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Review Article

Harnessing Plant-derived Exosomes for Targeted Cancer Therapy: A Green Alternative in Drug Delivery

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Abstract

Plant-derived exosomes (PDEs) are natural extracellular vesicles that have better biological compatibility, low immunogenicity, and the capability to carry a variety of therapeutic agents which makes them promising therapeutics for various diseases, especially cancer. Several methodologies have been developed for the isolation of PDEs, including ultracentrifugation, immunoaffinity, size-based isolation, and precipitation, each with its advantages and limitations, which must be optimized for large-scale production. Due to PDEs' higher biocompatibility, stability, and broader capacity for encapsulation of bioactive compounds, they have been considered a safer alternative for cancer treatment compared to other types of exosomes. More specifically, surface engineering, membrane fusion, and genetic transformation can be performed on PDEs to enhance the efficiency of drug delivery, specific targeting, and capability of overcoming drug resistance. However, optimization challenges persist in large-scale production, drug loading efficiency, and safety and stability of the nanostructures. In addition to the lack of uniform protocols for their characterization, the intrinsic heterogeneity of PDEs further limits their clinical applications. Some clinical trials are in progress, though regulatory frameworks regarding PDEs as therapeutic agents are still in the process of development. Therefore, for the full impact of PDEs in cancer therapy to be realized, there is a need to overcome the low yields, heterogeneity, and poor drug-loading efficiency challenges. However, employing some strategies can increase the efficacy of drug therapy through genetic engineering, chemical modifications, and the development of multifunctional nanoplatform, continued research is expected to proliferate PDEs into wider fields of medicine.

Keywords: Drug delivery, Cancer therapy, Extracellular vesicles, PDEs, Theraputic Targets

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Introduction

Cancer is recognized as one of the leading causes of death in the world (1). According to the most recent data released by the International Agency for Research on Cancer (IARC), 19.96 million new cancer cases and 9.74 million cancer deaths were estimated worldwide in 2022, with demographic-based predictions indicating that the number of new cancer cases will exceed 35 million by 2050 (2). To combat cancer, traditional treatment methods (e.g., chemotherapy and radiotherapy) have been developed in clinical settings (3, 4). Although they have been effective and caused prolonged human life, they can lead to various side effects (e.g., cardio-, neuro-, gastro-, and nephrotoxicity) that further impact the patient's quality of life. Adverse effects of classical cancer treatments highlight the necessity for alternative treatments that not only target cancer cells but also reduce the side effects and further improve the cancer patient's quality of life (5). In this regard, researchers have investigated extracellular vesicles (EVs), a diverse group of cell-derived membranous structures that include microvesicles, exosomes, apoptotic bodies, and autosomes. EVs are released from different cells (e.g., blood cells, immune system cells, tumor cells, adult and embryonic stem cells) and found throughout various biological fluids (e.g., blood, urine, saliva, cerebrospinal fluid (CSF), breast milk, and seminal plasma) (6, 7). Functionally, they play a crucial role in intercellular communication, immunological regulation, coagulation, and disease etiology (8-15). Over the past years, exosomes, as a subpopulation of EVs, has gained interest, particularly in the field of cancer. Indeed, exosomes are used as cancer therapeutic tools in drug delivery due to their ability to deliver anti-cancer drugs straight to tumor cells, which increases their efficacy and decreases side effects compared to traditional chemotherapy methods (16-19).

Moreover, they can be modified to carry major histocompatibility complex (MHC) molecules and tumor antigens, making them suitable candidates for cancer vaccines (20, 21). Furthermore, exosomes can be derived from a variety of sources, such as animal products, body fluids, plants, bacteria, fungi, and parasites (22).

Over the past years, a particular class of exosomes called plant-derived exosomes (PDEs) has attracted interest for their potential to target biological substances. Furthermore, PDEs can address the issues regarding patient well-being and environmental impact with a non-toxic supply of anti-cancer drugs.

