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Plant-derived exosome-like nanoparticles as emerging bioactive compounds

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ABSTRACT

This review connects emerging research on plant-derived exosome-like nanoparticles (PDENs) with functional food science, highlighting opportunities to improve standardization, translational validation, and product development for gut-health applications.

PDENs are small (30–150 nm) lipid-bound vesicles derived from edible plants that are structurally and functionally similar to mammalian exosomes. They serve as natural carriers of bioactive molecules—including proteins, lipids, and miRNAs—supporting antioxidant, anti-inflammatory, and therapeutic effects, while also offering high stability, low toxicity, and cost-effective, high-yield production.

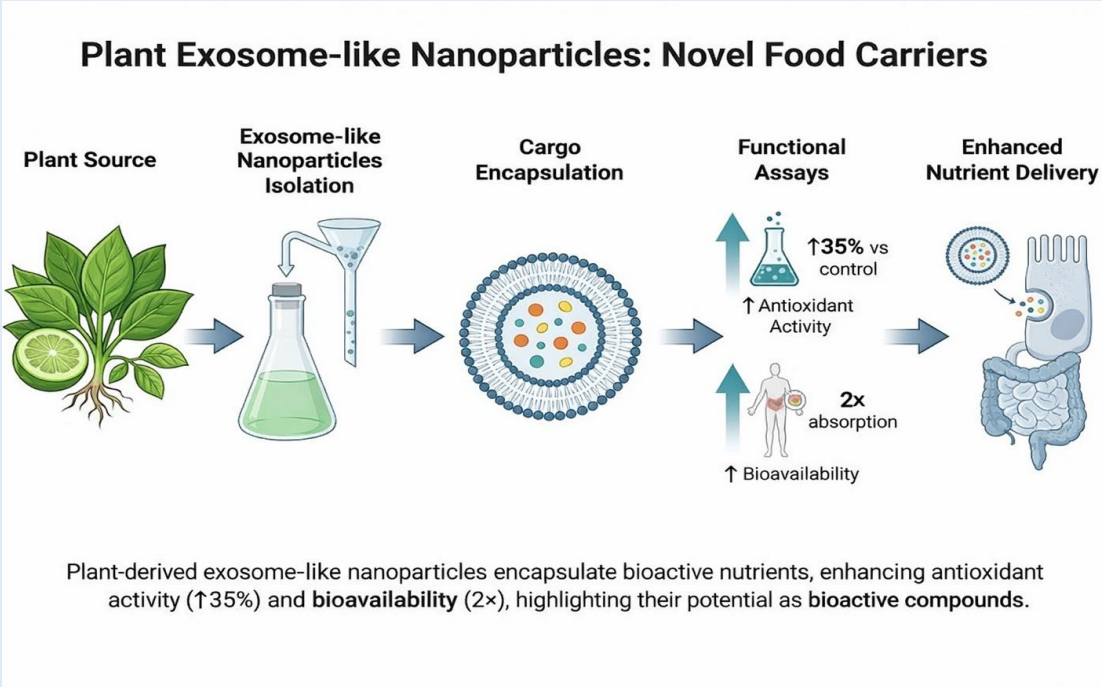
PDENs isolated from edible plants (e.g., ginger, grape, grapefruit, citrus, tea, aloe) carry bioactive cargo—lipids, proteins, metabolites, and nucleic acids—and may remain functionally active during gastrointestinal transit, enabling interactions at the intestinal interface. Interest is growing because PDENs may act as both intrinsic functional components and food-native delivery platforms that influence gut–immune outcomes. However, key uncertainties remain, including inconsistent terminology, scalable isolation and characterization, dosing conventions, stability in real food matrices, and the extent to which proposed cross-kingdom and microbiome-mediated mechanisms translate to humans.

This review evaluates the current evidence base with emphasis on gut inflammation, barrier resilience, mucosal immune balance, and microbiome-directed effects as functional food targets. It also addresses commercialization barriers such as plant- and processing-driven batch variability, co-isolated impurities that complicate functional attribution, and safety considerations for concentrated preparations. Finally, the article discusses how PDEN products fit within regulatory frameworks for novel and concentrated ingredients and proposes a practical development pathway

that prioritizes harmonized quality benchmarks, transparent reporting aligned with extracellular vesicle standards, and stepwise human feasibility studies using validated biomarkers.

Novelty: This review applies a functional food development framework to PDEN research by connecting vesicle characterization, food-grade formulation, regulatory planning, and biomarker-based human validation into one translational approach. It links emerging PDEN mechanisms in gut and immune health with practical product development needs, highlights key barriers such as inconsistent terminology, batch variability, dosing uncertainty, and limited human data, and proposes stepwise solutions to support evidence-based translation into functional food carriers for gut–immune support.

