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Herbal Modulators of the Human Sweet-Taste Receptor (TAS1R2 / TAS1R3)

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Abstract

The human sweet-taste receptor (STR), a heterodimer of the class-C GPCR subunits TAS1R2 (Taste Receptor Type 1 Member 2) and TAS1R3 (Taste Receptor Type 1 Member 3), is the pivotal molecular sensor of dietary sugars and an emerging metabolic regulator in extra-oral tissues. A striking

proportion of STR ligands originate from plants, encompassing diterpene glycosides (steviol glycosides), cucurbitane triterpenoids (mogrosides), triterpenoid saponins (gymnemic acids), flavanone derivatives (neohesperidin dihydrochalcone, eriodictyol), and intensely sweet proteins (thaumatin, brazzein, miraculin, curculin). These "herbal" molecules do far more than replace sucrose: they can act as full agonists, positive allosteric modulators, biased agonists, or competitive antagonists, thereby reshaping STR-mediated pathways that control incretin release, insulin secretion, and appetite. This review maps the chemistry, binding topography, and signalling bias of major botanical STR modulators; evaluates pre-clinical and clinical evidence for their metabolic effects; and discusses formulation tactics that exploit sweet-enhancing synergy or mitigate off-tastes. Safety and regulatory statuses are summarised, highlighting generally recognised as safe (GRAS) approvals for steviol glycosides, monk-fruit extracts, and recombinant sweet proteins, alongside the hypertensive risk of glycyrrhizin and the sweet-suppression utility of gymnemic acids. Analytical toolkits—including LC-MS/MS quantification, cell-based calcium assays, and human psychophysics—are outlined for rigorous characterisation.

Finally, the review identifies key knowledge gaps: the need for high-resolution STR–herbal co-structures, development of gut-restricted allosteric modulators, clarification of microbiome interactions, and precision-nutrition strategies that accommodate TAS1R polymorphisms. Collectively, botanical STR modulators represent a versatile pharmaco-nutritional arsenal with the potential to curb caloric sugar intake and ameliorate metabolic disease, provided that forthcoming research translates their promise into clinically validated interventions.

Keywords: Sweet-taste receptor; TAS1R2/TAS1R3; steviol glycosides; mogrosides; positive allosteric modulators; gymnemic acids; sweet proteins; biased agonism; incretin secretion; metabolic health

1 Introduction

Plants have supplied humankind with sweetness for millennia, from cane sugar to maple syrup. 21st-century nutrition, however, is dominated by the need to lower caloric sugar intake without sacrificing palatability and to find novel metabolic therapeutics for obesity and diabetes. The class-C G-protein–coupled sweet-taste receptor (STR), a TAS1R2/TAS1R3 heterodimer, is the molecular gatekeeper of sweet perception in the tongue and an increasingly appreciated metabolic modulator in gut, pancreas, adipose tissue, and bone.

A remarkably large fraction of STR ligands is *botanical* in origin: diterpene glycosides from *Stevia rebaudiana*, cucurbitane triterpenoids from monk fruit, flavanone derivatives from citrus, triterpenoid saponins from *Gymnema sylvestre*, and a whole family of intensely sweet plant proteins. Beyond acting as simple sugar substitutes, these "herbals" can function as positive allosteric modulators (PAMs), biased agonists, or competitive antagonists of the STR, with downstream consequences for insulin secretion, incretin release, and appetite regulation.

This review surveys the landscape of herbal STR modulators, integrating chemistry, receptor

pharmacology, metabolic physiology, formulation technology, safety, and future research priorities.

2 The Sweet-Taste Receptor in Brief

1. Structure. Each subunit possesses an extracellular Venus Flytrap Domain (VFD), a Cys-rich hinge, and a 7-transmembrane (7TM) bundle.
2. Ligand map. Sugars and many plant glycosides bind in the TAS1R2 VFD; small hydrophobic ligands (e.g., some flavanones) and PAMs often target the TAS1R3 7TM cavity.
3. Signalling bias. STR can couple to Gα_gustducin, Gα_s, Gα_q/11, or even Gα_i, permitting pathway-selective drug design.
4. Extraoral roles. In enteroendocrine L-cells it boosts GLP-1; in β-cells it potentiates insulin; in adipocytes it may influence lipogenesis.

Understanding where an herbal ligand binds and which pathway it favours is essential to predicting both taste and systemic outcomes.

3 Botanically-Derived Sweet Agonists

3.1 Steviol Glycosides (Stevia rebaudiana Bertoni)

Feature	Details
Chemical class	Ent-kaurene diterpene diglycosides
Major species	Stevioside, Rebaudioside A–M (Reb A most abundant)
Potency	200–400 × sucrose (threshold ≈ 40 μM)
Binding site	VFD (TAS1R2) + auxiliary contacts in 7TM
Metabolic notes	Glucose-independent insulinotropic effect; possible AMPK activation

Stevia extracts are standardized to ≥ 95 % steviol glycosides and are globally approved as food additives. Rebs D and M offer superior sensory profiles (less licorice after-taste) but are low-abundance compounds often manufactured by enzymatic glycosylation or fermentation.

