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REVIEW

Stability Challenges and Engineering Strategies of Plant-Derived Extracellular Vesicle-Like Particles: A Translational Perspective

Hengyi Li[1,*], Yuxiang Yan[1,2,*], Meifang Lin[1,2,*], Shijie Wang[1], Yating Su[1,2], Jinhan Guo[1,2], Youguang Lu[1,2], Xiaohang Chen[1,2], Dali Zheng[1]

[1]Fujian Key Laboratory of Oral Diseases, School and Hospital of Stomatology, Fujian Medical University, Fuzhou, People's Republic of China; [2]Department of Preventive Dentistry, School and Hospital of Stomatology, Fujian Medical University, Fuzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dali Zheng; Xiaohang Chen, Email dalizheng@fjmu.edu.cn; kqyx__cxh@163.com

Abstract: Plant-derived extracellular vesicle-like particles (PD-EVLPs), composed of a phospholipid bilayer enriched with lipids, proteins, metabolites, and RNA, have emerged as promising therapeutic agents with intrinsic bioactivity (eg, anti-inflammatory and wound healing activities) as well as biocompatible nanocarriers. However, before their clinical translation, a key challenge lies in ensuring their stability in biological environments and achieving effective accumulation at disease sites. On one hand, the lack of standardized isolation protocols and preservation strategies where non-standardized methods compromise yield-purity balance, freeze-thaw cycles induce lipid rearrangements that lead to vesicle fusion, and lyophilization-induced ice crystals disrupt membrane integrity, poses a significant barrier to maintaining the dispersity, structural integrity, and purity of PD-EVLPs affecting their ex vivo stability. On the other hand, extreme conditions in gastric and intestinal fluids during administration can easily cause PD-EVLPs to degrade and their content to leak, while in vivo circulation necessitates avoiding rapid immune clearance in order to accumulate at target sites, further challenging their stability and bioavailability. In this review, we comprehensively evaluate the entire PD-EVLPs pipeline from preparation to application, dissecting potential stability concerns at each stage, including isolation, storage conditions, structural composition, and administration routes. We also explore the contribution of engineering strategies to enhancing PD-EVLPs stability while considering potential risks associated with these modifications. By establishing a comprehensive framework, we aim to provide concrete guidance for standardizing PD-EVLPs preparation protocols and designing preclinical studies, thereby streamlining their translation from bench to bedside.

Plain Language Summary:

(1) From standardized isolation to preservation: Analyzing the impact of PD-EVLPs' preparation and storage on their stability, paving the way for industrial-scale production.
(2) Decoding structure and composition: Unveiling how the lipid bilayer structure and components of PD-EVLPs influence their stability, ensuring their efficacy in drug delivery.
(3) Engineering modifications and biomimicry: Exploring strategies to overcome the intrinsic stability limitations of PD-EVLPs and enhance their functionality for in vivo applications.

Keywords: plant-derived extracellular vesicle-like particles, stability, engineered modification, isolation, administration

Introduction

Plant-derived extracellular vesicle-like particles (PD-EVLPs) are natural nanovesicles obtained from various plant sources.[1] Terminology used to describe these vesicles has varied considerably, including nanovesicles, extracellular vesicles, exosome-like nanoparticles, and vesicle-like structures.[2] According to an up-to-date consensus[3] and for the sake

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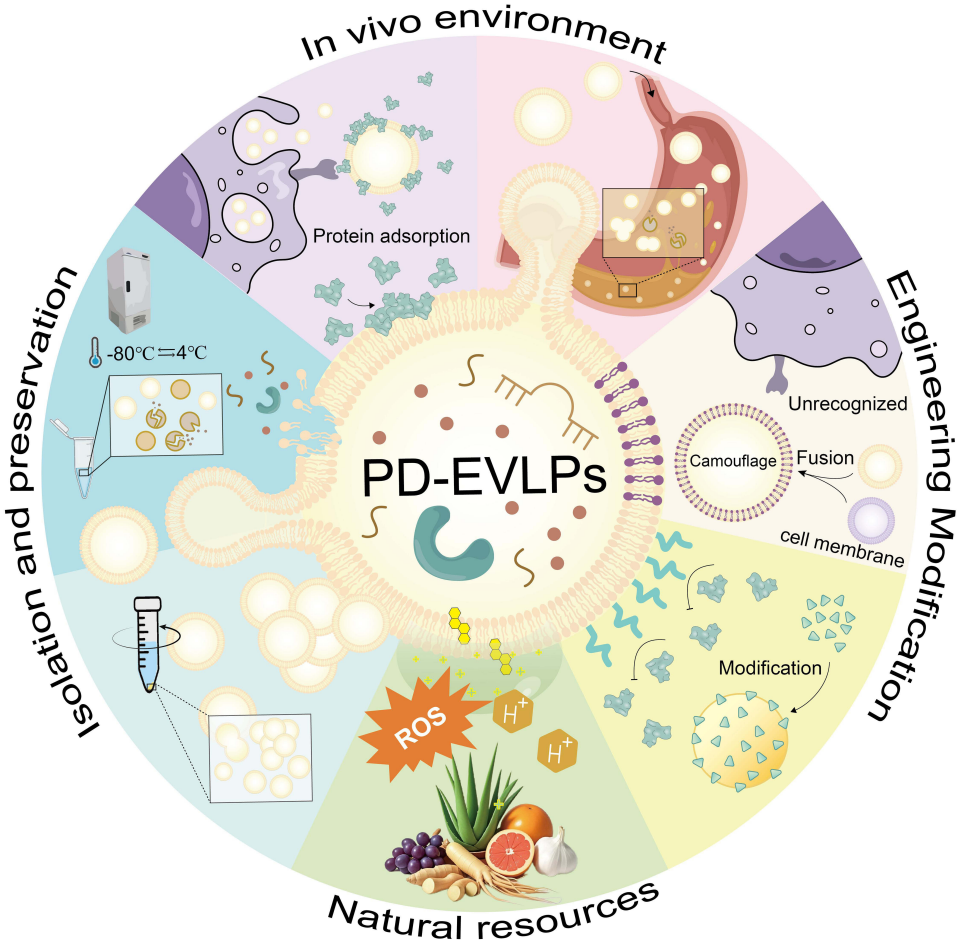
Graphical Abstract



of clarity and consistency, this review employs "PD-EVLPs" specifically to refer to vesicles isolated by plant tissue disruption, while those obtained via cell culture or vacuum extraction from plant organs are referred to as plant-derived extracellular vesicles (PDEVs).[2]

PD-EVLPs possess distinctive structural and biochemical characteristics, including a lipid bilayer encapsulating diverse bioactive molecules, such as lipids, proteins, metabolites, and nucleic acids[4,5] (Figure 1). Their intricate phospholipid bilayer structure confers superior biocompatibility and in vivo stability, while the encapsulated natural bioactive constituents provide therapeutic potential.[6] Collectively, these attributes render PD-EVLPs highly promising for biomedical applications, owing to their sustainability and cost-effectiveness as renewable resources derived from edible and medicinal plants,[7] efficient drug delivery capabilities resulting from enhanced cellular uptake,[8] intrinsic bioactivity,[4,9,10] and minimal immunogenicity risks compared to animal-derived extracellular vesicles.[11]

Despite these advantages, the stability of PD-EVLPs remains a significant yet underexplored challenge that could limit their translational potential. Studies have revealed variability in stability profiles, including aggregation tendencies,[12,13] size heterogeneity, and immune responses upon administration. For instance, tea flower-derived PD-EVLPs administered intravenously in mice elevated blood C3 complement levels, suggesting immunogenicity risks.[14] Conversely, PD-EVLPs enriched with phytosterols and polyphenols exhibit enhanced stability,[12] indicating that their composition plays a critical role in maintaining stability.

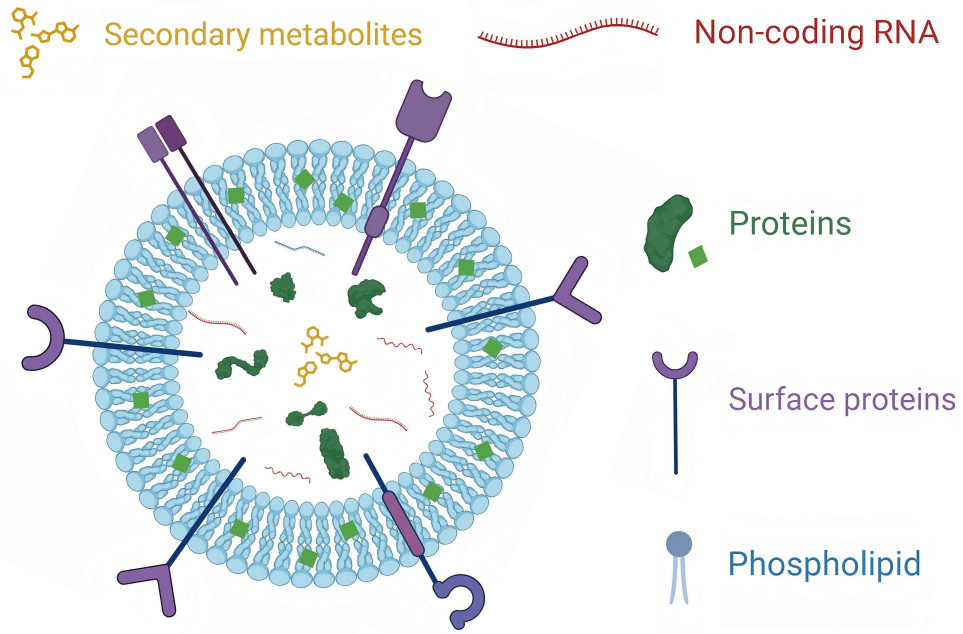


Figure 1 The distinctive structural and biochemical characteristics of PD-EVLPs. Reprinted from Langellotto MD, Rassu G, Serri C, et al. Plant-derived extracellular vesicles: a synergetic combination of a drug delivery system and a source of natural bioactive compounds. Drug Delivery Transl Res. 2025;15(3):831–845.[5]

Given these complexities, thoroughly assessing the stability of PD-EVLPs is imperative for successful clinical application. Stability variations may arise from numerous factors, including isolation methods,[12,15] storage conditions,[16] source plant variability,[17] and administration routes.[14] Therefore, this review thoroughly examines the critical factors influencing PD-EVLPs stability. Specifically, we assess current isolation and preservation techniques, investigate the molecular mechanisms underlying stability differences, examine the impact of administration routes, and explore engineering modifications to enhance PD-EVLPs stability. Through this comprehensive approach, the review aims to identify key challenges and propose strategies to optimize PD-EVLPs stability, thereby advancing their integration into biomedical research and facilitating their translational effectiveness.