Keywords: Plant-derived exosome-like nanoparticles; Intestinal barrier integrity; Gut inflammatory balance; Microbiome modulation; Food-grade standardization; MISEV-aligned characterization; Biomarker-based human studies; Functional ingredients; Gut-health applications



Graphical Abstract: Plant-derived exosome-like nanoparticles as emerging bioactive compounds.

INTRODUCTION

Functional ingredient science has traditionally emphasized isolated nutrients and discrete bioactive compounds that can be standardized, dosed, and linked to measurable biomarkers. This approach has supported early product development and claim substantiation because ingredient identity and exposure can be defined with reasonable precision. However, a growing body of research in food science and nutrition recognizes that biological outcomes are also influenced by food structure and naturally occurring supramolecular assemblies that affect stability, uptake, and site-specific interactions in the gastrointestinal tract. Within this broader evolution, nano- and micro-scale delivery strategies have been

explored to protect labile bioactives and improve functional performance in complex food matrices, while maintaining food-grade feasibility and safety expectations [1-2].

PDENs have emerged as a candidate class within this shift. They are lipid bilayer vesicle-like nanoparticles enriched from edible plant tissues and reported across common dietary sources including ginger, grape, grapefruit, citrus fruits, tea, and aloe [3-7]. PDEN preparations contain complex cargo, including lipids, proteins, metabolites, and nucleic acids, and are proposed to retain sufficient integrity during gastrointestinal transit to interact with intestinal epithelial surfaces, immune cells, and gut microbial communities [3-8]. The defining functional ingredient interest is that PDENs may serve as food-native carriers that integrate cargo protection and delivery with intrinsic bioactivity, potentially enabling gut-localized "quick outcome" endpoints such as inflammatory tone and barrier resilience [3-7].

A central hypothesis in this field is cross-kingdom communication, in which vesicle-associated cargo, including lipids and small RNA species, influences mammalian and microbial targets after ingestion. Although the strength and generalizability of cross-kingdom signaling remain debated and are highly sensitive to methodological controls, multiple studies support the plausibility of intestinal uptake and measurable effects in preclinical gut inflammation models [4-8]. These outcomes align closely with translational goals in bioactive compound development because they are mechanistically anchored to the gut interface and can be evaluated using biomarker-driven study designs [9-10].

This review positions PDENs as emerging functional ingredient innovation candidates, with an emphasis on their role as functional carriers for gut–immune outcomes. The article summarizes PDEN structure and composition, evaluates plausible mechanisms and evidence, and discusses commercialization barriers, including standardization, manufacturing feasibility, safety, and regulatory classification. Regulatory context is discussed using the EU Novel Food framework and US GRAS and dietary supplement claim substantiation resources as representative pathways relevant to innovation translation [11-14].

Methodology: This narrative review synthesizes key studies on plant-derived exosome-like nanoparticles (PDENs) with a focus on their relevance to functional ingredient science and gut-health applications. Literature was collected from electronic databases including PubMed, Scopus, Web of Science, Google Scholar, and the FFHDJ journal database. Search terms included combinations such as "plant-derived exosome-like nanoparticles," "PDENs," "PELNs," "edible plant extracellular vesicles," "plant nanovesicles," "functional ingredient carriers," "gut inflammation," "microbiome modulation," and "cross-kingdom signaling," with filters for English-language publications from 2013 to 2026. Priority was given to peer-reviewed original research, reviews, and studies with mechanistic or translational relevance. Selection criteria emphasized edible plant sources, gut-related outcomes, characterization rigor (e.g., MISEV alignment), and bioactive compound implications.

Plant-derived exosome-like nanoparticles: Plant-derived exosome-like nanoparticles (PDENs) are nanoscale, membrane-bound vesicular structures enriched from edible plant tissues, including fruits, vegetables, and medicinal plants. They are commonly described as lipid bilayer nanoparticles, with reported size distributions often ranging from tens to a few hundred nanometers, although measurements vary across studies due to differences in plant source, separation workflows, and analytical methods [3-8]. The term "exosome-like" is typically used based on size, morphology, and cargo patterns rather than definitive

proof of endosomal biogenesis in the source plant cells, which is rarely demonstrated for food-derived preparations. For this reason, operational definitions and transparent characterization are essential, especially when positioning PDENs as functional ingredients rather than purely experimental fractions [8-10,15-19].

