A Critical Narrative Review of the Gut–Brain and Microbiome Disruptive Potential of Non-Nutritive Sweeteners and Emulsifiers

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Abstract

Non-nutritive sweeteners (NNS) and dietary emulsifiers are widely used in processed foods marketed as low-calorie, sugar-free, or gut-friendly. While considered safe under current toxicological standards, emerging evidence suggests these additives may disrupt gut microbiota, compromise intestinal and blood–brain barrier (BBB) integrity, and induce neuroimmune activation, raising concern about their inclusion in clinical nutrition products targeting the microbiome or brain health. To critically evaluate the mechanistic, preclinical, and clinical literature on the effects of commonly used NNS and emulsifiers on gut microbiota composition, microbial metabolism, intestinal permeability, BBB function, and neuroinflammation. This review aims to assess their suitability for inclusion in gut- and brain-targeted formulations. A narrative review approach was employed, synthesizing findings from randomized controlled trials, mechanistic animal and in vitro models, human observational studies, and regulatory reports. Compounds assessed include sucralose, aspartame, acesulfame potassium, saccharin, stevia, polysorbate 80 (P80), carboxymethylcellulose (CMC), lecithins, mono- and diglycerides, carrageenans, and food gums such as xanthan, guar, and gum arabic. Particular focus was given to studies involving gut barrier integrity, microbiome-mediated immune signaling, BBB permeability, and cognitive or metabolic outcomes. Multiple NNS and emulsifiers, including Ace-K, P80, and CMC, were found to impair glucose tolerance, reduce microbial diversity, increase production of pro-inflammatory microbial molecules (e.g., lipopolysaccharide, flagellin), and weaken epithelial and endothelial tight junctions. Notably, chronic Ace-K exposure altered hippocampal energy

metabolism and impaired memory in animal models. P80 and CMC disrupted BBB-related gene expression, induced astrocyte and microglial activation, and accelerated age-related cognitive decline. Even compounds considered inert or prebiotic in some contexts (e.g., gum arabic, sunflower lecithin) demonstrated dose- and context-dependent disruption in mechanistic models. Despite regulatory approval for general use, many NNS and emulsifiers exhibit mechanistic properties that may undermine microbiome balance, gut integrity, and neuroimmune resilience, particularly with chronic or high-dose exposure. These findings underscore the need for stricter evaluation of such compounds in clinical nutrition products, especially those targeting microbiome or neuroprotective benefits.

Keywords: non-nutritive sweeteners, dietary emulsifiers, gut microbiota, intestinal permeability, blood–brain barrier, neuroinflammation, gut–brain axis, microbial diversity

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Introduction

The widespread integration of non-nutritive sweeteners (NNS) and dietary emulsifiers into processed foods has raised important questions about their long-term effects on human health, particularly given emerging evidence that these additives may not be metabolically inert (Conz, Salmona, & Diomede, 2023; Miclotte et al., 2020). Disruptions in the gut microbiome composition and associated changes in intestinal and neuroimmune function are increasingly recognized as playing a pivotal role in metabolic, inflammatory, and neuropsychiatric conditions (Liu et al., 2022; Naimi et al., 2021). Nevertheless, regulatory safety assessments of food additives often overlook their impact on gut microbial ecology and the health of the gut–brain axis (Warner, 2024).

Recent advances in microbiome science and neurogastroenterology have illuminated the critical roles of gut microbiota in host metabolic regulation, immune function, and even central nervous system homeostasis via the gut-brain axis (Liu et al., 2022). Both NNS, such as sucralose, aspartame,

saccharin, and acesulfame potassium, and common dietary emulsifiers like polysorbate 80 and carboxymethylcellulose, have been shown in animal models and in vitro studies to alter microbial diversity, disrupt intestinal barrier integrity, modulate neuroimmune signaling, and potentially contribute to neuroinflammatory and metabolic disorders (Chassaing et al., 2015; Naimi et al., 2021). Notably, certain NNS and emulsifiers appear capable of influencing blood–brain barrier permeability and engaging pathways implicated in mood, cognition, and neuropsychiatric health (Burke & Small, 2015; Arnold et al., 2022).

Despite ongoing regulatory approval and widespread inclusion in food products, the context-dependent and at times irreversible impacts of these additives on the gut microbiome and related systemic processes underscore the need for a reevaluation of their long-term safety, especially in populations vulnerable to metabolic or neuropsychiatric diseases (Conz et al., 2023). The microbiome's role as a responsiveness hub and mediator of additive-host interactions suggests that both individual susceptibility and the cumulative effect of chronic exposure should be central considerations for future nutritional guidelines (Suez et al., 2022).

This review critically assesses the mechanistic, preclinical, and human data underlying the disruptive potential of NNS and dietary emulsifiers on the gut–brain axis. By synthesizing evidence from recent studies, our aim is to elucidate the microbiome-mediated pathways by which these ubiquitous food additives may impact host health and identify pressing gaps for further research and regulatory scrutiny.

Methods

This narrative review synthesizes and critically evaluates current evidence on the biological effects of non-nutritive sweeteners (NNS) and dietary emulsifiers on the gut microbiome, intestinal barrier function, neuroinflammation, and the gut–brain axis (Conz, Salmona, & Diomede, 2023; Naimi

et al., 2021). Rather than applying rigid inclusion and exclusion criteria, studies were selected based on their mechanistic relevance and contribution to emerging hypotheses regarding the microbiome–neuroimmune interface (Miclotte et al., 2020; Liu et al., 2022).

Peer-reviewed publications were identified through keyword-based searches in PubMed, Google Scholar, and ScienceDirect. Search terms included combinations such as “non-nutritive sweeteners,” “emulsifiers,” “gut microbiota,” “intestinal permeability,” “lipopolysaccharide,” “neuroinflammation,” “microglia,” “blood–brain barrier,” and “depression/anxiety.” Additional sources were identified by manually reviewing the reference lists of key reviews and seminal mechanistic studies (Miclotte et al., 2020; Conz et al., 2023).

The review prioritized studies elucidating molecular and physiological mechanisms, particularly those involving widely used dietary additives such as acesulfame potassium, sucralose, aspartame, saccharin, polysorbate 80, carboxymethylcellulose, and lecithins (Naimi et al., 2021; Liu et al., 2022). Animal and in vitro studies were included if they examined microbiome composition, gut barrier integrity, inflammatory markers, or neurobiological outcomes. Human clinical trials and observational studies were considered when they reported microbial, metabolic, or cognitive effects associated with these compounds (Conz et al., 2023).

Mechanistic investigations of key pathways—including toll-like receptor 4 (TLR4) signaling, nuclear factor kappa B (NF-κB) activation, cyclooxygenase-2 (COX-2), senescence-associated secretory phenotype (SASP), and mTORC1—were emphasized to construct a conceptual framework linking dietary exposures to systemic and central nervous system effects (Miclotte et al., 2020). Particular attention was given to studies reporting alterations in gut microbial metabolites, such as lipopolysaccharide (LPS), short-chain fatty acids (SCFAs), and flagellin, alongside neuroimmune outcomes including microglial activation and astrocytic reactivity (Miclotte et al., 2020).