Threats to PD-EVLPs Stability Posed by Isolation and Storage Conditions

The stability of PD-EVLPs is largely influenced by their isolation and storage conditions. Variations in the isolation methods, storage conditions, and media employed across different studies substantially limit the comparability and in-depth investigation of PD-EVLPs stability (Figure 2a–c and Table 1). Therefore, the establishment of standardized protocols is of great significance.

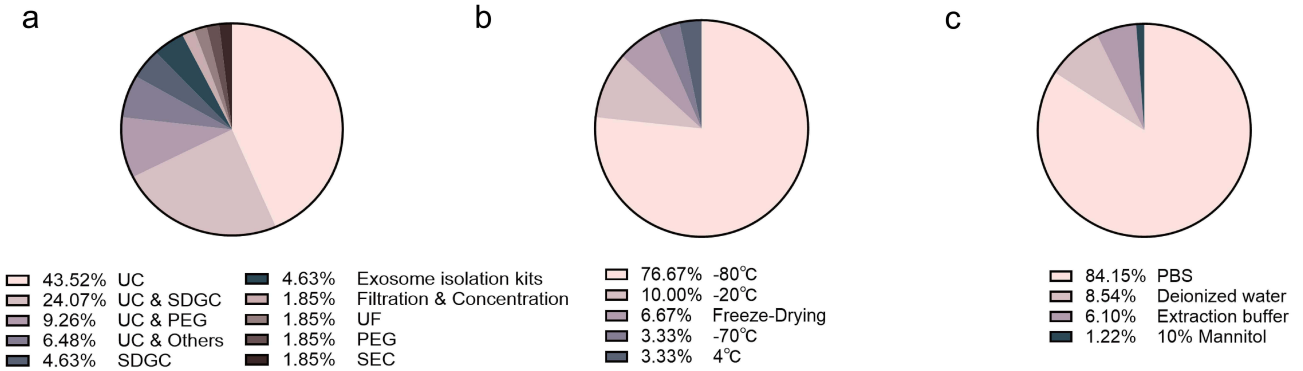


Figure 2 Isolation methods and storage methods of PD-EVLPs. (**a**) Proportion of PD-EVLPs isolation methods. (**b**) Proportion of different storage conditions for PD-EVLPs. (**c**) Proportion of various storage media used for PD-EVLPs preservation.

Abbreviations: UC, Ultracentrifugation; PEG, Polyethylene Glycol; UF, Ultrafiltration; SDGC, Sucrose Density Gradient Centrifugation; SEC, Size-Exclusion Chromatography.

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Table 1 The Isolation and Preservation of PD-EVLPs

Resource	Isolation Method	Storage Temperature	Storage Solvent	Reference
Broccoli	UC & SEC	−80 °C	PBS	[18]
	Exosome isolation kits	−80 °C	PBS	[19]
	UC	−80 °C	10% Mannitol	[20]
Tomato	UC	−80 °C	PBS	[21]
	UC	−80 °C	PBS	[22]
	UC	−80 °C	PBS	[23]
	UC	−20 °C	PBS	[24]
	UC & SEC	N.R	Extraction buffer	[25]
	UC & PEG	−80 °C	N.R	[26]
Piccadilly variety tomato	UC	N.R	Extraction buffer	[27]
Grapefruit	UC	−80 °C	PBS	[28]
	UC & SDGC	N.R	N.R	[8]
	UC & SDGC	N.R	N.R	[29]
	UC & SDGC	N.R	N.R	[30]
	PEG	N.R	N.R	[31]
Grape/Grapefruit/Ginger/Carrot	UC & SDGC	N.R	N.R	[32]
Lemon	UC	N.R	PBS	[33]
	UC	N.R	PBS	[34]
	UC & SDGC	N.R	N.R	[35]
	UC & SDGC	N.R	PBS	[36]
	PEG	−80 °C	Extraction buffer	[26]
	SDGC	N.R	PBS	[37]
	UC with 30% Sucrose Buffer	N.R	PBS	[38]
Apple	UC & PEG	−80 °C	N.R	[26]
	UC	N.R	PBS	[39]
Panax notoginseng	UC & SDGC	−80 °C	N.R	[40]
Ginseng	UC	N.R	N.R	[41]
	UC	N.R	Extraction buffer	[42]
	UC & SDGC	Freeze-Drying	N.R	[43]
	UC & SDGC	−80 °C	PBS	[44]
	SDGC / Exosome isolation kits/Combine	N.R	PBS	[45]
Centella asiatica	UC	−80 °C	PBS	[46]
Vitis vinifera kyoho	UC	−80 °C	PBS[	[47]
Cannabis strain	UC	N.R	N.R	[48]
Garlic	UC & SDGC	−80 °C	PBS	[49]
	UC & SDGC	N.R	PBS	[50]
	UC	−80 °C	PBS	[51]
	UC	−80 °C	PBS	[52]
Tangerine	UC	−20 °C	PBS	[53]
Pueraria lobata root	UC & SDGC	N.R	PBS	[54]
Pomegranate	N.R	N.R	PBS	[55]
	SEC	N.R	PBS	[56]
Sesame leaves	UF	−80°C	PBS	[57]
Oyster mantle	UC & SDGC	N.R	PBS	[58]
Orange	UC & SDGC	N.R	PBS	[59]
	UC	N.R	PBS	[60]
Citrus clementina	UC with 30% Sucrose Buffer	N.R	Extraction buffer	[61]
Kiwi	UC & SDGC	−80 °C	PBS	[62]
Avocado/Kiwi/ Orange/Plum	Exosome isolation kits	N.R	PBS	[63]
Kiwi/Lemon/Grapefruit/Blood orange	UC	−80 °C	N.R	[64]
Actinidia arguta	UC	−80 °C	PBS	[65]
Aloe	UC	−20 °C	PBS	[66]
	UC	−80 °C	PBS	[67]
	UC	−80 °C	PBS	[68]
	UC & UF	−70 °C	PBS	[69]

(*Continued*)

Table 1 (Continued).

Resource	Isolation Method	Storage Temperature	Storage Solvent	Reference
Morus nigra L. leaves	UC & SDGC	−80 °C	PBS	[70]
Momordica charantia	UC	−80 °C	PBS	[71]
Artemisia annua branches and leaves	UC	−80 °C	PBS	[72]
Kaempferia parviflora	UC & SDGC	−80 °C	PBS	[73]
	UC & SDGC	−80 °C	PBS	[74]
Solanum nigrum L. berries	UC & PEG	−8 °C	Deionized water	[75]
Carica papaya L. fruit	UC & PEG	4 °C	N.R	[76]
Houttuynia cordata	UC	−80 °C	PBS	[77]
Ginger	N.R	N.R	N.R	[78]
	SDGC	−80 °C	PBS	[79]
	UC & SDGC	4 °C	N.R	[80]
	SDGC	N.R	PBS	[81]
	UC & SDGC	N.R	PBS	[82]
Arabidopsis thaliana leaves	UC & PEG	N.R	PBS	[83]
Ecklonia cava	UC	Freeze-Drying	N.R	[84]
Black cumin	SDGC	Freeze-Drying	N.R	[85]
Salvia miltiorrhiza	UC & SDGC	Freeze-Drying	N.R	[86]
Portulaca oleracea L.	UC & SDGC	−80 °C	PBS	[87]
Blueberry	UC	N.R	PBS	[88]
	UC	−80 °C	PBS	[89]
Dandelion	UF	N.R	Deionized water	[90]
Eriobotrya japonica	UC & SDGC	N.R	N.R	[91]
Mulberry fruit	UC & SDGC	−80 °C	PBS	[92]
Pachyrhizus erosus	UC & PEG	N.R	Deionized water	[93]
Olive vegetation water	UC & Optiprep DGC	N.R	PBS	[94]
Brucea javanica	UC	−80 °C	PBS	[95]
Biyang floral mushrooms	UC	−80 °C	PBS	[96]
Atractylodes lancea rhizome	Exosome isolation kits	−70 °C	Deionized water	[97]
Dendrobium	UC & SDGC	N.R	PBS	[98]
Goldenberry	UC & PEG	N.R	Deionized water	[99]
Sweet basil leaf	UC	N.R	PBS	[100]
Allium tuberosum	UC & PEG	−80 °C	PBS	[101]
Sunflower Seedling	UC	−20 °C	PBS	[102]
Strawberry	UC	−80 °C	N.R	[103]
	UC	−80 °C	PBS	[104]
Apis mellifera bee pollen/Honey and royal jelly	UC	−80 °C	PBS	[105]
Sweet orange/Lemon/Grapefruit/Bitter orange	UC	−80 °C	PBS	[106]
	UC	−80 °C	PBS	[107]
Sweet oranges	UC	−20 °C	PBS	[108]
Tartary buckwheat	UC	−80 °C	PBS	[109]
Salvia dominica hairy roots	UC	−80 °C	Deionized water	[110]
Hemp (roots/seeds/sprouts/leaves)	UC	N.R	PBS	[111]
Cabbage	UC/UC & PEG/SEC	N.R	PBS	[7]
Turmeric	UC & SDGC	N.R	N.R	[112]
Sap of D. Morbifera trees	Filtration & Concentration	−80 °C	PBS	[113]
Leaves and stems of D. Morbifera	Filtration & Concentration	−80 °C	PBS	[114]
Acerola	UC/ Exosome isolation kits	N.R	PBS	[115]
Cannabis plants	UC	N.R	N.R	[48]
White beech/Brown Beech/White Button/Shiitake	UC	N.R	PBS	[116]
Celery root	UC & PEG	N.R	N.R	[117]
Corn	UC with 30% Sucrose Buffer	N.R	Deionized water	[118]

Abbreviations: UC, Ultracentrifugation; PEG, Polyethylene glycol; UF, Ultrafiltration; SDGC, Sucrose density gradient centrifugation; SEC, Size-Exclusion Chromatography.

