Emerging Low-Calorie Sweeteners in Diabetes Management: A Comprehensive Review of Rare Sugars, Polyols and Natural Compounds Including Stevioside, Rebaudiosides, Mogrosides and Tagatose

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***Abstract*—The increasing incidence of Type 2 Diabetes Mellitus in the world today makes the need to establish better glycemic management approaches to replace the traditional pharmacotherapy. Both functional and natural sweeteners have low glycemic properties and other complementary metabolic effects in a variety of ways. The features of the sweeteners investigated in this detailed review are the molecular characteristics that include the stereochemistry, glycosidic structure and hydrogen bonding patterns that define the physicochemical properties and receptor interactions. We discuss functions of formulations such as viscosity modulation, effects of osmotic pressure and water activity control which affect drug delivery and stability.The review is a critical analysis of the interactions of sweeteners with glucose regulation involving intestinal transporters (SGLT1, GLUT2), sweet taste receptor signaling (TAS1R2/TAS1R3), and gut microbiota pathways that mediate short-chain fatty acid formation and incretin secretion. Such sophisticated formulation techniques as microencapsulation, nanoencapsulation, stimuli-responsive hydrogel and co-delivery system are addressed because of their potential effect to increase bioavailability and therapeutic effectiveness. The translatability of sweetener-based interventions is evidenced by novel dosing systems (e.g., oromucosal systems), 3Dprinted formulations, and functional beverages. The role of biofunctional excipients of polymers, cyclodextrins and mucoadhesive systems in enhancing the solubility of drugs, stability and targeted action is investigated. Clinical data indicate that there are small curious but reproducible impacts of plant-based interventions on glycemic indicators with stevia and monk fruit showing glycemic impartiality. Some of the factors that are considered under safety include microbiome impacts, metabolomics profiling, and regulatory frameworks that focus on product standardization and quality control. Future trends emphasize the adoption of artificial intelligence in the area of sweetener design, customized nutrition strategies, and the increased pharma integration with the use of sophisticated detection methods.**

***Index Terms*—Sweeteners, Diabetes, Stereochemistry, glycemic index**

I. INTRODUCTION

The increase in the prevalence of metabolic diseases such as obesity and type 2 diabetes worldwide has boosted the urgency in developing effective policies to curb the consumption of excess sugar intake because excessive consumption of added sugars is closely linked to insulin resistance, cardiovascular diseases and metabolic imbalances and, as such, reducing sugar intake is a priority area of concern in the context of health policies (Dragomir et al., 2025). Despite the fact that though diabetes mellitus is still a significant health burden worldwide and many patients fail to sustain glycemic control in the longterm despite modern pharmacotherapy (Husak et al., 2026), dietary modification continues to be the cornerstone of prevention and management, but pharmacotherapy has now grown even as many patients struggle to sustain long-term glycemic control because of such factors as adverse effects, weight effects, cost, and adherence issues, the current practice has prompted a focus on individualized, combination therapy that targets glycem The role of sweeteners, such as artificial, natural, and polyolbased sweeteners, in this case is to deliver the sensation of sweetness without any substantial caloric content and their action has demonstrated a range of implications such as the replacement of the taste experience, but their effects are not limited to that, they interact with sensory systems, intestinal nutrient sensing, and systemic metabolic regulation, which, however, are interconnected in a brain-guttaste axis (Juen et al., 2025; Heng and Qiuming, 20 The contributions of sweeteners to this end cannot be completely understood within a single disciplinary framework that focuses on the chemical structure, biochemical processing, receptor signaling and interactions with microbiome; the syntheses that have been done so far, however, have predominantly included either broad groups of medicinal plants or individual agents, at the expense of integrating complementary plant-based approaches to diet and supplementation (Husak et al., 2026), which underscores a real gap in the research that is the focus of the present review.

II. SWEETENER ARCHITECTURE: CHEMICAL ARCHITECTURE OF SWEETENERS.

2.1. Stereochemistry and glycosidic topology

Glycosidic bond cleavages catalyzed by glycoside hydrolases are over 17 orders of magnitude faster, and there are over 180 sequence-defined families of them (Overkleeft et al., 2026). The differences in stereochemistry, especially, the anomeric carbons, affect an enzyme recognition and receptor binding. The sugars that are found naturally have a stereochemical structure that is perfectly digested by the enzyme glycosidases, and many of the artificial sweeteners are engineered to resist enzymatic breakdown, where their contribution to calories is insignificant. There is also stereochemical orientation of the binding affinity with the TAS1R2/TAS1R3 receptor complex (Juen et al., 2025).

2.2. Hydrogen bonding and hydration

Hydrogen bonding is an important factor that determines the solubility of sweeteners, their stability and receptor interaction. Sweet molecules are normally functionally grouped with molecules that can form large hydrogen networks with water and biology large molecules and dictate hydration dynamics and dissolution behavior. At the molecular scale, hydrogen bonding facilitates the recognition of ligands in the sweet taste receptor, and the interactions of sweeteners and amino acid residues in the TAS1R2 binding pocket are mainly promoted by the hydrogen bonding and the electropotential complement (Juen et al., 2025).

2.3 Structure-sweetness-metabolism correlation.

The connection of sweetness with molecular structure is regulated by physicochemical and biological characteristics such as the size of the molecule, its polarity, flexibility, as well as functional group composition.Generally, high-intensity sweeteners undergo structural adjustments that contribute to receptor binding, but not metabolic decay to produce high levels of sweetness with insignificant calories (Dragomir et al., 2025). Metabolic pathways depend on structural differences: digestible carbohydrates are subjected to enzyme hydrolysis, polyols are partially metabolized and artificial sweeteners are usually passed on to the excreta unchanged.