While this review does not claim to be exhaustive, it aims to reflect the current state of the evidence, highlighting relevant mechanistic pathways, clinical implications, and pressing areas for further investigation. The selected studies represent a focused yet diverse body of literature that contributes to a deeper understanding of how common food additives may influence host physiology via microbiome–brain interactions (Naimi et al., 2021; Miclotte et al., 2020).

Results

Effects of Non-Nutritive Sweeteners (NNS) on the Gut Microbiome and Metabolism

Monk fruit extract (MFE) has demonstrated promising short-term metabolic effects in randomized controlled trials, such as reductions in postprandial glucose (10–18%) and insulin responses (12–22%). However, its long-term safety and broader applicability remain uncertain. A recent PRISMA-guided systematic review of five high-quality RCTs found no serious adverse events; notably, none of these trials assessed the impact of MFE on gut microbiota, intestinal permeability, or neurocognitive outcomes. Furthermore, the trials were generally of short duration and involved ethnically homogenous populations from Asia and North America, limiting the global relevance of the findings. This raises concerns that genetic and dietary differences across populations may affect metabolic responses and that underrepresentation could mask variability in efficacy or safety profiles (Kaim & Labus, 2025).

Although MFE is approved for use in the United States, China, and Canada, the European Food Safety Authority (EFSA) has withheld authorization, citing insufficient toxicological and mechanistic data. Subchronic animal studies have reported safety concerns, including a 90-day toxicity study in which high-dose male rats exhibited decreased testis weight and irreversible tubular degeneration and atrophy—deemed potentially adverse by the EFSA Panel (Younes et al., 2019). This regulatory divergence underscores the contradiction between localized acceptance based on preliminary findings

and the need for more rigorous, long-term safety data (Kaim & Labus, 2025). Claims regarding the antioxidant and anti-inflammatory benefits of MFE's bioactive mogrosides remain unsubstantiated in prospective human studies, and the "natural health" image associated with MFE appears to outpace the current empirical support. Given unresolved issues such as the lack of microbiome or brain-health outcomes, as well as the potential for contamination with bulking agents like erythritol or maltodextrin, it is scientifically prudent to exclude MFE from gut- or neuro-targeted health products until comprehensive, long-term, and more demographically diverse studies are available (Kaim & Labus, 2025).

A landmark multi-arm randomized controlled trial by Suez et al. (2022) evaluated the metabolic and microbiome-mediated effects of four widely used non-nutritive sweeteners—sucralose, saccharin, aspartame, and stevia—in 120 healthy, NNS-naïve adults. Even at doses below the accepted daily intake, sucralose and saccharin significantly impaired glycemic control, as indicated by increased glucose incremental area under the curve (iAUC) during oral glucose tolerance testing. Aspartame and stevia did not elicit major glycemic changes. All four NNS produced distinct alterations in both gut and oral microbiome composition and function, as indicated by shotgun metagenomic sequencing; these changes were absent in controls, demonstrating active interactions with host microbes. Further, microbiomes transplanted from "top responders" (those most metabolically affected by NNS) into germ-free mice reproduced similar glycemic impairments, confirming a causal link between NNS-induced microbiome changes and host metabolism. Plasma metabolomics also revealed shifts in metabolites—including TCA cycle intermediates and amino acids—that correlated with impaired glucose tolerance and altered microbial pathways. Notably, individual responses to NNS were highly variable and dependent on baseline microbiome composition, underscoring the personalized nature of NNS effects (Suez et al., 2022)

These findings challenge the traditional assumption that NNS are metabolically inert, indicating a more complex and individualized safety profile than previously believed. Even stevia and aspartame, which did not impair glycemia, drove significant functional shifts in the microbiome, suggesting broader potential health implications. The authors propose the microbiome functions as a "responsiveness hub," through which NNS-host interactions are mediated—a dynamic process inconsistent with the conventional view of NNS as biologically neutral (Suez et al., 2022)

A review by Ruiz-Ojeda et al. (2019) synthesized experimental and clinical evidence, concluding that sucralose, saccharin, and stevia consistently altered gut microbiota composition. Saccharin and sucralose induced notable dysbiosis, reducing beneficial genera such as Lactobacillus and Bifidobacterium and, in animal models, were linked to proinflammatory responses and impaired glucose tolerance. Steviol glycosides were generally considered compatible with the microbiome but showed weak antimicrobial effects and Bacteroides modulation. In contrast, polyols like isomalt, lactitol, and maltitol demonstrated bifidogenic properties, while erythritol and mannitol appeared mostly neutral but potentially disruptive at high doses due to osmotic changes. Nevertheless, conclusions were limited by reliance on animal and observational studies, which precludes definitive causal inference. Most human studies on NNS are short-term, underpowered, lack diversity, and rarely include long-term metabolic or microbiome endpoints—indicating a need for more robust research.

The Suez et al. (2022) study represents a critical advance, demonstrating that even low-dose exposure to sucralose and saccharin can impair glycemic control via microbiome-mediated pathways. All four sweeteners altered gut and oral microbiota, and fecal microbiota transplantation (FMT) from high-responding individuals into germ-free mice reproduced these glycemic impairments, establishing causality. Notably, the metabolic effects of NNS were highly individualized, depending on baseline microbiome composition. Such evidence challenges the prevailing narrative that NNS are metabolically

inert and underscores the need for patient-specific safety assessments. Given the scarcity of long-term, well-powered human trials and the mechanistically plausible microbiome–host interactions, current safety recommendations—especially for gut-targeted products—may warrant reconsideration in microbiome-sensitive populations.

Functional and Compositional Microbiome Effects of NNS: Insights from Metaproteomics and Systematic Reviews

Recent metaproteomic data have intensified scientific scrutiny over the use of non-nutritive and sugar-substitute sweeteners in microbiome-targeted applications. Wang (2021) utilized the RapidAIM high-throughput culturing and metaproteomic platform to examine the effects of 20 commonly used sweeteners—including monk fruit extract, stevia glycosides, and various sugar alcohols—on the taxonomic and functional profile of human gut microbiota in an ex vivo model. All tested sweeteners induced genus-level compositional shifts, with certain compounds such as monk fruit extract, stevioside, rebaudioside A, and several polyols causing notable functional changes across all five donor microbiomes. Particularly, these included altered expression of microbial enzymes involved in butyrate production, notably within key genera such as Faecalibacterium, Roseburia, and Eubacterium. While disruption levels varied among sweeteners and between microbiomes, glycoside and sugar alcohol classes were consistently associated with modulation of metabolic pathways linked to short-chain fatty acid biosynthesis. Given butyrate's vital role in intestinal barrier integrity, immune regulation, and host–microbiota signaling, these findings raise concerns about the implications of habitual sweetener consumption for gut homeostasis. Although the study stops short of clinical conclusions, it contributes to a growing body of evidence that many non-nutritive sweeteners are not microbiota-inert and may exert off-target effects on microbial function that go beyond simple taxonomic alterations.

