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From Plant-Derived Extracellular Vesicles to Precision Nanomedicine: Engineering Natural Vesicular Systems for Targeted Drug Delivery

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Abstract: Plant-derived extracellular vesicles (PDEVs) have emerged as an attractive class of naturally occurring nanocarriers that combine the biological functionality of extracellular vesicles with the accessibility, scalability, and chemical diversity of plant sources. These nanoscale lipid-bilayer vesicles contain proteins, lipids, nucleic acids and plant-derived metabolites and can participate in intercellular and potentially cross-kingdom communication. Increasing evidence indicates that PDEVs can function not only as naturally bioactive nanoparticles but also as engineered delivery systems for small-molecule drugs, proteins and nucleic acids. Their membrane composition, intrinsic cellular uptake, gastrointestinal stability and possibility of oral or intranasal administration provide characteristics that are attractive for precision nanomedicine. However, differences in plant source, tissue, cultivation conditions and isolation strategy can substantially influence vesicle composition, yield, purity and biological activity. Recent engineering approaches have therefore focused on controlled drug loading, membrane reassembly, surface ligand functionalization, hybridization with synthetic nanomaterials and process intensification. Preclinical studies have demonstrated applications in cancer, inflammatory bowel disease, neurological disorders, wound repair and other conditions. Nevertheless, clinically relevant development remains constrained by limited standardization, incomplete understanding of biodistribution and pharmacokinetics, scalability, storage stability, critical quality attributes and regulatory classification. This mini-review discusses the transition of PDEVs from naturally occurring plant nanovesicles to engineered precision nanomedicine platforms, emphasizing biogenesis, composition, isolation, characterization, cargo loading, targeting, therapeutic applications, manufacturing and translational requirements.

Keywords: Plant nanovesicles; drug delivery; precision nanomedicine; targeted delivery; nanopharmaceutics; RNA delivery

1. Introduction

Extracellular vehicles (EVs) are membrane-enclosed particles released from cells and capable of transporting proteins, lipids, nucleic acids and other bioactive molecules between cells [1–5]. Although EV research initially concentrated on mammalian systems, plant-derived vesicular systems have increasingly attracted attention as biologically active nanoparticles and potential drug delivery platforms [8–15]. Early observations of vesicular structures in plant apoplastic fluids provided evidence that plants possess extracellular membrane-bound particles analogous in some respects to mammalian EVs [9,10]. Subsequent studies demonstrated that vesicle-like particles can be isolated from edible plants and may retain proteins, lipids, RNA and secondary metabolites with biological activity in mammalian cells [11,12].

The terminology used for these particles remains heterogeneous. Terms such as plant-derived extracellular vesicles (PDEVs), plant-derived vesicles (PDVs), plant-derived nanovesicles (PDNVs), edible plant-derived exosome-like nanoparticles (EPDENs) and exosome-like nanoparticles have all appeared in the literature. Current EV recommendations encourage investigators to avoid assigning a precise biogenetic origin when this has not been experimentally established and instead use operationally defined terminology [6,7]. This distinction is particularly relevant for plant preparations because conventional isolation methods frequently enrich heterogeneous nanoscale populations rather than a single molecularly defined EV subtype.

PDEVs are attractive for nanomedicine for several reasons. Plants are abundant and readily cultivated, some plant materials are already incorporated into human diets, and plant-derived preparations can provide large quantities of vesicular material without dependence on mammalian cell culture [11–15]. In addition, PDEVs may exhibit intrinsic biological effects derived from their endogenous cargo while simultaneously acting as carriers for externally introduced therapeutics [13–16]. Such dual functionality creates the possibility of a delivery paradigm in which the carrier is itself pharmacologically active.

The emerging concept of precision nanomedicine extends this idea further. Rather than treating PDEVs as passive natural nanoparticles, current research increasingly seeks to engineer their size, lipid composition, surface chemistry, loading capacity, tissue distribution and release behavior. Such engineering can involve passive optimization, membrane modification, targeting ligands, nucleic-acid loading, drug encapsulation, hybridization with synthetic nanomaterials and process engineering [19–22].

The objective of this review is therefore to examine the transition from naturally occurring PDEVs to engineered precision nanomedicine. Particular emphasis is placed on the relationship between vesicle biology and pharmaceutical performance, the engineering strategies used to enhance targeting and loading, representative therapeutic applications, and the manufacturing and regulatory issues that must be solved before clinical translation.

2. Biological Basis of Plant-Derived Extracellular Vesicles

2.1 Biogenesis and heterogeneity

Plant cells release heterogeneous extracellular vesicles through more than one intracellular route. Evidence from Arabidopsis and other plant systems supports contributions from multivesicular bodies (MVBs), plasma-membrane-derived budding and specialized secretory compartments [8–10]. Tetraspanins such as TET8 and TET9 have been associated with specific plant EV populations, whereas other marker proteins identify different subpopulations [8,10], seen in Figure 1. The existence of multiple vesicle-generating pathways is important for nanomedicine because vesicles isolated from different tissues or by different methods cannot automatically be assumed to have equivalent compositions. Environmental stress, pathogen exposure, tissue type, developmental stage and cultivation conditions can alter vesicle release and molecular cargo [8,11–13]. Consequently, a future pharmaceutical product based on PDEVs will require control of both the biological source and the downstream manufacturing process.