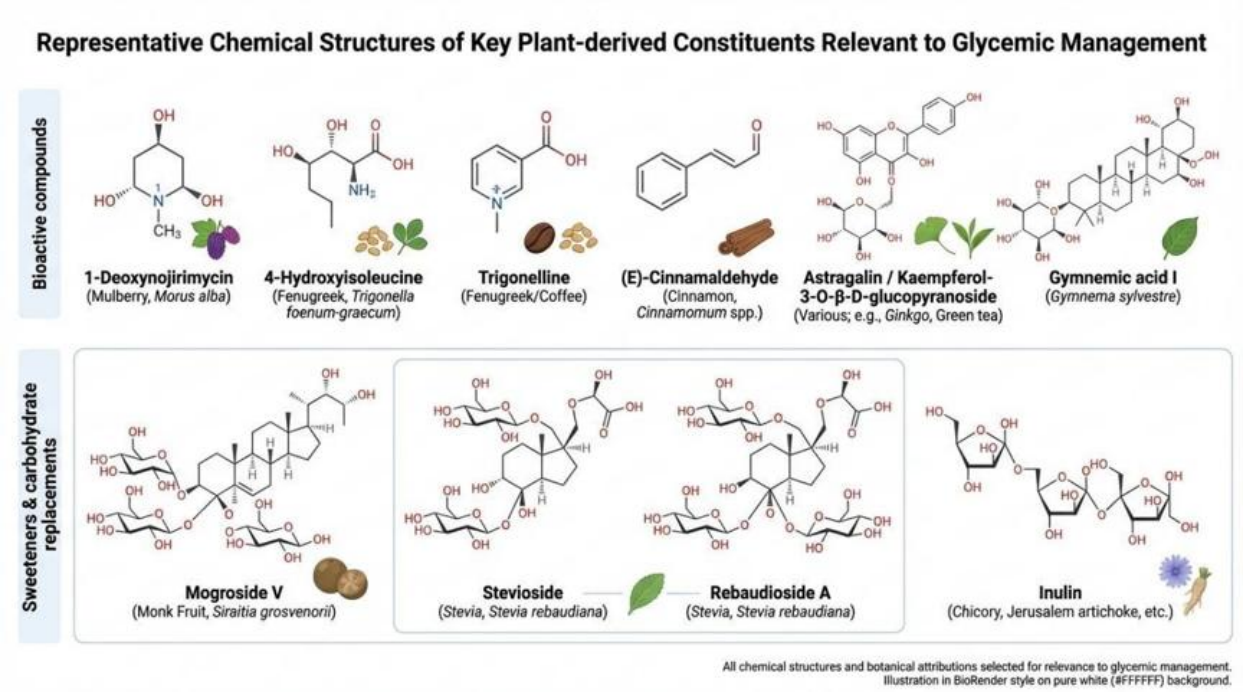

Figure 1: Representative chemical structures of key sweetener constituents

Table 1 Molecular descriptors and physiochemical properties of natural and functional sweetners (Dragomir et al., 2025; Sievenpiper et al., 2025)

Sweetener	Type	Relative Sweetness	Glycemic Index	Key Structural Features
Sucrose	Natural sugar	1×	High (~65)	Disaccharide
Aspartame	Artificial	180–250×	~0	Dipeptide ester
Sucralose	Artificial	600×	0	Chlorinated derivative
Saccharin	Artificial	300–500×	0	Sulfonamide
Stevia (Reb A)	Natural	200–300×	0	Glycoside
Xylitol	Polyol	1×	Low (~7)	Sugar alcohol
Erythritol	Polyol	0.7×	0	Sugar alcohol

III. MOLECULAR MECHANISMS BEYOND GLYCEMIC INDEX

3.1 Transporter interaction (SGLT1, GLUT2)

The environment in which the cells are cultured influences SGLT1 and GLUT2 transporter interactions. The sodium-glucose cotransporter-1 (SGLT-1) is the transporter involved in the transportation of glucose in the small bow using sodium-dependent transport and the release of the GLP-1, which controls the insulin secretion, gastric emptying, and satiety (Heng & Qiuming, 2026). The intestinal sugar sensing is characterized by the taste-receptor signaling in the gut epithelium, which T1R3 and the gustducin regulate SGLT1 expression in reaction to the luminal sugars. A variety of flavonoids may suppress the GLUT2-mediated glucose absorption in experimental models, but it has not been directly proven in humans yet (Husak et al., 2026). Transport of Glucose across the intestine includes the action of SGLT1 and GLUT2 in apical and basolateral membrane respectively. In vivo experiments have demonstrated that absorption rates seem to be higher than the theoretical potential of these transporters so that glucose transport may happen through other pathways, which can include passive processes (BaechLaursen et al., 2025). The block of SGLT1 transport resulted in a 60% reduction in glucose uptake whereas the block of GLUT2 resulted in an 80 percent decrease in glucose uptake. Combined luminal SGLT1 and GLUT2 blockade resulted in glucose absorption of about 30 percent, which could be considered a strong paracellular contribution (Bæch-Laursen et al., 2025).