They have also demonstrated cancer-preventive action, with fewer side effects than conventional treatments. In addition, they can deliver bioactive molecules directly to cancer cells that inhibit growth and metastasis. In fact, PDEs are also considered a safer choice for cancer treatment because they are associated with fewer adverse effects. They are also more cost-effective and readily available, especially in resource-limited settings (23-25).

PDEs can therefore be used as a substitute for current medication delivery methods. However, despite their advantages, they have some disadvantages that will be discussed. In addition, the therapeutic applications of PDEs will also be investigated, which may further emphasize their potential in the treatment of cancer.

Biogenesis of PDEs

Plant-derived nanovesicle biological compounds are unique based on the original cell, which contain proteins, small RNAs, and metabolites. The biogenesis pathway of both plant-derived nanovesicles and exosomes is similar, as plant nanovesicles are linked to TETRASPANIN 8/TETRASPANIN 9 generated by multivesicular bodies (MVBs). In addition, Exocyst-positive organelle (EXPO), a double-membrane structure, is another pathway of exosome biogenesis. However, despite limited research on the biogenesis of plant-derived nanovesicles, evidence suggests at least three distinct pathways which are shown in Fig. 1(26-29). Endosomal-derived exosomes are confirmed by analyzing vesicles liberated by immune cells (e.g., B lymphocytes and dendritic cells) and are generated by the association of late endosomes with multivesicular bodies (MVBs), which are released in the extracellular milieu by exocytosis. The endosomal sorting complex required for transport (ESCRT) is composed of four complexes: ESCRT-0, -I, -II, and -III, which have fused proteins like VSP4, VAT1, ATPase, and TSG101. The formation of EXO through an ESCRT-independent mechanism has been documented, implicating ceramide biosynthesis in this process. (26, 30-33).

Isolation, purification, and characterization of PDEs from plants and fruits

Isolation and purification

PDEs can be excreted from different parts of plants, such as seeds, roots, stems, fruits, and leaves (36). Usually, the isolation techniques for extracting and purifying PDEs consist of homogenization of plant tissues, centrifugation, and filtration processes (37). The isolation of PDEs, particularly, involves various techniques, including centrifugal ultrafiltration (UF), size exclusion chromatography (SEC), differential ultracentrifugation (DUC), gradient ultracentrifugation (GUC), polymer-based precipitation, and immunoaffinity techniques (Table 1) (26, 37).

Physicochemical characterization

PDE's particle size ranges from 10 to 1000 nm and shares physicochemical characteristics with animal-derived exosomes. When observed under electron microscopy, they have a saucer- or cup-shaped morphology, despite variations due to fixation, dehydration, and staining procedures. Moreover, particle sizes and potentials vary depending on the plant source of PDEs. Exosomes of wheat and ginger origin range in size from 40 to 100 nm, while those of grapefruit and ginger origin average 250 nm.

PDEs usually have a negative surface charge, which means they do not aggregate and are mutually exclusive. Moreover, the protein portions of the PDEs consist of transmembrane and other lipid membrane proteins, while phospholipids and glycerol make up the lipid composition. Furthermore, exogenous mRNAs and non-coding miRNAs control intracellular RNA and protein levels as well as affect gene expression and structural roles after they enter recipient cells. Additionally, it has been shown that PDEs' physicochemical properties stay stable in vitro tests that mimic the gastrointestinal route, which means that they could be given through oral drug delivery systems (81-84).