PDEN cargo reflects plant origin and commonly includes membrane lipids, proteins, metabolites, and nucleic acids, including small RNA species frequently described as microRNA-like sequences [3-7]. This multicomponent nature distinguishes PDENs from classic functional food ingredients defined primarily by a single dominant bioactive compound. From a translational standpoint, PDENs are best conceptualized as integrated bioactive systems in which structure and cargo are intrinsically linked, and ingredient identity is therefore dependent on source material and manufacturing specifications rather than a single chemical marker [3,8-9].

A critical practical consideration is that PDEN preparations vary across studies. Agricultural conditions, storage, tissue selection, extraction, and enrichment methods can all shift yield and cargo composition, and co-isolated plant macromolecules may contribute to observed effects if purity controls are insufficient [8-9]. For bioactive compound development, PDENs should therefore be defined by source, process, and physicochemical specifications, including size distribution, particle concentration, morphology confirmation, and representative compositional fingerprints that support batch-to-batch consistency [8-10].

Mechanistic basis for PDEN bioactivity and carrier function: The proposed functional relevance of PDENs depends on three mechanistic pillars: partial stability during gastrointestinal transit, interaction or uptake at the intestinal interface, and downstream modulation of host and/or microbiome-associated pathways. Several studies suggest that plant-derived vesicle-like nanoparticles can retain functional integrity under gastrointestinal-like conditions sufficiently to reach intestinal sites where they can interact with epithelial surfaces and immune cell compartments, although stability is expected to be source- and formulation-dependent and must be validated for each intended product matrix [3-7, 20-22].

Uptake or interaction with intestinal targets is a repeated theme in landmark PDEN studies. Grapefruit-derived nanovesicles have been reported to target intestinal macrophage populations and to act as carriers for bioactive delivery to intestinal immune compartments, while grape-derived vesicle-like nanoparticles have been associated with effects on intestinal cell populations relevant to mucosal maintenance [3-5]. Ginger-derived nanoparticles have been widely reported for gut-directed effects in preclinical colitis models, supporting the plausibility of local gut activity as a functional endpoint [7]. Together, these data support the translational relevance of gut-localized outcomes, which are typically more feasible for functional ingredient evaluation than systemic pharmacokinetic endpoints [3-7].

At the pathway level, PDENs have been proposed to modulate inflammatory signaling and barrier resilience through mechanisms involving immune tone regulation, oxidative stress responses, and epithelial repair processes. A complementary mechanism involves microbiome interactions, including proposed vesicle–microbe effects mediated by vesicle lipids or nucleic acids, which may indirectly influence mucosal immunity and barrier function [6]. The microbiome-directed hypothesis is particularly attractive for functional food positioning because it supports “ecosystem modulation” rather than single-target pharmacology; however, it also raises the standard for mechanistic controls and reproducibility [6-9,23-25].

Because PDENs are frequently described using extracellular vesicle terminology, methodological rigor should align with established EV reporting standards. The Minimal Information for Studies of Extracellular Vesicles (MISEV) guidelines emphasize transparent reporting of pre-analytical variables, separation workflows, characterization, and appropriate controls for contaminants and functional attribution, all of which are directly relevant for credible functional food translation [8-9].

PDENs as Potential Carriers for Prebiotic-Like Effects and Considerations for Allergen Transport: PDENs may serve as natural carriers for bioactive payloads, including potential indirect support for prebiotic-like effects by protecting or delivering microbiome-modulating compounds (e.g., lipids or metabolites) that influence gut microbiota composition. While direct evidence for PDEN-prebiotic synergy remains emerging and requires further validation, this aligns with microbiome-directed functional ingredient strategies. Separately, concerns exist regarding whether PDEN preparations could inadvertently transport allergenic proteins (e.g., pathogenesis-related proteins from source plants). Rigorous purity controls and source selection (e.g., low-allergen plants) are essential to mitigate this risk, particularly for concentrated preparations intended for broad consumption. These aspects underscore the need for allergen screening and compositional profiling in product development.

