The Sweetener Problem: What "Natural" Doesn't Mean — Microbiome-Mediated Metabolic and Neurophysiological Risk

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1. Introduction: Reassessing Biological Inertness in the Colonic Niche

The food industry positions non-nutritive and low-calorie sweeteners as metabolic alternatives to sugar because they provide sweetness with little or no acute glycemic effect. Plant-derived high-intensity sweeteners, including steviol glycosides, mogrosides, and thaumatin, are often marketed as especially benign because they are "natural." Yet natural origin does not establish biological neutrality. These compounds differ substantially in absorption, metabolism, microbial transformation, and colonic exposure, and some require gut microbial activity as part of their biological fate.

Regulatory assessments have historically focused on acute toxicity, genotoxicity, carcinogenicity, and acceptable daily intake thresholds, concluding that approved sweeteners are safe within established ADIs (Conz et al., 2023; Magnuson et al., 2016). This framework remains important, but it does not fully resolve a different question: whether repeated exposure to biologically active sweeteners can alter gut microbial metabolism, host-microbe signaling, barrier integrity, glucose regulation, or neuroendocrine function in ways that vary across individuals.

This distinction matters because the gut microbiome is not a passive compartment. It participates in immune regulation, short-chain fatty acid production, bile acid metabolism, enteroendocrine signaling, epithelial barrier maintenance, and metabolic homeostasis. A compound that is minimally caloric or glycemically neutral in the short term may still interact with this ecosystem. For many sweeteners, especially those reaching the colon intact or requiring microbial metabolism, the assumption that "not sugar" means "biologically inert" is increasingly difficult to defend.

This review synthesizes mechanistic, preclinical, and clinical evidence on the microbiome-mediated effects of high-intensity and polyol sweeteners, distinguishing between synthetic compounds such as sucralose, saccharin, and acesulfame-K, and plant-derived glycosides such as stevia and monk fruit. The central argument is deliberately measured. The current ADI-based safety paradigm does not adequately account for person-specific, microbiome-dependent responses or long-term functional outcomes. However, the magnitude and clinical significance of these effects vary substantially by chemical class, host baseline microbiome, metabolic status, and exposure context.

The evidence is strongest for saccharin and sucralose, mechanistic-to-preliminary for several other compounds, and incomplete, mixed, or superficially reassuring for others. This review therefore argues for calibrated caution rather than a blanket claim of harm. Non-nutritive sweeteners should not be assumed to be metabolically inert simply because they are low-calorie, non-glycemic, or naturally derived.

2. The Strongest Human Evidence: Saccharin, Sucralose, and the Microbiome as a Responsiveness Hub

The most rigorous human evidence comes from the randomized controlled trial by Suez et al. (2022), in which 120 healthy adults who were strict non-consumers of NNS were randomized to saccharin, sucralose, aspartame, or stevia, at doses below the ADI, or to glucose-vehicle and no-supplement controls, for two weeks. Saccharin and sucralose significantly impaired glycemic responses; all four sweeteners produced distinct changes in the stool and oral microbiome and the plasma metabolome. Critically, transplanting stool from the most-affected human “responders” into germ-free mice reproduced the donors’ glycemic impairments, establishing a microbiome-dependent causal mechanism rather than a direct pharmacologic effect (Suez et al., 2022). An earlier study by the same group demonstrated saccharin-induced glucose intolerance in mice and in a small human cohort, also transmissible by microbiota transfer (Suez et al., 2014).

Two nuances matter for accurate interpretation. First, in Suez et al. (2022), stevia altered microbial function but did not impair glycemic control at the cohort level, a point often lost in secondary summaries. Second, responses were highly individualized and tracked with baseline microbiome configuration, positioning the microbiome as a "responsiveness hub" that determines whether a given exposure is consequential (Suez et al., 2022). This individual variability is the paper's central clinical insight: population-average safety data can obscure meaningful risk in susceptible hosts.

