# 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 a 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; Chassaing et al., 2022).

Ethanol-based vanilla extracts employ ethanol, typically 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 (U.S. FDA standard of identity for vanilla extract, 21 C.F.R. § 169.175). 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 (21 C.F.R. § 101.22; Cox et al., 2021). These carriers are necessary from a

manufacturing standpoint because pure vanilla oleoresins are viscous, poorly soluble, and prone to oxidation. Thus, these agents act as solvents, humectants, bulking agents, and, in the case of the mono- and diglycerides, emulsifiers, 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 creates a state of persistent exposure even when individual doses remain within regulatory limits. This chronic exposure, or acute exposure in vulnerable metabolically challenged patients, is detrimental because these detergent-like physicochemical properties allow direct interaction with the intestinal epithelium and microbial communities, where they alter microbial composition and elevate pro-inflammatory LPS and flagellin (Naimi et al., 2021) and, in animal and controlled-feeding models, disrupt the mucus barrier and downregulate epithelial tight-junction proteins such as ZO-1 and occludin (Chassaing et al., 2022; Panyod et al., 2024). 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; Ghosh et al., 2020; 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 linked, in animal models, to anxiety-like behavior 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 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.

**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 |

| Aspect | Vanilla Bean Powder | Reconstituted "Natural Flavor" |
|---|---|---|
| Solubility Behavior | Disperses naturally; no solubilization required | Requires carrier emulsification for uniform mixing |
| Shelf Life | 12–18 months (cool, dry storage) | 24–36 months |
| Sensory Appearance | Natural brown hue with visible bean specks | Clear or uniform white appearance |
| Biological Impact | Free of carriers implicated in dysbiosis; not shown to disrupt the barrier | Contains carriers implicated in gut dysbiosis and mucosal disruption (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 (21 C.F.R. § 101.22; Cox et al., 2021). 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 conventional no-observed-adverse-effect levels. 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: The Science of Gut Microbiome Preservation

Vanilla bean powder delivers its 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 (Naimi et al., 2021).

Vanilla bean powder is a preferable 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 avoids the carriers and solvents implicated in dysbiosis and mucosal disruption (Naimi et al., 2021; Chassaing et al., 2022).

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 carrier-free flavor 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 (Cox et al., 2021).

However, these same components directly interact with the gut microbiota. They alter microbial composition and elevate LPS and flagellin bioactivity (Naimi et al., 2021) and, in vivo, compromise mucosal barrier integrity and permit bacterial encroachment into the inner mucus layer (Chassaing et al., 2022; Panyod et al., 2024). 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, 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, in animal models, to anxiety-like behavior and cognitive decline (Arnold et al., 2022; Holder et al., 2019; Zhang et al., 2024).

### 2.4 Comparative Summary

| Component | Vanilla Bean Powder | "Natural Vanilla Flavor" (Processed/Reconstituted) |
|---|---|---|
| Primary Ingredient | Dried, ground whole vanilla beans | Vanilla flavor components extracted via solvents (Cox et al., 2021) |
| Need for Carriers/Solvents | None; the whole-bean matrix provides integrity | Required to dissolve, stabilize, and improve texture for shelf life (Cox et al., 2021) |
| Typical Carriers/Solvents | None | Ethanol, glycerin, maltodextrin |
| Microbiome Implication | Contains no carriers implicated in dysbiosis | Carriers such as maltodextrin disrupt microbial balance and promote inflammatory signaling (Naimi et al., 2021; Chassaing et al., 2022) |

### 2.5 What Vanilla Bean Powder Contributes — and What It Does Not

By eliminating maltodextrin and the emulsifying glyceryl esters, the carrier compounds most consistently implicated in additive-driven dysbiosis, and by carrying no residual ethanol, vanilla bean powder removes the excipients of genuine concern. Glycerin is a separate case: it is benign at flavoring levels, so its absence is a matter of simplicity rather than safety. Its clearest and best-supported advantage is therefore *what it avoids* rather than what it adds. Beyond avoidance, whole vanilla bean also contributes:

1. **Naturally occurring plant fiber and polyphenol/vanillin bioactives** retained in the intact bean matrix.
2. **Preclinical microbiome signals:** in high-fat-diet mice, vanillin (the principal vanilla flavor compound, tested in isolation) improved gut microbiota composition, increased short-chain fatty acid production, and reduced LPS, IL-6, and TNF-α while improving insulin sensitivity and glucose tolerance (Guo et al., 2018). This is animal evidence using isolated vanillin at doses

well above what a flavoring amount of vanilla bean powder delivers; it is not proof of a prebiotic effect in humans.

3. **Absence of detergent-like carriers** that otherwise deplete keystone SCFA-producing taxa and increase inflammatory potential (Naimi et al., 2021; Panyod et al., 2024).