3.2 Signaling of sweet taste receptors.

The perception of sweetness starts with the stimulation of the TAS1R2/ TAS1R3 heterodimeric GPCR (Juen et al., 2025). Cryo-electron microscopy has shown that the ligands, like sucralose and aspartame, can bind to the Venus flytrap domain of TAS1R2 in a common pocket, which causes changes in conformation, which trigger intracellular signaling pathways. The receptor has a low level of affinity with natural sugars, but it is highly sensitive to artificial sugars, hence their high level of perceived sweetness despite low concentration. Other than receptor binding, the diffusion of sweeteners through the oral mucin layer affects the kinetics of the perception of sweetness. The research on the diffusion of sucrose, erythritol, and stevioside across mucin suggests that the diffusion rate of these sweeteners at pH of 5.0 or 7.0 is relatively quick, and the diffusion is related to the molecular weight of the sweeteners and their reactions with mucin (Li et al., 2025). The results of rheological and QCMD provide evidence to indicate that hydrogen bonding and hydrophobic interactions are significant factors in the binding of mucin and sweetener. A highly pore size when mucin is homogeneous facilitates the diffusion of sweetener through the mucin layer at a pH of 5.0 or 7.0, and at these pH, comparatively weak mucin-sweetener interactions generally contribute to the fast rate of penetration and thus the pleasurable sensation of sweetness is perceived (Li et al., 2025).

3.3 Gut microbiota pathways

Sweeteners also have an impact on the composition and work of gut microbiota, which has an impact on metabolic regulation. High levels of non- nutritive additives in diets have been linked to a change in microbial diversity and activity (Erickson et al., 2025). Gut microbes partially ferment polyols, with the resulting metabolites having effects on the host metabolism, and artificial sweeteners can change microbial composition without much metabolism. Such interactions can influence the glucose tolerance, satiety signaling and systemic inflammatory. The metabolic effects brought by gut microbiota mediate the response of interventions that involve a high-fiber intake. The resistant carbohydrates and nondigestible polysaccharides are transported to the colon and are fermented to yield short-chain fatty acids, including acetate, propionate and butyrate (Husak et al., 2026). The short-chain fatty acids also enhance the secretion of GLP-1 through the free fatty acid receptor, and glucose tolerance in mechanistic systems, as well as being associated with the activation of AMPK and insulin sensitivity at the systemic level. This route is best applicable in inulin-type fructans of Jerusalem artichoke and in viscous and fermentable fructose of fenugreek (Husak et al., 2026).

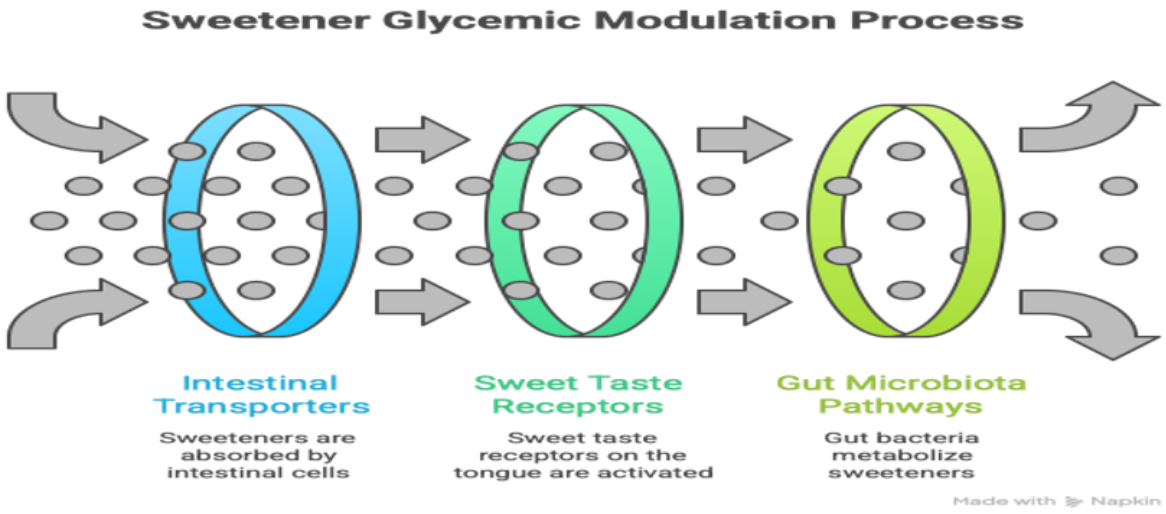

Figure 2. Multi-level mechanisms of glycemic modulation by sweeteners involving intestinal transporters, sweet taste receptors, and gut microbiota pathways

IV. RHEOLOGY/MICROENVIRONMENTAL EFFECTS.

4.1 Viscosity modulation

The viscosity of sugars and polyols increases due to hydrogen bonding and structuring of water, which adds a texture, mouthfeel, and stability to the formulation. Polyols and some natural sweeteners offer volatility and viscosity like sucrose, which are necessary to support the structure of food systems (Dragomir et al., 2025). There are also little direct effects of artificial sweeteners since few people use them but indirect effects on the rheological properties when mixed with bulking agents. Viscous soluble fiber of fenugreek galactomannan also elevates the viscosity of the digesta and restricts the availability of α-glucosidase to carbohydrate substrates at the brush border. This decreases glycolysis of carbohydrates to free glucose and retards the occurrence of glucose in the blood, thus limiting postprandial hyperglycemia (Husak et al., 2026).

4.2 Osmotic pressure effects

Sweeteners affect the osmotic balance because of changes in the concentration of solutes. Sugars and polyols can form high concentrations that provide a high osmotic pressure, which influences the process of cellular hydration, microbial growth, and transport. Osmotic effects find their importance in pharmaceutical preparations to regulate the release of drugs and the maintenance of isotonic conditions. High osmotic pressure may prevent the growth of microbes, which will lack water. Polyols and fermentable fibers are partially fermented by microbes and the resulting metabolites may modify the metabolism of the host. Conversely, not all artificial sweeteners are broken down in the gastrointestinal tract, but they still have access to microbial communities and can modify them and their roles (Husak et al., 2026).