2.2 Molecular composition

PDEVs contain a lipid bilayer surrounding a complex molecular cargo. Proteomic studies have identified cytosolic proteins, enzymes, stress-associated proteins and cell-wall-

related proteins within plant EV preparations [11,12]. Cell-wall remodeling enzymes, including glucosidases, pectin-related enzymes and other hydrolases, may contribute to vesicle movement through the plant extracellular matrix [11]. The lipid composition of PDEVs differs from that of many mammalian EVs. Plant-derived vesicles can contain phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamine (PE), monogalactosyldiacylglycerol (MGDG), digalactosyldiacylglycerol (DGDG), sterols and plant-specific sphingolipids [11,13]. These lipids are not simply structural components; they can influence membrane stability, cellular recognition, cargo association and release behavior. Ginger-derived nanovesicles, for example, have been reported to contain high proportions of phosphatidic acid, contributing to their distinctive membrane properties [19], also seen in Figure 1. PDEVs may also carry mRNAs, microRNAs, small RNAs and metabolites [11–15]. Importantly, lipophilic phytochemicals may be preferentially associated with the vesicular membrane, whereas hydrophilic metabolites are less consistently detected [11]. Thus, the pharmacological activity of a PDEV preparation may reflect a combination of endogenous lipids, nucleic acids, proteins and phytochemicals rather than one purified active molecule.

2.3 From natural bioactivity to pharmaceutical functionality

The multifunctionality of PDEVs creates a fundamental distinction from conventional synthetic nanocarriers. A conventional liposome is normally designed to be pharmacologically inert, whereas a PDEV may simultaneously deliver its endogenous cargo and an externally loaded therapeutic [13–15]. Ginger-derived vesicles, citrus-derived vesicles and other edible-plant nanovesicles have demonstrated anti-inflammatory, antioxidant or anticancer effects independently of externally added drugs [22,23]. This endogenous biological activity may provide therapeutic synergy, but it also complicates pharmaceutical development. Batch-to-batch differences in plant cultivar, cultivation conditions or metabolite content could influence efficacy even when particle concentration and size appear similar [16–18]. For precision nanomedicine, therefore, biological composition must become a controllable product attribute rather than an uncontrolled natural variable.

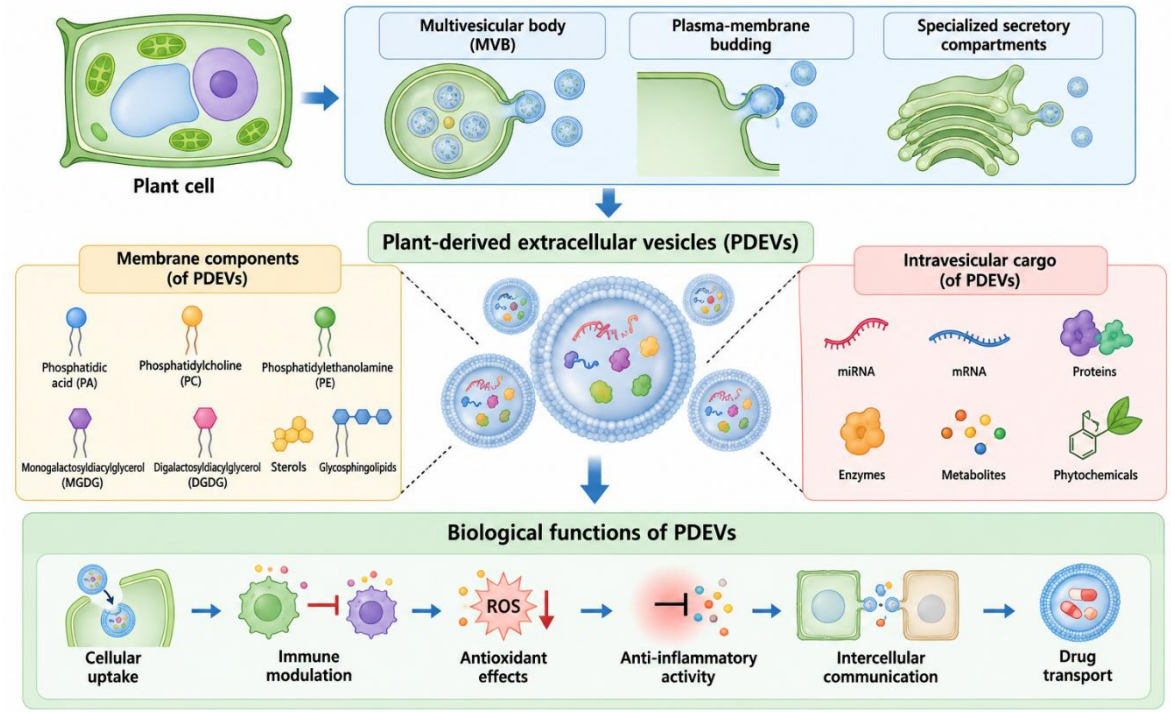

Figure 1. Biogenesis, Molecular Composition and Functional Architecture of PDEVs.

