# Natural and Non-Nutritive Sweeteners: Comprehensive Bioactive Profiles, Extraction Methodologies, Health Implications, and Industrial Applications in Metabolic Disease Management

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*Abstract*—**Excessive consumption of refined sucrose and high-fructose corn syrup has driven a global surge in noncommunicable metabolic disorders, including type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, and clinical obesity. In response, human nutrition, pharmacology, and food engineering have increasingly shifted focus toward natural and non-nutritive sweeteners as therapeutic and functional alternatives. This comprehensive manuscript delivers an exhaustive review of natural sugar sources (date palm, grapes, sweet sorghum, raw sugarcane, honey, agave syrup, sugar beet, and maple syrup), non-nutritive high-intensity natural sweeteners (thaumatin, glycyrrhizin, monk fruit mogrosides, and steviol glycosides), semi-synthetic flavonoid derivatives (neohesperidin dihydrochalcone), and rare nutritive carbohydrates and polyols (D-tagatose, D-allulose, trehalose, erythritol, mannitol, and maltitol). We evaluate their molecular structures, green and conventional extraction protocols, microencapsulation technologies, receptor-level sweet synergy mechanisms, and broad-spectrum biological activities including antioxidant, anti-inflammatory, hepatoprotective, and immunomodulatory effects. Furthermore, this manuscript examines detailed case studies, including the hepatoprotective mechanisms of NHDC against Paraquat-induced acute liver injury, longitudinal epidemiological evaluations of artificial sweetener exposure and type 2 diabetes risk in the NutriNet-Santé cohort, the dual metabolic paradox of synthetic sweeteners in glycemic control, the neuro-behavioural reward dysregulation driving hyperphagia in obesity, a crossover clinical trial comparing honey, sucrose, and HFCS55, and the ethnopharmacological synergistic co-administration of Stevia rebaudiana with saxagliptin. Ultimately, this work synthesizes current scientific evidence, addresses technological formulation hurdles, and establishes a strategic roadmap for integrating functional natural sweeteners into mainstream food science and clinical metabolic management.**

*Index Terms*—**Steviol Glycosides, Monk Fruit, Metabolic Syndrome, Type 2 Diabetes Mellitus, Hepatoprotection, Microencapsulation, Synergy, Glycemic Control, Natural Sweeteners, case studies.**

## I. INTRODUCTION

Sugar, primarily in the form of sucrose derived from sugar beet and sugar cane, has dominated human diets since the 18th century, largely eclipsing traditional natural options like honey. In recent years, global sucrose consumption has surged, reaching 174 million metric tons in 2018–2019. However, this sharp increase in excessive sugar intake has raised severe public health concerns worldwide. Extensive research links high dietary sugar consumption directly to an elevated risk of noncommunicable diseases, including cardiovascular disease, obesity, dental caries, and type 2 diabetes mellitus.[1]

Diabetes mellitus is a chronic metabolic lifestyle disorder characterized by persistent hyperglycemia, which arises from deficits in insulin secretion, insulin action, or both. Insulin, a vital hormone produced by the beta (β) cells of the pancreatic islets, plays a central role in regulating blood glucose homeostasis. The condition manifests primarily in two forms: Type 1 diabetes, an autoimmune disorder causing complete β-cell destruction and absolute insulin deficiency influenced by genetic factors like the HLA complex and environmental triggers, and Type 2 diabetes, a progressive disease driven by insulin resistance and β-cell dysfunction linked to oxidative stress, elevated fatty acids, and amyloid deposition.[2]

Managing chronic hyperglycemia is essential because unmanaged diabetes leads to severe microvascular and macrovascular complications. Up to half of diabetic

patients suffer from diabetic neuropathy, experiencing pain, numbness, and heightened risks of foot ulcers and amputations, while diabetic retinopathy frequently results in severe visual impairment or blindness. Additionally, affected individuals face elevated risks of end-stage renal failure and cardiovascular events, particularly stroke. Management typically relies on oral hypoglycemic agents alongside comprehensive lifestyle modifications.

To mitigate these health risks, natural sweeteners derived from plants, seeds, roots, fruits, and honey have emerged as promising alternatives to refined sucrose. Structurally diverse, these natural compounds encompass diterpenes such as steviol glycosides from Stevia rebaudiana, triterpenes like mogrosides from Monk fruit (Siraitia grosvenorii), citrus-derived flavonoid derivatives such as Neohesperidin Dihydrochalcone (NHDC), oligosaccharides, and sweet proteins. Nonnutritive options like stevia and monk fruit offer sweetness hundreds of times potent than sucrose while delivering key bioactive properties. Beyond serving as low-calorie sugar substitutes, natural sweeteners exhibit remarkable therapeutic and biological activities, including anti-inflammatory, antioxidant, anti-hyperglycemic, anti-tumor, and antibacterial effects. Consequently, these compounds are attracting substantial interest across the pharmaceutical, cosmetic, and health food industries. This review provides a comprehensive overview of natural sweeteners classified by structural type, exploring their extraction methods, physicochemical properties, biological applications, and prospective roles in functional foods and therapeutic strategies.[1], [2], [3]

## II. NATURAL SOURCES OF SUGAR: HEALTH BENEFITS, BIOACTIVE PROFILES, AND DIETARY APPLICATIONS

The growing public interest in personal health and long-term wellness has driven a significant increase in consumer demand for low-calorie and nutrient-dense alternatives to conventional refined sugar. In response, modern food science and nutrition research have increasingly focused on replacing refined sucrose with sugars derived from natural sources that can be effortlessly incorporated into solid, semi-solid, and liquid food formulations. Unlike refined table sugar, which provides empty calories devoid of essential nutrients, unrefined sugars obtained from natural plant-based sources contain a rich spectrum of bioactive compounds, essential minerals, dietary fibers, antioxidants, and protective phytochemicals. These naturally occurring components work synergistically to reduce systemic inflammation and enhance endothelial function. The nutritional value and overall antioxidant potential of these natural sugars are heavily influenced by the degree of industrial processing and purification they undergo. Research indicates that substituting unrefined sugars for highly processed white sugar offers marked dietary advantages, largely due to the retention of high phenolic and flavonoid content. Furthermore, epidemiological studies suggest that weight gain in adults is inversely associated with the intake of naturally occurring plant sugars, emphasizing their potential to support sustainable health outcomes.



Date palm (Phoenix dactylifera) represents one of the most prominent natural sugar sources and has been cultivated for thousands of years across Africa and the Middle East for its nutritional and socioeconomic value. With over 5,000 cultivated varieties worldwide, dates vary in morphological characteristics and nutrient composition, with prominent varieties like Dhakki and Aseel driving major agricultural markets. Dates are exceptionally rich in carbohydrates predominantly easily digestible glucose and fructose alongside moisture, proteins, dietary fibers, and minimal fat.

To produce traditional date palm sugar, the collected sap is filtered and boiled over controlled heat until it concentrates into a thick, pourable liquid before being set into molds. Beyond providing sweetness, date fruit syrup serves as a highly functional substitute for sucrose. Clinical and preclinical research demonstrates

that dates contribute substantially to human health through multiple mechanisms. The high fiber content of date fruit significantly reduces gastrointestinal transit time, promoting bowel regularity and colonic bacterial homeostasis while inhibiting the proliferation of colon cancer cells. The fruit is also an abundant source of vital minerals including copper, iron, calcium, magnesium, and potassium delivering approximately 15% of the recommended daily allowance in a standard 100-gram serving, alongside generous amounts of B-complex vitamins. Additionally, the complex mixture of flavonoids, steroids, carotenoids, and polyphenols in dates provides potent free-radical scavenging capacity, hepatoprotective activity against toxic insults, nephroprotective effects against tubular damage, and significant anti-hyperlipidemic activity that helps prevent fatty liver changes.[4]



Grapes (Vitis vinifera) are another globally crucial fruit crop whose high natural sugar content renders them an effective alternative sweetener. Soluble solids in ripe grapes consist primarily of glucose and fructose in a balanced one-to-one ratio, though fructose concentrations predominate in overripe fruit. Because fructose possesses a significantly higher relative sweetness intensity than sucrose, smaller total amounts are needed to achieve equivalent levels of sweetness in food and beverage products.

Beyond their primary carbohydrates, fresh grape juices contain essential organic acids, minerals, pectic substances, and diverse phenolic compounds that contribute both functional stability and health benefits. Similarly, sweet sorghum (Sorghum bicolor) has emerged as a promising, environmentally non-polluting crop that yields a nutrient-dense juice containing sucrose, glucose, fructose, and various minor sugars alongside a rich profile of amino acids and essential macro- and microelements such as potassium, calcium, and manganese.

The syrup extracted from sweet sorghum closely resembles natural honey in its biologically active constituents and demonstrates significant utility across baking and confectionery industries as a partial or full sucrose replacement. Additionally, sweet sorghum contains unique phytochemicals like tannins, which modulate digestive enzyme activity, and polycosanols, which support cardiac function and improve lipoprotein ratios. Being naturally gluten-free, sweet sorghum products provide a safe, highly nutritious alternative for individuals suffering from celiac disease or gluten sensitivity.[4]



Sugarcane (Saccharum species) remains the primary raw material for industrial sweetener production worldwide, but raw sugarcane juice and its unrefined derivatives contain extensive health-promoting properties that are routinely stripped away during refined sugar processing. Historically valued in Ayurvedic and traditional medicine systems for treating conditions ranging from anemia and jaundice to respiratory ailments and general debility, sugarcane extracts are now recognized for their strong antioxidant, immunomodulatory, anti-stress, and liver-protective properties.

Unrefined sugarcane products, such as jaggery (or Gur), are produced by concentrating sugarcane juice without synthetic additives, bleaching agents, or chemical preservatives. Jaggery retains up to 85% sucrose along with substantial quantities of vitamins

A, C, and D2, alongside a rich mineral complex featuring calcium, magnesium, potassium, iron, phosphorus, and zinc. Compared to white table sugar, jaggery offers rapid yet sustained energy release while actively preventing insulin resistance and abdominal fat accumulation. Its complex carbohydrate structure and natural iron content make it a superior functional ingredient for traditional sweets, baked goods, and dairy products. Furthermore, sugarcane processing by-products like molasses exhibit high antioxidant activity and lipid peroxidation inhibition, partially due to beneficial Maillard reaction products formed during thermal processing.[4], [5]

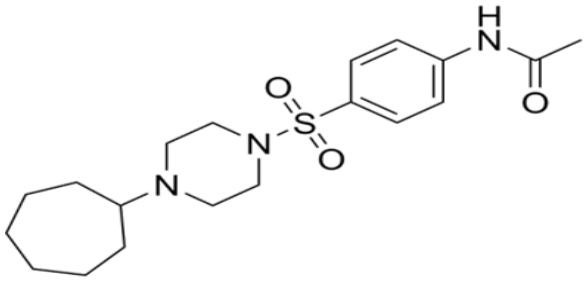


Honey is a complex, naturally occurring sweetener produced by honeybees from floral nectar or honeydew, consisting of roughly 200 distinct chemical constituents. Monosaccharides dominate its composition with fructose accounting for over 38% and glucose representing approximately 30% accompanied by disaccharides, water, organic acids, enzymes, vitamins, minerals, and bioactive phenolic compounds. Honey has long formed the cornerstone of apitherapy, serving as a powerful therapeutic agent against oxidative stress, cardiovascular disease, hepatic impairment, and cellular aging. The prebiotic oligosaccharides naturally present in honey stimulate the growth of beneficial gut microbiota such as Lactobacillus and Bifidobacterium species, improving colonic health and immune function.