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Impact of Isolation Processes on PD-EVLPs Purity and Dispersibility, and Potential Solutions

Currently, the primary methods for isolating PD-EVLPs include ultracentrifugation, density gradient centrifugation, size exclusion chromatography (SEC), ultrafiltration, and polymer-based precipitation (eg, polyethylene glycol [PEG] precipitation).[119,120] Among these, differential ultracentrifugation combined with density gradient centrifugation remains the most widely used technique at the laboratory scale due to its cost-effectiveness, high separation efficiency, high recovery rate, and suitability for large-scale sample processing.[121]

Techniques and Challenges in PD-EVLPs Isolation

Several PD-EVLPs isolation techniques have been developed.[122] Size-exclusion chromatography (SEC) preserves vesicle integrity but requires specialized equipment, such as high-performance liquid chromatography (HPLC) systems equipped with specific columns and detectors to accurately separate and quantify nanovesicles based on their size, and is primarily suitable for small-scale, high-purity PD-EVLPs research, such as proteomic and content analyses.[7] PEG precipitation reduces vesicle aggregation risks but introduces polymer contaminants, complicating subsequent purification steps.[123] Meng et al exploited the natural negative charge of PD-EVLPs for separation via electrophoretic dialysis in a shorter time; however, similar to ultrafiltration,[124] membrane fouling can reduce yield over time. He et al employed antibody-based immunoaffinity isolation targeting specific proteins on Arabidopsis-derived nanovesicles, achieving high-purity nanovesicles.[125] However, this method is costly and requires the development of plant-specific antibodies, limiting its broad applicability. Although each method has its own merits, they remain inferior to ultracentrifugation (UC) for large-scale applications.

The differential ultracentrifugation process for PD-EVLPs typically involves several steps[11] (Figure 3): (1) mechanical disruption of plant materials using a juicer to obtain plant juice, followed by filtration to remove large particulate residues; (2) sequential centrifugation of the filtrate at different centrifugal forces (3000–10,000×g) at 4 °C for 10–60 minutes to remove large precipitates, cellular debris, and dead cells; (3) ultracentrifugation of the supernatant (100,000–150,000×g) for over one hour to obtain a PD-EVLPs pellet. Due to the presence of non-vesicular contaminants in the pellet, many studies further employ density gradient centrifugation to enhance PD-EVLPs purity.[120,126] Despite these additional steps, vesicle-like

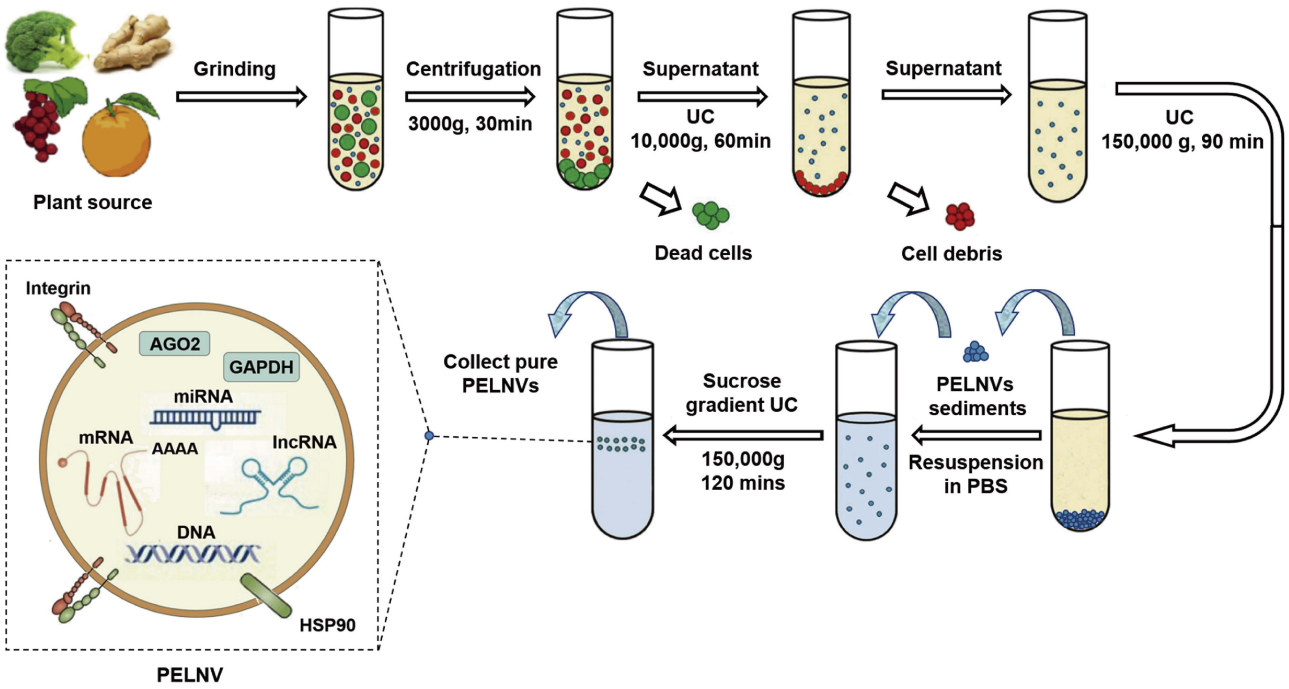

Figure 3 General isolation process of PD-EVLPs. Reprinted from Molecular Therapy: 29/1, Dad HA, Gu TW, Zhu AQ, et al. Plant exosome-like nanovesicles: emerging therapeutics and drug delivery nanoplatforms. 13-31, Copyright 2021 with permission from Elsevier.[11]

Abbreviations: PELNVs, Plant Exosome-Like Nanovesicles; UC, Ultra-Centrifugation; PBS, Phosphate Buffered Saline; AGO, Argonaute; GAPDH, Glyceraldehyde-3-Phosphate Dehydrogenase; mRNA, Messenger RNA; miRNA, MicroRNA; DNA, Deoxyribonucleic Acid; lncRNA, Long Non-coding RNA; HSP, Heat Shock Protein.

contaminants of similar density remain, posing a threat to PD-EVLPs stability. Additionally, prolonged exposure to extreme centrifugal forces can lead to vesicle aggregation,[127] potentially affecting stability.

Optimized Approaches for Improving PD-EVLPs Isolation

Concerns over nanovesicles aggregation following prolonged high-speed centrifugation have been previously raised in extracellular vesicle research. Given that PD-EVLPs are often present in higher quantities in plant extracts, aggregation may be even more pronounced. For example, Mu et al used 150,000×g centrifugation for 90 minutes, while Kim et al applied 100,000×g for 70 minutes, resulting in uneven vesicle size distribution, with some exceeding 1,000 nm in diameter, making them prone to rapid immune clearance in vivo.[32,69] Chen's research group found that optimizing centrifugation speed and duration effectively reduced aggregation and enhanced dispersibility.[12] Additionally, protective agents such as trehalose have been shown to reduce vesicle size from an average of 631.4 nm to 380.4 nm following ultracentrifugation.[128] However, compared to adding trehalose during the resuspension stage, introducing trehalose prematurely during the centrifugation stage may interfere with impurity removal, counteracting its stabilizing effects. Most alternative separation methods except ultracentrifugation are limited by their separation principles and costs, making it difficult to overcome the constraints of large-scale production. Thus, in the future, optimizing PD-EVLPs isolation technologies will require breakthroughs in several key areas: (1) refining ultracentrifugation parameters, particularly adjusting speed and duration, to minimize aggregation while maintaining purity and recovery rates; (2) developing alternative separation techniques, such as microfluidic-based isolation,[129] to mitigate contamination risks and enhance efficiency; (3) enhancing the adaptability of standardized workflows by adjusting buffer systems and preprocessing strategies based on plant characteristics to improve PD-EVLPs stability and functionality. These optimizations will facilitate the efficient isolation and large-scale production of PD-EVLPs, while supporting their stability.

Preservation Strategies for Maintaining the Structural Integrity of PD-EVLPs

Post-isolation preservation of the structural integrity of PD-EVLPs integrity is crucial for their clinical translation. The International Society for Extracellular Vesicles (ISEV) recommends storing extracellular vesicles (EVs) in PBS at −80 °C.[130] Although most studies currently adopt −80 °C as the storage temperature and PBS as the preservation medium, whether these conditions are optimal for maintaining PD-EVLPs stability remains to be determined.

Challenges of Aggregation and Fusion During Storage

Multiple studies indicate that PD-EVLPs tend to aggregate or fuse during storage.[16,131] Chen et al reported that *Rehmannia glutinosa*-derived extracellular vesicle-like particles (RG-EVLPs) aggregated and fused after two weeks at 4 °C or −20 °C, with further deterioration observed at all temperatures over two months.[16] Even under −80 °C conditions repeated freeze-thaw cycles can compromise PD-EVLPs stability. In the study by Nemidkanam et al, *Kaempferia parviflora*-derived extracellular vesicle-like particles (KP-EVLPs) exhibited size increases from 300.3 ± 49.65 nm to 387.1 ± 97.53 nm after a single freeze-thaw cycle, with further enlargement to 391.9 ± 111.1 nm upon multiple cycles.[74] These findings suggest that freeze-thaw cycles may induce structural alterations, potentially impairing PD-EVLPs bioactivity and drug delivery efficacy. Collectively, these results indicate that simply relying on low temperatures might not effectively protect PD-EVLPs.

Recent studies have demonstrated that formulations containing 1,3-butylene glycol (TMO) significantly enhance *Dendropanax morbifera* leaf-derived extracellular vesicles (LDEVs) stability at 4 °C compared to untreated LDEVs.[131] Another study using depth filtration with size exclusion chromatography demonstrated that cellulose-based membranes could serve as a stable storage matrix, maintaining vesicle integrity at 4 °C.[132] These findings suggest that incorporating preservatives and alternative storage matrices may broaden the potential industrial applications of PD-EVLPs by improving their storage stability.

Role of Cryoprotectants and Lyophilization

Lyophilization, a widely used method for preserving food and various biological materials, has also been applied in the clinical use of apoptotic vesicles derived from mammals.[133] This approach often involves cryoprotectants to mitigate freeze-thaw damage, with mannitol demonstrating effectiveness in maintaining EV integrity during the freeze-drying

process.[134] Similarly the choice of cryoprotectants significantly influences extracellular vesicle stability during freezing. For example, compared to PBS alone, the addition of human serum albumin and trehalose (PBS-HAT) improves EV stability under −80 °C storage, mitigating freeze-thaw cycle damage.[135] Luo et al reported that lipid vesicles preserved with trehalose maintained better size stability at −40 °C than those with sucrose, highlighting trehalose's superior protective effects.[136] Trehalose also prevents aggregation during subsequent room-temperature storage,[137] although lyophilization can sometimes induce membrane damage or protein denaturation, necessitating further refinement.

