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Review Article

Plant-derived extracellular vesicles in allergic diseases: From immunomodulatory nanotherapeutics to environmental allergen carriers

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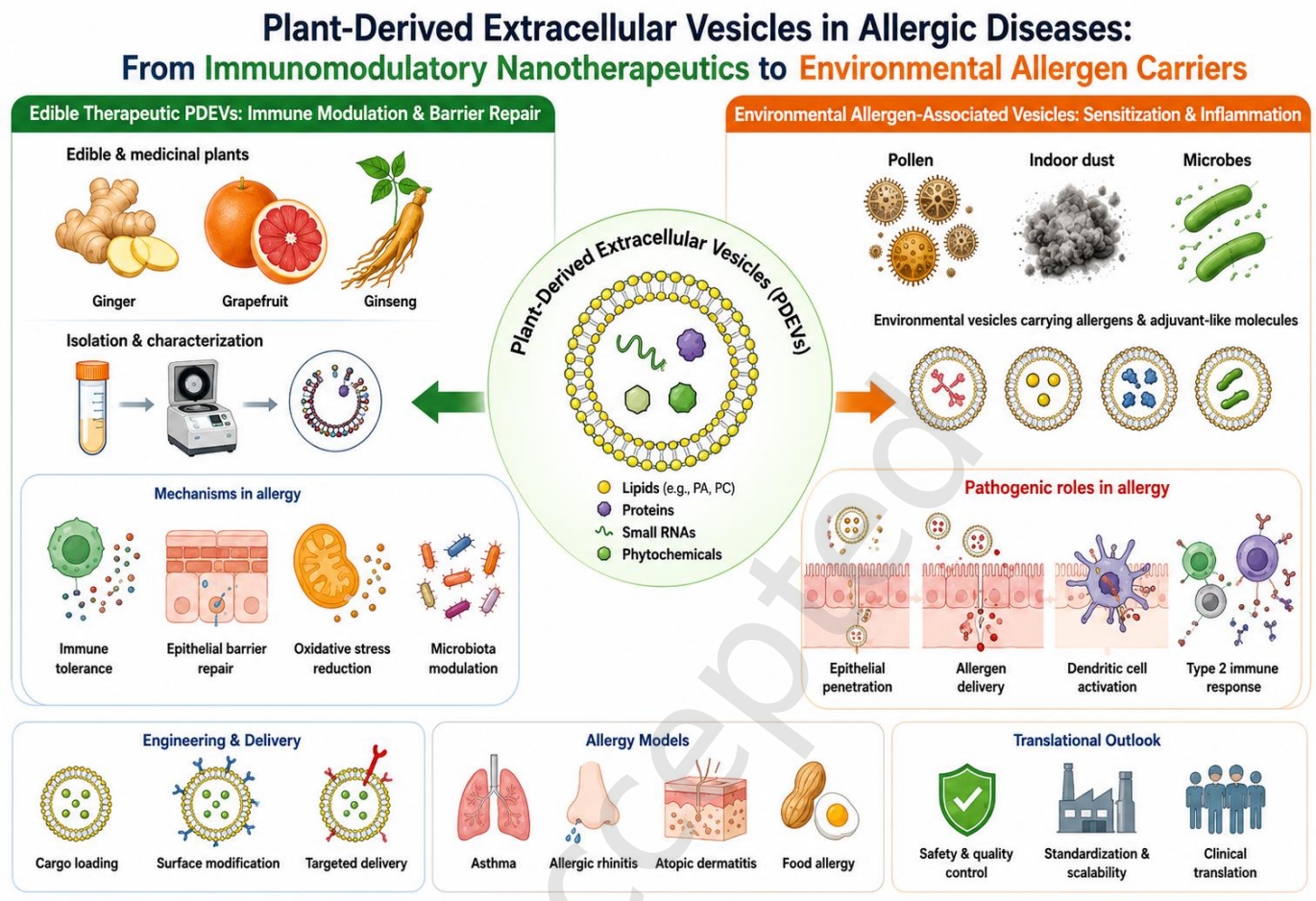

This review distinguishes therapeutic PDEVs from environmental allergen-associated vesicles and provides a comprehensive framework encompassing immune regulation, nanotherapeutic engineering, and clinical translation in allergic diseases.

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ABSTRACT: Plant-derived extracellular vesicles (PDEVs) are increasingly investigated as naturally bioactive nanovesicles and as carriers for exogenous therapeutics. Their lipids, proteins, small RNAs, and secondary metabolites can influence immune-cell function, epithelial integrity, oxidative stress, and host-microbiota interactions. However, the relevance of this evidence to allergic disease is uneven. Direct allergy-specific evidence currently includes a limited number of preclinical studies, most notably Aster yomena callus-derived EVs in allergic asthma, whereas many mechanistic claims are extrapolated from colitis, infection, cancer, vascular, or wound-healing models. In parallel, environmental vesicles can promote disease rather than resolve it. Pollen-derived vesicles (pollensomes) and allergen-bearing EVs in indoor dust can protect and co-deliver allergenic proteins, lipid mediators, oxidases, and adjuvant-like signals, thereby facilitating epithelial exposure and type 2 immune activation. This review critically integrates these opposing vesicle contexts. We summarize PDEV biogenesis, isolation, composition, characterization, engineering, loading, and biodistribution; distinguish direct allergic-disease evidence from indirect mechanistic support; and place vesicle actions within the epithelial alarmin-ILC2-Th2-IgE axis and regulatory T-cell, regulatory B-cell, and IgG4-associated tolerance. We further define critical quality attributes, allergenicity testing, release criteria, regulatory considerations, and patient-stratification requirements. PDEVs may offer useful opportunities for allergy nanomedicine, but their translation will require source-specific characterization, rigorous potency and safety assays, and avoidance of unqualified extrapolation from non-allergic models.

KEYWORDS: plant-derived extracellular vesicles (PDEVs); allergic diseases; environmental allergen carriers; immune tolerance; nanotherapeutics; quality control

1 Introduction

Allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and food allergy, arise from maladaptive immune responses to otherwise harmless environmental or dietary antigens and affect a substantial proportion of the global population [1-6]. Their pathogenesis is not explained by a single Th2 pathway. Barrier disruption in the airway, skin, or intestinal epithelium permits allergen access and promotes the release of thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. These epithelial alarmins activate dendritic cells (DCs) and group 2 innate lymphoid cells (ILC2s), which amplify IL-4-, IL-5-, and IL-13-dominated inflammation, IgE class switching, mast-cell and basophil activation, eosinophil recruitment, mucus production, and tissue remodeling [7-10]. The relevant barrier should therefore be specified according to disease context rather than described generically as the skin barrier.

Antihistamines, corticosteroids, leukotriene-pathway inhibitors, and biologics targeting IgE or type 2 cytokines can provide effective disease control, but their effects are often treatment-dependent and vary across endotypes [11-13]. Allergen immunotherapy (AIT) remains the principal disease-modifying intervention because it can increase the activation threshold of mast cells and basophils, expand allergen-specific regulatory T cells (Tregs) and regulatory B cells (Bregs), enhance IL-10 and TGF-beta signaling, suppress IgE responses, and favor blocking IgG4 antibodies. Nevertheless, treatment duration, adherence, allergen selection, adverse-event risk, and incomplete or heterogeneous responses limit broad implementation [12]. These constraints motivate delivery systems that can improve local exposure while supporting, rather than merely suppressing, immune tolerance.

Extracellular vesicles (EVs) are membrane-bound particles that transfer proteins, lipids, metabolites, and nucleic acids between cells. Mammalian extracellular vesicles (MEVs) released by immune and structural cells can regulate antigen presentation, epithelial responses, and communication among DCs, mast cells, eosinophils, T cells, and ILC2s in allergic inflammation [14-20]. EV biology also extends beyond host-derived vesicles. Pollen, microorganisms, and indoor dust contain or release nanoscale vesicles that transport allergens and immunostimulatory cofactors [21-24]. Thus, EVs can participate in either immune regulation or sensitization depending on their source, composition, route of exposure, and recipient-cell context.

In this review, plant-derived extracellular vesicles (PDEVs) is used as the primary umbrella term for nanoscale vesicles isolated from plant tissues. Terms such as plant EV-like nanoparticles, exosome-like nanoparticles (ELNs), ginger-derived ELNs (GELNs), and ginseng-derived ELNs (GENs) are retained only when they reflect the nomenclature of the cited study. Edible-plant PDEVs are discussed as candidate

therapeutic preparations [25-29], whereas pollen-derived vesicles, indoor-dust EVs, and microbial EVs are treated as distinct environmental exposure classes [21, 22, 30]. This distinction is essential because edible origin does not guarantee non-immunogenicity, and environmental vesicles should not be assumed to be therapeutically interchangeable with food-derived PDEVs.

We provide a critical, evidence-weighted overview of PDEV biogenesis, separation, characterization, intrinsic bioactivity, engineering, cargo loading, administration, and biodistribution. Particular emphasis is placed on distinguishing direct data from allergic asthma, rhinitis, dermatitis, food allergy, or AIT models from indirect mechanistic evidence generated in other inflammatory diseases. Figure 1 integrates these therapeutic and pathogenic vesicle contexts within an evidence-weighted framework spanning source, cargo, exposure route, biological outcome, engineering, and clinical translation.

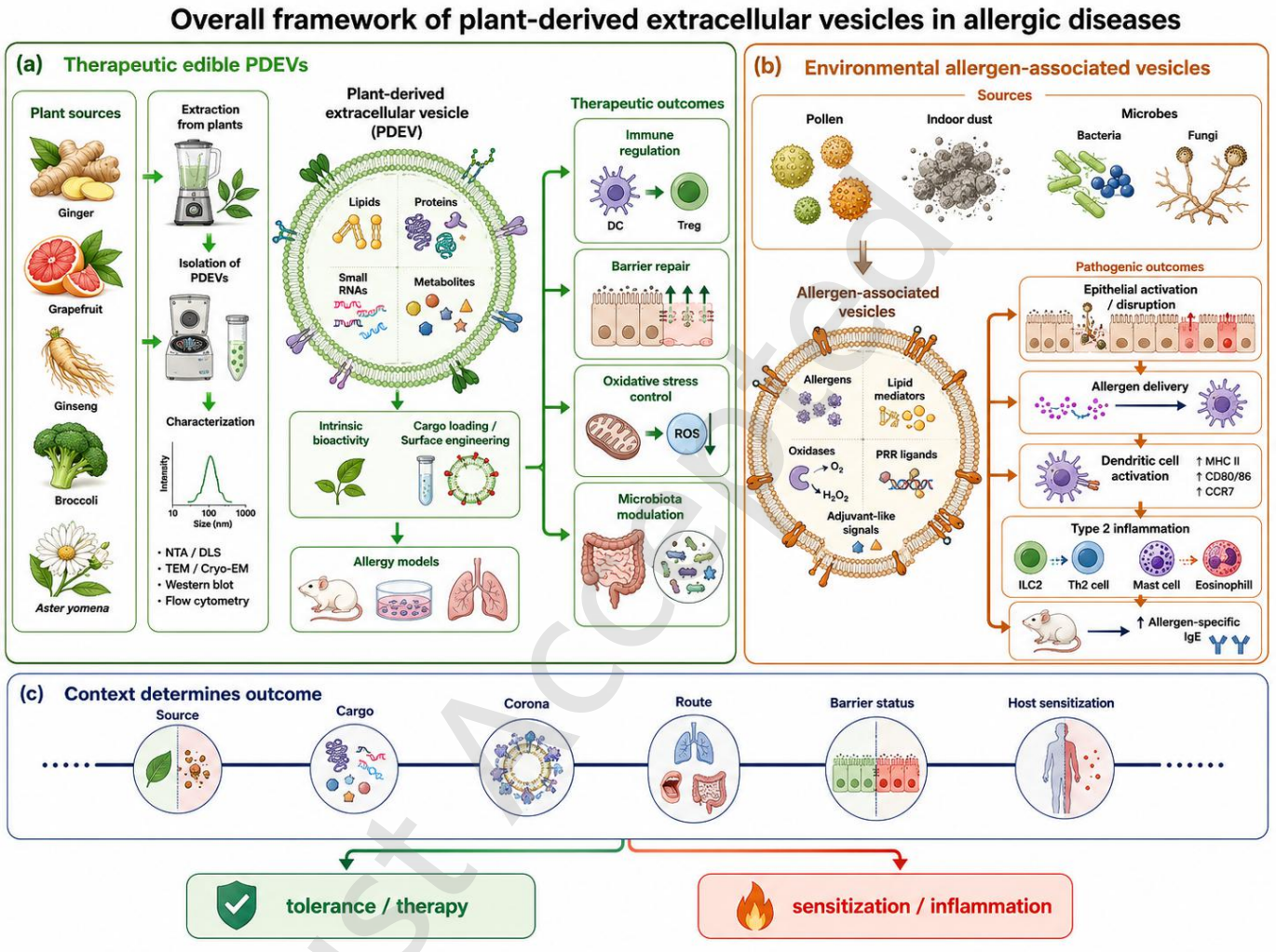

Figure 1. Conceptual framework of plant-associated vesicles in allergic diseases. (a) Edible and medicinal-plant-derived extracellular vesicles (PDEVs) are investigated as immunomodulatory agents and therapeutic nanocarriers. (b) Pollen-derived vesicles, indoor-dust extracellular vesicles, and microbial vesicles can transport allergens and adjuvant-like signals that promote epithelial activation and sensitization. (c) Biological outcome is determined by vesicle source, cargo, exposure route, epithelial-barrier status, and host sensitization.

Against this conceptual background, the following section defines the structural, compositional, and functional attributes of PDEVs.

2 Overview of PDEVs

PDEVs are broadly defined as lipid-bilayer nanovesicles that are either naturally released by plant cells or recovered from plant tissues through controlled processing [31, 32]. Their cargos comprise proteins, lipids, small RNAs, and diverse secondary metabolites. Compared with mammalian extracellular vesicles, PDEVs frequently exhibit source-dependent enrichment in phosphatidic acid and plant-associated membrane lipids, including glycolipids such as digalactosyldiacylglycerol (DGDG), monogalactosyldiacyl- glycerol (MGDG), and glycosyl inositol phosphorylceramides (GIPCs), as well as phytosterols. They may additionally carry flavonoids and other plant secondary metabolites that contribute to their intrinsic biological activities [26, 33-36]. Importantly, preparations obtained from homogenized tissues can contain both naturally secreted vesicles and vesicle-like nanoparticles generated or remodeled during extraction. Accordingly, source tissue, processing history, isolation method, and evidence of vesicular identity should be reported explicitly rather than assuming that every nanoscale particle is an exosome [32]. These source-dependent structural components and their principal biological functions are summarized in Figure 2.

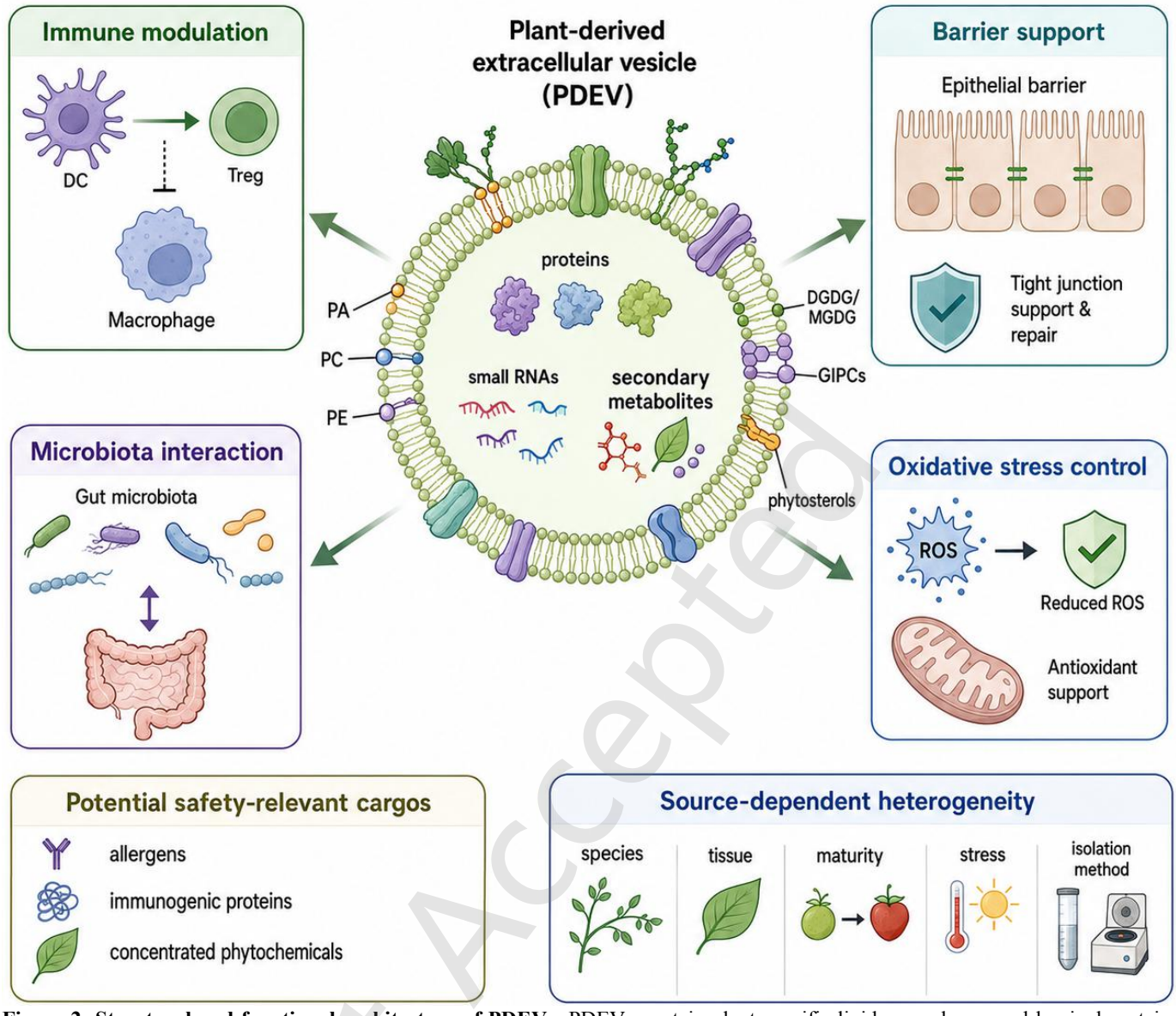

Figure 2. Structural and functional architecture of PDEVs. PDEVs contain plant-specific lipids, membrane and luminal proteins, small RNAs, and secondary metabolites that may influence vesicle stability, cellular uptake, immune regulation, epithelial repair, oxidative stress, and microbiota interactions. Their composition and activity vary with plant species, tissue, physiological state, and production process.

The biological origins and operational classification of these heterogeneous vesicle populations are considered next.

2.1 Biogenesis and Classification of PDEVs

PDEV biogenesis remains less completely defined than mammalian EV biogenesis. Current evidence supports several plant secretory routes, including multivesicular-body (MVB) and exocyst-positive organelles (EXPOs) associated pathways, whose relative contributions may depend on cell or tissue type, developmental context, and exposure to biotic or abiotic stress (Figure 3) [37-42].

The MVB-associated pathway is currently the best-supported route of plant EV biogenesis. Intraluminal vesicles are generated through inward budding of endosomal membranes and are subsequently released when MVBs fuse with the plasma membrane [43-48]. Plant proteins involved in cargo recognition, endosomal sorting, lipid trafficking, vesicle tethering, and membrane fusion—including RNA-binding proteins, TET8, COPI-associated machinery, Rab GTPases, and exocyst components—contribute to cargo loading and EV secretion. Nevertheless, the biogenetic origins of several plant EV subpopulations remain unresolved, and their correspondence with mammalian exosome or ectosome categories is incomplete [40, 49, 50].

Plants also use specialized secretory mechanisms. Vacuole-associated pathways can release defense-related vesicles enriched in antimicrobial cargos, whereas EXPOs represent a plant-specific unconventional secretion route that becomes prominent during stress, pathogen challenge, or tissue injury [41, 44].

