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Plant-Derived Exosome-Like Nanoparticles: Advances in Therapeutic Applications and Drug Delivery

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Received: 17 Feb 2026 | Revised: 15 Mar 2026 | Accepted: 02 Apr 2026 | Published: 12 Apr 2026

Abstract

Background: Plant-derived exosome-like nanoparticles (PELNs) are nanoscale vesicles secreted by plant cells that contain lipids, proteins, RNAs, and secondary metabolites. Increasing evidence indicates that these vesicles can deliver plant-derived molecules into mammalian cells and modulate biological processes, including inflammation, oxidative stress, and immune responses.

Scope of the Review: This review summarizes current knowledge of PELNs, including their biogenesis, molecular composition, isolation and characterization strategies, cellular uptake mechanisms, and reported therapeutic applications. Representative examples from medicinal plants, such as ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), and tea (*Camellia sinensis*), are discussed to illustrate their biological activity and their potential as natural nanocarriers. Their physicochemical stability, biocompatibility, and low immunogenicity support ongoing investigation for both oral and systemic delivery.

Challenges and Future Prospects: Despite growing interest, several challenges remain, including the lack of standardized isolation and purification protocols, variability in vesicle composition, and limited regulatory frameworks. Advances in omics-based analyses and functional validation will be essential to clarify mechanisms of action and improve reproducibility.

Conclusion: PELNs represent a rapidly developing research area at the interface of natural products and nanomedicine. Although current evidence is largely preclinical, these vesicles may contribute to the development of safe and effective therapeutic strategies with further validation.

Keywords: plant-derived exosome-like nanoparticles; extracellular vesicles; medicinal plants; cross-kingdom communication; RNA-mediated regulation; drug delivery systems; immunomodulation; nanomedicine

How to cite this article: Lu Zhan, Xuqin Huang, Bowen Chang, Qian Li, Li Zhang, Songping Xie, Jie Huang. Plant-Derived Exosome-Like Nanoparticles: Advances in Therapeutic Applications and Drug Delivery. *Botanical Drugs*. 2026;1:04.

<https://doi.org/10.65239/botanicaldrugs.2026.04>

ISSN: 3142-9386

1. Introduction

Botanical drugs have long contributed to human health and remain an important source of therapeutic agents. Many clinically used compounds, including paclitaxel and artemisinin, originate from plants and illustrate the continued relevance of natural products in drug discovery [1,2]. In addition to isolated compounds, botanical preparations often contain multiple bioactive constituents that may act on different molecular targets, a feature that has attracted continued interest in the treatment of complex and chronic diseases [3,4].

Despite these advantages, several limitations restrict the broader clinical application of botanical drugs. Traditional formulations such as decoctions, powders, and tinctures frequently exhibit poor solubility and limited stability [5]. Variability in plant sources, cultivation conditions, and extraction processes can result in inconsistent composition across batches, making standardization challenging [6]. In addition, many phytochemicals are susceptible to degradation in the gastrointestinal environment, which reduces systemic exposure and may limit therapeutic efficacy [7].

Recent studies have identified plant-derived nanovesicles as a potential approach to address some of these limitations. Nanoscale vesicles isolated from plants typically range from 30 to 150 nm in diameter and consist of a lipid bilayer enclosing proteins, lipids, nucleic acids, and small molecules [8]. These vesicles have been reported in a variety of edible and medicinal plants, including ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), and tea (*Camellia sinensis*) [9–11]. Their membrane structure can protect encapsulated compounds and facilitate uptake by recipient cells [12].

However, the terminology used in this field remains inconsistent. Terms such as "exosomes," "exosome-like nanoparticles," and "extracellular vesicles" are often used interchangeably. In this review, the term plant-derived exosome-like nanoparticles (PELNs) is used preferentially, because plant vesicles have not been conclusively shown to satisfy the criteria established for mammalian exosomes by the International Society for Extracellular Vesicles (ISEV) [13].

Accumulating experimental evidence suggests that PELNs can be internalized by mammalian cells through mechanisms such as endocytosis and membrane fusion [14,15]. Their cargo has been associated with modulation of inflammatory signaling, oxidative stress responses, and immune activity in preclinical models [16–18]. However, the extent to which plant-derived RNAs exert functional gene regulatory effects in mammals remains under debate, and conflicting findings have been reported [19–22].

This review provides an overview of plant-derived vesicles, focusing on their biogenesis, molecular composition, isolation and characterization methods, cellular uptake mechanisms, and therapeutic applications.