3. The 2023 WHO Position

In May 2023, the World Health Organization advised that non-sugar sweeteners not be used as a means of achieving weight control or reducing the risk of non-communicable diseases (World Health Organization, 2023). This was a conditional recommendation based on low-certainty evidence, drawn from a systematic review of more than 280 studies (Rios-Leyvraz & Montez, 2022). The review concluded that short-term trials show, at most, trivial weight effects, while longer-term observational data associate habitual NNS use with higher risks of type 2 diabetes, cardiovascular disease, and mortality, associations that may be partly confounded by reverse causation (Rios-Leyvraz & Montez, 2022). The recommendation reflects an absence of demonstrated long-term benefit and a possibility of harm, not proof of harm; commentators have noted the evidence base warrants cautious interpretation (Khan et al., 2023). Even on this conservative reading, the WHO position marks a shift away from treating NNS as inert.

3.1 A Necessary Counterweight: The SWEET Trial

The EU-funded SWEET trial is the strongest recent randomized counterweight to a broad harm narrative and should be acknowledged directly. In adults with overweight or obesity who first completed a low-energy weight-loss phase, participants lost 10.1 ± 3.6 kg before entering the maintenance intervention. Over the following year, replacing sugar-rich products with "sweetener and sweetness-enhancer" (S&SE) products produced a modest additional weight-maintenance advantage of

1.6 kg (P = 0.03) and was associated with increased abundance of short-chain fatty acid–associated taxa, leading the authors to conclude that prolonged S&SE use within a healthy diet may be a safe strategy for obesity management (Pang et al., 2025).

Several features limit how far this conclusion can be generalized. First, the weight effect was a substitution-and-adherence finding layered on prior diet-induced weight loss; it does not demonstrate that non-nutritive sweeteners independently cause weight loss or improve metabolic health. Second, the S&SE intervention was not an isolated NNS exposure. By the trial's own definition, it included high-potency sweeteners, polyols, slowly digestible carbohydrates, and inulin-type oligosaccharides, which are established fermentable substrates. Therefore, the favorable microbiota signal cannot be attributed specifically to non-nutritive sweeteners. Third, the microbiome outcome was primarily compositional and inferential: increased SCFA-associated taxa do not prove increased SCFA production, absorption, host utilization, barrier protection, or mitochondrial benefit.

Finally, SWEET did not directly assess the endpoints most relevant to gut-barrier and metabolic safety, including intestinal permeability, tight-junction integrity, LPS translocation, inflammatory proteomics, mitochondrial function, or host-microbe signaling. Nor did it include post-intervention follow-up sufficient to assess durability or delayed effects. SWEET therefore provides useful evidence that this structured sugar-substitution strategy did not produce obvious harm on measured outcomes over one year. It does not establish that NNS are biologically inert, independently beneficial, or adequate for long-term gut-metabolic safety assessment.

A further limitation is that sweeteners are rarely consumed alone. In real-world diets, they are co-exposed with medications, caffeine, flavor compounds, preservatives, emulsifiers, and other xenobiotics. Blasche et al. (2026) showed in vitro that common xenobiotics can modify gut bacterial responses to low-calorie sweeteners. For example, the steviol-related compound isosteviol inhibited the

butyrate-producing bacterium *Roseburia intestinalis* only in combination with duloxetine, not alone. This does not establish human harm, and the in vitro design limits clinical inference. However, it directly challenges isolated-compound safety thinking and supports the need for long-term studies that assess mixture effects, microbial function, metabolomics, barrier integrity, and host-response endpoints.

4. Synthetic Non-Nutritive Sweeteners

4.1 Aspartame

Aspartame is rapidly and almost completely hydrolyzed in the small intestine to L-aspartate, L-phenylalanine, and methanol, so little intact compound reaches the colon (Magnuson et al., 2016). Its risk profile therefore differs from that of colon-persistent sweeteners. In a maternal rat model, low-dose aspartame (with an obesogenic diet) altered gut microbiota, metabolism, and mesolimbic reward signaling in dams and offspring (Nettleton et al., 2020). In the human RCT of Ahmad et al. (2020), aspartame produced no significant change in gut microbiome composition at realistic intakes. Aspartame's evidence is thus mixed, with animal signals in developmental or obesogenic contexts and largely neutral short-term human microbiome data.

