DOI: 10.26599/FSHW.2026.9251265

Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Food-Derived Extracellular Vesicles: Biogenesis Mechanisms, Functional Characteristics, and Therapeutic Potential for Disease Treatment

Qi Shen[a,b,c], Weizhong He[d], Yujie Chen[a,b,c], Xin Lü[a,b,c*], Cheng Wang[d,*]

[a]*College of Food Science and Engineering, Northwest A&F University, Yangling, 712100, Shaanxi, China*

[b]*Shaanxi Engineering Research Centre of Dairy Products Quality, Safety and Health, Yangling, Shaanxi, China*

[c]*National Yangling Agricultural Comprehensive Engineering Technology Research Center, Yangling, Shaanxi, China*

[d]*Xinjiang Academy of Agricultural Sciences, Urumqi 830091, Xinjiang, China*

ABSTRACT: Food-derived extracellular vesicles (FDEVs) are a class of naturally occurring nanoscale bioactive carriers found in various edible plant and animal-derived foods. With their low immunogenicity, high biocompatibility, and innate targeting capabilities, FDEVs have emerged as promising candidates for disease prevention, health promotion, and food-based therapeutic delivery strategies. Growing evidence indicates that these vesicles play crucial roles in supporting multiple physiological functions relevant to human health. This review systematically integrates recent advances in FDEVs biogenesis mechanisms, isolation and purification techniques, and physicochemical and biological characterization, emphasizing validated mechanisms and preclinical evidence in anti-tumor, anti-inflammatory, and hypoglycemic effects. Furthermore, we explore the potential of FDEVs as natural, safe, and efficient nanocarriers for functional foods and precision nutrition interventions. We also analyze key bottlenecks hindering their translation, including the lack of scalable separation processes and standardized quality control systems. Addressing these challenges is crucial for advancing FDEVs as next-generation functional food active ingredients, offering novel strategies to improve population health and develop targeted nutritional interventions.

Keywords: Food-derived extracellular vesicles; Isolation and extraction; Therapeutic effects; Drug delivery potential; Translational challenges; Plant-specific markers; Large-scaleproduction; Targeted modification

1. Introduction

Food-derived extracellular vesicles (FDEVs) are membrane-bound nanostructures ubiquitously present in various dietary sources, including milk, edible plants, cereals, and edible fungi. These nanovesicles typically exhibit a saucer-like morphology with diameters ranging from approximately 30 to 200 nm[1,2], positioning them as naturally occurring nanoscale drug delivery systems. FDEVs possess heterogeneous molecular compositions and interact with biological systems via distinct mechanisms[3]. Increasing evidence demonstrates that plant-based diets confer significant health benefits; FDEVs not only encapsulate endogenous bioactive compounds but also exhibit cross-kingdom regulatory capacity[4,5], which underpins

***Corresponding author**
xinlu@nwsuaf.edu.cn; wangchengxj321@sina.com

Received 26 October 2025
Received in revised from 1 December 2025
Accepted 21 April 2026

their unique potential in synthetic biology, nanomedicine, and personalized therapeutic applications(Figure 1).

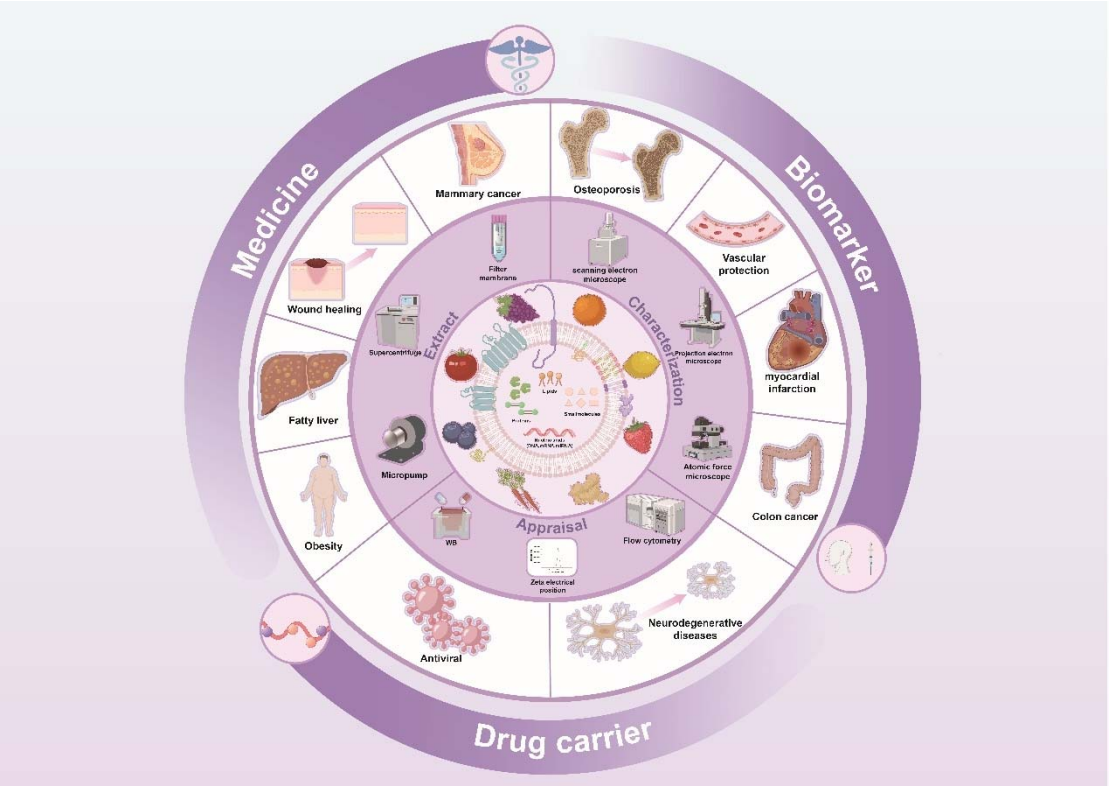


Fig.1 Food-derived extracellular vesicles (FDEVs) are natural nanocarriers that promote health and reduce the risk of associated diseases. Following isolation and characterization, they serve as targeted delivery vehicles to transport bioactive payloads to sites of inflammation, oxidative stress, and metabolic homeostasis regulation. Their applications span functional food development, biomarker discovery, and therapeutic interventions for cardiovascular, skeletal, metabolic, and neuroprotective benefits.

Compared to mammalian exosomes, FDEVs offer distinct advantages as biocompatible nanocarriers for biomedical applications: (1) The structural barrier of the plant cell wall significantly reduces pathogen-associated molecular patterns (PAMPs) on FDEVs[6], thereby lowering immunogenicity and minimizing the risk of cytokine storm following systemic administration, substantially enhancing clinical safety[7]; (2) Edible plants naturally contain bioactive phytochemicals, such as polyphenols, flavonoids, saponins, and alkaloids[8,9], which can be endogenously encapsulated within FDEVs, conferring intrinsic therapeutic potential without requiring additional chemical modification; (3) The abundant availability and cost-effectiveness of plant biomass facilitate scalable production of FDEVs, positioning them as economically viable platforms for large-scale nanotherapeutic manufacturing. Recent studies have demonstrated that FDEVs derived from fruits (grapes[10], strawberries[11], lemons[12]), vegetables (ginger[13], bitter melon[14], yam[15]), and cereals (rice[16], sorghum bicolor[17]) exhibit beneficial bioactivities across multiple preclinical disease models.

FDEVs modulate cellular signaling pathways through their unique biomolecular cargo and cellular uptake mechanisms. FDEVs from citrus[18], papaya[19], and ginger[20] attenuate inflammation by upregulating anti-inflammatory gene expression, while grapefruit[8] and lemon[12] derivatives demonstrate potent antitumor activity through multiple pathways. Notably, lemon-derived FDEVs inhibit nephrolithiasis progression[21], suppress gastric cancer growth[12], prevent viral infections[22], and exert potent antioxidant and anti-

inflammatory effects[23]. Furthermore, nanovesicles isolated from organically cultivated plants often yield higher particle concentrations and enhanced antioxidant capacities compared to conventional sources. Organic production transcends the mere avoidance of synthetic chemical inputs; it emphasizes locally adapted ecological processes and biogeochemical cycles to preserve biodiversity and promote long-term ecological sustainability. In recent comparative analyses, nanovesicles were isolated from organically and conventionally cultivated fruits of four species—kiwifruit (Actinidia chinensis), lemon (Citrus limon), grapefruit (Citrus paradisi), and blood orange (Citrus sinensis 'Blood Orange')—and characterized by nanoparticle tracking analysis (NTA) and colorimetric assays for total antioxidant capacity. Organic cultivation yielded significantly greater numbers of nanovesicles across all tested species: 22% more in A. chinensis ($P < 0.001$), 36% more in C. limon ($P < 0.05$), 39% more in C. paradisi ($P < 0.05$), and 49% more in C. sinensis 'Blood Orange' ($P < 0.0001$), relative to conventional counterparts. Cultivation system also affected vesicle morphology: nanovesicles from organic fruits exhibited a smaller mean diameter than those from conventional fruits ($P < 0.05$)[24,25]. These findings indicate that agricultural practice can influence both the abundance and physical properties of plant-derived nanovesicles.

This review comprehensively examines the biogenesis, molecular composition, isolation methodologies, and physicochemical characterization of FDEVs, along with their biological functions and therapeutic applications in preclinical disease models, including inflammatory, metabolic, cardiovascular, cerebrovascular, and oncological conditions. Furthermore, we analyze emerging trends and future research directions for FDEV-based nanotherapeutics, proposing translational strategies to accelerate clinical implementation of FDEVs in precision medicine.

2. Biogenesis and cargoes of FDEVs

2.1 Exosomal biogenesis

Studies have identified three primary pathways involved in the biogenesis of FDEVs: the multivesicular body (MVBs) pathway, the extracellular-positive organelle (EXPO) pathway, and the vesicles pathway[26–28](Figure 2). However, it is crucial to note that a unified biogenesis pathway for EVs derived from plants, animals, and edible fungi has not yet been fully standardized. Milk extracellular vesicles (EVs) may originate from two sources: they can be secreted directly by mammary epithelial cells, or released from cellular crescents associated with milk fat globules, which contain exosome-like vesicles [29].Unlike animal cells, secretion in plant and fungal cells is hindered by the presence of the plant cell wall. necessitating specialized mechanisms for vesicular release that are currently the subject of active investigation.