3.2 Mogrosides (Siraitia grosvenorii, “monk fruit”)

Cucurbitane triterpene glycosides (mogroside V, VI, etc.) deliver 150–250-fold sweetness with a clean taste and serve both as agonists and weak PAMs for sucrose. Animal studies indicate reduced fasting glucose and improved hepatic antioxidant status after chronic administration.

3.3 Glycyrrhizin (Glycyrrhiza glabra, licorice root)

An oleanane triterpenoid diglucuronide, glycyrrhizin is ≈ 50-fold sweeter than sucrose but exhibits a pronounced bitter/liquorice note due to simultaneous activation of the TAS2R14 bitter receptor. Metabolically, chronic excess can cause pseudo-aldosteronism via 11β-HSD2 inhibition; thus formulation levels are limited.

3.4 Phyllodulcin (Hydrangea macrophylla var. thunbergii)

A dihydroisocoumarin with ~400× sweetness, phyllodulcin is stable at high temperatures and low pH, making it attractive for beverages. Molecular docking and mutagenesis point to an inter-domain (VFD/CRD) pocket unique to small phenolic agonists.

3.5 Neohesperidin Dihydrochalcone (NHDC) – citrus flavanone derivative

NHDC is produced by catalytic hydrogenation of bitter neohesperidin from *Citrus aurantium* peels. It:

- Tastes 500–1 600× sweeter than sucrose.
- Acts as both an agonist (low micromolar) and a potent PAM—raising the EC_{50} of sucrose, sucralose, or stevia by 5–15-fold.
- Binds deeply in the TAS1R3 7TM cavity (Servant et al., 2020).

3.6 Natural Sweet Proteins

Protein	Botanical source	Sweetness vs. sucrose	Pharmacology
Thaumatin	*Thaumatococcus daniellii* (West African katemfe)	3 000× (threshold 50 nM)	Orthosteric VFD agonist; large interface
Brazzein	*Pentadiplandra brazzeana* (Oubli berry)	500–2 000×	Heat-stable, pH-stable
Miraculin	*Synsepalum dulcificum* (Miracle berry)	Taste-modifying; turns sour into sweet	pH-dependent PAM/agonist that requires acidic condition
Curculin	*Curculigo latifolia*	~550× + taste-modifier	Dual agonist/PAM

Recombinant expression in *E. coli*, *Pichia pastoris*, or plant cell cultures is solving supply constraints, and the proteins' low caloric contribution (< 4 kcal · g^{-1}) makes them promising for clean-label sugar reduction.

4 Botanical STR Antagonists and Sweet-Suppression Agents

4.1 Gymnemic Acids (*Gymnema sylvestre*, "gurmar")

These dammarane-type triterpenoid saponins competitively block sucrose and stevia binding sites, abolishing sweet perception for up to 60 min when applied lingually. Mechanistically they interact with aromatic residues (F562, W566) at the entrance of the TAS1R2 VFD, preventing "clamshell" closure.

Clinical pilot studies show:

- Acute reduction in sugary snack consumption post-lozenge.
- Modest post-prandial glucose blunting in type-2 diabetics.

4.2 Gurmarin

A 35-mer peptide also from *Gymnema*, gurmarin selectively inhibits rodent but not human STR—an instructive example of species divergence.

4.3 Miscellaneous Herbal Inhibitors

1. Ziziphin (triterpene saponin from *Ziziphus jujuba*) – transient sweet suppression.
2. Hodulcin (isocoumarin glycoside from *Hydrangea*) – partial antagonist/agonist depending on concentration.

Such agents are being explored as behavioral aids in sugar-reduction programs.

5 Herbal Positive Allosteric Modulators & Synergists

Beyond NHDC, several plant flavanones and chalcones increase the apparent sweetness of sugars by 20–50 %.

Compound	Source plant	Structural motif	PAM effect
Eriodictyol	*Eriodictyon californicum* (yerba santa)	Flavanone O-glycoside	3–5× sucrose potentiation
Homoeriodictyol	same	7-methoxy flavanone	Masking of bitter & salt tastes, minor STR potentiation
Hesperetin derivatives	*Citrus* spp.	Di-hydroxy flavanone	Mild PAM

These molecules bind within or adjacent to the 7TM sodium pocket; their relatively low intrinsic sweetness mitigates calorie concerns while enabling flavour-house "sweetness enhancers."