These distinct biogenetic routes generate compositional heterogeneity. Vesicles derived from leaves, roots, fruits, pollen, or cultured callus should therefore not be treated as a single product class. For allergy applications, this heterogeneity is biologically consequential because the same broad category of plant vesicle may contain anti-inflammatory metabolites, intact allergens, oxidases, or adjuvant-like lipids [51].

Although size-based terms such as exosome-like vesicles and microvesicles are widely used in plant-vesicle research, particle size alone cannot determine biogenetic origin. Reported PDEV preparations typically contain particles of approximately 30–200 nm but often display broader heterogeneous distributions influenced by source material, isolation procedures, and

analytical platforms [52-55]. A functional classification integrating tissue origin, biogenesis, cargo composition, and biological activity provides greater insight into PDEV heterogeneity. Defense-associated vesicles carry antimicrobial molecules, signaling vesicles contain regulatory RNAs/proteins, and nutrient-associated vesicles transport lipids and metabolites [33, 56, 57]. Translational development requires coupling these descriptors with quantitative product specifications.

PDEVs can also be classified by botanical source, including fruits, vegetables, crops, medicinal plants, callus cultures, and pollen [33, 56, 58]. However, source-based classification should consider cultivar, tissue, growth conditions, harvest stage, storage, and processing, as these factors influence vesicle yield, composition, allergenicity, and biological activity. In allergy research, pollen-derived vesicles should be distinguished from edible-plant PDEVs because they represent fundamentally different exposure contexts and immunological functions. Taken together, current evidence favors a multidimensional classification based on botanical source, presumed biogenesis, molecular composition, target cell, and biological function rather than particle size alone (Figure 3)

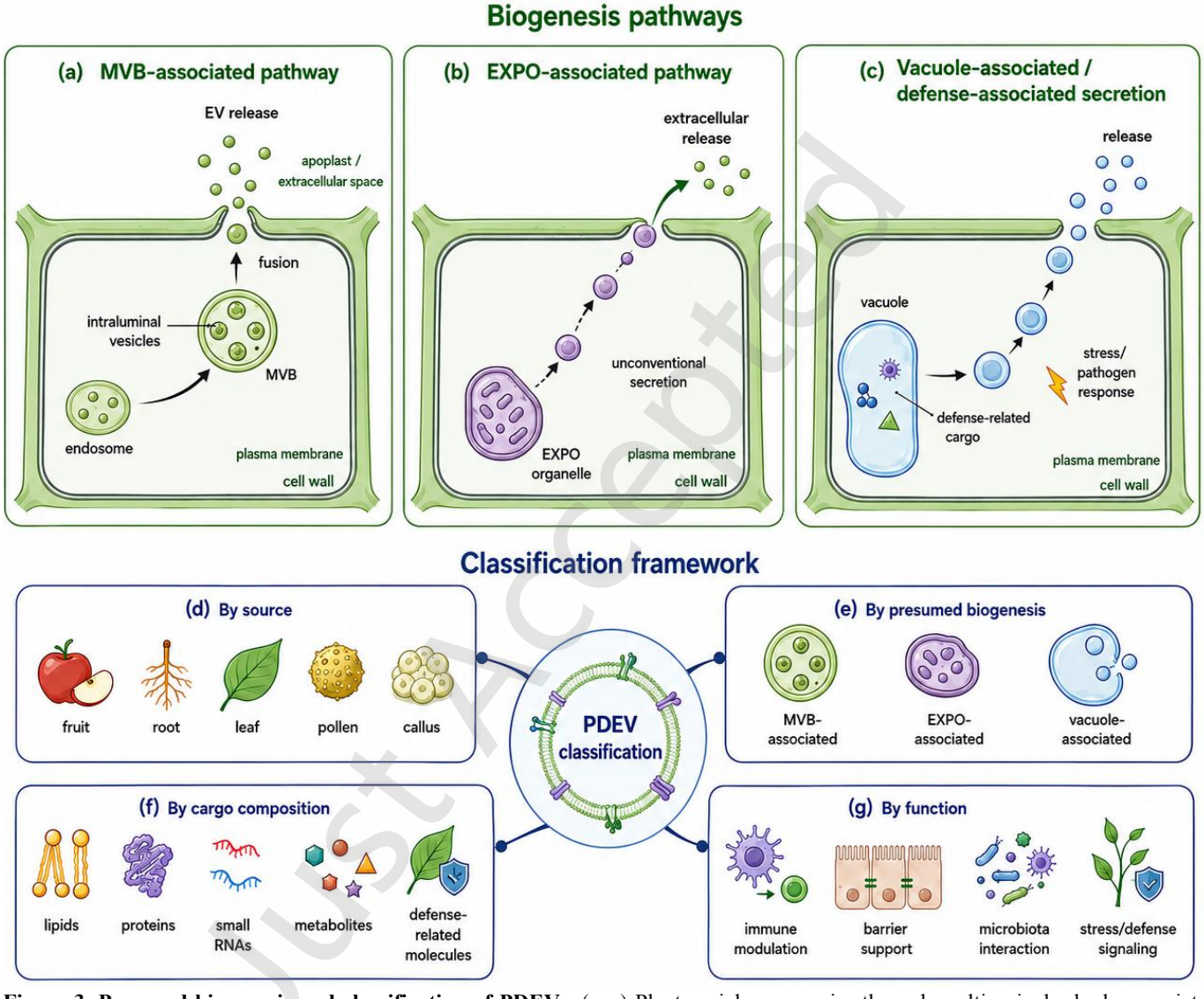

Figure 3. Proposed biogenesis and classification of PDEVs. (a–c) Plant vesicles may arise through multivesicular-body-associated secretion (a), exocyst-positive organelles(b), or vacuole-related pathways(c). (d-g) PDEVs can be classified according to botanical source(d), presumed biogenesis(e), molecular composition(f), target cell, and biological function(g); vesicles recovered from disrupted tissues should not be assigned an endosomal origin without experimental evidence.

Because tissue disruption and downstream processing can further reshape the recovered particle population, the principal isolation and purification strategies are examined next.

2.2 Separation and Preparation of PDEVs

PDEV isolation generally combines clarification with one or more enrichment and polishing steps. Ultracentrifugation (UC, both differential and density gradient), ultrafiltration (UF), size-exclusion chromatography (SEC), polymer precipitation, tangential-flow filtration (TFF), electrophoresis-coupled dialysis (ELD), microfluidics, and affinity capture have all been used (Figure 4). No single method simultaneously maximizes yield, purity, structural integrity, and scalability. The operating principles, advantages, limitations, suitable applications, and essential reporting parameters of the major isolation and purification methods are compared in Table S1 in the Electronic Supplementary Material (ESM). Method selection should therefore be linked to the intended use: exploratory omics, mechanistic cell studies, animal dosing, or clinical-grade production. Current best practices often employ hybrid approaches combining multiple techniques (e.g., UF with SEC) to optimize both yield and purity, with method selection guided by specific application requirements, available resources, and desired vesicle characteristics. Comparative attributes of the major isolation methods and representative source-specific

preparation workflows are provided in Tables S1 and S2, respectively, in the ESM.

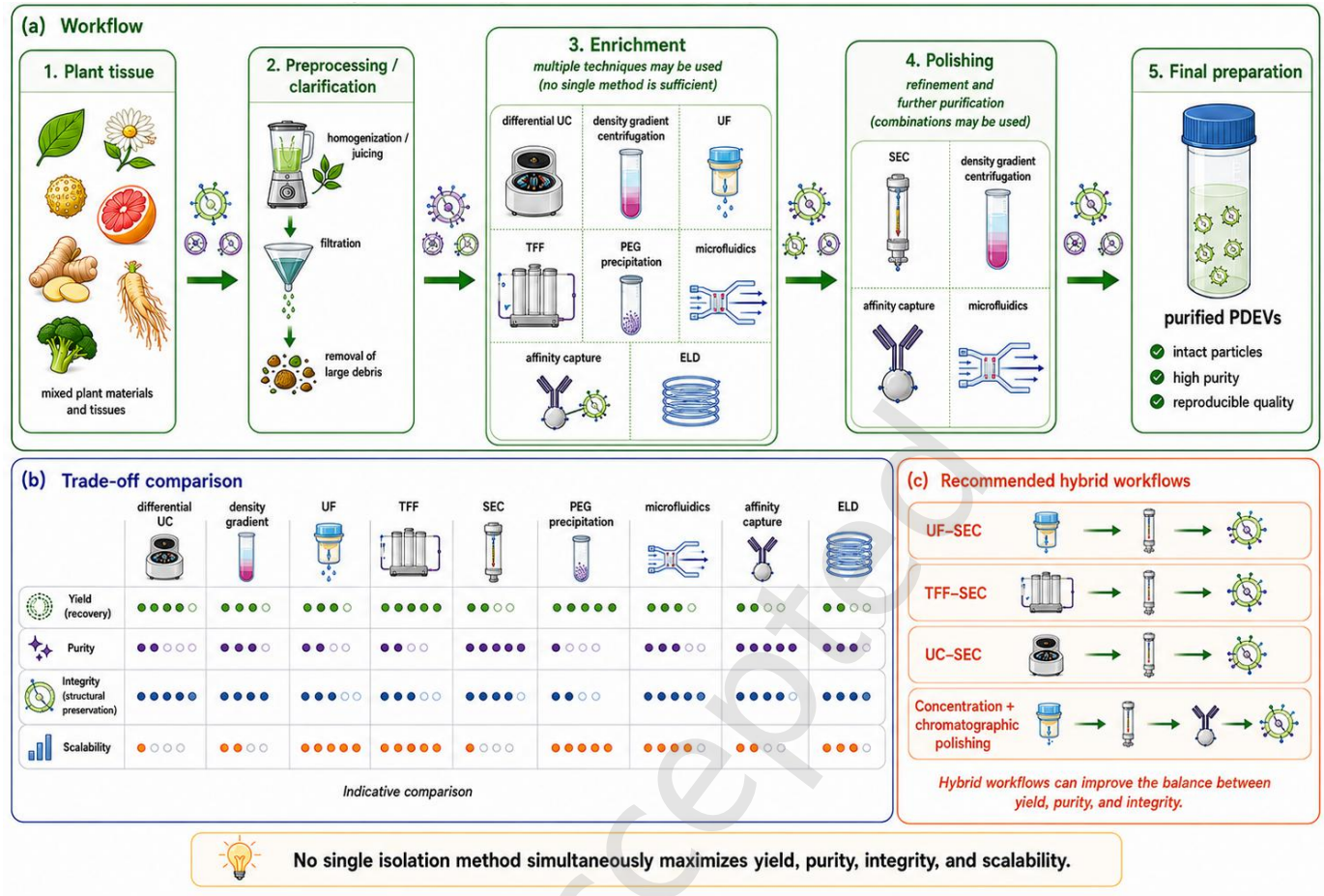

Figure 4. Isolation and purification strategies for PDEVs. (a) Plant tissues undergo preprocessing, clarification, enrichment, and polishing to obtain PDEV preparations. (b) Centrifugation, ultrafiltration, tangential-flow filtration, size-exclusion chromatography, precipitation, microfluidics, and affinity-based approaches provide different balances among recovery, purity, vesicle integrity, throughput, and scalability. (c) Hybrid workflows separate concentration from purification and facilitate process control.

The operating principles, major limitations, and reporting requirements of the individual methods are discussed below.

2.2.1 UC

UC remains widely used because it is accessible and can process relatively large volumes [59]. Differential UC removes cells, fibers, and larger particles before high-speed pelleting, whereas density-gradient centrifugation separates particles according to buoyant density [60]. The approach is time-intensive and operator-dependent, and prolonged high g-forces can promote aggregation, deformation, or co-pelleting of protein and polysaccharide contaminants. UC should therefore not be described as an unconditional gold standard; recovery, purity, and functional integrity must be measured for each protocol [61, 62].

2.2.2 Polymer-Based Precipitation

Polymer-based precipitation, most commonly with polyethylene glycol (PEG), reduces particle solubility and enables simple processing without specialized ultracentrifuges [57, 63]. Its principal limitation is non-specific co-precipitation of soluble proteins, polysaccharides, nucleic acids, and polymer residues, which can confound particle counts and biological assays [64, 65]. Precipitation is therefore best used as a concentration step followed by orthogonal purification rather than as a stand-alone method for mechanistic or translational studies.

2.2.3 UF

UF separates particles by membrane cutoff, whereas TFF directs feed parallel to the membrane and is more amenable to scale-up. Key process parameters include membrane chemistry, molecular-weight cutoff, transmembrane pressure, shear rate, flow, concentration factor, and diafiltration volume. Adsorption and fouling can reduce recovery, while excessive pressure or shear may alter vesicle structure. TFF combined with SEC or another polishing step is a practical route for scalable preparation, provided that membrane-associated losses and product comparability are quantified [66].

2.2.4 Size exclusion chromatography (SEC)

SEC separates larger vesicles from smaller soluble molecules through a porous matrix and generally preserves particle morphology and biological activity [67-69]. It is well suited to polishing because it removes a substantial fraction of free protein and small-molecule contaminants. Limitations include sample dilution, finite loading capacity, column-to-column variation, and the need to define fraction-collection windows. Pre-concentration by UF or TFF is frequently required [70].

2.2.5 Immunoaffinity capture (IC)

IC provides high specificity when a validated surface antigen is available. Mammalian tetraspanins such as CD9, CD63, and CD81 are not universal PDEV markers, which limits direct transfer of MEV protocols [71]. TET8-positive vesicles and proteins such as PEN1 have been used in selected plant systems [40, 49], but no marker currently identifies all therapeutically relevant PDEVs. Affinity methods are therefore useful for studying defined subpopulations, not for establishing total PDEV yield or universal identity.

2.2.6 Other Techniques

ELD can shorten processing time and has been applied to lemon- and bitter-melon-derived preparations, but membrane fouling, aggregation, and recovery variability remain concerns [72]. Automated systems such as EXODUS and commercial columns may improve throughput [73, 74], yet proprietary materials and incomplete disclosure can hinder comparability. Independent validation against orthogonal particle, protein, lipid, and functional assays is required before these methods are adopted for release testing.

Integrated workflows usually provide the best balance between recovery and purity. Examples include UF-SEC, UC-SEC, and concentration followed by density-gradient or chromatographic polishing [70, 75, 76]. For each workflow, investigators should report input mass or volume, recovery, particle concentration, size distribution, particle-to-protein and particle-to-lipid ratios, residual plant macromolecules, and a disease-relevant potency assay.

2.3 Structure and Composition of PDEVs

PDEVs generally appear spherical or, after conventional negative-staining electron-microscopy preparation, cup-shaped because of dehydration-associated vesicle collapse. Many reported preparations contain predominant particle populations within approximately 30–200 nm, although broader distributions, including particles larger than 200 nm, are common and depend on the plant source, isolation procedure, and measurement method [77, 78]. Their membranes contain PA, phosphatidylcholine (PC), phosphatidylethanolamine (PE), plant-associated glycolipids, and, in some preparations, phytosterols. These lipids contribute to membrane curvature, vesicle stability and fusion behavior, and can mediate selective interactions with mammalian cells and microorganisms (Figure 5) [33, 34, 58].

PA can promote negative membrane curvature and facilitate lipid-dependent vesicle uptake, in some cases through interactions with specific lipid-binding proteins. In contrast, PC-rich membranes may exhibit distinct cellular or microbial uptake preferences and trafficking or biodistribution profiles [79-81]. Lipid unsaturation modulates membrane fluidity, oxidation susceptibility, cargo retention, and interaction with serum proteins. Consequently, the PA:PC ratio and broader lipidomic signature should be treated as potential critical quality attributes rather than descriptive compositional data alone.

Reported PDEV proteins include heat-shock proteins, annexin-like proteins, aquaporins, metabolic enzymes, and plant defense or trafficking proteins [37, 82, 83]. Some may support vesicle stability or uptake, whereas others can be immunogenic or allergenic. Proteomic analysis should therefore include both candidate identity markers and source-specific allergen screening.

PDEVs are known for their nucleic acid cargo, which includes small RNAs, microRNA-like RNAs, messenger RNAs, and other RNA species. Cross-kingdom regulation has been proposed for several preparations, including effects on NF-kappaB- and MAPK-related pathways [84, 85]. However, functional attribution requires demonstration of RNA integrity, intravesicular localization, dose, delivery to recipient cells, target engagement, and loss-of-function rescue; sequence detection alone is insufficient.

Plant secondary metabolites, including flavonoids, polyphenols, terpenoids, and other phytochemicals, may contribute antioxidant or anti-inflammatory activity [58]. Their co-localization with vesicular lipids and RNAs creates opportunities for multimodal activity but also complicates mechanism assignment, potency testing, and toxicological interpretation.

Composition varies with species, cultivar, tissue, season, stress, maturity, storage, and extraction conditions [40, 86]. This variability can be exploited for source selection, but it is a major obstacle to reproducible manufacturing. Source provenance and process control must therefore be integrated with multi-omics and functional characterization. Representative source-dependent lipid, protein, RNA, secondary-metabolite, and allergy-relevant compositional features are summarized in Table S3 in the ESM.

2.4 Characterization

PDEV characterization should combine orthogonal methods because each assay measures a different property and is vulnerable to specific artifacts. Nanoparticle tracking analysis (NTA) estimates particle size and concentration, whereas dynamic light scattering (DLS) is more sensitive to large particles and reports an intensity-weighted hydrodynamic diameter (Figure 5) [28, 87-91]. Particle-to-protein or particle-to-lipid ratios can support purity assessment, but no universal cutoff has been validated across plant sources [33, 92-95].

Transmission electron microscopy (TEM) provides high-resolution morphology but can introduce dehydration-related artifacts. Cryogenic TEM better preserves native structure, while atomic force microscopy provides complementary surface and mechanical information [96, 97]. Differences between NTA, DLS, TEM, and cryo-TEM are expected and should not be interpreted as assay failure; the measurement principle and sample preparation must be reported.

Method-specific contaminants also require attention. PEG-dextran aqueous two-phase systems can leave polymer residues, microfluidic platforms can have low throughput or device-dependent recovery, and high-pressure homogenization may generate membrane fragments that resemble vesicles [98, 99]. Negative controls should include process blanks and non-vesicular fractions to distinguish PDEV-specific effects from soluble plant components or materials introduced during processing.

Identity and function should be assessed through complementary proteomic, lipidomic, transcriptomic, and metabolomic analyses together with surface-protein measurements and potency assays [58, 100-112]. Candidate plant markers such as TET8 or PEN1 are informative only in defined species and subpopulations. Consistent with MISEV2023 principles, investigators should document source, collection, separation, particle characterization, contaminant assessment, dose normalization, and functional controls [53]. Collectively, these orthogonal measurements define a source-specific framework for PDEV identity, purity, stability, safety, and biological potency, as summarized in Figure 5.