2. Biogenesis and Molecular Composition of Plant-Derived Exosome-Like Nanoparticles

Plant-derived exosome-like nanoparticles (PELNs) are nanoscale vesicles generated within the endomembrane system of plant cells. Their biogenesis involves the formation of multivesicular bodies (MVBs), in which intraluminal vesicles (ILVs) are produced through inward budding of the endosomal membrane and subsequently released into the extracellular or apoplastic space upon fusion of MVBs with the plasma membrane [23,24]. This process shares key mechanistic similarities with extracellular vesicle formation in mammalian systems, although plant-specific regulatory pathways and cellular contexts introduce distinct features [25].

The generation of ILVs is regulated, at least in part, by the endosomal sorting complexes required for transport (ESCRT), including ESCRT-I, ESCRT-II, and ESCRT-III, as well as associated proteins such as VPS4 and ALIX [26]. In plant systems, ESCRT components have been implicated in membrane remodeling, cargo selection, and vesicle trafficking. In addition to ESCRT-dependent mechanisms, alternative pathways involving plant-specific membrane proteins have been described. For example, tetraspanin proteins such as TET8 have been associated with vesicle formation and cargo loading, particularly under stress or pathogen-related conditions [27,28]. The trans-Golgi network (TGN), which functions as an early endosome in plant cells, also plays an important role in vesicle trafficking by integrating endocytic and secretory pathways and contributing to the release of extracellular vesicles [29].

The molecular composition of PELNs reflects their biological origin and functional roles. The lipid bilayer membrane is enriched in phosphatidic acid, phosphatidylcholine, phosphatidylethanolamine, and phytosterols, rather than cholesterol, which is more prominent in mammalian vesicles [30–32]. These lipid components contribute to membrane curvature, vesicle stability, and resistance to environmental stress, and they may influence vesicle–cell interactions and uptake efficiency in recipient cells.

Proteomic analyses have revealed that PELNs contain a diverse range of proteins involved in stress responses, metabolism, and vesicle transport. Commonly identified proteins include heat shock proteins (e.g., HSP70 and HSP90), annexins, and enzymes associated with redox regulation [33,34]. These proteins may contribute not only to vesicle stability but also to the biological activity of PELNs following uptake by recipient cells. Notably, plant vesicles do not consistently express canonical mammalian exosome markers such as CD9, CD63, or CD81, highlighting differences in molecular signatures across kingdoms.

PELNs also carry a variety of RNA species, including microRNAs, small interfering RNAs, and other non-coding RNAs. RNA loading into vesicles is thought to involve selective sorting mechanisms during vesicle formation, potentially mediated by RNA-binding proteins and sequence-specific recognition processes [35–37]. These RNA molecules are relatively stable within the vesicular environment and may be protected from degradation under physiological conditions. While some studies have suggested that plant-derived RNAs can exert regulatory effects in mammalian cells, others have reported limited or inconsistent evidence, indicating that the functional significance of these RNAs remains an area of ongoing investigation [19–22].

Overall, PELNs share fundamental structural characteristics with mammalian extracellular vesicles, including nanoscale size, a lipid bilayer membrane, and the capacity to transport bioactive molecules. At the same time, their plant-specific composition and biogenesis pathways confer unique physicochemical properties and biological functions, supporting their emerging role in cross-kingdom communication and therapeutic applications (see Figure 1).

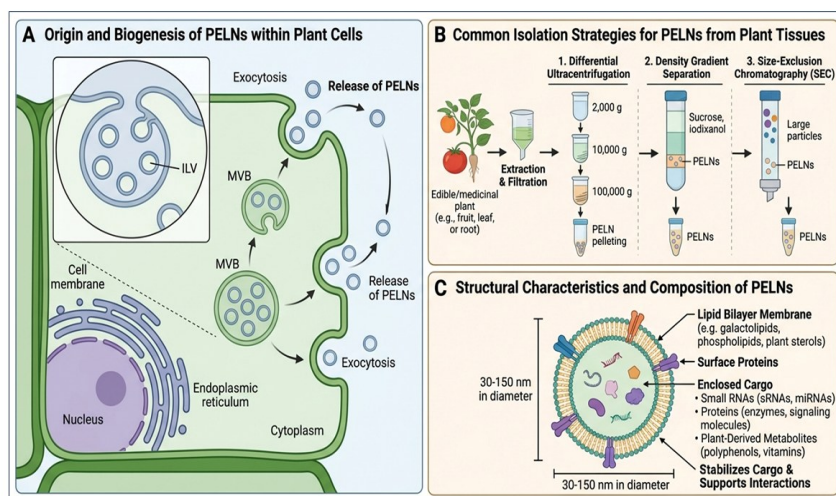


Figure 1. Overview of Plant-Derived Exosome-Like Nanoparticles. Schematic overview of the origin, isolation, and structural characteristics of plant-derived exosome-like nanoparticles (PELNs). PELNs are formed within the endosomal system of plant cells through the generation of multivesicular bodies and subsequent release of intraluminal vesicles. Vesicles can be isolated from edible or medicinal plant tissues using approaches such as differential ultracentrifugation, density gradient separation, or size-exclusion chromatography. Structurally, PELNs typically range from 30 to 150 nm in diameter and consist of a lipid bilayer enclosing proteins, lipids, small RNAs, and plant-derived metabolites.