6 Metabolic Consequences of Herbal STR Modulation

6.1 Gut Incretin Axis

- Steviol glycosides and mogrosides administered intraluminally elevate GLP-1 secretion in mouse enteroid cultures by 1.5–3-fold (Kyriazis et al., 2014).
- Sweet proteins, due to their macromolecular size, have limited intestinal permeability and mainly act luminally, still adequate to stimulate L-cell STRs.

6.2 Pancreatic β-Cell Insulin Secretion

Isolated human islets express STR mRNA and respond to 10 μM Rebaudioside A with a 40 % amplification of glucose-stimulated insulin secretion (GSIS). Stevia's insulinotropic effect is preserved in GLUT2-knockout mice, indicating a receptor-rather-than-transporter mechanism.

6.3 Energy Intake and Satiety

Clinical trials:

- A 290 kcal reduction in ad-libitum lunch observed in healthy volunteers after a pre-load beverage sweetened with 12 mg steviol glycosides relative to sugar control.
- Gymnemic acid lozenges lowered ice-cream consumption by 23 % compared with placebo (n = 60, crossover design).

6.4 Cardio-Metabolic Biomarkers

Meta-analyses suggest small but significant reductions in HbA1c (-0.24 %) and systolic blood pressure (-4 mmHg) after chronic stevia use; monk-fruit data remain preliminary.

7 Safety, Toxicology, and Regulatory Status

Herbal agent	Acceptable Daily Intake (ADI)	Key safety notes
Steviol	0–4 mg kg^{-1} d^{-1} (as steviol	No genotoxicity; caution in hypotensive

Herbal agent	Acceptable Daily Intake (ADI)	Key safety notes
glycosides	equivalents)	therapy
Mogroside V	0–2 mg kg^{-1} d^{-1} (provisional)	Limited reproductive tox data
NHDC	0–5 mg kg^{-1} d^{-1}	Mild GI discomfort at high doses
Glycyrrhizin	0.2 mg kg^{-1} d^{-1} (EU)	Risk of hypertension, hypokalemia
Gymnemic acids	No ADI; GRAS for oral care	Limited systemic exposure

Sweet proteins are regarded as *generally recognized as safe* (GRAS) when produced under good manufacturing practice, but allergenicity assessments are mandatory for recombinant sources.

8 Analytical & Bioassay Toolkits

1. HPLC-MS/MS with multiple reaction monitoring (MRM) for quantifying multi-glycoside stevia extracts.
2. Fluo-4 or G-CaMP calcium imaging in TAS1R2/3-transfected HEK293 cells permits rapid potency ranking.
3. NanoBiT G-protein recruitment assays dissect bias toward Gα_s vs. Gα_q.
4. Human psychophysics panels (ASTM E679 ascending concentration) remain the gold standard for sweetness equivalence factors.

9 Formulation Considerations

• After-taste masking. Blends of Rebs M + NHDC attenuate Stevia's metallic notes.
• Synergy rules. Sub-additive interactions occur between stevia and mogroside, whereas additive or supra-additive synergy can be engineered with PAMs such as eriodictyol.
• Thermal stability. Sweet proteins denature > 80 °C; encapsulation in pullulan/trehalose matrices extends shelf-life in baked goods.
• pH-dependent behaviour. Miraculin requires pH < 6 to exert taste-modifying activity; beverage formulators exploit this with citric acid buffering.

10 Research Gaps & Future Directions

1. High-resolution structures of STR bound to steviol glycosides and mogroside V are lacking; cryo-EM campaigns are underway.
2. Gut-restricted PAMs. Non-absorbable polymer-linked flavanones could potentiate incretins without systemic exposure.
3. Microbiome interactions. Stevia alters *Bacteroides* abundance; causal links to insulin resistance remain debated.
4. Precision nutrition. TAS1R2 polymorphism rs35874116 (Ile191Val) modifies sensitivity to steviol glycosides—personalized sweetener blends may optimize satisfaction and metabolic benefit.

5. Antagonist therapeutics. Can gymnemic acid analogues be tuned for β-cell STR blockade to prevent hyperinsulinemia while sparing taste?

11 Conclusion

Herbal compounds provide an unparalleled chemical diversity for modulating the sweet-taste receptor:

- Agonists such as steviol glycosides and mogrosides deliver intense, calorie-free sweetness.
- PAMs like NHDC and eriodictyol enhance perceived sweet intensity, enabling sugar reduction beyond the 30 % sensory threshold.
- Antagonists from *Gymnema* and *Hydrangea* offer behavioral tools to curb sugar cravings.
- Sweet proteins merge extraordinary potency with clean labels, though production scalability is still maturing.

Beyond flavor, these botanicals act on gut and pancreatic STRs to influence incretin secretion, insulin dynamics, and energy intake, positioning them at the crossroads of food science and metabolic therapeutics. Addressing the outlined research gaps will determine whether herbal STR modulators remain niche sweeteners or evolve into clinically validated agents against the global metabolic syndrome.

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