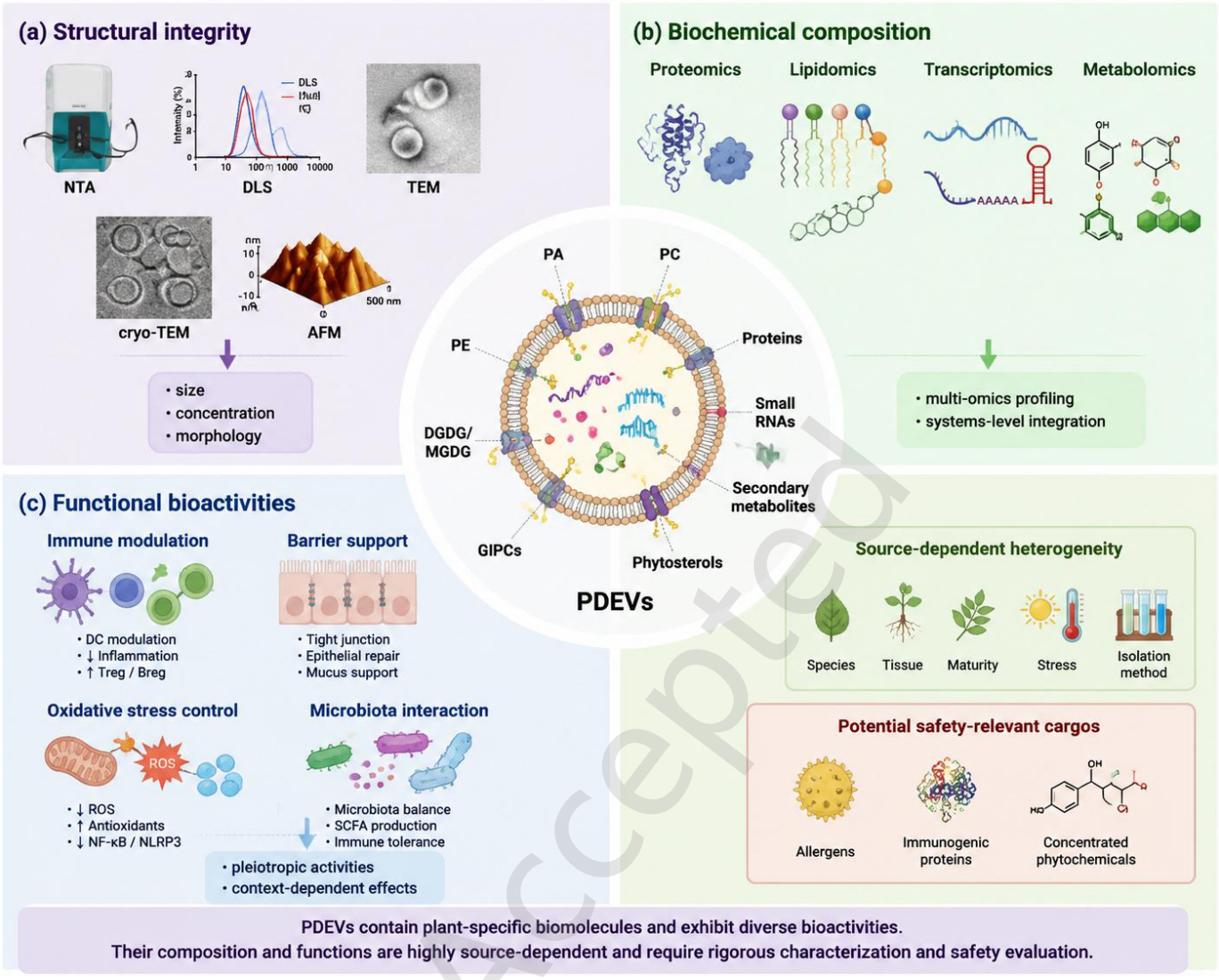

Figure 5. Characterization and critical quality attributes of PDEVs. (a) Orthogonal physical methods determine particle size, concentration, morphology, and surface charge. (b) Proteomic, lipidomic, transcriptomic, and metabolomic analyses establish source-specific molecular profiles. (c,d) Purity, membrane integrity, storage stability, allergen content, biological potency, and process-related contaminants should be incorporated into identity and batch-release testing.

Once product identity and quality have been established, the potential advantages and translational limitations of PDEVs can be evaluated more rigorously.

2.5 Advantages and Applications of PDEVs

PDEVs offer several potential advantages, including renewable plant sources, intrinsic bioactive cargos, compatibility with oral or local administration, and amenability to engineering. Reported yields vary widely among grape, grapefruit, ginseng, tomato, ginger, and other sources [58, 113-116], but values cannot be compared without standardized input mass, extraction efficiency, particle counting, and purity criteria. Edible origin may support tolerability, yet it does not establish safety. Most published data are short-term cell or rodent studies, and source-specific allergens, pesticides, mycotoxins, heavy metals, microbial contamination, and concentrated secondary metabolites remain relevant hazards [58, 59, 62, 77, 113, 117-119].

The lipid bilayer and food matrix can protect selected RNAs and small molecules against heat, saliva, and simulated gastrointestinal digestion [72, 120-129]. Stability nevertheless depends on pH, ionic strength, protein content, storage temperature, freeze-thaw cycles, lyophilization, and formulation. Claims of superior stability over synthetic liposomes should be restricted to directly matched experiments because composition and assay conditions differ [119].

Cellular uptake and organ distribution vary with administration route and composition. Intravenous or intraperitoneal administration often produces liver and spleen signals, whereas oral preparations can remain in the gastrointestinal tract and interact with intestinal macrophages, stem cells, and microbiota [113, 119, 124, 130-132]. Intranasal administration can increase respiratory or brain-associated signals in selected models, but fluorescent labels may dissociate from vesicles. Biodistribution should therefore be confirmed with orthogonal labeling or cargo-tracking methods.

Lipid composition can contribute to biological selectivity. PA-enriched ginger- and turmeric-derived nanoparticles have been associated with uptake by Lactobacillaceae, whereas PC-rich garlic- and grapefruit-derived preparations show different microbial and hepatic trafficking patterns [33, 129]. These observations support a role for lipid composition in tropism, but they should not be generalized across preparations without direct lipidomics and biodistribution studies. Fluorescent imaging is useful for screening but is susceptible to autofluorescence, dye transfer, and limited tissue penetration [133]. Taken together, PDEVs offer several practical and biological opportunities, but these remain inseparable from source variability, analytical uncertainty, allergenicity, stability, and manufacturing

constraints (Figure 6).

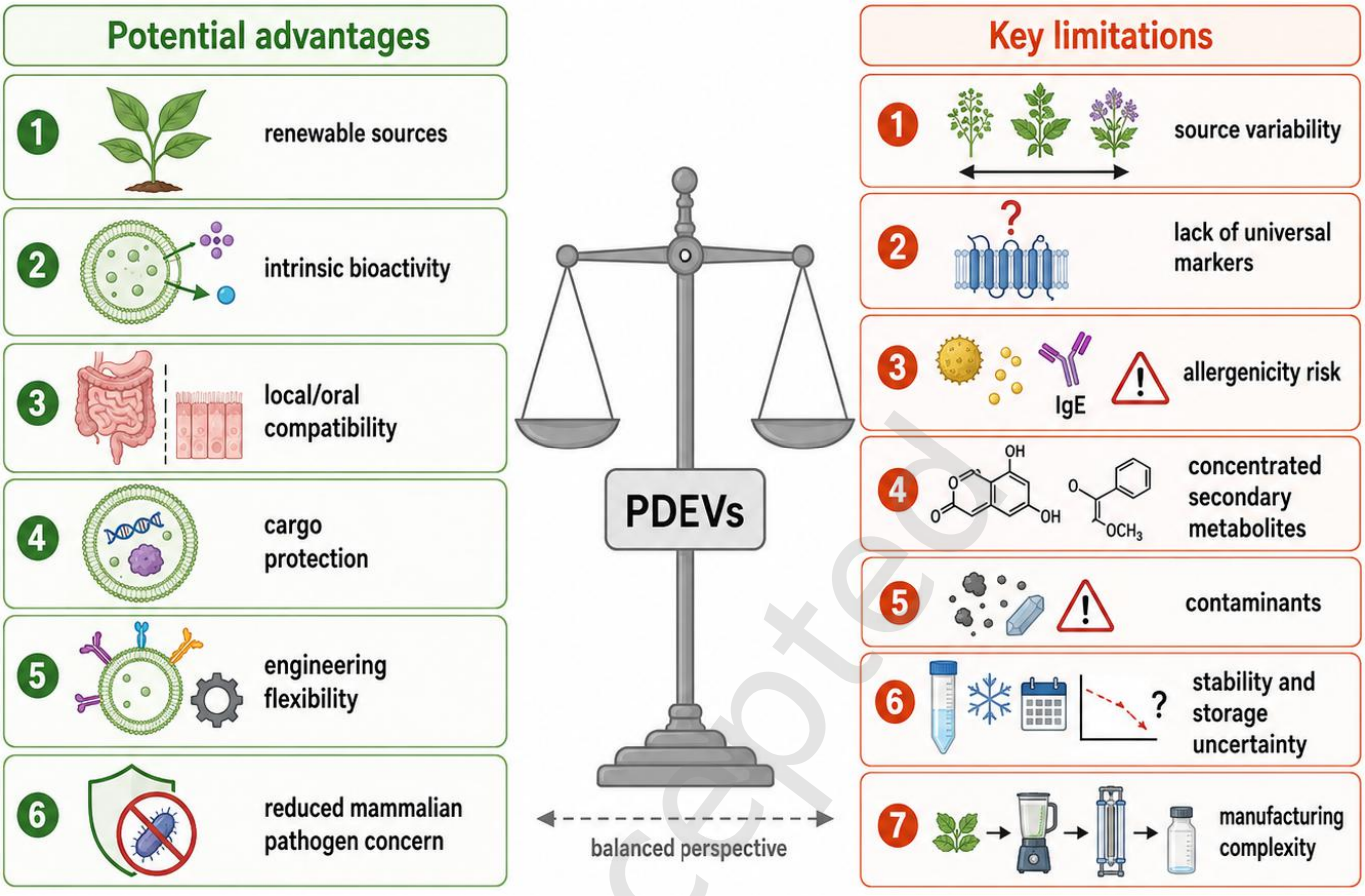

Figure 6. Potential advantages and translational limitations of PDEVs. PDEVs may provide renewable source materials, intrinsic bioactivity, cargo protection, local or oral delivery potential, and engineering flexibility. These attributes must be balanced against source variability, the absence of universal identity markers, contaminant and allergen risks, concentrated secondary metabolites, uncertain long-term stability, and manufacturing complexity.

These product-level considerations provide the foundation for evaluating how PDEVs may influence allergy-relevant biological pathways.

3 Mechanisms of PDEVs in allergic diseases

The clinical need for improved allergy therapeutics does not by itself establish PDEV efficacy. Current pharmacological and biological treatments can control symptoms and reduce exacerbations, but tolerance induction remains difficult and disease mechanisms differ among type 2-high, type 2-low, barrier-dominant, and mixed endotypes [13, 134-141]. MEVs play a role in communication problems in allergies and asthma [20, 142-145]. PDEV mechanisms must therefore be evaluated with allergy-relevant endpoints rather than inferred solely from general anti-inflammatory activity.

Candidate PDEV actions can therefore be organized into four interconnected axes—immune reprogramming, epithelial-barrier restoration, oxidative-stress control, and microbiota modulation—as summarized in Figure 7. These axes are biologically plausible, but the strength of evidence differs. Direct allergy-specific studies are limited, whereas many supporting observations originate from colitis, infection, cancer, vascular injury, or wound-healing models. This distinction is maintained throughout the following sections.

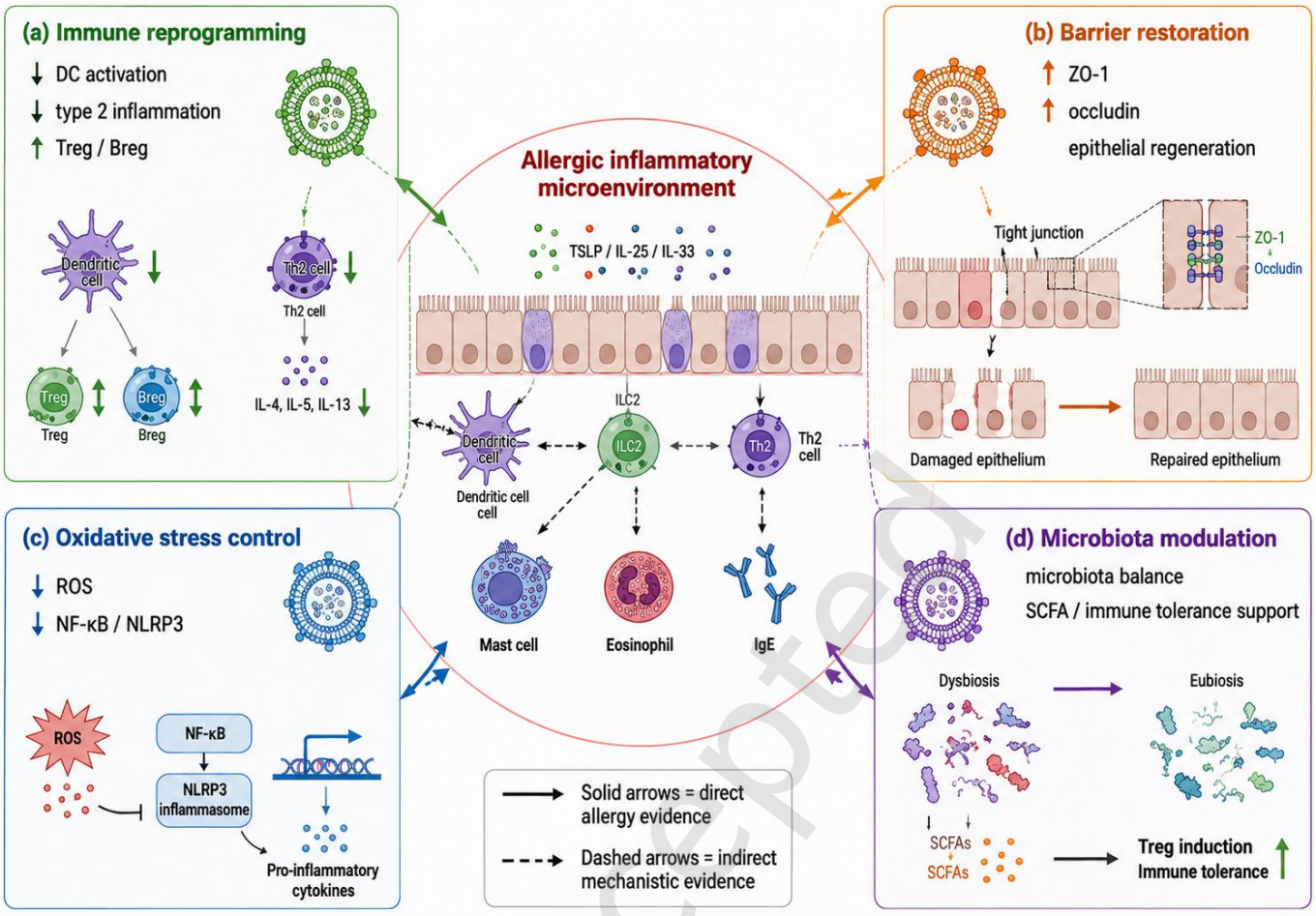

Figure 7. Allergy-relevant mechanisms proposed for therapeutic PDEVs. PDEVs may influence allergic disease through four interconnected axes: immune reprogramming(a), epithelial-barrier restoration(b), oxidative-stress control(c), and microbiota modulation(d). Solid arrows indicate relationships supported directly in allergy-related models, whereas dashed arrows denote mechanistic support derived mainly from non-allergic inflammatory models.

The following subsections evaluate each axis while distinguishing direct allergy-specific evidence from mechanistic findings derived from non-allergic inflammatory models.

3.1 Immune Reprogramming Axis

Immune dysregulation is a defining feature of allergic diseases and reflects coordinated epithelial, innate, and adaptive immune circuits rather than a single, fixed immune-memory program. Epithelial alarmins, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, activate dendritic cells (DCs) and group 2 innate lymphoid cells (ILC2s), thereby promoting type 2 inflammation. IL-4 drives Th2 differentiation and IgE class switching, IL-5 supports eosinophil survival and activation, and IL-13 contributes to mucus hypersecretion and barrier dysfunction. Allergen-bound IgE activates mast cells and basophils, whereas repeated exposure sustains allergen-specific memory B- and T-cell populations [146-149]. In contrast, regulatory T cells (Tregs) and regulatory B cells (Bregs) restrain effector responses through IL-10, TGF-β, inhibitory receptors, and the induction of allergen-blocking IgG4 during successful AIT [7, 9, 12, 150]. These pathways provide the cellular and humoral framework for evaluating PDEV-mediated immune regulation.

EVs can modify antigen presentation and recipient-cell transcription through surface-associated signals and transferred RNA, lipid, protein, and metabolite cargos [151-154]. Within this framework, PDEVs act as cargo- and context-dependent modulators of innate and adaptive immunity. DCs represent a prominent responsive population. Broccoli-derived nanoparticles activate AMP-activated protein kinase in intestinal DCs and promote a regulatory phenotype in experimental colitis [155]. More directly relevant to allergy, Aster yomena callus-derived EVs suppress DC maturation and antigen-presenting activity, reduce downstream $CD4^+$ and $CD8^+$ T-cell responses, and alleviate airway hyperresponsiveness and type 2 inflammation in experimental allergic asthma [156]. This study currently provides the strongest direct evidence for PDEV-mediated immune modulation in allergy, although it remains a single, source-specific preclinical example.

Macrophages are another well-documented PDEV-responsive population. Grapefruit-, turmeric-, and other edible plant-derived nanovesicles are preferentially taken up by intestinal macrophages and induce anti-inflammatory or tissue-repair programs characterized by reduced NF-κB or MAPK signaling, lower TNF-α, IL-6, IL-1β, and nitric oxide production, and increased HO-1, Nrf2, or IL-10 activity [124, 157-164]. In tumors, however, macrophage reprogramming may proceed in the opposite direction. Ginseng-derived nanoparticles promote antitumor macrophage polarization through TLR4–MyD88 signaling [113], whereas Artemisia annua-derived nanovesicles can activate cGAS–STING or NF-κB/PPARγ-associated pathways, depending on the preparation and tumor model, thereby restoring inflammatory macrophage activity and enhancing T-cell recruitment [165, 166]. In acute lung injury and viral pneumonia, Artemisia annua-derived nanovesicles instead restore alveolar-macrophage mitochondrial fitness and limit excessive inflammation [167]. PDEVs may also act directly on lymphocytes, as celery-root-derived vesicles suppress activated $CD4^+$ T-cell signaling and inflammatory

cytokine production in vitro [168]. Collectively, these findings demonstrate that PDEV effects are bidirectional and are determined by botanical source, molecular cargo, recipient-cell identity, tissue microenvironment, and disease context. Most of the available mechanistic evidence, however, derives from colitis, cancer, or acute inflammatory injury rather than allergy. These studies establish biological plausibility but cannot substitute for direct testing in airway, skin, or food-allergy models. Although not an EV study, Dendropanax morbifera leaf extract suppressed NF-κB and MAPK signaling in LPS-stimulated macrophages and reduced serum IgE, skin thickening, and mast-cell accumulation in DNCB-induced atopic dermatitis, providing source-level evidence for its anti-inflammatory and antiallergic potential but not direct evidence of PDEV-mediated activity [162]. Moreover, the conventional M1/M2 macrophage framework oversimplifies tissue-specific myeloid heterogeneity, and some plant vesicles can enhance DC maturation, Th1 responses, or $CD8^+$ T-cell activation [169]. Direct evidence that PDEVs expand allergen-specific Tregs, induce Bregs, suppress mast-cell or basophil degranulation, reduce eosinophil survival, regulate ILC2 activity, or simultaneously decrease allergen-specific IgE while promoting allergen-blocking IgG4 remains limited. Mammalian EV studies provide relevant mechanistic benchmarks: mast-cell-derived EV miR-103a-3p can enhance ILC2-derived IL-5, whereas EVs generated during allergen immunotherapy can suppress ILC2 activity and increase IL-10 [150, 170]. These observations identify important assay systems but do not establish equivalent effects for PDEVs.

Future allergy-focused PDEV studies should therefore evaluate epithelial alarmins, DC activation and antigen presentation, ILC2 abundance and function, mast-cell and basophil degranulation, eosinophilia, allergen-specific Th2/Treg balance, Breg responses, serum IgE and IgG4, and disease-specific physiological outcomes such as airway resistance, skin-barrier integrity, or intestinal permeability. Rechallenge and treatment-withdrawal experiments will also be essential to distinguish transient anti-inflammatory activity from durable immune tolerance.

3.2 Epithelial Barrier Restoration Axis

Epithelial dysfunction is central to asthma, allergic rhinitis, atopic dermatitis, and food allergy because it increases allergen access and alarmin release [171]. The relevant tissue must be specified: airway epithelial barrier in respiratory allergy, epidermal barrier in atopic dermatitis, and intestinal epithelial barrier in food allergy. PDEVs have been reported to support epithelial survival and repair in several non-allergic injury models [172].