3. Isolation, Purification and Characterization

Isolation is one of the most consequential steps in PDEV development because the procedure determines not only yield but also purity, particle composition and downstream functionality [16–18]. Methods adapted from mammalian EV research include differential ultracentrifugation, density-gradient centrifugation, ultrafiltration, tangential-flow filtration (TFF), size-exclusion chromatography (SEC), precipitation, aqueous two-phase systems and immunoaffinity approaches [16–18].

3.1 Differential and density-gradient ultracentrifugation

Differential ultracentrifugation remains one of the most frequently used laboratory methods. Sequential centrifugation removes cell debris and larger structures before high-speed sedimentation enriches nanoscale vesicles. Density-gradient centrifugation using sucrose or iodixanol can subsequently improve separation according to buoyant density [16–18]. The principal advantages are familiarity and relatively high recovery. However, high-speed centrifugation is time-consuming, equipment-intensive and susceptible to co-pelleting of non-vesicular proteins, aggregates and other particles. Repeated pelleting can also contribute to vesicle aggregation or loss of structural integrity [16–18].

3.2 Ultrafiltration and tangential-flow filtration

Ultrafiltration provides a size-based concentration approach, while TFF offers greater potential for scale-up and continuous or semi-continuous processing [16,17]. TFF is particularly attractive for pharmaceutical manufacturing because it can be integrated with concentration, diafiltration and buffer exchange without repeated ultracentrifugation. Nevertheless, membrane fouling, vesicle retention and concentration polarization require optimization. The choice of membrane material, pore size or molecular-weight cutoff and operating pressure can substantially influence recovery and vesicle integrity [16–18].

3.3 Size-exclusion chromatography

SEC is a relatively gentle polishing technique in which vesicles are separated from smaller soluble contaminants on the basis of hydrodynamic size [16,17]. It is particularly useful when preservation of vesicle structure is critical. Its main limitations are finite column capacity, dilution of the recovered product and difficulties associated with processing very large volumes.

3.4 Polymer precipitation and alternative approaches

Polyethylene glycol (PEG)-based precipitation is inexpensive and convenient and can recover large quantities of vesicle-like material. However, co-precipitation of proteins and other soluble contaminants can reduce purity [16,17]. Recent studies have investigated pH-assisted PEG precipitation, electrophoretic separation and combinations of TFF with chromatographic purification to improve recovery and process compatibility [40,45,49]. A 2026 experimental protocol further illustrates the movement toward reproducible integrated workflows combining differential centrifugation, filtration, ultrafiltration, ultracentrifugation and density-gradient purification, followed by particle-size and zeta-potential characterization [49].

Table 1. Comparative evaluation of major PDEV isolation and purification strategies **[16–18,40,45,49].**

Isolation method	Main principle	Relative yield	Purity	Scalability	Major advantages	Main limitations
Differential ultracentrifugation	Sedimentation by size/density	High	Moderate	Low–moderate	Established, widely accessible in EV laboratories	Expensive equipment, long processing time, co-pelleting

Density-gradient centrifugation	Separation by buoyant density	Moderate	High	Low	Improved purification and analytical quality	Laborious and difficult to scale
Ultrafiltration	Membrane-based size separation	Moderate–high	Moderate	Moderate–high	Rapid concentration and buffer exchange	Membrane fouling and vesicle retention
TFF	Pressure-driven membrane processing	High	Moderate–high	High	Continuous processing and manufacturing compatibility	Requires process optimization and specialized equipment
SEC	Hydrodynamic size exclusion	Moderate	High	Moderate	Gentle processing and good removal of soluble contaminants	Limited column capacity and product dilution
PEG precipitation	Reduced solubility/aggregation	Very high	Low–moderate	High	Low cost and simple operation	High co-precipitation of non-EV material
Immunoaffinity capture	Ligand–marker recognition	Low	Very high	Low	High molecular specificity	Expensive, low recovery, marker dependence

3.5 Characterization and critical quality attributes

PDEV characterization should integrate multiple orthogonal techniques. Nanoparticle tracking analysis or related particle-sizing methods can determine size distribution and particle concentration, while transmission electron microscopy or cryo-electron microscopy provides morphological information. Additional characterization should include zeta potential, protein and lipid content, RNA profiling, metabolomics and, where appropriate, functional assays [6,7,45,47,49]. For future clinical development, critical quality attributes (CQAs) should encompass at least: particle concentration and size distribution; vesicle morphology and membrane integrity; protein, lipid and nucleic-acid composition; residual plant-derived impurities; sterility and bioburden; endotoxin and microbial contamination; pesticide, heavy-metal and environmental contaminant control; potency and biological activity; cargo loading and release characteristics; and storage stability. Such multiparametric characterization is consistent with the broader evolution of EV quality standards promoted by MISEV recommendations [6,7].