3. Separation, Purification and Characterization Techniques

The isolation of plant-derived exosome-like nanoparticles (PELNs) requires methods tailored to the structural complexity of plant tissues and the presence of abundant polysaccharides, pigments, and secondary metabolites. Among the available approaches, differential ultracentrifugation (DUC) remains one of the most widely used techniques for vesicle enrichment. This method typically involves sequential centrifugation steps combined with filtration to remove cellular debris, large organelles, and insoluble

components prior to high-speed centrifugation for vesicle collection [38–40]. Although broadly applied, DUC may co-isolate protein aggregates and heterogeneous particle populations, which can affect downstream analyses.

To improve purity, density gradient centrifugation (DGC) using sucrose or iodixanol gradients is frequently employed. This approach separates particles based on buoyant density, allowing enrichment of vesicle populations within a defined density range. However, DGC is relatively time-consuming and requires careful optimization, limiting its applicability for large-scale or high-throughput studies [41]. As an alternative, size-exclusion chromatography (SEC) has been widely adopted to separate vesicles from soluble proteins and small metabolites based on hydrodynamic size. SEC offers the advantage of preserving vesicle integrity by avoiding high centrifugal forces, although it may result in lower yield and often requires subsequent concentration steps [42].

Tangential flow filtration (TFF) has emerged as a promising method for scalable isolation and purification of PELNs. By allowing continuous flow parallel to the filtration membrane, TFF reduces membrane fouling and enables efficient concentration and buffer exchange. This method is particularly suitable for processing large volumes of plant extracts and is increasingly considered for translational and industrial applications [43].

Following isolation, comprehensive characterization of PELNs is essential to confirm vesicle identity, assess purity, and evaluate physicochemical properties. Transmission electron microscopy (TEM) is commonly used to visualize vesicle morphology, typically revealing spherical or cup-shaped structures enclosed by a lipid bilayer [44]. Cryo-electron microscopy can further preserve native structure and reduce artifacts associated with sample preparation. Nanoparticle tracking analysis (NTA) provides quantitative measurements of particle size distribution and concentration, while dynamic light scattering (DLS) can be used to assess polydispersity, although it is less reliable for heterogeneous samples [45].

In addition to morphological characterization, biochemical and molecular analyses are widely employed to define vesicle composition. Proteomic and lipidomic approaches allow identification of vesicle-associated proteins and lipids, while RNA sequencing can profile small RNA content. These techniques provide insights into vesicle heterogeneity and potential functional properties. However, the absence of universally accepted plant-specific vesicle markers remains a limitation, and standardized criteria for defining PELNs are still under development.

Overall, each isolation and characterization method presents specific advantages and limitations in terms of yield, purity, scalability, and structural preservation. The selection of appropriate methodologies should therefore be guided by the intended downstream applications, whether for mechanistic studies, functional assays, or translational development.

4. Cellular Uptake and Cross-Kingdom Communication Mechanisms

Plant-derived exosome-like nanoparticles (PELNs) interact with mammalian cells through multiple internalization pathways, reflecting the diversity of vesicle–cell interactions. Reported mechanisms include clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis, and lipid raft–dependent uptake [46–49]. The relative contribution of each pathway may depend on vesicle size, lipid composition, surface charge, and the physiological state of recipient cells. These uptake processes enable PELNs to cross cellular membranes and deliver their molecular cargo into intracellular compartments.

Following internalization, PELNs are typically trafficked through the endosomal system. Early endosomes mature into late endosomes and may subsequently fuse with lysosomes, where partial degradation can occur, or release vesicular cargo into the cytosol [50–52]. The efficiency of endosomal escape is considered a critical factor influencing the biological activity of vesicle-associated molecules. Lipid composition, particularly the presence of phosphatidic acid and other fusogenic lipids, may facilitate membrane fusion events and promote intracellular delivery.

A central topic in this field is the potential for cross-kingdom communication mediated by PELNs. Several studies have suggested that plant-derived small RNAs, including microRNAs such as miR-168a, can be

detected in mammalian systems and may modulate gene expression [53]. However, these findings remain controversial. Independent studies have reported limited or undetectable uptake of dietary plant microRNAs and questioned their functional relevance *in vivo* [54–56]. Variability in experimental design, detection sensitivity, and biological context may contribute to these discrepancies. As a result, the concept of RNA-mediated cross-kingdom regulation should be interpreted with caution, and further rigorous validation is required (see Figure 2).