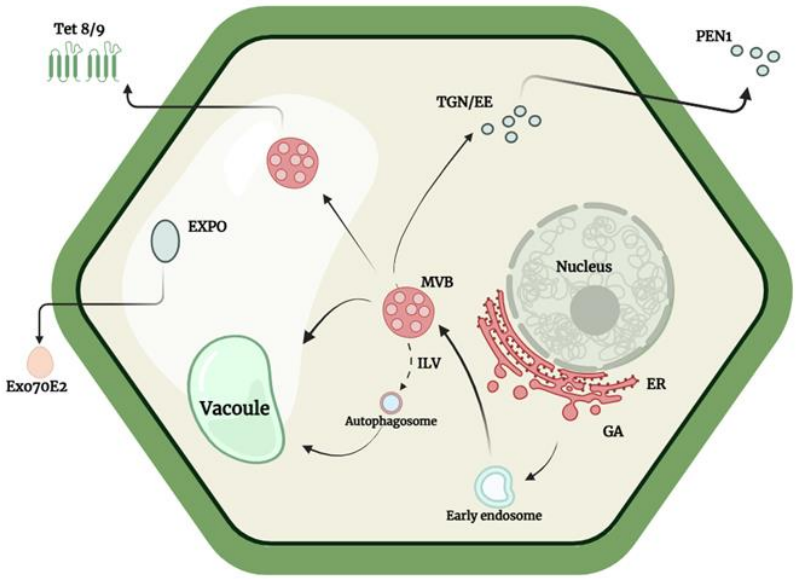

Figure 1. Different Biogenesis pathways of plant-derived nanovesicles. The intraluminal vesicles (ILV)s are generated when the early endosomes integrate with the surrounding membrane layer. They encapsulate exosomes within the multivesicular bodies (MVBs), which subsequently fuse with the plasma membrane and release the contents into the extracellular space. PDEs associated with tetraspanin 8/tetraspanin 9 (TET8/TET9) are secreted from MVBs. Some PDEs are formed by association of penetration 1 (PEN1). Another subpopulation of PDVs is derived from exocyst-positive organelles (EXPO) (26, 34, 35)(Abbreviation: ER, Endoplasmic Reticulum; EXPO, Exocyst-Positive Organelles; GA, Golgi Apparatus; ILV, Intraluminal Vesicles; MVBs, Multivesicular Bodies; PEN1, Penetration1; TGN/EE, Trans-Golgi Network/Early Endosome; TET8/TET9, tetraspanin 8/tetraspanin 9.)

Biochemical characteristics

PDEs contain a wide range of biomolecules, including lipids, nucleic acids, and proteins which share similarities with exosomes-derived animals. However, both have different biological functions, which makes it easier to find active ingredients and their roles. The primary constituents of PDEs are lipids, which can be categorized into glycerolipids and phospholipids. Exosomes generated from animals are abundant in cholesterol and sphingolipids, whereas PDEs are plentiful in phospholipids and plant lipids. Phosphatidic acid is the principal compound implicated in mitosis in plants and can stimulate vesicle fusion. Other plant-derived lipids in PDEs may be essential for interspecies signaling. Lipids possess biological functions, including the inhibition of Porphyromonas gingivalis monocyte proliferation. The lipid composition in exosome-like nanovesicles from various plant sources differs, exhibiting varying ratios of K-derived exosomes to phosphatidic acid (83, 85-89).

Safety and toxicological studies

Exosomes have attracted attention as a means of intercellular communication because of their biocompatibility and natural source. Still, safety issues have restricted its widespread application in medical aspects.

Before their application in practical settings, PDEs must be thoroughly safety-evaluated. Research indicates that PDEs can regulate biological processes like proliferation, differentiation, and apoptosis; hence they are rather vital for treating diseases and healing injured tissues. From medicinal plants, exosomes were separated and their therapeutic impacts on triple-negative breast cancer as well as possible underlying molecular pathways were investigated. Moreover, the findings of a series of animal tests clearly showed that these therapeutic PDEs have great biological safety in vivo and do not cause appreciable toxicity on important organs. Thus, the findings offer significant safety data for the application of medicinal plant exosomes in the field of cancer treatment (90). They also provide a safer option than exosomes generated from mammals due to their low toxicity and immunogenicity. They exhibit biocompatibility, which makes them suitable for drug delivery systems and medical applications. In vitro tests of murine models' liver, spleen, and renal tissues have revealed no harm. PDEs also have antioxidant properties that protect against oxidative stress-generated damage. E.g., Exocomplex®—a mix of PDEs—restored redox equilibrium in mice exposed to hydrogen peroxide and lowered oxidative stress indicators free from any recorded harm. PDEs are considered safe and beneficial for therapeutic uses with few negative side effects because of their anti-inflammatory and anti-cancer properties (23, 34, 81, 91-99). PDEs have shown antioxidant and anti-inflammatory properties which reveals their protective potential against various diseases without causing toxicity (81). For instance, Beta vulgaris-derived exosomes have been shown to alleviate doxorubicin-induced cardiotoxicity without adverse effects (92). Moreover, exosomes derived from Asparagus cochinchinensis showed significant antitumor activity without side effects in a hepatoma carcinoma model (100). Though PDEs have complex architecture and many applications, further study is needed to address safety issues using them.