4.2 Sucralose

Sucralose is a chlorinated disaccharide that is highly stable and poorly absorbed; the majority of an ingested dose reaches the colon unchanged (Magnuson et al., 2016; Ruiz-Ojeda et al., 2019). In Suez et al. (2022), two weeks of sucralose impaired glycemic responses in healthy adults, and the phenotype was transmissible to germ-free mice by fecal transfer. Animal studies report reductions in beneficial taxa and enrichment of Proteobacteria, with a murine model linking Splenda/sucralose to Crohn's-like ileitis (Rodriguez-Palacios et al., 2018). A distinct and well-characterized concern is sucralose-6-acetate, an impurity and intestinal metabolite of sucralose: Schiffman et al. (2023) found it to be genotoxic (clastogenic) and to impair intestinal barrier integrity in human colonic epithelium,

with induction of inflammation- and oxidative-stress-related genes. This is among the strongest mechanistic reasons for caution with sucralose and is directly relevant to barrier integrity.

4.3 Saccharin

Saccharin is only partially absorbed, leaving a substantial fraction to interact with colonic microbes (Ruiz-Ojeda et al., 2019). Both mouse and human data indicate that saccharin impairs glucose tolerance through microbiome-mediated mechanisms, with the phenotype transferable to germ-free mice (Suez et al., 2014, 2022). Alongside sucralose, saccharin shows the most consistent dysbiotic and glycemic signal among tested NNS.

4.4 Acesulfame Potassium (Ace-K)

Ace-K is highly absorbed and largely excreted unchanged, which historically suggested minimal colonic interaction. However, long-term exposure in mice produces a distinct neuro-metabolic profile: Cong et al. (2013) reported that chronic Ace-K impaired hippocampal glycolysis and memory, depleted ATP, and dysregulated TrkB–BDNF signaling in hippocampal neurons. These are animal findings at sustained exposure; their translation to human dietary intake is unestablished but warrants monitoring.

4.5 Neotame and Advantame

Neotame is an N-substituted aspartame derivative of very high potency. Shil et al. (2024) reported that neotame damaged intestinal epithelial cells, increased apoptosis and permeability, and enhanced the pathogenicity (adhesion, invasion, biofilm formation) of model gut bacteria such as *E. coli* and *Enterococcus faecalis*, with effects mediated via the T1R3 sweet-taste receptor. These are in vitro/model findings at defined concentrations rather than human data. For advantame, microbiome data are essentially absent, and structural analogy to neotame is a hypothesis, not evidence.

5. "Natural" High-Intensity Sweeteners: Where the Evidence Is Genuinely Thin

Stevia, monk fruit, thaumatin, and neohesperidin dihydrochalcone (NDC) are frequently marketed as natural and implicitly safer. This framing is not scientifically justified, but neither is the opposite claim of demonstrated harm. For most of these compounds, the honest position is that long-term, functionally-resolved human data are lacking.

5.1 Steviol Glycosides (Stevia)

Steviol glycosides are not absorbed intact; colonic bacteria (notably *Bacteroides*) hydrolyze them to steviol, which is then absorbed (Ruiz-Ojeda et al., 2019). On genotoxicity, the regulatory consensus is important and often misstated: after reviewing the in-vitro and in-vivo database, EFSA (2010) and JECFA concluded that steviol glycosides are not genotoxic in vivo and established an ADI of 4 mg/kg body weight/day (steviol equivalents). Early positive in-vitro signals for steviol or its metabolites were not considered relevant to human exposure. Steviol glycosides should therefore not be described as genotoxic.