A recent systematic review by Conz, Salmona, and Diomede (2023) reinforces growing concerns about the impact of non-nutritive sweeteners (NNS) on the gut microbiota. Synthesizing human clinical

trials and animal studies from the past decade, the authors found that widely consumed NNS—including aspartame, sucralose, saccharin, and acesulfame-K—can alter gut microbial composition and metabolic activity. Some short-term human studies reported negligible or no changes in microbial diversity, whereas others found shifts in microbial taxa and function, notably after exposure to saccharin and sucralose. In contrast, animal models more consistently demonstrated pronounced dysbiosis, marked by reductions in beneficial bacteria such as Lactobacillus, Bifidobacterium, and Clostridium, along with increases in potentially pathogenic taxa like Proteobacteria and Escherichia coli. These microbial changes often co-occurred with increased intestinal permeability, inflammation, and compromised gut barrier integrity. The authors emphasize that, although NNS are widely approved based on toxicological data, their effects on the gut microbiome remain insufficiently understood, especially in the context of long-term and habitual use. Notably, the review underscores the need for more robust, long-term, and standardized human studies to clarify the microbiological and metabolic consequences of NNS use, as well as to address individual variation in microbiome responsiveness.

Further analysis from Conz et al. (2023) highlighted the divergence in findings among existing studies. While some human trials found no major effects of aspartame or sucralose, others, including the landmark RCT by Suez et al. (2022), identified distinct microbiome and metabolic disruptions, particularly for sucralose and saccharin. Animal studies were more consistent, revealing that NNS-induced dysbiosis generally involved reductions in beneficial taxa and enrichment of pro-inflammatory or potentially pathogenic bacteria, together with heightened inflammatory markers and increased gut barrier permeability. Importantly, NNS reach the colon intact, allowing direct interaction with the gut microbiota; nonetheless, risk assessment is complicated by high interindividual variability in response.

The findings of Wang (2021) further corroborate that stevia glycosides, monk fruit extract, and sugar alcohols significantly alter microbial functional pathways, particularly those linked to butyrate

production. Together with Ruiz-Ojeda et al. (2019), whose review documented compositional shifts and signs of preclinical inflammation associated with common sweeteners, these data collectively undermine the notion that NNS are microbiota-inert. Despite broad regulatory acceptance, the evidence suggests that these sweeteners may exert subtle but biologically relevant effects on host–microbiota interactions, especially in metabolic and gut health contexts. This calls for individualized, long-term, and mechanistically grounded research, rather than generalized safety assumptions. See Table 1 for a comparative summary of key reviews and experimental studies.

Table 1: Comparative Summary of Key Reviews and Experimental Studies on the Effects of Non-Nutritive Sweeteners on the Gut Microbiome

Topic	Wang (2021, MSc)	Ruiz-Ojeda et al. (2019)	Conz et al. (2023)
Study Type	Metaproteomic, mechanistic, in vitro	Narrative review (experimental + clinical)	Systematic review of human + animal studies
Sweeteners Analyzed	20 (incl. stevia, monk fruit, polyols, NAS)	Mixed sweeteners (NAS + polyols + glycosides)	Focused on 4 most common: aspartame, ACE-K, sucralose, saccharin
Butyrate Effects	Strong emphasis on disrupted butyrogenic enzymes	Not emphasized	Not directly addressed—but mentions shifts in SCFA producers
Conclusion	Natural sweeteners not inert; strong caution urged	Preclinical signs of harm, human data inconsistent	Mixed human evidence, but significant dysbiosis in animals
Clinical Risk Framing	Functional impairment, ex vivo	Caution due to inconsistency and short durations	Advocates for individualized response model and better trials

Effects of Dietary Emulsifiers on Gut Microbiota and Metabolic Health

A recent in vivo and in vitro study by Panyod et al. (2024) systematically evaluated the effects of four widely consumed emulsifiers—lecithin, sucrose fatty acid esters, carboxymethylcellulose (CMC), and mono- and diglycerides (MDGs)—on metabolic health and gut microbiota composition in mice.

The findings revealed that sucrose fatty acid esters and CMC significantly disrupted glucose homeostasis, inducing hyperglycemia, hyperinsulinemia, and elevated HOMA-IR scores. Both emulsifiers also promoted substantial gut microbiota dysbiosis, depleting beneficial taxa such as *Muribaculaceae*, *Faecalibaculum*, and *Parasutterella* and enriching disease-associated genera, including *Blautia* and *Clostridium sensu stricto 1*.

Lecithin induced a milder metabolic response but still altered microbial composition, notably increasing Streptococcus—a genus linked to inflammatory processes—while depleting Oscillibacter and Turicibacter, taxa associated with butyrate production and intestinal homeostasis. MDG intake was associated with impaired lipid and glucose metabolism, elevated circulating lipopolysaccharide (LPS), and reduced microbial evenness, suggesting an increased risk of systemic inflammation. Notably, while lecithin, CMC, and sucrose esters did not disrupt the intestinal mucus barrier or promote epithelial invasion, MDGs significantly decreased the distance between luminal bacteria and epithelial cells, raising concerns about mucosal barrier compromise and chronic inflammation. Collectively, Panyod et al. (2024) emphasize that all tested emulsifiers significantly altered gut microbiota α- and β-diversity, and these shifts correlated with key features of metabolic dysregulation. These results suggest that emulsifiers—once presumed safe under GRAS standards—may contribute to metabolic syndrome via microbiota–host interactions, underscoring the need to reevaluate their widespread inclusion in ultra-processed foods.

Although lecithin, particularly from sunflower sources, is often promoted as a cleaner alternative to synthetic emulsifiers, emerging evidence challenges its presumed neutrality on the gut microbiome. Even though lecithin produced milder metabolic disturbances compared to CMC or MDGs in Panyod et al.'s (2024) study, it still significantly altered microbial community structure, increasing pro-inflammatory genera and reducing beneficial butyrate producers. Furthermore, these changes in gut

microbiota α- and β-diversity were paired with features of metabolic dysregulation. Consequently, inclusion of lecithin—even in its sunflower-derived form—may not be advisable in clinical-grade formulations aimed at supporting gut health or reducing inflammation, particularly in populations with underlying metabolic or gastrointestinal vulnerabilities (Panyod et al., 2024).

In a preliminary in vitro study, Dufrusine et al. (2023) examined the cellular and inflammatory effects of two commonly used food emulsifiers (EMI and EMII) on Caco-2 intestinal epithelial cells and THP-1-derived macrophages. Compared to extra virgin olive oil controls, both emulsifiers significantly increased Caco-2 cell proliferation and migration, as demonstrated by MTT and wound healing assays—behaviors indicative of early inflammatory and tumorigenic activity. Emulsifier exposure led to a marked increase in interleukin-6 (IL-6) secretion and, in the case of EMI, also strongly induced CCL2 expression, both cytokines central to intestinal inflammation and implicated in the pathogenesis of inflammatory bowel disease. Conditioned media from emulsifier-treated Caco-2 cells further amplified IL-6 release by macrophages, suggesting a secondary pro-inflammatory effect via epithelial–immune cell signaling. These findings reinforce growing concerns about emulsifier-triggered mucosal immune activation, highlighting that even “technologically necessary” emulsifiers may pose inflammatory risks with chronic exposure. Dufrusine et al. (2023) argue for revisiting current food safety assessments to incorporate endpoints sensitive to chronic immune perturbations, beyond conventional toxicological parameters.