4.3 Water activity

Microbial stability and shelf life are controlled by water activity (aw). Sweeteners especially sugars and polyols suppress microbial growth by interfering with free water molecules, lowering the water activity and increasing the stability of the product. Even though the effect of the artificial sweeteners is minimal with the minimal usage rates, in many cases, they are included in combination with bulk sweeteners, which adjust the water activity jointly.

Table 2. Rheological and microenvironmental effects of sweeteners in pharmaceutical formulations (Dragomir et al., 2025)

Parameter	Effect of Sweeteners	Mechanism	Application
Viscosity	Increased (sugars/polyols)	Hydrogen bonding, water structuring	Syrups, gels
Osmotic Pressure	Increased	Solute concentration	Preservation, drug delivery
Water Activity	Decreased	Water binding	Shelf-life stability
Mouthfeel	Enhanced	Bulk and texture contribution	Food products
Stability	Improved	Reduced Microbial growth	Pharmaceuticals

V. FORMULATION STRATEGIES.

5.1 Encapsulation techniques

Microencapsulation has become a strategic tool of conventional importance to improve the stability and functional activity of sensitive bioactive compounds especially natural antioxidants that are very sensitive to heat, light and oxygen elimination. These ecological sensitivities become a big constraint when it comes to their direct integration into pharmaceutical and nutraceutical systems (Nedjip & Yucegonul, 2025). The use of encapsulation technologies helps to establish a protective barrier around the active compounds and improve the physicochemical stability of the compounds, as well as allow the release profiles to be controlled. The processing methods and good choice of wall materials have a major influence on the overall formulation performance, release kinetics, and efficiency of encapsulation (Nedjip & Yucegonul, 2025). Nanoencapsulation refers to carriers of nanoscale that do not cause the destruction of sensitive nutrients and ensure better absorption due to a higher degree of solubility, controlled release, mucoadhesion, and lymphatic transportation (Hao et al., 2025). Cyclodextrins have inclusion complexes with numerous drug molecules, which have been applied to drugs such as enhancement of dissolution rate, bioavailability and stability. It has been demonstrated that 2 -cyclodextrin can be used in emulsion systems to enhance physical stability via interfacial

complexation with the oil phase, minimizing globule coalescence and increasing storage stability over time. Emulsions made in the laboratory with 1.5% β-cyclodextrin have demonstrated maximum physical stability (Gonugunta et al., 2025).

5.2 Stimuli-responsive systems

Hydrogels are very promising materials, particularly in drug delivery applications due to their biocompatibility, biodegradability, and stimuli-responsiveness (hydrogels have three-dimensional networks of polymers). Their ability to entrap medicinal substances and release them in a controlled, sustained, or targeted way has triggered extensive research and commercial interest. It is worth noting that chitosan-based hydrogels have attracted attention because of their excellent antibacterial, biodegradable, pH-sensitive, and biocompatible characteristics that render them the most suitable in targeted and oral delivery of drugs. The chemically modified chitosan hydrogels can be precisely engineered to achieve drug release kinetics and degradation, and respond to different stimuli, including pH, temperature, light, electric and magnetic fields (Yadav & Mishra, 2026). Thermoresponsible biocompatible gels impregnated with microparticles of poly (lactic-co -glycolic) acid (PLGA) enable regulated release of bioactive chemicals possessing antibacterial properties. Topical administration can be used in wound healing as the gel formulations are thermoresponsive and can be gelated at physiological temperatures (Dahiya et al., n.d.). A topical hydrogel system to treat diabetic foot ulcer has been created using a naringenin-ferulic acid beeswax-based nano constructs as a part of a pH- and temperature-reactive system. Streptozotocin-induced diabetic rats in vivo were shown to have a wound closure rate of 93.2 ± 3.4% after day 15 (Emad et al., 2025).

5.3 Co-delivery systems

Diabetes mellitus is multifactorial, and it has many related complications that necessitate the creation of specific therapeutic approaches, which are not limited to pharmacological treatments. This should take into consideration not only the optimal glycemic control but also the oxidative stress, chronic inflammation, and pancreatic 86 -cell dysfunction (Ababei-Bobu et al., 2026). The design of the nano formulations that are able to encapsulate two or more drugs is especially promising. Contrary to the administration of individual encapsulated drugs, co-encapsulation would allow targeting the same cells or tissue compartment and would lead to coordinated pharmacodynamic effects (Ababei-Bobu et al., 2026). The co-delivery of miR-21-3p antagomir and aflibercept is in a novel light-responsive hydrogel that is based on hyaluronic acid methacryloyl. The hydrogel simply crosslinks in situ when exposed to light, which is characterized by high ocular biocompatibility and duration of drug release of 45 days (Ni et al., 2025).

Table 3. Advanced formulation systems and their functional advantages in glycemic modulation (Nedjip & Yucegonul, 2025)

Encapsulation Method	Key Advantages	Suitable Sweetener Types	Release Profile	Application Focus
Spray drying	High efficiency, scalable	Polyols, natural extracts	Immediate to sustained	Powders, tablets
Lyophilization	Preserves heat-sensitive compounds	Stevia, monk fruit	Controlled	Oral disintegrating forms
Coacervation	High encapsulation efficiency	Polyphenolrich extracts	pH-triggered	Targeted intestinal delivery
Fluidized Bed coating	Uniform particle size	Sugar alcohols	Delayed	Modifiedrelease granules
Interfacial polymerization	Robust barrier properties	Functionalized sweeteners	Stimuliresponsive	Smart delivery systems

VI. NOVEL DOSAGE FORMS

6.1 Oromucosal systems

Intraoral drug delivery system is a promising way of overcoming diverse barriers related to the traditional use of per-oral drug delivery. These delivery systems offer a chance to treat diseases of the oral cavity and other diseases both systemically and locally (Mortazavi et al., 2025). The oral cavity is an easily accessible point of drug delivery, with highly

permeable mucosal tissues, and also, therapeutic agents can be accurately localized. In situ gelling formulations are gelled during contact with the mucosal surface, which allows them to be retained over time and act locally and enhance bioavailability as well as regulate the release of drugs into the body (Prashar et al., 2025). Hydroxypropyl methylcellulose (HPMC), Carbopol and sodium alginate have been studies to provide in situ gelling oromucosal formulations with a desirable viscosity, gelation time and mucoadhesive characteristics. The formulations based on HPMC exhibited the most regulated release profile with an initial burst release that happens in the first hour and a constant release of the drug up to 12 hours (Prashar et al., 2025).