Therapeutic applications

Because of the unique advantages compared to synthetic or animal-derived exosomes, PDEs are becoming a very promising tool in therapy. One of the major benefits taken by PDEs includes the ability to avoid toxicity related to synthetic or animal-derived exosomes due to their plant origin(81, 101, 102). They have shown significant potential in various therapeutic applications because of their special characteristics and possible benefits over traditional methods (23, 24, 103, 104). A significant reason for the growing interest in PDEs is because of their low toxicity, great biocompatibility, and less immunogenicity which makes them appropriate for therapeutic usage (23, 37). Being produced on large scales, PDEs also prove suitable for widespread therapeutic use. They can serve effectively in the delivery of many therapeutic agents such as bioactive molecules, including small interfering RNAs, into the target cells (105). Their targeted delivery reduces systemic toxicity and enhances therapeutic efficacy. Besides, PDEs have attributes that enhance the penetration and retention of therapeutic agents in tissues, cell cycle arrest, induction of apoptotic pathways, and antimetastatic properties inhibiting the growth and spread of cancer

cells (23, 37). However, several clinical trials are currently underway to evaluate the efficacy of PDEs and solve the challenges in cancer therapy (106, 107).

Beyond cancer treatment, PDEs are also applied in the delivery of anti-inflammatory agents to gut epithelium cells and the reprogramming of gut microbiota, thus playing an important role in the treatment of cancer and other diseases (5, 108). For instance, citrus limon-derived nanovesicles efficiently deliver antioxidant and anti-inflammatory agents to human cells. Therefore, it has the potential to modulate gut microbiota and bile acid resistance, supporting IBD treatment (109). Methotrexate from grapefruit-derived nanovesicles can be incorporated directly into intestinal cells for ease of administration in colitis (110). Also, the bitter melon EVs can work synergistically alongside a chemotherapy drug to reduce tumor size and inflammation in a mouse model of oral cancer. Ginseng-derived EVs can also alter macrophage polarization; therefore, they are beneficial for therapies against brain cancer. Moreover, ginger-derived EVs can inhibit pro-inflammatory cytokines are and thus be effective in combating colitis-associated cancer. As another example, tea leaf- and flower-derived EVs, by generating of reactive oxygen species and modulation of microbiota, can mitigate colon tumors and breast cancer metastasis(5). Grape exosome-like nanoparticles also deliver therapeutic agents to intestinal stem cells and promote mucosal regeneration (111). However, the therapeutic potential of PDEs is thus proved to be even above and beyond inflammation and cancer treatment. Nanovesicles have even shown promise, such as of tea flowers and edelweiss, as potential carriers of selective delivery to targeted cancer cells and antioxidants for skin rejuvenation (112, 113). Accordingly, it can be dedicated that PDEs can deliver therapeutic agents with high efficiency, low toxicity, and minimal immune response, which can make them an ideal candidate for the treatment of various disease. Also, they may even enhance the treatment strategies while paving the way for safer and more effective therapies in the future (114).

PDEs as novel drug carriers in delivery systems for cancer treatment

Comparison of exosome sources and functions

Different types of exosomes have specific biological characteristics and functional capacities due to different derived sources. For instance, PDEs might facilitate signaling, transport biomolecules, and have different anti-inflammatory, antioxidative, and anti-tumorigenic effects (115). On the other hand, mammalian-derived exosomes are important for immune modulation, tumor progression, and cellular homeostasis because they contain proteins, lipids, and RNAs that have effects on the behavior of recipient cells (116-119). Moreover, engineered or synthetic exosomes are designed for drug targeting to enhance efficacy while reducing side effects (120, 121). In addition, milk-derived exosomes also attracted considerable interest due to their beneficial health impact especially on neonates as nutrition and for immunity (122, 123) Additionally, bacterial-derived exosomes are also essential in the formation of biofilms and antibiotic resistance and possession of phage toxins, as