On the microbiome, the evidence is mechanistic and mixed. In the RapidAIM ex-vivo metaproteomic study, stevioside, rebaudioside A, and monk fruit extract altered microbial function despite modest compositional change; they shared a reduction in one enzyme (annotated COG1509) within the lysine-to-butyrate pathway and reduced *Roseburia* abundance, but they also increased microbial extracellular-structure (type IV pilus) functions, which the author interpreted as potentially supporting competitive exclusion of pathogens (Wang, 2021). The largest butyrate-pathway changes in that dataset were driven by sugar alcohols, some of which *increased* butyrate. A recent in-vitro study underscores that isosteviol (a steviol derivative) is biologically active but with a mixed, context-dependent profile: on its own it *promoted* the probiotic *Lactobacillus gasseri*, and its inhibition of the butyrate producer *Roseburia intestinalis* emerged only in combination with a co-consumed drug rather than in isolation (Blasche et al., 2026; discussed further in Section 7). Alongside these mixed in-vitro

signals, two randomized human trials found that daily stevia for 4–12 weeks did not alter gut microbiota diversity (Kwok et al., 2024; Singh et al., 2024), nor fecal SCFA concentrations where these were measured (Kwok et al., 2024), and rebaudioside has shown hepatoprotective, not hepatotoxic, effects in a model of diet-induced steatohepatitis (Bhattacharjee et al., 2020). The balanced conclusion is that stevia is biologically active in the gut but that evidence of net harm in humans is not established.

5.2 Mogrosides (Monk Fruit Extract)

Mogroside V is the principal sweetener in monk fruit extract. EFSA (2019) did not authorize monk fruit extract in the EU, concluding that the available data, including on the genotoxicity of microbial aglycone metabolites, were insufficient to complete the safety assessment (EFSA Panel, 2019). This is a genuine data gap, not a demonstrated hazard. Short-term human data show reduced postprandial glucose and insulin relative to sucrose (Tey et al., 2017). Claims that monk fruit causes hepatic injury, elevates serum LPS, or drives steatosis are not supported by studies of monk fruit; the emulsifier trials sometimes cited for these effects (e.g., carboxymethylcellulose) did not test monk fruit and cannot be used to characterize it. The defensible position is precautionary on the basis of missing long-term data, not asserted harm.

5.3 Thaumatin and Neohesperidin Dihydrochalcone (NDC)

Thaumatin is a sweet protein presumed to be digested to amino acids in the small intestine; no human or animal studies have examined its microbiome effects, and no long-term toxicity data exist (Ruiz-Ojeda et al., 2019). NDC increases *Lactobacillus* and lactic-acid production in vitro (Ruiz-Ojeda et al., 2019); human microbiome trials are lacking, and proposed adverse effects in dysbiotic contexts remain hypothetical. For both, safety is assumed rather than demonstrated — a legitimate reason for caution in products intended for daily use.

6. Sugar Alcohols (Polyols): The Real Trade-off Is Dose and Tolerance

Polyols are partially fermented nutritive sweeteners marketed as "gut-friendly." The accurate picture is neither "prebiotic" nor "toxic," but dose-dependent. At realistic intakes they are poorly absorbed osmotic agents: sorbitol is malabsorbed in a majority of adults at ~10 g and causes bloating and diarrhea at ~20 g/day (Ruiz-Ojeda et al., 2019; Conz et al., 2023). On the microbiome, several polyols can *increase* butyrate production in ex-vivo and in-vitro systems — in the RapidAIM metaproteomic dataset, sugar alcohols such as sorbitol and isomalt promoted butyrate-synthesis pathways in *Faecalibacterium*, and xylitol supports *Anaerostipes*-mediated butyrate production (Wang, 2021; Ruiz-Ojeda et al., 2019). This contradicts a blanket claim that polyols suppress butyrate. The honest trade-off is gastrointestinal tolerance and osmotic effects at higher doses, with microbiome effects that are compound- and dose-specific rather than uniformly harmful.