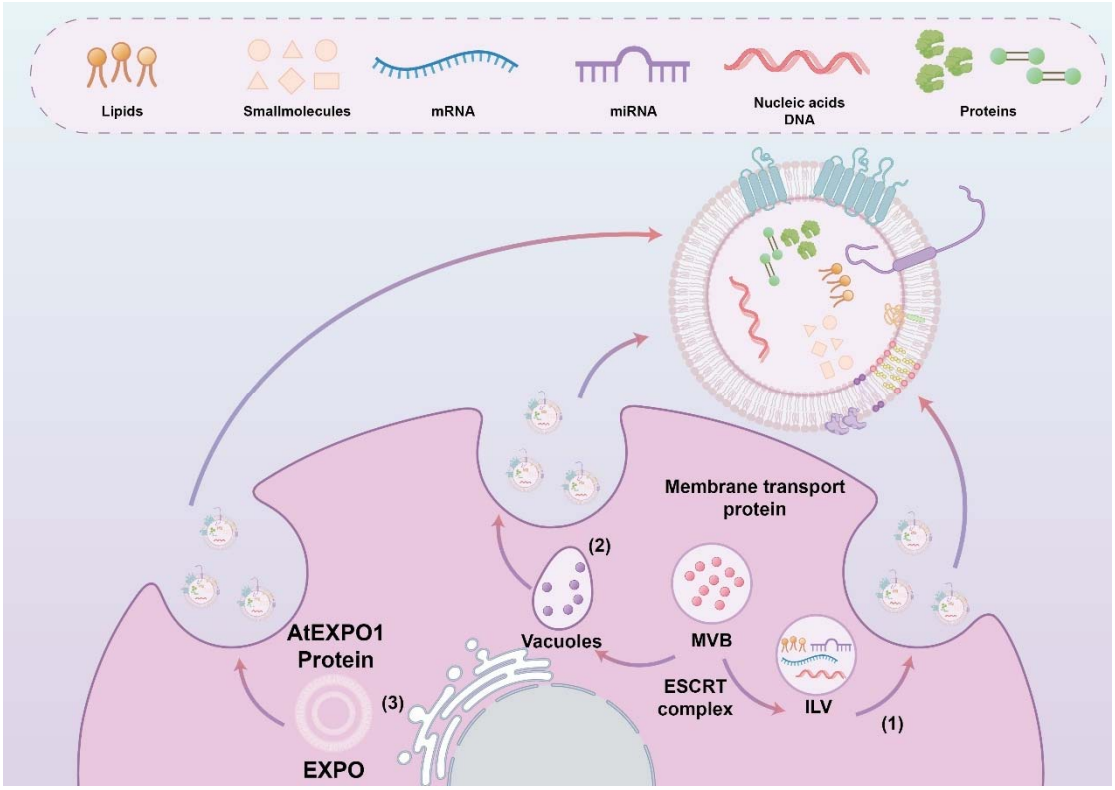


Fig. 2 Mechanism of nanovesicle formation. (1) Multivesicular body pathway; (2) Vesicles pathway; (3) Extracellular-positive organelle pathway.

MVBs and their contents exhibit two distinct fates: one is being directionally transported to lysosomes for degradation, and the other is being delivered to the cell surface, followed by fusion with the plasma membrane. A critical step in MVB formation, where protein sorting occurs, involves the maturation of intraluminal vesicles[30]. This process is largely mediated by the endosomal sorting complex required for transport (ESCRT) machinery, which consists of four protein complexes (ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III) and the associated AAA ATPase VPS4. ESCRT-0 components, including Hrs (hepatocyte growth factor-regulated tyrosine kinase substrate) and TSG101 (tumor susceptibility gene 101), together with ESCRT-I component STAM1, promote the recognition and sequestration of ubiquitinated cargo into nascent ILVs. Depletion of these components markedly reduces exosome secretion. By contrast, knockdown of ESCRT-III–associated factors (CHMP4C, VPS4B, and VTA1) has been reported to increase exosome release, suggesting that these proteins help regulate the balance between degradative and secretory MVB destinies. In addition to ESCRT-dependent sorting, ESCRT-independent mechanisms have been described, involving tetraspanins (CD9, CD63, CD82, and Tspan8) and the syndecan–syntenin–ALIX pathway. In the latter, syntenin binds ALIX to couple heparan sulfate proteoglycans to ESCRT-associated membrane remodeling and thereby facilitate cargo sorting[31]. Regarding animal EVs, milk EVs, while their biogenesis primarily involves the MVB pathway, the specific regulatory factors are complex and still under investigation.

EXPOs are double-membraned, spherical organelles that merge with the plasma membrane to release vesicles[28,32]. This pathway is a plant-specific unconventional secretion mechanism, reflecting the uniqueness of plant cells in vesicles secretion. The molecular regulation of the EXPO pathway involves plant-specific genes such as Arabidopsis thaliana EXPO1 (AtEXPO1), which encodes a membrane-associated protein

essential for the formation and trafficking of EXPO structures. AtEXPO1 facilitates the unconventional secretion of soluble proteins lacking signal peptides, a process distinct from the canonical ER-Golgi secretory pathway. Unlike the ESCRT-dependent MVB pathway predominant in animal cells, the EXPO pathway operates independently of ESCRT machinery, highlighting fundamental differences in vesicle biogenesis mechanisms between plant and animal kingdoms[33].

The extent of exosome release is cell type-dependent and can be regulated by different cellular conditions or external factors[34]. Specifically, various cellular stress conditions profoundly modulate FDEVs secretion through distinct molecular mechanisms. For instance, irradiation, cisplatin treatment, hypoxia exposure, and endoplasmic reticulum (ER) stress can all increase exosome release[35]. Hypoxia-induced activation of hypoxia-inducible factor 1-alpha (HIF-1α) has been reported to enhance small extracellular vesicle (sEV) release by upregulating the expression of RAB27A, which controls exosome secretion[36]. These stress-responsive changes in FDEV release underscore their role in cellular homeostasis and intercellular stress communication. Crucially, during these biogenesis processes, specific biomolecules, including proteins, lipids, and nucleic acids, are selectively sorted and loaded into the vesicles. The composition of this molecular cargo defines the biological function of FDEVs.

2.2 FDEVs cargoes

The specific molecular components encapsulated within FDEVs, collectively termed "cargoes," are critical determinants of their biological functions and therapeutic potential. These cargoes are selectively packaged during the biogenesis processes, making FDEVs natural nanocarriers capable of delivering diverse biomolecules. It is worth noting that the biological activity of FDEVs is indeed a complex and intricate system; it is not determined by a single internal cargo, but rather shaped by the composition of the vesicle membrane and the synergistic interactions among the internal biomolecules[37]. This synergy profoundly influences the stability, tissue tropism, cellular uptake, and critical endosomal escape of PDEVs, ultimately determining the bioavailability and functional efficacy of the ribonucleic acid (RNA), proteins, and metabolites they carry within recipient cells[38].

2.2.1 Proteins

Exosome composition varies depending to their cellular or tissue origin; however, all exosomes，Including FDEVs, consistently contain membrane transporters and fusion proteins (such as GTPases, annexins, and flotillin), heat shock proteins (HSP70 and HSP90), tetraspanins (CD9, CD63, CD81, and CD82), proteins involved in MVB biosynthesis (Alix and TSG101), and lipid-associated proteins[39,40]. The proteins CD9, CD63, CD81, HSP70, TSG101, and Alix are notably enriched in exosomes, commonly used as exosome markers[39], and essential for intercellular communication and signaling. Of note, these proteins are integral to intercellular communication and cellular functions. Several studies have reported that the cytosolic proteins in PDVLNs include the enzymes involved in cell wall remodeling and that they provide antifungal and antibacterial defenses against invading pathogens[41].

2.2.2 RNAs

RNAs in FDEVs primarily comprise mRNAs, miRNAs, and small RNAs (sRNAs). Both mRNAs and non-coding RNAs (ncRNAs) can regulate protein expression in recipient cells, influencing cellular morphology and function[42]. miRNAs, a specific class of small ncRNAs, are pivotal in the posttranscriptional regulation of protein levels and participate in various physiological and pathological processes, including cell proliferation, metabolism, and immune responses[43]. Plant-based exosomal miRNA (which protects RNase) was shown to be delivered to humans in a cross-kingdom fashion[44]， these exosome-derived miRNAs can regulate intercellular signaling pathways[45]; inducing functional alterations that impact on tumor progression and metastasis [46]. The encapsulation of these RNAs within the FDEV lipid bilayer effectively protects them from enzymatic degradation, thereby enhancing their stability and bioavailability in target cells[47]. This inherent protection mechanism positions FDEVs as highly promising natural nanocarriers.

2.2.3 Lipids and metabolites

The primarily phosphatidic acid (PA), phosphatidylglycerol (PG), phosphatidylcholine (PC), phosphatidylinositol (PI), and phosphatidylethanolamine (PE), are fundamental components of FDEVs[43,48,49]. In addition, glycolipids in plant cytoplasmic membranes, such as dilactosyl diacylglycerol (DGDG), monogalactosyl diacylglycerol (MGDG), and monogalactosyl monoacylglycerol (MGMG), are also important components of FDEVs[31]. These lipids are crucial for the organizing and regulating the cell membrane structure and function. The phospholipid bilayer effectively shields endogenous miRNAs, proteins, and other active molecules from enzymatic degradation and acidic environments. Research indicates that lipids in FDEVs contribute to microbiota regulation in two ways: by facilitating cell-specific uptake of the nanovesicles[50] and regulating the microbiota[51].

FDEVs are rich in secondary metabolites. For example, citrus nanovesicles contain high levels of fructose, citric acid, glucose, sucrose, inositol, and various monosaccharides and disaccharides and their derivatives[8]. Similarly, lemon-derived exosome-like nanoparticles include active compounds such as eriocitrin, quercetin, vicenin-2, naringin, hesperidin and limonoids, like limonin [23]. Most of these natural compounds exert beneficial roles, such as anti-inflammatory[52]; anti-oxidant[53,54].

3. Extraction methods and quality control for FDEVs

Extracellular vesicles (EVs) from different sources exhibit significant heterogeneity in composition and physicochemical properties, necessitating the selection of an appropriate extraction method for each source. In addition, extraction methods vary in recovery and purity, and processing may compromise vesicle membrane integrity. Therefore, establishing reproducible and scalable extraction strategies that minimize damage, together with a systematic quality control framework, is a critical prerequisite for obtaining high-quality FDEVs and supporting subsequent mechanistic studies, formulation development, and clinical evaluation.

3.1 FDEVs extraction methods

A variety of FDEVs extraction methods have been reported. In this paper, we briefly summarize the advantages and disadvantages of these techniques, as shown in Table 1. Currently, ultracentrifugation and sucrose density gradient centrifugation are the main methods by which FDEVs are extracted[55], .These methods offer high purity and relatively standardized protocols; however, they are cumbersome and time consuming, require specialized ultrahigh speed centrifuges. The choice of isolation technique significantly dictates the physical characteristics and biological potency of the resulting vesicles. For instance, field emission scanning electron microscopy (FESEM) analysis reveals that ultrafiltration (UF) isolates vesicles with higher morphological and size variability compared to precipitation and UC methods. Dynamic light scattering (DLS) measurements further confirm these differences, with mean diameters of FDEVs isolated via UF, precipitation, and UC recorded at 122, 89, and 60 nm, respectively. Critically, these structural variations translate to differences in bioactivity; AlamarBlue assays demonstrate that FDEVs obtained through UF, precipitation, and UC increase the viability of damaged cells by 11%, 15%, and 22%, respectively[56]. This suggests that while multiple centrifugation steps in the UC method may lead to some nanoparticle loss, the higher purity and structural integrity achieved often result in superior functional performance compared to other methods (Figure 3).

