Mechanistic Links Between Non-Nutritive Sweeteners, Intestinal Permeability, and Metabolic Endotoxemia

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1. Executive Summary

Non-nutritive sweeteners (NNS), including plant-derived sweeteners such as steviol glycosides (stevia) and mogrosides (monk fruit), are widely consumed as sugar substitutes. While regulatory bodies deem them toxicologically safe at established intake levels, the assumption of complete biological inertness is increasingly questioned. This reassessment is informed by the 2023 World Health Organization (WHO) guideline, which conditionally recommends against using non-sugar sweeteners for weight control or disease prevention, citing a lack of evidence for long-term benefit and the possibility of undesirable metabolic effects (WHO, 2023).

This paper synthesizes evidence that NNS are not necessarily inert but can act as bioactive compounds that interact with the gut ecosystem. Because these compounds are largely unabsorbed in the small intestine, they reach the colon where they become substrates for microbial metabolism. Ex-vivo functional studies indicate that plant-derived sweeteners can shift microbial metabolic activity, including reduced activity in a butyrate-synthesis pathway and reduced *Roseburia,* while also enriching other butyrate-associated taxa, so the net functional signal is mixed rather than uniformly adverse (Wang, 2021). Separately, human randomized trials have established that, for certain NNS such as saccharin and sucralose, microbiome alterations can be causally linked to personalized impairments in glucose tolerance; the same trial found that stevia did not impair glycemic control at the cohort level (Suez et al., 2022).

Importantly, the human evidence is not one-directional. Several short-term trials in healthy adults report neutral effects on overall microbiome composition, and the large, publicly funded SWEET trial found that a sweetener-substitution strategy within a healthy diet did not cause harm and supported

weight-loss maintenance over one year, though its intervention combined sweeteners with prebiotic fibres and polyols, so its favourable microbiota shift cannot be credited to the sweeteners themselves (Pang et al., 2025). At the same time, most NNS trials have not measured intestinal permeability or endotoxemia, the endpoints predicted by the mechanistic literature, leaving a genuine gap rather than a settled answer. Given the established role of metabolic endotoxemia in insulin resistance and inflammation (Cani et al., 2007), the biological activity of these compounds in the gut warrants continued scrutiny and, for a microbiome-focused product, a precautionary posture under acknowledged uncertainty.

2. Introduction: Public Health Context and the WHO Position

Cardiometabolic diseases, driven largely by the rising global prevalence of obesity and insulin resistance, represent a major public health challenge. In response, NNS have been widely promoted as tools for reducing the caloric and glycemic burden of modern diets. However, their long-term efficacy and safety remain subjects of ongoing scientific and regulatory debate.

In May 2023, the World Health Organization issued a guideline advising that non-sugar sweeteners not be used for weight control or for reducing the risk of non-communicable diseases (WHO, 2023). The recommendation was conditional and based on evidence the WHO characterized as low certainty. Its supporting review included more than 280 studies and found that short-term randomized trials sometimes show modest weight reductions, while longer-term observational studies associate habitual NNS intake with higher risks of type 2 diabetes, cardiovascular disease, and mortality. However, those associations are vulnerable to reverse causation and residual confounding, since individuals at higher metabolic risk are also more likely to use sugar substitutes (Rios-Leyvraz & Montez, 2022).

Two points are therefore important. First, the WHO guideline is not a toxicological ban and does not replace regulatory acceptable daily intake limits. Second, it remains contested. Some nutrition

researchers argue that the guideline underweighted randomized substitution trials, in which NNS replace sugar, and relied too heavily on observational evidence that cannot fully separate cause from risk-marker behavior (Khan et al., 2023). This paper therefore treats the WHO position as a cautious public-health signal, not as settled proof of harm.

This shift reframes NNS from presumptively inert sugar replacements to biologically active dietary components whose long-term systemic effects remain insufficiently characterized. Assessing the biological plausibility of the observational associations requires examining the mechanistic pathways through which NNS interact with the gut microbiome and host metabolic systems, while keeping in mind that plausible mechanisms are not, by themselves, evidence of harm at dietary exposures.

