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Research Article

Herbal-Based Exosomal Drug Delivery System

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ABSTRACT

Herbal-based exosomal drug delivery systems (H-Exo-DDS) represent a novel and promising strategy that merges the therapeutic potential of herbal medicines with the innate nanocarrier properties of exosomes. Exosomes are nanosized extracellular vesicles (30–150 nm) capable of transporting bioactive molecules, including proteins, lipids, nucleic acids, and metabolites across biological barriers, and they have been widely explored for enhancing drug delivery efficacy due to their biocompatibility and stability. Plant-derived exosome-like nanoparticles (PELNs) from fruits, vegetables, and herbs exhibit low immunogenicity, enhanced safety, and environmental sustainability, making them attractive carriers for herbal bioactives and therapeutic agents. Isolation techniques such as differential ultracentrifugation, density gradients, size-exclusion chromatography, and ultrafiltration are adapted to extract exosomes from plant tissues, while drug loading methods including passive incubation, electroporation, and surface functionalization enable efficient encapsulation and controlled release. Mechanistically, H-Exo-DDS enhance bioavailability and cellular uptake of herbal compounds and can modulate cellular pathways, including immune responses and inflammation, through both cargo delivery and endogenous bioactive effects. Advantages of these systems include excellent biocompatibility, scalability from edible plant sources, and potential dual action of carrier plus intrinsic biological activity; however, challenges remain in standardizing isolation, ensuring reproducibility, evaluating pharmacokinetics, and navigating regulatory frameworks for clinical translation. Future research should focus on optimizing purification, validating therapeutic outcomes in vivo, and clarifying safety profiles to advance H-Exo-DDS toward clinical application.

.INTRODUCTION

Herbal medicines have been used for centuries in traditional medical systems such as Ayurveda, Siddha, Unani, and Traditional Chinese Medicine for the prevention and treatment of various diseases. Despite their proven therapeutic potential, many herbal bioactive compounds suffer from poor aqueous solubility, low oral bioavailability, chemical instability, and rapid

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metabolism, which significantly limit their clinical efficacy (Patra et al., 2018; Mohanraj & Chen, 2006). To overcome these limitations, nanotechnology-based drug delivery systems have gained considerable attention for enhancing the pharmacokinetic and pharmacodynamic profiles of herbal medicines (Kumari et al., 2010). Among various nanocarriers, exosomes have emerged as promising natural delivery vehicles due to their unique biological origin and physicochemical properties. Exosomes are nanosized lipid bilayer vesicles (30–150 nm) secreted by almost all cell types, including mammalian, bacterial, and plant cells, and are involved in intercellular communication by transporting proteins, lipids, nucleic acids, and metabolites (Théry et al., 2002; Kalluri & LeBleu, 2020). Their intrinsic biocompatibility, low immunogenicity, and ability to cross biological barriers make exosomes attractive candidates for drug delivery applications (El Andaloussi et al., 2013). Recently, plant-derived exosomes or exosome-like nanoparticles (PELNs) have gained significant interest for herbal drug delivery. These vesicles can naturally encapsulate phytochemicals and protect them from enzymatic degradation, thereby improving stability, cellular uptake, and therapeutic efficacy (Mu et al., 2014; Wang et al., 2022). Owing to their edible origin, scalability, and safety profile, plant-based exosomal systems represent a novel and efficient platform for the targeted delivery of herbal bioactive compounds.

2. EXOSOMES: AN OVERVIEW

Exosomes are small extracellular vesicles with a diameter ranging from 30 to 150 nm, generated through the inward budding of endosomal membranes to form multivesicular bodies (MVBs). Upon fusion of MVBs with the plasma membrane, exosomes are released into the extracellular environment, where they participate in intercellular communication by transferring bioactive cargo between cells (Théry et al., 2002; Kalluri & LeBleu, 2020). Exosomes possess a highly organized and biologically active molecular composition that reflects their cellular origin and physiological functions. They are surrounded by a lipid bilayer membrane enriched with phospholipids, cholesterol, sphingomyelin, ceramides, and glycolipids, which provide structural stability and protect the internal cargo from enzymatic degradation in extracellular environments (Raposo & Stoorvogel, 2013). This lipid architecture contributes to membrane curvature, vesicle rigidity, and enhanced stability during circulation, while also facilitating cellular uptake via endocytosis or membrane fusion. The protein cargo of exosomes plays a crucial role in their biological activity and targeting capabilities. Exosomes are enriched with conserved marker proteins such as tetraspanins (CD9, CD63, CD81), which are widely used for exosome identification and are involved in vesicle formation and membrane organization. Heat shock proteins (HSP70 and HSP90) support protein folding and stress responses, while integrins, cytoskeletal proteins, and membrane transport proteins contribute to vesicle trafficking, adhesion, and intracellular signaling (Kalluri & LeBleu, 2020).