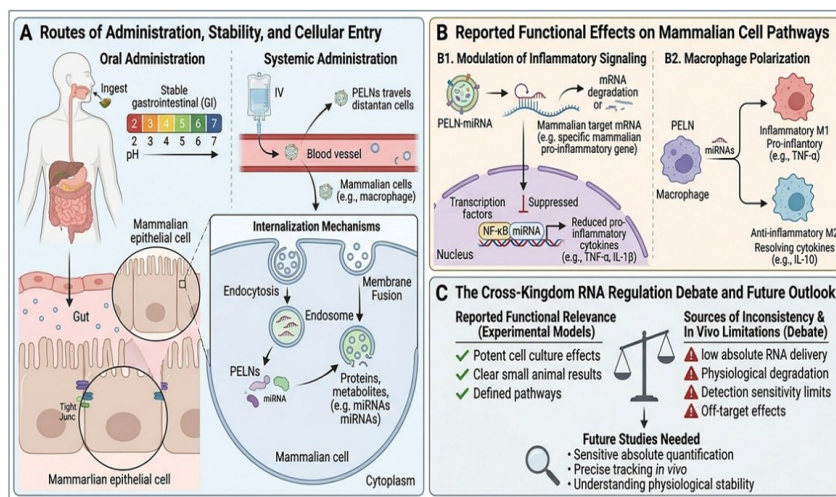


Figure 2. RNA-Mediated Cross-Kingdom Communication. Schematic representation of proposed RNA-mediated cross-kingdom communication by plant-derived exosome-like nanoparticles (PELNs). Following oral or systemic administration, PELNs may remain stable in the gastrointestinal environment and be internalized by mammalian cells through endocytosis or membrane fusion. Vesicle-associated small RNAs, including miRNAs, have been reported to interact with intracellular pathways and to be associated with modulation of inflammatory signaling, macrophage polarization, and epithelial barrier function in experimental models.

In addition to RNA cargo, PELNs carry lipids, proteins, and small molecules that may contribute to biological effects following cellular uptake. Lipid components can interact with membrane receptors or alter membrane dynamics, while vesicle-associated proteins and enzymes may influence intracellular signaling pathways, including those related to oxidative stress and immune responses [57–60]. These combined effects suggest that PELNs function not only as passive carriers but also as active modulators of cellular processes.

Overall, while the ability of PELNs to enter mammalian cells and deliver bioactive cargo is well supported by experimental evidence, the efficiency, specificity, and mechanistic basis of cross-kingdom communication remain incompletely understood. Continued investigation into uptake pathways, intracellular trafficking, and cargo functionality will be essential for clarifying their biological significance and therapeutic potential.

5. Therapeutic Applications of Plant-Derived Exosome-Like Nanoparticles

Accumulating evidence indicates that plant-derived exosome-like nanoparticles (PELNs) exhibit diverse biological activities and can function as carriers for bioactive molecules. Their relative stability in the gastrointestinal environment, low immunogenicity, and availability from edible plant sources have supported growing interest in their potential therapeutic applications. Current studies can be broadly categorized into intrinsic biological activities, engineered delivery systems, and emerging translational applications.

5.1. Intrinsic Biological Activities

5.1.1. Anti-inflammatory and antioxidant effects

Anti-inflammatory activity represents one of the most extensively studied properties of PELNs. Vesicles derived from ginger have been shown to reduce the expression of pro-inflammatory cytokines, including TNF- α , IL-6, and IL-1 β , while increasing anti-inflammatory mediators such as IL-10 in macrophages [61]. These effects are associated with suppression of NF- κ B signaling and improvement of epithelial barrier function in experimental colitis models. In parallel, vesicles derived from other plant sources, including carrot and citrus species, have been linked to reduced oxidative stress in recipient cells. This effect is likely mediated by the delivery of antioxidant enzymes and plant-derived metabolites that regulate intracellular redox balance [62–64]. Together, these findings support a role for PELNs in modulating inflammatory and oxidative pathways, although most evidence remains derived from *in vitro* or animal models.

5.1.2. Anticancer activity

PELNs have also been investigated in cancer-related contexts. Vesicles derived from citrus and grape have been reported to inhibit tumor cell proliferation and induce apoptosis in experimental models, potentially through modulation of signaling pathways such as Wnt/ β -catenin and activation of caspase cascades [65,66]. In addition to direct effects on tumor cells, PELNs may influence the tumor microenvironment. Their lipid composition and bioactive cargo have been associated with modulation of immune cell activity, including macrophage function. However, these observations are largely preclinical, and their relevance to human disease remains to be established.