Sandall et al. (2020) conducted a two-part investigation into the effects of common food emulsifiers on intestinal inflammation in mice, as well as the feasibility of a low-emulsifier diet in individuals with Crohn’s disease. In the animal model, chronic administration of CMC, polysorbate-80 (P80), soy lecithin, or gum arabic over twelve weeks led to reduced colonic length—a surrogate marker of intestinal inflammation—with the most pronounced effects observed for CMC and P80. These

emulsifiers were also associated with increased body weight and adipose tissue, indicating metabolic consequences beyond inflammation alone. The parallel human feasibility study demonstrated that adults with stable Crohn's disease maintained high adherence to a low-emulsifier diet for two weeks, successfully eliminating 65 food additives. Adherence resulted in improved gastrointestinal symptoms, enhanced food-related quality of life, and preserved nutritional adequacy. Participants found the intervention acceptable and sustainable. Sandall et al. (2020) conclude that a broad range of emulsifiers —including some not previously studied in vivo—may contribute to gut inflammation, and that restrictive low-emulsifier diets are feasible and safe, warranting further clinical evaluation in inflammatory bowel disease populations (Sandall et al., 2020).

Context- and Dose-Dependence of Natural Emulsifiers and Dietary Gums

Although alginate and its oligosaccharide derivatives (AOS) have demonstrated promising preclinical effects, the current evidence base does not support their inclusion in clinical-grade formulations intended to modulate the human gut microbiome, particularly in individuals with inflammatory or metabolic disorders. In a 15-day animal study, oral administration of calcium alginate aerogels in rats produced no detectable toxicity and modestly shifted microbial composition, most notably increasing Clostridia and Bacteroidia—taxa often associated with butyrate production (Al-Najjar et al., 2021). Similarly, a narrative review by Zhang, Wang, and Li (2023) highlighted anti-inflammatory and prebiotic effects of purified AOS in animal models, including increased short-chain fatty acid (SCFA) production and enrichment of beneficial taxa such as *Akkermansia*, *Lactobacillus*, and *Faecalibacterium*. However, these findings derive primarily from short-term, preclinical studies with limited translational relevance for chronic human use. No long-term human clinical trials have evaluated alginate emulsifiers or oligosaccharides for safety, microbiome modulation, or efficacy in conditions such as inflammatory bowel disease or metabolic dysfunction. Furthermore, alginate's

biological effects may vary substantially with molecular weight, purity, degree of polymerization, and formulation context. Given the absence of validated human data, unclear dose–response relationships, and the need for rigorous characterization of functional outcomes, alginate should not be considered microbiota-targeted or functionally active in the context of clinical nutrition or therapeutic interventions. While no evidence currently suggests harm, the lack of robust, long-term safety and efficacy data renders alginate unsuitable for daily use in microbiome-focused formulations, especially for vulnerable populations (Al-Najjar et al., 2021; Zhang et al., 2023).

A recent mechanistic study by Naimi et al. (2021) systematically evaluated the direct effects of 20 commonly used dietary emulsifiers on human gut microbiota using the MiniBioReactor Array (MBRA) in vitro model (see Table 2 for details). While established synthetic emulsifiers such as carboxymethylcellulose (CMC) and polysorbate 80 (P80) were confirmed to induce long-lasting, deleterious shifts in microbial composition and pro-inflammatory activity, the study revealed that many other emulsifiers—including dietary gums (*guar*, *xanthan*, *gum arabic*, *locust bean*), maltodextrin, carrageenans, diacetyl tartaric acid esters of mono- and diglycerides (DATEM), and glyceryl stearate—exerted similarly harmful effects. These included reductions in microbial diversity, suppression of beneficial taxa (e.g., *Faecalibacterium*, *Oscillibacter*, *Lachnospiraceae*), and increased production of lipopolysaccharide (LPS) and flagellin, both key pro-inflammatory microbial molecules. Metatranscriptomic analysis demonstrated broad suppression of microbial gene expression, particularly in pathways essential for mucosal health. Although soy and sunflower lecithin exhibited comparatively milder effects in this model, they were not entirely inert. Naimi et al. (2021) concluded that most tested emulsifiers negatively altered gut microbiota composition and function in ways that may predispose to chronic inflammation, particularly under conditions of habitual or cumulative exposure.

Even compounds traditionally considered benign—such as *gum arabic*, which has shown dose-dependent prebiotic effects in human trials by promoting *Bifidobacterium*, *Lactobacillus*, and SCFA production—elicited dysbiotic and pro-inflammatory responses under high-dose or isolated exposure in vitro. These responses included decreased microbial diversity and increased flagellin production, suggesting that natural emulsifiers are not universally microbiota-friendly, particularly when consumed outside traditional or whole-food contexts (Naimi et al., 2021). The authors emphasized that many positive human trials test such ingredients as targeted supplements, often in individuals with low baseline fiber intake and minimal additive exposure, whereas ultra-processed food environments can produce frequent, multi-emulsifier exposures at levels sufficient to tip the microbial balance toward dysbiosis (Naimi et al., 2021).

This distinction is particularly relevant for *gum arabic* and *guar gum*, both generally regarded as safe and marketed as microbiome-enhancing fibers. Naimi et al.'s (2021) results do not necessarily contradict prior clinical findings but indicate that gut microbiota responses are dose-, duration-, and co-exposure dependent. What may be beneficial when consumed intermittently or as a standalone supplement may become disruptive under chronic, cumulative exposure—particularly in combination with other additives that share inflammatory potential. While dietary gums may retain functional value in specific clinical or supplement contexts, their classification as universally benign emulsifiers is no longer tenable. Their microbiome impact should be considered contextual, conditional, and highly individualized. Future research is needed to define safe dose thresholds, characterize additive–additive synergies, and assess habitual consumption risks across diverse populations (Naimi et al., 2021).

Table 2: Microbiome Impact Matrix: Mechanistic Evaluation of 20 Common Emulsifiers (Naimi et al., 2021)

Emulsifier	Human Clinical Evidence	Preclinical/Mechanistic Evidence	Microbiome Impact Summary	Key References
Sodium Carboxymethylcellulose (CMC)	No clinical gut RCTs	Reduces diversity, ↑ LPS/flagellin, compositional shifts	Strongest dysbiosis signature in MBRA model	Naimi et al., 2021
Polysorbate-80 (P80)	No clinical gut RCTs	Mucus thinning, LPS ↑, microbial shifts	Potent inducer of dysbiosis and inflammation	Naimi et al., 2021
Soy Lecithin	No clinical gut RCTs	Mildest effect in study, slight compositional impact	Weak but detectable microbiota effects	Naimi et al., 2021
Sunflower Lecithin	No clinical gut RCTs	Increased flagellin expression, minor shifts	Milder than synthetic emulsifiers, not inert	Naimi et al., 2021
Maltodextrin	No clinical gut RCTs	Reduced diversity, LPS ↑, inflammatory potential	Marked gene suppression and dysbiosis risk	Naimi et al., 2021
Propylene Glycol Alginate	No clinical gut RCTs	Gene suppression and community restructuring	Not inert in microbiome context	Naimi et al., 2021
Iota Carrageenan	No clinical gut RCTs	Pro-inflammatory signaling ↑, community shifts	Strong microbial disruption and inflammation potential	Naimi et al., 2021
Kappa Carrageenan	No clinical gut RCTs	Significant dysbiosis and immune activation	Similar effects to iota carrageenan	Naimi et al., 2021
Lambda Carrageenan	No clinical gut RCTs	Inflammatory markers ↑, reduced diversity	Effects similar to other carrageenans	Naimi et al., 2021
Xanthan Gum	No clinical gut RCTs	Significant diversity loss, pro-inflammatory changes	Mechanistically disruptive	Naimi et al., 2021
Gum Arabic	Supported by human RCTs (Calame et al., 2008)	In vitro: ↓ diversity, ↑ flagellin	Context- and dose-dependent; prebiotic in humans, disruptive in vitro	Calame et al., 2008; Naimi et al., 2021
Guar Gum	No clinical gut	Reduces diversity, ↑ LPS,	Not microbiota-neutral under	Naimi et al., 2021