Furthermore, human clinical trials demonstrate that honey consumption actively supports weight management by reducing total body weight, fat mass, serum triglycerides, and low-density lipoprotein (LDL) cholesterol while modestly increasing protective high-density lipoprotein (HDL) cholesterol. Finally, sugar beet (Beta vulgaris) serves as another major commercial source of natural sucrose, accumulating high sugar concentrations within its fleshy taproots. The water-insoluble byproduct of sugar beet extraction beet pulp is exceptionally rich in dietary fibers with desirable water-retention capabilities and a uniquely low phytate content, ensuring that it does not hinder essential mineral absorption in the human digestive tract. Collectively, these natural sugar sources offer a multifaceted approach to human nutrition, replacing nutrient-void refined sucrose with functional, disease-preventing compounds.[5]

## III. NON-NUTRITIVE NATURAL SWEETENERS: OVERVIEW AND APPLICATIONS

Non-Nutritive Sweeteners (NNS) are natural or synthetic compounds that deliver intense sweetness while providing minimal to zero caloric energy. As global health challenges like obesity, type 2 diabetes, and metabolic syndrome continue to rise, NNS have gained immense popularity as functional alternatives to refined sucrose. Among naturally derived non-nutritive options, thaumatin, glycyrrhizin, monk fruit extract, stevia, and neohesperidin dihydrochalcone (NHDC) stand out for their exceptional sweetness potency and distinct health benefits.[6]




3.1 Thaumatin

Thaumatin (E957) is an intensely sweet, non-nutritive natural protein extracted from the arils of the katemfe fruit (Thaumatococcus daniellii Bennett), native to West Africa. It primarily consists of two sweet-tasting proteins, designated as thaumatin I and thaumatin II, which possess molecular masses of 22,209 Da and 22,293 Da, respectively. Structurally, thaumatin II is composed of a single polypeptide chain containing 207 amino acid residues. It is celebrated for its extraordinary sweetness potency, eliciting a sweet perception even at extremely low threshold concentrations of approximately 50 nM (roughly

2,000 to 3,000 times sweeter than sucrose). Driven by its dual functionality as a high-intensity sweetener and flavor modifier, the global thaumatin market is expanding rapidly, with an estimated compound annual growth rate (CAGR) of 6.1% over the 2023–2030 period.[6]

According to Commission Regulation (EU) No 231/2012, commercial thaumatin is conventionally produced via acidic aqueous extraction of the plant's arils followed by ultrafiltration to isolate and concentrate the protein fractions. However, direct extraction from wild plant harvests presents notable economic constraints. To address these recovery costs and supply fluctuations, biotechnological research has focused on the bioproduction of recombinant thaumatin using genetically engineered microorganisms and transgenic plants, offering a scalable, cost-effective alternative.[6], [7]

Thaumatin's exceptional sweetness intensity and flavor-enhancing capabilities have led to extensive research regarding its application across a wide spectrum of food matrices. In bakery products, thaumatin effectively compensates for sucrose reduction while preserving structural integrity. Research indicates that reducing sucrose by 25% to 35% in biscuit formulations combined with thaumatin minimally alters dough rheology while improving physical attributes like firmness, consistency, and hardness, which enhances baked crunchiness and overall mouthfeel. In fruit preserves, thaumatin performs remarkably well; low-sugar mixed fruit jams containing a sucralose-thaumatin blend (1:0.6 ratio) achieve sensory acceptability identical to traditional sucrose-sweetened jam. Similarly, adding thaumatin to guava jam increases product cohesiveness, suggesting favorable chemical interactions between the sweet protein and the pectin gel network. In dairy systems, thaumatin provides unique structural and temporal advantages. In mango-flavored skyr yogurt, adding 0.11% thaumatin preserves consistency and syneresis comparable to sucrose controls while increasing product cohesion. Furthermore, combining this sweet protein with an acidic yogurt matrix prolongs sweetness perception in the mouth. In strawberry petit Suisse cheese, a 2:1 blend of thaumatin and sucralose at 0.018% allows for a 17% reduction in required sucrose while maintaining the target sweetness intensity. Thaumatin also remains stable under acidic conditions, serving as an effective flavor enhancer in savory applications such as salted, pickled, and processed tomato products stored at low pH (pH = 3.1) for up to six months without loss of sweetness, despite a mild characteristic aftertaste in pickled formulations.

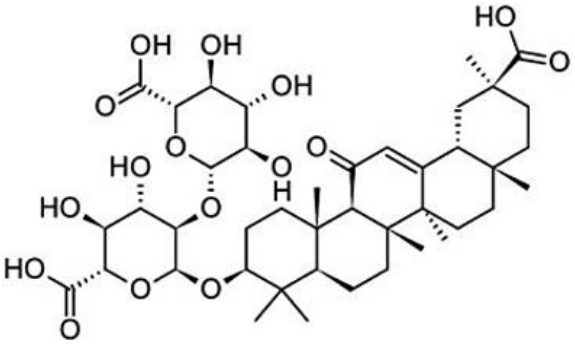
Despite its versatility across solid and semi-solid foods, thaumatin's application in commercial beverages remains limited due to molecular interactions with food colorants. Thaumatin carries a net positive electrostatic charge at typical beverage pH levels. When combined with negatively charged synthetic dyes, electrostatic attraction leads to the formation of insoluble dye-protein complexes, causing precipitation, loss of color intensity, or a mutual decrease in perceived sweetness.[6]

3.2 Glycyrrhizin

Glycyrrhizin (E958) is a naturally occurring triterpene saponin derived from the roots and rhizomes of licorice (Glycyrrhiza glabra L., as well as G. uralensis, G. inflata, G. echinata, and G. lepidota). Structurally, it consists of two molecules of glucuronic acid conjugated with glycyrrhetinic acid, conferring an intensely sweet taste estimated to be 50 to 200 times sweeter than sucrose. Beyond its high-intensity sweetening capacity, glycyrrhizin possesses functional amphiphilic properties that allow it to act as an effective emulsifier, foaming agent, and gel-forming compound in complex food systems. When applied as a sucrose replacer in baked goods and confectioneries, it distinctly influences physical and sensory attributes. In cake formulations, glycyrrhizin enhances aeration by increasing specific volume, though it causes noticeable crumb browning alongside reductions in lightness, redness, and yellowness. In toffee preparations, substituting up to 50% of sucrose with glycyrrhizin maintains optimal textural parameters and a favorable flavor profile without imparting unacceptable bitterness, although higher replacement levels trigger persistent off-flavors. Driven by consumer demand for low-calorie functional ingredients, the global glycyrrhizin market is expanding at a projected compound annual growth rate (CAGR) of 6.8% over the 2023–2030 period.

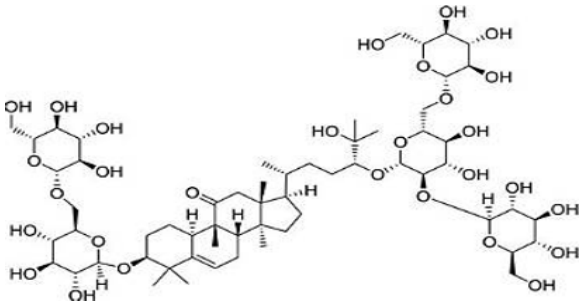
The extraction and isolation of glycyrrhizin encompass both conventional and emerging technological approaches designed to yield crude licorice extract (LE) or high-purity mono-ammonium

glycyrrhizate (MAG). Standard separation methods utilize hot water under ambient pressure and alkaline pH (dilute ammonia solution) or aqueous alcohols like methanol and ethanol. In a typical isolation protocol, powdered G. glabra root is mixed with dilute ammonia at a 1:40 solid-to-solvent ratio and autoclaved, after which the supernatant is filtered and chilled. To isolate purified crystalline MAG, the crude extract is concentrated using a rotary evaporator, treated with ethanol at a 3:1 (v/v) ratio to separate the alcoholic layer, and subsequently acidified with sulfuric acid to induce acid precipitation. The resulting white MAG crystals are vacuum-dehydrated into a stable powder suitable for low-calorie food and pharmaceutical applications. Beyond traditional liquid extraction, modern green chemistry alternatives such as ultrasound-assisted extraction, supercritical carbon dioxide ($CO_2$), and superheated subcritical water extraction have been introduced to improve extraction yield, shorten processing time, and minimize solvent usage.[4], [6], [12]



Biologically, glycyrrhizin and crude licorice extracts demonstrate diverse metabolic and organ-protective activities. Recognized as Generally Recognized as Safe (GRAS) by the United States Food and Drug Administration (US FDA), oral administration of glycyrrhizin in long-term in vivo animal models yields notable hypolipidemic and metabolic benefits. Experimental findings show that ingestion of glycyrrhizin significantly reduces serum total lipids (TL), triglycerides (TG), and very-low-density lipoproteins (VLDL) without adversely altering total cholesterol or high-density lipoprotein (HDL) levels. Furthermore, it exerts marked hepatoprotective activity by lowering serum liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and acid phosphatase (ACP) and enhancing renal function indicators such as creatinine and uric acid. Histopathological evaluations confirm the preservation of normal hepatic and renal cellular architectures with no tissue damage at non-toxic therapeutic doses. Broadly, licorice phytochemicals exhibit significant antiviral, anti-inflammatory, anti-tumor, antimutagenic, antioxidant, and antihepatotoxic effects.[13].[14]

Despite its nutritional and pharmacological advantages, the consumption of licorice extracts and their phytochemical constituents presents critical pharmacokinetic considerations, particularly regarding herb-drug interactions. Hydroethanolic extracts from various Glycyrrhiza species and isolated bioactives have been shown to significantly affect nuclear receptor activation and drug-metabolizing enzymes. Specifically, licorice extracts enhance the transcriptional activity of the pregnane X receptor (PXR) and aryl hydrocarbon receptor (AhR) by more than two-fold, leading to the upregulation and increased enzyme activity of key cytochrome P450 isoforms, primarily CYP3A4 and CYP1A2. Studies reveal that G. echinata induces up to a four-fold increase in CYP3A4 activity, whereas G. uralensis and G. inflata induce up to 18-fold and 16-fold increases in CYP1A2 activity, respectively. Among individual constituents, glabridin, licoisoflavone



A, glyasperin C, glycycoumarin, and formononetin drive these interactions, with glabridin acting as a particularly potent activator of PXR (6-fold) and AhR (27-fold). Consequently, co-administration of licorice formulations accelerates the metabolic clearance of substrate drugs; for instance, G. uralensis and its marker compound glycycoumarin significantly increase the clearance of antiretroviral drugs such as rilpivirine and dolutegravir. Similarly, G. glabra increases dolutegravir metabolism by 2.8-fold. These interactions demonstrate that while licorice derivatives offer valuable therapeutic properties, their potential to alter the pharmacokinetics and clearance of concurrent

medications warrants careful clinical monitoring.[6], [7].