In addition to lipids and proteins, exosomes encapsulate a diverse range of nucleic acids, including microRNAs (miRNAs), messenger RNAs (mRNAs), long non-coding RNAs, and DNA fragments. These nucleic acids are protected from degradation and can be functionally transferred to recipient cells, where they regulate gene expression and cellular behavior. The discovery of exosome-mediated RNA transfer highlighted their role as genetic messengers in intercellular communication (Valadi et al., 2007). Furthermore, exosomes contain bioactive metabolites, enzymes, and signaling molecules

that enhance their functional versatility. The synergistic presence of lipids, proteins, nucleic acids, and metabolites enables exosomes to function not only as passive carriers but also as active modulators of biological processes, making them highly promising platforms for advanced drug delivery and therapeutic applications.

Plant-Derived Exosomes

Plant-derived exosomes, also known as plant exosome-like nanoparticles (PELNs) or plant extracellular vesicles, are naturally occurring nanosized vesicles isolated from edible plants and medicinal herbs such as ginger, turmeric, grape, aloe vera, ginseng, citrus fruits, and tea leaves (Mu et al., 2014). These vesicles closely resemble mammalian exosomes in size, morphology, and structural organization, possessing a lipid bilayer membrane capable of encapsulating a wide range of biomolecules, including proteins, lipids, nucleic acids, and secondary metabolites (Zhang et al., 2016). Their plant origin makes them inherently biocompatible, biodegradable, and suitable for repeated administration. One of the most distinctive advantages of plant-derived exosomes is their exceptional stability in harsh gastrointestinal conditions. Unlike many synthetic nanocarriers, PELNs can withstand acidic pH, digestive enzymes, and bile salts, allowing effective oral delivery without significant degradation (Mu et al., 2014). Several studies have demonstrated that plant-derived exosomes can cross the intestinal epithelial barrier via endocytosis and transcytosis, leading to improved absorption and tissue distribution of encapsulated herbal bioactives (Zhang et al., 2016). This property is particularly beneficial for herbal compounds that normally suffer from poor oral bioavailability. Plant-derived exosomes also play a unique role in cross-kingdom communication. They can transport plant microRNAs, lipids, and metabolites into mammalian cells, where these cargos modulate gene expression, immune responses, and inflammatory signaling pathways (Wang et al., 2022). This phenomenon not only highlights their role as delivery vehicles but also demonstrates their intrinsic biological activity. For example, ginger-derived exosomes have been shown to suppress pro-inflammatory cytokines and protect against intestinal inflammation and liver injury, while grape-derived vesicles promote intestinal stem cell proliferation and mucosal regeneration (Mu et al., 2014; Zhang et al., 2016). In addition to their therapeutic effects, plant-derived exosomes exhibit low immunogenicity and minimal toxicity, making them safer alternatives to synthetic nanoparticles. Their scalable isolation from dietary plants and medicinal herbs further enhances their translational potential. The dual functionality of plant-derived exosomes—as both bioactive therapeutic agents and natural drug delivery carriers—positions them as a promising platform for advanced herbal drug delivery systems and future clinical applications (Wang et al., 2022).

3. HERBAL BASED EXOSOMAL DRUG DELIVERY SYSTEM

Herbal-based exosomal drug delivery systems (H-Exo-DDS) involve the use of plant-derived exosomes or exosomes loaded with herbal bioactive compounds to enhance therapeutic efficacy, targeting ability, and safety profiles. Plant extracellular vesicles (EVs), including exosome-like nanoparticles, are increasingly explored as natural nanocarriers due to their biocompatibility, biodegradability, low immunogenicity, ability to cross biological barriers, and inherent stability in physiological environments, making them suitable for both oral and systemic administration (Zhuang et al., 2015; Mu et al., 2014). Plant-derived exosomes facilitate

efficient cellular uptake and systemic distribution of cargo, addressing common limitations of herbal phytochemicals such as poor water solubility, rapid metabolism, and low oral bioavailability (Wang et al., 2022; Zhang et al., 2016). The concept integrates traditional herbal medicine with advanced nanobiotechnology by harnessing the intrinsic therapeutic activities of plant vesicles alongside their capacity to encapsulate and deliver phytochemicals (such as curcumin, polyphenols, flavonoids, and saponins) directly to target tissues while protecting them from degradation and minimizing off-target effects. By combining the intrinsic bioactivity of plant-derived exosomes with engineered payload delivery, H-Exo-DDS offers a synergistic approach that enhances therapeutic outcomes in a range of diseases, including inflammation, cancer, metabolic disorders, and gastrointestinal conditions (Mu et al., 2014; Wang et al., 2022).