5.1.3. Metabolic and immune regulation

Several studies have suggested that PELNs can affect metabolic and immune processes. Vesicles derived from grapefruit and ginger have been reported to accumulate in hepatocytes and immune cells, where they are associated with changes in lipid metabolism and inflammatory signaling pathways [67–69]. PELNs have also been linked to macrophage polarization toward anti-inflammatory phenotypes under experimental conditions. These findings suggest potential roles in metabolic disorders such as obesity and fatty liver disease, although the underlying molecular mechanisms require further clarification.

5.1.4. Regenerative effects

PELNs have been explored in regenerative medicine models, where they have been associated with enhanced cell proliferation, tissue repair, and extracellular matrix remodeling. Vesicles derived from plant sources such as grape, aloe, and ginger have been reported to promote the proliferation of fibroblasts, keratinocytes, and mesenchymal cells, processes relevant to wound healing and tissue regeneration [70–72]. In addition, vesicles carrying specific RNA species and bioactive lipids may support osteogenic differentiation and reduce oxidative stress in damaged tissues. While these findings are promising, they remain largely confined to preclinical models (see Figure 3 and Table 1).

5.2. Engineered Delivery Applications

Beyond their intrinsic biological activity, PELNs have been investigated as delivery platforms for therapeutic agents. Their lipid bilayer structure can protect encapsulated molecules from enzymatic degradation, while their surface properties facilitate cellular uptake. Plant-derived vesicles have been used to deliver small-molecule drugs, proteins, and nucleic acids in experimental systems. For example, vesicles derived from grapefruit have been employed to deliver chemotherapeutic agents such as paclitaxel and doxorubicin, resulting in improved drug stability and reduced systemic toxicity in preclinical models [73–75]. Surface modification strategies have also been explored to enhance targeting efficiency. Functionalization with ligands or peptides has been reported to increase uptake by specific cell types, supporting the potential of engineered PELNs for targeted delivery. Nevertheless, most studies remain at the proof-of-concept stage, and further work is needed to evaluate pharmacokinetics, biodistribution, and long-term safety.

Table 1. Plant-Derived Exosome-Like Nanoparticles (PELNs): Sources, Cargo, and Reported Biological Activities.

Plant Source	Major Cargo Components	Experimental Model	Reported Biological Activities	Proposed Mechanisms
Ginger (<i>Zingiber officinale</i>)	miRNAs, lipids (phosphatidic acid), proteins	DSS-induced colitis; macrophages	Reduced intestinal inflammation; modulation of cytokine production	Associated with inhibition of NF- κ B signaling and macrophage polarization
Grapefruit (<i>Citrus paradisi</i>)	Lipids, flavonoids, small RNAs	Tumor models; hepatocytes	Enhanced drug delivery; modulation of lipid metabolism	Vesicle uptake by target cells; interaction with metabolic pathways
Grape (<i>Vitis vinifera</i>)	Polyphenols, proteins, RNAs	Colon cancer models; epithelial cells	Inhibition of tumor cell proliferation; antioxidant effects	Associated with modulation of Wnt/ β -catenin signaling and oxidative stress pathways
Turmeric (<i>Curcuma longa</i>)	Curcuminoids, enzymes, miRNAs	Cancer cell lines; inflammatory models	Induction of apoptosis; reduction of oxidative stress	Linked to caspase activation and regulation of redox balance
Carrot (<i>Daucus carota</i>)	Antioxidant enzymes, lipids	Macrophages; epithelial cells	Reduction of ROS levels; anti-inflammatory effects	Delivery of antioxidant components and modulation of cellular stress responses
Broccoli (<i>Brassica oleracea</i>)	Sulforaphane-related compounds, RNAs	Macrophages; intestinal cells	Modulation of immune responses	Associated with regulation of inflammatory signaling pathways
Aloe (<i>Aloe vera</i>)	Polysaccharides, proteins, RNAs	Fibroblasts; wound healing models	Promotion of cell proliferation and tissue repair	Linked to enhancement of cell growth and extracellular matrix remodeling
Lemon (<i>Citrus limon</i>)	Flavonoids, lipids	Microbiome-related models	Modulation of gut microbiota composition	Interaction with microbial metabolic pathways
<i>Arabidopsis thaliana</i>	miRNAs (e.g., miR-159, miR-168), proteins	<i>In vitro</i> and experimental systems	Detection of plant-derived RNAs in recipient systems	Proposed involvement in RNA transfer; functional relevance remains under debate
Tea (<i>Camellia sinensis</i>)	Polyphenols, catechins, RNAs	Oxidative stress models	Antioxidant activity; cellular protection	Associated with redox regulation and cellular stress response pathways