6.2 3D printing

Additive manufacturing (or three-dimensional printing, 3D printing) can be used to create personalized dental delivery systems by additively printing layers of materials based on a computer assisted design system, allowing dose optimization based on patient-specific values such as age, weight, and disease severity (Białek et al., 2025). Several additive manufacturing technologies have been created to be used in pharmaceuticals:

- Fused Deposition Modelling (FDM): It uses thermoplastic materials; cannot use active ingredients that are thermally unstable.
- Stereolithography (SLA): This uses photopolymerization of liquid resins that allow high-resolution structures and no thermal degradation. Semisolid Extrusion (SSE): Extrudes paste-like or gel-based materials under low processing conditions, which is applicable to heat sensitive compounds and soft dosage forms.
- Embedded 3DP (e-3DP): Permits printing of elastomeric reservoir; permits dissociation of API and taste-masking excipients.
- SSE printing has been used to create buccal and mucoadhesive films with antifungal or antiretroviral drugs, the formulations of which exhibit quick disintegration, great mucosal adhesion, and improved drug permeability (Białek et al., 2025).

Antifungal drugs miconazole was printed on buccal films using SSE printer; the time of disintegration was observed to be less than 10 min. Chitosan nanoparticles with dolutegravir prepared by spray drying were printed on buccal films, and the disintegration time was found to be less than 10 min (Bialeck et al., 2025). Gummies and chewable tablets manufactured by SSE or embedded 3DP methods have shown that active ingredients (paracetamol, ranitidine, or metformin) could be incorporated successfully without loss of print fidelity, organoleptic properties and controlled release.

6.3 Functional beverages

Antioxidant-based functional drinks that utilize natural ingredient sources have become a possible dietary intervention approach towards the increasing degenerative disease, such as cardiovascular diseases, atherosclerosis, and diabetes mellitus (Dewi, 2025). Increased health consciousness by consumers has led to attraction towards substitute food products that can be preventative as well as acceptable in terms of their sensory characteristics. Pigeon pea, cinnamon and lime peel formulations of instant tea bags have been studied in terms of their chemical properties and sensorial attributes as functional drinks based on antioxidants. Functional group characterization by FTIR, moisture, pH, sugar content, antioxidant activity, and organoleptic analysis were used as analytical parameters. The findings showed that the moisture content of all formulations was between 6.97% and 8.56, and the analysis of antioxidant capacity revealed that all formulations are very active (Dewi, 2025). The factor of soluble sugars is one of the factors that determine the quality of sweetness in plant-derived beverages. Specific metabolomics applications can be used to systematically measure sugar profiles and their connection to sensory outcomes (Li et al., 2025). In comparative research on six key types of tea, sensory assessment revealed a rating of sweetness as follows; green tea > yellow tea > dark tea > oolong tea > black tea > white tea. The metabolomics profiling revealed 26 metabolites of differences in sugars, with the major contributors being sucrose, inositol, D-fructose, glucose and Darabinitol, which play a major part in distinguishing the sweetness properties.

