Minimally Processed Vanilla Bean Powder Versus "Natural Vanilla Flavor": Implications for Gut Microbiome Preservation and Food Safety

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1. Introduction

The demand for clean-label, microbiome-friendly formulations in the functional food and clinical nutrition sector has intensified scrutiny of both primary and auxiliary ingredients (these are supporting agents added for technological or sensory reasons and not for nutrition, which may make the product stable or more palatable). Vanilla is one of the world's most widely utilized flavor profiles, which is typically delivered as an ethanol-based extract, a reconstituted "natural flavor" formulated with multiple carriers, or as minimally processed vanilla bean powder (reconstituted means to chemically and mechanically reconstructed product designed to imitate the natural flavor profile while remaining shelf stable and easily mixed into processed food). While the "natural flavor" designation is widely accepted for its cost-effectiveness and regulatory flexibility, its inclusion of solvents and carriers raises increasing concern regarding long-term effects on gut barrier integrity and microbial homeostasis (Naimi et al., 2021; Conz et al., 2023).

Ethanol-based vanilla extracts employ ethanol, which typically are at concentrations of 35–40% by volume, as a solvent to dissolve and stabilize vanilla's complex aromatic compounds (e.g., vanillin, phenols) during maceration and aging (EFSA Panel on Food Additives and Flavourings, 2019). Reconstituted "natural flavor" systems, by contrast, incorporate multi-component carriers such as glycerol, propylene glycol, maltodextrin, and mono-/diglycerides to standardize flavor intensity, enhance water solubility, and extend shelf life, particularly in spray-dried or liquid concentrate applications (Cox et al., 2020; Younes et al., 2019). These carriers are necessary from a manufacturing

standpoint because pure vanilla oleoresins are viscous, poorly soluble, and prone to oxidation. Thus, carriers act as emulsifiers and stabilizers, ensuring a homogeneous, flowable product suitable for consistent dosing across processed food and beverage matrices.

However, accumulating evidence demonstrates that these substances, though currently Generally Recognized as Safe (GRAS), are not inert with respect to mucosal integrity and gut microbial compositional homeostasis, particularly under chronic dietary exposure. As daily intake patterns have shifted toward chronic micro-exposures, the distinction between “safe” levels and cumulative biological stress has become increasingly blurred. Continuous low-dose ingestion through multiple daily sources like coffee sweeteners, flavored yogurts, protein powders, and pharmaceuticals all which create a state of persistent exposure even when individual doses remain within regulatory limits. This chronic exposure or acute exposure with vulnerable metabolically challenged patients is detreimental as these detergent-like physicochemical properties allow direct interaction with the intestinal epithelium and microbial communities, where they compromise epithelial tight junctions (e.g., ZO-1, occludin), disrupt the mucus barrier, and alter microbial composition (Naimi et al., 2021; Chassaing et al., 2022). Such disruptions enable bacterial encroachment into the normally sterile inner mucus layer, facilitating translocation of lipopolysaccharide (LPS) and flagellin into systemic circulation. These microbial components activate Toll-like receptor 4 (TLR4) signaling, promoting chronic low-grade inflammation (metabolic endotoxemia) that manifests as insulin resistance, hyperglycemia, and hyperinsulinemia (Cani et al., 2007; Panyod et al., 2024).

The ensuing dysbiosis is characterized by depletion of short-chain fatty acid (SCFA)-producing genera such as *Faecalibacterium* and *Roseburia, which* further impairs vagal signaling and diminishes secretion of appetite-regulating peptides (GLP-1, PYY). Simultaneously, systemic LPS can cross a compromised blood–brain barrier, activating microglia and astrocytes and initiating neuroinflammation

associated with anxiety, depression, and cognitive decline (Arnold et al., 2022; Holder et al., 2019; Zhang et al., 2024). These findings underscore that flavor carriers, although historically treated as technologically necessary and acutely safe, can exert cumulative, microbiome-mediated effects that extend far beyond their intended functional role.