7. Mechanistic Pathways: What Is Established and What Is Extrapolated

Where sweeteners do perturb the microbiome, the mechanistic through-line is plausible: reduced butyrate availability can weaken barrier function, and barrier compromise can raise exposure to lipopolysaccharide (LPS), which activates TLR4 signaling implicated in insulin resistance (Cani et al., 2007). In Suez et al. (2022), sucralose "responders" showed upregulated microbial purine-biosynthesis and energy-harvest pathways correlating with impaired glycemic control, a genuine functional finding. However, three cautions are essential for accuracy. First, saccharin and sucralose are the compounds with the strongest human functional data; extending these mechanisms wholesale to stevia, monk fruit, thaumatin, or polyols is extrapolation. Second, specific figures that have circulated in secondary summaries — a ">40% suppression of butyryl-CoA:acetate CoA-transferase" and "stevia/monk-fruit LPS-biosynthesis induction" — are not found in the primary source (Wang, 2021) and are not asserted here. Third, emulsifier studies (Chassaing et al., 2015, 2022; Naimi et al., 2021;

Panyod et al., 2024) characterize *emulsifiers*, not sweeteners, and cannot be used to assign LPS, mucus-erosion, or hepatic effects to any sweetener.

A further limitation cuts across all of this evidence: sweeteners are rarely consumed in isolation, yet they are almost always tested that way. A recent in-vitro systems-biology study challenges the assumption that they can be evaluated as isolated, inert compounds. Blasche et al. (2026) screened 39 commercial sweeteners against 25 human gut bacterial strains, alone and in combination with four commonly co-consumed compounds (advantame, caffeine, vanillin, and the antidepressant duloxetine). About three-quarters of the sweeteners affected the growth of at least one strain individually, and more than 100 sweetener–xenobiotic interactions emerged in combination. The most pronounced was isosteviol combined with duloxetine, which synergistically inhibited *Roseburia intestinalis* and *Parabacteroides merdae*, altered microbial metabolite output, and shifted epithelial-cell cytokine secretion (IL-6, IL-8) in a synthetic gut community. These are in-vitro findings in selected strains and synthetic communities, not human outcomes, and isosteviol is a steviol-related compound rather than a stand-in for every stevia product. The implication for safety assessment is nonetheless substantive: real-world exposure occurs in mixtures — sweeteners alongside caffeine, flavor compounds, food additives, and long-term medications — and conventional testing of single compounds under simplified conditions can miss interaction effects on microbial growth, metabolite output, and host-cell signaling. This is a core reason short-term, isolated-compound trials are an incomplete basis for long-term safety claims.

8. Neurophysiological Considerations

Extra-oral sweet-taste receptors (T1R2/T1R3) are expressed in enteroendocrine cells and modulate GLP-1 and GIP secretion (Jang et al., 2007; Margolskee et al., 2007); chronic non-caloric stimulation may, in some models, blunt this incretin signaling, though human findings are mixed (Burke & Small, 2015). Among sweeteners, Ace-K is distinctive in producing central effects after

chronic exposure in mice — impaired hippocampal energy metabolism and memory — and mass-spectrometric measurement detected acesulfame potassium in brain tissue, with cortical levels near 10 µg/ml and controls below the limit of detection, leading the authors to conclude it crosses the blood–brain barrier (Cong et al., 2013). Beyond this direct effect, the proposition that sweetener-induced dysbiosis drives neuroinflammation, blood–brain-barrier breakdown, sarcopenia, or cognitive decline is, at present, mechanistic extrapolation: the animal evidence for those endpoints comes primarily from **emulsifier** exposures (e.g., polysorbate-80 and carboxymethylcellulose), not sweeteners, and should be presented as an adjacent hypothesis rather than an established sweetener effect.