Candidate mechanisms include increased expression or organization of tight-junction proteins such as ZO-1 and occludin, reduced oxidative injury, enhanced epithelial migration, and modulation of inflammatory signaling [173]. For allergy translation, these observations should be validated by transepithelial electrical resistance, permeability assays, ciliary function, mucus production, alarmin release, and allergen-translocation measurements in disease-relevant airway, skin, or intestinal models.

Some PDEV preparations also promote angiogenesis or tissue regeneration through pathways involving VEGF and other repair mediators [174]. Such effects may aid wound healing, but excessive angiogenesis or fibroproliferation could be undesirable in chronic airway remodeling or dermatitis. Barrier repair and structural remodeling should therefore be evaluated separately.

Evidence from cutaneous wound healing and intestinal injury supports a link between inflammation resolution and epithelial regeneration [175]. Nevertheless, repair in sterile wounds or colitis is indirect mechanistic evidence for allergy and should not be presented as proof of therapeutic efficacy in atopic dermatitis, asthma, or food allergy.

3.3 Oxidative Stress Regulation Axis

Oxidative stress amplifies allergic inflammation by damaging epithelial cells, activating NF-kappaB and NLRP3 pathways, and increasing alarmin and cytokine release [176, 177]. It can also alter allergens and epithelial lipids, thereby changing immunogenicity.

PDEVs can contain flavonoids, polyphenols, glutathione-related metabolites, and other antioxidant cargos that reduce reactive oxygen species in cell and animal models [129, 178]. These effects are mechanistically relevant to allergy, but antioxidant assays should be linked to allergen exposure, epithelial function, and immune outcomes rather than reported only as changes in generic oxidative markers.

Source-specific potency and dose are critical. A preparation that reduces oxidative stress at one concentration may become cytotoxic or pro-oxidant when secondary metabolites are concentrated. Orthogonal chemical analysis and dose-response testing are therefore required [100].

3.4 Microbiota-Mediated Modulation Axis

Microbiota dysbiosis is associated with food allergy, atopic dermatitis, and asthma, although causal relationships are context-dependent [179-181]. Because orally administered PDEVs can interact with intestinal bacteria and immune cells, microbiota-mediated effects are particularly relevant to food allergy and systemic immune regulation.

PDEV lipids and metabolites can influence bacterial growth, nutrient use, and spatial localization, while vesicle uptake may differ among bacterial taxa [33, 182, 183]. These interactions may alter short-chain fatty acids, bile-acid metabolism, epithelial integrity, and tolerogenic immune circuits. Antibiotic-treated, germ-free, and microbiota-transfer experiments are needed to establish causality.

Plant small RNAs have also been proposed to regulate microbial genes [184]. Because sequence abundance, stability, and target engagement can be low, cross-kingdom RNA claims require rigorous controls. Microbiota shifts observed in colitis or metabolic disease should be treated as hypothesis-generating for allergy until accompanied by allergen-specific immune and clinical endpoints.

3.5 Environmental vesicles as allergen carriers

Environmental vesicles differ fundamentally from edible therapeutic PDEVs. Pollen-derived vesicles (pollensomes), allergen-bearing EVs in indoor dust, and bacterial or fungal EVs can transport intact allergens together with lipids, proteins, nucleic acids, oxidases, and microbial pattern-recognition receptor ligands [22, 185-191].

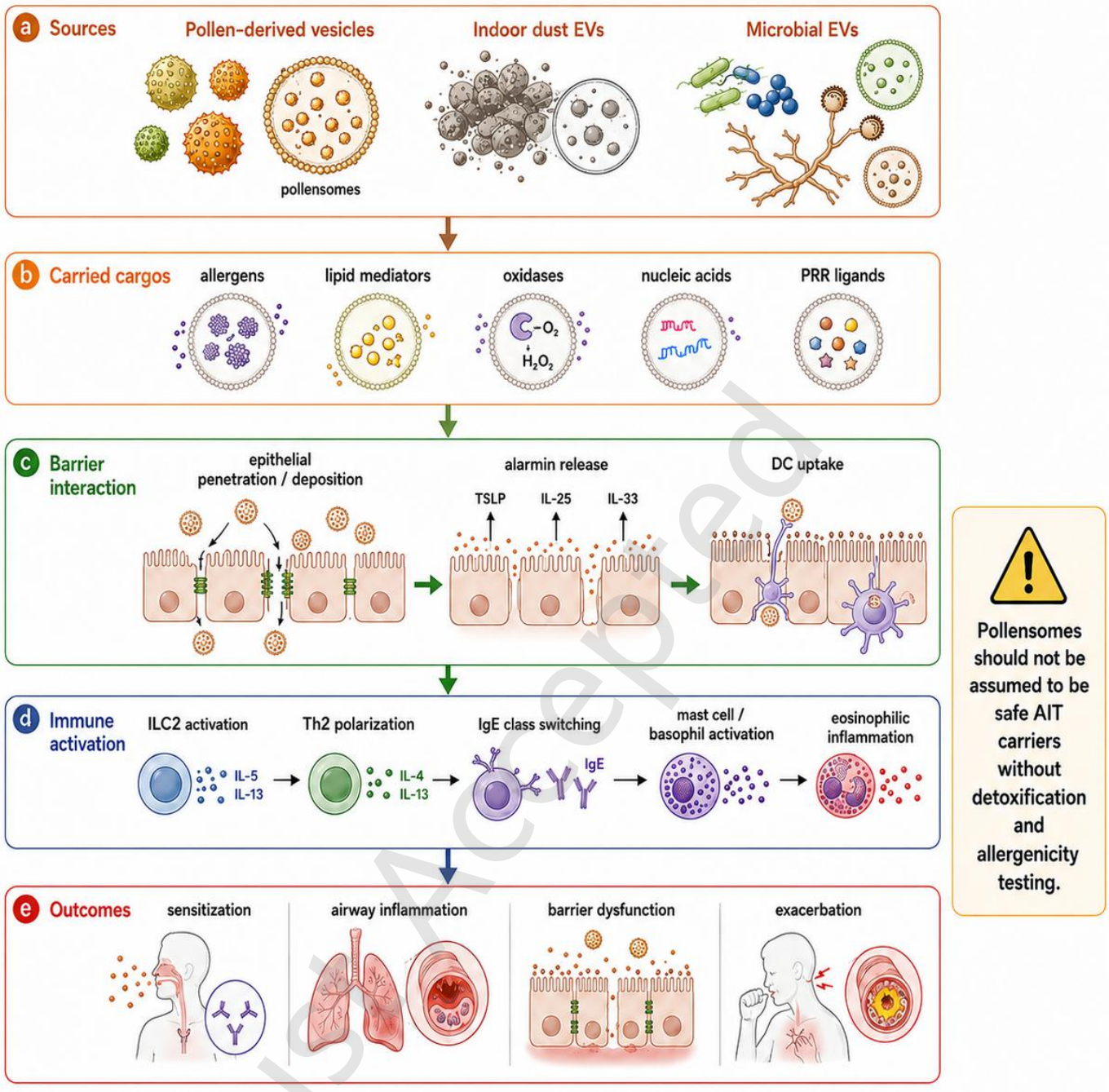

Figure 8. Environmental vesicles in allergen sensitization and allergic inflammation. Pollen-derived vesicles, indoor-dust extracellular vesicles, and microbial vesicles (a) can co-deliver allergens, lipid mediators, oxidases, and pattern-recognition-receptor ligands (b) to epithelial surfaces (c). Barrier activation and alarmin release can promote dendritic-cell and group 2 innate lymphoid-cell activation, type 2 immunity, immunoglobulin E production, and mast-cell, basophil, and eosinophil responses(d-e). Their potential use in allergen immunotherapy requires prior control of allergenicity and adjuvant activity.

The lipid bilayer can protect these cargos and facilitate epithelial deposition or uptake by DCs. Pollensomes from allergenic plants bind patient IgE and can activate basophils, while recent experimental evidence directly links pollen-derived EVs with allergic airway inflammation [185, 191, 192]. These data support a pathogenic carrier role rather than a generic plant-vesicle effect. New evidence shows that environmental exposure does more than just trigger a reaction by the immune system. It also leaves a lasting impact, shaping how likely a person is to develop allergies [193]. In this context, EVs may play a key role in communicating environmental signals. We suggest that EVs from plants could be used as controllable nanoplatforms to trigger a positive immune response, which could transform allergic inflammation into immune tolerance.

The immune system does not distinguish therapeutic from allergenic vesicles solely by botanical origin. Recognition is shaped by surface glycans and proteins, allergen density, lipid composition, particle size and charge, acquired protein corona, co-delivered danger signals, route of exposure, epithelial condition, and host sensitization. Allergenic vesicles can trigger epithelial TSLP, IL-25, or IL-33, activate pattern-recognition pathways, and deliver antigen to DCs in an inflammatory context. In contrast, selected edible PDEVs may deliver anti-inflammatory lipids, small RNAs, or metabolites to gut macrophages, epithelial cells, or microbiota. These are tendencies, not immutable categories; source, dose, processing, and recipient phenotype can reverse the outcome.

Pollensomes should therefore not be proposed as AIT carriers

without qualification [192]. Their natural allergen packaging could improve antigen delivery, but the same vesicles may contain allergenic proteins, pollen-associated lipid mediators, oxidases, and adjuvant-like signals that enhance sensitization or provoke immediate reactions. Before any AIT application, pollensomes would require component-resolved allergen profiling, IgE-binding assays, basophil-activation testing, epithelial and innate immune assays, standardized detoxification or engineering, and demonstration of a favorable tolerance-to-reactogenicity window. The resulting sequence—from environmental vesicle exposure and epithelial activation to type 2 immune amplification and sensitization—is summarized in **Figure 8**. Because this pathogenic exposure framework should not be conflated with therapeutic PDEV efficacy, the following section defines an explicit hierarchy for interpreting the available evidence.

3.6 Evidence hierarchy and disease-specific interpretation

The available literature supports an evidence hierarchy rather than a uniform conclusion of anti-allergic efficacy. Direct evidence is defined here as testing in an allergic disease or AIT model with allergy-specific outcomes. Indirect evidence includes anti-inflammatory, barrier, microbiota, loading, or targeting data from other diseases. The evidence hierarchy and permitted interpretation of the available studies are summarized in **Table 1**. Figure 9 distills this evidence hierarchy into three principal interpretive levels: direct allergy-specific evidence, indirect mechanistic evidence, and engineering or platform feasibility.

Table 1 Evidence hierarchy for interpreting plant-derived extracellular vesicle studies in allergic diseases

Evidence class	Operational definition	Representative examples	Preferred allergy-relevant outcomes	Permitted interpretation	Principal limitation
Direct therapeutic allergy evidence	A defined PDEV preparation is tested in an allergic disease or allergen-immunotherapy model using allergy-specific outcomes.	Aster yomena callus-derived EVs in murine allergic asthma; localized engineered PDEV systems in experimental atopic dermatitis [115, 156, 194, 195].	Airway hyperresponsiveness; eosinophilia; mucus; epithelial alarmins; mast-cell/basophil activation; allergen-specific IgE/IgG4; barrier function; durable response after withdrawal.	Supports efficacy only for the tested source, formulation, route, dose, and model.	Evidence remains sparse and predominantly preclinical; durable allergen-specific tolerance has not been established.
Direct environmental allergy evidence	Environmental vesicles are directly linked to allergen carriage, sensitization, or allergic inflammation.	Olive pollensomes with IgE binding and basophil activation; indoor-dust EV sensitization; pollen-derived EVs promoting allergic airway inflammation [185, 186, 191, 192].	Allergen content; IgE binding; basophil activation; epithelial alarmins; type 2 cytokines; airway inflammation; sensitization.	Supports a pathogenic carrier role for the specific environmental vesicle context.	Cannot be generalized to purified edible PDEVs; exposure matrix, co-factors, and host sensitization are critical.
Indirect mechanistic evidence	PDEVs are tested in non-allergic inflammatory, injury, metabolic, cancer, or infectious models.	Broccoli, grapefruit, turmeric, grape, Portulaca, garlic chive, tea, and other preparations in colitis, acute lung injury, vascular injury, cancer, or wound repair [155, 157, 164, 167, 172, 196-204].	NF-κB/MAPK/NLRP3 signaling; macrophage or dendritic-cell phenotype; oxidative stress; epithelial repair; microbiota changes.	Establishes biological plausibility and candidate mechanisms only.	Shared pathways do not prove control of allergen-specific IgE, type 2 memory, reactogenicity, or durable tolerance.
Engineering/platform evidence	A study demonstrates cargo loading, targeting, membrane engineering, hybridization, or biodistribution outside allergy.	RNA, small-molecule, ligand, aptamer, membrane-fusion, and reconstituted plant-lipid systems in cancer, colitis, vaccination, or other models [106, 205-221].	Loading capacity; encapsulation efficiency; release; target-cell uptake; organ distribution; formulation stability.	Supports technical feasibility and informs design selection.	Does not establish anti-allergic efficacy, safety in sensitized hosts, or superiority over conventional carriers.
Preliminary human observation	Uncontrolled or exploratory human use without a rigorously characterized clinical-grade product.	Topical rose stem cell-derived exosome formulations in mixed dermatologic indications, including atopic dermatitis [222].	Symptoms; local tolerability; exploratory clinical observations.	Hypothesis-generating only.	Uncontrolled design, mixed indications, uncertain product identity, and lack of comparator prevent efficacy conclusions.

AIT, allergen immunotherapy; EV, extracellular vesicle; PDEV, plant-derived extracellular vesicle.

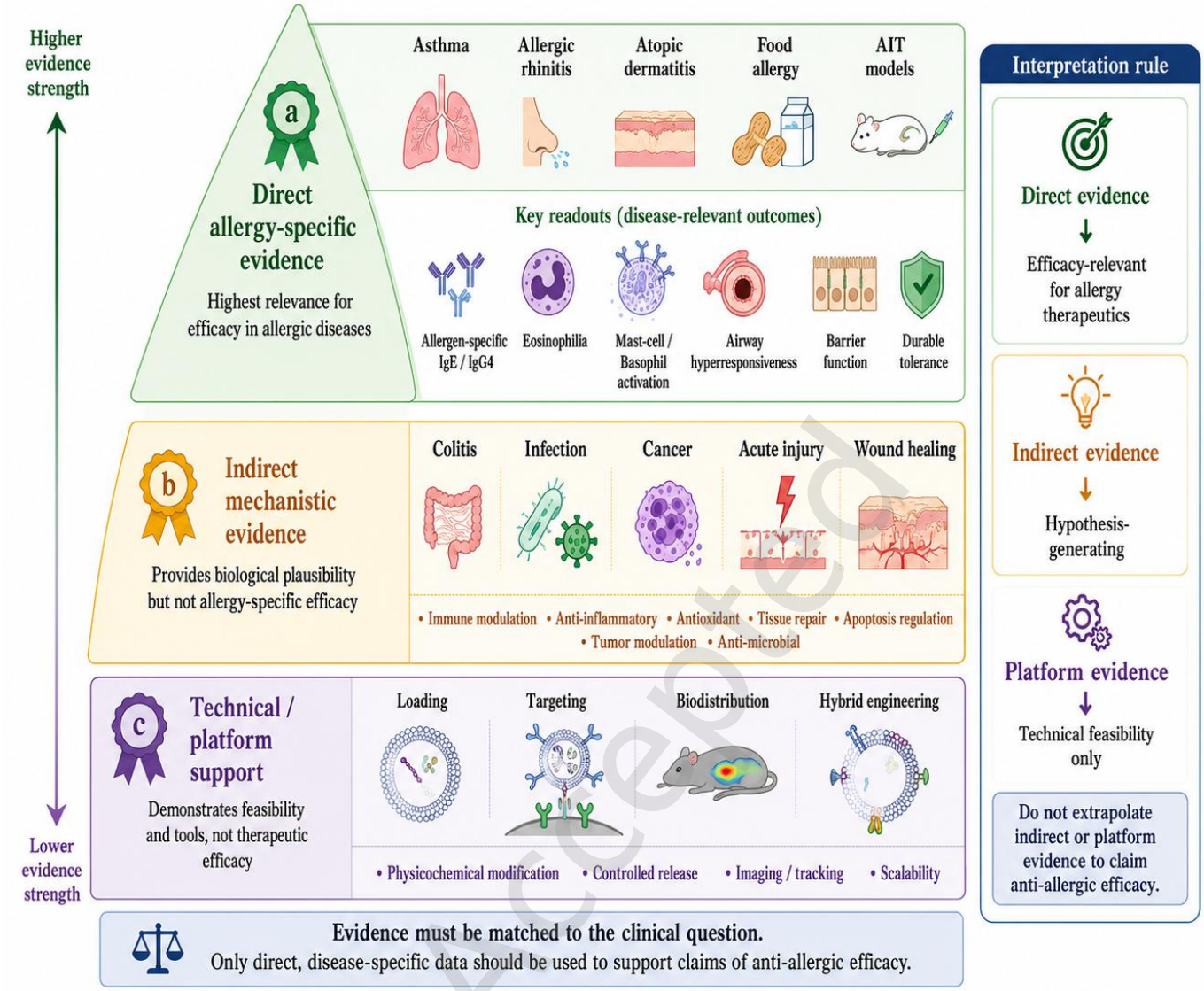

Figure 9. Evidence hierarchy for PDEVs in allergic diseases. Direct evidence comprises studies in asthma, allergic rhinitis, atopic dermatitis, food allergy, anaphylaxis, or allergen-immunotherapy models (a). Findings from colitis, cancer, infection, tissue injury, and other inflammatory models provide indirect mechanistic support (b), whereas loading, targeting, and biodistribution studies primarily demonstrate technical feasibility (c). Therapeutic claims should be interpreted according to this evidence hierarchy.

Using this framework, the following section evaluates PDEVs as intrinsic therapeutic agents and as platforms for exogenous cargo delivery.

4 PDEVs as Therapeutic Agents and Delivery Platforms for Allergic Diseases

PDEVs are attractive nanotherapeutic candidates because the vesicle itself can be biologically active and can also protect exogenous cargo. Nevertheless, the therapeutic literature is dominated by non-allergic disease models. Allergy-specific claims should therefore be restricted to direct evidence, while other findings are presented as mechanistic or platform support.

4.1 PDEVs as intrinsic bioactive agents: direct and indirect evidence

PDEVs carry bioactive small RNAs, lipids, proteins, and secondary metabolites that can regulate inflammatory signaling, redox homeostasis, immune-cell function, and tissue repair. Although direct evidence in allergic diseases remains limited, studies in colitis, metabolic inflammation, acute lung injury, and other inflammatory disorders provide mechanistic support for their potential use in allergy. These models involve pathways also relevant to allergic pathology, including NF-κB and MAPK activation, NLRP3 inflammasome signaling, oxidative stress, mitochondrial dysfunction, epithelial-barrier injury, and dysregulated antigen-presenting cells. The clearest direct evidence is provided by Aster yomena callus-derived EVs, which modulated DC and T-cell responses and improved outcomes in a murine allergic-asthma model [156]. This study links a defined plant-vesicle preparation to an allergy-specific disease context and supports further evaluation of airway inflammation, IgE, eosinophilia, epithelial alarmins, and tolerance. By contrast, pollen-derived vesicles are discussed as pathogenic environmental carriers in Section 3.5 and should not be combined with therapeutic PDEVs under a single anti-allergic category [185, 191, 192].

Most other PDEV studies provide indirect mechanistic support. Across these models, PDEVs frequently restrain excessive myeloid-cell activation. Ginger-, Portulaca oleracea-, garlic chive-, ginseng-, and grapefruit-derived vesicles reduce NF-κB-, MAPK-, or NLRP3-associated signaling, lower IL-1β, IL-6, IL-12, TNF-α, nitric oxide, and pyroptosis, and in some settings enhance IL-10, antioxidant defenses, or mitochondrial fitness [20, 58, 196-198]. In intestinal inflammation, Momordica charantia-, broccoli-, turmeric-, ginger-, tea-, nut-, and grapefruit-derived vesicles further promote tolerogenic dendritic-cell programs, macrophage restraint, microbiota regulation, and epithelial-barrier repair [33, 155, 157, 164, 199-

203]. Blueberry- and ginger-derived vesicles also mitigate vascular or pulmonary inflammation, supporting broader effects on epithelial and innate immune homeostasis [70, 204]. These pathways are relevant to allergy because oxidative stress, inflammasome activation, barrier dysfunction, and dysregulated antigen-presenting cells amplify disease in the airway, skin, and intestine.