	RCTs	compositional disruption	mechanistic testing	
Locust Bean Gum	No clinical gut RCTs	Reduces evenness, alters microbiota structure	Microbial disruption with inflammatory signal increases	Naimi et al., 2021
Agar Agar	No clinical gut RCTs	Modest impact on composition/diversity	Weaker effect than other gums, but still present	Naimi et al., 2021
DATEM	No clinical gut RCTs	Reduces evenness, diversity; long-lasting changes	Industrial additive with lasting microbiome impact	Naimi et al., 2021
Hydroxypropyl Methyl Cellulose (HPMC)	No clinical gut RCTs	Suppresses microbiota gene expression	Mechanistically concerning	Naimi et al., 2021
Sorbitan Monostearate	No clinical gut RCTs	Alters inflammatory gene expression	Limited data, but mechanistically disruptive	Naimi et al., 2021
Mono- and Diglycerides	No clinical gut RCTs	Minimal shifts in MBRA, structurally similar to disruptive agents	Minimal effects observed, but caution still warranted	Naimi et al., 2021
Glyceryl Stearate	No clinical gut RCTs	Reduced *Faecalibacterium*, ↑ LPS, flagellin	One of the more disruptive agents	Naimi et al., 2021
Glyceryl Oleate	No clinical gut RCTs	Moderate alpha diversity loss, minor shifts	Less severe than stearate, but not inert	Naimi et al., 2021

Impact of Emulsifiers and Non-Nutritive Sweeteners on Blood–Brain Barrier Integrity and Neuroinflammation

A growing body of evidence indicates that both dietary emulsifiers and non-nutritive sweeteners (NNSs) can compromise blood–brain barrier (BBB) integrity and promote neuroinflammation through a combination of direct central effects and indirect gut microbiota–mediated pathways (Zhang et al., 2024; Arnold et al., 2022; Cong et al., 2013; Burke & Small, 2015; Naimi et al., 2021).

Several commonly used emulsifiers, most notably polysorbate 80 (P80) and carboxymethylcellulose (CMC), have been shown to impair BBB integrity in animal models. Chronic dietary P80 exposure reduces key tight junction proteins—ZO-1 and Occludin—in BBB endothelial cells, as confirmed by immunofluorescence and Western blot analyses. Gene expression profiling further supports these structural findings: P80 and CMC downregulate *PCDHGA5* (encoding a cadherin-like adhesion protein critical for BBB stability), upregulate *ARNO* (enhancing vascular permeability), and elevate *SPARC* expression (linked to increased BBB permeability and endothelial inflammation). Collectively, these changes weaken barrier function, increasing the potential for peripheral toxins or immune mediators to access the brain (Zhang et al., 2024; Arnold et al., 2022).

Beyond barrier disruption, emulsifiers can initiate and sustain neuroinflammation. Chronic P80 intake activates both microglia and astrocytes, increases the proportion of neurotoxic C3+ GFAP+ astrocytes, and impairs microglial phagocytic capacity. These cellular changes occur alongside elevated levels of pro-inflammatory mediators—including IFN-γ, ICAM-1, IL-17, and CXCL12—following both direct exposure and microbiota transplantation from treated animals, indicating a gut–brain axis mechanism. Transcriptomic analysis reveals enrichment of immune-related pathways such as *PTGS2/COX2* and *MIF* in the amygdala and hypothalamus, consistent with persistent, low-grade neuroinflammation (Zhang et al., 2024; Arnold et al., 2022).

Impact of Non-Nutritive Sweeteners on BBB Integrity and Neuroinflammation

Among NNSs, acesulfame potassium (AceK/ACK) is distinctive in its ability to cross the BBB and accumulate in brain tissue after chronic exposure in mice. This direct neural penetration disrupts hippocampal energy metabolism and synaptic signaling—manifesting as decreased glycolysis, reduced ATP production, and diminished neurotrophic support (lower BDNF/TrkB and Akt/ERK pathway activity). While classical inflammatory markers are less consistently elevated, these neurometabolic disturbances create a permissive environment for neuroinflammatory cascades, cognitive decline, and heightened vulnerability to injury (Cong et al., 2013; Burke & Small, 2015).

Other NNSs—such as aspartame, saccharin, and sucralose—have not demonstrated robust BBB penetration or direct neuroinflammatory effects at typical human-relevant intakes. However, each has been associated with alterations in gut microbiota and host metabolic function, suggesting an indirect potential to modulate brain health via the microbiota–gut–brain axis (Burke & Small, 2015).

Role of the Gut Microbiota in BBB and Neuroimmune Modulation

Both emulsifiers and select NNSs can significantly reshape gut microbial communities, often increasing the abundance of pro-inflammatory signatures such as lipopolysaccharide (LPS) and flagellin. These microbiota-derived molecules activate systemic immune pathways that, in turn, influence BBB permeability and neuroinflammatory signaling. This indirect route—via microbiota–gut–brain communication—provides a mechanistically plausible and experimentally supported link between dietary additive exposure and central neuroimmune changes (Zhang et al., 2024; Naimi et al., 2021).

Summary

The available evidence supports a model in which dietary emulsifiers—particularly P80 and CMC—and certain NNSs, most notably AceK, impair BBB integrity either through direct effects on

endothelial junction proteins or indirectly via gut microbiota–mediated immune activation. These structural and functional disruptions are accompanied by neuroimmune activation and low-grade brain inflammation, with potential implications for cognitive function and neurological disease risk (Zhang et al., 2024; Arnold et al., 2022; Cong et al., 2013; Burke & Small, 2015; Naimi et al., 2021). Such findings highlight the need for ingredient-specific and population-specific safety assessments, especially in vulnerable individuals or those consuming these additives chronically.