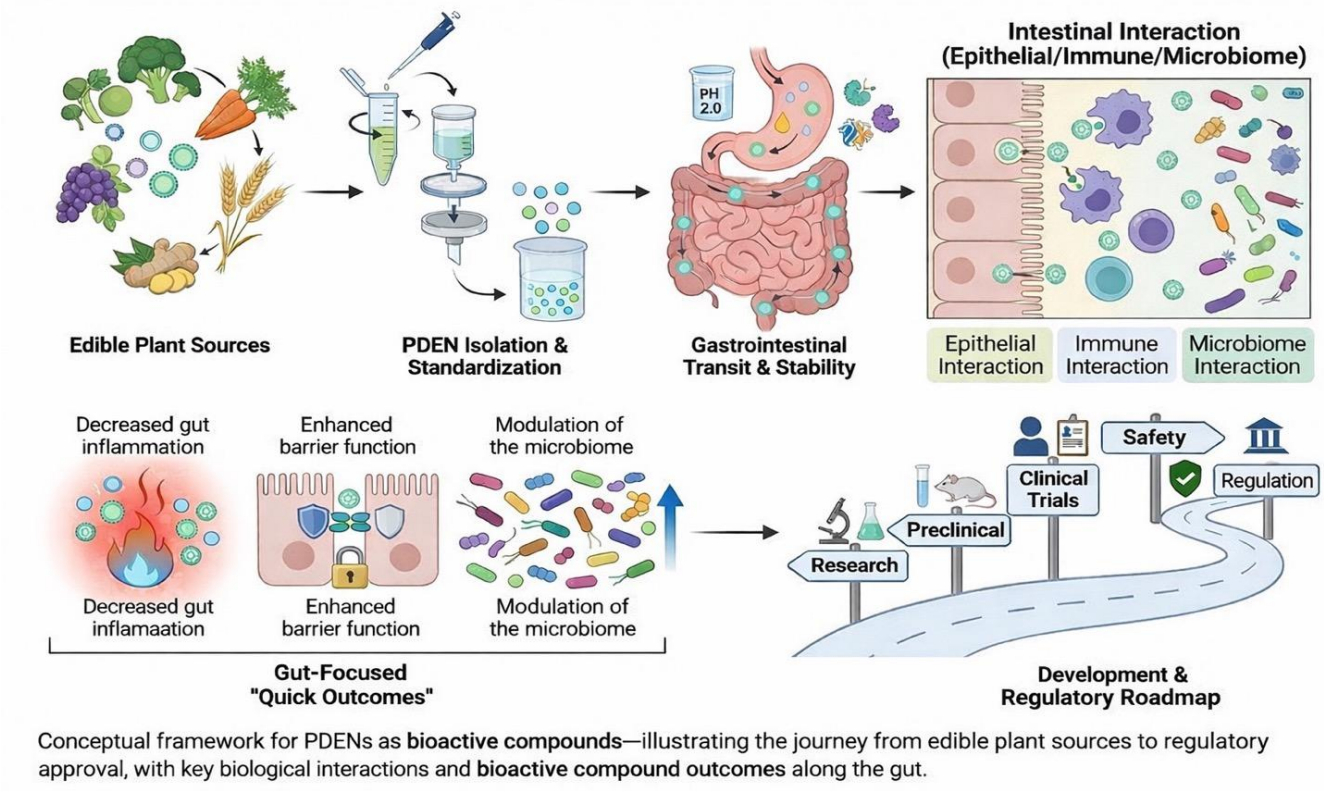


Figure 1. Proposed Mechanisms of PDEN Interaction at the Gut Interface

Current scientific evidence: The PDEN evidence base is currently strongest in cellular systems and animal models, with a major emphasis on intestinal inflammation and mucosal injury contexts. Foundational studies demonstrated that edible plant-derived vesicle-like nanoparticles can be isolated and characterized and may show biological activity after oral exposure. Grape-derived vesicle-like nanoparticles were reported to

influence intestinal cell populations and protect mice in DSS-induced colitis models, while grapefruit-derived nanovesicles were reported to deliver cargo to intestinal macrophage populations and support anti-inflammatory outcomes in gut-relevant contexts [3-4]. Additional studies advanced the cross-species signaling concept by reporting interactions between plant-derived nanoparticle preparations and mammalian cells after ingestion [5,26-28].

Ginger-derived nanoparticles represent a particularly prominent example due to extensive citation and mechanistic exploration in experimental colitis and colitis-associated cancer contexts. These studies support the plausibility of PDENs as natural delivery platforms for gut-localized effects and provide a rationale for functional food concepts centered on inflammatory balance and barrier integrity [7]. Separately, microbiome-focused work has proposed that plant-derived exosome-like nanoparticles and their RNA cargo may shape gut microbiota and downstream host mucosal immune pathways, although the extent to which these mechanisms generalize across sources and diets remains an area requiring continued validation and standardized methods [6].

For functional ingredient development, the key limitation is the translation gap from preclinical efficacy to reproducible ingredient definition, scalable manufacturing, safety assurance, and human feasibility trials using validated biomarkers. This gap is not unique to PDENs; it is a recurring challenge for complex ingredients and delivery systems, and it underscores the need to integrate PDEN research with standardized characterization frameworks and development models that emphasize dose, safety, and clinically meaningful endpoints [1-2,8-10,29-33].