4. Engineering PDEVs for Precision Drug Delivery

Natural PDEVs provide a starting platform, but precision nanomedicine generally requires engineering of **cargo, surface identity, pharmacokinetics and release behavior** [19–22], also seen in Figure 2.

4.1 Small-molecule loading

Hydrophobic drugs can often partition into the vesicular membrane, whereas hydrophilic molecules may require active loading. Sonication, extrusion, freeze–thaw cycling, electroporation, incubation and membrane reassembly are among the approaches explored for PDEV loading [19,20,44]. The landmark ginger-derived nanovector study demonstrated that plant lipids could be isolated, reassembled into nanovesicles and loaded with doxorubicin. Folic-acid functionalization further enabled receptor-mediated targeting to folate-receptor-positive colon cancer cells, and the formulation displayed pH-sensitive drug release [19]. This

study established a conceptual framework that remains highly relevant: **source → vesicle/lipid isolation → cargo loading → surface targeting → disease-specific delivery**.

4.2 Nucleic-acid loading

RNA delivery is particularly attractive because lipid membranes naturally protect nucleic acids from extracellular degradation. Ginger-derived and grapefruit-derived systems have been used to deliver siRNA or miRNA, illustrating the potential for plant vesicles to transport functional genetic cargo [20,22]. The brain-delivery study by Zhuang et al. demonstrated that folate-functionalized grapefruit-derived nanovectors could transport miR-17 by intranasal administration and reach a mouse brain tumor model [20]. The approach illustrates the ability of PDEV systems to combine a non-invasive route with ligand-mediated targeting.

4.3 Surface engineering

Targeting can be introduced through chemical conjugation, hydrophobic insertion or membrane association of ligands. Examples include folic acid, cyclic RGD peptides and other targeting components directed toward receptor-rich tumor or inflammatory tissues [19–21]. An important design principle is that surface engineering should alter biodistribution without destroying the intrinsic membrane properties responsible for biological compatibility and uptake. Excessive chemical modification may change membrane charge, aggregation behavior or protein adsorption.

4.4 Hybrid and composite systems

A newer direction combines plant EVs with synthetic nanoparticles or polymeric materials. One example is the ginger-EV/ZIF-8 system containing TNF-α siRNA for ulcerative colitis. In this system, ginger EVs provided gastrointestinal and macrophage-targeting properties, while ZIF-8 improved nucleic-acid loading and intracellular trafficking [28]. Such systems represent a transition from naturally occurring nanocarriers to hybrid precision nanomedicines in which each component contributes a defined function.