Table 1. Exosomes isolation methods. (**Abbreviations:** DUC, differential ultracentrifugation; GUC, gradient Ultracentrifugation; SEC, size exclusion chromatography; UF, centrifugal ultrafiltration)

Isolation method	Principle	Advantages	Disadvantages	Ref.
UF	Utilizes exosomes' physical properties like size and density. Uses centrifugal force to drive sample through pore-sized filter. Retains exosomes while allowing smaller molecules and debris. Can be combined with density gradient centrifugation for enhanced purity and yield.	High Purity and Yield Time Efficiency Scalability Convenience	Potential for Contamination Membrane Fouling Limited by Sample Type Initial Setup Cost	(38-41)
SEC	Separates molecules based on size. Utilizes porous bead column for liquid phase flow. Large molecules elute quickly, and smaller molecules elute slowly. Ideal for isolating exosomes with a 30-150 nm size range.	High purity Non-damaging Compatible with physiological conditions Scalable Reproducible	Low yield labor-intensive complex standardization limited capacity	(42-52)
DUC	Separates molecules based on size and density. Sequential centrifugation steps. Removes cells, debris, larger vesicles. Pellets exosomes.	Cost-Effective Widely Used High Purity	Time-Consuming Low Yield Contamination Equipment Requirement	(53-60)

GUC	Layering sample over density gradient medium. Subsequently subjecting to high-speed centrifugation. Exosomes migrate through gradient, and settle at density match. Allows separation from cellular debris and particles.	High Purity Reproducibility Preservation of Exosome Integrity	Time-Consuming Complexity Low Yield	(55, 61-63)
Polymer-based precipitation	Isolates exosomes by reducing solubility. Involves adding polymer solution, incubating, and centrifuging. Allows exosomes to aggregate.	Cost-effective High Yield Convenience Efficiency Enhanced Biological Activity	Purity Issues Size Distribution Contaminating Debris Optimization Required	(64-72)
Immunoaffinity techniques	Utilizes antibodies or affinity ligands. Binds to surface proteins on exosomes. Uses magnetic beads or solid supports coated with ligands.	High Specificity High Throughput Preservation of Exosome Integrity Compatibility with Downstream Analysis	High cost Limited by Antibody Availability Potential for Non-Specific Binding Scalability Issues	(73-80)

well as for transporting cargoes (124). Furthermore, fungal-derived exosomes are gaining recognition for their contributions in host-pathogen interaction and may harbor immunogenic components (125, 126). Finally, parasite-derived exosomes have been correlated with the evasion of the host's immune response favoring parasitic survival (Table 2.) (127).

PDEs in drug delivery systems

PDEs have gained attention in the last decade as carriers in drug delivery due to their biocompatibility, stability, and capability of encapsulating a variety of biomolecules (150). They share all the advantageous features of exosomes derived from mammalian cells but present some unique advantages, such as low immunogenicity and capability to encapsulate a wider range of bioactive compounds(151-153). The biogenesis of plant exosomes resembles mechanisms described for mammalian cells, such as multivesicular

body formation followed by the fusion of these bodies with the plasma membrane (152, 154, 155).

An important factor that influences the functionality of PDEs is their heterogeneous composition. Their heterogeneity PDEs is due to the identity of the parent cell and growth conditions and modulates functional properties. For instance, exosomes isolated from Moringa oleifera have been demonstrated to possess antioxidant activity and hence can be employed for the delivery of antioxidants against oxidative stress-related diseases (114, 156).

Regarding drug delivery, PDEs have been studied for drug delivery applications delivering small molecules, proteins, and nucleic acids. For instance, exosome-like nanovesicles derived from ginger enhance the internalization of bioactive compounds such as 6-shogaol toward active delivery in cancer therapy. In addition, ginseng-derived exosome-like nanovesicles cross the blood-brain barrier to deliver therapeutic agents into gliomas. Besides, it can target macrophage polarization associated with tumors into an anti-tumorigenic state within the tumor microenvironment. Nanovesicles derived from lemon can reach the tumor sites turn on the tumor-suppressing pathways and reduce the process of angiogenesis. Moreover, they increased the efficacy of chemotherapy when conjoined with targeting molecules such as folic acid (153, 157, 158).