Table 3: Dietary Emulsifiers & Non-Nutritive Sweeteners—Direct Evidence of Brain Impact

Compound/Class	Example/Additive & Dosing	BBB Disruption Evidence	Neuroinflammation Evidence	Key Mechanisms/Findings	References
Polysorbate 80 (P80)	1% in water, chronic (mice)	Decrease in ZO-1 & Occludin; increased ARNO; altered barrier gene network	Activation/morphological changes in microglia and astrocytes; increased pro-inflammatory cytokines	Gut microbiota dysbiosis; elevated bile acids (DCA); triggers ABCA1-mTORC1-SASP, impairs barrier	Zhang et al., 2024; Arnold et al., 2022
Carboxymethylcellulose (CMC)	1% in water, chronic (mice)	Decrease in PCDHGA5 (stabilizing protein); increase in SPARC in hypothalamus/amygdala	Elevation of immune gene expression (COX2/PTGS2, MIF) in the brain	Alters gene expression related to BBB integrity/inflammation in key brain areas	Arnold et al., 2022
Acesulfame potassium (AceK/ACK)	Chronic dietary intake (mice, high FDA limit)	Direct BBB crossing and accumulation in brain/cortex	Neurometabolic impairment in hippocampus, decreased ATP & glycolysis, reduced neurotrophic signaling (BDNF/TrkB); cognitive deficits	Inhibits glycolysis in brain, disrupts energy balance, reduces Akt/TrkB phosphorylation, impairs neurons	Cong et al., 2013; Burke & Small, 2015
Sucralose	Chronic (mice); physiologic & supra-physiologic	No current evidence for BBB crossing/disruption	No direct CNS neuroinflammation; does not impair memory or induce metabolic/inflammatory changes in mouse brain	Most sucralose is not absorbed, does not act on insulin/leptin/metabolic brain endpoints at tested doses	Cong et al., 2013; Burke & Small, 2015
Saccharin	Variety of food uses; animal/human data	No robust evidence for BBB crossing/disruption	Alters gut microbiota; can induce glucose intolerance via gut-brain-microbiota axis, but no direct neuroinflammation	Effects appear to be mediated through microbiota changes; CNS impact indirect rather than direct	Burke & Small, 2015 Tsan et al. (2022).

Compound/Class	Example/Additive & Dosing	BBB Disruption Evidence	Neuroinflammation Evidence	Key Mechanisms/Findings	References
			evidence		
Aspartame	Variety of food uses; animal/human data	No robust evidence for BBB crossing/disruption	Affects gut microbiota/metabolic interactions; possible subtle behavioral effects in some settings	Rapidly metabolized to aspartic acid, phenylalanine, and methanol; not shown to directly alter brain barrier or inflammation	Cong et al., 2013; Burke & Small, 2015
Stevia (rebaudioside A/steviol glycosides)	Early life, FDA-limit doses (rats)	No direct BBB disruption measured	No direct neuroinflammation measured; impairs hippocampal-dependent memory	Impaired memory and altered sugar-motivated behaviors; ↓ Tas1r2/Tas1r3 expression; gene pathway changes in hippocampus	Tsan et al. (2022). These are animal studies

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Key:

- ↓ = decreased/reduced; ↑ = increased
- BBB = blood–brain barrier; CNS = central nervous system

Gut Barrier Dysfunction, Endotoxemia, and Blood–Brain Barrier Disruption: Mechanistic Insights

Intestinal barrier dysfunction is increasingly recognized as a pivotal factor in the development of systemic and neurological diseases, particularly in the context of dietary influences and gut microbiota alterations. The intestinal barrier consists of multiple protective layers—including intestinal alkaline phosphatase (IAP), mucus, epithelial cells, and antibacterial peptides—which collectively prevent the translocation of bacterial components such as lipopolysaccharide (LPS) into systemic circulation (Ghosh et al., 2020). Disruption of any of these layers, whether through dietary factors (e.g., high-fat diets, alcohol) or gut microbiome dysbiosis, can result in elevated circulating LPS and subsequent immune activation. This is accompanied by increased production of pro-inflammatory mediators such as TNFα, IL-1β, and IL-6, which can further impair barrier integrity and amplify inflammatory signaling (Ghosh et al., 2020).

Once the intestinal barrier is compromised, LPS enters systemic circulation, acting as a potent immune stimulant and contributing to metabolic endotoxemia and chronic inflammatory states. In both human and animal studies, excessive alcohol consumption has been associated with elevated serum LPS and monocyte activation markers, with the magnitude of increase proportional to alcohol intake; abstinence reverses these effects (Liangpunsakul et al., 2017). Similarly, in ruminants and other mammalian models, diets high in rapidly fermentable carbohydrates or non-physiological additives elevate gut-derived LPS, resulting in metabolic endotoxemia, chronic inflammation, and reduced organ function (Khiaosa-ard & Zebeli, 2018).

Chronic systemic exposure to LPS extends its impact beyond peripheral organs to the central nervous system. LPS-induced systemic inflammation can impair blood–brain barrier (BBB) integrity, with downregulation of tight junction proteins and endothelial adhesion molecules identified as central mechanisms (Chmielarz et al., 2024). Even at low concentrations, LPS primes microglia, creating a

persistent neuroinflammatory state implicated in neurodegenerative processes (Chmielarz et al., 2024). Experimental evidence shows that BBB vulnerability to LPS varies by brain region and involves both paracellular and transcytotic transport pathways; some disruption is reversible with cyclooxygenase inhibition (Banks et al., 2015). Inflammatory cytokines induced by systemic endotoxemia, including IL-1β, IL-6, and TNFα, further compromise BBB tight junctions and perpetuate neuroinflammatory cascades.

Across multiple models, dietary emulsifiers, synthetic additives, and certain non-nutritive sweeteners that alter gut microbial diversity or increase LPS-producing taxa produce effects consistent with those of high-fat diets and alcohol—namely, increased gut permeability, elevated systemic LPS, and downstream BBB disruption (Khiaosa-ard & Zebeli, 2018; Ghosh et al., 2020; Chmielarz et al., 2024). These findings collectively position gut barrier dysfunction and metabolic endotoxemia as key mechanistic links between diet-induced microbiota alterations and neuroinflammatory processes (Ghosh et al., 2020; Chmielarz et al., 2024; Banks et al., 2015).

From Gut Dysbiosis to Neuroinflammation: Emerging Evidence on Sweeteners and Emulsifiers in Modulating Brain Reward Circuits

Current research demonstrates that non-nutritive sweeteners (NNS) and dietary emulsifiers can disrupt the gut microbiome, with growing evidence linking these changes to downstream effects on brain function. These include neuroimmune activation, altered blood–brain barrier (BBB) integrity, and changes in cognitive and behavioral outcomes. While direct human evidence is limited, animal studies and mechanistic work suggest multiple plausible microbiota–gut–brain pathways through which these compounds may influence the central nervous system (CNS).

Alterations in Gut Microbiota Composition and Functional Potential Induced by Non-Nutritive Sweeteners and Emulsifiers

Non-nutritive sweeteners (NNS) and dietary emulsifiers have been consistently shown to disrupt the gut microbiome, altering both microbial diversity and metabolic function. Artificial sweeteners such as sucralose, aspartame, saccharin, and acesulfame potassium significantly reduce beneficial taxa, including *Bifidobacterium* and *Lactobacillus*, while promoting the overgrowth of potentially pro-inflammatory genera such as *Clostridiales* and *Bacteroides* (Suez et al., 2014; Conz et al., 2023; Liu et al., 2022; Naimi et al., 2021; Ivanovic & Dimitrijevic Brankovic, 2024). These compositional shifts often coincide with functional changes, including increased microbial production of lipopolysaccharide (LPS) and flagellin—potent immune activators that compromise gut barrier integrity (Xiong et al., 2023).