3. Mechanistic Pathways: How NNS Interact With the Gut Ecosystem

The biological activity of NNS, including stevia and monk fruit, originates in part from their interaction with the gut microbiota. Because these compounds are largely unabsorbed in the small intestine, they reach the colon where they become substrates for microbial metabolism.

3.1 Colonic Metabolism and Functional Microbial Shifts

Steviol glycosides (stevia) and mogrosides (monk fruit) are too large to be absorbed intact. Instead, they require microbial enzymes, particularly β-glucosidases produced by species such as *Bacteroides*, to cleave their sugar moieties and release the core aglycone molecules (steviol or mogroside aglycones) for absorption (Ruiz-Ojeda et al., 2019). This metabolic dependence makes the gut microbiome an active participant in the digestion of these compounds.

Microbiome research distinguishes between taxonomic composition (which organisms are present) and functional activity (what those organisms are doing). Because microbial communities exhibit functional redundancy and strain-level metabolic diversity, closely related taxa can perform

different biochemical roles, and community composition can appear stable while metabolic activity shifts. Consequently, taxonomic analyses based on 16S rRNA sequencing may not capture changes in microbial metabolism, gene expression, or host–microbe signaling (Shade & Handelsman, 2011; Costello et al., 2012; Zhao, 2025). This is a genuine methodological caveat, but it cuts both ways: unmeasured functional shifts may be adverse, neutral, or beneficial, and cannot be assumed to be harmful.

Applied to NNS, an ex-vivo study using the RapidAIM human-microbiome culturing platform found that stevia and monk fruit extracts altered microbial enzyme expression related to short-chain fatty acid metabolism and other central pathways even when large compositional shifts were not observed (Wang, 2021). This illustrates that an apparently stable composition can accompany functional remodeling; it does not, on its own, establish the direction or clinical significance of that remodeling.

3.2 Butyrate and Barrier Function

Butyrate is a primary energy source for colonocytes and supports intestinal barrier integrity: it promotes tight-junction protein expression, stimulates mucus production, and exerts anti-inflammatory effects (Bischoff et al., 2014). A reduction in butyrate availability is therefore a biologically coherent route by which any dysbiotic exposure could weaken barrier function.

In the RapidAIM ex-vivo platform, steviol glycosides and monk fruit extract altered microbial function despite modest compositional change: they reduced activity in a butyrate-synthesis pathway and reduced the butyrate producer *Roseburia*, while also enriching the butyrate producer *Butyricicoccus* and increasing microbial extracellular-structure (pilus) functions that the author interpreted as potentially beneficial (Wang, 2021). The net functional signal from this single ex-vivo thesis is therefore mixed rather than uniformly adverse, and should be described as such rather than as a

demonstrated suppression of butyrate. Whether a net reduction in butyrate availability occurs in vivo, and whether it is large enough to affect barrier function at dietary doses, has not been established.

3.3 Lipopolysaccharide (LPS) Signaling and Metabolic Endotoxemia

Metabolic endotoxemia refers to a chronic, low-grade elevation of circulating lipopolysaccharide (LPS) derived from Gram-negative gut bacteria. Even modest increases in circulating LPS can activate Toll-like receptor 4 (TLR4) signaling, initiating inflammatory pathways that contribute to insulin resistance and metabolic disease (Cani et al., 2007). Under normal conditions, the intestinal epithelial barrier limits translocation of bacterial endotoxin into the circulation. Two mechanistic routes by which NNS *could* influence this pathway are discussed below, with the caveat that neither has been demonstrated to raise circulating LPS in humans consuming plant-derived sweeteners.

Potential effects on LPS-related microbial activity. The strongest additive-related evidence for increased LPS bioactivity concerns *dietary emulsifiers* rather than sweeteners: in an ex-vivo human-microbiome model, emulsifiers such as carboxymethylcellulose and polysorbate-80 increased bioactive LPS and flagellin and reduced diversity (Naimi et al., 2021). For sweeteners specifically, associations between sucralose and enrichment of LPS-associated Proteobacteria come largely from animal and review data (Ruiz-Ojeda et al., 2019); the ex-vivo functional signal for stevia and monk fruit is mixed (Section 3.2) and does not establish increased LPS production for these plant-derived glycosides.