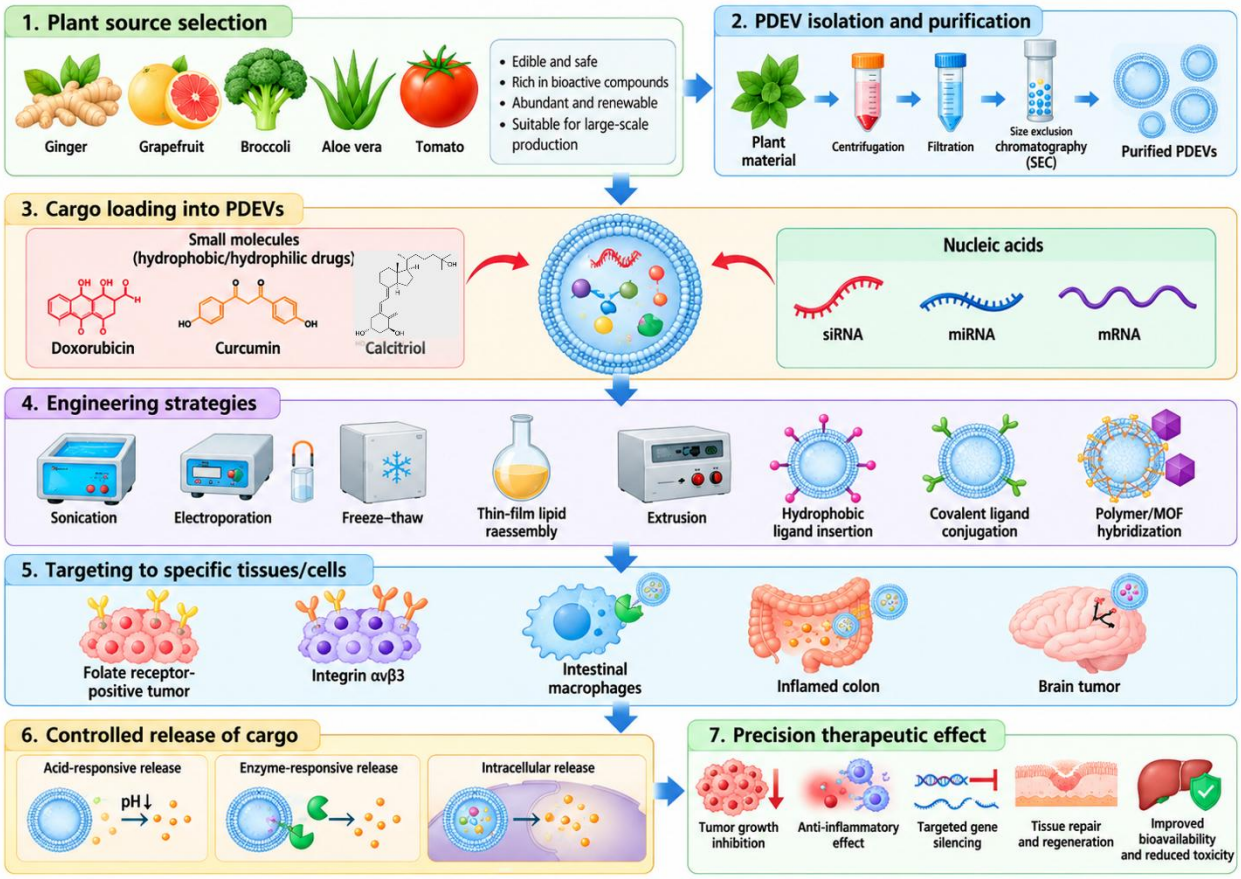

Figure 2. Engineering of PDEVs for Targeted Drug Delivery.

5. Targeting Mechanisms and Biodistribution

5.1 Intrinsic targeting

PDEVs may possess tissue preferences arising from membrane lipids, proteins and surface-associated molecules. This intrinsic tropism is particularly evident for gastrointestinal delivery, where orally administered vesicles can remain sufficiently stable to interact with intestinal tissues [22,29]. Plant lipid composition may influence uptake by specific immune-cell populations. Ginger and grapefruit nanovesicles have demonstrated interactions with intestinal macrophages and other gastrointestinal cells, suggesting that membrane identity can contribute to natural targeting [22].

5.2 Ligand-mediated targeting

Active targeting can be achieved by decorating vesicles with ligands that recognize receptors overexpressed by diseased cells. Folic acid has been investigated for folate-receptor-positive tumors, whereas RGD peptides can interact with integrin αvβ3 [19–21]. The objective is not merely greater accumulation, but increased probability of productive cellular uptake and intracellular cargo release.

5.3 Route-dependent biodistribution

The administration route strongly influences PDEV distribution. Intravenous administration commonly results in substantial liver and spleen exposure, whereas oral administration favors gastrointestinal tissues and can be particularly useful for intestinal disease [13–16,29]. Intranasal administration has been explored for brain delivery because it can partially bypass conventional systemic barriers [20]. However, fluorescent-label-based biodistribution data should be interpreted carefully because free dye or altered vesicles can confound localization. Future studies should use orthogonal labeling strategies and pharmacokinetic measurements that distinguish intact vesicles from released cargo [5,7].

6. Therapeutic Applications

6.1 Cancer therapy

Cancer is one of the most intensively investigated PDEV applications. Citrus-derived nanovesicles have demonstrated selective effects against malignant cells, including induction of apoptotic pathways and tumor-growth suppression [23]. Citrus vesicles have also shown activity against colorectal cancer models characterized by altered p53 signaling and macropinocytic uptake [25]. *Asparagus* cochinchinensis-derived vesicles have demonstrated anti-hepatocellular carcinoma activity with an emphasis on safety and regulation of apoptosis-associated pathways [24]. This is particularly relevant for liver-directed nanomedicine because plant-derived systems may provide opportunities to combine natural hepatopharmacological activity with targeted delivery. More recent studies have expanded the repertoire of therapeutic sources. Fingerroot-derived nanovesicles induced apoptosis and oxidative stress in colorectal cancer cells while displaying limited toxicity toward normal colon epithelial cells [26]. Broccoli extracellular vesicles enhanced the anticancer response to 5-fluorouracil and partially reversed chemoresistance in HT-29 colorectal cancer cells through effects involving the PI3K/Akt/mTOR axis [30]. Platycodon grandiflorum-derived vesicles have additionally shown activity against triple-negative breast cancer while modifying the tumor immune microenvironment and gut microbiota [31].

6.2 Combination therapy

PDEV systems can serve as biological adjuvants rather than merely drug containers. In a 3D-bioprinted triple-negative breast cancer model, Citrus limon-derived EVs used together with doxorubicin produced greater cytotoxicity than either treatment alone, while a hydrogel scaffold enabled sustained release [32]. Such approaches suggest that precision nanomedicine may increasingly involve multi-functional vesicle systems that combine endogenous plant bioactivity with a conventional anticancer agent.

