythritol as sucrose replacers in short-dough cookies: sensory, fracture, and acoustic properties. J Food Sci. 2013;78(5):S777–84.
35. Akesowan A. Quality of reduced-fat chiffon cakes prepared with erythritol-sucralose as replacement for sugar. Pak J Nutr. 2009;8(9):1383–6.
36. Martínez-Cervera S, Salvador A, Sanz T. Comparison of different polyols as total sucrose replacers in muffins: thermal, rheological, texture and acceptability properties. Food Hydrocoll. 2014;35:1–8.
37. Spies RD, Hoseney RC. Effect of sugars on starch gelatinization. Cereal Chem. 1982;59:128.
38. Rice T, Zannini E, Arendt EK, Coffey A. A review of polyols–biotechnological production, food applications, regulation, labeling and health effects. Crit Rev Food Sci Nutr. 2020;60(12):2034–51.
39. Canada G. Sugar alcohols (polyols) and polydextrose used as sweeteners in foods – food safety – health Canada. 2005. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/sugar-substitutes/sugar-alcohols-polyols-polydextrose-used-sweeteners-foods-food-safety.html.
40. Grembecka M. Sugar alcohols. Encyclopedia of analytical science. Amsterdam: Elsevier Ltd.; 2019. p. 290–9.
41. Tuncer D, Onen A, Yazici AR. Effect of chewing gums with xylitol, sorbitol and xylitol-sorbitol on the remineralization and hardness of initial enamel lesions in situ. Dent Res J. 2014;11(5):537–43.

42. Oza S, Patel K, Bhosale S, Mitra R, Gupta R, Choudhary D. To determine the effect of chewing gum containing xylitol and sorbitol on mutans streptococci and Lactobacilli count in saliva, plaque, and gingival health and to compare the efficacy of chewing gums. J Int Soc Prev Community Dent. 2018;8(4):354–60.
43. Kawanabe J, Hirasawa M, Takeuchi T, Oda T, Ikeda T. Noncariogenicity of erythritol as a substrate. Caries Res. 1992;26(5):358–62.
44. Jeon Y, Oh J, Cho MS. Formulation optimization of sucrose-free hard candy fortified with cudrania tricuspidata extract. Foods. 2021;10(10):1–17.
45. Bertelsen H, Jensen BB, Buemann B. D-tagatose--a novel low-calorie bulk sweetener with prebiotic properties. World Rev Nutr Diet. 1999;85:98–109.
46. Kim P. Current studies on biological tagatose production using L-arabinose isomerase: a review and future perspective. Appl Microbiol Biotechnol. 2004;65(3):243–9.
47. Karabinos JV. Psicose, sorbose and tagatose. Adv Carbohydr Chem. 1952;7(C):99–136.
48. Lee A, Storey DM. Comparative gastrointestinal tolerance of sucrose, lactitol, or D-tagatose in chocolate. Regul Toxicol Pharmacol. 1999;29(2 I):78–82.
49. Buemann B, Toubro S, Raben A, Blundell J, Astrup A. The acute effect of D-tagatose on food intake in human subjects. Br J Nutr. 2000;84(2):227–31.
50. Buemann B, Toubro S, Astrup A. D-tagatose, a stereoisomer of D-fructose, increases hydrogen production in humans without affecting 24-hour energy expenditure or respiratory exchange ratio. J Nutr. 1998;128(9):1481–6.
51. Buemann B, Toubro S, Raben A, Astrup A. Human tolerance to a single, high dose of D-tagatose. Regul Toxicol Pharmacol. 1999;29(2 I):66–70.
52. Buemann B, Toubro S, Astrup A. Human gastrointestinal tolerance to D-tagatose. Regul Toxicol Pharmacol. 1999;29(2 I):71–7.
53. Boesch C, Ith M, Jung B, Bruegger K, Erban S, Diamantis I, et al. Effect of oral D-tagatose on liver volume and hepatic glycogen accumulation in healthy male volunteers. Regul Toxicol Pharmacol. 2001;33(2):257–67.
54. Saunders JP, Donner TW, Sadler JH, Levin GV, Makris NG. Effects of acute and repeated oral doses of D-tagatose on plasma uric acid in normal and diabetic humans. Regul Toxicol Pharmacol. 1999;29(2 I):57–65.