By the formal ISAPP definition, a prebiotic is a substrate selectively utilized by host microorganisms to confer a health benefit (Gibson et al., 2017); vanilla bean powder has not been established at that level in human trials and should not be described as a clinically proven prebiotic. The accurate positioning is that its whole-bean fiber and vanillin-related bioactives make it a more microbiome-conscious flavor choice than carrier-based "natural flavor" systems or non-nutritive sweeteners — not that it actively feeds beneficial bacteria at flavoring doses.

A practical standard follows from this evidence, and it is not all-or-nothing. The carriers that warrant concern are the detergent-type emulsifiers and the bulking agent maltodextrin, which alter microbial composition and barrier function; the operative distinction is therefore not carrier versus no carrier, but benign, fully disclosed carrier versus hidden, barrier-active one. Where a small amount of carrier is needed to stabilize or disperse a real-vanilla extract, benign and fully declared options are categorically different from the excipients of concern: food-grade vegetable glycerin, which is a humectant rather than a surfactant and is not implicated in the emulsifier literature (Section 3.2), and acacia fiber (gum arabic), a fermentable soluble fiber that the ex vivo screen found only modestly active (Naimi et al., 2021), do not carry the barrier and microbiome liabilities of maltodextrin, glyceryl-ester emulsifiers, or an undeclared natural flavor blend. A formulation built on ground whole vanilla bean together with a minimal, disclosed, benign-carrier extract therefore meets the microbiome-protective and transparency objectives of this paper; it removes the excipients that matter without requiring that every carrier be eliminated.

### 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 source of exposure to carriers with demonstrated microbiome effects (Zhang et al., 2024). The evidence is strongest for what it avoids: vanilla bean powder's minimal processing sidesteps the demonstrated effects of synthetic carriers, making it a defensible default 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, glyceryl esters, and maltodextrin, have historically been treated as biologically inert within food matrices (Cox et al., 2021; 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). Glycerol is the benign exception in this group and is addressed separately in Section 3.2. 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 an ex vivo screen of 20 emulsifiers, including maltodextrin and glyceryl stearate, and showed that effects such as reduced microbial diversity and increased pro-inflammatory molecules (LPS and flagellin) are often persistent (non-reversible) and cumulative, 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 (21 C.F.R. § 169.175). At meaningful, consumption-level doses, ethanol is a well-established disruptor of the intestinal barrier: ethanol and its metabolite acetaldehyde alter tight-junction protein expression (ZO-1, occludin), increase intestinal permeability, and shift the microbiota toward pro-inflammatory taxa such as *Enterobacteriaceae* while suppressing butyrate-producing species such as *Faecalibacterium* and *Roseburia*, changes that amplify endotoxin translocation and low-grade systemic inflammation. This evidence, however, derives from alcohol *consumption* and doses on the order of grams per drink, not from the trace quantities left behind by a flavoring.

The amount of ethanol contributed by a vanilla flavoring is orders of magnitude smaller. Ethanol is volatile and a large fraction evaporates during any drying or heating step (though the common assumption that it "cooks off" completely is inaccurate; some residual can remain). Even so, the residual reaching a finished serving is measured in milligrams at most, which is far below any level shown to affect the human gut barrier. There is currently no evidence that residual ethanol at flavoring concentrations disrupts intestinal integrity, and this paper does not claim otherwise.

The relevant point for formulation is therefore not that trace ethanol is hazardous, but that it is an avoidable variable. Extract- and carrier-based "natural vanilla flavor" systems introduce ethanol by design, whereas minimally processed vanilla bean powder contains no added ethanol at all. For products intended for metabolically or gastrointestinally sensitive populations, eliminating the solvent entirely is a cleaner and more defensible choice than relying on the assumption that residual levels are low enough to be inconsequential.

### 3.2 Glycerol (Glycerin) Versus Glyceryl Esters

These are frequently confused because they share a root name, but they are different compounds with different biological behavior, and only one of them carries a microbiome concern. **Glycerol, commonly labeled glycerin, is a simple sugar alcohol** used as a solvent and humectant, a hygroscopic compound that binds water to prevent drying or crystallization. It has no fatty-acid component, does not act as a surfactant, and is absorbed and metabolized in the small intestine. At the levels used in flavorings, glycerin is not known to disrupt the intestinal barrier or the microbiota, and the emulsifier evidence discussed below does not apply to it. Its only notable dose-dependent effect is osmotic, like other polyols, large quantities can loosen stool, which is a tolerance issue, not barrier damage.

**Glyceryl esters are a distinct class**, formed by attaching one or more fatty acids to the glycerol backbone; mono- and diglycerides and glyceryl stearate are common examples. The fatty-acid tail gives these molecules surfactant (detergent-like) properties, which is what allows them to alter host–microbe interactions at the mucosal surface. It is this class, not glycerol itself, that is implicated in the emulsifier literature.