Emerging PDEN-Based Formulations and Applications Under Investigation: Although the majority of PDEN research remains at the preclinical stage, with most evidence derived from in vitro cellular models and animal studies (particularly DSS-induced colitis, gut inflammation, and microbiome modulation models), several landmark and follow-up investigations have begun to explore proof-of-concept formulations and potential functional food-relevant applications. These examples illustrate how PDENs could transition from isolated vesicle preparations to integrated ingredients or delivery platforms in food matrices.

Ginger-derived nanoparticles represent one of the most extensively studied cases, with multiple reports demonstrating their utility as natural bioactive carriers in experimental gut-health contexts. For instance, ginger-derived exosome-like nanoparticles have been administered orally in preclinical colitis models, where they exhibited protective effects on intestinal mucosa, reduced inflammatory injury, and improved barrier resilience—outcomes directly relevant to functional ingredient targets such as inflammatory balance and gut comfort [7]. These preparations have been conceptualized as potential functional ingredients in gut-directed nutraceuticals or supplements, leveraging their lipid- and metabolite-enriched cargo for localized activity during gastrointestinal transit.

Grapefruit-derived nanovesicles provide another prominent example, having been investigated as natural carrier platforms capable of targeted delivery to intestinal immune compartments, including macrophage populations. Studies have shown these vesicles can transport bioactive cargo to gut-associated lymphoid tissues, resulting in anti-inflammatory effects in relevant models [4]. This property has prompted exploration of grapefruit-derived PDENs as food-native delivery systems that could be incorporated into functional beverages, soft gels, or fortified foods aimed at supporting mucosal immune balance.

Grape-derived vesicle-like nanoparticles have similarly been reported to influence intestinal cell populations and confer protection in chemically induced colitis models, supporting their potential role in formulations designed to enhance mucosal maintenance and barrier function [3]. Conceptual applications include their use as intrinsic bioactive components in grape-based functional products (e.g., juices, extracts, or powders) where vesicle integrity during processing and transit could contribute to gut-protective outcomes.

Additional edible plant sources, such as citrus (e.g., lemon) and tea, have been examined for PDEN preparations enriched in antioxidant-related signaling components or mixed bioactive cargo with microbiome-linked effects [references in Table 1]. These have been proposed as candidates for incorporation into antioxidant-supportive beverages, microbiome-modulating teas, or synbiotic-like formulations, although such applications remain largely hypothetical pending scalable isolation, matrix stability data, and human feasibility confirmation.

Collectively, these investigational examples highlight PDENs' dual appeal as both intrinsic bioactive entities and natural carriers within food-grade contexts. However, they remain constrained by the same translational challenges discussed throughout this review: inconsistent dosing conventions, batch-to-batch variability from plant source and processing, co-isolated impurities requiring rigorous purity controls, limited stability testing in real food matrices, and the absence of robust human pilot data using validated biomarkers. Advancing these formulations toward product prototypes will require alignment with standardized characterization (e.g., MISEV guidelines), food-grade manufacturing feasibility, and stepwise human studies focused on gut-localized endpoints.

Table 1: compares representative PDEN sources, reported dosing approaches, and gut-related effectiveness outcomes, highlighting the translational gaps that must be addressed for functional food development.

PDEN source (resource)	Dominant cargo emphasis reported	Dose metric commonly reported in studies	Representative gut-related effectiveness outcome in preclinical models	Primary gap for functional ingredient translation
Ginger	Lipid- and metabolite-enriched vesicle fraction	Particle number and/or protein content; sometimes source-equivalent mass	Reduced intestinal inflammatory injury and improved mucosal resilience in colitis-related models	Standardized dosing convention and matrix stability data
Grapefruit	Vesicles used as natural carrier platform; lipid-rich membranes	Particle number and/or protein content	Delivery to intestinal immune compartments with anti-inflammatory effects in gut models	Scalable food-grade isolation and batch consistency benchmarks
Grape	Vesicle-associated bioactive cargo linked to mucosal support	Particle number and/or protein content	Support of intestinal protection in chemically induced colitis models	Purity controls to distinguish vesicle effects from co-isolates
Citrus (e.g., lemon)	Antioxidant-related signaling components; membrane lipids	Protein content and/or particle number	Activation of antioxidant/anti-inflammatory pathways with intestinal protective effects in experimental settings	Confirmation of reproducibility across cultivars and processing conditions
Tea	Mixed bioactive cargo with microbiome-linked hypotheses	Variable (often protein-based normalization)	Microbiome-associated modulation with downstream mucosal immune relevance (preclinical)	Mechanistic validation and diet-controlled study design for translation

Functional ingredient targets with "quick outcomes": A practical translational strategy is to focus PDEN product concepts on gut-localized endpoints that can be evaluated within relatively short time windows using biomarker-supported outcomes [34].