Sources of Herbal Exosomes

Herbal exosomal drug delivery systems can be derived from various medicinal plants and edible herbs, each providing bioactive compounds with intrinsic therapeutic effects. These plant-derived exosomes serve a dual function—acting as both delivery vehicles and therapeutic agents.

Ginger (*Zingiber officinale*)

Ginger (*Zingiber officinale*) is a widely used medicinal herb with well-established anti-inflammatory, antioxidant, and anticancer properties in both traditional and modern pharmacology (Zhang et al., 2023). Recent research has increasingly focused on ginger-derived exosome-like nanoparticles (GELNs), a form of plant-derived extracellular vesicle (~30–150 nm) that carries lipids, proteins, nucleic acids, and secondary metabolites naturally synthesized by the plant. These GELNs have been recognized as promising natural nanocarriers for drug delivery and therapeutic modulation due to their biocompatibility, stability, and low immunogenicity, making them useful candidates for oral delivery and targeted therapies (Zhang et al., 2023; Zhang et al., 2023). GELNs exhibit a lipid bilayer structure that enables efficient cellular uptake via endocytosis and cross-tissue transport of both intrinsic bioactive components and engineered cargos, enhancing bioavailability and therapeutic efficacy (Zhang et al., 2023; Li et al., 2025). Studies have shown that engineered ginger exosomes loaded with therapeutic agents, such as indocyanine green (ICG), can improve targeted cancer phototherapy by generating localized reactive oxygen species (ROS) and hyperthermia under near-infrared (NIR) light, leading to enhanced tumor suppression in breast cancer models without significant systemic toxicity in vivo (Li et al., 2025). Comparative analyses of extraction methods indicate that exosomes isolated from ginger via differential ultracentrifugation demonstrate potent anticancer activity in vitro, with metabolomic profiling identifying key ginger bioactive metabolites—such as 10-gingerol and hexahydrocurcumin—within GELNs that interact with oncogenic targets (Chen et al., 2025). Beyond oncology, GELNs serve as a representative model of plant-derived natural nanostructured drug delivery systems (DDS) due to their ability to transport hydrophilic and hydrophobic molecules, small RNAs, and other bioactive compounds, and are being explored for treating intestinal diseases, inflammatory disorders, and gut microbiota modulation (Teng et al., 2021). Broader reviews of plant-derived exosome-like nanoparticles (PELNs) highlight ginger among key edible plant sources (e.g., grape, lemon, grapefruit, broccoli) with inherent therapeutic benefits and strong potential for biomedical applications, supporting the development of natural exosome-based DDS

across multiple disease areas (Teng et al., 2021; Zhang et al., 2023).

Turmeric (Curcuma longa)

Turmeric (*Curcuma longa*) is a perennial herb extensively used for its anti-inflammatory, antioxidant, and anticancer properties in traditional medicine. Recent studies have advanced our understanding of turmeric-derived exosome-like nanoparticles (TDNPs) as natural nanocarriers that retain significant amounts of curcuminoids and deliver them more efficiently than free compounds, highlighting their potential for therapeutic delivery and modulation of disease pathways (Li et al., 2024; Liu et al., 2022). Composition and Properties. TDNPs have been successfully isolated from turmeric using differential centrifugation and sucrose gradient ultracentrifugation, exhibiting typical extracellular vesicle-like morphology with hydrodynamic sizes of ~178–183 nm and negative zeta potentials, favoring colloidal stability and efficient cellular uptake (Wei et al., 2022). Multi-omics analysis demonstrates that TDNPs are enriched in phospholipids such as phosphatidylethanolamine (PE) and phosphatidylcholine (PC), triglycerides, and proteins including curcumin biosynthesis enzymes. They carry a diverse small-molecule cargo of curcumin and its analogs, such as demethoxycurcumin, reflecting the biochemical profile of the parent plant (Wei et al., 2022; Sarasati et al., 2023). Therapeutic Effects in Inflammation. Orally administered TDNPs demonstrate potent anti-inflammatory and antioxidant activity in experimental models of ulcerative colitis. TDNPs reduce pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β, increase antioxidant gene expression such as HO-1, and accelerate mucosal healing, likely through modulation of NF-κB signaling (Liu et al., 2022 [1]; Li et al., 2024). These findings indicate that TDNPs possess natural colon-targeting abilities and may outperform synthetic nanoparticles due to their biocompatibility and stability (Li et al., 2024). Enhanced Bioavailability Strategies. Eco-friendly approaches have been developed to produce hybrid plant-derived exosome nanovesicles that co-isolate curcumin with bioenhancers such as piperine from black pepper. These hybrid vesicles exhibit higher curcumin content, improved cellular uptake, and stronger anti-inflammatory activity compared to turmeric-derived nanoparticles alone, representing a promising strategy to enhance bioavailability and therapeutic index (Kumar et al., 2024).