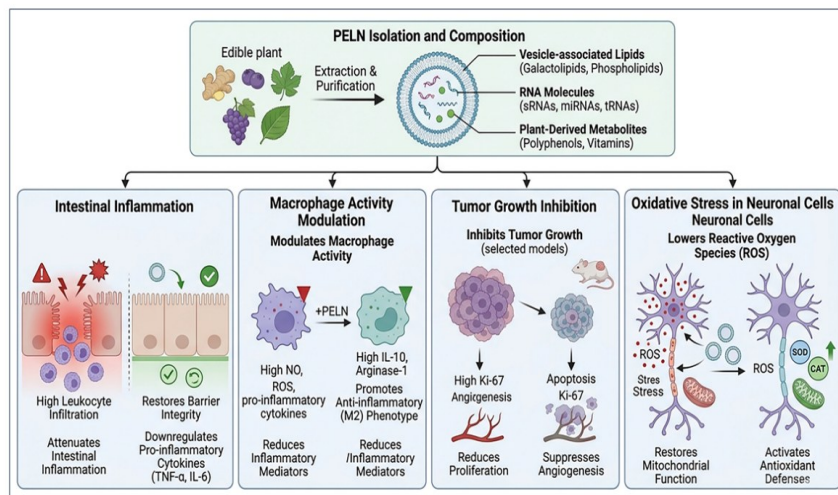


Figure 3. Pharmacological Effects in Different Disease Models. Schematic summary of the reported biological activities of plant-derived exosome-like nanoparticles (PELNs) in representative experimental systems. Reported effects include attenuation of intestinal inflammation, modulation of macrophage activity, inhibition of tumor growth in selected models, and reduction of oxidative stress in neuronal cells.

5.3. Emerging Applications

5.3.1. Oral delivery and gastrointestinal targeting

PELNs have attracted interest as oral delivery vehicles due to their relative stability under acidic and enzymatic conditions. Experimental studies suggest that these vesicles can persist within the gastrointestinal tract and interact with intestinal epithelial and immune cells, producing localized biological effects [76]. These properties may be advantageous for the development of therapies targeting intestinal diseases, although mechanisms of absorption and systemic distribution are not yet fully understood.

5.3.2. Microbiome modulation

Plant-derived vesicles have also been associated with modulation of gut microbiota composition and activity. Vesicles derived from ginger and citrus species have been reported to influence microbial growth and metabolic function in experimental systems [77–79]. These interactions may involve vesicle-associated lipids or RNA molecules that affect microbial pathways. However, the functional relevance of these findings *in vivo* remains to be clarified (see Figure 4 and Table 2).

6. Challenges, Standardization, and Regulatory Considerations

The rapid expansion of research on plant-derived exosome-like nanoparticles (PELNs) has highlighted several scientific and translational challenges that must be addressed before their broader clinical application can be realized. These challenges span methodological standardization, molecular characterization, manufacturing consistency, and regulatory classification.

A primary issue is the lack of standardized isolation and purification protocols. Current studies employ a variety of approaches, including differential ultracentrifugation, filtration, density gradient centrifugation, size-exclusion chromatography, and tangential flow filtration, often in different combinations. Variations in these procedures can result in differences in vesicle yield, purity, and composition, complicating comparisons across studies and limiting reproducibility [80]. In addition, co-isolation of non-vesicular components, such as protein aggregates or plant-derived macromolecules, remains a persistent concern.

Table 2. Comparative Characteristics of Conventional Plant Extracts and Plant-Derived Exosome-Like Nanoparticles (PELNs).

Plant Source	Major Cargo Components	Experimental Model	Reported Biological Activities	Proposed Mechanisms
Ginger (<i>Zingiber officinale</i>)	miRNAs, lipids (phosphatidic acid), proteins	DSS-induced colitis; macrophages	Reduced intestinal inflammation; modulation of cytokine production	Associated with inhibition of NF- κ B signaling and macrophage polarization
Grapefruit (<i>Citrus paradisi</i>)	Lipids, flavonoids, small RNAs	Tumor models; hepatocytes	Enhanced drug delivery; modulation of lipid metabolism	Vesicle uptake by target cells; interaction with metabolic pathways
Grape (<i>Vitis vinifera</i>)	Polyphenols, proteins, RNAs	Colon cancer models; epithelial cells	Inhibition of tumor cell proliferation; antioxidant effects	Associated with modulation of Wnt/ β -catenin signaling and oxidative stress pathways
Turmeric (<i>Curcuma longa</i>)	Curcuminoids, enzymes, miRNAs	Cancer cell lines; inflammatory models	Induction of apoptosis; reduction of oxidative stress	Linked to caspase activation and regulation of redox balance
Carrot (<i>Daucus carota</i>)	Antioxidant enzymes, lipids	Macrophages; epithelial cells	Reduction of ROS levels; anti-inflammatory effects	Delivery of antioxidant components and modulation of cellular stress responses
Broccoli (<i>Brassica oleracea</i>)	Sulforaphane-related compounds, RNAs	Macrophages; intestinal cells	Modulation of immune responses	Associated with regulation of inflammatory signaling pathways
Aloe (<i>Aloe vera</i>)	Polysaccharides, proteins, RNAs	Fibroblasts; wound healing models	Promotion of cell proliferation and tissue repair	Linked to enhancement of cell growth and extracellular matrix remodeling
Lemon (<i>Citrus limon</i>)	Flavonoids, lipids	Microbiome-related models	Modulation of gut microbiota composition	Interaction with microbial metabolic pathways
<i>Arabidopsis thaliana</i>	miRNAs (e.g., miR-159, miR-168), proteins	<i>In vitro</i> and experimental systems	Detection of plant-derived RNAs in recipient systems	Proposed involvement in RNA transfer; functional relevance remains under debate
Tea (<i>Camellia sinensis</i>)	Polyphenols, catechins, RNAs	Oxidative stress models	Antioxidant activity; cellular protection	Associated with redox regulation and cellular stress response pathways