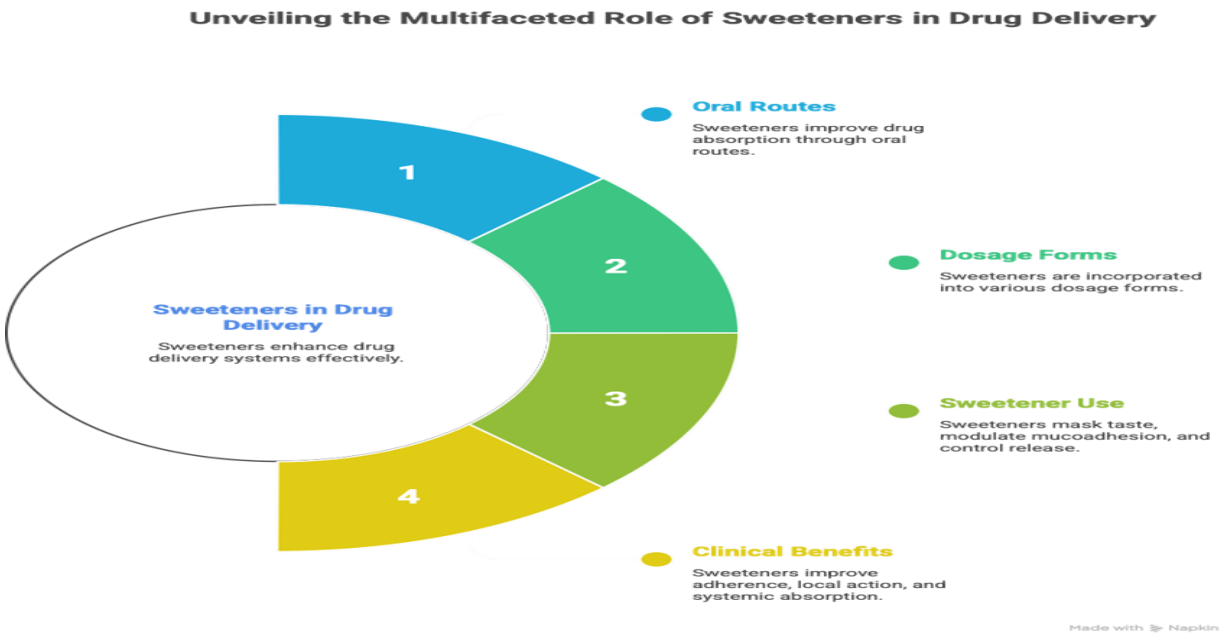

Figure 3. Incorporation of sweeteners into new dosage formats such as oromucosal delivery systems and individualized drug delivery systems. [Schematic illustrating: (1) Oral routes: sublingual, buccal, gingival; (2) Dosage forms: orodispersible tablets, films, gels; (3) Sweetener use: taste masking, mucoadhesion modulation, release control; (4) Clinical: better adherence, local action, systemic absorption.

VII. BIOFUNCTIONAL EXCIPIENT ROLE

7.1 Dual functionality

Pharmaceutical excipients have been developed as simple, chemically, and pharmacologically inert components, to vital functional constituents, which maximize the performance of a formulation (Qelliny et al., 2025). Historically, excipients were considered as substances that possessed sufficient bulk as well as even distribution of content that served to incorporate the active drug ingredient (API) into the formulation. Nonetheless, the technological progress in the pharmaceutical industry has enabled the discovery of excipients that can be utilized in particular functions that are not necessarily related to the volumetric adjustment. Biofunctional is the term used to mean excipients in pharmaceutical preparations that have biological activity or other functional properties outside of their traditional roles (Qelliny et al., 2025). Compared to the conventional excipients, biofunctional excipients play an active role in therapeutic effect or safety of the drug, as opposed to the basic excipients which are usually used to assist in drug production, stabilization of the API, or enhance the drug distribution and absorption.

7.2 Polymer interaction

Biofunctional excipients have been noted to be a number of polymers because of their dual purposes in drug manufacturing and increase in biofunctionality, including drug solubility (Qelliny et al., 2025).

Examples of available polymers are polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), hydroxy propyl methyl cellulose (HPMC), and methacrylate copolymer such as Eudragit polymers. Polyvinyl alcohol (PVA) is a synthetic polymer that is particularly water soluble and depends on the level of its hydrolysis and polymerization (Qelliny et al., 2025). The unusual combination of hydrophilic and hydrophobic groups enables PVA to become microstructured in the form of micelles and this aspect provides the best conditions to solubilize drugs that are poorly soluble. The chitosan is a natural and biocompatible biopolymer derived by the deacetylation of chitin that is frequently utilized to enhance the properties of the nanocarriers because it has high mucoadhesive aptitude and can confer positive surface charge (Ababei-Bobu et al., 2026). Cyclodextrins serve as biofunctional excipients since they establish an inclusion complex with hydrophobic molecules, which leads to a positive effect on the rates

of dissolution, bioavailability, and physical stability (Gonugunta et al., 2025). Polymers as the processed excipients are an important part of the production of parenteral pharmaceuticals, and the effectiveness and safety of the formulations heavily rely on the quality and the functionality of the excipients used (Basu et al., 2025).

7.3 Bioavailability impact

The solubility of drugs is an important factor in the pharmaceutical formulations, specifically in drug delivery through the oral route because the oral bioavailability is primarily determined by the absorption through the gastrointestinal tract (Qelliny et al., 2025). Biopharmaceutics Classification System (BCS) provides a structure which gives correlation between drug absorption and solubility and intestinal permeability. Although Class I compounds are prevalent in commercially available drugs, emerging drug targets exhibit a change in which a large portion of the drug candidates are Class II (high permeability and low solubility). Nanoencapsulation has many complementary methods to enhance the oral bioavailability of bioactive compounds (Hao et al., 2025). The nanoscale dispersion and surface modification are used to increase the solubility of poorly water-soluble nutraceuticals, whereas controlled release profiles are used to provide sustained therapeutic exposure. Mucoadhesive nanocarriers increase the residence time of absorption sites promoting increased uptake across intestinal epithelia.

Table 4. Sweetener–drug interactions and their impact on drug release and bioavailability (Qelliny et al., 2025)

xcipient Class	Examples	Mechanism of Action	Impact on Drug Performance	Application
Functional Polymers	PVA, PVP, PVP-VA	Micelle formation, hydrogen bonding, crystal growth inhibition	Enhanced solubility, reduced variability	ASDs, Hot- melt extrusion
Polyethylene Glycols	PEG (Macrogols)	Reduced solvent	Improved solubilization of	Solubility enhancement
		polarity, hydrophobic interactions	hydrophobic drugs	
Methacrylate Copolymers	Eudragit L, S, E	pH-dependent dissolution, ionizable carboxylic acid content	Controlled release, gastric delivery optimization	Targeted delivery
Cellulose Derivatives	HPMC, HPMCAS	Amphiphilic properties, stabilization of colloidal solution	Supersaturation maintenance, crystallization inhibition	Oral bioavailability
Biosurfactants	SLS, Saponins	Surface tension reduction	Cost-effective solubility enhancement	Limited by safety profile