In contrast, minimally processed vanilla bean powder requires no solvents, emulsifiers, or humectant carriers. It is produced through simple drying, curing, and mechanical grinding of whole vanilla beans, retaining the native aromatic matrix and natural vanillin–polyphenol complexes without the need for extraction or stabilization systems. Because its volatile compounds remain bound within the bean's lignocellulosic matrix, vanilla bean powder exhibits inherent oxidative stability and dispersibility when blended into dry formulations, eliminating the need for solvent-assisted solubilization or carrier addition. This processing simplicity minimizes chemical exposure, avoids carrier–microbiome interactions, and preserves the integrity of the flavor in its natural plant matrix. See figure 1 below comparing the two.

See Figure 1: Comparison of Carrier-Based "Natural Flavor" vs. Vanilla Bean Powder

Aspect	Vanilla Bean Powder	Reconstituted "Natural Flavor"
Processing Method	Dried and ground whole vanilla beans	Solvent extraction and spray-drying or emulsification
Matrix Structure	Intact lignocellulosic plant fibers preserve volatiles	Aromatic compounds isolated and recombined with carriers
Carriers/ Solvents Used	None	Ethanol, glycerol, maltodextrin, propylene glycol
Oxidative Stability	Naturally protected by plant polyphenols and fiber	Chemically stabilized via carrier encapsulation
Solubility Behavior	Disperses naturally; no solubilization required	Requires carrier emulsification for uniform mixing
Shelf Life	12–18 months (cool, dry storage)	24–36 months

Aspect	Vanilla Bean Powder	Reconstituted “Natural Flavor”
Sensory Appearance	Natural brown hue with visible bean specks	Clear or uniform white appearance
Biological Impact	Microbiome-neutral; no barrier disruption	Associated with gut dysbiosis and mucosal irritation (Naimi et al., 2021; Chassaing et al., 2022)

Thus, from both a food-safety and gut-microbiome preservation perspective, minimally processed vanilla bean powder represents a superior alternative to “natural vanilla flavor” systems. Its production avoids extractive solvents and carrier compounds that have been implicated in epithelial barrier dysfunction and dysbiosis, aligning with modern principles of clean-label formulation and functional ingredient transparency.

2. Vanilla Bean Powder vs. “Natural Vanilla Flavor”: The Processing Divide

2.1 Regulatory Context of “Natural Vanilla Flavor”

Under major international food additive frameworks, the designation *“natural vanilla flavor”* permits the use of ethanol as an extractive solvent, with glycerol, propylene glycol, and maltodextrin frequently employed as humectants, bulking agents, or stabilizers (EFSA Panel on Food Additives, 2019). These components are required to meet acute safety and purity standards; however, emerging toxicological and microbiological evidence indicates that safety evaluations should also account for their chronic and cumulative effects, particularly their interactions with gut microbial and epithelial homeostasis at doses well below the No Observed Adverse Effect Level (NOAEL) (Younes et al., 2019). This recognition has prompted renewed scrutiny of “natural flavor” systems as more than neutral excipients, reframing them as potential modulators of intestinal and metabolic health.

2.2 Vanilla Bean Powder: Why Vanilla Bean Powder is Far Superior: The Science of Gut Microbiome Preservation

Vanilla bean powder represents a fundamentally superior choice for gut health because it delivers bioactive compounds in their native matrix without introducing microbial disruptors. Unlike processed flavor systems, vanilla bean powder is simply dried and ground whole vanilla beans, a preparation method that preserves the natural food structure and eliminates the need for synthetic or semi-synthetic carriers that drive dysbiosis, inflammation, and metabolic dysfunction (EFSA Panel on Food Additives and Flavourings, 2019; Naimi et al., 2021).

Vanilla bean powder is a superior flavoring ingredient because it involves minimal processing, maintaining the integrity of the natural ingredient and avoiding the detrimental effects of added chemical carriers.