55. Normén L, Lœrke HN, Jensen BB, Langkilde AM, Andersson H. Small-bowel absorption of D-tagatose and related effects on carbohydrate digestibility: an ileostomy study. Am J Clin Nutr. 2001;73(1):105–10.
56. Roy S, Chikkerur J, Roy SC, Dhali A, Kolte AP, Sridhar M, et al. Tagatose as a potential nutraceutical: production, properties, biological roles, and applications. J Food Sci. 2018;83(11):2699–709.
57. Surapureddi SRK, Ravindhranath K, Kumar GSS, Chiliveri P, Sappidi SR. High resolution and high throughput analytical methods for D-tagatose and process related impurities using capillary electrophoresis. Anal Biochem. 2020;609(113981):1–10.
58. Hirst EL, Hough L, Jones JKN. Composition of the gum of Sterculia setigera: occurrence of D-tagatose in nature. Nature. 1949;4135:163–77.
59. Lindberg B. Studies on the chemistry of lichens. VIII. Investigation of a dermatocarpon and some Roccella species. 1955. Report No.: 6.
60. Mendoza MR, Olano A, Villamiel M. Chemical indicators of heat treatment in fortified and special milks. J Agric Food Chem. 2005;53(8):2995–9.
61. Adachi S. Formation of lactulose and tagatose from lactose in strongly heated milk. Nature. 1958;181(4612):840–1.
62. Troyano E, Martinez-Castro I, Olano A. Kinetics of galactose and tagatose formation during heat-treatment of milk. Food Chem. 1992;45(1):41–3.
63. Xu Z, Li S, Fu F, Li G, Feng X, Xu H, et al. Production of D-tagatose, a functional sweetener, utilizing alginate immobilized Lactobacillus fermentum CGMCC2921 cells. Appl Biochem Biotechnol. 2012;166(4):961–73.

64. Izumori K, Tsuzaki K. Production of d-tagatose from d-galactitol by Mycobacterium smegmatis. J Ferment Technol. 1988;66(2):225–7.
65. Manzoni M, Rollini M, Bergomi S. Biotransformation of D-galactitol to tagatose by acetic acid bacteria. Process Biochem. 2001;36(10):971–7.
66. Izumori K, Miyoshi T, Tokuda S, Yamabe K. Productoin of D-tagatose from dulcitol by Arthrobacter globiformis. Appl Environ Microbiol. 1984;48(5):1055–7.
67. Ravikumar Y, Ponpandian LN, Zhang G, Yun J, Qi X. Harnessing L-arabinose isomerase for biological production of D-tagatose: recent advances and its applications. Trends Food Sci Technol. 2021;107:16–30.
68. Roh HJ, Kim P, Park YC, Choi JH. Bioconversion of D-galactose into D-tagatose by expression of L-arabinose isomerase. Biotechnol Appl Biochem. 2000;31(1):1.
69. Acu M, Kinik O, Yerlikaya O. Probiotic viability, viscosity, hardness properties and sensorial quality of synbiotic ice creams produced from goat's milk. Food Sci Technol (Brazil). 2021;41(1):167–73.
70. Taylor TP, Fasina O, Bell LN. Physical properties and consumer liking of cookies prepared by replacing sucrose with tagatose. J Food Sci. 2008;73(3):S145–51.
71. Manley D. Part III types of biscuits. In: Manley D, editor. Technology of biscuits, crackers and cookies. 3rd ed. Boca Raton: CRC Press; 2000.
72. Lagast S, De Steur H, Schouteten JJ, Gellynck X. A comparison of two low-calorie sweeteners and sugar in dark chocolate on sensory attributes and emotional conceptualisations. Int J Food Sci Nutr. 2018;69(3):344–57.
73. Torrico DD, Tam J, Fuentes S, Viejo CG, Dunshea FR. D-tagatose as a sucrose substitute and its effect on the physico-chemical properties and acceptability of strawberry-flavored yogurt. Foods. 2019;8(7):256.
74. Bell L. Tagatose stability in beverages as impacted by composition and thermal processing. In: Preedy V, editor. Processing and impact on active components in food. Amsterdam: Elsevier Inc.; 2015. p. 605–12.
75. Acevedo W, Capitaine C, Rodríguez R, Araya-Durán I, González-Nilo F, Pérez-Correa JR, et al. Selecting optimal mixtures of natural sweeteners for carbonated soft drinks through multi-objective decision modeling and sensory validation. J Sens Stud. 2018;33(6):1–9.