6.3 Inflammatory bowel disease

The gastrointestinal tract represents a particularly attractive target because some edible plant vesicles exhibit relative stability under gastrointestinal conditions [22,29]. Ginger-derived systems can modulate inflammatory signaling, oxidative stress and macrophage responses [22]. The 2024 ginger-EV/ZIF-8/TNF-α-siRNA system represents a more advanced form of engineering. The vesicles facilitated colon and macrophage targeting, while the hybrid structure improved siRNA loading and intracellular activity [28]. These characteristics demonstrate how a natural vesicle can be integrated with a synthetic component to obtain tissue targeting, protective encapsulation and gene silencing within one platform.

6.4 Oral and gastrointestinal nanomedicine

Improving oral delivery is an important translational advantage of PDEVs. Studies of engineered plant vesicles have shown that surface or formulation modifications can increase intestinal retention and therapeutic activity [29]. Oral administration may be particularly attractive for colitis, intestinal inflammation and diseases in which gastrointestinal localization is itself therapeutically desirable.

6.5 Central nervous system delivery

The brain remains a difficult target for most nanoparticle systems because of biological barriers and limited drug penetration. Grapefruit-derived nanovectors carrying miR-17 demonstrated brain delivery following intranasal administration in mice and delayed brain-tumor growth [20]. These observations have stimulated broader interest in PDEV-based neurological delivery platforms.

Importantly, promising brain accumulation in animal models should not yet be interpreted as proof of efficient human blood–brain barrier penetration. Differences in nasal anatomy, mucus clearance, particle stability and receptor biology will need systematic investigation.

6.6 Wound repair and regenerative medicine

PDEVs are also being investigated as cell-free biomaterials for tissue repair. Aloe saponaria-derived EVs promoted fibroblast migration, endothelial tube formation and suppression of inflammatory mediators in vitro, supporting their potential in chronic wound repair [27]. Plant-vesicle-loaded polymeric wound materials have subsequently been investigated for diabetic wound healing, indicating a transition from soluble vesicle formulations toward biomaterial-integrated delivery systems [37].

6.7 Vaccines and nucleic-acid delivery

Plant-derived EVs may also protect nucleic acids during gastrointestinal exposure. Orange-derived EVs loaded with SARS-CoV-2 mRNA have been investigated as oral vaccine carriers, illustrating the possibility of using edible vesicles as non-invasive nucleic-acid delivery systems [38]. This area remains experimental, but it broadens the concept of PDEV precision nanomedicine beyond conventional chemotherapy toward vaccines, gene regulation and mucosal immunotherapy.

7. Manufacturing, Stability and Scale-Up

A major advantage attributed to PDEVs is source availability, but large-scale manufacture remains challenging. Production begins upstream with the selection, cultivation and harvesting of plant material. Genotype, plant age, environmental stress, season and post-harvest handling may influence vesicle abundance and cargo [11,15–18]. One strategy is to use controlled plant-cell suspension cultures or bioreactor systems instead of variable field-grown material. Another is to improve process control through TFF and chromatography. These approaches could reduce dependence on laboratory-scale ultracentrifugation [16–18,45,49]. Engineering itself must also be scalable. A targeting ligand that is effective at milligram scale but requires multiple low-throughput purification steps may not be practical for pharmaceutical manufacturing. Similarly, sonication or repeated freeze–thaw cycles may require process validation if used for commercial batches. Storage represents another unresolved problem. Cryopreservation, lyophilization and spray drying have been investigated for EVs, but vesicle aggregation, leakage and loss of biological activity remain concerns [15–18]. Stabilizers, cryoprotectants and formulation-specific packaging will therefore need systematic development.

8. Quality Control and Regulatory Considerations

PDEV products occupy an unusual position between biologics, advanced nanomedicine and botanical products. At present, no universally harmonized regulatory category has been established specifically for therapeutic PDEVs. Regulatory interpretation will likely depend on the source, degree of engineering, therapeutic cargo and intended indication [13–18]. The United States Food and Drug Administration has established a botanical drug development framework that emphasizes control of source material, manufacturing consistency, quality and evidence of reproducible therapeutic activity [50]. European regulatory guidance similarly recognizes the complexity of herbal medicinal products and emphasizes control of quality characteristics and manufacturing processes [51]. These principles are highly relevant to PDEV development because the natural source is itself part of the product. A formulation prepared from different cultivars or under different environmental conditions may contain different

lipids, proteins or phytochemicals. Accordingly, the phrase "natural product" cannot substitute for pharmaceutical standardization. A translational PDEV program should therefore establish a defined quality-by-design framework encompassing raw-material specifications, controlled cultivation, validated extraction, purification, particle characterization, cargo quantification, potency assays and stability testing [45–49].