Plant vesicles are not uniformly anti-inflammatory. Pollensomes and other pollen-derived particles can carry IgE-reactive allergens, lipid mediators, oxidases, and metabolites that promote epithelial activation, Th2 polarization, and allergic airway inflammation [23, 24, 185, 223, 224]. Thus, the biological outcome of PDEVs depends on botanical source, cargo composition, processing, dose, exposure route, and recipient-cell state. Current evidence supports selected PDEVs as potential multimodal regulators of inflammation, oxidative stress, microbiota, and barrier repair, but their superiority over conventional anti-inflammatory drugs and their capacity to induce durable allergen-specific tolerance remain unproven. Direct therapeutic and environmental allergy-relevant evidence is summarized in Table 2.

Table 2 Direct allergy-relevant evidence for therapeutic PDEVs and environmental allergen-associated vesicles.

Context	Vesicle source/ preparation	Model or evidence setting	Formulation/ route	Principal findings	Evidence-weighted interpretation
Therapeutic [156]	Aster yomena callus-derived EVs	Murine allergic asthma	Intrinsic PDEV; oral administration	Reduced dendritic-cell maturation and T-cell activation; improved airway hyperresponsiveness, type 2/Th17 inflammation, mucus-associated outcomes, and allergen-specific IgE.	Direct therapeutic evidence; strongest source-specific asthma study, but not an engineered pulmonary carrier.
Therapeutic [194]	Turmeric-derived nanovesicles	Experimental atopic dermatitis	Metal–polyphenol hydrogel; topical/local delivery	Improved local retention and skin hydration; reduced epidermal thickening and inflammatory stress; supported barrier repair.	Direct localized engineering evidence; formulation-specific.
Therapeutic [195]	Portulaca oleracea-derived nanovesicles	Experimental atopic dermatitis	Hyaluronic-acid/polysaccharide dissolving microneedles	Enhanced transdermal delivery; modulated macrophage polarization and inhibited NF-κB/STING-associated inflammation.	Direct localized engineering evidence; microneedles and vesicles must be evaluated with separate controls.
Therapeutic [115]	Grapefruit EVs fused with CCR6-expressing gingival mesenchymal-stromal-cell nanovesicles and loaded with CX5461	Psoriasis and atopic dermatitis models	Hybrid membrane-fusion system	Improved CCL20-rich inflammatory-skin targeting; reduced inflammatory cytokines and Th17 responses; increased Treg infiltration.	Direct allergy-relevant engineering evidence, but the product is a complex hybrid rather than a native PDEV.
Preliminary clinical [222]	Rose stem cell-derived exosome formulations	Mixed dermatologic case series, including atopic dermatitis	Topical formulation; product characterization limited	Reported symptomatic improvement across several skin indications.	Very-low-confidence human evidence; cannot establish PDEV efficacy or carrier-mediated benefit.
Environmental /pathogenic [185]	Olive-pollen pollensomes	Human sensitization assays	Natural pollen-derived vesicles	Carried major/minor pollen allergens; bound patient IgE; activated basophils and produced positive skin responses.	Direct evidence that vesicular packaging preserves allergenic activity.
Environmental /pathogenic [186]	Indoor-dust extracellular vesicles	Human airway-disease association	Environmental inhalation exposure	Sensitization to EV-associated antigens was associated with airway disease.	Supports disease association, but causality and allergen-specific mechanisms require further validation.
Environmental /pathogenic [191]	Small EVs released from germinated kiwi pollen	Pollen-vesicle characterization and immune relevance	Natural environmental vesicles	Demonstrated pollen-derived small-EV release and protein/cargo transport relevant to epithelial exposure.	Mechanistic environmental evidence; direct clinical allergenicity must be evaluated source by source.
Environmental /pathogenic [192]	Pollen-derived extracellular vesicles	Sensitized mouse allergic-airway model	Respiratory exposure	Promoted epithelial activation, type 2 cytokines, IgE production, and inflammatory-cell infiltration.	Direct pathogenic evidence that efficient airway deposition can amplify, rather than resolve, allergy.

Only studies with direct allergic-disease, human sensitization, or allergy-relevant environmental outcomes are included. Non-allergic mechanistic and engineering studies are summarized separately in the supplementary tables.
AD, atopic dermatitis; EV, extracellular vesicle; IgE, immunoglobulin E; PDEV, plant-derived extracellular vesicle; Treg, regulatory T cell.

4.2 PDEVs as Carriers of Exogenous Therapeutic Cargos

The lipid bilayer of PDEVs provides a versatile compartment for exogenous therapeutic cargos: hydrophilic molecules can be retained within the aqueous lumen, whereas hydrophobic compounds can partition into or associate with the membrane [28]. Reported loading approaches include passive co-incubation, electroporation, sonication, membrane permeabilization with saponin, freeze–thaw cycling, and osmotic treatment (Figure 10) [225]. Passive incubation is operationally simple and generally causes less membrane disruption, but its loading efficiency is often limited and surface adsorption may be difficult to distinguish from true encapsulation. Active methods can improve loading but may alter vesicle size, membrane integrity, colloidal stability, or cargo activity [28, 226]. Loading studies should therefore quantify both encapsulation efficiency and loading capacity, remove unbound cargo, distinguish luminal incorporation from surface association, and assess vesicle integrity and release kinetics after processing. Their mechanistic basis, indicative loading performance, advantages, limitations, and minimum analytical controls are compared quantitatively in Table 3.

Proof-of-concept studies have demonstrated that plant-derived vesicular platforms can deliver small molecules, proteins, and nucleic acids. Grapefruit-derived nanovesicles loaded with

methotrexate preferentially interacted with intestinal macrophages and improved local anti-inflammatory activity in experimental colitis [157]. For RNA delivery, ginger-derived nanovesicles decorated with folate-displaying three-way-junction RNA nanoparticles delivered survivin siRNA after intravenous administration and inhibited xenograft growth [205], whereas acerola-derived nanovesicles protected exogenous miRNA from enzymatic and physicochemical degradation and enabled oral delivery to the digestive tract [206]. Lipids isolated from plant-derived nanovesicles can also be reassembled into artificial nanovectors. Ginger-derived lipids were reconstructed into doxorubicin-loaded nanovectors that exhibited high drug-loading efficiency and pH-dependent release; folic acid functionalization further enabled targeted delivery to folate-receptor-expressing colon tumors [106]. However, such reassembled lipid nanoparticles should be distinguished from intact PDEVs because their composition, topology, and biological identity are modified during reconstruction.

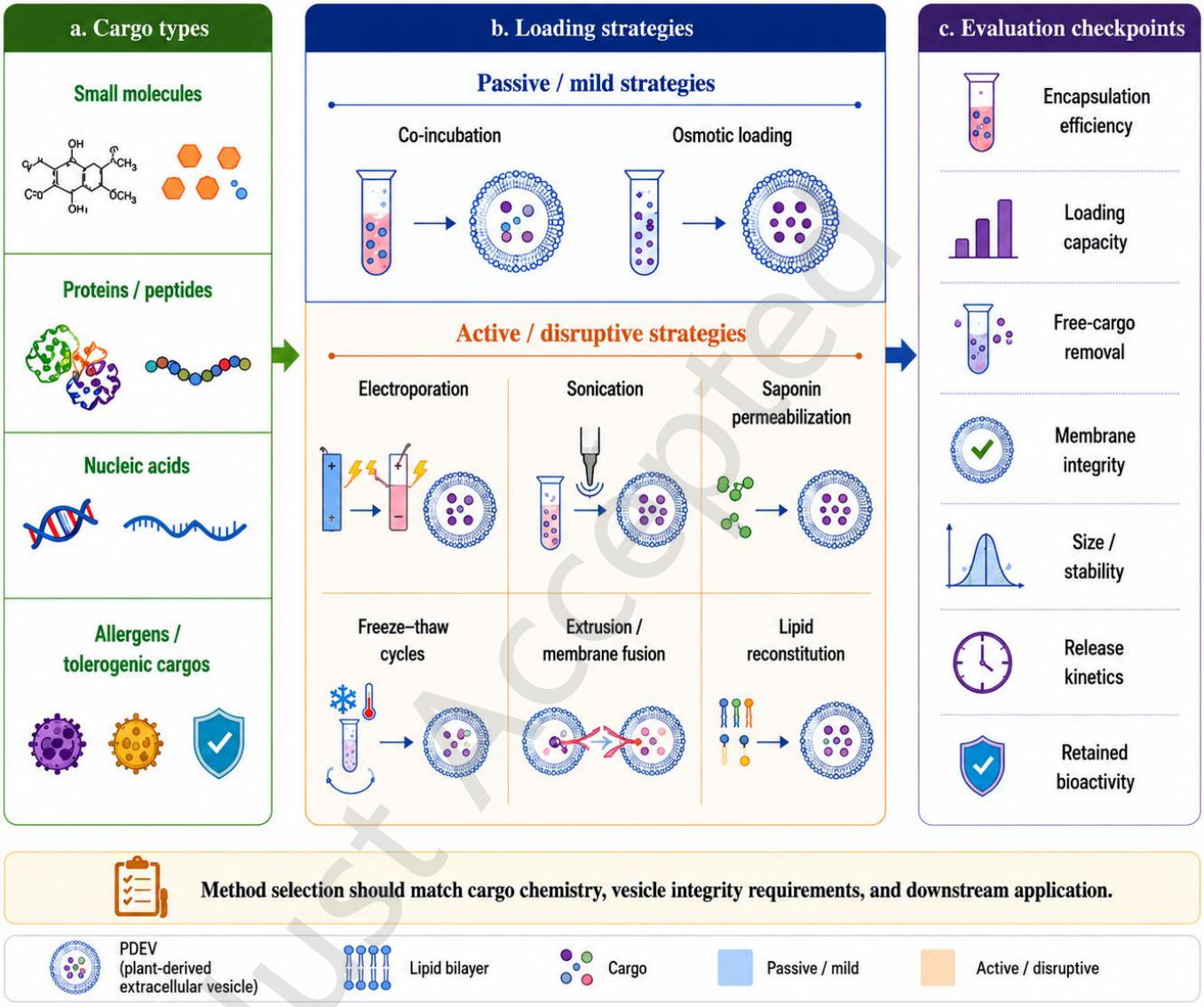

Figure 10. Exogenous cargo-loading strategies for PDEVs. (a) Small molecules, proteins, peptides, and nucleic acids can be incorporated into PDEVs or related plant-lipid nanovesicles. (b) Co-incubation, electroporation, sonication, freeze–thaw cycling, membrane permeabilization, osmotic loading, extrusion, and membrane fusion differ in cargo compatibility and membrane disruption. (c) Method selection should consider loading capacity, encapsulation efficiency, removal of free cargo, vesicle recovery, structural integrity, release kinetics, and retained biological activity.

Table 3. Practical comparison of exogenous cargo-loading strategies for PDEVs and related EV platforms.

Method	Mechanistic basis	Indicative reported performance*	Best-suited cargo	Advantages	Principal limitations	Required controls	Representative applications
Co-incubation/ passive loading	Cargo partitions into the membrane or diffuses along a concentration gradient.	~1–10% in many related-EV reports; substantially higher values have been reported for selected hydrophobic PDEV cargos.	Hydrophobic or amphiphilic small molecules; selected cargos with complexing agents.	Simple, mild, scalable, and generally preserves membrane structure.	Low/variable loading; long incubation; surface adsorption may be misclassified as encapsulation.	Remove free cargo; quantify loading capacity and encapsulation efficiency separately; distinguish luminal cargo from surface association.	MTX-loaded grapefruit nanovesicles and related small-molecule systems [157, 225, 226].

Electroporation	Electrical pulses create transient membrane pores.	~5–25% in heterogeneous EV studies; values are strongly protocol- and assay-dependent.	siRNA, miRNA, oligonucleotides, and other charged macromolecules.	Rapid and reagent-light; adaptable to nucleic acids.	Cargo precipitation, vesicle aggregation, membrane-protein loss, and recovery variability.	Cargo-only electroporation control; aggregation and precipitation assessment; post-loading purification; recovery and membrane-integrity testing.	General PDEV/EV engineering guidance and reporting standards [225, 227].
Sonication	Mechanical shear transiently disrupts and reorganizes the bilayer before membrane recovery.	~10–30% in comparative EV studies; higher study-specific values have been reported for optimized plant-vesicle formulations.	Hydrophobic drugs, selected proteins, and cargos requiring stronger incorporation.	Often higher incorporation than passive loading; may support sustained release.	Heat/shear damage, vesicle enlargement, endogenous-cargo loss, and altered membrane composition.	Temperature control; pre/post size and morphology; membrane integrity; retained cargo and intrinsic-vesicle activity.	General plant-vesicle loading and nanodrug literature [225-227].
Freeze–thaw cycling	Repeated phase transitions permeabilize or fuse membranes.	~5–20% in related-EV literature; no transferable universal value.	Proteins and small molecules that tolerate thermal cycling.	Equipment-light and technically simple.	Aggregation, leakage, broad size distribution, and cargo denaturation.	Optimize cycle number; quantify aggregation, recovery, leakage, and retained activity.	Used in EV/liposome hybridization and related loading workflows [225, 227].
Saponin permeabilization	Saponin–sterol interactions create transient membrane pores.	~10–20% in related-EV reports; plant-membrane transferability is uncertain.	Hydrophilic drugs, proteins, and enzymes.	Can improve macromolecule loading without high mechanical energy.	Residual saponin, membrane toxicity, leakage, and uncertain effects on plant-specific sterols.	Validated saponin-removal assay; hemolysis/cytotoxicity; membrane integrity and recovery.	General EV loading literature and reporting guidance [225, 227].
Osmotic loading	Osmotic gradients transiently alter membrane permeability.	~5–20% in heterogeneous reports.	Hydrophilic small molecules.	Low equipment burden and low cost.	Variable reproducibility, osmotic damage, leakage, and difficult process control.	Osmolality control; recovery; leakage during re-equilibration; size and potency after loading.	General plant-vesicle loading reviews [225, 226].
Extrusion/ membrane fusion	Mechanical extrusion or co-processing drives bilayer remodeling and membrane fusion.	~20–50% in related-EV/hybrid reports; highly formulation-specific.	Drugs, proteins, membrane components, and hybrid formulations.	High incorporation; enables coating, fusion, and simultaneous size homogenization.	Substantial membrane remodeling; loss or redistribution of endogenous cargo; increased product complexity.	Fusion confirmation; component stoichiometry; identity/purity; membrane integrity; free-partner removal; comparability with native PDEVs.	CCR6-directed skin hybrids and activated-leukocyte-coated grapefruit systems [115, 221].
Lipid extraction and reconstitution	Plant lipids are extracted and reassembled around cargo to form engineered nanovectors.	High study-specific loading can be achieved; values are not comparable with intact-PDEV methods.	Hydrophobic small molecules and defined synthetic/plant-lipid formulations.	Improved compositional control and cargo loading; can remove endogenous protein allergens.	The product is not an intact native PDEV; natural proteins/RNAs may be lost; regulatory identity changes.	Define lipid composition, cargo-to-lipid ratio, residual solvent, particle identity, release, and matched liposome controls.	Doxorubicin-loaded ginger-lipid nanovectors [106].

*The numerical ranges are indicative values aggregated from heterogeneous PDEV and related-EV reports. They are not universal specifications and should not be compared without matching the definitions of loading capacity, encapsulation efficiency, recovery, purification, cargo assay, and dose normalization. EV, extracellular vesicle; miRNA, microRNA; PDEV, plant-derived extracellular vesicle; siRNA, small interfering RNA.

These studies establish the technical feasibility of PDEV-mediated cargo delivery but are derived mainly from cancer and intestinal inflammation models. Translation to allergy should prioritize disease-relevant cargos, such as mast-cell stabilizers, topical or inhaled anti-inflammatory agents, barrier-repair molecules, and nucleic acids targeting TSLP, IL-33, IL-4Rα, or other type 2 inflammatory pathways. Delivery of allergen-derived peptides or proteins for tolerance induction requires particular caution because vesicular packaging may either promote tolerogenic presentation or increase allergen uptake and reactogenicity. Allergy-directed formulations should therefore be compared with free cargo, empty PDEVs, liposomes, and mammalian EVs at matched cargo and particle doses, with evaluation of epithelial alarmins, mast-cell and basophil activation, allergen-specific IgE and IgG4, off-target biodistribution, and repeated-dose safety. Current evidence supports PDEVs as adaptable experimental carriers but does not yet establish superiority over conventional delivery systems. Compared with some mammalian cell-derived EV platforms, plants may provide scalable raw materials and reduce the risk of transmitting mammalian pathogens. However, lower immunogenicity, reduced tumorigenic risk, superior stability, or improved delivery efficiency cannot be assumed across all PDEVs and must be demonstrated through source-specific characterization, matched controls, and comparative safety studies [157, 225, 228-230].

4.3 Current evidence for Engineered and Localized PDEV Delivery

Localized delivery is particularly attractive for allergic diseases because the major target organs—the skin, airway, and intestinal mucosa—are accessible to topical, inhaled, intranasal, or oral administration. Local retention may increase drug exposure at diseased barriers while limiting systemic immunosuppression. Emerging studies in atopic dermatitis illustrate three complementary engineering strategies: membrane fusion for inflammatory-site targeting, hydrogel incorporation for prolonged local retention, and microneedle-assisted delivery across the skin barrier.

For allergy treatment, the most compelling opportunities involve local delivery to the airway, skin, or intestine, protection of labile therapeutic cargos, and co-delivery of agents that suppress effector inflammation while promoting barrier repair or immune tolerance. Emerging studies in atopic dermatitis (AD) illustrate several engineering strategies. Grapefruit-derived exosome-like nanovesicles loaded with the immunosuppressant CX5461 were fused with CCR6-expressing nanovesicles derived from engineered gingival mesenchymal stromal-cell membranes, improving inflammatory-skin targeting and therapeutic activity in experimental AD [115]. Turmeric-derived nanovesicles incorporated into a metal–polyphenol hydrogel provided a locally retained, dual-repair system that reduced inflammatory stress and supported restoration of the damaged skin barrier [194]. Similarly, dissolvable microneedles composed of hyaluronic acid and Portulaca oleracea polysaccharides enhanced the transdermal delivery of P. oleracea-derived nanovesicles, which alleviated AD-associated inflammation by modulating macrophage polarization and inhibiting NF-κB- and STING-associated signaling [195]. Preliminary clinical observations have also been reported for topical rose stem cell-derived exosome formulations, including symptomatic improvement in an AD case; however, the uncontrolled case-series design, heterogeneous indications, and limited product characterization preclude conclusions regarding efficacy or carrier-mediated delivery [222].

Together, these studies define three complementary delivery strategies for cutaneous allergy: cargo loading combined with membrane-guided targeting, hydrogel-mediated local retention, and microneedle-assisted transdermal administration. Nevertheless, development should include dose-normalized comparisons with free cargo, empty biomaterials, liposomes, and mammalian EVs; rigorous assessment of vesicle identity, cargo release, skin penetration, off-target biodistribution, and repeated-dose safety; and allergy-specific evaluation of epithelial alarmins, barrier function, mast-cell and basophil activation, eosinophilia, and allergen-specific IgE and IgG4 responses [27, 231-234]. Current AD studies establish the feasibility of incorporating PDEVs into localized delivery systems but do not yet demonstrate their superiority over established carriers or their ability to induce durable allergen-specific tolerance. Representative intrinsic, localized, and cargo-delivery applications are summarized in Table S4 in the ESM.