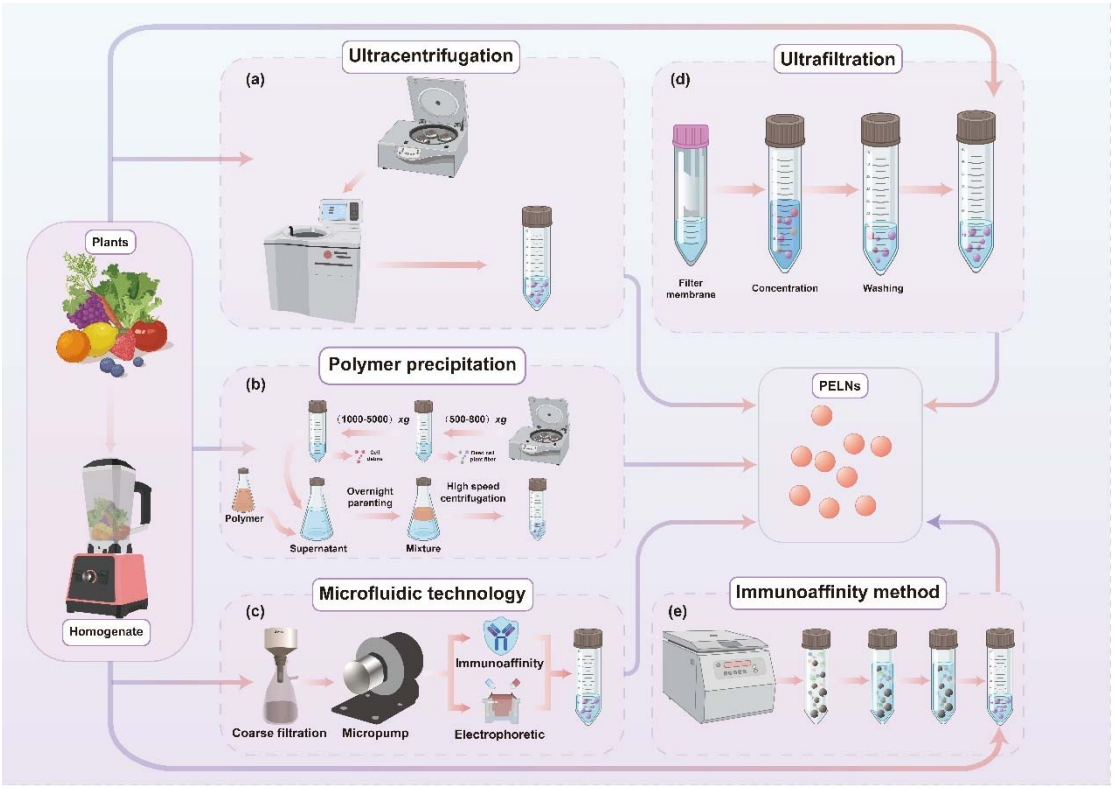


Fig.3 The isolation techniques of FDEVs. (a) Ultracentrifugation. (b) Polymer precipitation. (c) Microfluidic technology. (d) Ultracentrifugation. (e) Immunoaffinity capture.

Table 1 Comparison of different FDEVS extraction methods

Approaches	Separation principle	Advantages	Disadvantages	Source
Ultracentrifugation/ Sucrose density gradient ultracentrifugation	Based on differences in density, cellular debris are removed through stepwise centrifugation, and exosomes are ultimately precipitated using ultrahigh speed centrifugation.	no chemicals added; suitable for a wide range of plants.	Time consuming; requires expensive equipment; may disrupt the vesicle structure.	Grapefruit and tomato[9], Momordica charantia[57], Cabbage[58], Turmeric[59]
Polymer-based precipitation	Polymers are used to reduce exosome solubility, which leads to their precipitation, and the precipitate can be collected by low speed centrifugation.	Simple operation; suitable for large-scale applications; low cost.	Low purity; remaining polymer residue affects subsequent analyses.	Ginger[60], Garlic[61],[62]
Ultrafiltration	Large particles are removed and the exosomes are concentrated by gradient filtration through membranes with different pore sizes.	Time efficient; no need for centrifugation equipment; suitable for large volume samples.	Low purity; Risk of membrane clogging; possible loss of small exosomes.	Cabbage [63],Orange[18]
Size-exclusive chromatography	Particles of different sizes are separated using a porous gel column, wherein exosomes elute preferentially due to their large size.	High purity; preserves vesicle integrity; suitable for small samples.	High equipment cost; time consuming.	Broccoli[64],[65]
Microfluidics technology	Precise isolation of exosomes with a microfluidic chip.	High purity; high throughput; can be automated.	The need for expensive equipment; complex chip design; parameters need to be optimized.	[66,67]
Immunoaffinity capture	Exosomes are isolated using magnetic beads that specifically bind to surface markers of exosomes, such as the transmembrane protein CD63.	High purity; High specificity; capable of targeting specific subpopulations.	High costs; strong antibody dependence; potential omission of exosomes lacking markers.	[68],[69]
Asymmetrical flow field-flow fractionation	Asymmetrical field-flow fractionation applies a cross-flow perpendicular to the main channel flow, pushing exosomes and other particles towards a semi-permeable membrane wall to form an accumulation layer. Particles with different hydrodynamic sizes/diffusion coefficients reach distinct equilibrium heights within this layer due to the balance between cross-flow and Brownian motion, then elute sequentially based on their position in the parabolic velocity profile, achieving size-based separation.	Offers high resolution, broad separation range, label-free operation, gentle and rapid separation, excellent reproducibility, and high recovery rates.	High instrumentation and method development costs, sensitivity to operational parameters, and relatively limited throughput, coupled with potential membrane adsorption/fouling, can lead to sample loss and reproducibility issues.	[70,71]

3.2 Biosafety of FDEVs

FDEVs offer notable biosafety advantages over animal-derived vesicles, they do not carry zoonotic or human-specific pathogens[72], which makes them attractive as therapeutic delivery vehicles. However, this advantage depends critically on the quality of the source material. Raw plant materials from high-input, intensive agriculture can contain pesticide or fungicide residues, heavy metals, or mycotoxins, whereas organically cultivated and traceable inputs generally have lower contamination burdens[42]. Importantly, biosafety risk is determined not only by the presence of contaminants but also by how those contaminants interact with FDEVs. These interactions can be classified into three principal modes, governed by pollutant physicochemical properties and vesicle membrane composition: (1) Free molecules—contaminants exist as independent species in the FDEVs suspension and, under appropriate conditions, can be removed by standard isolation methods (e.g., ultracentrifugation, density-gradient separation, or polymer-based precipitation); (2) Surface adsorption-lipophilic or charged contaminants (for example, certain organophosphorus pesticides or polycyclic aromatic hydrocarbons) may adhere to the lipid bilayer via van der Waals, hydrophobic, or electrostatic interactions, forming relatively stable but reversible complexes; (3) Lipid encapsulation—highly lipophilic toxins or complexes that interact strongly with membrane components may become embedded within the hydrophobic region of the lipid bilayer, producing more stable, internalized complexes that can evade conventional purification and potentially gain entry into recipient cells via endocytic pathways[73]. Given these possibilities, a rigorous quality-control program is essential: at minimum it should include sterility testing for bacteria and fungi and quantitative endotoxin assays to exclude microbial contamination and pyrogenic risk, and for products intended for human use should also incorporate in vitro cytotoxicity testing on relevant normal human cell types at therapeutically relevant concentrations to inform subsequent in vivo and clinical translation.

4. Characterization and identification of FDEVs

FDEVs are usually spherical in shape when isolated and facilitate cell wall passage. The size of FDEVs is generally between 50 and 1,000 nm and varies according to plant origin and isolation technique[26,74]. Studies have shown that plant exosomes are similar in size and structure to mammalian exosomes[75]. Comprehensively characterizing of their structure and composition is crucial for understanding their functional mechanisms and ensuring their reliability and stability in practical applications. Common FDEVs characterization techniques include transmission electron microscopy (TEM), dynamic light scattering (DLS), and nanoparticle tracking analysis (NTA), which assess morphology, particle size, and zeta potential, respectively. In addition, can be analysed by western blotting and flow cytometry[3], Current research offers a far richer arsenal of markers for mammalian EVs, yet plant-specific markers remain scarce. This scarcity of specific molecular markers for FDEVs poses a significant challenge for their definitive identification, accurate quantification, and differentiation from other co-isolated nanoparticles or cellular debris. To systematically

identify FDEVs, we recommend a multiparametric characterisation strategy. On one hand, integrate evaluation of physical properties (size, morphology and ζ-potential) with molecular profiling (specific markers and cargo analysis) to confirm purity and functional integrity. On the other hand, alongside structural and compositional characterisation, perform functional assays that verify bioactivity to definitively establish FDEVs identity and demonstrate efficacy.

4.1 Ultrastructural characterization

The ultrastructures of FDEVs are typically characterized using TEM, scanning electron microscopy (SEM), or atomic force microscopy (AFM). These techniques are the most convenient and effective for observing and identifying the shapes of FDEVs.

TEM is a crucial technique for assessing the ultrastructure of FDEVs, offering images with nanoscale resolution that reveal the double-layer membrane and internal features of FDEVs[76]. In contrast, SEM is used for examining the surface morphology and three-dimensional structure of FDEVs, although its resolution is inferior to that of TEM[10]. Cryo-transmission electron microscopy (cryo-TEM) has an advantage over SEM and TEM, as it avoids the effects of dehydration and chemical fixatives by analyzing samples at very low temperatures without extensive fixation or staining[77]. AFM is a versatile and powerful technique for characterizing the morphology of nano- and submicron-sized materials[78]. AFM can nondestructively and clearly reveal the morphology and structure of FDEVs; however, this technique is more complicated to perform and has stringent sample surface requirements[79].

4.2 Particle size and zeta potential measurements

The particle size and zeta potential of FDEVs are typically assessed via DLS and NTA. These techniques determine the hydrodynamic size distribution and surface charge properties of exosomes, facilitating the analysis of their integrity and stability[80]. In addition to the techniques described above, exosomes can be characterized via a variety of other methods. Flow cytometry can be used to characterize exosomes by using fluorescently labeled antibodies that bind to specific antigens on the surface of the exosome followed by laser excitation for fluorescent signal detection[81,82]. Enzyme-linked immunosorbent assays (ELISAs) can be used to quantify specific proteins or other molecules in exosome samples via high-sensitivity and high-specificity antibody-based detection[83,84]. Techniques such as mass spectrometry[85] and RNA sequencing[86] can also be used for exosome identification, as these methods can offer insight into the functional roles of exosomes and their origins, providing a more comprehensive perspective in the study and application of exosomes.

4.3 Stability of FDEVs

In the quality-control framework for FDEVs, stability is a key evaluation metric. FDEVs stability is primarily influenced by storage temperature, freeze–thaw cycles, and pH. Notably, FDEVs demonstrate excellent intrinsic stability, particularly in the gastrointestinal environment, they can withstand gastric acidity (pH) and degradation by digestive enzymes such as pepsin and trypsin[87]. This resilience derives from their

native lipid bilayer, which effectively protects internal bioactive cargos (miRNAs and proteins), allowing intact delivery to and uptake in the intestine[88]. To further enhance production control, temporary immersion bioreactor systems (TIBS) combine plant tissue culture with airlift and hydraulic engineering principles to mimic plant physiological needs and enable standardized production of PDEVs in a highly controlled environment. TIBS not only substantially improves product stability but also mitigates the quality fluctuations commonly encountered in conventional preparation processes[89–91].

Storage conditions critically impact the quality of isolated PELNs, as maintaining membrane integrity is essential for preserving their biological activity. Generally, storage at temperatures below -70 ℃ is considered optimal for exosomes. To prevent membrane damage induced by freezing, cryoprotectants such as trehalose, dimethyl sulfoxide (DMSO), or glycerol are often employed. In contrast, storage at ambient temperatures above -25 ℃ is strongly discouraged due to rapid degradation[92].Current best practices recommend storage at in phosphate-buffered saline (PBS) to preserve the structural integrity of PELNs[93]. Previous research has demonstrated that plant-derived exosomes in liquid form remain stable at, with no significant alterations in particle size or morphology even after one year of storage[94]. Furthermore, while lyophilization facilitates storage and allows for convenient reconstitution, repeated freeze-thaw cycles must be avoided as they significantly diminish both exosome concentration and protein content. Notably, the stability of exosomes varies depending on their biological source and their response to different preservation processes.