- **Process:** Created by simply drying and grinding whole vanilla beans, this mechanical process preserves the native food matrix without chemical modification.
- **Composition:** It consists solely of the ground vanilla bean, containing no non-nutritive or synthetic additives.
- **Microbiome Impact:** This minimally processed approach aligns with dietary patterns known to support gut microbial diversity and mucosal health by avoiding chemical disruptors (Camilleri, 2021; Conz et al., 2023).

The key advantage of vanilla bean powder is that the whole-bean structure inherently provides oxidative and physical stability. Because the aromatic compounds remain embedded within plant fibers and natural polyphenolic complexes, no emulsifying agents, solvents, or humectants are required to achieve dispersibility or shelf stability. The result is a microbiome-neutral ingredient that aligns with the clean-label and functional-nutrition paradigm emphasizing minimal processing and biological compatibility.

2.3 “Natural Vanilla Flavor”: Chemical Dependency

In contrast, “natural vanilla flavor” and related reconstituted powders rely on complex processing and the inclusion of non-nutritive compounds (carriers and solvents) that have been linked to gut dysbiosis (Naimi et al., 2021; Conz et al., 2023). These carriers are indispensable from a manufacturing perspective because flavor extracts are viscous and poorly water-soluble; thus, agents such as ethanol, glycerol, and maltodextrin act as solvents, humectants, and stabilizers to improve texture, ensure homogeneous distribution, and extend shelf life in processed foods (EFSA Panel on Food Additives and Flavourings, 2019).

However, these same components directly interact with the gut microbiota. Their emulsifying and solvent properties compromise mucosal barrier integrity, downregulate tight-junction proteins, and permit bacterial encroachment into the inner mucus layer (Naimi et al., 2021; Chassaing et al., 2022). The resulting permeability facilitates the translocation of lipopolysaccharide (LPS) into systemic circulation, triggering TLR4-mediated inflammatory signaling and chronic low-grade endotoxemia, manifesting as insulin resistance, hyperglycemia, and hyperinsulinemia (Panyod et al., 2024; Chassaing et al., 2022). Furthermore, the accompanying dysbiosis, which marked by depletion of short-chain fatty acid (SCFA)-producing genera, impairs vagal signaling and reduces production of appetite-regulating peptides. Systemic LPS can also cross a compromised blood–brain barrier, activating microglia and inducing neuroinflammatory cascades linked to anxiety, depression, and cognitive decline (Arnold et al., 2022; Camilleri, 2021).

2.4 Comparative Summary

Component	Vanilla Bean Powder	“Natural Vanilla Flavor” (Processed/Reconstituted)
Primary	Dried, ground whole	Vanilla flavor components extracted via solvents (EFSA

Component	Vanilla Bean Powder	“Natural Vanilla Flavor” (Processed/Reconstituted)
Ingredient	vanilla beans	Panel on Food Additives and Flavourings, 2019)
Need for Carriers/Solvents	None; the whole-bean matrix provides integrity	Required to dissolve, stabilize, and improve texture for shelf life (EFSA Panel on Food Additives and Flavourings, 2019)
Typical Carriers/Solvents	None	Ethanol, glycerin, maltodextrin
Microbiome Implication	Supports balanced gut microbiota (Camilleri, 2021)	Carriers such as maltodextrin disrupt microbial balance and promote inflammatory signaling (Naimi et al., 2021; Chassaing et al., 2022)

2.5 What Thrives When You Choose Vanilla Bean Powder

By **eliminating maltodextrin, ethanol, and glycerin,** vanilla bean powder allows the gut microbiome to maintain homeostasis. The whole bean matrix provides:

1. **Natural polyphenols** that selectively feed beneficial *Bifidobacterium* species (Conz et al., 2023)
2. **Dietary fiber** that supports SCFA production by *Faecalibacterium* and *Roseburia*, strengthening barrier function
3. **Absence of detergent-like compounds** that otherwise deplete these keystone taxa and increase inflammatory potential (Panyod et al., 2024)

