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Mini Review

Plant-Derived Exosomes: A New Frontier in Natural Drug Delivery Systems

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Abstract

Plant-derived exosomes (PDEs), or plant-derived extracellular vesicles (PDEVs), are a new technology that has brought a revolution to the world of nanomedicine and nutraceutical delivery. These nanosized vesicles that naturally are released by several types of plant cells contain structural and functional similarities to mammalian exosomes and have several benefits, including biocompatibility, low immunogenicity, abundance, and affordability. PDEs represent a variety of biomolecules; lipids, proteins, RNAs and phytochemicals interacting with one another to mediate intercellular and interspecies communication. Their natural resistance in the gastrointestinal tract and penetration of biological barriers indicate their potential to deliver therapeutic factors in targeted cancers, inflammation, metabolic and neurodegenerative diseases. Recently, modification of PDE membranes has been successfully demonstrated to be effective in modifying the membranes to have a high drug loading speed, tissue targeting and controlled release. In addition, ginger, grape and broccoli are edible plants that offer safe and sustainable pool of PDE isolation.

Keywords: Plant-Derived Exosomes; Drug Delivery; Nanocarriers; Biocompatibility; Phytopharmaceuticals; Natural Nanoparticles

Introduction

Extracellular vesicles (EVs) are cellular nanoscale membrane-bound particles that are involved in cell-cell communication and transportation of lipids, proteins, nucleic acids and small metabolites. Although the initial EV studies were conducted on mammalian exosomes, the finding that plants also can release structurally and functionally related vesicles, also known as plant-derived exosome-like nanoparticles (PDENs), plant extracellular vesicles (P-EVs)

or plant-derived nanovesicles has presented a new opportunity in natural, biocompatible drug delivery platforms. PDENs have a number of physicochemical similarities to mammalian EVs (size range -30300nm, lipid bi-layer membrane) but are based on edible plants with benefits in safety, scalability and oral bioavailability [1-3].

Initial pioneering studies identifying EV-like particles in edible plants as well as the separation of EV-like particles in animal models showed that the vesicles can store bioactive lipids, proteins and plant small RNAs and deliver them to host cell signalling and immunity. Those results have presented evidence-of-concept that cross-kingdom communication is possible and indicated that PDENs have the potential to transport biologically active cargos to mammalian tissues after oral delivery. The fact that many PDENs have an edible origin decreases the toxicity and immunogenicity concerns that can be raised against them and make them appealing natural nanocarriers of therapeutic molecules [4,5].

During the last ten years, the expanding body of literature has defined the PDEN composition (lipidomes, proteomes, small RNAs and secondary metabolites), their inherent bioactivities (anti-inflammatory, antioxidant, anti-tumor), and their ability to encapsulate and deliver exogenous small molecules, nucleic acids and proteins. Small drug delivery and RNAs have been found to be successfully delivered using vesicles isolated in ginger, grapefruit, lemon, grape and broccoli among other fruits. Together these data suggest that PDENs offer natural therapeutic payloads to a modular loading capacity, and thus are potential therapeutic and diagnostic agents to oral therapeutics and gut-microbiome-modulation [4,5].

Translational PDENs have practical benefits over synthetic nanoparticles and mammalian EVs, including: (1) most source plants are edible and highly abundant, allowing cost-effective large-scale production; (2) PDENs have low immunogenicity and excellent gastrointestinal stability, allowing oral routes of delivery; and (3) the complex surface chemistry and lipid composition of PDENs have the potential to mediate cellular uptake and tissue targeting without excessive chemical modification. But not everything is easy - standardization of methods of isolation, heterogeneity of sources of plants, determination of biogenesis mechanisms in plants, cargo loading capacity, storage stability, and stringent safety and pharmacokinetic safety testing *in vivo*. The solution to these gaps is required to translate PDENs used in experimental systems into clinically useful natural drug delivery systems [6,7].

This review gives prevailing information on exosome-like vesicles produced by plants: their biogenesis and made-up, ways to isolate and load cargos, preclinical evidences about therapeutic delivery (oral and parenteral) and the significant technical and regulatory challenges that need to be overcome to allow clinical translation. It focuses on comparative advantages of PDENs, typical representatives of engineered PDEN formulations, and the priorities to be pursued in future studies to hasten the safe, reproducible, and effective application of plant-based vesicles in medication [7,8].