5 Disease-Oriented Engineering Strategies for PDEVs in Allergic Diseases

The engineering requirements of PDEVs differ substantially among asthma, allergic rhinitis, AD, and food allergy. Inhaled systems must tolerate aerosolization and penetrate airway mucus; nasal formulations must overcome mucociliary clearance; cutaneous platforms must cross the stratum corneum; and oral PDEVs must withstand gastrointestinal degradation while controlling allergen exposure. These disease-specific constraints require an integrated engineering framework that links botanical-source safety, cargo selection, cellular targeting, barrier-adapted formulation, and allergy-specific evaluation (Figure 11).

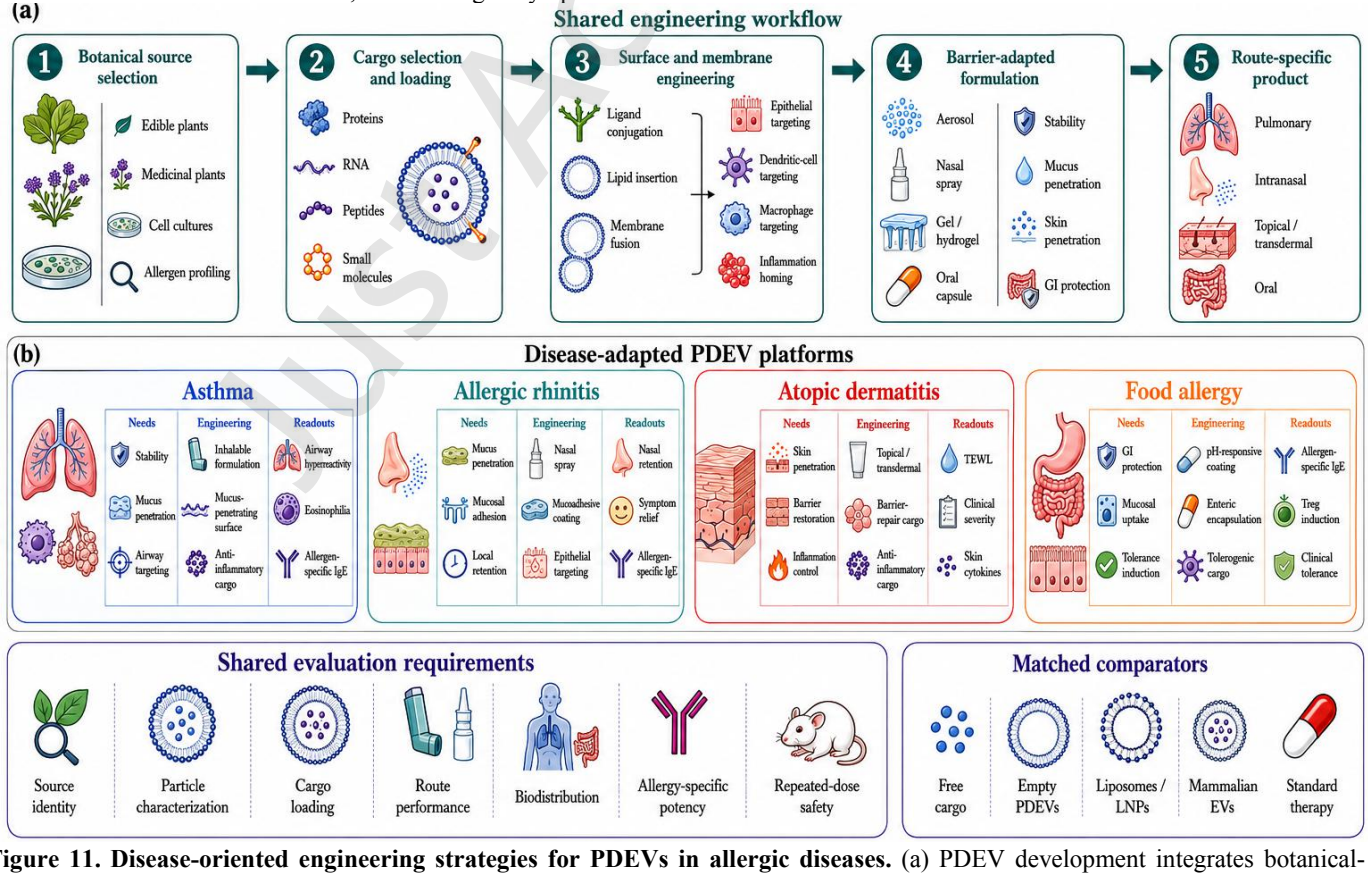

Figure 11. Disease-oriented engineering strategies for PDEVs in allergic diseases. (a) PDEV development integrates botanical-source selection, cargo loading, surface or membrane engineering, barrier-adapted formulation, and route-specific delivery. (b) Pulmonary, intranasal, topical or transdermal, and oral platforms require distinct design criteria for asthma, allergic rhinitis, atopic

dermatitis, and food allergy, respectively. Shared evaluation requirements include source identity, allergenicity, biodistribution, allergy-specific potency, matched comparators, and repeated-dose safety.

Most advanced strategies have been developed in cancer, colitis, vaccination, or other inflammatory models [106, 128, 205, 207-216]，and should be regarded as technical precedents rather than direct evidence in allergy. At present, direct engineering evidence is strongest in AD, whereas applications in allergic rhinitis and food allergy remain largely prospective. The current evidence status, preferred delivery route, dominant biological barriers, candidate cargos, and essential evaluation endpoints for each allergic disease are summarized in Table 4

Table 4. Disease-oriented engineering roadmap for PDEVs in allergic diseases.

Disease	Current evidence status	Preferred route/ formulation	Dominant delivery barriers	Candidate targets and cargos	Essential performance and efficacy readouts	Overall status
Asthma	Direct intrinsic efficacy from orally administered Aster yomena callus EVs; no established engineered inhaled PDEV product. Pollen EVs provide direct pathogenic airway evidence.	Pulmonary aerosol or carefully distinguished intranasal delivery; mucus-penetrating or airway-retentive formulation.	Aerosol stress; aerodynamic deposition; mucus diffusion; mucociliary clearance; post-nebulization membrane/cargo integrity.	Airway epithelial cells, dendritic cells, alveolar macrophages; anti-inflammatory RNAs, mast-cell stabilizers, epithelial-repair or antioxidant cargos.	Airway resistance; fine-particle deposition; epithelial alarmins; eosinophilia; mucus; mast-cell/basophil activation; allergen-specific IgE; withdrawal/rechallenge response.	Direct efficacy but limited engineering evidence.
Allergic rhinitis	No direct engineered-PDEV efficacy study identified in the current review.	Intranasal spray, thermoresponsive gel, or controlled-mucoadhesion system.	Rapid mucociliary clearance; mucus entrapment; limited residence; enzymatic degradation; accidental swallowing.	Nasal epithelial cells and local antigen-presenting cells; alarmin-suppressing, mast-cell-stabilizing, or tolerogenic cargos.	Nasal retention; epithelial uptake; TSLP/IL-25/IL-33; mast-cell activation; local symptoms; allergen-specific IgE; unintended sensitization.	Prospective application; platform evidence only.
Atopic dermatitis	Strongest direct engineering evidence: hybrid membrane targeting, turmeric-nanovesicle hydrogel, and Portulaca microneedles.	Topical hydrogel, dissolving microneedle, or inflammation-directed hybrid vesicle.	Stratum-corneum penetration; heterogeneous barrier damage; local retention; irritation; systemic escape.	Keratinocytes, skin dendritic cells, macrophages; anti-inflammatory, antioxidant, filaggrin/junction-supporting, or barrier-repair cargos.	Transepidermal water loss; filaggrin; epidermal/dermal penetration; epithelial alarmins; eosinophilia; mast cells; local/systemic exposure; repeated-dose irritation.	Most advanced allergy-directed engineering area.
Food allergy	No direct engineered-PDEV efficacy study identified; oral delivery precedents derive mainly from colitis and vaccine models.	Enteric coating, pH-responsive capsule, polysaccharide hydrogel, or intestinal-cell-targeting formulation.	Gastric acid; digestive enzymes; bile salts; intestinal mucus; premature allergen release; microbiota-dependent transformation.	M cells, CD103+ dendritic cells, CX3CR1+ phagocytes, epithelium; standardized allergen peptides combined with IL-10/IDO1/TGF-β-associated or regulatory-RNA cargos.	Gastrointestinal release; IgE cross-linking; basophil activation; anaphylaxis; Treg induction; barrier integrity; oral challenge; durable tolerance after withdrawal.	Prospective application with high sensitization-risk requirements.

Route-specific product development should use matched comparators, including free cargo, empty PDEVs, conventional liposomes or lipid nanoparticles, mammalian EVs, and standard therapy. IDO1, indoleamine 2,3-dioxygenase 1; TGF-β, transforming growth factor-β; TSLP, thymic stromal lymphopoietin.

5.1 Source selection and safety-oriented engineering

Botanical source is a critical design variable because plant species, cultivar, tissue, cultivation, processing, and isolation methods influence vesicular proteins, lipids, RNAs, metabolites, and biological activity. An edible or medicinal origin does not guarantee low allergenicity.

Strawberry-derived vesicles contain Fra a-related allergens with IgE-binding activity [217], while pollen-derived EVs can promote epithelial activation and allergic airway inflammation [192]. Therapeutic PDEVs should therefore originate from well-characterized, low-allergen plants and undergo allergen-focused proteomics, IgE-binding assays, mast-cell or basophil-activation testing, and evaluation in sensitized models.

For food allergy, endogenous plant allergens should be distinguished from intentionally loaded therapeutic allergens. The former represent a source-related safety risk, whereas standardized allergen peptides may be incorporated for tolerance induction only when their dose, release, and IgE-cross-linking potential are tightly controlled. Reconstituted plant-lipid carriers may reduce endogenous protein complexity but are not biologically equivalent to intact PDEVs.

5.2 Cargo engineering for inflammation control, barrier repair, and immune tolerance

PDEVs can accommodate hydrophilic and hydrophobic cargos through passive incubation, sonication, electroporation, membrane permeabilization, freeze–thaw cycling, extrusion, or lipid reconstitution. Because these procedures may affect vesicle integrity and cargo activity, studies should quantify loading efficiency, loading capacity, free-cargo removal, colloidal stability, and release kinetics.

Representative studies demonstrate delivery feasibility. Grapefruit-derived nanovesicles delivered methotrexate to intestinal macrophages [157]; broccoli-derived EVs protected exogenous miRNAs [218]; and orange-derived EVs delivered functional mRNA through oral and intranasal routes [219]. These studies support the platform concept but do not establish efficacy in allergy.

Potential anti-allergic cargos include corticosteroids, mast-cell

stabilizers, JAK inhibitors, antioxidants, and nucleic acids targeting TSLP, IL33, IL25, IL4RA, STAT6, or GATA3. Barrier-repair cargos may enhance filaggrin expression, epithelial junctions, antioxidant defenses, mitochondrial homeostasis, or tissue repair. Combining anti-inflammatory and barrier-restorative agents may be particularly valuable because epithelial injury promotes allergen penetration and alarmin release.

A more disease-modifying strategy would co-deliver standardized allergen peptides with IL-10-, IDO1-, or TGF-β-associated cargos or regulatory miRNAs. However, vesicular allergen delivery may promote either tolerance or sensitization. Accordingly, efficacy studies must assess mast-cell and basophil activation, allergen-specific antibodies, Treg induction, anaphylaxis, and protection after treatment withdrawal.

5.3 Surface and membrane engineering for allergy-relevant targeting

Surface modification can improve cellular uptake, mucosal interaction, local retention, and inflammatory-site homing. Available approaches include covalent ligand conjugation, lipid-anchor insertion, polymer coating, aptamer decoration, and membrane fusion (Figure 11) [225]. Although folate-, cRGD-, transferrin-, and aptamer-modified plant vesicles demonstrate technical feasibility in cancer, allergy-directed systems should target epithelial cells, dendritic cells, macrophages, keratinocytes, or intestinal antigen-presenting cells [106, 205, 207-209].

Hyaluronic-acid-functionalized red-cabbage EVs showed enhanced intestinal localization and interaction with epithelial and immune cells in colitis [220], providing a relevant precedent for oral mucosal targeting. Similarly, CX5461-loaded grapefruit vesicles fused with CCR6-expressing stromal-cell nanovesicles accumulated in CCL20-rich inflammatory skin [115]. Activated-leukocyte membrane-coated grapefruit nanovectors also demonstrated inflammation-directed trafficking [221].

These approaches may be adapted to allergic tissues, but membrane fusion and multi-ligand modification increase manufacturing complexity, immunogenicity concerns, and regulatory burden. Each modification should therefore produce a measurable advantage over unmodified PDEVs.

5.4 Barrier-specific formulation and localized delivery

5.4.1 Pulmonary delivery for asthma

Aster yomena callus-derived EVs reduced dendritic-cell activation, airway hyperresponsiveness, Th2/Th17 responses, mucus-associated markers, and allergen-specific IgE in experimental asthma [156]. However, these vesicles were used as intrinsic bioactive agents rather than engineered carriers.

Inhaled PDEVs should be optimized for aerosol stability, aerodynamic deposition, mucus penetration, lung retention, and uptake by airway epithelial or immune cells. Particle size, membrane integrity, aggregation, cargo retention, and activity should be assessed before and after nebulization. Intranasal mRNA-loaded orange EVs provide a respiratory-delivery precedent [219], but asthma-directed systems must suppress type 2 inflammation or induce tolerance rather than enhance immunity.

5.4.2 Nasal delivery for allergic rhinitis

No direct study has established engineered PDEVs for allergic rhinitis. Major challenges include mucociliary clearance, mucus entrapment, limited residence time, and accidental swallowing. Mucoadhesive polymers, thermoresponsive gels, and nasal sprays may prolong retention, although excessive mucoadhesion can limit epithelial penetration.

Orange-derived EVs demonstrate the feasibility of intranasal nucleic-acid delivery [219], but vaccine-induced mucosal immunity cannot be equated with allergic tolerance. Future studies should assess nasal retention, epithelial uptake, alarmin release, mast-cell activation, allergen-specific IgE, tolerogenic dendritic cells, and unintended sensitization.

5.4.3 Cutaneous delivery for atopic dermatitis

AD currently provides the strongest direct evidence for localized PDEV engineering. Dissolving microneedles containing Portulaca oleracea-derived nanovesicles improved transdermal delivery and alleviated AD by modulating macrophage polarization and suppressing NF-κB and STING signaling [195].

Turmeric-derived nanovesicles incorporated into a metal–polyphenol hydrogel enhanced local retention, reduced inflammatory and oxidative stress, and promoted skin-barrier repair [194]. Microneedles primarily improve barrier penetration, whereas hydrogels support retention and sustained release. Membrane-guided targeting, as demonstrated by CCR6-expressing hybrid vesicles [115], may further enhance lesion accumulation but requires direct validation in AD.

Relevant outcomes include skin penetration, local retention, transepidermal water loss, filaggrin expression, epithelial alarmins, eosinophilia, mast-cell activation, systemic exposure, and repeated-dose irritation.

5.4.4 Gastrointestinal delivery for food allergy

Direct evidence for engineered PDEVs in food allergy remains unavailable. Oral carriers must resist gastric acid, enzymes, bile salts, and intestinal mucus while preventing premature allergen release. Enteric coatings, pH-responsive capsules, polysaccharide hydrogels, and surface ligands may improve gastrointestinal stability and target M cells, CD103^+ dendritic cells, CX3CR1^+ phagocytes, or epithelial cells.

HA-modified red-cabbage EVs provide a precedent for intestinal targeting [220], whereas broccoli- and orange-derived vesicles support RNA loading and oral delivery [218, 219]. Future food-allergy formulations may co-deliver standardized allergen peptides with tolerogenic cargos, but should be evaluated for gastrointestinal release, IgE cross-linking, basophil activation, anaphylaxis, Treg induction, barrier integrity, and durable tolerance.

5.5 Hybrid and reconstituted plant-derived nanovectors

Hybrid systems combine plant vesicles with mammalian-cell membranes to acquire inflammatory-site homing properties, as demonstrated by CCR6-expressing fusion vesicles and activated-leukocyte-coated grapefruit nanovectors [115, 221]. Although potentially useful for allergic tissues, these systems increase compositional and regulatory complexity.

Reconstituted plant-derived nanovectors are generated by extracting and reassembling plant lipids. Ginger-derived lipids have been formulated into doxorubicin-loaded, pH-responsive, folate-targeted nanovectors [106]. Hybrid systems incorporating inorganic nanosheets, drug-lipid conjugates, or polymeric components can increase cargo capacity or responsiveness [215, 216]. For allergy, reconstitution may improve compositional control, aerosol or gastrointestinal stability, and removal of endogenous allergenic proteins. However, it may also eliminate natural anti-inflammatory and barrier-repair cargos. Native PDEVs, cargo-loaded PDEVs, reconstituted plant-lipid vesicles, and synthetic liposomes should therefore be compared at matched lipid and cargo doses. Representative ligand-display, surface-modification, membrane-fusion, coating, reconstitution, and hybrid-engineering strategies are summarized in Table S5 in the ESM.

5.6 Evaluation framework for allergy-directed PDEV engineering

In accordance with MISEV2023, studies should document botanical source, preprocessing, isolation, particle concentration and size, morphology, biochemical composition, and non-

vesicular contaminants [53]. Engineered formulations additionally require characterization of cargo loading, ligand density, free-cargo removal, membrane integrity, release kinetics, and storage stability.

Testing should be route specific: aerosol performance for inhaled formulations, mucus transport for nasal systems, penetration and retention for cutaneous platforms, and gastrointestinal stability for oral products. Biodistribution methods should distinguish intact vesicles from released cargo or free fluorescent labels.

Allergy-specific endpoints should include epithelial alarmins, mast-cell and basophil activation, eosinophilia, airway hyperresponsiveness, mucus production, skin or intestinal barrier function, allergen-specific antibodies, tolerogenic dendritic cells, Treg induction, and responses to repeated allergen challenge. Claims of durable tolerance require efficacy after treatment withdrawal.

Engineered PDEVs should also be compared with free cargo, conventional liposomes or lipid nanoparticles, mammalian EVs, and standard anti-allergic therapies at matched delivered doses. Their superiority in delivery, safety, stability, manufacturability, or allergen-specific tolerance remains to be established [235-238].

In a summer, PDEV engineering should align botanical source, cargo, target cell, biological barrier, and immune objective. Asthma requires aerosol-compatible pulmonary delivery; allergic rhinitis requires balanced nasal retention and mucus penetration; AD requires skin-barrier access and local retention; and food allergy requires gastrointestinal protection, allergen control, and tolerogenic antigen presentation. Each additional ligand, coating, biomaterial, or membrane component should be retained only when it provides a demonstrable improvement in efficacy, safety, or product consistency.

6 Route of Administration and Biodistribution

Administration route determines PDEV exposure, tissue retention, cellular uptake, and therapeutic outcome (Figure 12). Route selection should match the affected barrier and immune objective: pulmonary delivery for asthma, intranasal delivery for allergic rhinitis, topical or transdermal delivery for AD, and oral delivery for food allergy. Systemic administration is generally less suitable for these barrier-localized diseases unless multiorgan exposure or specific circulating immune-cell targeting is required. Direct evidence remains limited: oral PDEVs have shown activity in experimental asthma, and localized formulations have been evaluated in AD, whereas allergic-rhinitis and food-allergy applications remain largely prospective.

6.1 Oral delivery: food allergy and gastrointestinal immune modulation

Oral administration provides access to intestinal epithelial cells, macrophages, antigen-presenting cells, and the microbiota. Edible plant-derived nanoparticles have been detected in intestinal epithelial and immune-cell compartments, while ginger-derived nanoparticles preferentially accumulated in the intestine and colon [58, 124]. These findings support oral PDEV delivery but derive mainly from healthy or inflammatory-bowel-disease models rather than food allergy.

Oral formulations must withstand gastric acidity, enzymes, bile salts, and intestinal mucus while preserving vesicle and cargo integrity. Food-allergy applications should additionally prevent premature allergen release and promote delivery to epithelial cells, M cells, $CD103^+$ dendritic cells, or $CX3CR1^+$ phagocytes. Relevant studies should assess gastrointestinal stability, controlled release, IgE cross-linking, basophil activation, anaphylaxis, Treg induction, and durable tolerance.