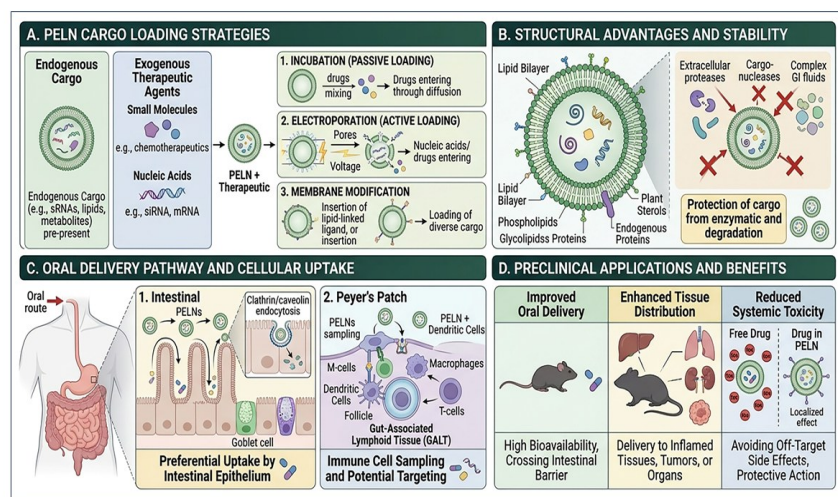


Figure 4. Plant-Derived Exosome-Like Nanoparticles as Drug Delivery Platforms. Schematic representation of plant-derived exosome-like nanoparticles (PELNs) as biomimetic nanocarriers for therapeutic delivery. The lipid bilayer structure contributes to the stability of encapsulated molecules and may protect cargo from enzymatic degradation.

Batch-to-batch variability represents another major obstacle. The composition of PELNs is influenced by multiple factors, including plant species, cultivar, growth conditions, harvest timing, and extraction methods. These variables can affect lipid composition, protein content, and RNA profiles, thereby influencing biological activity and safety characteristics [81]. Establishing robust quality control parameters is therefore essential. Parameters such as particle size distribution, zeta potential, lipid composition, RNA content, and functional bioactivity assays have been proposed, but consensus standards have not yet been established (see Table 3).

Another challenge relates to the identification of vesicle-associated markers. Unlike mammalian extracellular vesicles, which are commonly characterized using markers such as CD9, CD63, and CD81, plant-derived vesicles do not exhibit a universally accepted set of markers. Proteins such as tetraspanins, annexins, and heat shock proteins have been reported, but their expression can vary depending on plant species and physiological conditions [82]. This variability complicates efforts to define vesicle identity and to distinguish PELNs from co-isolated contaminants.

Stability and storage conditions also require further investigation. Repeated freeze–thaw cycles may compromise vesicle integrity and lead to degradation of associated biomolecules. Strategies such as lyophilization and the use of cryoprotectants have been explored to improve stability, but optimal conditions appear to be context-dependent and require systematic evaluation [83]. These considerations are particularly important for large-scale production and long-term storage.

From a translational perspective, scalable manufacturing remains a critical challenge. While methods such as tangential flow filtration offer potential for large-scale processing, reproducible production under good manufacturing practice (GMP) conditions has not yet been fully established. The development of standardized upstream and downstream processes will be essential for clinical translation.

Regulatory classification represents an additional complexity. PELNs do not fit neatly into existing categories such as conventional botanical products, biologics, or synthetic nanomedicines. Regulatory frameworks established by agencies such as the U.S. Food and Drug Administration and the European Medicines Agency primarily address well-defined chemical entities or traditional botanical extracts, rather than vesicle-based systems containing heterogeneous biomolecular cargo [84,85]. As a result, the appropriate classification and regulatory pathways for PELN-based products remain to be determined.