Potential effects on permeability. A net reduction in butyrate could, in principle, weaken barrier integrity and increase permeability to luminal endotoxin. More directly, experimental work shows that the artificial sweetener *neotame* induces intestinal epithelial cell death and barrier disruption (increased monolayer leak, reduced claudin-3) through a T1R3-dependent pathway in a cell model, and promotes pathogenic changes in model gut bacteria (Shil et al., 2024). This effect is specific to neotame and has not been demonstrated for stevia or monk fruit; it establishes that some sweeteners can act

directly on the epithelium, not that plant-derived glycosides do. The barrier, LPS-translocation pathway therefore remains biologically plausible for NNS as a class but unproven for stevia and monk fruit at dietary exposures.

3.4 Enteroendocrine and Receptor-Mediated Effects

Beyond microbiome-mediated routes, NNS may interact directly with host physiology. Sweet-taste receptors (T1R2/T1R3) are expressed not only on the tongue but also on enteroendocrine cells in the gastrointestinal tract, where their activation influences secretion of metabolic hormones such as glucagon-like peptide-1 (GLP-1). Findings in this area are mixed, and it remains hypothesized rather than established that chronic non-caloric receptor stimulation meaningfully disrupts the coordination between taste perception, nutrient sensing, and hormonal responses (Burke & Small, 2015).

4. Re-evaluating the Human Clinical Evidence

The human evidence on plant-derived sweeteners is genuinely mixed, and it does not, on balance, demonstrate harm. Several randomized trials in metabolically healthy adults report that daily stevia for 4–12 weeks does not significantly alter overall gut-microbiota α- or β-diversity or fecal short-chain fatty acid concentrations (Kwok et al., 2024; Singh et al., 2024). A 2023 review of human clinical trials and cross-sectional studies reached a consistent conclusion: across the controlled trials examined, only a minority showed significant microbiome changes, concentrated in saccharin and sucralose, and the authors stressed that the microbial response to sweeteners may be strongly mediated by an individual's baseline microbiota (Gauthier et al., 2023). The human evidence is therefore best described as mixed, rather than uniformly reassuring or uniformly concerning.

The large, publicly funded SWEET trial is an important data point, but it must be interpreted strictly within its design. After a shared low-energy-diet phase in which all completers lost 10.1 ± 3.6 kg, participants who then replaced sugar-rich products with "sweetener and sweetness-enhancer" (S&SE) products regained slightly less weight over the following year than those using sugar-

containing products (a 1.6 kg maintenance advantage; P = 0.029), and their microbiota showed increased short-chain fatty acid– and methane-producing taxa; the authors concluded that prolonged S&SE use within a healthy diet is a safe strategy for obesity management (Pang et al., 2025). Three features bound how far this can be read. First, the effect is a substitution-and-adherence result layered on diet-induced weight loss, the weight loss itself came from the low-energy diet, not the sweeteners. Second, and most importantly, the S&SE arm was not non-nutritive sweeteners in isolation: by the trial's own definition it also included polyols (e.g., erythritol, xylitol), slowly digestible carbohydrates (e.g., isomaltulose), and sweet fibres or inulin-type oligosaccharides, all established prebiotics, so the favourable increase in SCFA-associated taxa cannot be attributed to non-nutritive sweeteners specifically. Third, the microbiome finding is compositional (taxa *associated with* SCFA production), not a direct measurement of SCFA flux, barrier function, LPS, or endotoxemia, and the trial did not test individual compounds or follow participants after the intervention ended. The honest reading is two-sided: SWEET provides real reassurance that this substitution strategy did not cause harm on its measured outcomes, but it does not demonstrate that non-nutritive sweeteners themselves are metabolically beneficial or gut-protective, and it does not address the permeability and endotoxemia endpoints at the center of this paper.