2.6 Clinical Implications for Consumers:

The processed flavor system's impact is dose-dependent and cumulative. Carrier effects persist post-treatment, suggesting chronic dietary exposure leads to sustained microbial disruption (Naimi et al., 2021). For consumers with metabolic syndrome, anxiety, or inflammatory conditions, choosing vanilla bean powder eliminates a significant, hidden source of gut-brain axis disruption (Zhang et al., 2024). The evidence is unequivocal when using vanilla bean powder's minimal processing preserves gut microbial balance and avoids the proven harms of synthetic carriers, making it the only responsible choice for microbiome-conscious consumers and formulators.

3. Risks Associated with Conventional Solvents, Carriers, and Bulking Agents

The excipients commonly used in "natural flavor" systems, ethanol, glycerol, glyceryl esters, and maltodextrin, have historically been treated as biologically inert within food matrices (Cox et al., 2020; Conz et al., 2023). However, emerging data from human and animal models demonstrate that

these compounds are bioactive participants in gut–epithelial and microbiome interactions (Naimi et al., 2021; Panyod et al., 2024). Their effects, while often subtle at low concentrations, accumulate through chronic dietary exposure (Naimi et al., 2021; Chassaing et al., 2022) and can have disproportionate consequences in metabolically or immunologically vulnerable populations (Panyod et al., 2024; Camilleri, 2021). Naimi et al., 2021 examined *ex vivo* screen of 20 emulsifiers, including maltodextrin and glyceryl stearate, showed that effects like reduced microbial diversity and increased pro-inflammatory molecules (LPS and flagellin) are often persistent (*non-reversible*) and accumulate, confirming their bioactive nature, even for compounds like glyceryl stearate (Naimi et al., 2021).

3.1 Ethanol (Residual Solvents)

Ethanol is the predominant solvent used for food-grade vanilla extraction (EFSA Panel on Food Additives, 2019). While most ethanol evaporates during post-processing, residual concentrations up to 0.05% are legally permitted in finished food products (Younes et al., 2019). Although this threshold is considered safe under conventional toxicology frameworks, ethanol is biologically active even at trace levels.

Chronic or repeated low-dose ethanol exposure alters tight-junction protein expression (ZO-1, occludin) and increases intestinal permeability. It simultaneously drives microbial compositional shifts, favoring pro-inflammatory taxa such as *Enterobacteriaceae* while suppressing butyrate-producing species (*Faecalibacterium*, *Roseburia*) (Camilleri, 2021; Conz et al., 2023). These microbial changes amplify endotoxin release, impairing gut barrier integrity and promoting low-grade systemic inflammation, a precursor to metabolic endotoxemia. For individuals with already-compromised gut or metabolic health, even residual ethanol levels may therefore serve as an unrecognized trigger of mucosal dysfunction.

3.2 Glycerol and Glyceryl Esters

Glycerol functions as both a solvent and humectant, a hygroscopic compound that binds water to prevent drying or crystallization. Mono- and diglycerides (glyceryl esters) are used as emulsifiers to stabilize reconstituted flavor systems. While these compounds are efficient at maintaining product texture and shelf stability, they also exhibit surfactant-like properties that alter host–microbe interactions at the mucosal surface.

Experimental evidence from both murine and ex vivo human gut models shows that mono- and diglycerides disrupt the ecological balance of commensal bacteria, reducing alpha diversity and expanding pathobionts associated with epithelial inflammation (Naimi et al., 2021; Panyod et al., 2024). These emulsifiers stimulate epithelial secretion of pro-inflammatory molecules such as flagellin and lipopolysaccharide (LPS), which activate Toll-like receptor (TLR) signaling and drive chronic immune activation (Cani et al., 2007). Loss of barrier integrity allows bacterial lipopolysaccharide (LPS) and flagellin to translocate into systemic circulation. The resulting low-grade endotoxemia activates toll-like receptor 4 (TLR4) signaling, increasing cytokines such as IL-6 and TNF-α (Cani et al., 2007). Clinically, this manifests as insulin resistance, endothelial dysfunction, and fatigue, which are all hallmarks of metabolic syndrome. Such exposure undermines the gut’s anti-inflammatory tone, particularly in individuals with metabolic syndrome or high-fat dietary patterns, in whom mucosal resilience is already impaired.