5. Applications of FDEVs in disease treatment

FDEVs are structurally similar to mammalian exosomes, and both can efficiently transfer plant components, including small RNAs, into human cells to exert various therapeutic effects[95]. We summarize some of the applications of FDEVs in disease therapy in detail in Table 2. FDEVs are very promising tools for the treatment of a wide range of diseases, and their therapeutic potential has recently been demonstrated in several models, such as wound healing[96], periodontitis[97], and neurodegenerative disorder models[98]. In particular, owing to their endogenous origin, exosomes avoid immune recognition and clearance better than exogenous nanovesicles do[99] and could thus be used in the future as novel functional components of human disease therapeutics.

5.1 Inflammatory diseases

FDEVs show great potential as anti-inflammatory agents. Recent findings have demonstrated that edible exosome-like nanoparticles derived from *Portulaca oleracea* L. can effectively alleviate DSS-induced colitis by promoting the growth of *Lactobacillus reuteri* and increasing indole derivative levels, which activate the aryl hydrocarbon receptor (AhR) in conventional + T cells, downregulate expression, reprogram conventional + T cells into double-positive + T cells, and consequently decrease the expression of proinflammatory cytokines[100]. Grape exosome-like nanoparticles can be internalized by mouse intestinal stem cells, and their lipid components specifically phosphatidic acid (PA), Induce the proliferation of Lgr5hi intestinal stem cells via the Wnt/β-catenin pathway, thus preventing DSS-induced colitis[101]. Broccoli-derived

nanoparticles(BDNs), can target dendritic cells (DCs). After uptake, these BDNs, particularly their sulforaphane (SFN) components, activate AMP-activated protein kinase (AMPK) in DCs. This activation leads to the inhibition of DCs activation and the induction of tolerant DCs, thereby reducing the release of pro-inflammatory cytokines such as TNF-α, IL-12, and IFN-γ, while promoting anti-inflammatory responses. This entire process contributes to the amelioration of DSS-induced colitis in mice [102]. Moreover, researchers have shown that blueberry-derived exosome-like nanoparticles can increase the mitochondrial content in cells, inhibit MMP-1 production, decrease the expression of apoptosis-related proteins, promote the transcription of antioxidant enzymes through Nrf2, and protect cells from inflammatory damage via HMOX1 regulation[103]. Exosomal miR-7972 derived from fresh Rehmanniae Radix nanovesicles alleviated lipopolysaccharide (LPS)-induced lung inflammation and restored intestinal dysbiosis by targeting the GPR161-mediated Hedgehog pathway[104]. These studies revealed the molecular mechanisms by which FDEVs can modulate the inflammatory microenvironment through multiple components to exert synergistic effects, suggesting their considerable potential in anti-inflammatory therapy.

5.2 Metabolic diseases

In terms of regulating insulin resistance, the oral administration of ginger-derived nanoparticles (GDNPs) to mice fed a high-fat diet (HFD) significantly improved the host's glucose tolerance and insulin response. Mechanistically, the GDNPs induce the expression of miR-375 and VAMP7, which subsequently regulate the expression of AhR, thereby preventing HFD-induced insulin resistance[105]. Another study revealed that natural exosome-like nanoparticles in mung bean sprouts could reduce oxidative stress by activating the PI3K/Akt signaling pathway. This activation upregulates GLUT4 and Nrf2, downregulates GSK-3β, and promotes the production of antioxidant enzymes such as HO-1 and SOD. These nanoparticles, referred to as MELNs, activate the PI3K/Akt signaling pathway and inactivate GSK-3β, thereby slowing the progression of type 2 diabetes in a HFD/streptozotocin (STZ)-induced mouse model[106]. Tangerine peel-derived exosome-like nanovesicles significantly improved glycolipid metabolism by modulating genes related to glucose and lipid metabolism (UCP1, FGFR4, PRDM16, PGC-1α, Tmem26, Cpt1, Cpt2, and PPAR-α), thereby reducing lipid accumulation in 3T3-L1 and AML-12 cells[107]. Overall, plant exosome nanoparticles from various sources regulate insulin resistance and metabolic processes through multiple mechanisms, providing new strategies and potential drug carriers for the treatment of metabolic diseases.

5.3 Tumors

FDEVs have also demonstrated significant advantages in tumor therapy. For example, the protein components within fig exosome-like nanoparticles (FELNs) have been shown to downregulate the expression of the key gene RN7SL1 in breast cancer cells. This downregulation of RN7SL1 consequently inhibits the proliferation of breast cancer cells, thereby suppressing the progression of breast cancer bone metastasis[108]. Ginseng-derived exosome-like nanoparticles (GENs) exhibit significant therapeutic effects against gliomas by actively penetrating the blood-brain barrier (BBB) and modulating the tumor microenvironment (TME).

Specifically, GENs, which contain bioactive components including miR396f, inhibit glioma progression by downregulating key apoptosis-related genes like c-MYC. Furthermore, GENs enhance the recruitment of M1 macrophages to the TME, induce T cell activity, and suppress regulatory T cells, thereby orchestrating a favorable anti-tumor immune response both in vitro and in vivo. Positions GENs as promising candidates for inhibiting glioma progression and regulating tumor-associated macrophages (TAMs) both in vitro and in vivo.[109]. Cucumber-derived nanovesicles (CDNVs) inhibited the proliferation of human non-small cell lung cancer cells by inhibiting signal transduction and transcription 3 activation activators, generating reactive oxygen species, promoting cell cycle arrest, and activating the caspase pathway. These CDNVs exhibited strong anticancer effects in vitro and in vivo and did not show any significant toxicity to the visceral organs of mice on the basis of their ability to reduce the tumor growth rate[110]. Nanoparticles originating from different species present unique mechanisms of tumor cell proliferation inhibition, microenvironment remodeling and metastasis control by carrying specific bioactive molecules.

5.4 Cardiovascular diseases

FDEVs have therapeutic potential by regulating intracellular physiological processes through the intercellular transport of bioactive molecules. Both in vitro and in vivo studies have validated the intrinsic therapeutic functions of FDEVs in various diseases. FDEVs are also widely used in the field of cardiovascular disease therapy. For example, miRNA164a/b-5p in *Solanum lycopersicum*-derived exosome-like nanovesicles reduces the expression of Keap1 mRNA, which increases the nuclear translocation of Nrf2, enhances the expression of antioxidant genes, and mitigates oxidative stress, thereby alleviating restenosis after vascular injury[111]. The ability of *Momordica charantia* L.-derived exosome-like nanovesicles (MC-ELNs) against doxorubicin (DOX) cardiotoxicity in vivo and in vitro is based on the mechanism by which these MC-ELNs restore the DOX-induced ubiquitination and degradation of p62 and promote cardiomyocyte survival[57]. *Panax notoginseng*-derived exosome-like nanoparticles(PDNs) attenuate cerebral ischemia/reperfusion (CI/R) injury by altering the phenotype of microglia from the proinflammatory M1 type to the anti-inflammatory M2 type, which is achieved through the activation of the PI3K/Akt signaling pathway. Furthermore, the lipids within PDNs have been identified as the major therapeutically effective components responsible for this microglia polarization and the amelioration of CI/R injury [112]. In addition, FDEVs can be used to treat other cardiovascular diseases, such as aortic dissection[113] and vascular calcification[114].

Table 2. Potential effects of FDEVs for disease treatment.

Sources	Condition(s) Treated or Function	In Vivo	In Vitro	Mechanism (s)	Ref
Grapes	Colitis	Lgr5+ intestinal stem cells	Lgr5-EGFP-IRES-CreERT2 mice	Promoted intestinal tissue regeneration and repair by promoting intestinal stem cell proliferation and activating the Wnt/β–catenin signaling pathway, thereby protecting mice from DSS-induced colitis.	[101]
Grapefruits	Breast cancer		Murine 4T1 BT cells and murine L929 noncancerous cells	Induced 90 % cell death by increasing ROS generation and inducing the apoptosis and necrosis cell death channels.	[115]
	Leukemias		U937, K562, HL-60, HEL and MV4-11 cells	ELPDNVs increased the ROS levels in both AML blast cells and U937 cells without affecting ROS storage in normal cells	[10]
	Colitis	Six-to-eight-week-old C57BL/6J male mice		Upregulated heme oxygenase-1 (HO-1) and inhibited IL-1β and TNF-α production in intestinal macrophages.	[116]
Blueberries	Nonalcoholic fatty liver disease	Male C57BL/6 mice	HepG2 cells	BELN supplementation prevented the formation of vacuoles and attenuated the accumulation of lipid droplets by inhibiting the expression of fatty acid synthase (FAS) and acetyl-CoA carboxylase 1 (ACC1).	[103]
	Vascular system protection		EA.hy926 cells	Three miRNAs in B-ELNs, miR-156e, miR-162, and miR-319d, may be responsible for the downregulation of PTGIS, MAPK14 and different isoforms of PDE, modulating the response to TNF-α.	[117]
Lemons	Gastric cancer	Four-to-six-week-old female BALB/c nude mice	AGS, BGC-823, and SGC-7901 cells	LDEVs mediate the production of reactive oxygen species and LDEVs can arrest gastric cancer cells in S phase, inducing apoptosis	[12]
	Clostridioides difficile infection	Mice were infected with *Clostridioides difficile*		LELNs increased the survival rates of LGG and STH in the gut, which lead to increased production of the AhR ligands I3Ald and I3LA and lactic acid. I3Ald and I3LA induced the expression of IL-22 to protect mice from *Clostridioides difficile* by activating the AhR pathway.	[22]
	Kidney stones	EG rats		LEVNs suppressed the CaOx-induced endoplasmic reticulum stress response in tubule cells, as indicated by homeostasis of specific signaling molecules and the restoration of subcellular function, thus indirectly inhibiting stone formation.	[21]
Carica papaya	Anti-Inflammatory effects		RAW 264.7 cells	LPS-induced RAW 264.7 cells treated with papaya PDEVs showed a decrease in NO production, the downregulation of the genes encoding the proinflammatory	[19]

				cytokines IL-1B and IL-6 at the mRNA level and the upregulation of the gene encoding the anti-inflammatory cytokine IL-10 at the mRNA level.	
Tangerine peels	Nonalcoholic fatty liver disease	Seven-week-old male C57BL/Ks mice and seven-week-old male C57BL/KsJ-db/db mice	VoLo and AML-12 cells	Tangerine-peel-derived exosome-like nanovesicles significantly improved glucose and lipid metabolism by inducing the expression of genes related to fatty acid β-oxidation and glycolysis.	[107]
Tomatoes	Cartilage regeneration		hASCs (PCS-500–011, ATCC, USA)	TELVs promoted COL 2, ACAN and SOX 9 expression and increased the potential for chondrogenic differentiation.	[118]
Ginger	Intestinal inflammation	Six-week-old male C57BL/6 mice	RAW264.7 macrophages	GELN-derived osa-miR164d regulated macrophage polarization and directly targets the 3′-UTR of TAB1, which regulates macrophage polarization by downregulating NF-κB.	[20]
	Liver damage	Six-to-eight-week -old 57BL/6j mice	Hepatocytes isolated from 8-week-old adult C57/B6 mice and TLR4-, TRIF-, MyD88-KO mice	Mediated the activation of nuclear factor erythroid 2-related factor 2 (Nrf2), which induced the expression of a group of liver detoxifying/antioxidant genes and inhibited the production of reactive oxygen species, contributing to liver protection.	
Yams	Osteoporosis prevention	C57BL/6 male (n = 10) and female (n = 10) mice	MC3T3-E1 cells	YNVs activated the BMP-2/p-p38-dependent Runx2 pathway.	[15]
Momordica charantia	Ischemic brain injury	Male Sprague–Dawley	Mouse hippocampal neuronal HT22 cells	MC-ELN treatment significantly activated the AKT/GSK3β signaling pathway and attenuated neuronal apoptosis in HT22 cells.	[14]
	Ameliorate doxorubicin-induced cardiotoxicity	Healthy 8-to-12-week-old male C57BL/6J mice And male Sprague–Dawley rats	H9c2 rat cardiomyocytes and MCF-7 human breast cancer cells	MC-ELNs suppressed DOX-induced p62 ubiquitination and degradation, and the recovered p62 bound to Keap1 to promote Nrf2 nuclear translocation and the expression of the downstream gene HO-1.	[57]
Rice	Reduce blood glucose levels	Five-week-old male ICR mice	DLD-1 human colorectal cancer cells, NB19 human neuroblastoma cells, and K562 human leukemia cells	hvu-MIR168-3p downregulated genes related to mitochondrial electron transport chain complex I in human cells and increased the protein and RNA expression levels of glucose transporter I, leading to a decrease in blood glucose levels.	[16]

6. FDEVs as drug carriers

FDEVs have demonstrated unique advantages in the field of drug delivery, mainly owing to their stability, biocompatibility, ability to permeate biological barriers, low toxicity and immunogenicity, and synergistic therapeutic effects[119]. Additionally, FDEVs are considered avant-garde, nonhazardous, environmentally friendly, and viable nanomedicine carriers. Because most FDEVs are derived from edible plants, they are generally considered to have a high safety profile, and numerous in vitro and in vivo tests have confirmed their safety.