Table 3. Strategies for Extract-Loaded Plant-Derived Exosome-Like Nanoparticles (PELNs) and Their Therapeutic Applications.

Plant Source	Major Cargo Components	Experimental Model	Reported Biological Activities	Proposed Mechanisms
Ginger (<i>Zingiber officinale</i>)	miRNAs, lipids (phosphatidic acid), proteins	DSS-induced colitis; macrophages	Reduced intestinal inflammation; modulation of cytokine production	Associated with inhibition of NF- κ B signaling and macrophage polarization
Grapefruit (<i>Citrus paradisi</i>)	Lipids, flavonoids, small RNAs	Tumor models; hepatocytes	Enhanced drug delivery; modulation of lipid metabolism	Vesicle uptake by target cells; interaction with metabolic pathways
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Lemon (<i>Citrus limon</i>)	Flavonoids, lipids	Microbiome-related models	Modulation of gut microbiota composition	Interaction with microbial metabolic pathways
<i>Arabidopsis thaliana</i>	miRNAs (e.g., miR-159, miR-168), proteins	<i>In vitro</i> and experimental systems	Detection of plant-derived RNAs in recipient systems	Proposed involvement in RNA transfer; functional relevance remains under debate
Tea (<i>Camellia sinensis</i>)	Polyphenols, catechins, RNAs	Oxidative stress models	Antioxidant activity; cellular protection	Associated with redox regulation and cellular stress response pathways

Finally, comprehensive safety evaluation is required. Although plant-derived vesicles have been associated with low immunogenicity in preclinical studies, systematic toxicological assessment is still needed. This includes evaluation of biodistribution, pharmacokinetics, long-term exposure, and potential off-target effects, particularly for engineered vesicles carrying therapeutic payloads.

Overall, addressing these challenges will require coordinated efforts to develop standardized methodologies, establish quality control criteria, and define regulatory pathways. Such advances will be essential for translating PELNs from experimental systems into clinically relevant therapeutic platforms.

7. Conclusions

Plant-derived exosome-like nanoparticles (PELNs) represent a distinct class of naturally derived nanovesicles with emerging relevance in drug delivery and therapeutic modulation. Their nanoscale structure, lipid bilayer composition, and capacity to transport proteins, lipids, and nucleic acids enable interactions with mammalian cells and contribute to a range of biological effects observed in experimental systems. Compared with many synthetic nanocarriers, PELNs offer advantages in biocompatibility, relative stability, and potential for oral administration, which have supported growing interest in their translational potential. Over the past decade, studies have demonstrated that PELNs can modulate inflammation, oxidative stress, tumor-associated processes, and tissue repair in preclinical models. In addition to their intrinsic biological activity, their use as delivery platforms for small molecules, nucleic acids, and other therapeutic agents has further expanded their potential applications. These findings suggest that PELNs may provide a framework for integrating natural product-based therapeutics with modern nanomedicine strategies.

Despite these advances, several limitations remain. Current evidence is largely derived from *in vitro* experiments and animal studies, and clinical data are still lacking. In addition, variability in isolation methods, vesicle composition, and experimental conditions complicates cross-study comparisons and limits reproducibility. A more detailed understanding of vesicle biogenesis, molecular composition, and mechanisms of action will be essential for clarifying their functional roles and optimizing their use in therapeutic settings.

Future progress in this field will depend on the establishment of standardized methodologies for isolation, characterization, and quality control, as well as the development of scalable manufacturing processes. Advances in omics technologies, including proteomics, lipidomics, and RNA sequencing, are expected to provide deeper insights into vesicle composition and function, facilitating the identification of molecular signatures relevant to efficacy and safety. From a translational perspective, further work is required to define regulatory pathways, evaluate long-term safety, and assess clinical efficacy in human populations. Interdisciplinary collaboration across plant biology, nanotechnology, pharmacology, and clinical research will be critical to advancing this field.

In summary, while PELNs remain at an early stage of clinical development, they represent a promising area of investigation at the intersection of natural products and nanomedicine. Continued research will determine whether these vesicles can be developed into standardized, safe, and effective therapeutic platforms.

Author Contributions

Conceptualization: All authors; Writing – original draft: All authors; Writing – review & editing: All authors; Supervision: All authors. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Statement

Not applicable.

Data Availability

No new data were generated or analyzed in this study. Data sharing is not applicable to this article.

Funding

This research received no external funding.

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How to cite this article: Lu Zhan, Xuqin Huang, Bowen Chang, Qian Li, Li Zhang, Songping Xie, Jie Huang. Plant-Derived Exosome-Like Nanoparticles: Advances in Therapeutic Applications and Drug Delivery. *Botanical Drugs*. 2026;1:04.
<https://doi.org/10.65239/botanicaldrugs.2026.04>
ISSN: 3142-9386