3.3 Maltodextrin and Other Bulking Agents

Maltodextrin is widely used as a carrier and bulking agent in spray-dried flavor formulations. It ensures uniform powder dispersion, encapsulates volatiles, and contributes to product stability.

However, both preclinical and clinical data now demonstrate that maltodextrin consumption, even at low daily doses, exerts measurable effects on intestinal ecology and barrier function.

Chronic maltodextrin ingestion reduces beneficial microbial taxa, suppresses genes involved in mucin degradation and short-chain fatty acid (SCFA) synthesis, and increases the expression of pro-inflammatory and oxidative stress genes in epithelial cells (Naimi et al., 2021; Camilleri, 2021). These molecular effects mirror those induced by synthetic emulsifiers and are consistent with observed increases in bacterial adherence and translocation. Collectively, these responses erode the mucus layer's protective barrier and promote enteric inflammation, particularly when combined with diets low in fermentable fiber or rich in processed carbohydrates.

3.4 Vulnerability Amplification in Metabolic Disease

While regulatory evaluations often assume safety at low exposure thresholds, susceptibility to harm is not uniform across populations. In individuals with metabolic dysfunction, such as type 2 diabetes, obesity, insulin resistance, or hypertension, microbiome perturbations act not as mild disturbances but as inflammatory accelerants. The gut microbiome serves as a *"responsiveness hub"*, determining how environmental exposures translate into systemic effects (Suez et al., 2022).

In a controlled carrageenan human trial, overweight participants exhibited striking vulnerability: after only two weeks, they developed reduced whole-body and hepatic insulin sensitivity, increased circulating C-reactive protein (CRP) and IL-6, and greater intestinal permeability compared to lean controls. This BMI-dependent response highlights that preexisting metabolic dysfunction magnifies the effects of seemingly low-level exposures.

Similarly, emulsifier-induced dysbiosis has been shown to deplete butyrate-producing microbes, compromising intestinal barrier integrity and allowing LPS to enter systemic circulation. The resulting

metabolic endotoxemia directly interferes with insulin signaling in muscle and adipose tissue (Cani et al., 2007). For a diabetic or insulin-resistant individual, this barrier disruption can acutely worsen glycemic control and vascular inflammation.

The Chassaing et al. (2022) controlled-feeding trial further demonstrated that exposure to the emulsifier carboxymethylcellulose (CMC) caused rapid and profound changes in the fecal metabolome, depleting short-chain fatty acids and free amino acids critical for intestinal repair and anti-inflammatory signaling. These metabolic derangements occurred within days and were most pronounced in individuals with preexisting metabolic impairment, precisely those whose disease management depends on microbial metabolite homeostasis.

Collectively, ethanol, glycerol, glyceryl esters, and maltodextrin are non-inert excipients whose chronic ingestion has measurable impacts on gut barrier function, microbial diversity, and systemic inflammation. Their effects occur well below traditional toxicological thresholds and are amplified in metabolically or immunologically vulnerable populations. The persistence of these compounds in "natural flavor" systems introduces an unpredictable variable into food formulations intended for health-conscious or clinical consumers. Reconsideration of their GRAS status in light of microbiome and metabolome data is therefore warranted to ensure that *"natural"* truly aligns with *biological safety* and *functional neutrality.*

4. Scientific and Regulatory Considerations

4.1. Microbiome and Barrier Preservation

Recent ex vivo and animal studies using next-generation gut models such as the MiniBioReactor Array (MBRA) have clarified how even trace levels of common food excipients, such

as glyceryl stearate, mono-/diglycerides, and maltodextrin, affect host–microbiota homeostasis. These mechanistic data consistently demonstrate a loss of beneficial commensal diversity, increased microbial activation, and elevated pro-inflammatory signaling within hours to days of exposure (Naimi et al., 2021; Panyod et al., 2024).