NNS-induced dysbiosis is associated with reduced short-chain fatty acid (SCFA) production, impaired gut hormone signaling, and altered glucose metabolism (Suez et al., 2014; Conz et al., 2023). These effects disrupt bidirectional gut–brain communication, influencing satiety, reward perception, and motivational behaviors. For example, sucralose exposure in animal models increases expression of ΔFosB in the nucleus accumbens and amygdala, suggesting long-term alterations in neural reward circuitry, particularly when combined with heightened endocannabinoid activity (Salaya-Velazquez et al., 2020).

Gut Barrier Dysfunction and Systemic Endotoxemia

The intestinal barrier comprises multiple protective layers—including intestinal alkaline phosphatase (IAP), mucus, epithelial cells, and antimicrobial peptides—that collectively prevent translocation of microbial products into systemic circulation (Ghosh et al., 2020). Disruption of these layers, whether through dietary exposures such as high-fat diets, alcohol, synthetic additives, or NNS- and emulsifier-induced dysbiosis, facilitates the passage of LPS into the bloodstream, leading to

metabolic endotoxemia. This state is characterized by elevated circulating LPS and increased production of pro-inflammatory mediators including TNFα, IL-1β, and IL-6, which can further damage barrier integrity (Ghosh et al., 2020).

Human and animal studies demonstrate that dietary and lifestyle factors directly influence circulating LPS levels. Excessive alcohol consumption correlates with elevated serum LPS and monocyte activation, with effects reversing upon abstinence (Liangpunsakul et al., 2017). Similarly, in mammalian models, rapidly fermentable carbohydrate–rich diets and certain food additives elevate gut-derived LPS, promoting chronic inflammation and organ dysfunction (Khiaosa-ard & Zebeli, 2018).

Blood–Brain Barrier Disruption and Neuroinflammatory Priming

Once LPS enters systemic circulation, it exerts potent effects on the central nervous system (CNS) by impairing blood–brain barrier (BBB) integrity. LPS downregulates tight junction proteins and endothelial adhesion molecules, increasing paracellular permeability (Chmielarz et al., 2024). Even at low concentrations, LPS can prime microglia, creating a persistent pro-inflammatory state that contributes to neurodegenerative disease progression (Chmielarz et al., 2024). BBB disruption appears region-specific, involving both paracellular and transcytotic transport pathways, and can be partially reversed by cyclooxygenase inhibition (Banks et al., 2015). Pro-inflammatory cytokines generated during endotoxemia—IL-1β, IL-6, and TNFα—further degrade BBB structure and amplify neuroinflammation.

Neuroimmune Modulation by Emulsifiers

Common emulsifiers, including carboxymethylcellulose (CMC), polysorbate 80 (P80), lecithins, mono- and diglycerides, and carrageenans, reduce α-diversity, shift microbial communities toward mucus-degrading species, and increase gut permeability (Miclotte et al., 2020; Liu et al., 2022; Panyod

et al., 2024). Although lecithin—particularly sunflower-derived lecithin—is often marketed as a "clean" alternative to synthetic emulsifiers, emerging evidence challenges the assumption that it is microbiota-neutral.

Animal studies demonstrate that chronic P80 and CMC exposure induces microglial activation, astrocytic reactivity, and altered expression of BBB-regulating genes (Arnold et al., 2022, as cited in Capitano, n.d.; Zhang et al., 2024, as cited in Ivanovic & Dimitrijevic Brankovic, 2024). These neuroimmune changes correspond with behavioral outcomes such as increased anxiety-like behavior, reduced social interaction, and deficits in learning and memory (Holder et al., 2019; Xiong et al., 2023). Furthermore, emulsifier-induced shifts in hypothalamic and amygdala neuropeptide expression suggest secondary effects on reward and motivational pathways.

From Dysbiosis to Altered Brain Reward Circuits

Microbial metabolites and inflammatory mediators generated in dysbiotic states modulate brain function via the microbiota–gut–brain axis. Elevated LPS and flagellin activate Toll-like receptor (TLR) signaling, trigger systemic cytokine release, and impair BBB function (Naimi et al., 2021; Xiong et al., 2023). These immune-driven signals influence dopaminergic, serotonergic, and neuropeptide systems—key regulators of mood, reward sensitivity, and cognition (Warner, 2024; Conz et al., 2023).

Neuroimaging studies show that NNS activate reward-related brain regions, including the ventral striatum, but elicit weaker dopaminergic responses than sugar, potentially disrupting reward prediction error processing (Greenberg & St. Peter, 2021; Onaolapo & Onaolapo, 2018; Yang, 2010). Acesulfame potassium, uniquely, crosses the BBB and accumulates in the hippocampus and cortex, impairing mitochondrial function and memory (Cong et al., 2013).

Animal data further demonstrate that sweetener- or emulsifier-induced microbiota changes are linked to elevated brain inflammatory markers, decreased neurotrophic factor expression, and altered synaptic plasticity (Salaya-Velazquez et al., 2020; Nettleton et al., 2020, as cited in Conz et al., 2023). These effects are context-dependent, dose-dependent, and in some cases reversible with dietary modification or targeted microbiota interventions.

Collectively, these results provide converging evidence that both non-nutritive sweeteners and dietary emulsifiers can modulate gut microbiota composition, compromise gut and blood–brain barrier integrity, and influence neuroimmune and neurobehavioral outcomes through microbiota–gut–brain axis pathways. The mechanistic findings across animal and human studies, coupled with consistent patterns of microbial dysbiosis, inflammatory signaling, and neural changes, establish a strong foundation for interpreting the broader implications of these additives for metabolic, neurological, and behavioral health.

Discussion

The integration of non-nutritive sweeteners (NNS) and dietary emulsifiers into modern food systems has sparked renewed scrutiny regarding their long-term safety, particularly in the context of gut microbiota composition, intestinal and blood–brain barrier (BBB) integrity, and neuroimmune modulation. Traditionally perceived as metabolically inert and safe under toxicological guidelines, emerging mechanistic and clinical research challenges this assumption—highlighting context-dependent risks that are especially pronounced in microbiome-sensitive and metabolically vulnerable populations (Conz, Salmona, & Diomede, 2023; Naimi et al., 2021).

Summary of Key Findings

Consistent evidence across animal and human studies demonstrates that both NNS and emulsifiers can disrupt the ecological balance of the gut microbiome, decrease microbial diversity, and foster the expansion of pro-inflammatory taxa. This dysbiosis frequently leads to increased microbial production of immunostimulatory molecules such as lipopolysaccharide (LPS) and flagellin, which collectively impair the mucosal and endothelial tight junctions fundamental to gut and BBB integrity (Ruiz-Ojeda et al., 2019; Conz et al., 2023; Naimi et al., 2021). Once these barriers are compromised, LPS and other microbial components gain systemic access, activating peripheral immune responses and, ultimately, central neuroimmune pathways that underpin low-grade neuroinflammation—a recognized driver of neurodegenerative conditions, mood disorders, and altered reward processing (Ghosh et al., 2020; Chmielarz et al., 2024).

Mechanistic and Clinical Evidence

Seminal research by Suez et al. (2022) provides causal evidence that even low-dose exposures to common NNS such as sucralose and saccharin can significantly impair glycemic control via the gut microbiome. Their landmark trial and follow-up fecal microbiome transplantation experiments established that NNS-induced dysbiosis itself can precipitate host metabolic dysfunction, directly challenging the narrative that such sweeteners are biologically neutral. The highly individualized metabolic responses observed were contingent on baseline microbiome composition, highlighting the microbiome as a dynamic “responsiveness hub” and underscoring the need for tailored safety recommendations in clinical nutrition (Suez et al., 2022).