76. Rubio-Arraez S, Benavent C, Ortolá MD, Castelló ML. Influence of low glycaemic index sweeteners on antioxidant, sensory, mechanical, and physicochemical properties of a watermelon jelly. J Food Qual. 2018;2018:8412017.
77. Son YJ, Choi SY, Yoo KM, Lee KW, Lee SM, Hwang IK, et al. Anti-blooming effect of maltitol and tagatose as sugar substitutes for chocolate making. LWT Food Sci Technol. 2018;88:87–94.
78. Rojo-Poveda O, Barbosa-Pereira L, Orden D, Stévigny C, Zeppa G, Bertolino M. Physical properties and consumer evaluation of cocoa bean shell-functionalized biscuits adapted for diabetic consumers by the replacement of sucrose with tagatose. Foods. 2020;9(6):814.
79. Skytte UP. Tagatose in ready to eat cereals. American Association of Cereal Chemist, Inc. 2002;47(2):224–7.
80. Yang H-I, Ameer K, Eun J-B. Effects of different stevia-to-onion ratios and heating temperatures on physicochemical and sensory attributes of onion-stevia hot water extracts. Food Sci Technol. 2022;42:1–11.
81. Anker CCB, Rafiq S, Jeppesen PB. Effect of steviol glycosides on human health with emphasis on type 2 diabetic biomarkers: a systematic review and meta-analysis of randomized controlled trials. Nutrients. 2019;11(9):1965.
82. Singh SD, Rao GP. Stevia: the herbal sugar of 21st century. Sugar Tech. 2005;7(1):17–24.
83. Ameer K, Bae SW, Jo Y, Lee HG, Ameer A, Kwon JH. Optimization of microwave-assisted extraction of total extract, stevioside and rebaudioside-a from Stevia rebaudiana (Bertoni) leaves, using response surface methodology (RSM) and artificial neural network (ANN) modelling. Food Chem. 2017;229:198–207.

84. Bursać Kovačević D, Barba FJ, Granato D, Galanakis CM, Herceg Z, Dragović-Uzelac V, et al. Pressurized hot water extraction (PHWE) for the green recovery of bioactive compounds and steviol glycosides from Stevia rebaudiana Bertoni leaves. Food Chem. 2018;254:150–7.
85. Yu H, Yang G, Sato M, Yamaguchi T, Nakano T, Xi Y. Antioxidant activities of aqueous extract from Stevia rebaudiana stem waste to inhibit fish oil oxidation and identification of its phenolic compounds. Food Chem. 2017;232:379–86.
86. Koubaa M, Roselló-Soto E, Šic Žlabur J, Režek Jambrak A, Brnčić M, Grimi N, et al. Current and new insights in the sustainable and green recovery of nutritionally valuable compounds from Stevia rebaudiana Bertoni. J Agric Food Chem. 2015;63(31):6835–46.
87. Debnath M. Clonal propagation and antimicrobial activity of an endemic medicinal plant Stevia rebaudiana. J Med Plant Res. 2008;2(2):45–51.
88. Brahmachari G, Mandal LC, Roy R, Mondal S, Brahmachari AK. Stevioside and related compounds – molecules of pharmaceutical promise: a critical overview. Arch Pharm. 2011;344(1):5–19.
89. Brandle JE, Starratt AN, Gijzen M. Stevia rebaudiana: its agricultural, biological, and chemical properties. Can J Plant Sci. 1998;78(4):527–36.
90. Carakostas MC, Curry LL, Boileau AC, Brusick DJ. Overview: the history, technical function and safety of rebaudioside A, a naturally occurring steviol glycoside, for use in food and beverages. Food Chem Toxicol. 2008;46(7 Suppl):1–10.
91. Puri M, Sharma D, Barrow CJ, Tiwary AK. Optimisation of novel method for the extraction of steviosides from Stevia rebaudiana leaves. Food Chem. 2012;132(3):1113–20.
92. Azarpazhooh E, Rashidi H, Sharayei P, Behmadi H, Ramaswamy HS. Effect of flaxseed-mucilage and Stevia on physico-chemical, antioxidant and sensorial properties of formulated cocoa milk. Food Hydrocoll Health. 2021;1:100017.