The MiniBioReactor Array (MBRA) Model

The MBRA system is a high-throughput, ex vivo human gut simulator that maintains complex microbial communities under strictly anaerobic conditions derived from human fecal inocula (Naimi et al., 2021; Auchtung et al., 2015). This model allows compound-specific evaluation without the interindividual variability inherent to human trials.

Key analytical endpoints include:

- **Microbiota Composition (16S rRNA sequencing):** MBRA studies track alpha diversity (Evenness Index) and beta diversity (Jaccard, Weighted UniFrac) to assess compositional shifts. Synthetic emulsifiers such as carboxymethylcellulose (CMC) and polysorbate 80 (P80) have been shown to induce non-reversible changes in microbial structure and function (Naimi et al., 2021).
- **Pro-inflammatory Potential (TLR-Reporter Assays):** HEK-cell reporter lines expressing TLR4 or TLR5 quantify bioactive microbial ligands such as lipopolysaccharide (LPS) and flagellin. Multiple food additives, such as maltodextrin, carrageenans, xantham gum, sorbitan monostearate, and glyceryl stearate, significantly elevate these signals (Naimi et al., 2021).
- **Gene Expression (Metatranscriptomics):** RNA-seq reveals that emulsifiers alter microbial gene activity even when species abundance remains superficially stable. Maltodextrin,

propylene glycol alginate, and several carrageenans have produced statistically significant shifts in metabolic and stress-response gene expression (Naimi et al., 2021).

In Vivo and Barrier-Integrity Models

Complementary mouse and humanized-gut studies validate these microbial disturbances at the physiological level (Chassaing et al., 2022; Panyod et al., 2024).

- **Mucus-Layer Assessment:** Confocal microscopy and PAS staining reveal reduced separation between luminal bacteria and intestinal epithelial cells, so-called *bacterial encroachment,* following exposure to CMC or P80 (Panyod et al., 2024).
- **Intestinal Permeability (FITC-Dextran):** Oral tracer assays demonstrate that mono-/diglycerides raise circulating LPS and, in some cases, modestly increase permeability, while sucrose-fatty-acid esters show an upward trend (Panyod et al., 2024).
- **Metabolic and Systemic Effects:** Emulsifiers such as sucrose fatty acid esters and CMC provoke hyperglycemia, hyperinsulinemia, and metabolic-syndrome phenotypes, with dysbiosis (loss of SCFA producers) correlating directly with these outcomes (Panyod et al., 2024).

Together, these ex vivo and in vivo data form a coherent causal chain: dietary emulsifiers, including mono-/diglycerides, glyceryl stearate, and maltodextrin, disrupt microbiota composition, elevate LPS and flagellin bioactivity, and impair mucosal barrier integrity, culminating in systemic metabolic inflammation.

4.2. Residual Solvent and Additive Standards

Peer-reviewed regulatory science now recognizes that even trace residual solvents and processing aids can exert biological effects. Accordingly, for products aimed at sensitive or clinical

populations, including those with inflammatory or metabolic disorders, finished food matrices should target non-detectable ("ND") levels (validated ≤ 0.05%) of ethanol and other residual solvents (Younes et al., 2019).

Vulnerability Amplification in Metabolic Disease

Toxicological thresholds derived from healthy populations fail to account for susceptibility amplification in individuals with metabolic dysfunction. For those with type 2 diabetes, obesity, insulin resistance, or hypertension, gut dysbiosis acts as an inflammatory accelerant rather than a benign perturbation (Suez et al., 2022).