Two methodological points remain fair. First, many trials relied primarily on 16S rRNA sequencing, which characterizes composition better than function; higher-resolution shotgun metagenomics, metaproteomics, and metabolomics remain underused (Section 3.1). Where a favourable functional-relevant signal has appeared, SWEET's increase in SCFA-associated taxa, it is confounded by that trial's inclusion of prebiotic fibres and polyols and so cannot be credited to the sweeteners. Second, most NNS trials have not measured intestinal permeability, circulating LPS, or other endotoxemia markers predicted by the mechanistic literature. That gap means the specific permeability/endotoxemia hypothesis is untested in humans, neither supported nor refuted.

In contrast to composition-only studies, the landmark trial by Suez et al. (2022) used shotgun metagenomics and a personalized design. It showed that saccharin and sucralose impaired glycemic responses at below-ADI doses, that all four tested sweeteners (saccharin, sucralose, aspartame, stevia) altered microbial function, and, critically, that transplanting stool from human "responders" into germ-free mice reproduced the glucose impairment, establishing microbiome-mediated causality. The same trial found that stevia altered microbial function but did *not* impair glycemic control at the cohort level. This built on earlier work in which saccharin induced glucose intolerance in mice and in four of seven healthy human volunteers, with microbiota transfer supporting a microbial mechanism (Suez et al., 2014). The causal signal, in other words, is strongest for the synthetic sweeteners saccharin and sucralose, not for stevia.

The effects are also population-specific, not uniform. In a controlled substitution trial in Asian Indian adults, replacing sugar with sucralose altered gut-microbiome community structure and composition in participants with type 2 diabetes but produced no comparable change in adults with overweight or obesity and no diabetes (Haslam et al., 2025). This is direct human evidence that host metabolic status, not the compound alone, determines whether a microbiome response occurs, and it supports both the compound-specific and population-specific framing of this paper.

Taken together, the human evidence is genuinely two-directional and should be stated as such. The SWEET trial found that a sweetener-substitution strategy within a structured healthy diet did not cause harm and supported weight-loss maintenance (Pang et al., 2025), genuine reassurance on safety, though, as detailed above, its heterogeneous intervention (which combined sweeteners with prebiotic fibres and polyols) prevents attributing the microbiota benefit to the sweeteners themselves. Yet other controlled human studies show that responses differ by compound and by person, with saccharin and sucralose producing microbiome-linked impairments in glycemic responses in some individuals (Suez et al., 2014, 2022; Haslam et al., 2025). The WHO's 2023 guideline advises against using non-sugar

sweeteners for weight control or chronic-disease prevention, citing limited long-term benefit and possible undesirable associations, while itself being conditional and contested (WHO, 2023; Khan et al., 2023). The honest synthesis is that the evidence does not prove every NNS is harmful, but it also does not support treating them as metabolically inert or universally beneficial.

5. Funding Structures and Research Integrity

Interpretation of nutrition research is complicated by funding-related bias: systematic reviews show that industry-sponsored studies are more likely to report conclusions favorable to sponsor interests (Lesser et al., 2007; Lundh et al., 2017). This is a reason to weight independently funded work heavily, but the direction of that adjustment must be applied honestly. Some short-term stevia trials disclose industry funding or product provision; at the same time, the two largest independent, publicly funded investigations relevant here point in opposite directions. Suez et al. (2022) demonstrated microbiome-mediated glycemic harm for saccharin and sucralose (but not stevia), while the EU-funded SWEET trial found a sweetener-substitution strategy to be safe on its measured outcomes, with favourable microbiota shifts that its mixed intervention (sweeteners plus prebiotic fibres and polyols) prevents attributing to the sweeteners specifically (Pang et al., 2025). Independent funding therefore does not uniformly support a harm interpretation for plant-derived sweeteners; the honest reading is that the highest-quality independent evidence is mixed and, in SWEET's case, confounded by design.

6. Vulnerable Populations: A Plausible but Untested Concern

The metabolic impact of NNS may not be uniform across populations. Individuals with metabolic syndrome, type 2 diabetes, or NAFLD often exhibit gut-microbiome alterations, reduced abundance of butyrate-producing taxa, low-grade inflammation, and/or markers of impaired intestinal barrier function. In such individuals, a more permeable barrier may offer less protection against microbial products such as LPS, while a primed immune-metabolic state may amplify downstream inflammatory responses. The Suez trial's central finding, that responses to NNS are individualized and

influenced by baseline microbiome state, supports the biological plausibility of heightened susceptibility in some hosts.