9. Clinical and Regulatory Implications

For clinicians, the defensible synthesis is this: several commonly used sweeteners are biologically active in the gut and can influence microbiome function, glycemic response, or barrier integrity under specific conditions, most robustly saccharin and sucralose, with sucralose-6-acetate adding a genotoxicity and barrier concern. Effects appear person-specific and are plausibly magnified in individuals with obesity, type 2 diabetes, or gastrointestinal inflammation, in whom baseline dysbiosis and barrier compromise may reduce the margin of safety (Bischoff et al., 2014), though direct trials in these populations remain scarce. For other compounds, particularly monk fruit, thaumatin, and NDC, the issue is missing long-term human data rather than demonstrated harm.

This supports a precautionary, not alarmist, stance. Consistent with the WHO's conditional recommendation, prioritizing water and unsweetened options and gradually reducing sweet-taste exposure is the most defensible general guidance. Future safety assessment should incorporate functional endpoints, metaproteomics, SCFA output, intestinal permeability, and endotoxin markers, and microbiome-stratified trials in vulnerable populations, rather than relying solely on ADI thresholds derived from acute toxicology.

10. Conclusion

The evidence no longer supports treating non-nutritive and low-calorie sweeteners as uniformly inert. Controlled human studies and mechanistic experiments show that some compounds, most clearly saccharin and sucralose, can interact with the gut microbiome in ways that influence host glucose regulation, and that these responses are highly individualized (Suez et al., 2014, 2022). This individual variability is central: population-average neutrality does not exclude meaningful effects in microbiome-defined responders or metabolically vulnerable hosts.

For plant-derived glycosides, polyols, and other “natural” sweeteners, the evidence demands a more nuanced conclusion. These compounds should not be presumed harmful simply because they are sweeteners, but neither should they be presumed biologically neutral because they are natural, low-calorie, or regulatory-approved. Existing human studies are often short, conducted in relatively healthy populations, and limited to endpoints such as glycemia, microbiome composition, or fecal SCFAs. They rarely assess intestinal permeability, LPS translocation, inflammatory proteomics, mitochondrial metabolism, neuroendocrine signaling, or long-term effects in metabolically or gastrointestinally vulnerable groups.

The most defensible conclusion is therefore not alarmism, but humility. Sweeteners are chemically diverse, biologically active, and context-dependent. Some may be useful as sugar substitutes in specific dietary settings, while others may carry microbiome-mediated risks that are not captured by conventional ADI-based safety frameworks. Absence of demonstrated harm in short-term studies should not be mistaken for proof of long-term physiological compatibility.

Accordingly, avoiding isolated high-intensity sweeteners when they are not nutritionally necessary, especially in daily-use products intended for individuals with metabolic dysfunction, gastrointestinal vulnerability, or inflammatory burden, is a clinical reasonable precaution. This is not a

claim of proven injury. It is a refusal to equate regulatory permissibility, short-term glycemic neutrality, or incomplete microbiome testing with long-term biological safety.

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References

Ahmad, S. Y., Friel, J., & Mackay, D. (2020). The effects of non-nutritive artificial sweeteners, aspartame and sucralose, on the gut microbiome in healthy adults: Secondary outcomes of a randomized double-blinded crossover clinical trial. *Nutrients, 12*(11), 3408. https://doi.org/10.3390/nu12113408

Bhattacharjee, J., Salazar-Gonzalez, R. M., Park, S., Jang, A., Warren, M., Merritt, R., Michail, S., Bouret, S., & Kohli, R. (2020). Rebaudioside affords hepatoprotection ameliorating sugar-sweetened beverage-induced nonalcoholic steatohepatitis. *Scientific Reports, 10*(1), 6689. https://doi.org/10.1038/s41598-020-63688-z

Bischoff, S. C., Barbara, G., Buurman, W., Ockhuizen, T., Schulzke, J. D., Serino, M., Tilg, H., Watson, A., & Wells, J. M. (2014). Intestinal permeability — a new target for disease prevention and therapy. *BMC Gastroenterology, 14*, 189. https://doi.org/10.1186/s12876-014-0189-7