9. Safety, Immunogenicity and Pharmacokinetics

Preclinical studies generally suggest favorable tolerability for many edible plant-derived vesicle preparations, but broad claims of inherent safety should be avoided. Food consumption of a plant does not automatically establish the safety of a concentrated, intravenously administered or chemically modified vesicle product. Safety evaluation should include acute and repeated-dose toxicology, immunological profiling, complement-related effects, biodistribution, organ histopathology, reproductive considerations where relevant and the effects of formulation-associated materials such as polymers or metal-organic frameworks [20,28,39]. Pharmacokinetic studies are also underdeveloped. Essential parameters include systemic half-life, tissue distribution, clearance mechanism, cargo release and the relationship between intact vesicles and degraded or metabolized components [5,7]. Imaging alone cannot fully answer these questions. A particularly important question for future studies is whether repeated PDEV exposure changes immune recognition or tissue distribution. Long-term administration may generate biological responses that are not apparent in short-duration mouse experiments.

10. Current Limitations

Despite rapid progress, several limitations remain. First, PDEV preparations are biologically heterogeneous. Different plant species and isolation procedures can yield particles with substantially different molecular profiles [11–18]. Second, nomenclature and characterization remain inconsistent. The field has historically used "exosome," "nanovesicle," "nanoparticle" and "extracellular vesicle" interchangeably even when biogenesis was not demonstrated. The MISEV framework emphasizes the importance of operationally defining vesicle populations and documenting purification and characterization procedures [6,7]. Third, many studies remain preclinical and use small-animal models. Data on human pharmacokinetics, dose-response relationships and repeated administration are limited [13–18]. Fourth, engineered PDEV systems may lose some of the advantages of naturally occurring vesicles when multiple chemical or synthetic components are added. Increasing formulation complexity may also complicate regulatory classification and manufacturing.

Finally, the field needs comparative studies against established delivery platforms. Demonstrating that a PDEV formulation works is not sufficient for clinical translation; it should also be determined whether the PDEV provides measurable advantages in efficacy, safety, cost, scalability or patient convenience over liposomes, lipid nanoparticles or polymeric nanocarriers [41–43,56,57].

11. Future Directions: From Natural Vesicles to Precision Nanomedicine

The next stage of PDEV research should move from descriptive biology toward quantitative engineering, (summarize in Figure 3).

11.1 Source engineering

Controlled plant cultivation, plant-cell suspension systems and bioreactors may reduce compositional variability [15–18]. Manipulating plant metabolic pathways could ultimately allow production of vesicles with predetermined lipid or phytochemical profiles.

11.2 Rational membrane engineering

Rather than testing large libraries of modifications empirically, membrane composition could be linked systematically to uptake, biodistribution and cargo release. Plant-specific lipids may eventually serve as design elements rather than merely natural constituents.

11.3 Programmable targeting

Ligands such as folic acid, peptides, aptamers and antibodies can convert intrinsic PDEV tropism into more selective delivery systems [19–22]. Future work should determine optimal ligand density, orientation and linker chemistry.

11.4 Precision combination systems

Hybrid PDEV–polymer, PDEV–metal-organic framework, PDEV–hydrogel and PDEV–lipid nanoparticle systems may permit simultaneous control over targeting, loading and release [28,32,37]. These approaches could be particularly useful for combination therapy and tissue-specific delivery.

11.5 Artificial intelligence and multi-omics

Multi-omics can identify relationships among plant genotype, vesicle lipidomics, proteomics, RNA cargo and therapeutic activity. Machine-learning approaches could eventually predict which plant source and processing conditions will produce a desired biological phenotype.

11.6 Establishing PDEV critical quality attributes

The field needs internationally accepted reference preparations and quantitative CQAs for particle identity, purity, composition, potency and stability [45–49]. This would enable meaningful comparison across laboratories and facilitate regulatory discussions.

11.7 Clinical translation

The most realistic translational pathway is likely to begin with indications where the natural biodistribution of PDEVs is advantageous, such as gastrointestinal disease, mucosal delivery, topical repair or locally administered formulations. More complex intravenous and CNS applications will require considerably deeper pharmacokinetic, toxicological and manufacturing evidence [13–18,56–59].