6.1 Unique Exploration of FDEVs as Functional Food Ingredients

This review not only focuses on the potential of FDEVs as nanocarriers but further explores their unique application scenarios as functional food ingredients. FDEVs, as natural carriers of bioactive substances, hold vast promise in the field of customized diets and nutritional supplements. They can exert synergistic effects with other bioactive components in the diet (e.g., probiotics, polyphenols), thereby enhancing overall health benefits. For instance, polyphenolic compounds can be effectively encapsulated and delivered by FDEVs, improving their stability and bioavailability in the digestive tract[120]. In addition, FDEVs have potential as protective delivery vehicles for probiotics, potentially enhancing probiotic tolerance to harsh gastrointestinal conditions (e.g., gastric acid and bile salts). Some intrinsic components of FDEVs for instance, low-molecular-weight carbohydrates or other microbiota-accessible molecules could exert prebiotic-like effects and thereby support the growth and colonization of beneficial gut microbes, resulting in synergistic host benefits[121,122]. This multi-component synergistic action offers new insights for developing novel functional foods, enabling them to play a crucial role in personalized nutritional interventions.

6.2 Cargo loading and cellular Interaction mechanisms

Owing to their natural nanoscale vesicular structure, exosomes have good biocompatibility and oral safety and can cross biological barriers, including the BBB[123,124], and when used as drug carriers, FDEVs can exert synergistic therapeutic effects with drugs to enhance therapeutic efficacy. Vesicular drug delivery systems can be prepared using various methods, which can be broadly categorized into active loading and passive loading methods. These methods are chosen based on the nature of the drug payload, whether it is hydrophilic or hydrophobic[125]. To enhance loading efficiency, methods such as surface modification and cargo loading techniques (e.g., electroporation, ultrasonic treatment) can significantly improve their targeting specificity and drug encapsulation efficiency. Notably, multifunctional PELNs capable of synergistically delivering drugs and genetic material for combined therapy have greatly enhanced the feasibility of disease treatment[126]. However, FDEVs from different sources contain different components, which causes them to interact with drugs differently. Compared with synthetic nanoparticles and mammalian cell-derived exosomes, FDEVs are usually less toxic[42]. Citrus lemon-derived nanovesicles rapidly reach the tumor tissue within 15

minutes after injection and continue to accumulate for up to 24 h, remaining internalized by the tumor and retained in the tumor mass[127]. Similarly, intranasal and intraventricular administration of ginger-derived exosome nanoparticles resulted in their homing to mouse lung tissues, and they were detectable for up to 72 h after administration[128]. FDEVs, as emerging nanomedicine carriers, have promising applications in disease treatment. Future studies should focus on standardizing extraction techniques, performing in-depth analyses of their mechanisms of action, and optimizing their targeting effects to promote their application in the clinic.

The mechanisms by which FDEVs enter target cells can be divided into two categories. The first is direct plasma membrane fusion, in which the vesicle's lipid bilayer fuses with the target cell membrane, releasing the FDEVs-encapsulated proteins, nucleic acids, lipids and other bioactive molecules directly into the cytosol[129]. The second comprises various endocytic routes, including clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, and lipid-raft–mediated endocytosis. The specific endocytic pathway of FDEVs depends largely on their surface molecular composition and the physiological state of the recipient cells. For example, lipid components such as phosphatidic acid, phosphatidylcholine, and phosphatidylethanolamine, which are abundant on the surface of FDEVs, can mediate interactions with the cell membrane; meanwhile, certain glycoproteins and lectin-like substances play a key role in mediating other cell membrane interactions and the subsequent endocytosis process[130]. The preferred pathway largely depends on the molecular composition of the FDEV surface and the specific physiological state of the recipient cell[131].

6.3 Drug Delivery and Targeted Engineering Strategies

FDEVs present distinct advantages as targeted drug-delivery vehicles and can be engineered by multiple complementary strategies to deliver therapeutics to specific cells or tissues, thereby enhancing efficacy and reducing off-target effects. Two principal approaches are commonly pursued: (1) surface modification, where targeting moieties (monoclonal antibodies, receptor-binding peptides, or aptamers) are grafted onto the vesicle membrane to increase selective binding to receptors on target cells and to promote receptor-mediated endocytosis or membrane fusion for efficient intracellular delivery; (2) Host-engineering, in which the plant producer is genetically modified to secrete FDEVs that inherently display defined surface proteins or lipid modifications, thus conferring targeting specificity at the point of biogenesis[132,133]. For example, ginger exosome nanoparticles (GDENs) display ligands on their surface to deliver siRNA and inhibit tumors after intravenous injection[13]; ginger-derived nanovesicle-derived liposomes have been administered orally to deliver miRNA that targets intestinal bacteria in a mouse model of colitis[50]. A recent green tea-derived FDEVs platform enables oral delivery of antagomir-HAAPIR for aortic coarctation therapy[113], highlighting the promise of FDEVs for oral nucleic acid delivery. Collectively, these studies underscore the translational potential of FDEVs and support their further development for personalized therapeutic applications.

7. Summary and future outlook

FDEVs represent an emerging class of biocompatible nanocarriers with inherent biosafety, minimal immunogenicity, and demonstrated anti-inflammatory and antitumor activities in preclinical models. These attributes, coupled with their scalability and botanical source diversity, position FDEVs as promising candidates for precision nanomedicine and targeted molecular delivery. In addition, growing evidence suggests that FDEVs are not merely passive delivery vehicles, but may also function as bioactive mediators of cross-kingdom communication, thereby broadening their conceptual significance in nutrition science, immunology, and translational medicine. However, the clinical translation of FDEV-based therapeutics is contingent upon addressing three critical knowledge gaps:

First, mechanistic elucidation of FDEVs bioactivity at the molecular level remains incomplete. The precise molecular composition of FDEVs is heterogeneous and poorly characterized, hampering rational engineering efforts. Specifically, systematic quantification of bioactive cargo (proteins, regulatory miRNAs, lipid species, and small-molecule metabolites) and their individual contributions to cellular signaling remain unclear. Rigorous characterization of post-translational modifications, structure-activity relationships, and the synergistic effects among multiple cargo components is essential for rational optimization of FDEV-based therapeutics. Future studies should therefore combine multi-omics profiling with functional validation to identify the dominant bioactive components and clarify whether therapeutic efficacy depends on single molecules or cooperative cargo networks.

Second, the molecular mechanisms governing cross-kingdom communication and cellular targeting are insufficiently characterized. The molecular mechanisms governing how FDEVs navigate biological barriers, achieve cellular tropism, and maintain systemic bioavailability in a heterologous host are poorly understood. Identifying membrane-resident ligands that dictate tissue targeting is a prerequisite for engineering FDEVs with enhanced therapeutic index and reduced off-target accumulation.

Third, the absence of standardized protocols for FDEVs isolation, characterization, and quality control is a major barrier to clinical development. The absence of consensus-based isolation methodologies and validated bioactivity reference standards leads to inter-study variability and complicates quality control.

Addressing these bottlenecks through multi-omics integration and cross-disciplinary collaboration is imperative. Transitioning FDEVs from a research-stage topic to a core component of functional foods and precision medicine necessitates a shift from descriptive profiling to rigorous, mechanism-driven validation. Establishing scalable, sustainable production systems and harmonized quality benchmarks will be pivotal in delivering FDEVs-based solutions for disease prevention and health promotion.

Acknowledgements

This work was Supported by the earmarked fund for CARS(CARS-25); Supported by the earmarked fund for XARS (XARS-06).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Consent for publication

All of the author has read the journal policies and submit this manuscript in accordance with those policies.

Competing interests

The authors declare no competing interests

References

[1] C. Yi, L. Lu, Z. Li, et al., Plant-derived exosome-like nanoparticles for microRNA delivery in cancer treatment, Drug Deliv. and Transl. Res. 15 (2025) 84–101. https://doi.org/10.1007/s13346-024-01621-x.

[2] D. Ratnadewi, C.H. Widjaja, A. Barlian, et al., Isolation of native plant-derived exosome-like nanoparticles and their uptake by human cells, HAYATI J Biosci 30 (2022) 182–192. https://doi.org/10.4308/hjb.30.1.182-192.

[3] S.-J. Fan, J.-Y. Chen, C.-H. Tang, et al., Edible plant extracellular vesicles: An emerging tool for bioactives delivery, Front. Immunol. 13 (2022) 1028418. https://doi.org/10.3389/fimmu.2022.1028418.

[4] A. Sha, Y. Luo, W. Xiao, et al., Plant-derived exosome-like nanoparticles: A comprehensive overview of their composition, biogenesis, isolation, and biological applications, IJMS 25 (2024) 12092. https://doi.org/10.3390/ijms252212092.

[5] Y. Han, X. Guo, Z. Ji, et al., Colon health benefits of plant-derived exosome-like nanoparticles via modulating gut microbiota and immunity, Critical Reviews in Food Science and Nutrition (2025) 1–21. https://doi.org/10.1080/10408398.2025.2479066.

[6] W. Zhang, F. Zhao, L. Jiang, et al., Different pathogen defense strategies in arabidopsis: More than pathogen recognition, Cells 7 (2018) 252. https://doi.org/10.3390/cells7120252.

[7] B.D. Rutter, R.W. Innes, Extracellular vesicles isolated from the leaf apoplast carry stress-response proteins, Plant Physiol. 173 (2017) 728–741. https://doi.org/10.1104/pp.16.01253.

[8] C. Stanly, M. Alfieri, A. Ambrosone, et al., Grapefruit-derived micro and nanovesicles show distinct metabolome profiles and anticancer activities in the A375 human melanoma cell line, Cells 9 (2020) 2722. https://doi.org/10.3390/cells9122722.

[9] A. Kilasoniya, L. Garaeva, T. Shtam, et al., Potential of plant exosome vesicles from grapefruit (citrus × paradisi) and tomato (solanum lycopersicum) juices as functional ingredients and targeted drug delivery vehicles, Antioxidants 12 (2023) 943. https://doi.org/10.3390/antiox12040943.