Based on the success of PDEs, Plant-derived exosome-like nanoparticles (PELNs) have also emerged as great candidates. PELNs and PDEs do possess several features, making them stand out in different ways; yet, both structures still share some features: biocompatibility, stability, and encapsulation of bioactive compounds. This overlap suggests that they can both utilized in drug delivery and therapy but may offer distinct advantages depending on their intended use (36). Functionally, the PELNs have excellent encapsulation and delivery properties. They can encapsulate and deliver bioactive molecules such as proteins, RNA, DNA, or chemotherapeutics by either a passive or active loading method. In passive loading, the dependence is on the diffusing of the molecules into vesicles, whereas active loading morphologically alters vesicles to favor the encapsulation process. PELNVs have shown drug delivery effectiveness in various studies. For instance, nanovesicles derived from grapefruit showed anti-tumor effects, while nanovesicles from ginger delivered anti-tumor agents into colon cancer cells. PELNs stabilize these compounds with improved therapeutic and antioxidative properties that may enhance the effectiveness of drug delivery and reduce undesirable side effects in cancer treatment (159).

The unique features of PELNs and PDEs make them excellent carriers for modern therapies such as chemotherapy, RNA-based treatments, and small-molecule drugs. By using them, drugs can be protected and accurately delivered to the targeted sites in the body and avoid degradation in the body, which should enhance personalized medicine and treatment effectiveness (158).

Modification and transformation of PDEs

Clinical applications of EVs face various challenges such as poor loading efficiencies, rapid clearance from the circulation, and limited scalability. Similarly, as PELN surface is enriched with special plant proteins and

lipids which partly limits their internal space and load capacity. The limited targeting ability and small loading capacity of PELNs reduce their efficiency. Therefore, to use their maximum therapeutic effect, modifications such as surface engineering, membrane fusion, bionic nanotechnology, and synthetic liposome integration may be helpful (159, 160). For instance, to improve EV targeting, researchers decorated the membranes of EVs with polyethylene glycol (PEG)-conjugated ligands. The nanobodies specific for epidermal growth factor receptor (EGFR) were coupled to the PEG-phospholipid derivatives, yielding nanobody-PEG-micelles that could be incorporated into EV membranes through a temperature-dependent "post-insertion" mechanism. Modifying EVs with PEG did not affect the morphology and composition of EVs but significantly improved their EGFR-specific binding and prolonged the circulation time in mice from 10 to well over 60 minutes (161). Similarly, polymer-drug conjugates can be chemically engineered to have a mixture of hydrophilic and hydrophobic blocks for improving drug loading efficiency as well as drug release profiles (162). For instance, the conjugation of hydrophobic anticancer drugs, such as doxorubicin, to hydrophilic polymers has improved solubility and reduced off-target effects. Careful selection of the chemical composition and architecture allows fine-tuning of properties toward superior therapeutic outcomes (163).

Another essential element in any efficient cancer treatment is targeting specificity. In this regard, surface functionalization can be helpful. Functionalization of the PDE surface with appropriate ligands or antibodies that recognize tumor-specific markers will result in improvement in their targeting efficiency (164). Chemical coupling techniques involve the binding of peptides, proteins, or compounds to vesicle membranes, enhancing targeting and stability without affecting the integrity of vesicles (159). Most notably, the inclusion of folic acid, which binds to folate receptors overexpressed on many cancer cells, has been studied as a strategy to enhance tumor targeting. The binding of folic acid can provide specific targeting of colon receptor cells with reduced drug decomposition in non-target areas, thus increasing the effectiveness of the treatment (159, 165).