To overcome the sensory limitations of glycyrrhizin specifically its delayed sweetness onset and lingering licorice aftertaste recent biotechnological strategies have focused on its enzymatic conversion into glycyrrhetic acid 3-O-mono-β-D-glucuronide (GAMG). GAMG is an advanced derivative that exhibits a significantly higher sweetness potency (5 to 1,000 times sweeter than glycyrrhizin and sucrose, respectively) alongside a cleaner, superior taste profile with minimal aftertaste. The biocatalytic conversion of glycyrrhizin to GAMG is carried out under mild reaction conditions using β-glucuronidases (β-GUS). To improve biocatalytic efficiency, thermal stability, and enzyme reusability, various immobilization strategies have been developed to confine β-GUS enzymes onto or within solid support matrices via physical entrapment, ionic adsorption, or covalent bonding. Purified β-GUS from Aspergillus terreus has been successfully immobilized through entrapment in alginate gels, while recombinant β-GUS from Aspergillus oryzae Li-3 has been immobilized via adsorption onto zinc oxide nanoparticles. Additionally, β-GUS derived from Patella vulgata has been effectively stabilized using mixed-matrix carriers composed of biomimetic silica and magnetic nanoparticles. These immobilization systems enhance enzyme stability across wider pH and temperature ranges, facilitating scalable, efficient GAMG production for high-value sweetener and pharmaceutical applications.[4], [5],

3.3 Monk fruit

Monk fruit (Siraitia grosvenorii), a dioecious perennial plant endemic to subtropical China, has emerged as a high-potency non-nutritive sweetener (NNS) approved by the US Food and Drug Administration (FDA) and European Food Safety Authority (EFSA). Extracted from the fruit of the Cucurbitaceae family, monk fruit sweetener provides intense sweetness with negligible caloric value, making it an attractive component for weight management, glycemic control, and cardiometabolic disease prevention. Unlike several other natural high-intensity sweeteners, monk fruit extract is widely appreciated for delivering a clean taste without leaving a sharp bitter or metallic aftertaste. Driven by expanding consumer demand for low-calorie natural foods, the global market for monk fruit sweeteners is projected to register a compound annual growth rate (CAGR) of 4.8% from 2023 to 2031. The principal sweet constituents of monk fruit are cucurbitane-type triterpene glycosides known as mogrosides, with mogroside V serving as the primary bioactive molecule. Delivering a sweetness intensity approximately 100 to 250 times greater than sucrose, mogrosides also exhibit valuable therapeutic properties, including antitussive, anti-asthmatic, hepatoprotective, glucose-lowering, and immunomodulatory activities. Commercial recovery of these functional compounds typically involves aqueous extraction from fresh fruit, filtration, and selective resin concentration.[15], [16]

To meet rising industrial demand and secure mass-scale propagation of elite germplasm, plant tissue culture techniques have been optimized for S. grosvenorii. Supplementing Murashige and Skoog (MS) growth media with functionalized gold nanoparticles (AuNPs) significantly influences in vitro shoot proliferation and plantlet development. Research demonstrates that supplementing MS medium with citrate- and cetyltrimethylammonium bromide (CTAB)-coated AuNPs across a concentration range of 10 to 100 μM differentially regulates morpho-physiological and biochemical responses. Monk fruit explants propagated on MS medium supplemented with 40 μM CTAB-coated AuNPs exhibit maximum shoot proliferation, root development, and physiological performance. Conversely, growth parameters decrease to minimum levels in media containing 100 μM citrate-coated AuNPs. Gene expression analyses reveal that the morphological enhancement observed under 40 μM CTAB-coated AuNP treatment directly correlates with the marked upregulation of key auxin and jasmonic acid signaling genes, specifically YUC9 and ARF8. These findings establish a reliable, high-efficiency protocol for nanoparticle-mediated micropropagation and elicitation of monk fruit planting stock.[17]

In food formulation, the thermal stability and favorable sensory profile of monk fruit extract make it a versatile substitute for refined sucrose across various solid, semi-solid, and liquid matrices. In bakery applications, such as sucrose- and gluten-free cupcakes formulated with soy flour to replace wheat flour, incorporating monk fruit extract successfully eliminates refined sugar while reducing batter viscosity. This viscosity reduction is particularly

advantageous for soy-based formulations, which are otherwise prone to high density and excessive tightness. Adding natural hydrocolloid gums derived from quince seed (Cydonia oblonga) and psyllium husk (Plantago ovata) alongside monk fruit sweetener further improves the specific volume, porosity index, and moisture retention of baked cupcakes. Similarly, in extruded cranberry-infused breakfast cereals composed of rice flour, cranberry pomace, and soy flour, optimizing the zero-calorie sweetening profile with up to 5% monk fruit extract enhances overall palatability and consumer preference without compromising structural extrusion parameters.

Monk fruit extract also demonstrates functional utility in gelled confections and dessert matrices. When evaluated in green tea agar jellies at sucrose-equivalent substitution levels ranging from 25% to 100%, combining monk fruit extract with stevia alters physical and sensory characteristics. Increasing the sugar replacement level decreases total soluble solids while increasing gel firmness and lightness. Low-sugar jellies prepared with monk fruit and stevia exhibit lower syneresis compared to full-sucrose controls, a physical outcome attributed to a denser gel network with smaller microscopic pores. Sensory evaluations indicate that while a complete 100% replacement of sucrose imparts a slight off-flavor, partial substitution levels at 50% and 75% yield optimal taste, aroma, and overall acceptability, balancing sweetness intensity with a pleasing texture.[18]

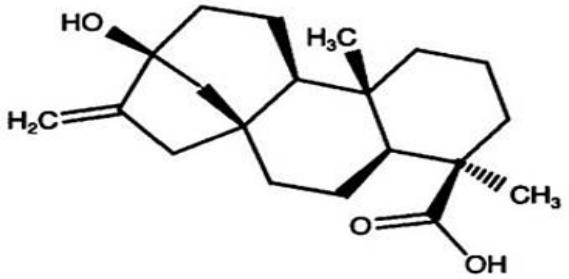
In cultured dairy systems, monk fruit extract serves as an effective sweetening agent that preserves structural stability and microbial viability. In camel milk yogurt formulations sweetened with monk fruit extract at concentrations up to 2.54 g/L, higher inclusion levels (1.27 g/L and 2.54 g/L) lower product pH and increase apparent viscosity over a 42-day cold storage period. Crucially, the addition of monk fruit sweetener does not adversely affect the viable counts or growth kinetics of key probiotic starter cultures, including Streptococcus thermophilus, Lactobacillus bulgaricus, and Lactobacillus acidophilus. Furthermore, incorporating monk fruit extract at low concentrations (0.1% or less) in standard yogurt matrices provides sufficient sweetness to completely replace sucrose while maintaining microstructural integrity, yielding low-glycemic dairy products tailored for diabetic consumers. [14], [15]

Beyond bakery, confectionery, and dairy applications, monk fruit extract functions as a protective functional ingredient in savory thermal processing. In traditional culinary preparations like braised pork, adding mogrosides during thermal stewing helps preserve overall meat quality. Mogrosides act as active antioxidants during cooking, mitigating both protein and lipid oxidation. Consequently, the inclusion of monk fruit extract reduces drip loss and cooking loss during high-temperature processing while preserving desirable volatile flavor compounds and fatty acid profiles. Collectively, these findings highlight monk fruit extract not only as a potent, non-caloric sugar substitute, but also as a bioactive additive that enhances the structural, physical, and nutritional qualities of processed functional foods.[6], [13],

3.4 Stevia

Steviol glycosides (E960) are non-nutritive natural sweeteners extracted from the leaves of Stevia rebaudiana Bertoni, a plant species belonging to the Asteraceae family. These glycosides consist of a complex mixture of sweet-tasting compounds, primarily comprising stevioside (5–10%), rebaudioside A (2–5%), rebaudioside C (1%), rebaudiosides D, E, and F (0.2%), and dulcoside A (0.5%). Among these individual constituents, rebaudioside A exhibits the sweetest profile and the cleanest taste, while the combined mixture of steviol glycosides delivers a sweetening power approximately 300 times greater than that of sucrose. Because steviol glycosides contribute negligible caloric energy and do not induce spikes in blood glucose levels, they represent a safe sugar alternative for individuals suffering from diabetes mellitus. Beyond their primary sweetening function, these natural compounds possess valuable pharmacological and nutraceutical properties, including anti-inflammatory, cardiotonic, anti-cancer, anti-hypertensive, and antioxidant activities. Reflecting the rapid rise in global demand for natural zero-calorie ingredients, the stevia market size was estimated at USD 0.84 billion in 2024 and is projected to reach USD 1.36 billion by 2029, expanding at a compound annual growth rate (CAGR) of 10.12% during the forecast period. Driven by these desirable attributes, scientific research has focused extensively on optimizing membrane-based extraction and purification methods such as microfiltration, ultrafiltration, nanofiltration, diafiltration, and their

combined cascades to maximize glycoside recovery yields from green leaves while studying their technological performance across various food and beverage systems.[16], [19]




In bakery products, steviol glycosides have been successfully applied as partial sucrose replacers, enhancing both the nutritional profile and the sensory acceptability of baked matrices. Experimental trials demonstrate that substituting up to 50% of sucrose with stevia in biscuit formulations preserves key physicochemical attributes, including diameter, thickness, spread ratio, mass, volume, bulk density, and structural compression force, while maintaining favorable sensory metrics like color, flavor, texture, and overall consumer acceptability. Similarly, oatmeal cookies formulated by replacing 25% to 50% of refined sugar with stevia extract exhibit desirable aroma profiles, optimal consistency, balanced sweetness, and characteristic crunchiness. However, exceeding this substitution threshold (at 75% and 100% replacement levels) adversely impacts sensory quality, introducing an undesirable bitter or metallic aftertaste, altering crumb appearance, and degrading baked texture due to the loss of sucrose's bulk and caramelization properties.[20], [21]

In dairy and frozen dessert systems, stevia functions as an effective functional sweetening agent that supports the growth of beneficial microorganisms while maintaining structural stability. In low-calorie yogurt preparations, combining stevia with sucralose yields a balanced sweetening system that alters neither the baseline physicochemical properties (such as pH and titratable acidity) nor the growth kinetics of starter probiotic cultures. In frozen desserts, steviol glycosides have been utilized alone or blended with reduced levels of sucrose to formulate functional low-calorie chocolate ice cream. Formulations containing high-purity rebaudioside A (97%) perform comparably to full-sucrose controls across visual appearance, aroma, flavor, melting rate, texture, and overall consumer acceptability. Conversely, in lactose-free chocolate ice cream matrices, the inclusion of stevia requires careful flavor modulation, as the absence of lactose can heighten the perception of lingering bitter off-notes, leading to decreased consumer acceptance scores if not properly balanced with flavor enhancers. [18], [19]