Blasche, S., Periwal, V., Beristain Covarrubias, N., Lindell, A., Roux, I., Kamrad, S., Mozzachiodi, S., Bradley, R., Ozgur, H., Ramachandran, B., Benes, V., & Patil, K. R. (2026). Common

xenobiotics modulate gut microbial responses to low-calorie sweeteners in vitro. *Molecular Systems Biology*. https://doi.org/10.1038/s44320-026-00225-6

Burke, M. V., & Small, D. M. (2015). Physiological mechanisms by which non-nutritive sweeteners may impact body weight and metabolism. *Physiology & Behavior, 152*(Pt B), 381–388. https://doi.org/10.1016/j.physbeh.2015.05.036

Cani, P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J. F., Gibson, G. R., Casteilla, L., … Burcelin, R. (2007). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes, 56*(7), 1761–1772. https://doi.org/10.2337/db06-1491

Cong, W. N., Wang, R., Cai, H., Daimon, C. M., Scheibye-Knudsen, M., Bohr, V. A., Turkin, R., Wood, W. H., Becker, K. G., Moaddel, R., Maudsley, S., & Martin, B. (2013). Long-term artificial sweetener acesulfame potassium treatment alters neurometabolic functions in C57BL/6J mice. *PLoS ONE, 8*(8), e70257. https://doi.org/10.1371/journal.pone.0070257

Conz, A., Salmona, M., & Diomede, L. (2023). Effect of non-nutritive sweeteners on the gut microbiota. *Nutrients, 15*(8), 1869. https://doi.org/10.3390/nu15081869

EFSA Panel on Food Additives and Flavourings (FAF). (2019). Safety of use of monk fruit extract as a food additive in different food categories. *EFSA Journal, 17*(12), 5921. https://doi.org/10.2903/j.efsa.2019.5921

European Food Safety Authority (EFSA) Panel on Food Additives and Nutrient Sources added to Food (ANS). (2010). Scientific opinion on the safety of steviol glycosides for the proposed uses as a food additive. *EFSA Journal, 8*(4), 1537. https://doi.org/10.2903/j.efsa.2010.1537

Jang, H. J., Kokrashvili, Z., Theodorakis, M. J., Carlson, O. D., Kim, B. J., Zhou, J., … Egan, J. M. (2007). Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like

peptide-1. *Proceedings of the National Academy of Sciences, 104*(38), 15069–15074. https://doi.org/10.1073/pnas.0706890104

Khan, T. A., Lee, J. J., Ayoub-Charette, S., Noronha, J. C., McGlynn, N., Chiavaroli, L., & Sievenpiper, J. L. (2023). WHO guideline on the use of non-sugar sweeteners: A need for reconsideration. *European Journal of Clinical Nutrition, 77*(11), 1009–1013. https://doi.org/10.1038/s41430-023-01314-7

Kwok, D., Scott, C., Strom, N., Au-Yeung, F., Lam, C., Hutton, T., Wolever, T. M. S., & Chakrabarti, A. (2024). Comparison of a daily steviol glycoside beverage compared with a sucrose beverage for four weeks on gut microbiome in healthy adults. *The Journal of Nutrition, 154*(4), 1298–1308. https://doi.org/10.1016/j.tjnut.2024.01.032

Magnuson, B. A., Carakostas, M. C., Moore, N. H., Poulos, S. P., & Renwick, A. G. (2016). Biological fate of low-calorie sweeteners. *Nutrition Reviews, 74*(11), 670–689. https://doi.org/10.1093/nutrit/nuw032

Margolskee, R. F., Dyer, J., Kokrashvili, Z., Salmon, K. S., Ilegems, E., Daly, K., … Shirazi-Beechey, S. P. (2007). T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1. *Proceedings of the National Academy of Sciences, 104*(38), 15075–15080. https://doi.org/10.1073/pnas.0706678104