Long-Term Preservation of PD-EVLPs via Optimized Technology and Source Selection

Any optimization strategy for preservation must control for plant-of-origin effects when assessing PD-EVLP stability. Some plants exhibit show stability in storage. *Olea europaea* L.-derived extracellular vesicle-like particles (OE-EVLPs) exhibit exceptional resilience to high temperatures (70 °C, 1 hour), a wide pH range (5–10), and mechanical stress (50–100 nm extrusion), enabling stable storage at 4°C for one month and long-term preservation with 25 mM trehalose.[138] Liquid nitrogen freezing followed by 80 °C storage represents a relatively effective preservation method for PD-EVLPs. However, significant variations in preservation efficacy exist across plant species. For instance, Rehmannia glutinosa-derived nanovesicles exhibit substantial aggregation and reduced bioactivity after two months under these conditions.[16] In contrast, nanovesicles from *Dioscorea spp*. (yam[139]) and *Brucea javanica*[95] maintain stability for at least six months under the same conditions, highlighting inherent interspecies differences in PD-EVLP stability (Table 2).

Table 2 Administration Methods, Particle Size and Surface Charge of PD-EVLPs

Resource	Method of Administration	Size	Charge	Cryoprotectant	Reference
Aloe	IV	137.4	–6.6	N.R	[15]
Aloe	IV	138.7	–7.4	N.R	[12]
Aloe	IV	181	N.R	N.R	[68]
Arctic bilberries	TP	30~200	–19	Cellulose-based membranes	[132]
Beta vulgaris	IP	125.2	N.R	N.R	[140]
Broccoli	In vitro	191.6	–15.85	N.R	[141]
Brucea javanica	IV	104.6	–9.2	N.R	[95]
Carrot	In vitro	143.9	–10.2	N.R	[142]
Celery	IP, Caudal Vein Injection	50 - 200	–34.24	N.R	[143]
Complex exosomes	PO	N.R	N.R	N.R	[144]
Dendropanax morbifera leaves	N.R	30~200	N.R	1,3-butylene glycol (TMO)	[131]
Edible tea flowers	IV, PO	131	–7.6	N.R	[14]
Garlic	PO, IG	N.R	N.R	N.R	[145]
Garlic	PO	N.R	N.R	N.R	[49]
Garlic	In vitro	191.8	–31	N.R	[146]
Garlic chive	PO, IV	N.R	N.R	N.R	[50]
Ginger	PO	294.1	–29.7	N.R	[147]
Ginger	IV	N.R	N.R	N.R	[148]
Ginger	IV	146	–5.16	N.R	[149]
Ginger	N.R	115.8	–12	N.R	[150]
Ginger	N.R	N.R	–31.94	N.R	[143]
Ginseng	IV, IC	151.6	–17.9	N.R	[44]
Ginseng	IP	344.8	–25.4	N.R	[151]
Ginseng	TP	N.R	N.R	N.R	[152]
Ginseng	TP	144.1	–27.4	N.R	[153]
Ginseng	TP	215.25	–34.7	N.R	[154]
Gouqi	IM	N.R	N.R	N.R	[155]
Grape	PO		N.R	N.R	[156]

(*Continued*)

Table 2 (Continued).

Resource	Method of Administration	Size	Charge	Cryoprotectant	Reference
Grape	N.R	N.R	–34.47	N.R	[143]
Grapefruit	IP	113.4	N.R	N.R	[157]
Grapefruit	IP, IV, IM, IN	N.R	N.R	N.R	[8]
Honey	IP	148	–13.7	N.R	[158]
Lemon	IP	N.R	N.R	N.R	[159]
Lemon	PO, IG	180.5	N.R	N.R	[37]
Lemon	N.R	N.R	–34.21	N.R	[143]
Momordica charantia	IV	N.R	N.R	N.R	[160]
Orange	IP	101.4	N.R	N.R	[59]
Orange	PO, IG	N.R	N.R	N.R	[60]
Orange	PO, IM, IN	N.R	N.R	N.R	[161]
Orange	PO, IG	N.R	N.R	N.R	[162]
Panax notoginseng	IV	151.3	–8	N.R	[40]
Plant hairy roots	IT	180	–10.4	N.R	[110]
Pomegranate	PO	161.4	N.R	N.R	[55]
Pueraria lobata	IP	N.R	N.R	N.R	[163]
Pueraria lobata	PO	N.R	N.R	N.R	[54]
Rice bran	IP	N.R	N.R	N.R	[164]
Shiitake Mushroom	IP	N.R	N.R	N.R	[116]
Simply Ginger	Intra-airway Administration	N.R	N.R	N.R	[165]
Tangerine	In vitro	255	–16.3	N.R	[166]
Tea leaves	PO	140	–14.6	N.R	[167]
Turmeric	PO	177.9	–21.7	N.R	[112]
Turmeric	PO	204.6	–21.3	N.R	[112]
Yam	PO	168	N.R	N.R	[139]

Abbreviations: PO, Oral Administration; IV, Intravenous Injection; IC, Intracranial Injection; IP, Intraperitoneal Injection; IT, Intratumoral Injection; IG, Intragastric Administration; IN, Intranasal Administration; IM, Intramuscular Injection; TP, Topical Administration;

With lyophilization already implemented in clinical applications of mammalian vesicles, refining this technique for PD-EVLPs holds great promise.[133] Systematic investigation of critical parameters, including cryoprotectant formulations, drying cycles, and residual moisture control, will enable the development of standardized lyophilization protocols that maximize PD-EVLPs stability while minimizing structural damage and contamination risks. In addition, selecting plant sources with higher intrinsic stability could further improve storage feasibility, thereby promoting broader clinical and industrial applications.

Contributions of Characteristics and Composition to the Stability of PD-EVLPs

The biological functions and application potential of PD-EVLPs are closely tied to their unique structural and chemical composition. As natural drug delivery carriers, PD-EVLPs not only rely on their morphology and size for efficient in vivo distribution, but also on their membrane composition—specifically certain lipids and bioactive molecules—which directly influence their stability, targeting capability, and interactions with biological fluids.[10,138]

PD-EVLPs Characteristics: Protecting Its Bioactive Cargo

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) are the primary tools for analyzing the morphology and ultrastructure of PD-EVLPs. Studies have shown that PD-EVLPs exhibit diverse shapes, including spherical, disc-like, or cup-shaped structures[15,30,140,168] (Figure 4). This structural diversity may be associated with their functional roles in biological systems, such as material exchange, intercellular communication, or the transport of specific bioactive molecules. Size distribution is typically analyzed using nanoparticle tracking analysis (NTA) and dynamic light scattering (DLS). Compared to PDEVs (30–150 nm in diameter) derived from cell culture supernatants, the preparation of PD-EVLPs involves mechanical disruption methods such as grinding and sonication, which directly fracture plant cell membranes and organellar

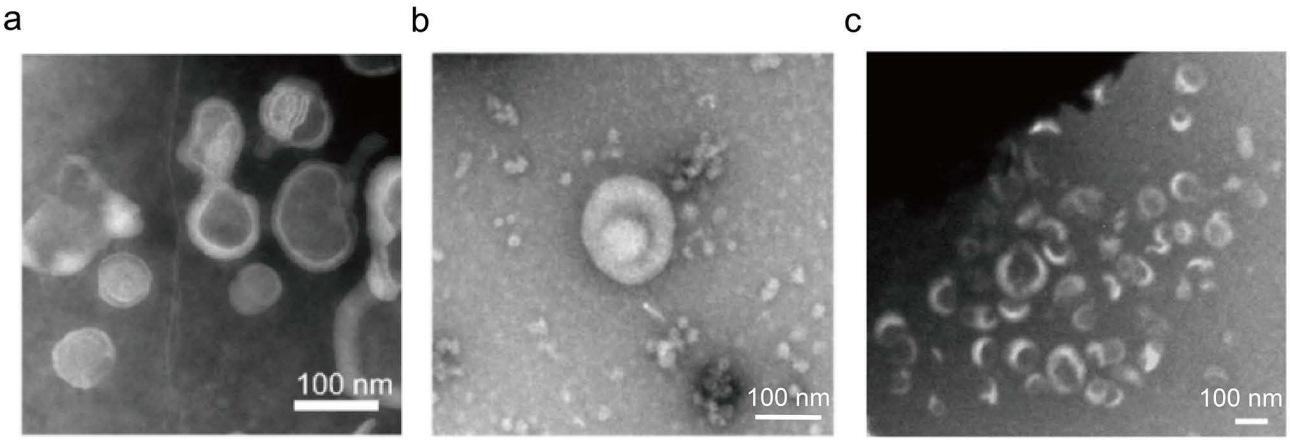

Figure 4 The TEM figures of PD-EVLPs with different morphology. (**a**) PD-EVLPs which are spherical shape. Reprinted with permission from Niu W, Xiao Q, Wang X, et al. A biomimetic drug delivery system by integrating grapefruit extracellular vesicles and doxorubicin-loaded heparin-based nanoparticles for glioma therapy. Nano Lett. 2021;21 (3):1484–1492. Copyright 2021 American Chemical Society.[30] (**b**) PD-EVLPs which are cup-shaped. Reprinted from Cai J, Pan J. Beta vulgaris-derived exosome-like nanovesicles alleviate chronic doxorubicin-induced cardiotoxicity by inhibiting ferroptosis. Journal of Biochemical and Molecular Toxicology. 2024;38(1):e23540. © 2023 Wiley Periodicals LLC. (**c**) PD-EVLPs which are saucer- or cup-shaped. (The scale bars in the above figures are all 100 nm) Reprinted with permission from Zeng L, Shi W, Wang H, et al. Codelivery of π-π stacked dual anticancer drugs based on aloe-derived nanovesicles for breast cancer therapy. ACS Appl. Mater. Interfaces. 2022;14 (24):27686–27702. Copyright 2022 American Chemical Society.[15]

membranes (including chloroplasts, vacuoles, and endoplasmic reticulum). These fragmented membranes spontaneously reassemble into vesicles through a process lacking the biological regulation inherent in conventional biogenesis of PDEVs, resulting in heterogeneous size distributions and a propensity for membrane fusion that generates larger vesicles. Consequently, PD-EVLPs typically exhibit diameters ranging from 40 to 200 nm[64,169] (Figure 5a and Table 2).