Fruit preserves, jellies, and jams formulated with steviol glycosides offer viable dietary alternatives for health-conscious consumers and individuals managing chronic non-communicable diseases such as obesity, metabolic syndrome, and type 2 diabetes. Sensory studies evaluating stevia-sweetened fruit products including pumpkin, strawberry, and blackberry jams, as well as coconut jelly indicate that partial sucrose replacement maintains the desirable gel structure, texture, spread ability, and overall consumer acceptability without inducing significant syneresis or phase separation. Furthermore, the high thermal and chemical stability of steviol glycosides across a broad pH spectrum ensures that their sweetening efficiency remains uncompromised during high-temperature boiling and pasteurization processes typical of commercial jam production.[16], [17],

The beverage sector represents one of the largest commercial applications for steviol glycosides worldwide. Between 2010 and 2017, over 300 distinct tea-based beverage products featuring stevia were introduced to the global market. In low-calorie iced teas, stevia is now utilized as frequently as artificial alternatives like sucralose. Furthermore, major global beverage manufacturers, including The Coca-Cola Company, have reformulated flagship soft drink lines to incorporate steviol glycosides into their product portfolios, meeting consumer demand for naturally sweetened, zero-calorie carbonated soft drinks, juices, and flavored waters. Overall, steviol glycosides stand out as versatile, clinically safe, and commercially robust non-nutritive natural sweeteners capable of serving as functional sugar substitutes across bakery, dairy, confectionery, and beverage applications.[6], [16], [19], [20], [22], [23]

Extraction of stevia

The optimization of extraction protocols for Stevia rebaudiana Bertoni leaves reveals that both the choice of extraction technique and the solvent composition exert a profound, statistically significant influence on the total extract yield, phytochemical retention,

antioxidant capacity, and broad-spectrum antibacterial efficacy of the resulting bioactive preparations.

When comparing conventional room-temperature agitation via a shaker against thermal extraction using a Soxhlet apparatus across diverse solvent systems encompassing absolute ethanol, 80% aqueous ethanol, 50% aqueous ethanol, and pure distilled water overall gravimetric extract yield is consistently higher under Soxhlet extraction. This occurs because elevated extraction temperatures effectively facilitate plant matrix cell wall disruption and enhance solute diffusion across matching solvent polarities. Across both methodologies, binary hydroethanolic mixtures specifically an 80/20 ethanol-to-water ratio yield the maximum total extract mass, peaking significantly under thermal Soxhlet processing, whereas absolute ethanol results in the lowest recovery gravimetrically. This contrast underscores the critical role of solvent polarity in liberating target solutes from the raw plant matrix.[21]

However, despite the higher quantitative gravimetric yields achieved through thermal Soxhlet extraction, non-thermal room-temperature shaker agitation preserves significantly higher concentrations of thermolabile bioactive phytochemicals by preventing the thermal degradation and oxidation of sensitive structures during prolonged boiling cycles. Consequently, maximum total phenolic content (TPC) and total flavonoid content (TFC) are achieved using the 80% hydroethanolic solvent via shaker extraction, demonstrating substantial increases in TPC over Soxhlet counterparts. Conversely, water-only extracts perform the poorest across both methods, recording the lowest overall TPC and TFC values.[21]

The preservation of these polyphenols and flavonoids directly dictates downstream antioxidant performance, which is rigorously evaluated through 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging, and cupric reducing antioxidant capacity (CUPRAC) assays, where lower effective concentration ($EC_{50}$ or $ECA_{0.50}$) values indicate superior free radical inhibition and electron-donating reducing power. In these evaluations, the 80% aqueous ethanolic shaker extract consistently exhibits superior antioxidant potency, recording the lowest $EC_{50}$ values for DPPH (ranging between 0.41 and 1.04 mg/ml) and ABTS assays, as well as the highest cupric reducing capability via CUPRAC. This performance significantly outperforms all Soxhlet-derived extracts, whose elevated thermal exposure diminishes radical scavenging thresholds. While positive controls such as BHA demonstrate higher baseline antioxidant effects than plant extracts, the strong statistical correlation between total phenolic content and radical scavenging activity confirms that phenolic acids, flavonoids, and associated glycosides function via both hydrogen atom donation and single-electron transfer mechanisms.[21]

Furthermore, these phytochemical profiles directly translate into potent antibacterial properties against both Gram-positive (Staphylococcus aureus and Enterococcus faecalis) and Gram-negative (Escherichia coli and Pseudomonas aeruginosa) foodborne pathogenic strains. Specifically, the 80% aqueous ethanolic extract obtained via shaker agitation exhibits significantly the highest zone of inhibition against all tested bacterial strains at a concentration of 50 mg/ml, outperforming both thermal Soxhlet extracts and pure aqueous or 50% hydroethanolic preparations. Mechanistically, plant polyphenols such as chlorogenic acids and associated flavonoids disrupt bacterial cell walls through the lipophilic interaction of their benzene ring structures and polar hydroxyl functional groups, which readily penetrate microbial membranes, bind to intracellular proteins, and crosslink with essential enzymes to induce cell lysis and mortality.[21]

The superior efficacy of cold shaker extracts compared to hot Soxhlet extracts further supports the conclusion that key antibacterial constituents in Stevia rebaudiana leaves are inherently heat-labile, suffering structural inactivation when subjected to extended high-temperature extraction. Although antibacterial activity operates in a dose-dependent manner with 50% and 80% aqueous ethanolic shaker extracts maintaining high efficacy against S. aureus even at reduced concentrations down to 12.5 mg/ml water-only extracts occasionally demonstrate notable inhibitory zones against S. aureus and E. coli.[21]

Ultimately, advanced chromatographic profiling via HPLC-ESI-Q-TOF-MS confirms that non-thermal shaker extraction using an 80% aqueous ethanol solvent system represents the optimal, most effective industrial protocol for maximizing the recovery of bioactive polyphenols, flavonoids, and steviol glycosides, yielding high-performance natural extracts with exceptional antioxidant and antimicrobial utility

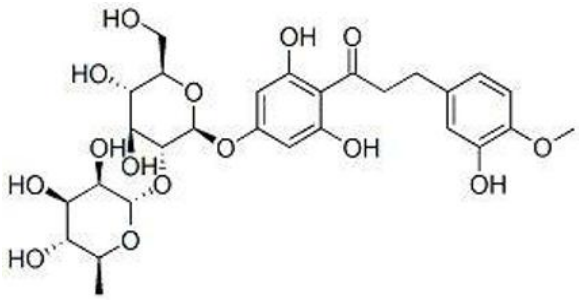
for functional food preservation and pharmaceutical applications.[21]

## IV. SEMI-SYNTHETIC SWEETENER

A separate section is devoted to a semi-synthetic glycoside chalcone, neohesperidin dihydrochalcone (DC), produced by the catalytic hydrogenation under alkaline conditions of neohesperidine from bitter orange (Citrus aurantium) or of naringin obtained from grapefruit [6] Semi-Synthetic and Bulk Sweeteners: Neohesperidin DC, Rare Sugars, and Functional Carbohydrates

### 4.1 Neohesperidin Dihydrochalcone (NHDC, E959)

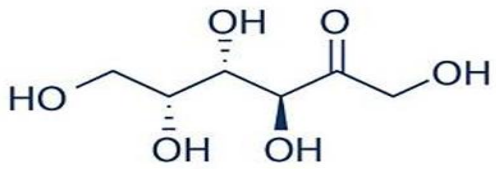
Neohesperidin dihydrochalcone (NHDC, E959) is an intense semi-natural flavonoid glycoside sweetener derived from bitter orange (Citrus aurantium). Driven by expanding applications in functional foods, the global market for NHDC is projected to grow at a compound annual growth rate (CAGR) of 4.6% from 2023 to 2030. Recent pharmacological studies highlight its notable metabolic benefits, including the suppression of triacylglycerol accumulation, lipogenesis, and adipogenesis, alongside the down-regulation of pro-inflammatory cytokines and the inhibition of subcutaneous lipid accumulation. To recover its precursor, neohesperidin, both conventional and modern extraction methods are employed, such as hydrodistillation, Soxhlet extraction, microwave-assisted, supercritical fluid, and ultrasound-assisted extractions.




For industrial food applications, determining the thermal and chemical stability of high-intensity sweeteners during processing and storage is critical. Research confirms that NHDC remains highly stable when incorporated into cultured dairy matrices like yogurt, withstanding both thermal pasteurization and lactic acid fermentation. At the maximum authorized concentration of 50 mg/kg, NHDC does not impair the acidification rate of starter bacteria, maintaining its structural integrity over 6 weeks of refrigerated storage at 3 °C. Furthermore, thermal evaluations demonstrate that NHDC (0.001% w/w) withstands heat treatments of 102–106 °C for 35–40 minutes and retains its sweetening potency over 18 months of room-temperature storage in blackcurrant jam preparations. In citrus juice-based soft drinks (orange, lemon, apple, and pineapple), NHDC (10 mg/L) displays exceptional stability during pasteurization, experiencing a minor concentration loss (-8%) only under extreme acidic conditions (pH 2.0 in lemon beverages). In carbonated lemonade, NHDC (0.1% w/w) remains stable for up to one year at room temperature under light or dark conditions, as well as after 3 months of accelerated thermal storage at 40 °C. [24], [25]

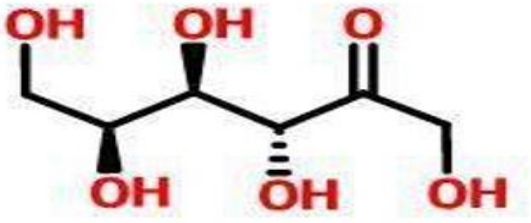
### 4.2 Bulk Sweeteners and D-Tagatose (E963)

Bulk sweeteners, or nutritive sweeteners, comprise sugars and sugar alcohols (polyols). Polyols occur naturally in fruits, vegetables, and fermented foods, or can be synthesized via the catalytic hydrogenation of monosaccharides and disaccharides. Because polyols are incompletely absorbed in the human gastrointestinal tract, they deliver fewer calories and lower glycemic responses than sucrose, making them popular in low-calorie formulations. However, high dietary intakes of sugar alcohols can trigger gastrointestinal discomfort, including flatulence and symptoms associated with irritable bowel syndrome.[6]