This remains a plausible hypothesis rather than a demonstrated effect. Few long-term NNS trials have specifically enrolled metabolically vulnerable populations with endpoints focused on intestinal permeability, LPS translocation, inflammatory proteomics, mitochondrial function, or host-microbe signaling. SWEET, conducted in adults with overweight or obesity, did not detect harm on its measured outcomes and provides an important counterweight. However, it does not rule out unmeasured barrier, endotoxemia, or host-metabolic effects in susceptible subgroups. The susceptibility concern is therefore a reason for targeted research and cautious formulation in clinical or metabolically vulnerable populations, not a basis for asserting universal harm.

7. Integrated Interpretation

Current evidence does not indicate that stevia or monk fruit are acutely toxic at commonly consumed doses, and the best-powered human data do not demonstrate net harm from plant-derived sweeteners. What the evidence does support is that NNS are biologically active rather than inert: they are metabolized by gut microbes and can shift microbial function. For the plant-derived glycosides specifically, that functional signal is mixed, some potentially adverse (reduced butyrate-pathway activity, reduced *Roseburia*) and some potentially beneficial (enrichment of *Butyricicoccus*). The apparently favourable microbiota shift in the SWEET trial cannot be added to the beneficial column for sweeteners, because that trial's intervention also delivered prebiotic fibres and polyols.

The strongest causal human evidence of metabolic harm concerns the synthetic sweeteners saccharin and sucralose (Suez et al., 2022), not stevia or monk fruit. The specific hypothesis at the center of this paper, that plant-derived NNS raise intestinal permeability and circulating LPS in humans, remains biologically plausible but untested, because the relevant endpoints have not been

measured in the trials conducted to date. Plausibility plus absent data is a case for further study and measured caution, not a demonstration of risk.

8. Conclusion

The classification of stevia and monk fruit as biologically *inert* is inconsistent with current microbiome research: mechanistic and ex-vivo studies show these compounds interact with the microbiota and can alter metabolic pathways. That is different from showing they are harmful. For the synthetic sweeteners saccharin and sucralose, human trials link microbiome-mediated changes to individualized impairments in glucose tolerance (Suez et al., 2022). For stevia and monk fruit, definitive human evidence of increased intestinal permeability or metabolic endotoxemia does not exist, and the largest independent trial to examine sweetener use in a healthy diet found it safe and associated with beneficial microbiota shifts (Pang et al., 2025).

Two things are true at once, and the honest position holds both: the absence of demonstrated harm is not proof of neutrality, many trials are short, conducted in healthy adults, and reliant on compositional rather than functional or barrier endpoints, and the available functional and clinical data, where they exist, have not established harm for plant-derived sweeteners and have in places been favorable. A prudent public-health strategy consistent with the WHO guidance is to prioritize reducing overall sweet-taste preference rather than assuming that substitution with any NNS is either risk-free or harmful.

Future research should move beyond compositional analyses to incorporate functional metagenomics, metabolomics, and, most importantly, direct measurement of intestinal permeability and circulating LPS, particularly in metabolically vulnerable populations, since these are the endpoints the mechanistic hypothesis actually predicts and the ones current trials omit.

From a clinical and formulation standpoint, the principle of non-maleficence supports acting cautiously where mechanisms are plausible, effects are compound- and person-specific, and long-term,

endpoint-appropriate human data are absent. The brand position follows directly and should be stated without overreach: TLC PureOrigin™ does not claim that the science proves all non-sugar sweeteners are harmful. The evidence is mixed, compound-specific, and person-specific. Some trials show no measurable harm, while others show microbiome and glucose-response changes, most consistently with saccharin and sucralose or in metabolically vulnerable groups. Because non-sugar sweeteners are optional in a protein powder, TLC PureOrigin™ chooses not to use them. This is a precautionary formulation choice made in full view of evidence (including the SWEET trial) that does not demonstrate harm, reflecting a preference for minimally processed ingredients and whole-food matrices over highly purified sweetener extracts, pending the higher-resolution, endpoint-appropriate human research that would actually resolve the question.

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