93. Bender C, Graziano S, Zimmermann BF. Study of Stevia rebaudiana Bertoni antioxidant activities and cellular properties. Int J Food Sci Nutr. 2015;66(5):553–8.
94. Lemus-Mondaca R, Vega-Gálvez A, Rojas P, Stucken K, Delporte C, Valenzuela-Barra G, et al. Antioxidant, antimicrobial and anti-inflammatory potential of Stevia rebaudiana leaves: effect of different drying methods. J Appl Res Med Aromat Plants. 2018;11:37–46.
95. Ntalli N, Kasiotis KM, Baira E, Stamatis CL, Machera K. Nematicidal activity of Stevia rebaudiana (Bertoni) assisted by phytochemical analysis. Toxins. 2020;12(5):1–17.
96. Takahashi K, Matsuda M, Ohashi K, Taniguchi K, Nakagomi O, Abe Y, et al. Analysis of anti-rotavirus activity of extract from Stevia rebaudiana. Antivir Res. 2001;49(1):15–24.
97. Jeppesen PB, Gregersen S, Poulsen CR, Hermansen K. Stevioside acts directly on pancreatic β cells to secrete insulin: actions independent of cyclic adenosine monophosphate and adenosine triphosphate-sensitive K PLUS_SPI -channel activity. Metab Clin Exp. 2000;49(2):208–14.
98. Momtazi-Borojeni AA, Esmaeili S-A, Abdollahi E, Sahebkar A. A review on the pharmacology and toxicology of steviol glycosides extracted from Stevia rebaudiana. Curr Pharm Des. 2016;23(11):1616–22.
99. Chatsudthipong V, Muanprasat C. Stevioside and related compounds: therapeutic benefits beyond sweetness. Pharmacol Ther. 2009;121(1):41–54.
100. Jyoti J, Kaur M, Mishra V, Mittal A. Sweet future of stevia: a magical sweetener. Asian J Pharm Clin Res. 2018;11(2):36–42.
101. Goyal SK, Samsher, Goyal RK. Stevia (Stevia rebaudiana) a bio-sweetener: a review. Int J Food Sci Nutr. 2010;61(1):1–10.
102. Serio L. La Stevia rebaudiana, une alternative au sucre. Phytothérapie. 2010;8(1):26–32.
103. Abou-Arab EA, Abou-Arab A, Abu-Salem F. Physico-chemical assessment of natural sweeteners steviosides produced from Stevia rebaudiana bertoni plant. Afr J Food Sci. 2010;4(5):270–81.
104. Lemus-Mondaca R, Vega-Gálvez A, Zura-Bravo L, Kong AH. Stevia rebaudiana Bertoni, source of a high-potency natural sweetener: a comprehensive review on the biochemical, nutritional and functional aspects. Food Chem. 2012;132(3):1121–32.

105. Kaushik R, Narayanan P, Vasudevan V, Muthukumaran G, Antony U. Nutrient composition of cultivated stevia leaves and the influence of polyphenols and plant pigments on sensory and antioxidant properties of leaf extracts. J Food Sci Technol. 2010;47(1):27–33.
106. Gaweł-Bęben K, Bujak T, Nizioł-Łukaszewska Z, Antosiewicz B, Jakubczyk A, Karaś M, et al. Stevia rebaudiana Bert. leaf extracts as a multifunctional source of natural antioxidants. Molecules. 2015;20(4):5468–86.
107. Ruiz-Ruiz JC, Moguel-Ordoñez YB, Segura-Campos MR. Biological activity of Stevia rebaudiana Bertoni and their relationship to health. Crit Rev Food Sci Nutr. 2017;57(12):2680–90.
108. Žlabur JŠ, Dobričević N, Brnčić M, Barba FJ, Lorenzo JM, Franco D, et al. Evaluation of the behavior of phenolic compounds and steviol glycosides of sonicated strawberry juice sweetened with stevia (Stevia rebaudiana Bertoni). Molecules. 2019;24(7):1202.
109. de Carvalho MW, Arriola NDA, Pinto SS, Verruck S, Fritzen-Freire CB, Prudêncio ES, et al. Stevia-fortified yoghurt: stability, antioxidant activity and in vitro digestion behaviour. Int J Dairy Technol. 2019;72(1):57–64.