In addition, the surface charge of PD-EVLPs significantly influences their biodistribution and clearance rate. In the circulatory system, cationic vesicles exhibit the fastest clearance, followed by anionic vesicles, whereas neutral or slightly negatively charged vesicles have the longest half-life.[170] Due to the presence of phosphate groups on the phospholipid membrane surface of PD-EVLPs, which undergo ionization in physiological buffer environments, and the embedding of negatively charged proteins (eg, aspartic acid residues) on the membrane surface,[171] most PD-EVLPs carry

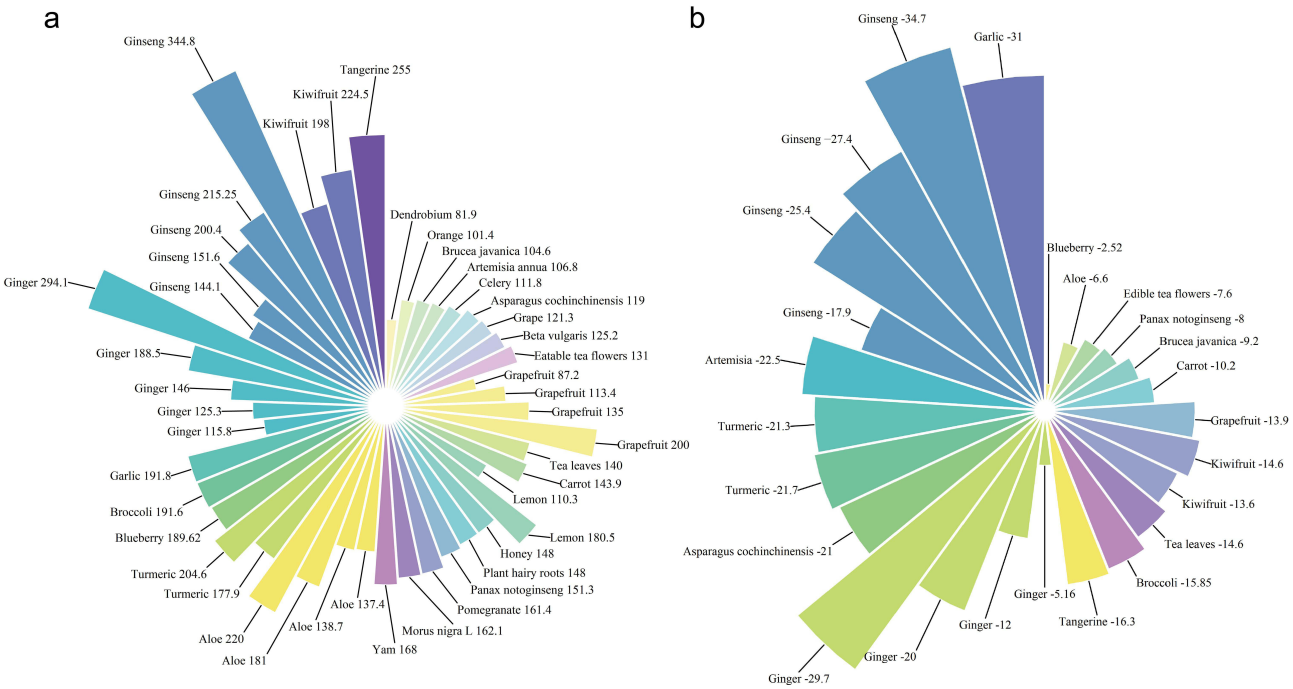

Figure 5 The size and surface charge of PD-EVLPs. (This figure is based on the data from Table 2) (**a**) The size of PD-EVLPs. (**b**) The surface charge of PD-EVLPs.

a net negative charge, typically exhibiting zeta potentials ranging from −30 mV to near-neutral (Figure 5b and Table 2), which helps mitigate phagocytosis by hepatic Kupffer cells, thereby extending their circulation time in vivo.[172] This property provides a key advantage for PD-EVLPs as drug carriers, by ensuring their resistance to rapid clearance in the circulatory system. It is noteworthy that there are inter-study variations in both particle size and charge when investigating PD-EVLPs from the same plant (Figure 5), highlighting the necessity of establishing standardized isolation and storage protocols. Only by enhancing reproducibility and minimizing batch-to-batch variability can the clinical translation of PD-EVLPs be further advanced.

PD-EVLPs Composition: Protective Role of the Phospholipid Bilayer and Bioactive Compounds

The phospholipid bilayer of PD-EVLPs not only provides intrinsic protection for encapsulated bioactive molecules but also plays a pivotal role in maintaining vesicle stability and functionality.[168] Phosphatidylcholine (PC) is a key structural component of PD-EVLPs membranes and is essential for membrane stability.[21] Studies have shown that PD-EVLPs with higher PC content tend to exhibit greater stability and prolonged circulation time in vivo.[173,174]

The primary phospholipid composition of PD-EVLPs varies with plant source. For instance, EVLPs derived from *Panax ginseng*,[44] *aloe vera*,[12] and tea leaves[167] exhibit high PC content. Meanwhile, tea flower-derived nanovesicles are enriched in phosphatidylserine (PS), which may reduce macrophage-mediated exosome clearance.[14] Additionally, *Panax ginseng*-derived nanovesicles predominantly contain diglyceride monoglyceride (DGMG, 59.4%), phosphatidylethanolamine (PE, 16.8%), and ceramide (Cer, 13.8%). Studies suggest that these components affect macrophage polarization and contribute to immune regulation.[151]

Beyond phospholipid, PD-EVLPs are rich in phytosterols and other bioactive compounds, such as antioxidants, which regulate membrane fluidity regulation and promote ordered arrangement of phospholipids.[65] Zeng et al found that *aloe*-derived nanovesicles, which contain *aloe*-emodin and β-sitosterol, exhibit superior antioxidant capacity and stability compared with synthetic liposomes (Figure 6).[12] These findings suggest that the complex composition of PD-EVLPs likely underpins enhanced stability and biological functionality.

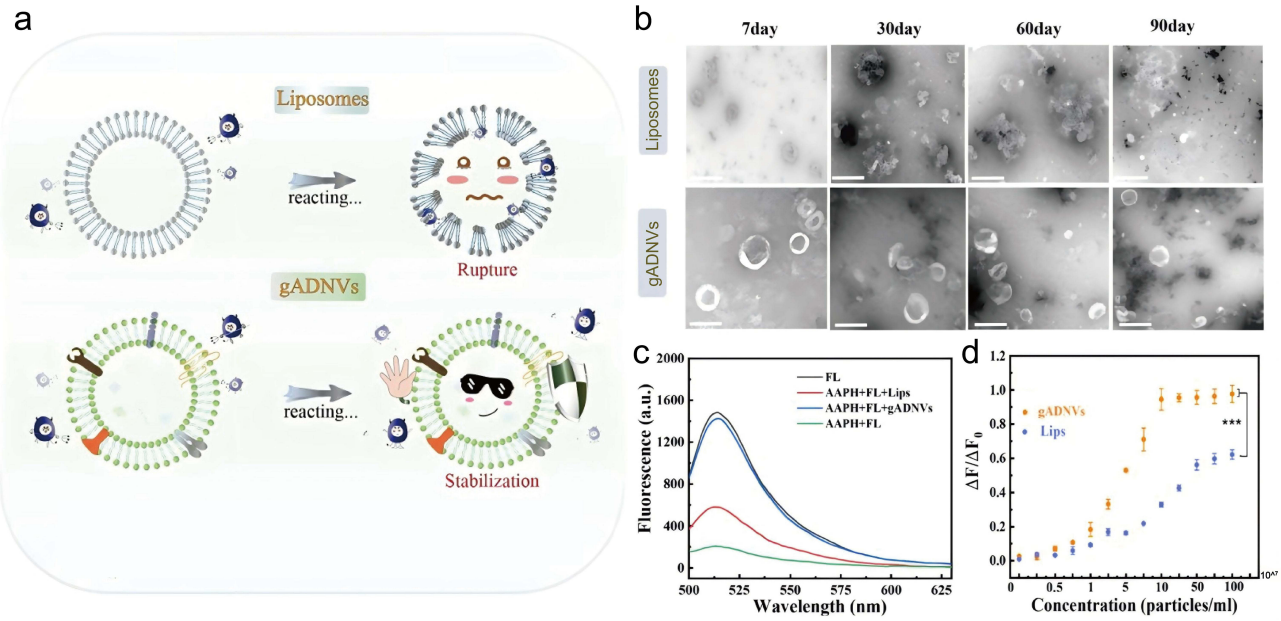

Figure 6 The comparison of stability between gADNVs and liposomes. (**a**) The stability comparison between Liposomes and ADNVs under different conditions. (**b**) TEM images of gADNVs and liposomes at different storage time points. Scale bar is 100 nm. (**c**) Fluorescence recovery assay comparing gADNVs and liposomes. (**d**) Antioxidant activity of gADNVs and liposomes. $\Delta F/\Delta F_0$ indicates the relative change in fluorescence intensity; *** indicates p <0.001, and the difference is statistically highly significant. Reprinted from Zeng L, Wang H, Shi W, et al. Aloe derived nanovesicle as a functional carrier for indocyanine green encapsulation and phototherapy. J Nanobiotechnol. 2021;19(1):439.[12]
Abbreviations: gADNVs, *Aloe*-derived nanovesicles from the gel; Lips, liposomes; FL, Fluorescence.