Among emerging nutritive alternatives, D-tagatose (E963) is a low-calorie rare ketohexose that occupies a valuable niche due to its anti-diabetic properties and prebiotic effects on beneficial gut microbiota. The global tagatose market is expected to expand at a CAGR of 5.2% from 2023 to 2033. Because natural occurrence is limited, tagatose is manufactured via chemical or enzymatic isomerization of D-galactose. In bakery formulations, complete substitution of

sucrose with tagatose (100 g/500 g dough) in cocoa bean shell biscuits slightly alters physical dimensions (diameter of 6.12 cm vs 6.51 cm for sucrose; thickness of 0.92 cm vs 0.86 cm) and reduces crispness due to its lower solubility, which creates a denser gluten network and limits post-baking crystallization. Nevertheless, partial replacement yields highly favorable results. Blending sucrose and tagatose (25–50%) in cookie dough maintains dough rheology and finished hardness similar to full-sucrose controls while imparting a desirable darker crust color through enhanced Maillard browning and reducing required baking times, offering potential energy savings.[6]




In vanilla-flavored muffins, a 1:1 replacement of sucrose with tagatose preserves core physical parameters including volume, firmness, cohesion, adhesion, and springiness while maintaining high consumer purchase intent. Similarly, low-level additions (1–2%) in cinnamon muffins, lemon cookies, and chocolate cakes render the sweetener sensory-indistinguishable from sucrose in consumer triangle tests. In cultured dairy products, replacing up to 80% of sucrose with tagatose in strawberry yogurt preserves core physicochemical parameters (°Brix, pH, titratable acidity, viscosity, and water-holding capacity). Crucially, 100% tagatose inclusion significantly preserves color brightness ($L^*$ and $b^*$ values) in strawberry yogurt over 28 days of refrigerated storage at 4 °C compared to sucrose controls. In chocolate manufacturing, substituting sucrose with tagatose (47 g/100 g) enhances long-term shelf stability by exerting anti-blooming effects, delivering lower-calorie dark chocolate with superior acceptability, texture, and minimal lingering bitterness compared to stevia-sweetened alternatives.[6]

4.3 D-Allulose

D-Allulose is a rare low-calorie ketohexose monosaccharide that delivers approximately 70% of the sweetness of sucrose with a caloric density of just 0.4 kcal/g. Widely recognized as Generally Recognized as Safe (GRAS) in the United States and exempt from "added sugars" labeling, the global allulose market is projected to grow at a CAGR of 11.7% from 2022 to 2032. Industrially, allulose is produced via enzymatic conversion of fructose derived from starch, whey, or hemicellulosic waste streams. Clinically, allulose regulates key physiological functions, suppressing postprandial blood glucose spikes, improving serum lipid profiles, reducing visceral fat accumulation, and enhancing reactive oxygen species scavenging capacity.

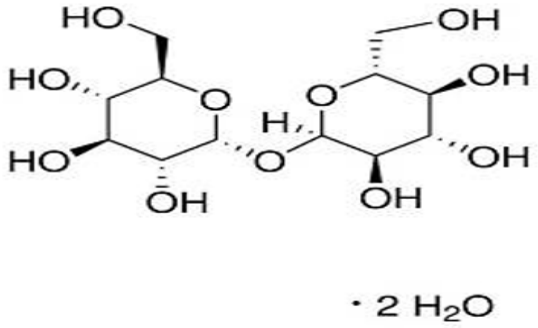
In bakery matrices, allulose participates actively in Maillard browning. In pound cake formulations, increasing allulose substitution elevates the crust browning index, with 25% inclusion achieving overall acceptability scores identical to sucrose controls. In cupcakes, allulose exhibits greater water-holding capacity than sucrose, reducing early moisture evaporation during baking; however, because it does not delay starch gelatinization, it can yield denser crumb structures with higher firmness and lower springiness. In baked meringues, allulose creates finer air bubble microstructures, increasing product crunchiness and boosting total antioxidant activity.

Beyond baking, allulose modifies gelling behaviors in confectionery and savory matrices. Adding 10–30% allulose to starch-based gels reduces retrogradation and extends product shelf life. In heat-induced surimi gelation, allulose significantly enhances gel strength and water-holding capacity compared to sucrose or sorbitol by promoting disulfide and non-disulfide protein crosslinking. In gelatin-based soft candies (10–40% w/w allulose), it retains higher moisture levels, maintaining a softer texture over 28 days of storage. Furthermore, in plant-based dairy, substituting 50% of sucrose with allulose in fermented soy yogurt yields superior consumer preference scores, supports higher lactic acid bacteria counts, and maintains optimal acid profiles.[6]

4.4 Trehalose

Trehalose is a naturally occurring disaccharide composed of two glucose units joined by an $\alpha, 1 \rightarrow 1$-glycosidic linkage, found across plants, fungi, insects, and yeasts. Driven by its widespread adoption as a stabilizing functional food additive, its global market is projected to expand at a CAGR of 5.34% over the 2020–2025 period. Because direct extraction from natural biomass is labor-intensive and low-yielding,

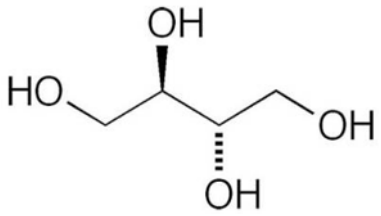
commercial trehalose is manufactured primarily via multi-enzyme biotransformations from starch substrates.



Possessing roughly 50% of the sweetening power of sucrose, trehalose is valued for its unique metabolic and physiological behavior. It induces a significantly lower insulin response than standard mono- and disaccharides by facilitating a slower, more sustained release of glucose into the bloodstream. Beyond its nutritional profile, trehalose functions as a powerful molecular stabilizer, protecting native protein conformations, enzymes, lipids, and complex carbohydrates against thermal denaturation, desiccation, and osmotic stress. In food processing, trehalose is widely utilized at 5% concentrations in confectionery and frozen foods as an effective cryoprotectant. In premium ice cream manufacturing, complete replacement of sucrose with trehalose significantly reduces the melting rate, increases product firmness, and allows for higher extrusion temperatures during frozen processing without compromising structural overrun or mouthfeel.[6]

4.5 Erythritol

Erythritol (E968) is a naturally occurring four-carbon sugar alcohol (polyol) abundant in various fruits (e.g., grapes, melons, and pears), mushrooms, seaweeds, and traditional fermented foods and beverages, including wine, beer, soy sauce, sake, and miso paste. Industrially, erythritol is produced on a large scale through fermentation processes driven by osmophilic yeasts such as Moniliella species or Trichosporonoides megachiliensis as well as select lactic acid bacteria, including Oenococcus oeni, Leuconostoc mesenteroides, and L. sanfranciscencis. As a non-caloric and non-glycemic sweetener, erythritol possesses a unique chemical structure that allows it to pass through the human body without impacting blood glucose or insulin levels, as it is absorbed in the small intestine and excreted unchanged in urine. This clinically safe metabolic profile makes erythritol an ideal sugar surrogate for individuals managing diabetes, obesity, and metabolic disorders, fueling a global market expansion projected to grow at a compound annual growth rate (CAGR) of 6.5% between 2023 and 2030.[26]



In food technology and modern bakery applications, erythritol serves as a prominent structural and functional substitute for refined sucrose, though its distinct physical properties particularly its lower water solubility, high crystallization tendency, and pronounced endothermic cooling effect profoundly influence dough rheology, batter aeration, and final baked texture. In cake formulations, erythritol yields varied structural outcomes depending on the specific batter system. In chiffon cake recipes, replacing sucrose with erythritol at concentrations ranging from 25% to 100% maintains batter specific gravity, baked cake volume, and crumb moisture content while producing a lighter brown crust due to reduced Maillard browning, yielding sensory scores for color, tenderness, and moistness comparable to sucrose controls. Similarly, in angel food cakes, a 50% replacement level optimizes sugar-egg white complex unfolding to achieve peak foam expansion, dense crumb geometry, and favorable post-baking physical parameters, while kinetic digestion models indicate that erythritol incorporation blunts glucose release and supports postprandial glycemic management in vivo. Conversely, in sponge cakes and white layer cakes, full sucrose substitution by erythritol increases egg liquid viscosity, reduces foam stability, lowers cake volume, and increases post-baking hardness (+96.8%), frequently imparting a gritty batter texture and a cooling, slightly bitter throat sensation due to incomplete dissolution during mixing.[27]

In muffin processing, erythritol demonstrates contrasting technological behavior depending on the presence of stabilizing hydrocolloids. Standard comparative trials against other polyols (such as

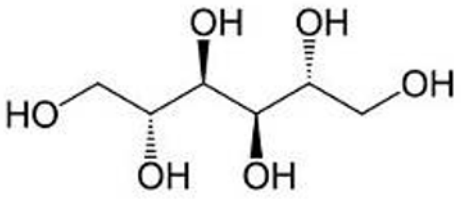
maltitol, sorbitol, and isomalt) often rank erythritol lower in solitary sucrose replacement due to significant shifts in batter rheology and delayed starch gelatinization temperatures during heating. However, when applied to Spanish muffin formulations, erythritol successfully increases batter gas retention, elevating air bubble density and achieving final muffin heights superior to sucrose controls. This structural stabilization occurs because erythritol preserves batter elasticity under heat while raising the thermosetting threshold; further incorporating hydrocolloid thickening agents like xanthan gum fully aligns the dough consistency, volume, and cell structure with conventional sucrose-based muffin standards.[28], [29]

The application of erythritol in cookies, biscuits, and delicate confections highlights both its processing stability and its mechanical limitations. In Danish cookies, erythritol remains chemically stable during high-temperature baking; incorporating up to 50% erythritol maintains baseline moisture, protein, fat, ash content, and structural hardness, matching control levels across flavor, crispness, and overall consumer acceptability metrics. However, in short-dough cookies and hard biscuits, higher replacement ratios can worsen structural fracture behavior, resulting in excessively hard, brittle doughs due to rapid post-baking polyol recrystallization. In contrast, delicate aerated confections show exceptional structural adaptability to erythritol. In sucrose-free macarons, incremental erythritol addition improves batter rheology and dough stability, with higher dosages (60 g) delivering maximum shell volume, improved mechanical resistance, and extended shelf-life. Similarly, in sucrose-free meringues formulated with whey protein isolate (WPI), a 1:1 erythritol-to-WPI ratio stabilizes the liquid foam network, minimizes spreading kinetics during baking, and maintains a uniform, fine-pored aerated crumb structure with enhanced surface smoothness. [21]

In frozen dairy systems, erythritol stands out as an exceptional functional bulk sweetener, providing significant calorie reduction, structural firmness, and low-glycemic properties. In low-GI coconut milk ice cream, replacing 12% sucrose with erythritol (19.51% w/w for sweetness equivalence) yields overall consumer acceptability scores five times higher than control samples, while optimizing serum phase viscoelasticity, overrun, and thermal resistance. In artisanal ice cream processing, replacing sucrose with erythritol reduces total caloric density by 23% to 45%. The lower water solubility and distinct freezing-point depression characteristics of erythritol require slightly longer freezing cycles and higher extrusion temperatures, resulting in an increased initial firmness and a markedly slower, more controlled melting rate due to the slow breakdown of amorphous solid states formed during freezing. Furthermore, in vanilla-flavored ice cream formulations, erythritol increases serum viscosity, lowers meltdown percentages, and enhances overall flavor perception and visual nuance, solidifying its role as a premier functional polyol for low-calorie frozen desserts.[6], [29]