110. Bukolt KF, Ramirez N, Saenz A, Mirza K, Bhaduri S, Navder K. Effect of low glycemic index stevia-benefiber sweetener on the physical, textural and sensory qualities of oatmeal raisin cookies. J Food Process Technol. 2019;10(8):804.
111. Rodriguez Furlán LT, Campderrós ME. The combined effects of Stevia and sucralose as sugar substitute and inulin as fat mimetic on the physicochemical properties of sugar-free reduced-fat dairy dessert. Int J Gastron Food Sci. 2017;10:16–23.
112. Wan ZL, Wang JM, Wang LY, Yang XQ, Yuan Y. Enhanced physical and oxidative stabilities of soy protein-based emulsions by incorporation of a water-soluble stevioside-resveratrol complex. J Agric Food Chem. 2013;61(18):4433–40.
113. López V, Pérez S, Vinuesa A, Zorzetto C, Abian O. Stevia rebaudiana ethanolic extract exerts better antioxidant properties and antiproliferative effects in tumour cells than its diterpene glycoside stevioside. Food Funct. 2016;7(4):2107–13.
114. Chen J, Xia Y, Sui X, Peng Q, Zhang T, Li J, et al. Steviol, a natural product inhibits proliferation of the gastrointestinal cancer cells intensively. Oncotarget. 2018;9(41):26299–308.
115. Boonkaewwan C, Ao M, Toskulkao C, Rao MC. Specific immunomodulatory and secretory activities of stevioside and steviol in intestinal cells. J Agric Food Chem. 2008;56(10):3777–84.
116. Gao J, Brennan MA, Mason SL, Brennan CS. Effect of sugar replacement with stevianna and inulin on the texture and predictive glycaemic response of muffins. Int J Food Sci Technol. 2016;51(9):1979–87.
117. Graebin CS. The pharmacological activities of glycyrrhizinic acid ("glycyrrhizin") and glycyrrhetinic acid. In: Reference series in phytochemistry. Cham: Springer International Publishing; 2018. p. 245–61.
118. Matsuoka K, Miyajima R, Ishida Y, Karasawa S, Yoshimura T. Aggregate formation of glycyrrhizic acid. Colloids Surf A Physicochem Eng Asp. 2016;500:112–7.
119. Schmid C, Brockhoff A, Shoshan-Galeczki YB, Kranz M, Stark TD, Erkaya R, et al. Comprehensive structure-activity-relationship studies of sensory active compounds in licorice (Glycyrrhiza glabra). Food Chem. 2021;364:130420.
120. Zhang Q, Gao B, Xiao Y, Yang H, Wang Y, Du L, et al. Purification and characterization of a novel β-glucuronidase precisely converts glycyrrhizin to glycyrrhetinic acid 3-O-mono-β-D--glucuronide from plant endophytic Chaetomium globosum DX-THS3. Int J Biol Macromol. 2020;159:782–92.
121. Pandey DK, Ayangla NW. Biotechnological aspects of the production of natural sweetener glycyrrhizin from Glycyrrhiza sp. Phytochem Rev. 2018;17(2):397–430.
122. Wang HL, Li YX, Niu YT, Zheng J, Wu J, Shi GJ, et al. Observing anti-inflammatory and anti-nociceptive activities of glycyrrhizin through regulating COX-2 and pro-inflammatory cytokines expressions in mice. Inflammation. 2015;38(6):2269–78.
123. Michaelis M, Geiler J, Naczk P, Sithisarn P, Leutz A, Doerr HW, et al. Glycyrrhizin exerts antioxidative effects in H5N1 influenza A virus-infected cells and inhibits virus replication and pro-inflammatory gene expression. PLoS One. 2011;6(5):e19705.

124. Duan E, Zhang B, Liang X, Jing H, Liu C, Zhang F, et al. Effects of glycyrrhizin on the growth cycle and ATPase activity of PRRSV-2-infected MARC-145 cells. Res Vet Sci. 2021;138:30–8.
125. Huang YC, Kuo CL, Lu KW, Lin JJ, Yang JL, Wu RSC, et al. 18α-Glycyrrhetinic acid induces apoptosis of HL-60 human leukemia cells through caspases- and mitochondria-dependent signaling pathways. Molecules. 2016;21(7):872.
126. Domitrović R, Potočnjak I. A comprehensive overview of hepatoprotective natural compounds: mechanism of action and clinical perspectives. Arch Toxicol. 2016;90(1):39–79.