Orally administered Aster yomena callus-derived EVs reduced airway hyperresponsiveness, Th2/Th17 responses, mucus-associated factors, and allergen-specific IgE in experimental asthma [156]. However, this finding indicates systemic or gut–lung immune modulation rather than proven lung-specific biodistribution.

6.2 Intranasal and pulmonary delivery: asthma and allergic rhinitis

Intranasal delivery provides direct access to the nasal mucosa and, depending on formulation and dosing technique, may also expose the lower airway. Orange-derived EVs carrying exogenous mRNA have demonstrated the feasibility of respiratory mucosal nucleic-acid delivery [219]. As this platform was developed for vaccination, it should not be regarded as evidence of tolerance induction in allergic rhinitis or asthma.

For allergic rhinitis, major barriers include mucociliary clearance, mucus entrapment, limited residence time, enzymatic degradation, and swallowing. Mucoadhesive sprays or in situ-forming gels may prolong retention, although excessive mucus binding can restrict epithelial penetration. Studies should distinguish superficial mucus retention from uptake by epithelial cells or local antigen-presenting cells.

For asthma, intranasal instillation should be distinguished from true pulmonary delivery. Nebulized or dry-powder PDEVs require assessment of aerosol output, aerodynamic particle size, fine-particle fraction, lung deposition, vesicle integrity, and cargo retention. Cellular biodistribution should identify uptake by airway epithelial cells, macrophages, and dendritic cells rather than rely only on whole-lung fluorescence.

Source safety is also critical. Intranasally administered pollen-derived EVs promoted epithelial activation, type 2 inflammation, IgE production, and inflammatory-cell infiltration in sensitized mice [192]. Efficient airway deposition therefore does not imply therapeutic benefit.

6.3 Topical and transdermal delivery: atopic dermatitis

Localized skin delivery can increase lesion exposure while reducing systemic immunosuppression, but passive topical application is limited by the stratum corneum and variable barrier disruption.

Dissolving microneedles containing Portulaca oleracea-derived nanovesicles improved transdermal delivery and alleviated experimental AD through regulation of macrophage polarization and suppression of NF-κB and STING signaling [195]. Turmeric-derived nanovesicles incorporated into a metal–polyphenol hydrogel enhanced local retention, reduced inflammatory and oxidative stress, and promoted barrier repai [194]. Microneedles primarily improve penetration, whereas hydrogels support retention and sustained release.

Cutaneous biodistribution should quantify epidermal and dermal penetration, local residence, target-cell uptake, cargo release, and systemic exposure. Surface fluorescence alone should not be interpreted as tissue delivery, and barrier status should be documented because acute, chronic, excoriated, and intact skin may produce different distribution profiles.

6.4 Systemic administration: limited indications in localized allergy

Intravenous administration increases systemic exposure but commonly results in hepatic and splenic clearance by the mononuclear phagocyte system. Grapefruit lipid-derived nanovectors showed substantial liver deposition influenced by circulating EVs and hepatic macrophages [239]. Although these particles were reconstituted plant-lipid nanovectors rather than intact PDEVs, the findings illustrate the importance of blood interactions in systemic distribution.

Because asthma, allergic rhinitis, AD, and food allergy primarily involve accessible barrier tissues, intravenous delivery is generally less disease-concordant than local administration.

Where systemic delivery is used, studies should assess protein-corona formation, complement activation, circulating stability, liver and spleen uptake, target-tissue accumulation, and repeated-dose immunogenicity.

6.5 Physicochemical determinants of biodistribution

Biodistribution is governed by administration route and vesicle properties, including size, charge, membrane composition, aggregation, and cargo loading. Because engineering, storage, and formulation can modify these features, distribution should be assessed using the final product in disease-relevant models that reflect inflammation-induced changes in barriers, receptors, and immune-cell recruitment.

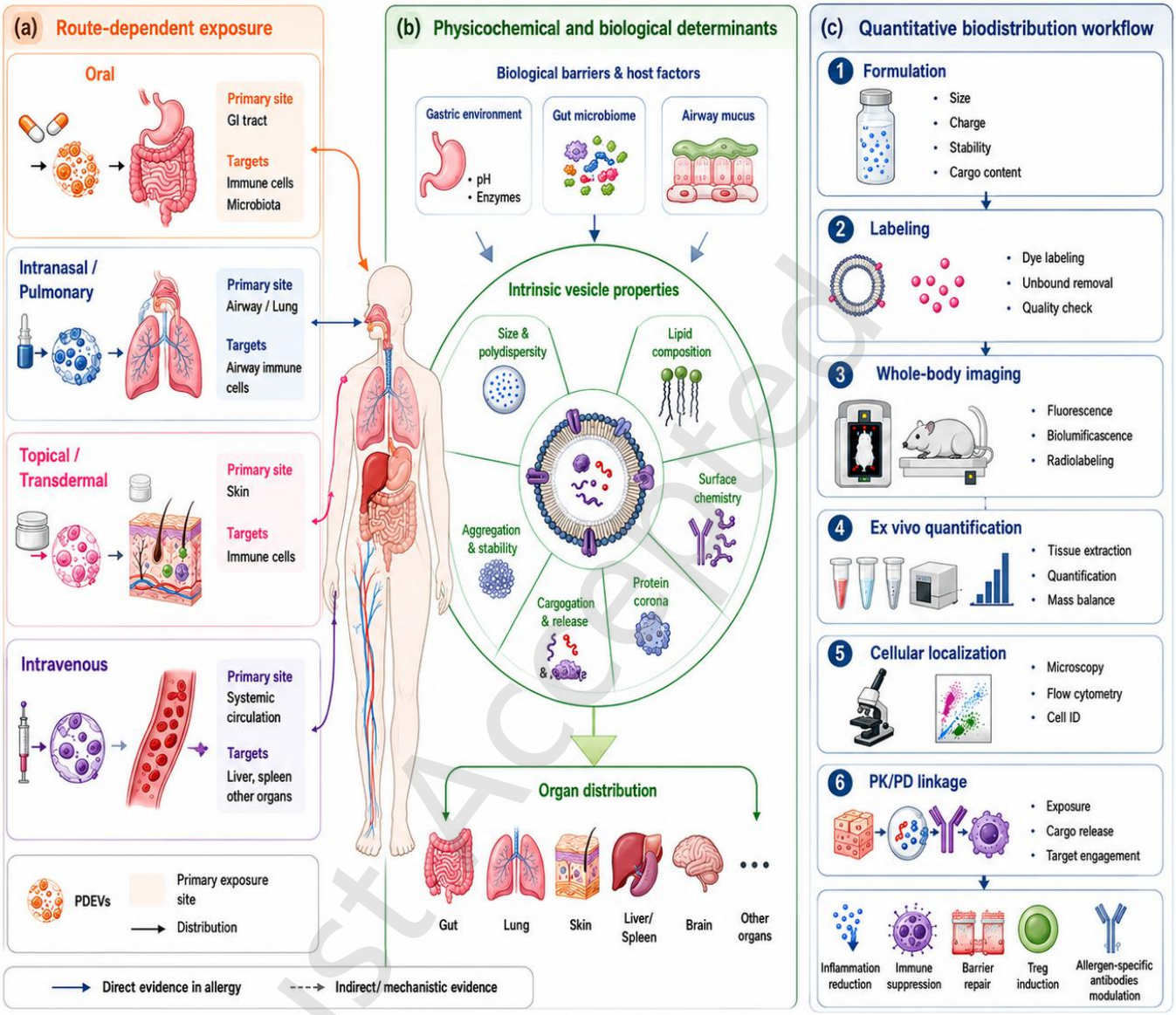

Figure 12. Administration routes and determinants of PDEV biodistribution. (a) Oral, intranasal or pulmonary, topical or transdermal, and intravenous administration generate distinct gastrointestinal, respiratory, cutaneous, and systemic exposure patterns. (b) Particle size, lipid composition, surface chemistry, protein-corona formation, aggregation, cargo loading, biological barriers, microbiota, and host phenotype collectively determine tissue distribution and cellular uptake. (c) Reliable biodistribution assessment requires labeling controls, quantitative tissue analysis, cellular localization, intact-vesicle or cargo tracing, and linkage of exposure to pharmacodynamic outcomes.

Single lipophilic-dye imaging is insufficient because dyes may dissociate, aggregate, or transfer to lipoproteins and cell membranes. Reliable studies should include dye-only controls, removal of unbound tracer, labeling-stability testing, and complementary or dual-label methods that distinguish vesicle membrane from therapeutic cargo [240]. Dose should be normalized by at least two measures, such as particle number and lipid, protein, or cargo mass.

Whole-body imaging should be combined with ex vivo tissue quantification, microscopy, flow cytometry, cargo-specific assays, or radiolabeling. Importantly, tissue fluorescence does not establish intact-vesicle delivery or functional cargo release. Biodistribution should therefore be linked to pharmacodynamic endpoints, including epithelial alarmins, mast-cell and basophil activation, eosinophilia, barrier restoration, allergen-specific antibodies, tolerogenic dendritic cells, and Treg induction.

Route selection should follow the anatomical and immunological requirements of each allergic disease: oral delivery for food allergy and intestinal tolerance, intranasal delivery for allergic rhinitis, pulmonary aerosol delivery for asthma, and topical or transdermal administration for AD. Oral PDEVs may also exert systemic immune effects, but these should not be interpreted as organ-specific targeting without direct evidence. Across all routes, robust conclusions require route-adapted formulation testing, quantitative tissue and cellular biodistribution, and methods that distinguish intact

PDEVs from released cargo and free tracers. **Figure 12** integrates the route-dependent exposure patterns, vesicle-intrinsic physicochemical properties, biological barriers, host factors, and analytical controls that collectively determine PDEV biodistribution. These route- and property-dependent uncertainties lead directly to the product-definition, quality-control, safety, manufacturing, and regulatory priorities discussed in the following section.

7 Perspectives on PDEVs and future challenges

Clinical translation requires more than demonstration of anti-inflammatory activity. The principal bottlenecks are source and product definition, batch consistency, mechanism-linked potency, scalable manufacturing, storage stability, biodistribution, allergenicity, and a regulatory strategy aligned with the final composition and intended use.

7.1 Standardization and Quality Control

PDEV standardization is challenging because no universal plant-vesicle marker is analogous to a validated pan-EV marker, and candidate proteins such as TET8 or PEN1 identify only selected sources or subpopulations. Raw-material variables and processing can change particle yield and cargo composition. A clinical-grade product should therefore be defined by a panel of critical quality attributes (CQAs), not by a single marker or TEM image. MISEV2023 provides general rigor principles, but PDEV-specific source controls, contaminant testing, potency assays, and release criteria are additionally required [53, 227]. Clinical readiness remains early, and no allergy-specific PDEV product has established regulatory approval. A proposed CQA-based characterization and batch-release framework for clinical-grade PDEVs is presented in **Table 5**.

Table 5. Proposed critical quality attributes and release framework for clinical-grade PDEVs

CQA domain	Attributes to control	Recommended analytical strategy	Proposed release principle	Translational relevance
Source identity and traceability	Species/cultivar authentication; tissue; cultivation conditions; harvest stage; geographic origin; storage and preprocessing history.	Botanical authentication, voucher specimen or genomic barcoding where appropriate; supplier and batch records.	Identity must match the defined source specification; changes require comparability assessment.	Controls source-dependent allergens, lipids, metabolites, potency, and contamination.
Product identity	Evidence that the preparation contains membrane-bound plant vesicles rather than only fragments or soluble co-isolates.	Orthogonal morphology and particle assays; membrane-integrity testing; source-specific candidate markers; detergent sensitivity; negative/process controls.	Use a source-specific identity panel; no single universal PDEV marker is sufficient.	Prevents classification based solely on size or a TEM image.
Particle attributes	Particle concentration, size distribution, polydispersity, morphology, surface charge, aggregation, and membrane integrity.	NTA plus DLS; TEM/cryo-TEM; AFM where useful; zeta potential; aggregation and integrity assays.	Predefined source- and formulation-specific ranges; use at least two orthogonal sizing/structure methods.	Influences stability, mucus diffusion, uptake, clearance, and biodistribution.
Purity and process residuals	Soluble proteins, polysaccharides, free nucleic acids, non-vesicular lipids, plant debris, PEG/dextran, solvents, detergents, free cargo, and unbound ligands.	Particle-to-protein and particle-to-lipid ratios; chromatography; targeted assays for process reagents; process blanks; non-vesicular fractions.	Source- and process-specific limits; absence of a universal particle-to-protein cutoff should be acknowledged.	Reduces false attribution of activity and limits toxicity from co-isolates.
Molecular composition	Lipid, protein, RNA, and metabolite fingerprints; allergen content; ligand density and cargo localization for engineered products.	Lipidomics, proteomics, transcriptomics/small-RNA profiling, metabolomics; targeted allergen assays; nuclease/protease protection; surface-ligand quantification.	Fingerprint similarity to qualified reference lots within predefined multivariate ranges.	Supports batch consistency, identity, mechanism, and safety.
Potency	Mechanism-linked biological activity relevant to the intended allergic disease and route.	Disease-specific cell assays: epithelial alarmins/barrier function, dendritic-cell activation, mast-cell/basophil activation, macrophage response, Treg-related activity, or cargo target engagement.	One qualified potency assay plus orthogonal supportive assays; acceptance range linked to in vivo activity.	Separates general anti-inflammatory effects from clinically relevant allergy mechanisms.
Allergenicity and immunogenicity	Source-plant allergens, cross-reactive proteins/glycans, IgE binding, basophil/mast-cell activation, complement activation, and cytokine release.	Allergen-focused proteomics; database matching; patient-serum IgE binding; basophil activation; mast-cell assays; complement and cytokine panels.	Negative or predefined low-risk profile for the intended population; sensitized subgroups may require exclusion or stratification.	Critical because edible origin does not guarantee non-immunogenicity.
General safety	Cytotoxicity, hemolysis, off-target immune stimulation, organ toxicity, local irritation, and repeat-dose toxicity.	In vitro cytotoxicity/hemolysis; acute and repeat-dose studies; route-specific local tolerance; clinical chemistry, histology, and recovery after withdrawal.	No unacceptable dose- or route-related toxicity at the proposed exposure margin.	Addresses concentrated secondary metabolites and non-physiological exposure routes.
Microbiological and chemical quality	Bioburden, sterility where required, endotoxin/pyrogenicity, mycotoxins, pesticides, heavy metals, and adventitious contaminants.	Compendial microbiological tests; endotoxin/pyrogen tests; targeted chemical-contaminant panels.	Limits should reflect route and product category; parenteral products require the most stringent controls.	Controls raw-material and manufacturing hazards.
Stability	Particle size, aggregation, membrane integrity, cargo retention, molecular fingerprint, and potency during storage, transport,	Real-time and accelerated stability; freeze–thaw challenge; container-closure compatibility; stability-indicating potency and release assays.	Shelf life supported by stability-indicating CQAs, not particle count alone.	Freezing, lyophilization, spray drying, and excipients can alter product quality.

	reconstitution, and freeze–thaw.			
Batch comparability and release	Consistency after scale-up, site change, process change, formulation change, or engineering modification.	Statistical/multivariate comparison of identity, purity, composition, potency, safety, and stability attributes; qualified reference lot.	Predefined comparability protocol and deviation handling; failure of a critical attribute blocks release.	Provides a practical path toward GMP manufacture and regulatory interaction.

No universal clinical acceptance limits have been validated for PDEVs. Specifications should therefore be source-, process-, formulation-, route-, and indication-specific and justified using qualified reference lots. CQA, critical quality attribute; DLS, dynamic light scattering; GMP, good manufacturing practice; NTA, nanoparticle tracking analysis; PDEV, plant-derived extracellular vesicle; TEM, transmission electron microscopy.

7.2 Mechanistic Uncertainty

Mechanistic uncertainty is intensified by the complexity of PDEV cargos. A biological effect may arise from vesicular lipids, small RNAs, proteins, metabolites, soluble co-isolates, or their combination. Causal studies should use detergent-plus-nuclease protection assays, cargo depletion or inhibition, fractionated controls, process blanks, uptake blockade, target-engagement measurements, and rescue experiments. Allergy-specific potency assays should distinguish broad suppression from tolerance, including durability after treatment withdrawal and allergen rechallenge. Pollensomes should be evaluated for both immunogenic and tolerogenic outcomes rather than presumed to improve AIT.

7.3 Manufacturing and Scalability

Scalable production requires controlled cultivation or sourcing, standardized tissue processing, closed clarification, TFF or equivalent concentration, chromatographic polishing, aseptic handling, and validated storage. Freezing, lyophilization, spray drying, and formulation additives can each alter aggregation, membrane integrity, and potency. Regulatory classification is likely to be case-specific because no dedicated FDA or EMA pathway exists for PDEVs. A minimally processed botanical preparation may draw on botanical or herbal-medicinal-product principles, whereas purified, engineered, or drug-loaded vesicles may be regulated as a more complex drug, biological, nanomedicine, or combination product depending on composition, manufacturing, and intended action [241]. Early engagement with regulators is therefore essential.

7.4 Safety and Sensitization Risk

Safety cannot be inferred from edible origin. Concentration and purification can enrich secondary metabolites to pharmacological or toxic levels, and plant proteins may cause de novo sensitization or cross-react with existing IgE, particularly in patients with an atopic background. Relevant risks include immediate hypersensitivity, complement activation, cytokine release, hemolysis, off-target immune stimulation, microbiological contamination, pesticide or mycotoxin carryover, and toxicity after repeated dosing.

A risk-based program should include source-specific allergen proteomics, serum IgE binding, basophil-activation or mast-cell assays, epithelial and innate immune responses, acute and repeat-dose toxicology, local tolerance, biodistribution, and recovery after treatment withdrawal. Environmental pollen or dust vesicles require especially stringent controls because allergen carriage is integral to their biology [22, 185, 191, 192].

7.5 Patient stratification and clinical development

Patient selection should reflect both disease endotype and source-specific sensitization. Relevant variables include type 2-high versus non-type 2 inflammation, dominant target organ, current asthma or dermatitis control, allergen-specific IgE profile, cross-reactive carbohydrate determinants, sensitization to the source plant, history of anaphylaxis, microbiome context, and concomitant biologic or immunotherapy use. For a PDEV derived from a potentially allergenic plant, prescreening with component-resolved diagnostics and ex vivo basophil testing may be necessary.

Early clinical studies should use well-characterized products, sentinel dosing, route-appropriate local monitoring, pharmacokinetic or biodistribution biomarkers, and predefined stopping rules for hypersensitivity. Clinical endpoints should include not only symptom control but also allergen-provocation thresholds, rescue-medication use, epithelial biomarkers, IgE/IgG4, Treg/Breg or ILC2 signatures, and durability after treatment discontinuation. Such stratification will be essential to identify patients in whom a PDEV platform provides a favorable benefit-risk profile.

8 Conclusions

PDEVs occupy an unusual position between natural bioactive products and engineered nanocarriers. Their lipids, RNAs, proteins, and metabolites can modulate inflammatory signaling, epithelial repair, oxidative stress, and microbiota interactions, while their membranes can protect therapeutic cargo. These properties justify continued investigation in allergy, but current direct therapeutic evidence is limited and is substantially weaker than the broader literature from non-allergic inflammatory models.

The environmental-vesicle literature provides the counterpoint to this therapeutic promise. Pollensomes and indoor-dust EVs can carry allergens and immunostimulatory cofactors that promote sensitization and airway inflammation. The relevant distinction is therefore not simply therapeutic versus pathogenic plant origin, but a context-dependent combination of source, cargo, corona, route, dose, barrier state, and host sensitization.

Progress toward clinical application will depend on evidence-weighted claims, standardized CQAs and release tests, quantitative loading and biodistribution methods, allergy-specific potency assays, rigorous allergenicity assessment, and patient stratification. With these safeguards, selected PDEVs may become useful components of precision allergy nanomedicine; without them, broad extrapolation risks obscuring both their therapeutic opportunities and their sensitization hazards.

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Data availability

Not applicable.

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Declaration of competing interest

All the contributing author(s) report(s) no conflict of interests in this work.