In overweight subjects from the carrageenan trial, only two weeks of exposure reduced hepatic insulin sensitivity, increased C-reactive protein and IL-6, and heightened intestinal permeability relative to lean controls, demonstrating BMI-linked vulnerability. Similarly, emulsifier-induced dysbiosis diminishes butyrate-producing microbes, weakening barrier function and permitting LPS translocation. This metabolic endotoxemia directly impairs insulin signaling in adipose and muscle tissue (Cani et al., 2007).

The Chassaing et al. (2022) controlled-feeding study further confirmed that ingestion of CMC rapidly depletes health-promoting short-chain fatty acids and amino acids in the fecal metabolome, metabolites essential for intestinal repair and anti-inflammatory regulation. These effects were most pronounced in metabolically compromised participants, underscoring the need for revised exposure limits that integrate microbiome and metabolic-risk endpoints.

4.3. Ingredient Labeling and Consumer Transparency

Whole vanilla bean powder, composed solely of dried and ground vanilla pods, offers a benchmark for regulatory transparency. Its absence of hidden carriers, solvents, or bulking agents aligns fully with “clean label” principles and with EU and North American labeling requirements for excipient disclosure and allergen declaration (EFSA Panel on Food Additives, 2019; Conz et al., 2023). By contrast, reconstituted “natural flavors” obscure additive complexity behind a single regulatory term, impeding informed consumer choice and complicating clinical nutrition labeling. The adoption of **c**arrier-free, minimally processed flavor ingredients thus represents both a scientific and ethical imperative for manufacturers targeting gut- and metabolic-health markets.

5. Conclusion

The cumulative evidence from mechanistic, microbiological, and regulatory perspectives supports the exclusive selection of minimally processed vanilla-bean powder as a flavoring agent in food matrices intended for health-conscious and metabolically sensitive populations. In contrast to “natural vanilla flavor” systems, which include ethanol-based extracts, concentrates, and carrier-dependent blends, vanilla-bean powder avoids exposure to residual solvents, emulsifiers, and humectants now recognized to disrupt gut microbial ecology, compromise epithelial integrity, and provoke chronic low-grade inflammation.

Mechanistic studies employing the MiniBioReactor Array, metatranscriptomics, and controlled in vivo models demonstrate that additives such as maltodextrin, mono-/diglycerides, and glyceryl stearate are not inert; they elicit quantifiable biological responses at concentrations far below conventional toxicological thresholds. These findings demand a paradigm shift toward microbiome-

aware safety evaluation, one that values functional integrity of host–microbe interactions as highly as absence of systemic toxicity.

Current GRAS and EFSA frameworks, built around the "average healthy adult," fail to capture the amplified sensitivity of vulnerable populations, including those with metabolic disease, gut dysbiosis, or age-related immune decline. Controlled feeding trials (Chassaing et al., 2022; Suez et al., 2022) reveal that even short-term exposure to emulsifiers can reduce insulin sensitivity, elevate C-reactive protein and IL-6, and increase intestinal permeability in overweight individuals. Integrating susceptibility weighting and microbiome endpoints into regulatory evaluation would ensure exposure limits reflect real-world biological diversity rather than theoretical averages.

Equally urgent is the need for transparency and traceability in compound ingredients. Current labeling exemptions for "natural flavors" obscure carriers, solvents, and humectants that may undermine gut health. Requiring full excipient disclosure would empower consumers, support clinicians in dietary guidance, and drive manufacturers toward carrier-free, minimally processed reformulations, with pure vanilla-bean powder serving as the model standard.

Looking forward, food safety must evolve from a purely toxicological discipline to a systems-biology framework that safeguards human–microbial symbiosis. Incorporating microbial-ecology metrics, barrier-function assays, and metabolomic signatures into additive evaluation will redefine what qualifies as "safe" in the 21st century. This transition toward microbiome-protective regulation will better align public-health policy with emerging evidence from gut biology and position clean-label, minimally processed ingredients as the scientific and ethical gold standard for functional-food innovation.

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