127. Han JB, Wu Y, Wang S, Yi L, Qiu R, Zhou H, et al. Chemical constituents and chemotaxonomic study of Glycyrrhiza glabra L. Biochem Syst Ecol. 2020;92:104130.
128. Isbrucker RA, Burdock GA. Risk and safety assessment on the consumption of Licorice root (Glycyrrhiza sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. Regul Toxicol Pharmacol. 2006;46(3):167–92.
129. Gomaa AA, Abdel-Wadood YA. The potential of glycyrrhizin and licorice extract in combating COVID-19 and associated conditions. Phytomed Plus. 2021;1:100043.
130. Nassiri Asl M, Hosseinzadeh H. Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. Phytother Res. 2008;22(6):709–24.
131. Böttcher S, Drusch S. Saponins – self-assembly and behavior at aqueous interfaces. Adv Colloid Interf Sci. 2017;243:105–13.
132. Dargel C, Hannappel Y, Hellweg T. Heating-induced DMPC/glycyrrhizin bicelle-to-vesicle transition: a X-ray contrast variation study. Biophys J. 2020;118(10):2411–25.
133. Hosseini MS, Ebrahimi M, Abadía J, Kadkhodaei S, Amirian R. Growth, phytochemical parameters and glycyrrhizin production in licorice (Glycyrrhiza glabra L.) grown in the field with saline water irrigation. Ind Crop Prod. 2022;177:114444.
134. Wang ZY, Nixon DW. Licorice and cancer. Nutr Cancer. 2001;39(1):1–11.
135. Ruschitzka F, Quaschning T, Noll G, DeGottardi A, Rossier MF, Enseleit F, et al. Endothelin 1 type A receptor antagonism prevents vascular dysfunction and hypertension induced by 11β-hydroxysteroid dehydrogenase inhibition: role of nitric oxide. Circulation. 2001;103(25):3129–35.
136. Bailly C, Vergoten G. Glycyrrhizin: an alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome? Pharmacol Ther. 2020;214:107618.
137. Alagawany M, Elnesr SS, Farag MR. Use of liquorice (Glycyrrhiza glabra) in poultry nutrition: global impacts on performance, carcass and meat quality. Worlds Poult Sci J. 2019;75(2):293–303.
138. Račková L, Jančinová V, Petríková M, Drábiková K, Nosáľ R, Stefek M, et al. Mechanism of anti-inflammatory action of liquorice extract and glycyrrhizin. Nat Prod Res. 2007;21(14):1234–41.
139. Vorobyova VI, Skiba MI, Shakun AS, Nahirniak SV. Relationship between the inhibition and antioxidant properties of the plant and biomass wastes extracts – a review. Int J Corros Scale Inhib. 2019;8(2):150–78.
140. Hayashi H, Sudo H. Economic importance of licorice. Plant Biotechnol. 2009;26(1):101–4.
141. I--Food C, Services H. CFR – Code of Federal Regulations Title 21 CFR – Code of Federal Regulations Title 21 Tariq Al-Jallad CFR – Code of Federal Regulations Title 21 Tariq Al-Jallad. US Food & Drug Administration. 2014;(d):5–6. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm.
142. Qiu X, Chen S, Liu G, Yang Q. Quality enhancement in the Japanese sea bass (Lateolabrax japonicas) fillets stored at 4 °C by chitosan coating incorporated with citric acid or licorice extract. Food Chem. 2014;162:156–60.
143. Jiang J, Zhang X, True AD, Zhou L, Xiong YL. Inhibition of lipid oxidation and rancidity in precooked pork patties by radical-scavenging licorice (Glycyrrhiza glabra) extract. J Food Sci. 2013;78(11):C1686–94.
144. Zhang H, Kong B, Xiong YL, Sun X. Antimicrobial activities of spice extracts against pathogenic and spoilage bacteria in modified atmosphere packaged fresh pork and vacuum packaged ham slices stored at 4 °C. Meat Sci. 2009;81(4):686–92.

145. Al-Turki AI, El-Ziney MG, Abdel-Salam AM. Chemical and anti-bacterial characterization of aqueous extracts of oregano, marjoram, sage and licorice and their application in milk and labneh. J Food Agric Environ. 2008;6(1):39–44.