4.6 Mannintol-

Mannitol (E421) and maltitol (E965) are functional sugar alcohols (polyols) widely utilized as alternative bulk sweeteners in health-conscious, low-calorie, and diabetic food formulations. Mannitol is unique as the only non-hygroscopic compound in its class, featuring zero glycemic and insulinemic indices that make it ideal for strict diabetic diets, while occurring naturally in small quantities across pumpkins, celery, carrots, pineapples, and seaweeds. Maltitol, found naturally in chicory, corn, wheat, and potatoes, delivers approximately 90% of the sweetness of sucrose alongside desirable texture-developing properties. Industrially, apart from erythritol, most polyols are produced via the catalytic hydrogenation of reducing sugars, enzymatic conversion, or microbial fermentation, with global market projections for mannitol and maltitol expanding at CAGRs of 7.1% and 6.2%, respectively, through 2033.[6]




In food processing and bakery applications, maltitol consistently demonstrates superior performance as a sucrose surrogate compared to mannitol, particularly in short-dough and sponge cake matrices. In sugar-free biscuit preparations, maltitol-based formulations achieve high flavor and consumer acceptance scores, enhancing product diameter despite inducing greater

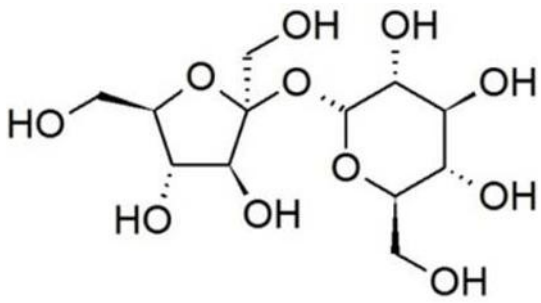
hardness and fragility. In sponge cakes, maltitol closely replicates the rheological properties, volume, crumb softness, and golden color of sucrose controls, whereas mannitol yields dense, poor-quality cakes with low sensory acceptability. However, in confectionery jellies, substituting up to 50% w/w of table sugar with either mannitol or maltitol preserves baseline pH, acidity, soluble solids (°Brix), and sensory consistency, despite slightly elevated syneresis values.[6]

In yeast-leavened dough systems, such as burger buns, incorporating polyols alters both dough rheology and finished baked characteristics. Polyols lower yeast fermentation yields, reducing total dough development (-37% to -81%) and gas release (-62% to -87%), while delaying gluten network formation (+50% to +161%) and reducing extensibility (-14% to -18%). While maltitol maintains standard pasting properties, mannitol requires a higher pasting temperature (+15 °C). High polyol concentrations lead to decreased specific volume (-30% to -48%), harder crumb structures (+135% to +678%), and pale crusts due to diminished Maillard browning; nevertheless, halving table sugar content (50% replacement) with these polyols remains a viable strategy for producing high-quality, reduced-sugar yeast-leavened goods.[6]

## V. NEUTRITIVE SWEETENERS

### 5.1 Honey

Honey is a complex, nutrient-dense natural sweetener produced by honeybees (Apis mellifera) from the nectar of flowering plants or honeydew secretions. Composed predominantly of simple monosaccharides specifically fructose and glucose alongside water, trace proteins, free amino acids, organic acids, vitamins, minerals, and bioactive phytochemicals, honey serves as a rich source of biological antioxidants. The exact chemical composition and therapeutic potency of honey vary significantly depending on its botanical source, geographical origin, climatic conditions, and processing methods. Beyond its traditional use as a dietary sugar substitute, honey has gained extensive scientific recognition in modern functional food research, oncology, and pharmacological science due to its broad spectrum of biological activities, which include antimicrobial, anti-inflammatory, antioxidant, wound-healing, and chemo preventive properties.[30]




Biologically, honey demonstrates potent anti-cancer and chemo preventive efficacy across various in vitro cellular models and in vivo animal studies. A prominent mechanism underlying its anti-tumor activity is the induction of programmed cell death (apoptosis) in malignant cells. For instance, Tualang honey has been shown to activate the mitochondrial apoptotic pathway in breast cancer cell lines, such as MDA-MB-231 and MCF-7, by upregulating the activity of executioner and initiator enzymes, specifically caspase-3/7 and caspase-9, while simultaneously inducing a loss of mitochondrial membrane potential. Furthermore, Tualang honey exhibits a notable synergistic effect when co-administered with conventional chemotherapeutic agents like tamoxifen. This synergy allows for a reduction in the effective dosage of tamoxifen required for tumor suppression, thereby minimizing drug-induced toxicity and adverse side effects in breast cancer management. Long-term in vivo rat models confirm that oral administration of Tualang honey at doses ranging from 0.2 to 2 g/kg over a 150-day period significantly inhibits the development and progression of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumors. In clinical observations involving postmenopausal breast cancer patients receiving daily honey supplementation, measurable alterations in physiological parameters including elevated levels of serum alanine aminotransferase (ALT), creatinine, leukocytes, and platelets have been documented, reflecting systemic metabolic responses.[31], [32]

In addition to breast cancer models, honey exerts marked antiproliferative effects on liver and ascites malignancies. When human hepatoma cells (HepG2) are treated with a 20% honey solution over a 72-hour period, a time- and dose-dependent reduction in cell viability occurs alongside an increase in total cellular antioxidant status and caspase-3 expression. Concurrently, honey treatment decreases the

concentration of radical nitrogen oxide ($NO^{\cdot}$) in culture supernatants. Because reactive nitrogen species can promote hepatic injury through lipid peroxidation and oxidative stress while inhibiting normal apoptotic pathways, the scavenging of $NO^{\cdot}$ by honey antioxidants plays a critical role in halting tumor initiation and promotion. Similarly, coriander honey demonstrates strong chemopreventive capacity in Ehrlich Ascites Carcinoma (EAC) models. In EAC-bearing mice, administration of coriander honey reduces both ascites fluid accumulation and viable tumor cell counts, leading to significant tumor size reduction and prolonged animal survival. This anti-tumor action is directly linked to honey's ability to modulate cellular redox states, as treated models show reduced levels of lipid peroxidation alongside restored concentrations of reduced glutathione (GSH).[33]

The anti-inflammatory activity of honey is another major contributor to its therapeutic versatility. Honey systematically downregulates key serum pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), across various systemic inflammatory conditions and malignancies. In animal models of acute liver injury, honey mitigates hepatocyte necrosis induced by acetaminophen (APAP) by inhibiting TNF-α converting enzyme activity and regulating the balance between pro-inflammatory cytokines and anti-inflammatory mediators like interleukin-10 (IL-10). In gastric ulcer models, honey administration lowers gastric tissue concentrations of IL-1β, IL-6, and TNF-α while elevating protective IL-10 levels. Furthermore, in diabetic models, honey suppresses nuclear factor kappa B (NF-κB) signaling pathways, thereby suppressing circulating levels of TNF-α, IL-6, IL-1β, and transforming growth factor-beta (TGF-β). In neuroinflammatory disease models, honey similarly suppresses central inflammatory markers, protecting neuronal architecture from cytokine-mediated damage.[34]

Distinct honey mono-florals possess specialized bioactivities attributed to unique phytochemical marker compounds. Manuka honey, derived from Leptospermum scoparium, is renowned for its superior wound-healing and tissue-regenerative properties. Manuka honey protects cells against intracellular reactive oxygen species (ROS) accumulation, lipid oxidation, and protein degradation while preserving mitochondrial functionality and stimulating cell proliferation. Mechanistically, it activates the adenosine monophosphate-activated protein kinase (AMPK), nuclear factor erythroid 2-related factor 2 (Nrf2), and antioxidant response element (ARE) pathway. This signaling cascade triggers the transcriptomic upregulation of endogenous antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), enhancing tissue antioxidant defenses and accelerating cutaneous wound closure. Meanwhile, buckwheat honey (Fagopyrum esculentum Moehch) displays exceptionally high phenolic content and total antioxidant capacity, exceeding that of Manuka honey, alongside strong broad-spectrum antibacterial activity against foodborne pathogens.[35]

To isolate and characterize the heat-sensitive polyphenolic compounds responsible for these biological activities, precise extraction protocols must be executed. Because honey consists primarily of dense sugars that interfere with analytical instrumentation, polyphenols must be separated without applying temperatures above 50 °C, as excessive heat triggers thermal degradation of delicate flavonoids and phenolic acids. Standard extraction approaches utilize either liquid-liquid extraction (LLE) with organic solvents such as ethyl acetate, ethanol, or chloroform, or solid-phase extraction (SPE). In SPE protocols, honey is first dissolved in an aqueous hydrochloric acid solution adjusted to pH 2, then passed through octadecyl-grafted ($C_{18}$) or polymeric Amberlite resins to retain phenolic analytes while washing away sugars. The adsorbed polyphenols are subsequently eluted, concentrated to dryness under a vacuum at 40 °C, and reconstituted in methanol or water-methanol mixtures before high-performance liquid chromatography (HPLC) analysis coupled with UV and mass spectrometry detection. Through these sophisticated analytical techniques, the diverse antioxidant and therapeutic constituents of honey continue to be validated for functional food and pharmaceutical development.[3]

5.2 Agave syrup, also widely known as agave nectar or agave sap concentrate, is a prominent natural sweetener that emerged in the commercial food market post-1990 as a popular plant-based and vegan alternative to traditional sweeteners such as refined

sucrose and honey. Produced primarily from Mexican agave species such as Agave tequilana Weber var. Azul (blue agave), Agave salmiana, Agave mapisaga, and Agave atrovirens agave plants thrive in arid and semi-arid environments by utilizing crassulacean acid metabolism (CAM) photosynthesis to adapt to periodic water scarcity. Central and Northern America, particularly Mexico as the recognized center of diversity and origin, boast deep historical roots in agave cultivation and consumption dating back to pre-Columbian times. In contemporary food manufacturing, the growing consumer demand for clean-label, natural ingredients has driven the widespread adoption of agave syrup, though this shift requires rigorous evaluation of its nutritional profile, health implications, industrial applications, and chemical quality parameters.[36], [37]




Obtaining high-quality agave syrup depends fundamentally on harvesting fully matured plants, typically between 6 to 10 years of age, to ensure maximum carbohydrate storage within the core or "piña" of the plant. The commercial conversion of raw agave into syrup follows two distinct processing pathways: traditional sap concentration and industrial fructan hydrolysis. The traditional artisanal method involves collecting the natural plant sap, known as aguamiel or mead, and concentrating it via thermal evaporation. While this technique preserves natural flavors, exposure to high heat exceeding 100 °C alters the sugar composition through thermal degradation and non-enzymatic browning reactions. Conversely, the industrial manufacturing process crushes harvested agave piñas to extract a fructan-rich juice, which is then subjected to partial or total acid or enzymatic hydrolysis at controlled temperatures around 80 °C. Glycosidic enzymes, such as inulinases and β-fructosidases, catalyze the breakdown of complex agavin-type fructans into free monosaccharides, predominantly fructose. Subsequent evaporation at temperatures above 95 °C yields a viscous syrup with total soluble solids ranging from 65 to 84 °Brix, a pH between 3.6 and 5.8, and a moisture content typically between 17% and 30%. To verify product authenticity and prevent economic adulteration with cheaper commercial sweeteners, advanced analytical methods such as high-performance liquid chromatography (HPLC) and proton nuclear magnetic resonance ( $^{1}$H-NMR) spectroscopy are routinely employed.[38]