VIII. CLINICAL OUTCOMES

8.1 Glycemic response

Plant-derived interventions are found to have a modest and heterogeneous clinical effect in glycemic management (Husak et al., 2026). Most reproducible ones are seen in mulberry leaf extracts supplemented with 1-deoxynojirimycin (DNJ) that reliably inhibits post prandial glucose excursions by competitive inhibition of intestinal intestinal 1,5-bisphosphoglucose (1,5-bisphosphoglucose) hydrolases. Reductions in postprandial glucose and insulin are dose-dependent and occur at effective doses of 6 to 18mg DNJ equivalent. In the case of cinnamon (Cinnamomum spp.), meta-analyses suggest that there are small loses in fasting plasma glucose and HbA1c in patients with type 2 diabetes, and that the effects are greater when the dose is higher, which is above 2 g/day (Husak et al., 2026). Randomized trials on the use of fenugreek (Trigonella foenum-graecum) supplementation show an increase in fasting glucose, postprandial glucose, HbA1c, and lipid parameters are modified. Meta-analyses of randomized trials have identified significant decreases in fasting blood glucose, postprandial glucose and glycated hemoglobin with gymnema sylvestre supplementation. Monk fruit mogrosides and steviol glycosides are the most promising options since they are glycemically neutral and can be used to decrease the glycemic load in the diet without undermining the palatability (Husak et al., 2026). Sources of inulin type fructans e.g. Jerusalem artichoke, have small-to-moderate effects with long-term use, but could be limited by gastrointestinal tolerability of higher doses.

8.2 Hormonal effects

A number of plant compounds affect incretin signaling and insulin secretion in a glucose-dependent manner. The 4-hydroxyisoleucine derived through the process of fenugreek promotes insulin secretion when glucose concentrations are high in the presence of the insulinotropic agent, and does not cause hypoglycemia in normoglycemic preclinical models (Husak et al., 2026). Experimental evidence has implicated steviol glycosides as glucose-dependent insulinotropic signals through TRPM5 channel potentiation of β-cells. The nutrient-sensing role of sweet-taste receptors expressed on enteroendocrine cells forms a mechanistic framework of subtle incretin effects of certain sweet tasting plant compounds (Husak et al., 2026). Nevertheless, transporter modulation or incretin enhancement in humans has yet to be directly confirmed with most botanicals and such mechanisms are to be viewed as facilitating and not driving clinical effectuality's.

8.3 Long-term outcomes

One of the major limitations in the existing evidence base is the lack of long-term randomized trials on standard preparations and permanent endpoints, including glycated hemoglobin (Husak et al., 2026). Numerous clinical investigations are focused on short-term fasting or postprandial reactions instead of long-term glycemic regulation and heterogeneity between products makes it challenging to compare cross-studies. When it comes to safety concerns, such as possible interaction with hypoglycemic drugs and gastrointestinal tolerance at higher doses, such trials are not consistently reported (Husak et al., 2026). Therefore, interventions that can be derived out of the plants can most effectively be used as a supplement in personalized, evidence-based glycemic management and not as a substitute to known pharmacotherapy.

Table 5. Clinical evidence on glycemic and metabolic outcomes of functional sweeteners and plantderived botanicals (Husak et al., 2026)

Intervention	Primary Mechanism	Glycemic Outcome	Evidence Strength	Key Considerations
Mulberry leaf (DNJ)	α-glucosidase inhibition	↓ Postprandial glucose	Moderate (acute trials)	Dose dependent; minimal side effects
Cinnamon	Enzyme inhibition, PI3K-AKT modulation	↓ Fasting glucose, ↓ HbA1c (≥2 g/day)	Moderate (meta-analyses)	Species variability; dose dependent
Fenugreek	Fiber viscosity, 4OH-Ile insulinotropic	↓ Fasting/postprandial glucose, ↓ HbA1c	Moderate (RCTs)	GI tolerability at high doses
Gymnema	Sweet receptor modulation, α-glucosidase inhibition	↓ Fasting/postprandial glucose, ↓ HbA1c	Moderate (meta-analyses)	Standardization of gymnemic acids
Stevia (Reb A)	Sucrose substitution, TRPM5 modulation	Glycemically neutral	Strong (acute substitution trials)	Aftertaste; formulation challenges
Monk fruit (mogrosides)	Sucrose substitution	Glycemically neutral	Moderate (acute trials)	Limited Longterm data
Inulin-type fructans	Microbiota fermentation, SCFA production	Small-moderate ↓ fasting glucose	Moderate (sustained intake)	GI tolerability limits dose

IX. SAFETY AND REGULATION

9.1 Metabolomics

Sweetness quality is a major issue in functional foods and beverages produced by plants, and soluble sugars are one of the determinants. Specific metabolomics methods allow evaluating sugar profiles and their connection to sensory effects in a systematic way (Li et al., 2025). Sensory assessment and electronic tongue analysis relative to comparison of six prominent types of tea made of the same cultivar revealed that green tea was rated higher than yellow tea as far as sweetness was concerned followed by dark tea, oolong tea, black tea, and white tea. Metabolomics profiling was found to profile 26 different sugar metabolites, with the major players being sucrose, inositol, d fructose, glucose, and d arabinitol to differentiate the sweetness attributes between the tea varieties.

9.2 Microbiome effects

Artificial sweeteners and some compounds of plant origin are non-nutritive components of diet that affect the composition and activity of gut microbiota (Husak et al., 2026). Polyols and fermentable fibers are partially fermented by microbes to generate metabolites with the potential to modulate host metabolic processes, whereas other artificial sweeteners can remodel microbial composition with little metabolism. Such communications can influence the process of glucose metabolism, inflammatory, and the general health of the metabolism.