146. Mocanu G-D, Rotaru G, Botez E, Gîtin L, Andronoiu D-G, Nistor O, et al. Sensory evaluation and rheological behavior of probiotic dairy products with Rosa canina L. and Glycyrriza glabra L. extracts. Innov Rom Food Biotechnol. 2009;4:32–9.
147. Maghamian N, Goli M, Najarian A. Ultrasound-assisted preparation of double nano-emulsions loaded with glycyrrhizic acid in the internal aqueous phase and skim milk as the external aqueous phase. LWT. 2021;141:110850.
148. Azami T, Niakousari M, Hashemi SMB, Torri L. A three-step sensory-based approach to maximize consumer acceptability for new low-sugar licorice-chocolate-flavored milk drink. LWT. 2018;91:375–81.
149. Aly AM, Al-Alousi L, Salem HA. Licorice: a possible anti-inflammatory and anti-ulcer drug. AAPS PharmSciTech. 2005;6(1):E74.
150. Sidhu P, Shankargouda S, Rath A, Hesarghatta Ramamurthy P, Fernandes B, Kumar SA. Therapeutic benefits of liquorice in dentistry. J Ayurveda Integr Med. 2020;11:82–8.
151. Asha MK, Debraj D, Dethe S, Bhaskar A, Muruganantham N, Deepak M. Effect of flavonoid-rich extract of Glycyrrhiza glabra on gut-friendly microorganisms, commercial probiotic preparations, and digestive enzymes. J Diet Suppl. 2017;14(3):323–33.
152. Han Y, Pang X, Zhang X, Han R, Liang Z. Resource sustainability and challenges: status and competitiveness of international trade in licorice extracts under the Belt and Road Initiative. Glob Ecol Conserv. 2022;34:e02014.
153. van der Wel H, Loeve K. Isolation and characterization of thaumatin I and II, the sweet-tasting proteins from Thaumatococcus daniellii Benth. Eur J Biochem. 1972;31(2):221–5.
154. Liu JJ, Sturrock R, Ekramoddoullah AKM. The superfamily of thaumatin-like proteins: its origin, evolution, and expression towards biological function. Plant Cell Rep. 2010;29(5):419–36.
155. Ming D, Hellekant G. Brazzein, a new high-potency thermostable sweet protein from Pentadiplandra brazzeana B. FEBS Lett. 1994;355(1):106–8.
156. Faus I. Recent developments in the characterization and biotechnological production of sweet-tasting proteins. Appl Microbiol Biotechnol. 2000;53(2):145–51.
157. Yamashita H, Theerasilp S, Aiuchi T, Nakaya K, Nakamura Y, Kurihara Y. Purification and complete amino acid sequence of a new type of sweet protein with taste-modifying activity, curculin. J Biol Chem. 1990;265(26):15770–5.
158. Morris JA, Martenson R, Deibler G, Cagan RH. Characterization of monellin, a protein that tastes sweet. J Biol Chem. 1973;248(2):534–9.
159. Joseph JA, Akkermans S, Nimmegeers P, Van Impe JFM. Bioproduction of the recombinant SWEET protein thaumatin: current state of the art and perspectives. Front Microbiol. 2019;10(APR):695.
160. de Jesús-Pires C, Ferreira-Neto JRC, Pacifico Bezerra-Neto J, Kido EA, de Oliveira Silva RL, Pandolfi V, et al. Plant thaumatin-like proteins: function, evolution and biotechnological applications. Curr Protein Pept Sci. 2019;21(1):36–51.
161. Science of Thaumatin. Available from: http://www.thaumatin.com/science-of-thaumatin.
162. Pereira CTM, Pereira DM, de Medeiros AC, Hiramatsu EY, Ventura MB, Bolini HMA. Skyr yogurt with mango pulp, fructooligosaccharide and natural sweeteners: physical aspects and drivers of liking. LWT. 2021;150(April):112054.
163. Firsov A, Shaloiko L, Kozlov O, Vainstein A, Dolgov S. Tomatoes expressing thaumatin II retain their sweet taste after salting and pickling processing. J Sci Food Agric. 2021;101(12):5286–9.
164. De Souza VR, Pinheiro ACM, Carneiro JDDS, Pinto SM, Abreu LR, Menezes CC. Analysis of various sweeteners in petit suisse cheese: determination of the ideal and equivalent sweetness. J Sens Stud. 2011;26(5):339–45.