From a carbohydrate perspective, agave syrup is predominantly composed of simple monosaccharides, with fructose accounting for up to 70% to 88% of its total sugar profile, complemented by smaller quantities of glucose, sucrose, and minor polyols like mannitol and inositol. Historically, high-fructose syrups were favored for diabetic nutrition due to their low glycemic index (GI values between 10 and 19). However, modern clinical research indicates that excessive dietary fructose intake even at moderate levels directs fructose heavily to the liver via GLUT-5 and GLUT-2 transporters, contributing to adverse health outcomes such as gut dysbiosis, hypertriglyceridemia, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), and heightened cardiovascular risk. Furthermore, thermal processing of agave syrup generates reactive dicarbonyl compounds, including glyoxal, diacetyl, and particularly high concentrations of methylglyoxal. These reactive molecules interact with amino acid residues during prolonged storage or heat exposure to form dietary advanced glycation end-products (AGEs) like carboxymethyllysine and carboxymethylcysteine. The consumption of dietary AGEs is linked to disrupted incretin hormone secretion, elevated systemic inflammation, and plasma protein glycosylation. Despite these metabolic and thermal transformation concerns, agave syrup retains a more complex chemical matrix than synthetic high-frequency corn syrup due to the presence of residual unhydrolyzed fructans, essential micronutrients, and functional phytochemicals.[33]

Beyond simple sugars, agave syrup retains valuable secondary metabolites derived from the original plant material. Residual fructans consist of linear and

branched polymers joined by β-2,1 and β-2,6 glycosidic linkages that exhibit prebiotic, antimicrobial, and immunomodulatory properties supporting beneficial gut microbiota, though they may trigger digestive discomfort in sensitive consumers. Additionally, agave syrup contains steroidal saponins, notably magueyoside B and kammogenin tetraglycoside, which demonstrate antioxidant, antimycotic, and anticancer activities in physiological models by reducing cell viability in Caco-2 and HepG2 cancer cell lines. The syrup also features a profile of phenolic compounds predominantly ellagic acid and catechins which contribute to radical scavenging capacity. Furthermore, unrefined and artisanally produced agave syrups retain an impressive array of essential minerals, including significant concentrations of potassium, sodium, calcium, magnesium, and iron, governed by local soil conditions and processing intensity. [38]

In commercial food manufacturing, agave syrup has been successfully integrated into diverse food matrices as a functional sucrose substitute. In bakery products, research demonstrates that agave syrup can replace up to 75% of sucrose in muffins without compromising physical or sensory properties. Similarly, white bread formulations incorporating agave syrup alongside roselle flour exhibit higher dietary fiber, phenolic compounds, anthocyanins, and antioxidant capacity, while granola bars successfully utilize agave syrup to reduce sucrose content by 10% without altering consumer appeal. In beverage applications, agave syrup has been combined with rice syrup, fruit juice, and electrolytes in specialized sports drinks designed for rapid hydration. Within confectionery, the addition of agave syrup and pectin to white-tea candies increase dry matter and browning while improving elasticity and reducing hardness without diminishing antioxidant capacity, and it has served as a base ingredient for functional jellies and low-sugar chocolates. Ultimately, while agave syrup offers valuable technological and sweetening advantages for food reformulation, its overall health impact represents a delicate balance between its favorable low glycemic index and bioactive constituents versus its high concentration of dietary fructose and thermal processing byproducts. [38]

4.3 Maple syrup is a prized natural delicacy and sweetener produced primarily by boiling and concentrating the xylem sap collected from mature maple trees (Acer species), most notably the sugar maple (Acer saccharum Marsh.). Canada stands as the world's largest producer of maple products, responsible for nearly 71% of global production, with the province of Quebec serving as the heart of the industry and housing thousands of dedicated producers.




Recognized as a superior alternative to refined white sugar, maple syrup is valued not only for its distinct, complex flavor profile but also for its nutritional composition, which includes essential minerals and a high concentration of bioactive phenolic compounds possessing demonstrated antioxidant, anti-radical, anti-mutagenic, and anti-cancer properties. Furthermore, compared to other caloric sweeteners such as dextrose, corn syrup, and brown rice syrup, maple syrup elicits lower postprandial glucose and insulin responses, making it a physiologically advantageous sweetener in modern human diets.[39]

The harvesting of maple sap occurs seasonally during late winter and early spring, driven by the natural freeze-thaw cycles that generate internal trunk pressure and cause watery xylem sap to flow. Because the sap typically contains only 2% to 3% sugar, roughly 40 liters of raw sap must be collected and boiled to evaporate excess water and yield a single liter of finished syrup standardized to approximately 66% sugar content (66 °Brix). Beyond its predominant sugar, sucrose, the complex flavor and functional properties of maple syrup arise from a delicate matrix of organic acids, amino acids, oligosaccharides, volatile aromatic compounds, and minerals, alongside naturally occurring microflora from the sap. The chemical composition of the sap varies depending on geographical origin, soil characteristics, and seasonal

progression, with syrup color typically darkening as harvesting advances from early spring to late season.[39]

To protect consumers, ensure fair market competition, and maintain high standards of authenticity, maple syrup quality is strictly regulated and graded by international and national authorities, such as the Canadian Food Inspection Agency (CFIA) and the United States Department of Agriculture (USDA). Regulatory frameworks classify maple syrup based on physical and sensory parameters, particularly color intensity and light transmittance measured at 560 nm. Canadian regulations establish two primary categories Grade A and Processing Grade with Grade A further divided into four distinct color classes: Gold (delicate taste), Amber (rich taste), Dark (strong taste), and Very Dark (robust taste). High-quality Grade A syrups must be free of turbidity, sediment, and uncharacteristic fermentation flavors, maintaining a moisture content strictly below 10% to ensure microbial stability. Interestingly, consumer preferences often lean toward darker syrups, which possess richer, more robust caramel and spicy flavor notes while containing significantly higher concentrations of health-promoting phenolic compounds than lighter grades. Beyond sucrose, maple syrup contains over 250 minor chemical constituents. Its inorganic profile is rich in essential macro- and micro-elements, including calcium, potassium, magnesium, zinc, phosphorus, manganese, sodium, and iron, which are routinely quantified using advanced atomic absorption spectroscopy (AAS) and inductively coupled plasma mass spectrometry (ICP-MS). Its amino acid profile features notable concentrations of D-alanine and other D-amino acids generated during thermal processing via the Maillard reaction, alongside seasonal fluctuations in glutamic acid, histidine, methionine, and asparagine. Carbohydrate profiling utilizing high-performance liquid chromatography (HPLC), hydrophilic interaction chromatography coupled with charged aerosol detection (HILIC-CAD), and capillary electrophoresis reveals a diverse array of oligosaccharides and fructosyl oligosaccharides. Phenolic compounds have garnered intense scientific interest, with more than 100 distinct phenolics identified through nuclear magnetic resonance (NMR) spectroscopy and high-performance liquid chromatography coupled with diode-array detection (HPLC-DAD).[40]

As the commercial value of maple syrup has expanded globally, the economic incentive for food fraud specifically the adulteration of pure maple syrup with inexpensive refined cane or beet sugars has driven the development of advanced analytical authentication tools. Techniques such as infrared (IR) spectroscopy, isotope ratio mass spectrometry (IRMS), and elemental fingerprinting via ICP-MS are increasingly deployed to detect fraudulent blending and verify product purity. Concurrently, ongoing research continues to refine processing technologies to maximize the retention of bioactive compounds, safeguarding the functional integrity of maple syrup as it transitions from a traditional regional delicacy into a globally recognized functional food ingredient.[33], [41]

## VI. MICROENCAPSULATION OF SWEETENERS: TECHNOLOGICAL STRATEGIES AND FOOD APPLICATIONS

Microencapsulation represents a vital technological strategy for overcoming the inherent processing and sensory limitations of natural and high-intensity sweeteners, such as thermo-sensitivity, high hygroscopicity, excessive reactivity, and lingering bitter or licorice aftertastes. By enclosing active sweetening agents within protective wall materials using techniques such as spray drying, coacervation, fluid bed coating, or cyclodextrin inclusion, microencapsulation enhances thermal stability, shields compounds against moisture, masks off-flavors, and improves handling by converting viscous liquids into free-flowing powders. For instance, neohesperidin dihydrochalcone (NHDC) exhibits a lingering aftertaste that can restrict its commercial usage; however, molecular inclusion with β-cyclodextrin (β-CD) or γ-cyclodextrin (γ-CD) significantly suppresses this unwanted aftertaste and optimizes the sweetness onset time, creating a clean sensory profile comparable to sucrose across carbonated beverages, baked goods, dairy products, and confectioneries. Similarly, microencapsulation via fluidized bed systems or polymeric matrices (such as polyvinyl acetate and natural resins) protects the delicate protein structure of thaumatin from thermal denaturation during processing, preserving its sweetness and enabling

controlled release in chewing gums and confections. In the case of glycyrrhizin, complex coacervation using chickpea protein isolate and Persian gum achieves over 90% encapsulation efficiency, successfully masking its characteristic yellowish-brown color and bitter licorice aftertaste in beverage formulations. Conversely, microencapsulation is rarely applied to bulk sweeteners like polyols, as their lower relative sweetness power means that encapsulation could undesirably diminish their bulking and sweetening functionality in food matrices.[6]