Gut inflammatory balance is a rational target because multiple PDEN studies report anti-inflammatory outcomes in gut injury models, and gut inflammatory tone can be assessed using stool-based inflammatory markers and symptom-oriented outcomes in appropriately designed feasibility studies [3-4,7]. Barrier resilience is similarly strategic because intestinal permeability and mucosal defense are connected to symptom profiles and immune activation and can be evaluated using established barrier-related biomarker strategies alongside microbiome profiling when appropriate [1-2,7,35-37].

Mucosal immune support is another plausible target, particularly where PDEN preparations are reported to influence intestinal immune cell compartments such as macrophages. In functional ingredient settings, the most responsible framing is support of healthy immune balance rather than disease claims, unless supported by robust clinical evidence consistent with claim regulations [3-4,14]. Finally, microbiome optimization is a differentiating opportunity given the proposal that PDENs can act as microbiome-directed vesicle ingredients. However, microbiome claims require careful substantiation and conservative language, and studies should be designed to separate diet effects from PDEN-specific effects while using reproducible manufacturing specifications [6,8-9,38-39].

Table 2: Overview of key gut-health–related bioactive compound targets for plant-derived exosome-like nanoparticles, highlighting proposed mechanisms of action and the primary translational priorities required for product development.

Bioactive compound target ("quick outcome")	Mechanistic rationale at the gut interface	Feasible efficacy readouts (human-ready)	Primary translation priority
Gut inflammatory balance support	Immune tone modulation and attenuation of pro-inflammatory signaling at the intestinal mucosa	Symptom scores; stool inflammatory markers; targeted cytokine panels (pilot trials)	Standardized dosing and purity controls
Intestinal barrier resilience support	Support of epithelial integrity and mucosal repair processes	Barrier-related biomarker panels; gut comfort outcomes	Stability in the final food matrix and shelf-life
Mucosal immune modulation support	Interaction with gut-associated immune compartments (e.g., macrophage-associated responses)	Immune biomarkers aligned to claim type; tolerability outcomes	Conservative claim strategy + substantiation plan
Microbiome-directed optimization	Vesicle–microbe interactions and microbiome-mediated downstream mucosal effects	Microbiome profiling linked to symptoms/biomarkers	Diet-controlled study design + batch consistency

Technical challenges: Terminology remains inconsistent across the PDEN literature, with "exosomes," "exosome-like nanoparticles," and "extracellular vesicles" used variably. For functional ingredient manuscripts and commercialization, conservative terminology that avoids overclaiming biogenesis is preferred, paired with operational definitions and transparent characterization [8-9,40].

Isolation and purification methods remain a substantial barrier. Ultracentrifugation and density-based separations are common in research contexts but may not translate cleanly to scalable food-grade manufacturing. Moreover, variation in workflows can

change the composition of the final preparation and introduce co-isolated components that confound functional attribution. These constraints highlight the need for standardized, scalable separation workflows and finished-product specifications that support reproducibility [8-9,41].

Characterization depth is uneven across studies. Because PDEN preparations may include plant debris, protein aggregates, and other non-vesicular components, credibility depends on reporting metrics that enable reviewers and regulators to evaluate identity and purity. MISEV-style recommendations provide an appropriate benchmark for separation reporting and characterization that supports functional claims [8-9,42].

Dose definition is another persistent challenge. PDEN dosing is variably reported as particle number, protein mass, or plant mass equivalents. For product development, dose must be tied to reproducible QC metrics. A feasible approach is dual specification, combining particle concentration and an orthogonal compositional fingerprint or potency proxy that is stable across batches and linked to the intended mechanism [8-10,43].

Regulatory and safety considerations: Regulatory classification depends on jurisdiction and intended use. In the European Union, concentrated and extracted PDEN preparations may be evaluated under the Novel Food framework, which governs foods not consumed to a significant degree prior to relevant dates and requires an authorization dossier addressing identity, production process, composition, specifications, intended uses, and safety data [11]. In the United States, PDEN ingredients intended for conventional foods may seek a GRAS pathway if safety under intended conditions of use can be established through generally available evidence, while dietary supplement positioning may involve structure/function claim notification and substantiation expectations [12-14].

A key safety principle is that edibility of the source plant does not automatically establish safety for concentrated PDEN preparations. Concentration altered exposure patterns, and extraction-related contaminants may change risk profiles. As a result, product development typically requires contaminant controls, stability and degradation profiling, and tolerability evidence appropriate for the intended exposure level and population [11-13].