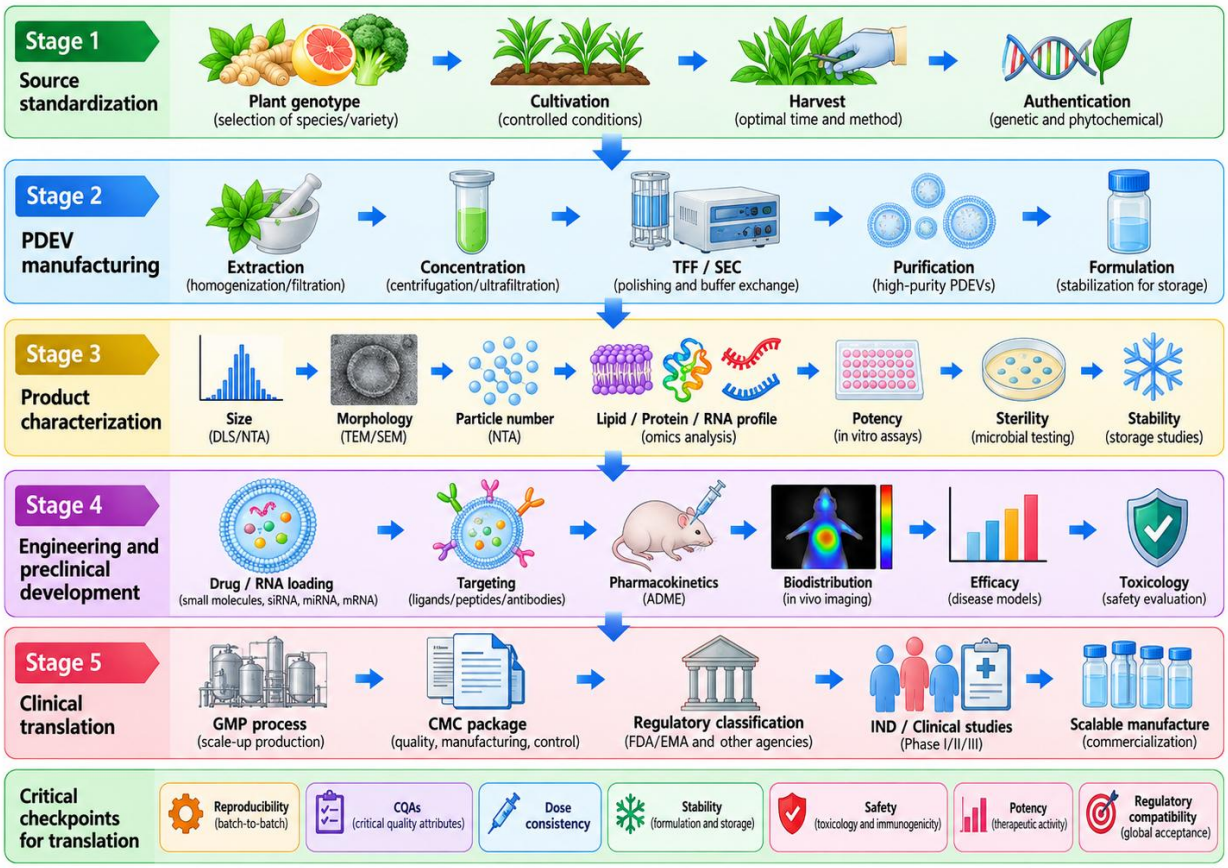

Figure 3. Translational Pipeline from Plant Source to PDEV Precision Nanomedicine.

12. Conclusion

Plant-derived extracellular vesicles have progressed from relatively poorly characterized plant membrane particles to increasingly sophisticated biological nanocarriers. Their value arises from the convergence of several properties: a naturally derived lipid membrane, biologically active endogenous cargo, potential gastrointestinal stability, flexible loading capacity and the possibility of scalable production. Preclinical studies have already shown that PDEVs can transport doxorubicin, siRNA, miRNA and other therapeutic agents and can contribute intrinsic anti-inflammatory, antioxidant, anticancer or regenerative effects. Engineering strategies such as folate targeting, peptide conjugation, membrane reassembly, ZIF-8 hybridization and biomaterial integration are moving the field toward functional precision nanomedicine.

However, the transition from promising nanoparticle to pharmaceutical product will depend less on additional proof-of-concept studies and more on standardization, reproducibility, quantitative pharmacology, manufacturing control and regulatory definition. Current recommendations for EV characterization, together with botanical-drug quality principles, provide useful foundations, but PDEV-specific standards will ultimately be required. The most important future opportunity is therefore not simply to harvest vesicles from plants, but to engineer plant-derived vesicular systems as predictable pharmaceutical entities. The convergence of controlled plant biotechnology, membrane engineering, targeted delivery, multi-omics, advanced manufacturing and precision pharmacology could establish PDEVs as a distinctive class of sustainable nanomedicines.

Author Contributions

Ashok Kumar Rajpoot and Vivek Kumar: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing Original Draft, Writing Review & Editing, Validation, Supervision, and Final Approval of the Manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Form
PDEV	Plant-Derived Extracellular Vesicle
EV	Extracellular Vesicle
MVB	Multivesicular Body
DUC	Differential Ultracentrifugation
SEC	Size-Exclusion Chromatography
UF	Ultrafiltration
TFF	Tangential Flow Filtration
PEG	Polyethylene Glycol
MISEV	Minimal Information for Studies of Extracellular Vesicles
GMP	Good Manufacturing Practice
RNA	Ribonucleic Acid
miRNA	MicroRNA
siRNA	Small Interfering RNA
DDS	Drug Delivery System
BBB	Blood–Brain Barrier

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