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Building upon the understanding of PD-EVLPs' composition-stability-function relationships, it is essential to contextualize their performance by comparing them with other widely used nanocarrier systems. PD-EVLPs, because their membrane composition, structure, and surface characteristics closely resemble those of cells, inherently possess biocompatibility and low immunogenicity. In contrast, polymer nanoparticles and liposomes, which are extensively studied nanocarriers, offer highly controllable architectures but encounter challenges such as multiple biological barriers and protein corona formation.[175,176] Moreover, they lack natural bioactive molecules. Studies have shown that polymer nanoparticles can become sequestered in endosomes or lysosomes after cellular uptake, hindering effective drug release and thereby limiting drug bioavailability.[177] Niosomes, known for their good stability and lower cost, are also potential candidates as nanocarriers. However, their stability depends significantly on the precise control of the cholesterol-to-surfactant ratio, and their preparation is relatively complex. Additionally, sterilization of niosomes presents challenges, as heat sterilization and membrane filtration are not suitable, potentially limiting their clinical translation.[178]

Elucidating Composition-Stability-Function Relationships in PD-EVLPs

Despite the promising stability and bioactivity of PD-EVLPs, their precise composition and stabilization mechanisms remain incompletely understood. Future studies should leverage high-throughput mass spectrometry and multi-omics analyses to comprehensively characterize the lipid, protein, and nucleic acid components of PD-EVLPs. Comparative studies should aim to identify key factors contributing to PD-EVLPs stability and elucidate how membrane composition influences vesicle stability, targeting properties, and drug delivery efficiency. Additionally, fluorescence tracing and in vivo imaging techniques should be employed to further investigate the distribution and degradation of PD-EVLPs under different physiological conditions, thereby enhancing their clinical feasibility. Advances in synthetic biology and nanotechnology could also facilitate PD-EVLPs engineering, such as surface ligand modifications or genetic modifications, to improve their therapeutic efficacy for specific diseases.

Disruptions to PD-EVLPs Stability Caused by Administration Routes

Different administration routes directly impact the stability, immune response, and delivery efficiency of PD-EVLPs in vivo. Oral administration allows gastrointestinal absorption and offers high safety, while intravenous injection enables rapid systemic distribution (Figure 7a). Localized delivery methods, such as transdermal patches or local injections, facilitate targeted delivery and help minimize systemic side effects.

Oral Administration: Overcoming Gastrointestinal Barriers for Stability and Absorption

As most PD-EVLPs originate from edible plants, oral administration is a common and practical delivery approach. Currently, many in vivo studies of PD-EVLPs have employed oral administration. Compared to intravenous injections, orally administered PD-EVLPs generally exhibit lower immunogenicity (Figure 7b).[14] However, the extreme pH levels, enzymatic degradation, and mucus clearance mechanisms within the gastrointestinal tract pose significant challenges to their stability. Studies have shown that PD-EVLPs from different plant sources undergo distinct volume changes in gastrointestinal fluids. For instance, grape-derived nanovesicles shrink in size, whereas *Zingiber officinale* (ginger)-derived nanovesicles expand.[112,156] These variations may influence the in vivo stability of PD-EVLPs; particles smaller than 10 nm are more likely to be cleared by the kidneys, while those exceeding 200 nm are more prone to phagocytosis by macrophages in the liver and spleen.[179]

Moreover, PD-EVLPs exhibit varying degrees of stability in the gastrointestinal environment. For example, lemon-derived nanovesicles have been shown to maintain their integrity for up to 12 hours in simulated gastric fluid.[124] Certain PD-EVLPs also carry natural membrane proteins, such as heat shock proteins, which provide partial resistance to proteolytic degradation.[12,174,180] Further investigation into PD-EVLPs stability and absorption mechanisms in the gastrointestinal tract will aid in optimizing oral delivery strategies. Additionally, numerous studies have shown that after oral administration, fluorescently labeled PD-EVLPs can reach various organs and exert effects, suggesting that these vesicles may withstand the harsh gastrointestinal environment.[139,145,162,174,181] However, a key issue remains in determining whether the detected vesicle signals still represent intact PD-EVLPs.

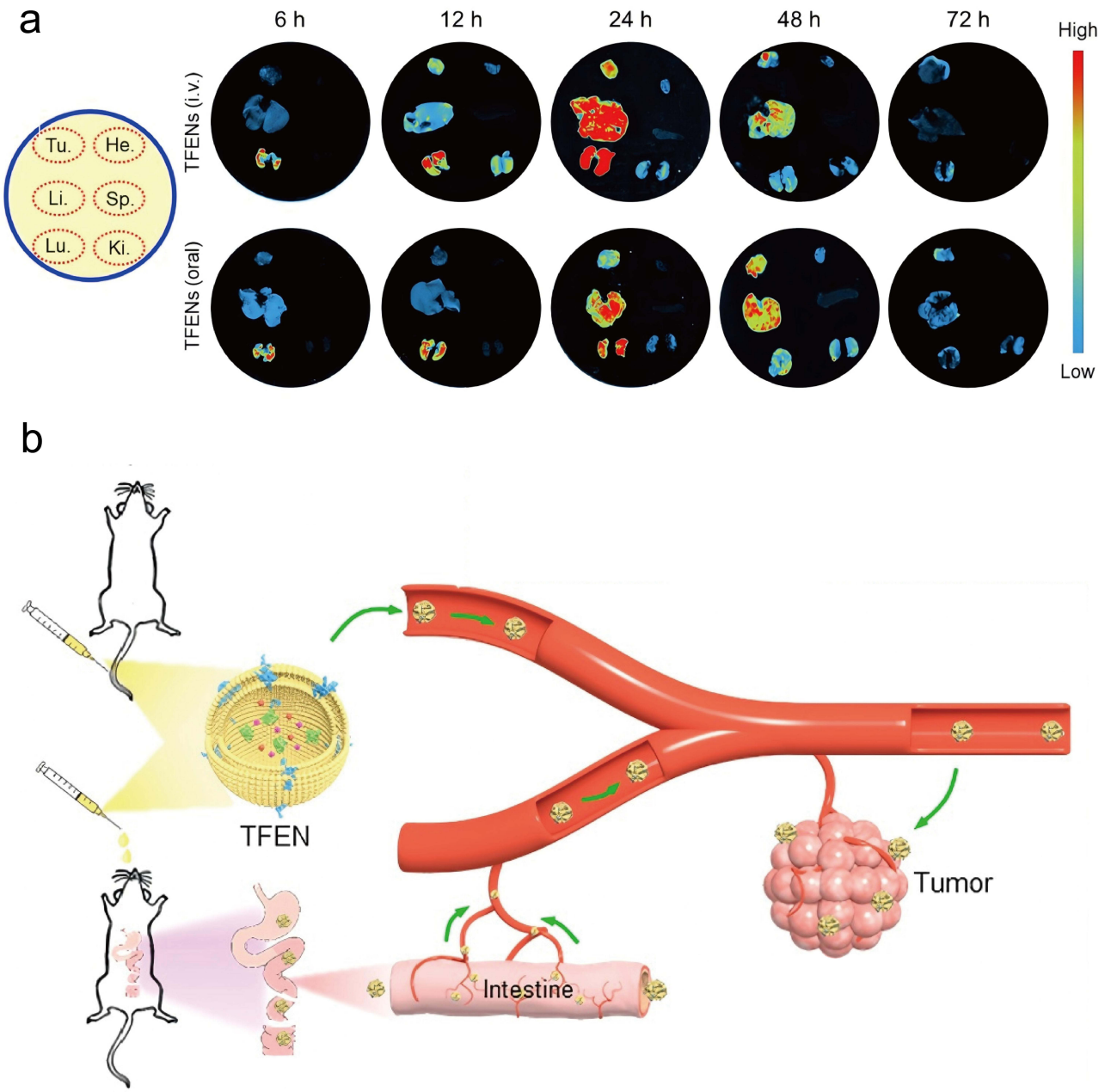

Figure 7 Edible tea tree flowers derived nanovesicles for drug delivery via different administration methods. (**a**) In vivo distribution of edible tea tree flowers derived nanovesicles under different administration methods. (**b**) Schematic representation and pros and cons of edible tea tree flowers derived nanovesicles under different administration methods. This article was published in Acta Pharmaceutica Sinica B, 12(2), Chen Q, Li Q, Liang Y, et al. Natural exosome-like nanovesicles from edible tea flowers suppress metastatic breast cancer via ROS generation and microbiota modulation. 907–923. Copyright Elsevier 2022.[14]
Abbreviations: I.v., intravenous tail; TFENs, tea flowers derived nanovesicles; Tu., tumor; He., heart; Li., liver; Sp., spleen; Lu., lung; Ki., kidney.

Intravenous Administration: Circulatory Fate and Strategies for Prolonged Stability

Intravenous injections are widely used for PD-EVLPs delivery due to their ability to rapidly introduce vesicles into systemic circulation. However, this route exposes PD-EVLPs directly to blood components, potentially triggering recognition and clearance by the mononuclear phagocyte system (MPS). Although PD-EVLPs possess a phospholipid bilayer that generally confers high biocompatibility and low immunogenicity, their distribution and clearance rates vary significantly among different sources. For example, tea tree flower-derived nanovesicles accumulate in the liver, lungs, and tumor tissues within six hours post-injection, reaching peak concentration at 24 hours, with some vesicles still detectable after 72 hours.[14] In

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contrast, certain PD-EVLPs, such as those derived from *Catharanthus roseus*[180] and *Panax ginseng*,[182] are rapidly eliminated by the liver and spleen, though the precise mechanisms governing their clearance remain unclear.

To extend PD-EVLPs circulation time and enhance therapeutic accumulation, strategies that prevent immune recognition have been explored. Blocking scavenger receptors (SRs) has been proposed to prolong blood retention and improve PD-EVLPs enrichment at tumor sites.[183] However, clinical translation of this approach faces challenges, as inhibiting MPS activity may increase the risk of infections.[184] Additionally, PD-EVLPs may form a protein corona in the bloodstream, which can alter their stability and biodistribution.[185] Future research should focus on optimizing PD-EVLPs surface modifications to enhance circulatory stability and therapeutic efficacy.