Biogenesis and characterization of plant-derived exosomes

Biogenesis Exosomes are nanosized extracellular vesicles (30150 nm) that are encircled in the multivesicular bodies and released into the extracellular domain. Endosomal sorting complexes that are necessary to facilitate transport (ESCRT)-dependent and independent pathways are involved in the biogenesis process and ensure selective incorporation of cargo [9]. Isolation Techniques popular for isolating proteins. In general, common methods of isolating proteins are: differential ultracentrifugation, density gradient centrifugation, ultrafiltration and size-exclusion chromatography. PDEs are also more concentrated with lipids that include phosphatidic acid and sterols that give it stability in the membrane and targeting capacity [10,11].

Therapeutic applications of plant-derived extracellular vesicles (PDEVs)

Recent studies on plant-derived extracellular vesicles (PDEVs) have demonstrated potential as a bio-nanocarrier in therapeutic delivery because of its inherent biocompatibility, oral stability, and natural source. Initial experiments showed that edible plant vesicles including ginger, grapefruit and grape could withstand

Table 1: Common Plant Sources and Cargo Types of PDEs.

Plant Source	Major Cargo Types	References
Ginger (*Zingiber officinale*)	Small RNAs (miRNAs), proteins (actin, tubulin), lipids (phosphatidic acid, phosphatidylethanolamine, phosphatidylcholine); bioactive metabolites such as gingerols and shogaols.	[12-14]
Grapefruit (*Citrus × paradisi*)	Proteins (heat shock proteins, membrane transporters), lipids (PC, PE), metabolites (naringenin, citric acid, sugars).	[15,16]
Tomato (*Solanum lycopersicum*)	Stress-response proteins (annexins, calmodulin), RNA species (mRNAs, miRNAs), membrane lipids.	[14,15]
Broccoli (*Brassica oleracea var. italica*)	Small RNAs, proteins, sulforaphane and other glucosinolates.	[16,17]
Apple (*Malus domestica*)	miRNAs, secondary metabolites (flavonoids, phenolic acids), membrane proteins.	[13,17]
Ginseng (*Panax ginseng*)	Proteins, phospholipids, triterpenoid saponins, small RNAs.	[3,17]
Sunflower/Olive (*Helianthus annuus*, *Olea europaea*)	Heat shock proteins, aquaporins, phospholipids, antioxidant metabolites (oleuropein).	[7,13]

the gastro intestinal digestive tract and deliver effective cargos to mammalian tissues, and regulate immune and metabolic responses [4,5]. An example of Ginger-derived PDEVs is selectively enriched in intestinal macrophage and epithelial cells and suppresses inflammation by inducing the Nrf2 pathway and inhibiting oxidative stress [5]. Nanovesicles derived using grapefruit have been demonstrated to target therapeutic agents such as curcumin and siRNA as well as chemotherapeutic drugs to the target tissues with little systemic toxicity [10,11]. These results point to PDEVs as natural, edible substitutes of synthetic nanocarriers to orally or parenterally administered drugs.

In addition to drug delivery, PDEVs have intrinsic biological functions that can be used to prevent and treat diseases. The antioxidative and anti-inflammatory actions of broccoli and lemon vesicles have been caused by their high level of plant miRNAs and bioactive metabolites, including sulforaphane and flavonoids [13,17]. Ginseng and *Aloe vera* PDEVs exhibit wound-healing, hepatoprotective, and neuroprotective activities that involve the regulation of cellular responses to stress and the expression of cytokines [3,11]. Also, there is a growing trend of evidence that plant vesicles are capable of interacting with the gut microbiota and inducing intestinal homeostasis and improving epithelial regeneration [4,7]. This type of multifunctionality (the combination of natural therapeutic constituents and vesicular delivery) makes PDEVs the optimal candidates to nutraceutical and pharmaco-botanical interventions.

New developments have expanded the use of PDEV to oncology, infectious disease and regenerative medicine. In cancer systems, vesicles derived out of grapefruit and ginger have been adapted to deliver anti-tumor drugs (e.g., doxorubicin, paclitaxel) and tumor-suppressive miRNAs, improving tumor targeting and reducing off-target toxicity [14,16]. PDEVs can also be used to deliver mRNA and siRNA, and so it is possible to gene-silence oncogenes and inflammatory mediators [15,16]. PDEV recipes are used in regenerative studies that stimulate the growth of dermal cells and angiogenesis, which increase wound healing [10]. Together, these results highlight the translational promise of PDEVs as a novel generation of natural and safe and multifunctional therapeutic nanocarriers which integrates biocompatibility with pharmacology.