[10] G. Castelli, M. Logozzi, D. Mizzoni, et al., Ex vivo anti-leukemic effect of exosome-like grapefruit-derived nanovesicles from organic farming—the potential role of ascorbic acid, IJMS 24 (2023) 15663. https://doi.org/10.3390/ijms242115663.

[11] F. Perut, L. Roncuzzi, S. Avnet, et al., Strawberry-derived exosome-like nanoparticles prevent oxidative stress in human mesenchymal stromal cells, Biomolecules 11 (2021) 87. https://doi.org/10.3390/biom11010087.

[12] M. Yang, X. Liu, Q. Luo, et al., An efficient method to isolate lemon derived extracellular vesicles for gastric cancer therapy, J Nanobiotechnol 18 (2020) 100. https://doi.org/10.1186/s12951-020-00656-9.

[13] Z. Li, H. Wang, H. Yin, et al., Arrowtail RNA for ligand display on ginger exosome-like nanovesicles to systemic deliver siRNA for cancer suppression, Sci Rep 8 (2018) 14644. https://doi.org/10.1038/s41598-018-32953-7.

[14] H. Cai, L.-Y. Huang, R. Hong, et al., Momordica charantia exosome-like nanoparticles exert neuroprotective effects against ischemic brain injury via inhibiting matrix metalloproteinase 9 and activating the AKT/GSK3β signaling pathway, Front. Pharmacol. 13 (2022) 908830. https://doi.org/10.3389/fphar.2022.908830.

[15] J.-H. Hwang, Y.-S. Park, H.-S. Kim, et al., Yam-derived exosome-like nanovesicles stimulate osteoblast formation and prevent osteoporosis in mice, Journal of Controlled Release 355 (2023) 184–198. https://doi.org/10.1016/j.jconrel.2023.01.071.

[16] Y. Akao, Y. Kuranaga, K. Heishima, et al., Plant hvu-MIR168-3p enhances expression of glucose transporter 1 (SLC2A1) in human cells by silencing genes related to mitochondrial electron transport chain complex I, The Journal of Nutritional Biochemistry 101 (2022) 108922. https://doi.org/10.1016/j.jnutbio.2021.108922.

[17] T. Chaya, A. Banerjee, B.D. Rutter, et al., The extracellular vesicle proteomes of *sorghum bicolor* and *arabidopsis thaliana* are partially conserved, Plant Physiology 194 (2024) 1481–1497. https://doi.org/10.1093/plphys/kiad644.

[18] S.P. Bruno, A. Paolini, V. D'Oria, et al., Extracellular vesicles derived from citrus sinensis modulate inflammatory genes and tight junctions in a human model of intestinal epithelium, Front. Nutr. 8 (2021) 778998. https://doi.org/10.3389/fnut.2021.778998.

[19] I. Iriawati, S. Vitasasti, F.N.A. Rahmadian, et al., Isolation and characterization of plant-derived exosome-like nanoparticles from carica papaya L. fruit and their potential as anti-inflammatory agent, PLoS ONE 19 (2024) e0304335. https://doi.org/10.1371/journal.pone.0304335.

[20] L. Yan, Y. Cao, L. Hou, et al., Ginger exosome-like nanoparticle-derived miRNA therapeutics: A strategic inhibitor of intestinal inflammation, Journal of Advanced Research (2024) S2090123224001309. https://doi.org/10.1016/j.jare.2024.04.001.

[21] L. Zhang, S. Li, M. Cong, et al., Lemon-derived extracellular vesicle-like nanoparticles block the progression of kidney stones by antagonizing endoplasmic reticulum stress in renal tubular cells, Nano Lett. 23 (2023) 1555–1563. https://doi.org/10.1021/acs.nanolett.2c05099.

[22] C. Lei, J. Mu, Y. Teng, et al., Lemon exosome-like nanoparticles-manipulated probiotics protect mice from C. diff infection, iScience 23 (2020) 101571. https://doi.org/10.1016/j.isci.2020.101571.

[23] S. Raimondo, O. Urzì, S. Meraviglia, et al., Anti-inflammatory properties of lemon-derived extracellular vesicles are achieved through the inhibition of ERK/NF-κB signalling pathways, J Cellular Molecular Medi 26 (2022) 4195–4209. https://doi.org/10.1111/jcmm.17404.

[24] M. Logozzi, R. Di Raimo, D. Mizzoni, et al., Nanovesicles from organic agriculture-derived fruits and vegetables: Characterization and functional antioxidant content, IJMS 22 (2021) 8170. https://doi.org/10.3390/ijms22158170.

[25] M. Logozzi, R. Di Raimo, D. Mizzoni, et al., The potentiality of plant-derived nanovesicles in human health—a comparison with human exosomes and artificial nanoparticles, IJMS 23 (2022) 4919. https://doi.org/10.3390/ijms23094919.

[26] I.M. Sall, T.A. Flaviu, Plant and mammalian-derived extracellular vesicles: A new therapeutic approach for the future, Front. Bioeng. Biotechnol. 11 (2023) 1215650. https://doi.org/10.3389/fbioe.2023.1215650.

[27] W. Halperin, W.A. Jensen, Ultrastructural changes during growth and embryogenesis in carrot cell cultures, Journal of Ultrastructure Research 18 (1967) 428–443. https://doi.org/10.1016/S0022-5320(67)80128-X.

[28] Y. Cui, W. Cao, Y. He, et al., A whole-cell electron tomography model of vacuole biogenesis in Arabidopsis root cells, Nature Plants 5 (2018) 95–105. https://doi.org/10.1038/s41477-018-0328-1.

[29] R. Sanwlani, P. Fonseka, S.V. Chitti, et al., Milk-derived extracellular vesicles in inter-organism, cross-species communication and drug delivery, Proteomes 8 (2020) 11. https://doi.org/10.3390/proteomes8020011.

[30] C. Villarroya-Beltri, F. Baixauli, C. Gutiérrez-Vázquez, et al., Sorting it out: Regulation of exosome loading, Seminars in Cancer Biology 28 (2014) 3–13. https://doi.org/10.1016/j.semcancer.2014.04.009.

[31] Y. Liu, C. Ren, R. Zhan, et al., Exploring the potential of plant-derived exosome-like nanovesicle as functional food components for human health: A review, Foods 13 (2024) 712. https://doi.org/10.3390/foods13050712.

[32] J. Wang, Y. Ding, J. Wang, et al., EXPO, an exocyst-positive organelle distinct from multivesicular endosomes and autophagosomes, mediates cytosol to cell wall exocytosis in *arabidopsis* and tobacco cells, The Plant Cell 22 (2011) 4009–4030. https://doi.org/10.1105/tpc.110.080697.

[33] Y. Cui, J. Gao, Y. He, et al., Plant extracellular vesicles, Protoplasma 257 (2020) 3–12. https://doi.org/10.1007/s00709-019-01435-6.

[34] N.P. Hessvik, A. Llorente, Current knowledge on exosome biogenesis and release, Cell. Mol. Life Sci. 75 (2018) 193–208. https://doi.org/10.1007/s00018-017-2595-9.

[35] L. Xiao, S. Hareendran, Y.P. Loh, Function of exosomes in neurological disorders and brain tumors, EVCNA (2021). https://doi.org/10.20517/evcna.2021.04.

[36] J. Tian, W. Chen, Y. Xiong, et al., Small extracellular vesicles derived from hypoxic preconditioned dental pulp stem cells ameliorate inflammatory osteolysis by modulating macrophage polarization and osteoclastogenesis, Bioact. Mater. 22 (2023) 326–342. https://doi.org/10.1016/j.bioactmat.2022.10.001.

[37] S. Hao, H. Yang, J. Hu, et al., Bioactive compounds and biological functions of medicinal plant-derived extracellular vesicles, Pharmacol. Res. 200 (2024) 107062. https://doi.org/10.1016/j.phrs.2024.107062.

[38] Z. Xu, Y. Xu, K. Zhang, et al., Plant-derived extracellular vesicles (PDEVs) in nanomedicine for human disease and therapeutic modalities, J. Nanobiotechnol. 21 (2023) 114. https://doi.org/10.1186/s12951-023-01858-7.

[39] L. Mashouri, H. Yousefi, A.R. Aref, et al., Exosomes: Composition, biogenesis, and mechanisms in cancer metastasis and drug resistance, Mol Cancer 18 (2019) 75. https://doi.org/10.1186/s12943-019-0991-5.

[40] L. Wang, J. Wu, S. Song, et al., Plasma exosome-derived sentrin SUMO-specific protease 1: A prognostic biomarker in patients with osteosarcoma, Front. Oncol. 11 (2021) 625109. https://doi.org/10.3389/fonc.2021.625109.

[41] G. Liu, G. Kang, S. Wang, et al., Extracellular vesicles: Emerging players in plant defense against pathogens, Front. Plant Sci. 12 (2021) 757925. https://doi.org/10.3389/fpls.2021.757925.

[42] H.A. Dad, T.-W. Gu, A.-Q. Zhu, et al., Plant exosome-like nanovesicles: Emerging therapeutics and drug delivery nanoplatforms, Molecular Therapy 29 (2021) 13–31. https://doi.org/10.1016/j.ymthe.2020.11.030.

[43] D. Li, Q. Tang, M. Yang, et al., Plant-derived exosomal nanoparticles: Potential therapeutic for inflammatory bowel disease, Nanoscale Adv. 5 (2023) 3575–3588. https://doi.org/10.1039/D3NA00093A.

[44] L. Zhang, D. Hou, X. Chen, et al., Exogenous plant MIR168a specifically targets mammalian LDLRAP1: Evidence of cross-kingdom regulation by microRNA, Cell Res 22 (2012) 107–126. https://doi.org/10.1038/cr.2011.158.

[45] S. Tan, L. Xia, P. Yi, et al., Exosomal miRNAs in tumor microenvironment, J Exp Clin Cancer Res 39 (2020) 67. https://doi.org/10.1186/s13046-020-01570-6.

[46] W. Zhou, M.Y. Fong, Y. Min, et al., Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis, Cancer Cell 25 (2014) 501–515. https://doi.org/10.1016/j.ccr.2014.03.007.

[47] S. Rawat, S. Arora, M.R. Dhondale, et al., Stability dynamics of plant-based extracellular vesicles drug delivery, J. Xenobiot. 15 (2025) 55. https://doi.org/10.3390/jox15020055.

[48] M. Zu, D. Xie, B.S.B. Canup, et al., 'green' nanotherapeutics from tea leaves for orally targeted prevention and alleviation of colon diseases, Biomaterials 279 (2021) 121178. https://doi.org/10.1016/j.biomaterials.2021.121178.

[49] V. Tinnirello, N. Rabienezhad Ganji, C. De Marcos Lousa, et al., Exploiting the opportunity to use plant-derived nanoparticles as delivery vehicles, Plants 12 (2023) 1207. https://doi.org/10.3390/plants12061207.

[50] Y. Teng, Y. Ren, M. Sayed, et al., Plant-derived exosomal MicroRNAs shape the gut microbiota, Cell Host & Microbe 24 (2018) 637-652.e8. https://doi.org/10.1016/j.chom.2018.10.001.

[51] X. Chen, L. He, C. Zhang, et al., Exploring new avenues of health protection: Plant-derived nanovesicles reshape microbial communities, J Nanobiotechnol 22 (2024) 269. https://doi.org/10.1186/s12951-024-02500-w.