Manufacturing hurdles: Manufacturing translation requires scalable, food-grade extraction and separation methods with validated hygienic controls and traceability. Batch-to-batch consistency is challenging because plant sources vary across season, cultivar, and storage. These sources of variability necessitate defined raw material specifications and in-process controls linked to finished-product quality metrics [8-10].

Formulation stability is critical because food processing conditions such as heat, shear, pH adjustment, and storage can disrupt vesicle integrity or shift cargo availability. Functional performance must be evaluated in the intended product format rather than only in isolated laboratory preparations, particularly when claims depend on gut delivery [1-2]. Finally, commercial viability requires cost-effective production. Using agricultural by-products may reduce input costs but increases the need for contaminant screening and tighter QC.

Standardization priorities: Translation of PDENs into functional foods requires harmonized separation workflows, standardized characterization reporting, and quality benchmarks that establish identity, purity, potency, and stability. EV reporting guidelines provide a strong foundation for technical standardization, while functional ingredient development frameworks emphasize aligning dose, safety, biomarkers, and efficacy evaluation to support credible product development [8-10, 44-45].

Clinical evidence needs: Human feasibility studies are necessary to establish tolerability, exposure realism, biomarker responsiveness, and preliminary efficacy signals. Trial design should prioritize validated biomarkers relevant to PDEN's proposed mechanisms, including inflammatory balance measures, barrier-related indicators, and microbiome endpoints where justified. Dose–response relationships and safety monitoring are essential for selecting product claims and for building regulatory-ready evidence packages [11-14].

Regulatory strategy: A pragmatic approach involves early regulatory pathway assessment to decide whether the ingredient is best positioned as a food ingredient, dietary supplement, or other category depending on jurisdiction. Evidence packages should be built around ingredient identity, manufacturing process controls, compositional specifications, dietary exposure estimates, and safety and substantiation narratives aligned with the relevant framework. EU Novel Food and US GRAS and claim substantiation guidance provide representative models for structuring this strategy [11-14].

Market development: Commercial success requires transparent consumer communication that avoids overstating cross-kingdom mechanisms and emphasizes measurable, realistic benefits. Target population identification and conservative early claims can reduce regulatory risk. Competitive positioning should clarify whether PDENs complement or differ from probiotics and prebiotics, particularly when microbiome-directed messaging is used [46-48]. Product format innovation should prioritize matrices where vesicle stability and dose delivery can be consistently validated.

Table 3: Alignment of PDEN translation needs with functional ingredient development steps.

Functional ingredient development step	PDEN translation need	Current gap
Ingredient identity & specifications	Source- and process-defined ingredient specifications with QC acceptance criteria	Harmonized QC package and batch-to-batch consistency benchmarks
Dosing strategy	Unified dose metric with serving-based exposure rationale	Inconsistent dosing units and limited dose–response justification
Mechanism & biomarkers	Mechanism-linked biomarker panel aligned to intended benefit	Human-relevant biomarker strategy and controlled functional attribution
Stability in final matrix	Processing and shelf-life stability in intended food format	Real-matrix stability data and potency retention criteria
Safety for intended use	Safety evaluation for concentrated preparations and exposure modeling	Safety dataset beyond edible-source assumption; contaminant/adulterant controls
Human feasibility & claims	Pilot human studies using standardized lots to support conservative claims	Limited human feasibility evidence and inconsistent manufacturing lots

Scientific Innovations: Future innovation may involve precision nutrition concepts in which PDEN selection or formulation is tailored to microbiome phenotype, although such applications remain research-stage and will face complexity in validation and regulatory acceptance. Enhanced PDEN strategies, such as biofortification or controlled cargo loading, may increase potency but may also increase regulatory burden because engineered features can shift classification expectations and safety requirements [11-14]. Exploration of underutilized plant sources and agricultural by-products may improve sustainability and cost-effectiveness, while expanding applications into

adjacent sectors such as animal nutrition may provide alternative translation pathways [49-52].

Research priorities: Priority research includes multi-omics characterization to define reproducible fingerprints, rigorous mechanistic studies with contamination controls, stability studies in realistic food processing conditions, and human feasibility trials using validated biomarker endpoints. Across all efforts, reproducibility and transparent reporting consistent with EV standards will be essential for credibility and translation [8-9,53].

DISCUSSION

The evidence synthesized in this review positions plant-derived exosome-like nanoparticles (PDENs) as a sophisticated class of bioactive compounds capable of mediating cross-kingdom communication. Unlike traditional isolated nutrients, PDENs function as synergistic biological units where the lipid membrane, proteins, and encapsulated RNA work together to influence host physiological pathways [5- 12]. The ability of these vesicles to remain functionally active during gastrointestinal transit and interact directly at the intestinal interface suggests they are more than mere metabolic byproducts; they are evolutionarily conserved delivery vehicles for bioactive cargo [22,41]. However, the transition from characterizing PDENs in laboratory settings to validating them as standardized bioactive ingredients requires addressing critical gaps in environmental sequestration and immunological safety.