Preclinical and clinical studies of plant-derived extracellular vesicles (PDEVs)

Pre-clinical investigations

There is preclinical evidence that PDEVs have potential as a therapeutic agent in a number of disease models. Exosome-like nanoparticles have been reported to be effective in the treatment

of inflammatory bowel disease and colitis-related cancer by decreasing pro-inflammatory cytokines like interleukin-6 and tumor necrosis factor-alpha [18]. Likewise, exosome-like nanoparticles made of grapefruit have also been investigated on the basis of their application in the treatment of osteoarthritis, as they have an effect on the inhibition of inflammation and the regeneration of the joints [19]. These articles emphasize the adaptability of PDEVs to treat various pathological conditions. Their natural source, and their capability to entrap a variety of bioactive molecules, put them in a vantage position whenever considering their use in future therapeutic interventions.

Clinical investigations

Although the preclinical data are encouraging, clinical trials of PDEVs are few. Nonetheless, their possible applications are becoming more interesting. Interestingly, an active registered clinical study is entitled Evaluation of Effects on Skin Quality of a *Centella asiatica* Extracellular Vesicle-based Skin Care Formulation (NCT06850935), and it is intended to determine the effect of plant-derived exosome-based formulations in skin care [20].

This trial is one of the major steps in bringing the therapeutic potential of PDEVs to clinical practice. Such studies will form important results that define the safety, efficacy, and regulation of PDEVs in human medicine.

Challenges and limitations of plant-derived extracellular vesicles (PDEVs)

Isolation and purification heterogeneity

One of the most critical challenges in PDEVs research is that there exists no single standardized method of isolating the PDEVs, and therefore the sizes, purity, and number of particles used in various studies vary. This lack of consistency makes it difficult to compare and repeat. Most of the existing methods, including ultracentrifugation, ultrafiltration, and precipitation, usually produce heterogeneous preparations, and it can influence the validity of the results of the experiments [7].

Scalability and production challenges

There is a major challenge of scaling up the production of PDEVs to therapeutic applications. Although plant-based systems have their benefits compared to mammalian cell cultures, their disadvantages are considered to be low yield and poor quality. These shortcomings make it difficult to move out of the laboratory research to clinical applications [21].

Immunogenicity and safety concerns

Despite the fact that the PDEVs are usually regarded as biocompatible, and less immunogenic than the mammalian-derived exosomes, the occurrence of plant-specific antigens or contaminants may trigger immune reactions. Also, there exists a possibility of transmitting pathogen sources, which is the safety concern that has to be carefully considered [22].

Regulatory and standardization issues

The use of PDEVs in clinical settings is limited because there are no standardized protocols for their production, characterization, and quality control. Without clear guidelines, it is difficult to ensure the safety, effectiveness, and consistency of PDEVs in therapy [10].

Limited clinical evidence

There are few clinical studies on PDEVs, despite encouraging preclinical data. The knowledge of their therapeutic potential and safety profile in clinical settings is restricted by the absence of extensive, carefully monitored human trials [23].

Conclusion

Exosomes derived from plants offer biocompatibility, stability, and therapeutic potential, making them a promising new frontier in natural drug delivery. PDEs are becoming a flexible platform for delivering medications, nucleic acids, and bioactive molecules, despite ongoing advancements in isolation, engineering, and characterization technologies. However, issues with standardization,

scalability, and regulation still exist. Targeted therapy and natural nanomedicine may be transformed by incorporating PDEs into pharmaceutical development. Looking ahead, advancing plant exosome research needs standardized methods for isolation and characterization to ensure reproducibility and safety. Using omics tools, nanotechnology, and bioengineering may help design custom PDEs that target more effectively and release in a controlled way. Exploring plant species diversity may uncover new exosomal components with unique therapeutic benefits. Additionally, working together with academia, industry, and regulatory agencies will be essential for turning laboratory findings into clinical-grade products. As interdisciplinary research continues, PDEs have great potential to transform targeted therapy, nutraceutical delivery, and natural nanomedicine.

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Conflict of Interest

The author(s) do not have any conflict of interest.

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