In the ex vivo human-microbiome (MBRA) screen, glyceryl stearate produced non-reversible reductions in microbial diversity and a lasting increase in bioactive LPS, while mono- and diglycerides produced more modest shifts (Naimi et al., 2021); complementary animal work links dietary emulsifiers of this type to reduced diversity, expansion of pro-inflammatory taxa, and mucus-barrier disruption (Panyod et al., 2024). Where these surfactant-like esters compromise barrier integrity, bacterial lipopolysaccharide (LPS) and flagellin can translocate into systemic circulation, activating TLR4 signaling and raising inflammatory cytokines such as IL-6 and TNF-α, the metabolic-endotoxemia pathway linked to insulin resistance (Cani et al., 2007). As with the other carriers

discussed here, these effects are most consequential 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 mechanistic 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 production and short-chain fatty acid (SCFA) synthesis, and increases the expression of pro-inflammatory and oxidative-stress genes in the microbial community (Naimi et al., 2021; Zangara et al., 2022; 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 may 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 randomized, double-blind crossover trial of carrageenan in twenty men, overall insulin sensitivity was unchanged, but a post hoc BMI interaction emerged: overweight participants developed

reduced whole-body and hepatic insulin sensitivity, elevated C-reactive protein (CRP) and IL-6, and greater intestinal permeability after two weeks, effects not seen in leaner participants (Wagner et al., 2024). This BMI-dependent response, a subgroup finding rather than an overall treatment effect, highlights that preexisting metabolic dysfunction can magnify the impact of seemingly low-level additive 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 could worsen glycemic control and vascular inflammation.

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

Collectively, dietary emulsifiers such as glyceryl esters, together with the bulking agent maltodextrin, are non-inert excipients whose chronic ingestion has measurable impacts on gut barrier function, microbial diversity, and systemic inflammation. Their effects occur at concentrations below traditional toxicological thresholds and are amplified in metabolically or immunologically vulnerable populations. Ethanol adds a separate, dose-dependent consideration: its barrier effects are well established at consumption-level intakes, whereas the residual amounts contributed by flavorings are far lower and not themselves shown to cause harm. Glycerol, by contrast, is a benign humectant at these levels and is not implicated. The persistence of the emulsifying and bulking carriers in "natural

flavor" systems nonetheless introduces an avoidable 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.

## 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 esters, 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. It models the microbial community in isolation and does not include host epithelium, so barrier and tight-junction endpoints are drawn from complementary in vivo work.

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, including maltodextrin, carrageenans, xanthan gum, sorbitan monostearate, and glyceryl esters, 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 esters, 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

A meaningful distinction should be drawn between additives and residual solvents. For dietary emulsifiers and bulking agents such as glyceryl esters and maltodextrin, controlled and mechanistic studies show measurable microbiome and barrier effects at the doses at which these compounds are actually consumed, which supports lower-exposure standards for products aimed at sensitive or clinical populations. For residual solvents such as ethanol, the situation is different: their biological effects are established at consumption-level intakes, but direct evidence of harm at the trace levels left behind by flavorings is lacking. On a precautionary basis, finished food matrices intended for inflammatory- or metabolic-disorder populations should still minimize residual solvents where practical and, better still, favor ingredients that avoid them entirely, a position grounded in precaution under uncertainty, not in demonstrated trace-level harm.

### Vulnerability Amplification in Metabolic Disease

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

In the carrageenan crossover trial, the overall effect on insulin sensitivity was null, but overweight participants showed reduced hepatic insulin sensitivity, higher C-reactive protein and IL-6,

and greater intestinal permeability after two weeks, a post hoc BMI-interaction effect rather than a population-wide one (Wagner et al., 2024). Similarly, emulsifier-induced dysbiosis diminishes butyrate-producing microbes, weakening barrier function and permitting LPS translocation, with the resulting metabolic endotoxemia impairing 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 alters the fecal metabolome, depleting short-chain fatty acids and amino acids relevant to intestinal repair and anti-inflammatory regulation. These effects were most pronounced in metabolically compromised participants, underscoring the case for 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. 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 carrier-free, minimally processed flavor ingredients thus represents both a scientific and ethical priority for manufacturers targeting gut- and metabolic-health markets.

## 5. Conclusion

The cumulative evidence from mechanistic, microbiological, and regulatory perspectives supports the preferential 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 below conventional toxicological thresholds. These findings support a shift toward microbiome-aware safety evaluation, one that values functional integrity of host–microbe interactions alongside the absence of systemic toxicity.

Current GRAS and EFSA frameworks, built around the "average healthy adult," may fail to capture the amplified sensitivity of vulnerable populations, including those with metabolic disease, gut dysbiosis, or age-related immune decline. Controlled human trials (Chassaing et al., 2022; Wagner et al., 2024) show that even short-term additive exposure can alter the gut metabolome and, in overweight individuals, reduce insulin sensitivity and raise inflammatory markers. Integrating susceptibility weighting and microbiome endpoints into regulatory evaluation would help ensure exposure limits reflect real-world biological diversity rather than theoretical averages.

Equally important is 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 encourage manufacturers toward minimally processed, fully disclosed reformulations, with whole vanilla bean and benign, declared carriers serving as a model standard.

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

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