This translational challenge aligns with several core stages of the Functional Food Center's 17-step functional food development framework, particularly the identification and standardization of the bioactive compound, clarification of mechanism of action, selection of mechanism-linked biomarkers, evaluation of stability in the intended food matrix, safety assessment for the target population, and eventual human efficacy testing to support responsible claims [40-42]. For PDEN-based strategies, progress toward functional food application therefore depends on defining reproducible vesicle specifications, linking their gut-directed effects to measurable biomarker outcomes, confirming stability during processing and gastrointestinal delivery, and establishing tolerability and feasibility in human studies before broad functional positioning can be justified [38,40-42].

A central consideration regarding the bioactivity of PDENs is their capacity to act as biological archives of the plant's growth environment. Because PDENs utilize a robust lipid bilayer to protect their molecular cargo [18,33], they may inadvertently sequester and transport environmental pollutants, such as heavy metals or lipophilic pesticides, from the soil. This potential for "hitchhiking" contaminants necessitates a focus on microbiome-directed safety to ensure that these vesicles support gut-barrier resilience [29-31] without introducing harmful co-isolates that could induce dysbiosis. Recent research into ultra-low-dose prebiotics, such as lactulose, has demonstrated that significant microbiota modulation can be achieved in healthy adults while maintaining total gut comfort and an absence of gastrointestinal symptoms [57]. For PDENs to be successfully integrated into health protocols, future human clinical trials must prioritize establishing this balance between potent bioactivity and gastrointestinal tolerability [48,57].

The presence of allergenic proteins within PDENs, such as pathogenesis-related (PR) proteins, profilins, and lipid transfer proteins (LTPs), presents a "dual-nature" challenge for their application [55]. On one hand, these proteins pose a safety risk, particularly for individuals with pollen-food allergy syndrome, where cross-reactivity between pollen antigens and nanoparticle-bound food allergens can trigger unexpected systemic or even anaphylactic responses [54-55]. On the other hand, the unique structure of PDENs may offer a beneficial therapeutic pathway for oral tolerance induction. By

naturally encapsulating these proteins, PDENs could act as "masked" delivery vehicles that protect the allergen from immediate recognition by IgE antibodies in the oral cavity, instead allowing for controlled exposure to the gut-associated lymphoid tissue (GALT) [37,43]. This controlled delivery is a hallmark of successful oral immunotherapy, potentially "re-educating" the immune system toward a tolerogenic state [54].

Ultimately, the success of PDENs as bioactive compounds depends on acknowledging that their properties—including their stability and allergenicity—are not fixed. They are heavily influenced by the plant source, storage conditions, and the specific analytical methods used for assessment [56]. There is currently no universal method for evaluating the immunoreactivity of such complex matrices, a challenge also shared by other emerging bioactive frontiers, such as *Tenebrio molitor*-derived ingredients, which require rigorous standardization to ensure consumer safety [57]. Future research must adopt a multi-targeted approach to characterize the complex interplay between the nanoparticle's environmental history, its cargo, and the host's immune and microbial landscape [50-52].

CONCLUSION

Plant-derived exosome-like nanoparticles represent a promising and emerging approach to functional ingredient innovation that shifts the focus from isolated bioactives toward complex, naturally occurring nanostructures with intrinsic carrier potential. Preclinical findings support gut-focused applications, particularly in the areas of inflammatory balance, intestinal barrier resilience, and microbiome-associated outcomes. However, translation and commercialization remain constrained by inconsistent terminology, variable separation workflows, incomplete characterization, dosing ambiguity, and regulatory uncertainty. Progress in this field will depend on standardized manufacturing and quality control specifications, rigorous safety evaluation of concentrated preparations, and well-designed human feasibility studies that link PDEN exposure to validated biomarkers and conservative, evidence-based functional claims.

Abbreviations: PDENs, plant-derived exosome-like nanoparticles; EVs, extracellular vesicles; GI, gastrointestinal; IBD, inflammatory bowel disease; QC, quality control; GRAS, generally recognized as safe; EFSA, European Food Safety Authority; FDA, Food and Drug Administration; MISEV, Minimal Information for Studies of Extracellular Vesicles; OTC, over-the-counter; RNA, ribonucleic acid; miRNA, microRNA; DSS, dextran sulfate sodium; EU, European Union; US, United States.

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