Re-engineered plant-derived nano vectors have demonstrated increased safety and precision in drug delivery. For instance, ginger-derived exosomes effectively deliver Doxorubicin to colon tumor cells and have shown high internalization efficiency and tumor growth inhibition. They also reduce oxidative stress, suppress pro-inflammatory cytokines, and release Doxorubicin in response to the acidic tumor microenvironment, thereby minimizing side effects. In the large-scale production process, they will also be safe, biocompatible, and cost-effective, outperforming synthetic liposomes in biocompatibility, apoptosis induction, and pH-responsive drug release. Exosomes derived from grapefruit deliver folic acid and paclitaxel in colon cancer, whereas modified grape-derived exosomes with surface coatings have enhanced targeting and efficacy against colon and breast cancers. Hence, PDEs are of promising therapeutic interest due to their anti-cancerous properties, although much future research is still needed, especially on the miRNA of PDEs (166).

Beyond chemical modifications, there are some novel ways of enhancing the functionality of exosomes through genetic and biophysical transformations. Exosomes with specified characteristics, such as increased drug loading capability or intrinsic therapeutic effects, can be generated by genetic engineering in the source plants. For instance, genetic engineering in exosomes to express tumor-suppressing microRNAs within their exosomes is a way of offering a dual-modality of drug delivery and gene therapy (159, 167).

Biophysical techniques, such as sonication, extrusion, or electroporation, are also implemented to change the structure and composition of exosomes which can enhance the encapsulation efficiency of therapeutic agents, and change the size and surface charge of exosomes, thereby favoring cellular uptake. Regarding this, synthetic liposomes extend the internal space of PELNVs by using techniques such as extrusion and electroporation, which allow higher drug loading while maintaining their biological properties. when preparing polymer-drug conjugates, the molecular weight and branching of polymers are usually changed to control drug release kinetics (159, 168, 169).

However, drug resistance from cancer cells to standard therapies remains one of the major challenges that often obstruct the way to effective treatment. Modified PDEs may successfully override this barrier with new strategies of drug delivery. For instance, surface-engineered exosomes can deliver siRNA or miRNA that are capable of silencing genes associated with drug resistance in cancer cells (170).

Nonetheless, the modification of PDEs is not without its challenges. Most of the procedures cannot easily be scaled up because of the lack of standardized isolation methods (171). Furthermore, the long-term safety and the aspect of immunogenicity of carriers need to be examined with great care. The optimal balance between stability and kinetics of drug release remains complex to achieve (172). Therefore, more studies are needed regarding polymer-drug conjugates. Besides, advanced modification strategies developed for other EVs may be adapted to PDEs to enhance their therapeutic functionality. Thus, despite all the challenges, the therapeutic application of modified PDEs can be very significant. Advanced approaches in chemical modification, genetic engineering, and biophysical methods can be integrated to reform PDE as highly effective and targeted drug carriers. Strategic developments in surface functionalization, chemical engineering, and biophysical modifications will help PDEs overcome traditional limitations of therapies and offer safer, more precise, and more effective treatments to cancer patients (173).

Clinical trials

Heretofore, few clinical trials have been launched to explore the anti-tumor properties of PDEs, despite growing enthusiasm. The first study used grape-derived exosomes and looked into how well they could heal oral mucositis in head and neck cancer patients who were getting chemotherapy and radiation at the same time. It was a randomized, parallel-assigned intervention study that first measured pain levels associated with oral mucositis, which were assessed weekly during treatment and six months after completion of therapy. As a second goal, it compared the levels of

immune biomarkers in blood and mucosal tissue between the beginning of the study and when the radiation therapy was over (174). The other study used PDEs in delivering curcumin (the active ingredient in turmeric, which has shown that it can stop colon cancer from starting and stop the growth of colon cancer cell lines (175)) to colon cancer patients. It divided participants into three distinct groups. The first group received curcumin alone, the second group received curcumin conjugated with plant EVs, and the third group did not receive any treatment, serving as a control group. Seven days after they signed up, the participants were tested to see how much curcumin was in normal and cancerous tissue, how safe and well the treatments were tolerated, and how they affected colon cells, including how the immune system responded and how the cells used energy (176). Furthermore, more PDE-based clinical trials are needed to gain more knowledge for better cancer therapeutic solutions.