Localized Administration: Protecting Them from the Challenge of Stability

Localized administration refers to the delivery of therapeutic agents directly to the site of injury or disease, minimizing systemic exposure and reducing side effects. This approach can be applied to both localized effects (eg, skincare and antimicrobial) and more targeted systemic effects when necessary. For example, *Panax ginseng*-derived nanovesicles, when injected intradermally, are efficiently internalized by skin cells within 24 hours, demonstrating effective localized delivery to the skin.[154] Similarly, *aloe*-derived nanovesicles show strong skin penetration during non-invasive transdermal delivery, enabling targeted treatment of skin conditions.[12]

The high membrane fusion capability and mechanical stability of PD-EVLPs make them ideal carriers for both localized and systemic therapeutic effects. Membrane fusion capability enables these vesicles to effectively deliver therapeutic agents to the target cells by merging with cell membranes, thereby improving the bioavailability of the payload. Mechanical stability ensures that the vesicles retain their integrity during transit, protecting the encapsulated compounds from degradation and enhancing the efficacy of the treatment.[186]

While localized administration typically refers to direct action at the site of disease, in some cases, such as transdermal delivery, the therapeutic effect extends beyond the skin to deeper tissues. For instance, transdermal treatments for superficial nerve damage aim to achieve localized effects on the skin and underlying nerves. In contrast, direct gel implantation into the spinal cord for the treatment of spinal cord injury involves localized delivery to the site of injury, with the potential for systemic benefits, such as motor function recovery. EVLPs derived from plants like *Taraxacum officinale*(dandelion),[187] *Panax ginseng*,[153] and *sophora*[188] have been incorporated into hydrogel systems, demonstrating significant antimicrobial, neuroprotective, and motor function recovery effects. The hydrogel matrix ensures a controlled and gradual release, offering potential for long-term therapeutic outcomes in both chronic disease treatment and skincare applications.

Overcoming Biological Barriers: Precision Tracking and Microenvironment-Responsive Delivery of PD-EVLPs

Tracking PD-EVLPs in vivo remains challenging, as fluorescence labeling may misinterpret stability due to vesicle degradation. More precise methods, such as isotope labeling and photoacoustic imaging, could provide a clearer picture of their integrity and biodistribution. Beyond tracking, immune clearance—particularly by the mononuclear phagocyte system (MPS), poses a significant hurdle. However, activating the immune system may not necessarily be a bad thing, as it could also trigger tumor immunity.

Additionally, surface modifications such as biomimetic coatings can enhance tissue penetration and reduce immunogenicity.[189] Another key challenge is PD-EVLPs instability in acidic environments, which complicates oral delivery but could facilitate drug release in tumors. To address this, pH-responsive coatings could protect PD-EVLPs in the stomach while enabling controlled release in targeted acidic microenvironments, ultimately optimizing therapeutic efficacy.[149]

Optimizations in PD-EVLPs Stability Brought by Engineering Modifications

Engineering modifications aim to enhance the stability of PD-EVLPs by preventing immune recognition and optimizing surface interactions. Current mainstream strategies can be categorized into two major approaches for improving stability: biomimetic membrane camouflage and surface chemical modifications (Figure 8 and Table 3).

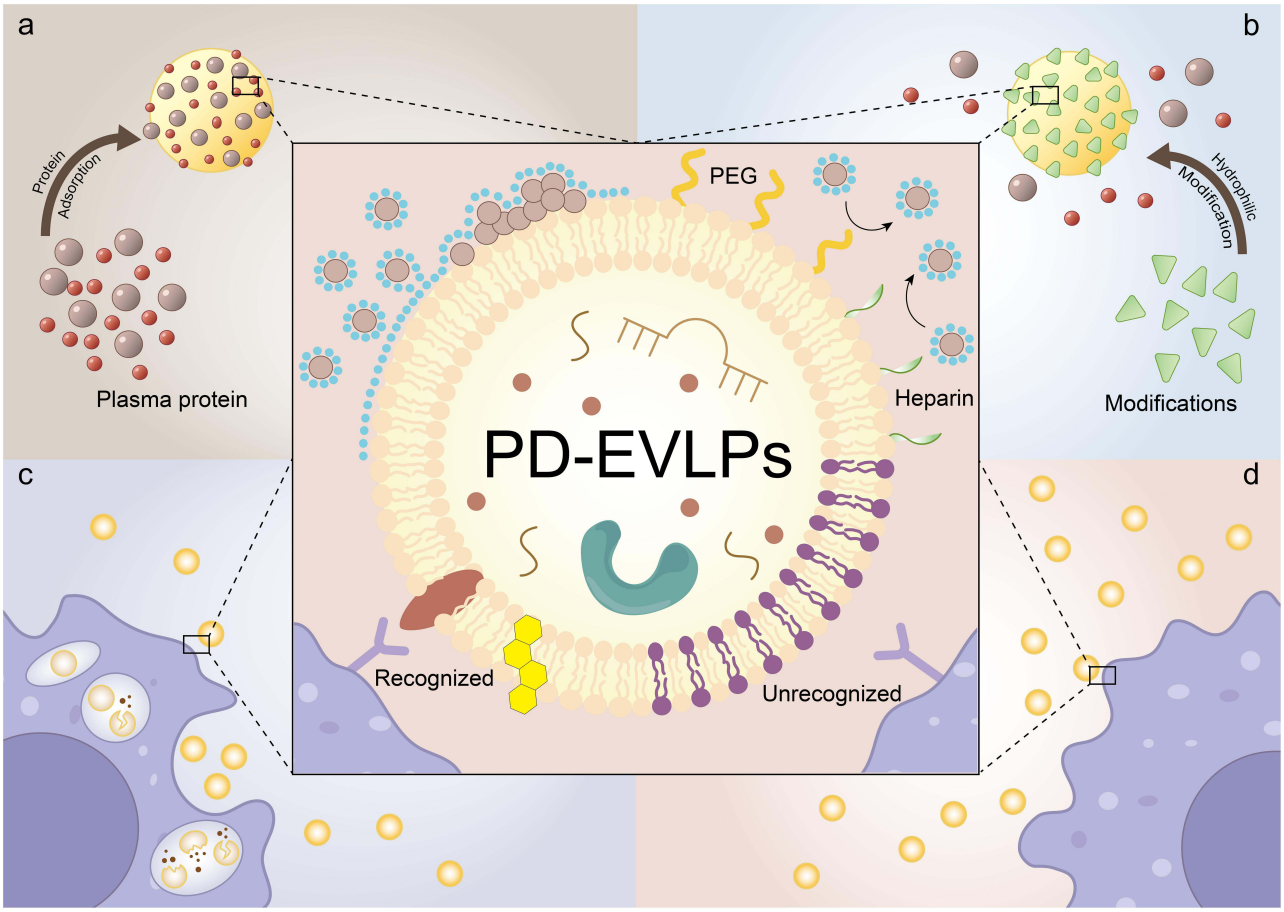

Figure 8 Current mainstream engineering modification methods. (**a**) The plasma protein adsorption of PD-EVLPs. (**b**) The reduction of plasma protein adsorption of PD-EVLPs after surface modifications. (**c**) The in vivo recognition and clearance of PD-EVLPs. (**d**) The immune evasion of PD-EVLPs after biomimetic membrane coating.
Abbreviation: PEG, polyethylene glycol.

Surface Modification to Inhibit Protein Adsorption on PD-EVLPs

Previous studies have confirmed that EVs are susceptible to plasma protein adsorption in bodily fluids, leading to the formation of a protein corona, which may accelerate their clearance and impair their targeting ability. Modulating the surface properties of PD-EVLPs, such as hydrophilicity and charge distribution, can significantly reduce nonspecific adsorption, thereby prolonging their circulation time in vivo. Among various approaches, PEG modification is the most widely used strategy. The hydrophilic polymer chains of PEG can form a dense hydration layer, generating steric hindrance that effectively prevents the adsorption of opsonins such as fibrinogen and immunoglobulins.[190] For instance, PEG-modified asparagus-derived nanovesicles demonstrated a 76% reduction in blood clearance rate and a 4.3-fold increase in tumor accumulation without inducing hepatic or renal toxicity.[183]

However, prolonged PEG exposure may lead to the accelerated blood clearance (ABC) phenomenon, where the immune system produces anti-PEG antibodies, resulting in rapid PD-EVLPs elimination[191,192] To mitigate this issue, researchers have explored alternative biocompatible molecules such as heparin to reduce immune rejection. Heparin competitively binds to the PD-EVLPs surface, creating steric hindrance that helps inhibit adsorption, prolonging circulation time. Additionally, its negative charge suppresses complement activation through electrostatic interactions.[193] In a glioblastoma model, heparin-modified PD-EVLPs exhibited a 3.2-fold increase in retention time, along with a 58% reduction in serum pro-inflammatory cytokine levels (C3a/C5a)[30] (Figure 9).

Surface charge modulation is another critical strategy. Introducing specific functional groups can adjust PD-EVLPs surface charge to near-neutral levels, minimizing electrostatic interactions with plasma proteins. In one study, polylysine, a positively charged polymer, was used to coat *Zingiber officinale* (ginger)-derived nanovesicles, successfully altering

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Table 3 Strategies for Modifying PD-EVLPs

Object	Plant	Modification	Modification	Linker	Targeting Ability	Ref
Stability	Ginger	Coating	Fucoidan (outer layer), ε-poly-lysine (middle layer)	–	Strengthen the biocompatibility and largely reduced the cardiotoxicity of free Dox Compared with the control mice, the fluorescence intensity in the tumor site of mice injected with modified EVLPs was 4.4 times higher after 24h, while the fluorescence intensity in the liver and spleen was greatly reduced.	[149]
	Asparagus cochinchinensis	Covalent coupling	PEG	–	Prolong the blood circulation time and increase the accumulation in tumor sites. In tumor tissues, the accumulated fluorescence intensity of modified drugs remained approximately three times that of unmodified counterparts during the 4–12 hour administration period. In circulation, the modified drug demonstrated tenfold higher fluorescence intensity at 4 hours post-administration compared to its unmodified counterpart. By 12 hours, while unmodified drugs had been nearly completely metabolized, the modified drugs maintained significantly elevated levels.	[183]
	Grapefruit	Covalent coupling	Heparin	–	Good anti-complement activation and circulation stability. The modified EVLPs had a higher maximum concentration after injection and a longer half-life of the loaded drug in the elimination phase, reaching 69.3h.	[30]
	Lemon	Covalent coupling	Heparin	EDC and NHS	Stability of blood circulation. The modified EVLPs had a higher maximum concentration after injection and a longer half-life of the loaded drug in the elimination phase, reaching 24h	[159]
	Herb	Covalent coupling	Chitosan and PEGylated graphene oxide	–	Increase the drug binding abilities and stability. After 10 days of preservation under the same conditions, the single-coupled EVLP was significantly aggregated, while the double-coupled EVLP still had particle morphology and biological activity.	[53]

Abbreviations: DOX, Doxorubicin; PEG, Polyethylene glycol; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; NHS, N-hydroxysuccinimide.

their originally negative charge.[149] This demonstrated that membrane fusion-based encapsulation could effectively regulate the electrostatic properties of PD-EVLPs.