[52] C. Song, J. Chen, X. Li, et al., Limonin ameliorates dextran sulfate sodium-induced chronic colitis in mice by inhibiting PERK-ATF4-CHOP pathway of ER stress and NF-κB signaling, International Immunopharmacology 90 (2021) 107161. https://doi.org/10.1016/j.intimp.2020.107161.

[53] R. Kumar, F. Akhtar, S.I. Rizvi, Hesperidin attenuates altered redox homeostasis in an experimental hyperlipidaemic model of rat, Clin Exp Pharma Physio 47 (2020) 571–582. https://doi.org/10.1111/1440-1681.13221.

[54] F. Bagheripour, S. Jeddi, K. Kashfi, et al., Metabolic effects of L -citrulline in type 2 diabetes, Acta Physiologica 237 (2023) e13937. https://doi.org/10.1111/apha.13937.

[55] C. Bai, J. Liu, X. Zhang, et al., Research status and challenges of plant-derived exosome-like nanoparticles, Biomedicine & Pharmacotherapy 174 (2024) 116543. https://doi.org/10.1016/j.biopha.2024.116543.

[56] F.J. Ansari, H.A. Tafti, A. Amanzadeh, et al., Comparison of the efficiency of ultrafiltration, precipitation, and ultracentrifugation methods for exosome isolation, Biochem. Biophys. Rep. 38 (2024) 101668. https://doi.org/10.1016/j.bbrep.2024.101668.

[57] C. Ye, C. Yan, S.-J. Bian, et al., Momordica charantia L.-derived exosome-like nanovesicles stabilize p62 expression to ameliorate doxorubicin cardiotoxicity, J Nanobiotechnol 22 (2024) 464. https://doi.org/10.1186/s12951-024-02705-z.

[58] J.Y. You, S.J. Kang, W.J. Rhee, Isolation of cabbage exosome-like nanovesicles and investigation of their biological activities in human cells, Bioactive Materials 6 (2021) 4321–4332. https://doi.org/10.1016/j.bioactmat.2021.04.023.

[59] Y. Wei, X. Cai, Q. Wu, et al., Extraction, isolation, and component analysis of turmeric-derived exosome-like nanoparticles, Bioengineering 10 (2023) 1199. https://doi.org/10.3390/bioengineering10101199.

[60] L. Yin, L. Yan, Q. Yu, et al., Characterization of the MicroRNA profile of ginger exosome-like nanoparticles and their anti-inflammatory effects in intestinal caco-2 cells, J. Agric. Food Chem. 70 (2022) 4725–4734. https://doi.org/10.1021/acs.jafc.1c07306.

[61] J. Liu, W. Li, Y. Bian, et al., Garlic-derived exosomes regulate PFKFB3 expression to relieve liver dysfunction in high-fat diet-fed mice via macrophage-hepatocyte crosstalk, Phytomedicine 112 (2023) 154679. https://doi.org/10.1016/j.phymed.2023.154679.

[62] S.P. Kalarikkal, G.M. Sundaram, Edible plant-derived exosomal microRNAs: Exploiting a cross-kingdom regulatory mechanism for targeting SARS-CoV-2, Toxicology and Applied Pharmacology 414 (2021) 115425. https://doi.org/10.1016/j.taap.2021.115425.

[63] J.Y. You, S.J. Kang, W.J. Rhee, Isolation of cabbage exosome-like nanovesicles and investigation of their biological activities in human cells, Bioactive Materials 6 (2021) 4321–4332. https://doi.org/10.1016/j.bioactmat.2021.04.023.

[64] L. Del Pozo-Acebo, M.-C. López De Las Hazas, J. Tomé-Carneiro, et al., Therapeutic potential of broccoli-derived extracellular vesicles as nanocarriers of exogenous miRNAs, Pharmacological Research 185 (2022) 106472. https://doi.org/10.1016/j.phrs.2022.106472.

[65] A. Gámez-Valero, M. Monguió-Tortajada, L. Carreras-Planella, et al., Size-exclusion chromatography-based isolation minimally alters extracellular vesicles' characteristics compared to precipitating agents, Sci Rep 6 (2016) 33641. https://doi.org/10.1038/srep33641.

[66] A. Liga, A.D.B. Vliegenthart, W. Oosthuyzen, et al., Exosome isolation: A microfluidic road-map, Lab Chip 15 (2015) 2388–2394. https://doi.org/10.1039/C5LC00240K.

[67] J. Bai, X. Wei, X. Zhang, et al., Microfluidic strategies for the isolation and profiling of exosomes, TrAC Trends in Analytical Chemistry 158 (2023) 116834. https://doi.org/10.1016/j.trac.2022.116834.

[68] W. Nakai, T. Yoshida, D. Diez, et al., A novel affinity-based method for the isolation of highly purified extracellular vesicles, Sci Rep 6 (2016) 33935. https://doi.org/10.1038/srep33935.

[69] Y. Huang, S. Wang, Q. Cai, et al., Methodological guidelines for isolation and purification of plant extracellular vesicles, (2021). https://doi.org/10.1101/2021.09.01.458648.

[70] H. Zhang, D. Lyden, Asymmetric-flow field-flow fractionation technology for exomere and small extracellular vesicle separation and characterization, Nat. Protoc. 14 (2019) 1027–1053. https://doi.org/10.1038/s41596-019-0126-x.

[71] S. Sitar, A. Kejžar, D. Pahovnik, et al., Size characterization and quantification of exosomes by asymmetrical-flow field-flow fractionation, Anal. Chem. 87 (2015) 9225–9233. https://doi.org/10.1021/acs.analchem.5b01636.

[72] J. Feng, Q. Xiu, Y. Huang, et al., Plant-derived vesicle-like nanoparticles as promising biotherapeutic tools: Present and future, Adv. Mater. 35 (2023) 2207826. https://doi.org/10.1002/adma.202207826.

[73] K. Goryunov, M. Ivanov, A. Kulikov, et al., A review of the use of extracellular vesicles in the treatment of neonatal diseases: Current state and problems with translation to the clinic, IJMS 25 (2024) 2879. https://doi.org/10.3390/ijms25052879.

[74] S. Zhang, Q. Wang, D.E.L. Tan, et al., Gut-liver axis: Potential mechanisms of action of food-derived extracellular vesicles, J of Extracellular Vesicle 13 (2024) e12466. https://doi.org/10.1002/jev2.12466.

[75] J. Mu, X. Zhuang, Q. Wang, et al., Interspecies communication between plant and mouse gut host cells through edible plant derived exosome-like nanoparticles, Molecular Nutrition Food Res 58 (2014) 1561–1573. https://doi.org/10.1002/mnfr.201300729.

[76] W. Chen, F. Zuo, K. Zhang, et al., Exosomal MIF derived from nasopharyngeal carcinoma promotes metastasis by repressing ferroptosis of macrophages, Front. Cell Dev. Biol. 9 (2021) 791187. https://doi.org/10.3389/fcell.2021.791187.

[77] I. Tatischeff, E. Larquet, J.M. Falcón-Pérez, et al., Fast characterisation of cell-derived extracellular vesicles by nanoparticles tracking analysis, cryo-electron microscopy, and raman tweezers microspectroscopy, J of Extracellular Vesicle 1 (2012) 19179. https://doi.org/10.3402/jev.v1i0.19179.

[78] D. Long, C. Yang, J. Sung, et al., Atomic force microscopy to characterize ginger lipid-derived nanoparticles (GLDNP), BIO-PROTOCOL 11 (2021). https://doi.org/10.21769/BioProtoc.3969.

[79] Y. Yuana, T.H. Oosterkamp, S. Bahatyrova, et al., Atomic force microscopy: A novel approach to the detection of nanosized blood microparticles, Journal of Thrombosis and Haemostasis 8 (2010) 315–323. https://doi.org/10.1111/j.1538-7836.2009.03654.x.

[80] J. Abello, T.D.T. Nguyen, R. Marasini, et al., Biodistribution of gadolinium- and near infrared-labeled human umbilical cord mesenchymal stromal cell-derived exosomes in tumor bearing mice, Theranostics 9 (2019) 2325–2345. https://doi.org/10.7150/thno.30030.

[81] R. Bano, F. Ahmad, M. Mohsin, A perspective on the isolation and characterization of extracellular vesicles from different biofluids, RSC Adv. 11 (2021) 19598–19615. https://doi.org/10.1039/D1RA01576A.

[82] V. Pospichalova, J. Svoboda, Z. Dave, et al., Simplified protocol for flow cytometry analysis of fluorescently labeled exosomes and microvesicles using dedicated flow cytometer, J of Extracellular Vesicle 4 (2015) 25530. https://doi.org/10.3402/jev.v4.25530.

[83] M. Logozzi, R. Di Raimo, D. Mizzoni, et al., Immunocapture-based ELISA to characterize and quantify exosomes in both cell culture supernatants and body fluids, in: Methods in Enzymology, Elsevier, 2020: pp. 155–180. https://doi.org/10.1016/bs.mie.2020.06.011.

[84] S. Yokoyama, A. Takeuchi, S. Yamaguchi, et al., Clinical implications of carcinoembryonic antigen distribution in serum exosomal fraction—measurement by ELISA, PLoS ONE 12 (2017) e0183337. https://doi.org/10.1371/journal.pone.0183337.

[85] J.J. Lai, Z.L. Chau, S. Chen, et al., Exosome processing and characterization approaches for research and technology development, Advanced Science 9 (2022) 2103222. https://doi.org/10.1002/advs.202103222.

[86] M. Elkommos-Zakhary, N. Rajesh, V. Beljanski, Exosome RNA sequencing as a tool in the search for cancer biomarkers, ncRNA 8 (2022) 75. https://doi.org/10.3390/ncrna8060075.

[87] X. Su, H. Wang, Q. Li, et al., Extracellular vesicles: A review of their therapeutic potentials, sources, biodistribution, and administration routes, Int. J. Nanomed. Volume 20 (2025) 3175–3199. https://doi.org/10.2147/IJN.S502591.

[88] M. Kim, H. Jang, W. Kim, et al., Therapeutic applications of plant-derived extracellular vesicles as antioxidants for oxidative stress-related diseases, Antioxidants 12 (2023) 1286. https://doi.org/10.3390/antiox12061286.

[89] F.-X. Shu, N.-X. Yang, F.-L. Yu, et al., Temporary immersion bioreactor system: An excellent strategy for preparing high-quality controlled extracellular vesicles from food and medicine homology plants, Food & Medicine Homology 2 (2025) 9420123. https://doi.org/10.26599/FMH.2025.9420123.

[90] F. Shu, S. Sarsaiya, L. Ren, et al., Metabolomic analysis of plant-derived nanovesicles and extracellular vesicles from *pinellia ternata*: Insights into a temporary immersion bioreactor system, Physiol. Plant. 176 (2024) e70016. https://doi.org/10.1111/ppl.70016.

[91] F. Shu, Y. Hu, S. Sarsaiya, et al., Plant-derived extracellular vesicles quality control: Key process progress and future research directions, Discover Nano 20 (2025) 233. https://doi.org/10.1186/s11671-025-04399-0.

[92] M.D. Langellotto, G. Rassu, C. Serri, et al., Plant-derived extracellular vesicles: A synergetic combination of a drug delivery system and a source of natural bioactive compounds, Drug Deliv. and Transl. Res. 15 (2025) 831–845. https://doi.org/10.1007/s13346-024-01698-4.

[93] M.A. Di Bella, Overview and update on extracellular vesicles: Considerations on exosomes and their application in modern medicine, Biology 11 (2022) 804. https://doi.org/10.3390/biology11060804.