Author contribution statement

S.B.L., J.Z.C. and R.L.: Data curation, project administration, validation, writing manuscript. Z.L., S.M.L., and Y.S.L: Data

curation, project administration, validation, literature curation, figures and tables preparation. X.R.S. and S.B.L.: Project administration, writing manuscript, funding acquisition. All the authors have approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

AI-assisted tools (open-AI: chatGPT5.5) were used only to support language refinement and the graphical design of selected illustrations. All scientific content, labels, accuracy, and final presentation were reviewed and edited the content as needed and take full responsibility for the content of the publication. No AI tool was used to generate, analyze, or interpret research data.

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Electronic Supplementary Material

Plant-derived extracellular vesicles in allergic diseases: From immunomodulatory nanotherapeutics to environmental allergen carriers

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Table S1 Comparative characteristics of PDEV isolation, enrichment, and purification methods

Method	Principle	Strengths	Key limitations	Recommended role	Critical process/reporting parameters
Differential ultracentrifugation [1-4]	Sequential sedimentation by increasing centrifugal force.	Accessible; handles moderate/large volumes; familiar workflow.	Time- and operator-intensive; aggregation/deformation; co-pelleting of proteins, polysaccharides, and debris.	Initial enrichment for research-scale preparations; should be followed by polishing for mechanistic or translational studies.	Rotor type, k-factor, g-force, time, temperature, braking, wash steps, recovery, and integrity.
Density-gradient centrifugation [2-4]	Separation by buoyant density in sucrose or iodixanol gradients.	Improves separation from soluble contaminants and dense particles.	Low throughput; lengthy; dilution; gradient-material carryover; recovery variability.	High-purity research preparations or orthogonal validation.	Gradient composition, fraction windows, density measurement, recovery, and removal of gradient medium.
Ultrafiltration [5]	Membrane-size cutoff retains vesicles while smaller solutes pass.	Rapid concentration; scalable in principle; no ultracentrifuge required.	Membrane adsorption, fouling, shear, concentration polarization, and filter-to-filter variability.	Concentration before SEC or another polishing method.	Membrane chemistry, molecular-weight cutoff, pressure, recovery, fouling, and extractables.
Tangential-flow filtration[5]	Feed flows parallel to the membrane, enabling scalable concentration and diafiltration.	More scalable and less clog-prone than dead-end filtration; compatible with closed processing.	Adsorption, shear, membrane fouling, and product loss; requires process optimization.	Preferred scalable concentration/diafiltration step before chromatographic polishing.	Flux, transmembrane pressure, shear rate, concentration factor, diafiltration volume, and membrane reuse.
Size-exclusion chromatography [6-9]	Porous matrix separates vesicles from smaller soluble molecules.	Preserves morphology and activity; removes free proteins and small molecules.	Sample dilution; finite loading capacity; column/fraction variability.	Polishing after UC, UF, or TFF; useful for mechanistic and translational preparations.	Column matrix, bed volume, sample load, fraction window, recovery, and column cleaning.
Polyethylene-glycol precipitation [10-13]	Polymer reduces particle solubility	Simple, inexpensive, high	Non-specific co-precipitation of	Concentration step only; should be	PEG molecular weight/concentrati

	and precipitates nanoscale material.	apparent recovery, and no specialized equipment.	proteins, polysaccharides, nucleic acids, and polymer residues.	followed by orthogonal purification.	on, incubation, polymer-removal assay, purity, and process blank.
Aqueous two-phase systems [14,15]	Partitioning between immiscible aqueous polymer phases.	Potentially rapid and scalable; mild processing.	Polymer residues, variable partitioning, and difficult standardization.	Exploratory enrichment followed by residue removal and orthogonal characterization.	Polymer composition, phase ratio, partition coefficient, residue testing, recovery, and potency.
Electrophoresis-coupled dialysis [16]	Electrical and membrane-based separation accelerates enrichment and contaminant removal.	Short processing time and reported application to selected fruit preparations.	Membrane fouling, aggregation, recovery variability, and limited independent validation.	Promising rapid method requiring comparison with established workflows.	Electrical settings, membrane properties, temperature, recovery, aggregation, and contaminant removal.
Microfluidic/automated platforms [17,18]	Micro-scale flow, filtration, acoustics, or proprietary capture modules.	Low sample volume, automation, and potential reproducibility.	Device-dependent recovery, low throughput for some systems, proprietary materials, and incomplete disclosure.	Method development, small-volume samples, or automated workflows after independent validation.	Device geometry, flow, throughput, recovery, carryover, extractables, and cross-platform comparability.
Affinity capture [19-21]	Specific binding to a validated vesicle-surface target.	High specificity for defined subpopulations.	No universal PDEV marker; biased recovery; ligand cost and possible functional alteration.	Mechanistic study of source-specific subpopulations, not total-PDEV quantification.	Target validation, binding capacity, elution, recovery, epitope accessibility, and negative controls.

No single method simultaneously maximizes yield, purity, integrity, and scalability. Hybrid workflows such as UF–SEC, TFF–SEC, and UC–SEC are generally more defensible than a single stand-alone enrichment step.
PDEV, plant-derived extracellular vesicle; SEC, size-exclusion chromatography; TFF, tangential-flow filtration; UC, ultracentrifugation; UF, ultrafiltration.

Table S2 Representative source-specific PDEV preparation and characterization workflows.

Plant source	Isolation	Polishing/purification	Reported characterization	Reported size (nm)
Arabidopsis thaliana cell culture [22]	UC	UF	SEM	90–250
Bitter melon [23]	DC	Sucrose density gradient + filtration	TEM; NTA	106
Cabbage [24]	DC	UF + anion-exchange FPLC	NTA; TEM	137.8
Cucumber [25]	UC	SEC	DLS; NTA; laser diffraction/light microscopy; SEM; AFM	167.0 ± 3.0
Honeysuckle [26]	UC	Sucrose density gradient	TEM	132.0 ± 0.3
Houttuynia cordata [27]	DC	Sucrose density gradient	TEM; NTA; DLS	58–228
Ginger [28]	DC	Sucrose density gradient	TEM; DLS	252.1 ± 5.5
Ginseng [29]	DC	Sucrose density gradient	DLS	>100 (reported)
Goji berry [30]	DC	Sucrose density gradient	TEM; NTA	171
Grapefruit [31]	DC	Sucrose density gradient	TEM	400
Kudzu root [32]	UC	UF	TEM; BCA	75.5 ± 10.2
Lemon [33]	UC	Aqueous two-phase system	NTA	172.8 ± 0.3
Mulberry leaf [34]	DC	NR	Q-Exactive mass spectrometry; BCA	110–150
Perilla [35]	UC	Density-gradient centrifugation	BCA	98.4 ± 1.3
Saffron tepal [36]	UC	Sucrose density gradient	TEM; NTA	210.1 ± 5.8
Strawberry [37]	DC	UF	TEM	30–191
Turmeric [38]	UC	Sucrose density gradient	TEM; AFM; DLS	177.9–204.6
Portulaca oleracea [39]	UC	Sucrose density gradient	TEM; NTA	122.3 ± 3.4

Reported sizes are not directly comparable because sample preparation, isolation, and measurement platforms differ. Size alone does not establish biogenesis or product identity. The original table mixed morphology, protein assays, and omics under a single 'morphology check' heading. The revised table separates purification from characterization and explicitly marks incomplete source

information. AFM, atomic force microscopy; BCA, bicinchoninic acid protein assay; DLS, dynamic light scattering; FPLC, fast protein liquid chromatography; NR, not reported; NTA, nanoparticle tracking analysis; SEC, size-exclusion chromatography; SEM, scanning electron microscopy; TEM, transmission electron microscopy; UC, ultracentrifugation; UF, ultrafiltration; DC, Differential centrifugation.

Table S3 Representative molecular composition of plant-derived and environmental plant-associated vesicles

Source	Representative lipids	Protein features	RNA cargo	Secondary metabolites/other cargos	Allergy and translational relevance
Ginger[40-42]	PA (~40% in selected reports); DGDG (~30–40%)	Relatively low protein content in selected preparations	≥125 miRNA-like species reported	6-Gingerol, 6-shogaol, and other phenolic bioactives; reported enrichment versus ginger flesh is preparation-specific	Potential microbiota/immune activity, but lipid and phytochemical concentrations require batch-specific quantification.
Grapefruit [43-45]	PE and PC prominent in selected preparations	Typical plant-vesicle proteins reported	Plant miRNAs, including source-specific sequences	Naringenin-related flavonoids, organic acids, sugars, and amino acids	Composition may influence intestinal macrophage uptake and systemic distribution; claims require direct lipidomics.
Lemon [46, 47]	PC/PE-rich phospholipid bilayer reported	Membrane and cytosolic proteins	mRNAs and miRNAs reported	NR in the original table	Product identity and residual soluble citrus compounds should be controlled, especially after industrial processing.
Grape [48, 49]	PE, PC, PA, DGDG, MGDG, PI, and PS reported	Relatively low protein content in selected preparations	miR-169-family enrichment reported	Procyanidins and other polyphenols	Supports multimodal activity, but RNA and polyphenol contributions require cargo-localization and depletion controls.
Broccoli [50-52]	PA, PE, and PC	Aquaporins and other membrane proteins reported	Plant miRNAs	Sulforaphane and related isothiocyanates reported	Potential dendritic-cell and intestinal effects; bioactivity cannot be attributed to vesicles without soluble-fraction controls.
Apple [53, 54]	PA, PE, and PC reported	General plant-vesicle proteins	Diverse miRNAs reported	Flavonoids and furanocoumarin-like phytochemicals reported in secondary sources	Requires primary-source confirmation and explicit screening for source-specific allergenic proteins.
Carrot [55]	PA, PE, and PC reported	General plant-vesicle proteins	miRNAs reported	NR in the original table	Illustrates source-dependent cargo but lacks sufficient quantitative data for comparative conclusions.
Tartary Buckwheat [56, 57]	TAG, PE, and PC reported	IgE-reactive allergens such as Fag t 1	NR	Chlorogenic acid (CGA); selenium nanoparticles (SeNPs)	Tartary buckwheat contains IgE-reactive allergens such as Fag t 1, source-specific

					allergen proteomics, IgE-binding, basophil-activation, and repeated-dose sensitization testing are required.
Pollen-derived vesicles [58-60]	Source-dependent pollen lipids and pollen-associated lipid mediators	Major/minor pollen allergens and oxidases	Nucleic acids reported in selected preparations	Adenosine and other pollen-associated small molecules may co-occur	Composition supports allergen protection, epithelial deposition, IgE recognition, and adjuvant-like activity; these vesicles should not be grouped with purified edible PDEVs.

Reported composition is strongly affected by species, tissue, growth conditions, preprocessing, isolation, and analytical platform. Presence does not establish intravesicular localization or functional dose. DGDG, digalactosyldiacylglycerol; MGDG, monogalactosyldiacylglycerol; miRNA, microRNA; NR, not reported; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine.

Table S4 Representative intrinsic, localized, and cargo-delivery applications of plant-derived vesicle platforms

Preparation/cargo	Plant source	Formulation or engineering	Model	Route	Principal outcome	Evidence class	Allergy relevance
Aster yomena callus EVs [61]	Aster yomena	Intrinsic PDEV	allergic asthma	Oral	Reduced dendritic-cell maturation, T-cell responses, airway hyperresponsiveness, type 2/Th17 inflammation, mucus, and allergen-specific IgE.	Direct allergy evidence	Supports source-specific asthma efficacy, not general PDEV efficacy.
Turmeric nanovesicles [62]	Turmeric	Metal–polyphenol hydrogel	ADs	Topical/ local	Improved local retention, hydration, epidermal morphology, inflammatory stress, and barrier repair.	Direct allergy engineering	Strong localized-delivery precedent.
Portulaca nanovesicles [39]	Portulaca oleracea	HA/polysaccharide dissolving microneedle	ADs	Transdermal	Improved delivery and reduced inflammation through macrophage and NF-κB/STING modulation.	Direct allergy engineering	Strong localized-delivery precedent.
CX5461-loaded hybrid vesicles [63]	Grapefruit EVs + gingival MSC nanovesicles	CCR6-directed membrane fusion	Psoriasis/ ADs	Systemic or formulation-specific route; verify from primary study	Improved inflammatory-skin targeting; reduced cytokines/Th17; increased Treg infiltration.	Direct allergy-relevant engineering	Complex hybrid; requires component-matched controls.
Rose stem cell exosome formulation [64]	Rose stem cell culture	Topical preparation	Mixed dermatologic case series	Topical	Exploratory symptomatic improvement.	Preliminary human observation	Insufficient for efficacy or carrier conclusions.
Methotrexate-loaded grapefruit nanovesicles [44]	Grapefruit	Drug-loaded bioactive nanovesicles	DSS colitis	Oral/local intestinal delivery	Enhanced intestinal-macrophage delivery and reduced systemic toxicity relative to free methotrexate.	Indirect/platform evidence	Relevant to local immunomodulatory cargo delivery, not proof in

							allergy.
Doxorubicin-loaded reconstituted plant-lipid nanovectors[65]	Ginger-derived lipids	Lipid extraction, reconstitution, and folate targeting	Colon cancer	Systemic	High cargo loading, pH-dependent release, and folate-receptor targeting.	Platform evidence	Reconstituted nanovector is not an intact native PDEV.
S1 mRNA-loaded orange EVs [66]	Orange juice	Exogenous mRNA loading	SARS-CoV-2 vaccination model	Oral/intranasal/intramuscular	Induced humoral and cellular immune responses.	Platform evidence	Respiratory/oral feasibility; vaccine immunity is not allergic tolerance.
Exogenous-miRNA-loaded broccoli EVs [52]	Broccoli	RNA cargo protection and delivery	Experimental delivery platform	Oral/intestinal context	Protected exogenous miRNA and supported delivery feasibility.	Platform evidence	Technical precedent for RNA delivery.
HA-modified red-cabbage EVs [67]	Red cabbage	Hyaluronic-acid surface engineering	Colitis-associated inflammation	Oral	Enhanced intestinal localization and interaction with epithelial/immune cells.	Indirect engineering evidence	Relevant precedent for food-allergy mucosal targeting.
Activated-leukocyte-coated grapefruit nanovectors [68]	Grapefruit-derived nanovectors	Leukocyte-membrane coating	Inflammatory tumor and colitis	Systemic	Used leukocyte trafficking pathways to enhance inflammatory-site homing.	Platform evidence	Potential inflammatory-site targeting but increased compositional/regulatory complexity.
Blueberry-derived nanovesicles with aspirin/curcumin [69]	Blueberry	Small-molecule-associated vesicle formulation	Caco-2 oxidative/ inflammatory model	In vitro	Modulated IL-8 and glutathione responses.	Indirect in vitro evidence	Mechanistic support only; no allergy-specific outcomes.
Balloon-flower-root hybrid vesicles with silymarin [70]	Balloon flower root	PDEV/liposome hybrid	Acetaminophen-induced liver injury	Systemic	Reduced inflammatory/apoptotic signaling and supported glutathione defenses.	Platform/indirect evidence	Demonstrates hybrid cargo delivery outside allergy.
Tartary-buckwheat EV-like nanovesicles + selenium nanoparticles [56]	Tartary buckwheat	Dual-carrier hybrid	Hyperglycemia/ diabetes model	Oral	Regulated intestine–liver glucose metabolism.	Platform/indirect evidence	Demonstrates hybrid oral delivery; unrelated to direct allergy efficacy.

The table separates direct allergy evidence from indirect mechanistic and platform evidence. Non-allergic studies should not be cited as proof of anti-allergic efficacy. EV, extracellular vesicle; HA, hyaluronic acid; MSC, mesenchymal stromal cell; PDEV, plant-derived extracellular vesicle.

Table S5 Representative surface, membrane, fusion, and hybrid-engineering strategies for plant-derived vesicle platforms

Engineering category	Source/ platform	Fabrication approach	Model	Reported engineering effect	Relevance and interpretation for allergy
Ligand display on intact vesicles [71]	Ginger exosome-like nanovesicles	Cholesterol-anchored three-way-junction RNA displaying folic acid; survivin siRNA cargo	Cancer xenograft	Ligand insertion enabled receptor-directed systemic RNA delivery and tumor suppression.	Shows modular ligand/cargo design; does not establish allergy targeting.
Mild surface functionalization [72]	Food-derived EVs	General chemical modification of surface molecules	Cell-targeting models	Improved target-cell recognition under mild conditions.	Potentially adaptable to allergy targets after source-specific safety

					and ligand-density testing.
Aptamer conjugation [73]	Grapefruit-derived nanovectors	Aptamer attachment through functionalized lipid/linker chemistry	HER2+ breast cancer	Improved receptor-specific uptake and antitumor delivery.	Technical precedent; aptamer immunogenicity, stability, and off-target binding require validation.
Integrin-directed engineering [74, 75]	Lemon/ orange-derived vesicle systems	cRGD-associated surface engineering and nanodrug assembly	Glioblastoma/o varian cancer	Enhanced integrin-mediated uptake, tumor accumulation, or transcytosis.	Cancer-specific targeting should not be extrapolated to allergic tissues without receptor validation.
Hyaluronic-acid surface modification [67]	Red-cabbage EVs	HA conjugation for intestinal localization	Colitis-associated inflammation	Improved intestinal localization and epithelial/immune-cell interaction.	Relevant precedent for oral mucosal delivery in food allergy.
Activated-leukocyte membrane coating [68]	Grapefruit-derived nanovectors	Extrusion/coating with activated leukocyte membranes	Inflammatory tumor and colitis	CXCR2/LFA-1-associated inflammatory-site homing.	Potential inflammation-directed delivery; complex identity and immunogenicity testing required.
CCR6-directed membrane fusion [63]	Grapefruit EVs + gingival MSC nanovesicles	Co-extrusion/fusion; CX5461 loading	Psoriasis and atopic dermatitis	Targeting to CCL20-rich inflamed skin; reduced Th17/cytokines and increased Tregs.	Most directly allergy-relevant hybrid-engineering example.
EV/ liposome hybridization [76]	Hydrangea macrophylla leaf EVs	Freeze–thaw liposome fusion with anti-inflammatory cargos	Skin-inflammation model	Generated a stable hybrid and reduced inflammatory mediators.	Topical-delivery precedent; not direct AD evidence unless tested in an AD model.
Neutrophil-membrane engineering [77]	Panax ginseng root EVs	Neutrophil-membrane coating; miR-182-5p cargo	Sepsis-induced acute lung injury	Enhanced inflamed-lung delivery and suppressed NOX4/Drp1/NLRP3 signaling.	Pulmonary inflammation precedent; sepsis is not allergic asthma.
Autologous tumor-membrane fusion [78]	Panax ginseng EV-like particles	Fusion with autologous tumor-cell membranes	Post-surgical tumor recurrence	Enhanced dendritic-cell activation, CD8+ responses, and immune memory.	Demonstrates bidirectional immunostimulation and warns against assuming all PDEVs are suppressive.
Inorganic hybridization [79]	Ginger-derived EVs	Pd–Pt nanosheet decoration/hybridization	Bacterial infection	Enabled reactive-oxygen/photothermal antibacterial activity.	Illustrates added functionality but substantially increases nanotoxicology and regulatory complexity.
Lipid extraction and reconstitution [65]	Ginger-derived lipids	Reassembled pH-responsive, folate-targeted doxorubicin nanovectors	Colon cancer	Improved cargo loading, release, and target uptake.	Useful for compositional control; product should not be labeled as an intact PDEV.
Structural droplet/ hybrid nanodrug [80]	Fruit-derived EV components	Hybridization with drug-lipid or nanomaterial components	Glioblastoma	Enhanced cargo delivery and tumor treatment in a complex engineered system.	Platform evidence; requires strict component identity, release, and safety testing.

The previous surface-modification and membrane-fusion tables were merged because many modern platforms combine ligand insertion, cargo loading, membrane fusion, coating, and reconstitution. Duplicate generic rows without a source-specific study were removed. AD, atopic dermatitis; EV, extracellular vesicle; HA, hyaluronic acid; MSC, mesenchymal stromal cell; PDEV, plant-derived extracellular vesicle.

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