"Camouflage" Strategies for Immune Evasion and Prolonged Circulation

Biomimetic membrane coating is an emerging strategy that confers PD-EVLPs with immune-evasion capability. For example, leukocyte membrane coating leverages leukocyte integrins, such as lymphocyte function-associated antigen-1 (LFA-1), and chemokine receptors to facilitate PD-EVLPs extravasation across vascular barriers, thereby targeting inflamed or tumor sites while avoiding complement activation.[189] Similarly, red blood cell (RBC) membrane coating has been widely applied in nanomedicine, because RBC membranes express cluster of differentiation 47 (CD47), a "do-not-eat-me" signal that reduces phagocytic clearance.[194] The PD-EVLPs fused with exogenous membranes can be therapeutic efficacy optimized through controlled-degradation design. Yang et al demonstrated that *Citrus limon*-derived extracellular vesicle-like particles achieve tumor-specific enrichment by embedding into the cell membrane of tumor cells, and undergo controlled degradation under acidic tumor microenvironment conditions, thereby promoting localized and sustained drug release.[195]

However, cross-species membrane fusion may alter the biological characteristics of PD-EVLPs by introducing novel antigens that trigger immune rejection. Additionally, significant lipid compositional differences between plant-derived

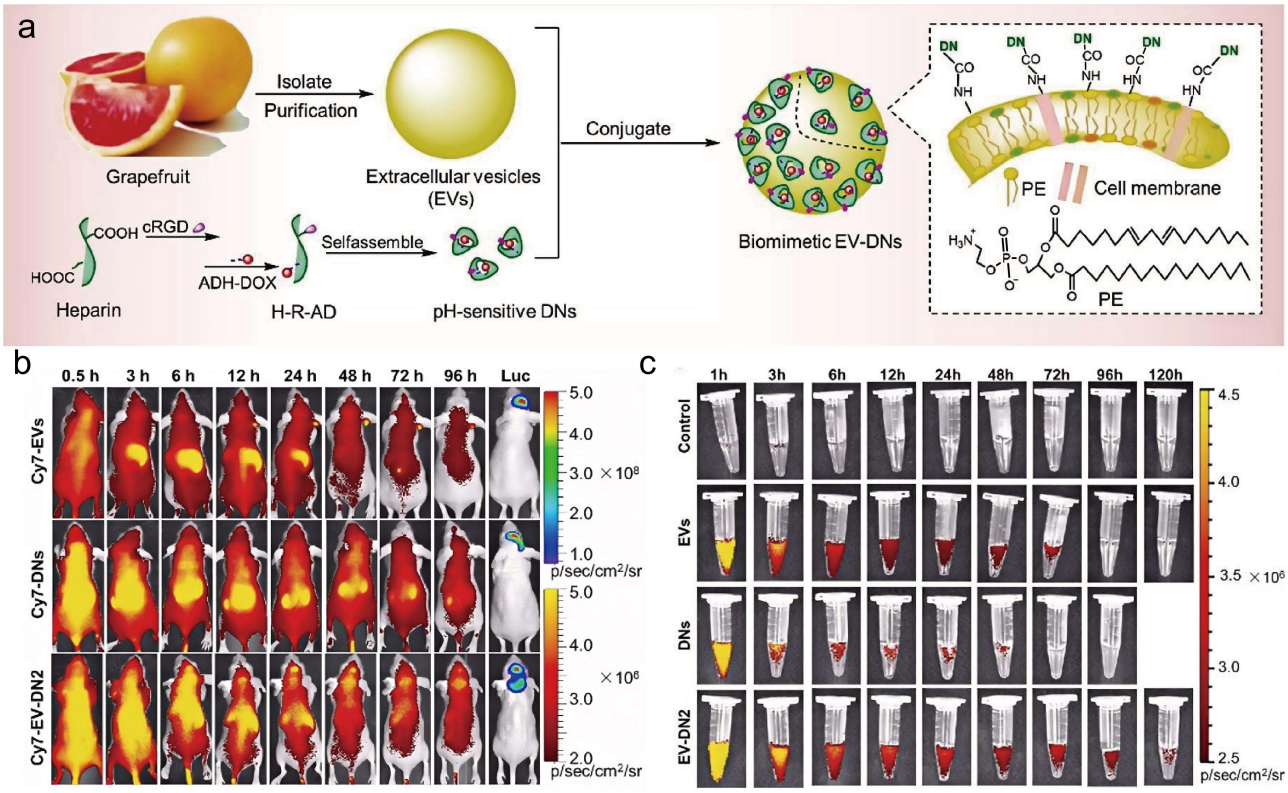

Figure 9 The example of prolonging the half-life of PD-EVLPs through modification. (**a**) The modification process of biomimetic EV-DNs. (**b**) Time-course in vivo fluorescence images of intracranial LN229-luc glioma-bearing mice following administration of different kinds of vesicle. (**c**) Time-course fluorescent imaging (IVIS) of rat serum after administration of different vesicles. Reprinted with permission from Niu W, Xiao Q, Wang X, et al. A biomimetic drug delivery system by integrating grapefruit extracellular vesicles and doxorubicin-loaded heparin-based nanoparticles for glioma therapy. Nano Lett. 2021;21(3):1484–1492. Copyright 2021 American Chemical Society.[30]
Abbreviations: cRGD, cyclic Arg-Gly-Asp; ADH, adipic acid dihydrazide; DOX, Doxorubicin; PE, phosphatidylethanolamine.

and mammalian vesicles may compromise membrane fusion stability and modification efficiency. These effects warrant further investigation.

Challenges and Future Directions in Engineering Modifications

Regardless of the modification approach used, it is crucial to consider the potential impact of these modifications on the intrinsic properties of PD-EVLPs. Changes in surface charge and modification density may affect the targeting ability of PD-EVLPs and therapeutic efficacy. Additionally, the distinct membrane compositions of plant-derived and animal-derived vesicles present a significant challenge, as many engineering strategies developed for mammalian extracellular vesicles may not be fully applicable to PD-EVLPs.

Future research should focus on evaluating the dynamic stability of PD-EVLPs in vivo and developing real-time monitoring technologies to track modification states within biological systems. Furthermore, proteomic analysis of PD-EVLPs interactions with biological components may provide new insights to optimize modification strategies. While these technologies remain largely experimental, their long-term safety and large-scale production feasibility should be further evaluated to facilitate clinical translation.

Key Considerations for Overcoming Stability Challenges

The clinical translation of PD-EVLPs hinges on overcoming a fundamental paradox: while their natural bioactivity and biocompatibility make them ideal drug carriers, their structural fragility and variability in physiological environments pose significant challenges. Stability is not a singular issue but an intricate interplay of vesicle composition, environmental interactions, and systemic processing. Addressing these challenges requires a paradigm shift—from merely

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optimizing storage conditions to redefining PD-EVLPs engineering by leveraging adaptive design principles, and rethinking their role within biological systems.

1. Stability should not be an afterthought but an intrinsic design principle – current efforts treat PD-EVLPs stability as a post-isolation issue, focusing on storage and preservation. A more fundamental approach would be engineering PD-EVLPs at the source level—genetically modifying plants to produce vesicles with inherently higher stability and optimized bioactive cargo. Meanwhile, rigorous validation of edited PD-EVLPs (eg, multi-omics profiling and functional assays) is essential before clinical translation to ensure their biocompatibility and bioactivity. Future collaborative efforts between plant biotechnologists and nanomedicine researchers will be pivotal in systematically addressing this question.
2. The immune system should be leveraged, not evaded – most modifications aim to enable PD-EVLPs to evade immune recognition. However, immune cells can be repurposed as active carriers, not just passive barriers. By exploiting the uptake of PD-EVLPs by macrophages these immune cells could serve as drug depots for sustained release within inflammatory microenvironments.
3. PD-EVLPs might not need to remain intact to be effective – Stability is typically equated with structural preservation, but in some cases, controlled degradation could enhance efficacy. If PD-EVLPs could be engineered to disassemble selectively at target sites, this might improve payload release efficiency and reduce off-target effects.
4. We are over-relying on extracellular vesicle paradigms from mammalian models – Many PD-EVLPs studies borrow strategies from mammalian EVs research without considering plant vesicles' distinct lipid compositions, structural properties, and evolutionary adaptations. A tailored stability framework specific to PD-EVLPs is necessary rather than forcing them into pre-existing EV models.
5. Current tracking methods create an illusion of stability – Most tracking studies rely on fluorescence labeling, assuming that detected signals represent intact PD-EVLPs. However, these signals could stem from degraded fragments, confounding stability assessments. More advanced degradation-sensitive tracking techniques are needed to truly measure PD-EVLPs integrity over time.
6. Stability challenges might require a paradigm shift from single-vesicle optimization to community-level engineering – Instead of stabilizing PD-EVLPs individually, they could be designed to function cooperatively, forming vesicle networks that enhance mutual stability, similar to biofilms or viral capsid assembly.
7. The goal should not just be stability, but controlled instability – The ideal PD-EVLPs should not be perfectly stable but rather exhibit "programmable degradation" tailored to different biological environments. A framework that integrates stability with controlled disassembly mechanisms could optimize PD-EVLPs performance across diverse applications.

Conclusion

PD-EVLPs show great promise as therapeutic agents and drug delivery vehicles due to their biocompatibility, bioactive cargo, and modifiability. However, stability remains a significant challenge that impedes their large-scale production, bioavailability, and clinical efficacy. Variations in lipid composition, storage conditions, and susceptibility to harsh physiological environments limit their functional lifespan. Engineering modifications, inspired by liposomal and exosomal technologies, offer potential solutions to enhance their stability. However, the long-term safety and scalability of these modifications remain areas requiring rigorous validation.

Future studies should prioritize developing standardized methods for PD-EVLP isolation, optimizing real-time monitoring of stability, and advancing targeted surface modifications to improve their functionality and lifespan. Moreover, overcoming challenges related to reproducibility, batch-to-batch variability, and large-scale production will be critical to their clinical translation. Only by ensuring both safety and stability can its potential for clinical application be validated in clinical trials. By focusing on these key areas, researchers can fully unlock the potential of PD-EVLPs for precision medicine and next-generation drug delivery.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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