Nettleton, J. E., Cho, N. A., Klancic, T., Nicolucci, A. C., Shearer, J., Borgland, S. L., … Reimer, R. A. (2020). Maternal low-dose aspartame and stevia consumption with an obesogenic diet alters metabolism, gut microbiota and mesolimbic reward system in rat dams and their offspring. *Gut, 69*(10), 1807–1817. https://doi.org/10.1136/gutjnl-2018-317505

Pang, M. D., Kjølbæk, L., Bastings, J. J. A. J., Andersen, S. S. H., Umanets, A., Sost, M. M., … Raben, A. (2025). Effect of sweeteners and sweetness enhancers on weight management and gut

microbiota composition in individuals with overweight or obesity: The SWEET study. *Nature Metabolism, 7*(10), 2083–2098. https://doi.org/10.1038/s42255-025-01381-z

Rios-Leyvraz, M., & Montez, J. (2022). *Health effects of the use of non-sugar sweeteners: A systematic review and meta-analysis*. World Health Organization.

Rodriguez-Palacios, A., Harding, A., Menghini, P., Himmelman, C., Retuerto, M., Nickerson, K. P., … Cominelli, F. (2018). The artificial sweetener Splenda promotes gut Proteobacteria, dysbiosis, and myeloperoxidase reactivity in Crohn's disease–like ileitis. *Inflammatory Bowel Diseases, 24*(5), 1005–1020. https://doi.org/10.1093/ibd/izy060

Ruiz-Ojeda, F. J., Plaza-Díaz, J., Sáez-Lara, M. J., & Gil, A. (2019). Effects of sweeteners on the gut microbiota: A review of experimental studies and clinical trials. *Advances in Nutrition, 10*(Suppl 1), S31–S48. https://doi.org/10.1093/advances/nmy037

Schiffman, S. S., Scholl, E. H., Furey, T. S., & Nagle, H. T. (2023). Toxicological and pharmacokinetic properties of sucralose-6-acetate and its parent sucralose: In vitro screening assays. *Journal of Toxicology and Environmental Health, Part B, 26*(6), 307–341. https://doi.org/10.1080/10937404.2023.2213903

Shil, A., Ladeira Faria, L. M., Walker, C. A., & Chichger, H. (2024). The artificial sweetener neotame negatively regulates the intestinal epithelium directly through T1R3-signaling and indirectly through pathogenic changes to model gut bacteria. *Frontiers in Nutrition, 11*, 1366409. https://doi.org/10.3389/fnut.2024.1366409

Singh, G., McBain, A. J., McLaughlin, J. T., & Stamataki, N. S. (2024). Consumption of the non-nutritive sweetener stevia for 12 weeks does not alter the composition of the human gut microbiota. *Nutrients, 16*(2), 296. https://doi.org/10.3390/nu16020296

Suez, J., Korem, T., Zeevi, D., Zilberman-Schapira, G., Thaiss, C. A., Maza, O., … Elinav, E. (2014). Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature, 514*(7521), 181–186. https://doi.org/10.1038/nature13793

Suez, J., Cohen, Y., Valdés-Mas, R., Mor, U., Dori-Bachash, M., Federici, S., … Elinav, E. (2022). Personalized microbiome-driven effects of non-nutritive sweeteners on human glucose tolerance. *Cell, 185*(18), 3307–3328.e19. https://doi.org/10.1016/j.cell.2022.07.016

Tey, S. L., Salleh, N. B., Henry, J., & Forde, C. G. (2017). Effects of aspartame-, monk fruit-, stevia- and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *International Journal of Obesity, 41*(3), 450–457. https://doi.org/10.1038/ijo.2016.225

Wang, W. (2021). *Studying changes of the human gut microbiome in response to sweeteners using RapidAIM* [Master's thesis, University of Ottawa]. uO Research. https://ruor.uottawa.ca/handle/10393/42337

World Health Organization. (2023). *Use of non-sugar sweeteners: WHO guideline*. World Health Organization.