[94] M. Tan, Y. Liu, Y. Xu, et al., Plant-derived exosomes as novel nanotherapeutics contrive glycolysis reprogramming-mediated angiogenesis for diabetic ulcer healing, Biomater. Res. 28 (2024) 0035. https://doi.org/10.34133/bmr.0035.

[95] M. Regente, G. Corti-Monzón, A.M. Maldonado, et al., Vesicular fractions of sunflower apoplastic fluids are associated with potential exosome marker proteins, FEBS Letters 583 (2009) 3363–3366. https://doi.org/10.1016/j.febslet.2009.09.041.

[96] W. Wu, B. Zhang, W. Wang, et al., Plant-derived exosome-like nanovesicles in chronic wound healing, IJN Volume 19 (2024) 11293–11303. https://doi.org/10.2147/IJN.S485441.

[97] Z. Zhang, Y. Yu, G. Zhu, et al., The emerging role of plant-derived exosomes-like nanoparticles in immune regulation and periodontitis treatment, Front. Immunol. 13 (2022) 896745. https://doi.org/10.3389/fimmu.2022.896745.

[98] T. Yang, A. Warner, S. Canham, et al., Exploring the therapeutic potential of blueberry-derived exosomes in neurodegenerative disease management, American Journal of Pharmaceutical Education 88 (2024) 100921. https://doi.org/10.1016/j.ajpe.2024.100921.

[99] Z. Jin, J. Na, X. Lin, et al., Plant-derived exosome-like nanovesicles: A novel nanotool for disease therapy, Heliyon 10 (2024) e30630. https://doi.org/10.1016/j.heliyon.2024.e30630.

[100] M. Zhu, H. Xu, Y. Liang, et al., Edible exosome-like nanoparticles from portulaca oleracea L mitigate DSS-induced colitis via facilitating double-positive CD4+CD8+T cells expansion, J Nanobiotechnol 21 (2023) 309. https://doi.org/10.1186/s12951-023-02065-0.

[101] S. Ju, J. Mu, T. Dokland, et al., Grape exosome-like nanoparticles induce intestinal stem cells and protect mice from DSS-induced colitis, Molecular Therapy 21 (2013) 1345–1357. https://doi.org/10.1038/mt.2013.64.

[102] Z. Deng, Y. Rong, Y. Teng, et al., Broccoli-derived nanoparticle inhibits mouse colitis by activating dendritic cell AMP-activated protein kinase, Molecular Therapy 25 (2017) 1641–1654. https://doi.org/10.1016/j.ymthe.2017.01.025.

[103] W. Zhao, Y. Bian, Q. Wang, et al., Blueberry-derived exosomes-like nanoparticles ameliorate nonalcoholic fatty liver disease by attenuating mitochondrial oxidative stress, Acta Pharmacol Sin 43 (2022) 645–658. https://doi.org/10.1038/s41401-021-00681-w.

[104] F.-S. Qiu, J.-F. Wang, M.-Y. Guo, et al., Rgl-exomiR-7972, a novel plant exosomal microRNA derived from fresh rehmanniae radix, ameliorated lipopolysaccharide-induced acute lung injury and gut dysbiosis, Biomedicine & Pharmacotherapy 165 (2023) 115007. https://doi.org/10.1016/j.biopha.2023.115007.

[105] A. Kumar, Y. Ren, K. Sundaram, et al., miR-375 prevents high-fat diet-induced insulin resistance and obesity by targeting the aryl hydrocarbon receptor and bacterial tryptophanase (*tnaA*) gene, Theranostics 11 (2021) 4061–4077. https://doi.org/10.7150/thno.52558.

[106] C. He, K. Wang, J. Xia, et al., Natural exosomes-like nanoparticles in mung bean sprouts possesses anti-diabetic effects via activation of PI3K/akt/GLUT4/GSK-3β signaling pathway, J Nanobiotechnol 21 (2023) 349. https://doi.org/10.1186/s12951-023-02120-w.

[107] J. Zou, Q. Song, P.C. Shaw, et al., Tangerine peel-derived exosome-like nanovesicles alleviate hepatic steatosis induced by type 2 diabetes: Evidenced by regulating lipid metabolism and intestinal microflora, IJN Volume 19 (2024) 10023–10043. https://doi.org/10.2147/IJN.S478589.

[108] D. Wang, H. Tian, J. Qian, et al., Mechanism study on fig exosome-like nanoparticles inhibiting the progression of bone metastasis in breast cancer., JCO 42 (2024) e12562–e12562. https://doi.org/10.1200/JCO.2024.42.16_suppl.e12562.

[109] J. Kim, Y. Zhu, S. Chen, et al., Anti-glioma effect of ginseng-derived exosomes-like nanoparticles by active blood–brain-barrier penetration and tumor microenvironment modulation, J Nanobiotechnol 21 (2023) 253. https://doi.org/10.1186/s12951-023-02006-x.

[110] T. Chen, B. Ma, S. Lu, et al., Cucumber-derived nanovesicles containing cucurbitacin B for non-small cell lung cancer therapy, IJN Volume 17 (2022) 3583–3599. https://doi.org/10.2147/IJN.S362244.

[111] H. Shen, M. Zhang, D. Liu, et al., *Solanum lycopersicum* derived exosome-like nanovesicles alleviate restenosis after vascular injury through the Keap1/Nrf2 pathway, Food Funct. 16 (2025) 539–553. https://doi.org/10.1039/D4FO03993A.

[112] S. Li, R. Zhang, A. Wang, et al., Panax notoginseng: Derived exosome-like nanoparticles attenuate ischemia reperfusion injury via altering microglia polarization, J Nanobiotechnol 21 (2023) 416. https://doi.org/10.1186/s12951-023-02161-1.

[113] Y. Liu, H. Qi, J. Zong, et al., Oral piwi-interacting RNA delivery mediated by green tea-derived exosome-like nanovesicles for the treatment of aortic dissection, Adv Healthcare Materials 13 (2024) 2401466. https://doi.org/10.1002/adhm.202401466.

[114] Y. Teng, J. He, Q. Zhong, et al., Grape exosome-like nanoparticles: A potential therapeutic strategy for vascular calcification, Front. Pharmacol. 13 (2022) 1025768. https://doi.org/10.3389/fphar.2022.1025768.

[115] J. Farheen, M.Z. Iqbal, Y. Lu, et al., Vitis vinifera kyoho-derived exosome-like nanoparticles-based drug delivery and therapeutic modalities for breast cancer therapy, Journal of Drug Delivery Science and Technology 92 (2024) 105332. https://doi.org/10.1016/j.jddst.2023.105332.

[116] B. Wang, X. Zhuang, Z.-B. Deng, et al., Targeted drug delivery to intestinal macrophages by bioactive nanovesicles released from grapefruit, Molecular Therapy 22 (2014) 522–534. https://doi.org/10.1038/mt.2013.190.

[117] M. De Robertis, A. Sarra, V. D'Oria, et al., Blueberry-derived exosome-like nanoparticles counter the response to TNF-α-induced change on gene expression in EA.hy926 cells, Biomolecules 10 (2020) 742. https://doi.org/10.3390/biom10050742.

[118] M. Yıldırım, N. Ünsal, B. Kabataş, et al., Effect of solanum lycopersicum and citrus limon–derived exosome-like vesicles on chondrogenic differentiation of adipose-derived stem cells, Appl Biochem Biotechnol 196 (2024) 203–219. https://doi.org/10.1007/s12010-023-04491-0.

[119] K. Shyu, B. Wang, W. Fang, et al., Hyperbaric oxygen-induced long non-coding RNA MALAT1 exosomes suppress MicroRNA-92a expression in a rat model of acute myocardial infarction, J Cellular Molecular Medi 24 (2020) 12945–12954. https://doi.org/10.1111/jcmm.15889.

[120] M. Ma, Q. Wu, T. Wang, et al., Therapeutic potential of extracellular vesicle-polyphenol nanoplatform in regenerative medicine, Nano Mater. Sci. (2025) S2589965125000534. https://doi.org/10.1016/j.nanoms.2025.05.008.

[121] Q. Gu, Y. Yin, X. Yan, et al., Encapsulation of multiple probiotics, synbiotics, or nutrabiotics for improved health effects: A review, Adv. Colloid Interface Sci. 309 (2022) 102781. https://doi.org/10.1016/j.cis.2022.102781.

[122] M. Shao, X. Jin, S. Chen, et al., Plant-derived extracellular vesicles -a novel clinical anti-inflammatory drug carrier worthy of investigation, Biomed. Pharmacother. 169 (2023) 115904. https://doi.org/10.1016/j.biopha.2023.115904.

[123] X. Xie, H. Wu, M. Li, et al., Progress in the application of exosomes as therapeutic vectors in tumor-targeted therapy, Cytotherapy 21 (2019) 509–524. https://doi.org/10.1016/j.jcyt.2019.01.001.

[124] L. Del Pozo-Acebo, M. López De Las Hazas, A. Margollés, et al., Eating microRNAs: Pharmacological opportunities for cross-kingdom regulation and implications in host gene and gut microbiota modulation, British J Pharmacology 178 (2021) 2218–2245. https://doi.org/10.1111/bph.15421.

[125] B.S. Lukhele, K. Bassey, B.A. Witika, The utilization of plant-material-loaded vesicular drug delivery systems in the management of pulmonary diseases, CIMB 45 (2023) 9985–10017. https://doi.org/10.3390/cimb45120624.

[126] K.M. Tembo, X. Wang, M. Bolideei, et al., Exploring the bioactivity of MicroRNAs originated from plant-derived exosome-like nanoparticles (PELNs): Current perspectives, J. Nanobiotechnol. 23 (2025) 563. https://doi.org/10.1186/s12951-025-03602-9.

[127] S. Raimondo, F. Naselli, S. Fontana, et al., *Citrus limon* -derived nanovesicles inhibit cancer cell proliferation and suppress CML xenograft growth by inducing TRAIL-mediated cell death, Oncotarget 6 (2015) 19514–19527. https://doi.org/10.18632/oncotarget.4004.

[128] S.P. Kalarikkal, G.M. Sundaram, Edible plant-derived exosomal microRNAs: Exploiting a cross-kingdom regulatory mechanism for targeting SARS-CoV-2, Toxicology and Applied Pharmacology 414 (2021) 115425. https://doi.org/10.1016/j.taap.2021.115425.

[129] N. Nueraihemaiti, D. Dilimulati, A. Baishan, et al., Advances in plant-derived extracellular vesicle extraction methods and pharmacological effects, Biology 14 (2025) 377. https://doi.org/10.3390/biology14040377.

[130] S.Q. Kim, K.-H. Kim, Emergence of edible plant-derived nanovesicles as functional food components and nanocarriers for therapeutics delivery: Potentials in human health and disease, Cells 11 (2022) 2232. https://doi.org/10.3390/cells11142232.

[131] J. Wei, Z. Ou, B. Tong, et al., Engineered extracellular vesicles as therapeutics of degenerative orthopedic diseases, Front. Bioeng. Biotechnol. 11 (2023) 1162263. https://doi.org/10.3389/fbioe.2023.1162263.

[132] C. Wu, J. Li, K. Huang, et al., Advances in preparation and engineering of plant-derived extracellular vesicles for nutrition intervention, Food Chem. 457 (2024) 140199. https://doi.org/10.1016/j.foodchem.2024.140199.

[133] L.-Y. Yang, C.-Q. Li, Y.-L. Zhang, et al., Emerging drug delivery vectors: Engineering of plant-derived nanovesicles and their applications in biomedicine, Int. J. Nanomed. Volume 19 (2024) 2591–2610. https://doi.org/10.2147/IJN.S454794.