## VII. HEPATOPROTECTIVE MECHANISMS AND ORGAN-DEFENSIVE POTENTIAL OF BIOACTIVE NATURAL SWEETENERS

Natural sweeteners and their associated phytochemical constituents extend far beyond simple sweetening roles, demonstrating profound hepatoprotective and organ-defensive properties against various toxic, oxidative, and inflammatory insults. For instance, date palm (Phoenix dactylifera) fruit is exceptionally rich in bioactive polyphenols, flavonoids, and carotenoids that contribute potent free-radical scavenging capacity alongside significant anti-hyperlipidemic activity, which actively helps prevent detrimental fatty liver changes and protects against toxic liver insults. Similarly, glycyrrhizin, a natural triterpene saponin derived from licorice roots (Glycyrrhiza species), exerts marked hepatoprotective and antihepatotoxic efficacy. Oral administration of glycyrrhizin significantly reduces serum total lipids, triglycerides, very-low-density lipoproteins, and key liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and acid phosphatase (ACP), while histopathological evaluations confirm the preservation of normal hepatic cellular architectures without tissue damage at non-toxic therapeutic doses. Furthermore, monk fruit (Siraitia grosvenorii) extract contains cucurbitane-type triterpene glycosides known as mogrosides, which deliver established hepatoprotective, glucose-lowering, and immunomodulatory activities that safeguard metabolic and hepatic health. In apitherapy, honey functions as a therapeutic agent that mitigates hepatocyte necrosis induced by hepatotoxins like acetaminophen (APAP) by suppressing TNF-α converting enzyme activity and regulating the delicate balance between pro-inflammatory cytokines and anti-inflammatory mediators such as interleukin-10. Advanced biomedical investigations have further elucidated these hepatoprotective mechanisms through dedicated toxicological case studies, such as the evaluation of neohesperidin dihydrochalcone (NHDC) an intense semi-natural flavonoid glycoside derived from bitter orange (Citrus aurantium) against Paraquat-induced acute liver injury in murine models. In this experimental framework, severe herbicide intoxication triggered massive oxidative stress, lipid peroxidation, glutathione depletion, and hepatocellular necrosis, accompanied by the activation of nuclear factor-kappa B (NF-κB) inflammatory cascades and mitochondrial-driven intrinsic apoptosis. Remarkably, oral pretreatment with NHDC profoundly mitigated acute hepatotoxicity by reducing serum ALT and AST leakage, preserving normal hepatic histological architecture, scavenging intracellular reactive oxygen species (ROS), and restoring depleted glutathione reserves alongside essential antioxidant enzymes like catalase, glutathione peroxidase, and glutathione-S-transferase. Mechanistically, NHDC exerted its potent anti-inflammatory effects by inhibiting IκBα phosphorylation to block p65 nuclear translocation and downregulate downstream pro-inflammatory mediators including COX-2, iNOS, TNF-α, IL-1β, and IL-6. Concurrently, NHDC suppressed mitochondrial-driven intrinsic apoptosis by restoring Bcl-2 levels, inhibiting Bax activation, and blocking the downstream proteolytic cleavage cascades of initiator caspase-9 and executioner caspase-3, thereby preventing cellular DNA fragmentation. Collectively, these findings establish that natural sweeteners and their semi-synthetic derivatives operate through multi-target pathways involving radical scavenging, anti-inflammatory regulation, and anti-apoptotic signaling to protect hepatic parenchyma from toxic stress.

## VIII. SYNERGISUM EFFECT OF NATURAL SWEETENERS

The synergistic effect of natural sweeteners encompassing nutritive simple sugars such as fructose, glucose, and sucrose, polyhydric alcohols like sorbitol, mannitol, and erythritol, natural high-potency steviol glycosides including stevioside and rebaudioside A, semi-synthetic citrus flavonoids like neohesperidin

dihydrochalcone (NHDC), botanical saponins like glycyrrhizin, and intensely sweet natural proteins such as thaumatin represents a critical phenomenon in modern food science and industrial formulation where the combined sensory sweetness intensity of a multi-component blend significantly surpasses the mathematical sum of its individual constituent components. Mechanistically, this cooperativity is governed by the human heterodimeric sweet taste receptor T1R2/T1R3, a class C G protein-coupled receptor (GPCR) that features distinct, spatially separate ligand-binding domains capable of accommodating structurally diverse molecules simultaneously. Specifically, natural monosaccharides and disaccharides interact primarily with the extracellular Venus Flytrap Modules (VFTMs) located on both the T1R2 and T1R3 subunits; in contrast, natural sweet-tasting proteins like thaumatin engage the Cysteine-Rich Domain (CRD) of T1R3, and flavor-modifying flavonoid derivatives like NHDC dock directly into allosteric pockets within the Transmembrane Domain (TMD) of T1R3. When structurally dissimilar natural sweeteners are combined in precise proportions, they bind concurrently to these non-overlapping orthosteric and allosteric sites, inducing cooperative conformational changes that stabilize the active signaling state of the receptor, lower the activation energy threshold, and amplify intracellular signal transduction cascades. Furthermore, compounds acting upon the TMD, such as NHDC, function as positive allosteric modulators that exponentially enhance the receptor's responsiveness to primary natural sugars or steviol glycosides present in the mixture. Beyond direct molecular receptor-level cooperativity, natural sweetener synergy is profoundly influenced by solution thermodynamics, hydration shell dynamics, and sensory masking mechanisms. Bulk natural sweeteners and polyols dominate the solvent matrix, altering water-structure dynamics and molecular packing in a manner that increases the mobility and diffusion efficiency of high-potency natural molecules toward tongue papillae and receptor binding pockets. Simultaneously, binary and polynary natural sweetener combinations effectively suppress the lingering bitter, metallic, astringent, or licorice-like off-tastes inherently associated with isolated high-potency extracts like rebaudioside-A or glycyrrhizin. By eliminating these sensory off-notes, the central nervous system processes the primary sweet signal without perceptual inhibition, thereby elevating net perceived sweetness. However, the manifestation of natural sweetener synergy is strictly concentration-dependent and bounded by human gustatory physiology; rigorous sensory evaluations utilizing modified isobole analysis demonstrate that synergistic enhancement is most pronounced at lower sucrose-equivalent concentrations (typically around 3% sucrose equivalence), whereas higher solute thresholds (exceeding 7% sucrose equivalence) suffer from receptor site saturation, steric hindrance, and cross-adaptation, causing synergistic yields to plateau, diminish, or give way to simple additivity and suppression. By utilizing modified isobole models (Method III) alongside advanced cell-based calcium mobilization assays and bioelectronic sensors, food scientists can precisely map these concentration-effect curves and optimize multi-component natural sweetener blends. This enables the food industry to formulate low-calorie, clean-label food products that maximize sweetness quality, eliminate undesirable aftertastes, and reduce overall caloric load without compromising consumer acceptability or exceeding established safety and regulatory thresholds.[42], [43]

## IX. EFFECTS OF NATURAL ALTERNATIVE SWEETENERS ON METABOLIC DISEASES

The use of natural alternative sweeteners as functional substitutes for sucrose can be beneficial in preventing and treating metabolic diseases. These sweeteners have been found to have varying effects on body weight, blood glucose, lipid metabolism, and anti-inflammatory pathways. It is important to note that the effects of natural alternative sweeteners may depend on the dose used. In general, natural alternative sweeteners appear to have more positive effects on glucose metabolism, lipid homeostasis, steatosis, and inflammation than sucrose. However, it is important to consider that there are some limitations to the current evidence, such as small sample sizes, short study durations, and a lack of clinical studies. While the available research provides valuable insights from cellular and animal models, the direct impact of these sweeteners on metabolic disease patients and their efficacy in clinical settings remain to be fully explored. The inclusion of well-designed clinical studies is necessary to provide more definitive

evidence and establish the effectiveness of natural alternative sweeteners in managing metabolic diseases. Therefore, further research is needed to fully understand the long-term effects of natural alternative sweeteners on metabolic diseases, including glucose homeostasis, lipid metabolism, and inflammation. Future studies should involve larger sample sizes of individuals with and without obesity or diabetes, and long-term evaluation of the effects of natural alternative sweeteners on metabolic disease. This will provide more robust evidence and contribute to a better understanding of the potential benefits and limitations of natural alternative sweeteners as a substitute for sucrose in the prevention and treatment of metabolic diseases.[44]

## X. APPLICATION OF NATURAL SWEETENERS

The application of natural sweeteners extends far beyond traditional sweetening roles, evolving into dynamic functional ingredients, culinary additions, and green reducing agents in advanced materials science. In the food and beverage sectors, natural alternatives such as maple syrup, agave syrup (AS), stevia, monk fruit (Siraitia grosvenorii), and glycyrrhizic acid provide innovative formulation solutions for creating low-calorie, nutrient-dense products. While pure maple syrup holds a modest market share globally, its unique bioactive profile, distinctive flavor, and functional attributes make it ideal for culinary and commercial uses ranging from classic pancake toppings, marinades, and glazes for root vegetables to specialty items like maple butter, flakes, jellies, and vinegar. Similarly, agave syrup has been successfully integrated into patented functional sports drinks for rapid hydration and electrolyte replenishment, as well as utilized in confectionery products like white-tea candies where incorporation with pectin enhances elasticity, optimizes texture, and reduces hardness without compromising antioxidant capacity. Furthermore, functional oligosaccharides such as galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), and xylo-oligosaccharides (XOS) serve as versatile texturizers, fillers, and prebiotics across infant formulas, dairy products, soups, cereals, snacks, and animal feeds. Beyond culinary matrices, natural high-potency sweeteners and botanical extracts have emerged as powerful green reagents in nanotechnology and materials science. Aqueous extracts of Stevia rebaudiana facilitate the eco-friendly synthesis of barium carbonate nanoparticles for biomedical applications, including cancer therapy. Likewise, natural extracts derived from Siraitia grosvenorii act as efficient reducing agents and stabilizers to synthesize stable silver nanoparticle/nitrogen-doped carbon dot nanocomposites. In a similar green engineering approach, glycyrrhizin is successfully employed to produce well-dispersed, highly stable spherical gold nanoparticles featuring a narrow size distribution and uniform functional coatings. This convergence of sensory reduction, metabolic wellness, and nanomaterial synthesis highlights the multifaceted industrial value of natural sweetening compounds in modern science and manufacturing.[3]

## XI. CONCLUSION

The comprehensive exploration of natural and semi-synthetic sweeteners highlights their immense potential as functional alternatives to refined sucrose, while simultaneously revealing the technical and physiological challenges that remain in modern food formulation. Completely replacing table sugar with natural sweeteners in complex food matrices such as baked goods, dairy, confectionery, and beverages presents ongoing hurdles due to variations in food chemistry, processing conditions, and sensory profiles. To overcome these limitations, current food science increasingly relies on binary and ternary sweetener blends (leveraging synergistic interactions among nutritive sugars, rare polyols, high-potency glycosides, and sweet proteins) alongside advanced microencapsulation technologies to mask off-tastes, enhance thermal and moisture stability, and improve industrial handling. Furthermore, beyond their primary sweetening roles, many natural sweeteners and botanical extracts exhibit profound biological activities, including anti-cancer, anti-inflammatory, antioxidant, antimicrobial, and prebiotic effects mediated through key cellular signaling pathways such as MAPK, PI3K/Akt, NF-κB, and mitochondrial apoptosis.

Despite these promising therapeutic and metabolic attributes, critical research gaps remain regarding human physiological impacts, gastrointestinal tolerance thresholds, and industrial production scalability. While natural compounds like stevia,

maple syrup, honey, agave syrup, and rare sugars offer distinct advantages over artificial sweeteners such as promoting satiety, avoiding carcinogenic risks, and providing essential bioactive phenolics and minerals issues like high dietary fructose loads, microbial fermentation of polyols in the colon, and the need for rigorous human clinical trials require careful navigation. Future research must prioritize elucidating the exact structure-function relationships, bioavailability, and molecular mechanisms of these bioactive ingredients, optimizing enzymatic production pathways, and scaling up sustainable functional applications. Ultimately, bridging these scientific and industrial divides will enable the successful integration of natural sweeteners into mainstream food and pharmaceutical sectors, satisfying consumer demand for clean-label, health-promoting ingredients while advancing global public health.

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