Converging systematic and mechanistic reviews further reinforce these concerns. Common sweeteners, including sucralose and acesulfame potassium, consistently reduce beneficial genera such as *Lactobacillus* and *Bifidobacterium*, while enhancing the prevalence of potentially pathogenic and

pro-inflammatory bacteria (Ruiz-Ojeda et al., 2019; Conz et al., 2023). Directly, certain additives downregulate key tight junction proteins (e.g., ZO-1, Occludin) and activate microglia and astrocytes, prompting the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Arnold et al., 2022). Indirectly, additive-induced intestinal permeability increases systemic exposure to LPS, which further compromises BBB integrity and amplifies neuroinflammatory signaling cascades (Banks et al., 2015; Ghosh et al., 2020; Chmielarz et al., 2024).

Neuropsychiatric and Behavioral Links

Beyond metabolic effects, these additives may influence mental health outcomes, including depression, anxiety, and altered reward processing. Animal models provide compelling evidence that both sucrose and saccharin modulate depression- and anxiety-like behaviors, particularly in the context of metabolic dysfunction. Kumar and Chail (2019) demonstrated that chronic sucrose consumption in diabetic mice exacerbated depressive and anxiety-like behaviors, likely via heightened oxidative stress, elevated corticosterone, and monoamine oxidase activity. In contrast, saccharin exposure mitigated these behavioral abnormalities and reduced stress biomarkers, suggesting a potentially protective role in metabolically compromised states.

Similarly, Holder et al. (2019) reported that prolonged exposure to emulsifiers—specifically carboxymethylcellulose (CMC) and polysorbate 80 (P80)—altered gut microbiota composition, induced low-grade intestinal inflammation, and led to sex-specific behavioral changes in mice. Male mice exhibited increased anxiety-like behavior in the open field test, while female mice showed diminished social interaction. These behavioral alterations were accompanied by region-specific changes in neuropeptides such as agouti-related peptide (AgRP) and α-melanocyte stimulating hormone (α-MSH), indicating that emulsifier exposure may disrupt central pathways involved in mood and social behavior regulation.

Mechanistically, chronic NNS exposure in rodents modulates dopamine signaling in the mesolimbic pathway, alters ΔFosB expression in the nucleus accumbens, and disrupts glucose and energy metabolism in reward-related brain regions (Salaya-Velazquez et al., 2020). Emulsifier-induced neuroinflammation can further hinder synaptic plasticity and memory (Arnold et al., 2022; Zhang et al., 2024). Notably, acesulfame potassium uniquely crosses the BBB, directly impairing hippocampal energy metabolism and reducing neurotrophic signaling, with consequences for both cognition and resilience to injury (Cong et al., 2013; Zhang et al., 2024).

Human Evidence and Microbiome Perspective

In humans, evidence remains preliminary and primarily correlational. Miller and Branscum (2021) found that college students reporting high stress consumed significantly greater amounts of NNS, although no direct association with anxiety was observed. These findings suggest a potential bidirectional relationship—where stress may increase NNS consumption, or vice versa—though causality cannot be established. From a microbiome perspective, smaller-scale studies suggest that artificial sweeteners and emulsifiers can promote dysbiosis, attenuate production of beneficial neuroactive metabolites such as short-chain fatty acids (SCFAs) and tryptophan derivatives, and increase systemically active inflammatory mediators—all of which can influence neuroendocrine signaling and brain function (Conz et al., 2023).

Variability Among Additives and Clinical Implications

Importantly, not all emulsifiers and gums are equally disruptive. While marketed “natural” or prebiotic agents such as gum arabic have shown beneficial effects in supplement trials, recent work makes clear that context, dose, and frequency of exposure are critical determinants of their impact (Calame et al., 2008; Naimi et al., 2021). High and chronic consumption, or intake within complex

ultra-processed food matrices, can shift their effect from adaptive to dysbiotic and pro-inflammatory (Naimi et al., 2021; Panyod et al., 2024).

Clinical Rationale for Avoidance in Prebiotic Formulations

From a clinical standpoint, the absence of definitive safety thresholds for many emulsifiers and gums warrants precaution, particularly in populations with existing dysbiosis, increased intestinal permeability, or inflammatory bowel conditions. Mechanistic and preclinical studies show that agents such as CMC, P80, guar gum, xanthan gum, gum arabic, and carrageenan can reduce microbial diversity, deplete beneficial taxa such as *Faecalibacterium*, and increase pro-inflammatory molecules like LPS and flagellin—especially with high, repeated, or cumulative exposure (Naimi et al., 2021). While some agents demonstrate prebiotic potential in controlled settings, their effects in real-world ultra-processed diets may differ markedly. Consequently, excluding potentially disruptive emulsifiers and gums from microbiome-targeted formulations aligns with a risk-averse, microbiome-preserving strategy aimed at supporting microbial diversity, mucosal integrity, and systemic health.

Future Research Directions

Given their ubiquity in modern diets and mounting concerns about possible harm, the absence of long-term, controlled human studies on NNS and emulsifiers represents a pressing research gap. Future work should prioritize longitudinal dietary intervention trials incorporating high-resolution microbiome sequencing, metabolomic and immunological profiling, and advanced neuroimaging to clarify dose–response relationships and reversibility upon withdrawal. Identifying vulnerable subgroups, establishing safe intake thresholds, and exploring mitigation strategies—such as targeted prebiotics, probiotics, or postbiotics—will be essential. In parallel, food labeling regulations and public health policies may require adaptation to limit cumulative additive exposure in at-risk populations and to inform consumers more effectively.

Conclusion

The evidence reviewed underscores the need for a paradigm shift in how non-nutritive sweeteners, emulsifiers, and certain dietary gums are evaluated within the context of gut and neuroimmune health. While historically regarded as inert under toxicological frameworks, emerging mechanistic and clinical findings reveal that these additives can disrupt microbial diversity, impair intestinal and blood–brain barrier integrity, and promote systemic and neuroinflammatory responses—particularly in individuals with pre-existing metabolic or gastrointestinal vulnerabilities.

The convergence of animal, human, and in vitro data points toward a common pathway of additive-induced dysbiosis and immune activation, with downstream implications for mood regulation, cognition, and metabolic control. Although some compounds, such as gum arabic, may exert context-dependent prebiotic effects, the absence of long-term, dose–response data and the potential for additive–additive interactions argue for a precautionary approach, especially in products marketed for gut or neurological support.

Clinically, this calls for ingredient selection grounded in both demonstrated benefit and minimal evidence of harm, alongside personalized risk assessments that consider baseline microbiome composition. Future research should prioritize rigorous, longitudinal human studies integrating high-resolution microbiome sequencing, metabolomics, and neuroimaging to clarify safety thresholds and identify strategies to mitigate risk.

Until such evidence emerges, erring on the side of microbiome preservation, through the exclusion of potentially disruptive additives,represents not only a prudent formulation strategy but also an ethical imperative for safeguarding both metabolic and mental health in an ultra-processed food environment.

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