9.3 Regulatory issues

Plant-derived interventions were limited to clinical practice because of heterogeneity in plant species and chemotypes, extraction and processing, product standardization, dosing, trial duration, and outcome selection (Husak et al., 2026). The issue of safety such as possible interactions with glucoselowering drugs are also not consistently provided in the same level of reporting. In turn, the regulatory guidance is based on individualized use in evidence-based frameworks, and it refers to the quality of products, the standardization of their constituents, and the observance of adverse effects or interactions of drugs. Licensing authorities believe that the accepted sweeteners are safe under the acceptable daily intake, but there is new evidence that they may be linked to changes in metabolism (Dragomir et al., 2025). The idea of the variability in the personal responses due to the genetic and microbiome composition, and dietary context is to emphasize that personalized nutrition approaches are necessary.

Table 6. Safety profile, acceptable daily intake, and regulatory status of major sweeteners (Dragomir et al., 2025; Sievenpiper et al., 2025)

Sweetener	Regulatory Status	Safety Considerations	Metabolic Concerns
Artificial Sweeteners	Generally Recognized as Safe (GRAS) within ADI	Potential metabolic alterations debated	Microbiome interaction debated
Natural Sweeteners	Generally Recognized as Safe (GRAS)	Generally, well tolerated	Minimal metabolism
Polyols	Generally Recognized as Safe (GRAS)	GI tolerance at high doses	Partial fermentation

X. FUTURE DIRECTIONS

10.1 Smart sweeteners

New directions in nanoencapsulation are co-encapsulation of synergistic ingredients and customized nutrition methods based on a specific metabolic profile (Hao et al., 2025). Co-encapsulation approaches allow the delivery of sweeteners in parallel with other bioactive compounds that are complementary like antioxidants or anti-inflammatory agents in the same delivery medium.

10.2 AI design

The rising consumer trend of healthier and sustainable sugars alternatives to the traditional sugars has sparked a lot of innovation in designing the artificial sugars (Xie et al., 2025). Artificial intelligence has proven to be a revolutionary research and development resource in developing new sweeteners and heavily a multidimensional approach to the overlap between computational procedures and sweetener development. AI uses in the discovery of sweeteners may be viewed as spanning the wide range of virtual screening, in particular, the structural description of the sweet taste receptor. Molecular dynamics simulation and structure-based virtual screening synergy is also one of the major strategies that can be used to enhance the efficiency and accuracy of the identification of the potential sweetener. Moreover, the application of AI has the potential to forecast the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles of sweeteners, which is an essential factor in gaining a complete understanding of their pharmacokinetic response as well as their safety margins.

10.3 Personalized systems

The genetic makeup, microbiomes and dietary contexts of individual responses to sweeteners vary, which explains why people require personalized nutrition (Sievenpiper et al., 2025). One is to be careful not to generalize that all sweeteners will behave in a similar fashion because they differ in their chemical makeup and may have dissimilar consequences on satiety signalling, gut microbiota, and metabolic results.

10.4 Pharma integration

The further development of the sweetener detecting technology is necessary to be applied in the food industry and the quality and safety of the products are to be ensured (Cheng et al., 2026). Combining strong methods of analysis with formation science will assist in the creation of the next generation of sweeteners concurrently balancing sensory sensation and metabolic safety.

XI. CONCLUSION

The sweeteners are a complex and dynamic interaction of the science of nutrition, biology, chemistry and even pharmaceutical science that are spreading their effects much further than mere taste perception to the regulation of metabolism, the diet of the gut microbiota, the general effects of systemic inflammatory reactions, and the health outcomes. The varying interaction with sweet taste receptors (TAS1R2/TAS1R3), intestinal transporters of glucose (SGLT1, GLUT2), and metabolism that finally defines their glycemic effect and therapeutic capacity is determined by the molecular architecture of sweeteners, which is regulated by stereochemistry, hydrogen bonding networks, and glycosidic topology. Natural sweeteners, including steviol glycosides and mogrosides, polyols, including erythritol and xylitol, are glycemic neutral, and have structural and functional properties that are needed in pharmaceutical preparations. Plant-derived bioactive compounds such as 1deoxynojirimycin of mulberry, 4-hydroxyisoleucine of fenugreek and gymnemic acids of Gymnema sylvestre exhibit multidiverse activity including the inhibition of 1-deoxynojirimycin, insulinotropic actions, as well as the signaling of sweet taste receptors. Combined with novel and advanced delivery technologies, including nano encapsulated formulations, stimuli-responsive hydrogels, and 3D-printed dosage forms, these compounds are suggested to have a higher bioavailability, selective delivery kinetics, and better patient compliance. Clinical evidence, though showing a relatively small and disparate effects, indicates the reproducible benefits of particular plant-derived interventions. The evidence base is, however, limited by the heterogeneity in standardizing the product, the mode of extraction, the length of trials and the choice of outcomes thereby necessitating the research of longterm randomized controlled trials with standard preparations and lasting outcomes. The safety factors include possible changes in metabolism, intestinal microbiome, gut gastrointestinal tolerability at high doses, and potential drug-nutrient interactions with glucose-lowering drugs. Regulatory measures focus on personal use as part of evidence-based practices, whereby the focus is placed on product quality, standardization of constituents, and checking of adverse effects. Future studies should focus on clarifying interindividual differences in sweetener responses in the context of genetic polymorphisms, microbiome composition, and dietary conditions; understanding long-term metabolic outcome by metabolomics and metagenomics techniques; building customized nutrition plans that incorporate genetic, epigenetic, and microbiome data; enhancing artificial intelligence tools to screen and predict ADMET effects; and designing smart sweeteners with co-encapsulated synergistic bioactives to exert multifunctional therapeutic effects. The integration of nanotechnology, biotechnology and computational sciences into nutritional and pharmaceutical studies make functional sweeteners central figures in the development of precision medicine in the management of diabetes.

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