Conclusion

PDEs, known as drug-delivery tools, have gained increasing attention due to their biological compatibility and their ability to carry a variety of medications (24). They provide a sustainable and healthy source for treatments that resolve both patient well-being and environmental issues (177). Advanced engineering techniques could refine their targeting mechanisms to allow much more precise delivery to specific cells. Notably, the efficacy of PDEs multiplies when they are loaded with drugs in nanoparticles and can target delivery to diseased cells. One of the examples can be the techniques that consist of attaching monoclonal antibodies to the exosomes which will enable the exosomes to be more specific (23, 24). With these developments, the direction of future studies will be more toward multifunctional platforms that can serve a wide range of therapeutic purposes. In fact, such platforms are supposed to offer a variety of treatments, ranging from photothermal therapy to gene therapy and chemotherapy. Moreover, PDEs are important in biological functions such as immunological defense, cell communication, and gene regulation (178). Beyond cellular communication, they provide an adaptable platform for diverse applications in functional nutrition and medical treatment and as carriers of pharmaceuticals (179, 180). The properties of PDEs such as natural origin, biocompatibility, and medicinal potential, have attracted the attention of researchers and scientists (181).

One of the most important applications of PDEs is in the targeted therapy of cancer. The capacity to deliver a variety of drugs is an efficient approach for precision medicine, and their biocompatibility reduces the possibility of immune reactions. The potential for therapy is further supported by their anti-tumor activities, presumably attributed to the specific biomolecular load. PDE solves a major limitation of mammalian exosomes by providing a plentiful and renewable source for large-scale synthesis (23, 34, 181).

While developments are promising, significant challenges remain in research on PDEs. The lack of standardized protocols for their characterization and classification, inherent heterogeneity, and limitations in current isolation techniques are some of the obstacles (23, 34). Overcoming these challenges will require further optimization

of the extraction methodologies, more understanding of the molecular mechanisms behind the anti-tumor action of PDEs, and extensive in vivo studies to assess their efficacy. Additionally, communication between researchers and healthcare professionals is essential to increase the potential of plant-derived exosomes as a cancer treatment. In this regard, to ensure PDEs' successful translation into medical practice, establishing standardized regulatory frameworks and clinical testing protocols will also be important (182, 183).

Drug transportation remains one of the primary functions of PDEs. New approaches for improving PDEs' drug delivery capabilities were actively explored in research studies. The approaches would include loading PDEs with therapeutic compounds, enhancing their stability, and targeting effectiveness (184). Additionally, plenty of patents have been granted for novel uses of PDEs in modern pharmaceuticals (185). PDEs offer cost-effective solutions for large-scale production, as plant materials are easy to acquire and their procedures for extraction are simple. The inherent stability and low side effects of PDEs make them a promising alternative to traditional exosomes thus making them cost-effective in therapeutic applications. Besides their biomedical applications, PDEs have also harnessed their potential for regenerative therapies and drug delivery systems. However, significant challenges remain, including the lack of a well-defined regulatory framework, unstandardized methods for isolating and characterizing PDEs, and the difficulty of achieving the most cost-effective large-scale production (52, 114, 186).

Notably, recent investigations have revealed new therapeutic possibilities for PDEs. For instance, the inhibitory effects of plant-derived exosomal microRNAs on lung inflammation induced by SARS-CoV-2 Nsp12-containing exosomes have been investigated by a project (187-189). PDEs also can have an essential role in treating multiple sclerosis (190). Moreover, PDEs are increasingly used in gene therapy by offering a novel approach to delivering genetic material to target cells (191). On the other hand, using the exosome process to stop the growth of mammary cells and induce apoptosis in cows has been the focus of another group of studies (192). Their findings may potentially be applied in human treatments in the future. In cancer research, PDEs have garnered particular interest, especially for pancreatic cancer and triple-negative breast cancer (184, 190, 193). Overall, exosomes have great potential for the treatment of various illnesses (190).

Conflict of interest

The authors have no conflict of interest to declare.

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