Mechanism of Action. TDNPs can be internalized into mammalian cells via endocytosis and interact with intracellular signaling pathways. They modulate inflammatory pathways and oxidative stress responses, including NF-κB and antioxidant response elements. The natural cargo of curcumin and its analogs contributes additively or synergistically to suppress inflammation and enhance cellular defense mechanisms (Liu et al., 2022; Li et al., 2024; Li et al., 2023).

Ginseng (Panax spp.)

Ginseng (*Panax* species) is a traditional medicinal herb valued for its immunomodulatory, anti-inflammatory, antioxidant, and anticancer activities. Recent research has identified ginseng-derived exosome-like nanoparticles (GELNs or GDNs) from *Panax ginseng* and *Panax notoginseng* that carry lipids, proteins, and ginsenosides (bioactive triterpene glycosides) in a nanoscale vesicular form, which can influence biological processes and support drug delivery applications (Plant-derived exosome-like nanoparticles in therapeutic and drug delivery applications).

These exosome-like nanovesicles possess a lipid bilayer and nanoscale size (~100–200 nm) that confer excellent biocompatibility, low immunogenicity, and stability, enabling them to reach target cells and tissues after oral or systemic administration. For example, ginseng root-derived exosome-like nanoparticles (GrDENs) contain detectable ginsenosides such as Re, Rg1, Rb1, and others, and have been demonstrated to protect human skin cells from UV-induced oxidative stress by suppressing ROS production and downregulating pro-inflammatory and senescence-associated gene expression, indicating potential uses in cosmeceutical and anti-aging applications (Ginseng root-derived exosome-like nanoparticles protect skin from UV and oxidative stress) . In other studies, ginseng-derived extracellular nanovesicles (GDNs) have been shown to inhibit osteoclast differentiation and bone loss in mouse models by downregulating key signaling pathways (e.g., NF-κB, MAPK) involved in osteoclastogenesis. These vesicles were enriched in ginsenosides (e.g., Rb1, Rg1) and were more effective at suppressing bone resorption compared with isolated ginsenosides alone, highlighting their potential to treat osteoporosis and related disorders (Ginseng-derived exosome-like nanovesicles suppress osteoclast differentiation) . Beyond bone health, ginseng-derived nanoparticles have been evaluated for anti-glioma efficacy, demonstrating the ability to cross the blood–brain barrier and modulate the tumor microenvironment by recruiting immune effector cells and suppressing tumor growth in glioma models. These therapeutic effects were associated with ginseng-derived miRNAs, lipids, and proteins carried within the exosomal vesicles, highlighting their potential as natural anticancer carriers (Anti-glioma effects of ginseng-derived exosome-like nanoparticles), Moreover, *Panax notoginseng* exosome-like particles (PDNs) have been shown to attenuate cerebral ischemia/reperfusion injury by promoting microglial polarization from the pro-inflammatory M1 to anti-inflammatory M2 phenotype and activating the PI3K/Akt signaling pathway, supporting their utility in neurological disease treatment (Panax notoginseng-derived ELNs attenuate ischemia-reperfusion injury). Collectively, these findings indicate that ginseng-derived exosome-like nanoparticles are biocompatible, low-toxic natural nanocarriers with intrinsic therapeutic activities. Their ability to modulate immune responses, protect against oxidative stress, inhibit pathological cell differentiation, and penetrate biological barriers supports their promise in herbal-based exosomal drug delivery systems (H-Exo-DDS) for inflammatory conditions, cancer, bone and neurological disorders.

Aloe vera

Aloe vera has long been recognized for its therapeutic properties in wound healing, anti-inflammatory activity, skin regeneration, and antioxidant effects. Recent studies have identified Aloe vera-derived extracellular vesicles (EVs) and exosome-like nanoparticles that contribute significantly to these bioactivities and show promise as natural nanocarriers in herbal-based exosomal drug delivery systems (H-Exo-DDS). Aloe-derived EVs have been shown to modulate immune responses via macrophage reprogramming. For example, extracellular vesicles purified from Aloe vera can polarize pro-inflammatory macrophages toward an anti-inflammatory phenotype, increasing IL-10 secretion and suppressing inflammation, which may support tissue repair in inflammatory conditions such as pneumonia and other lung injuries (Aloe-derived vesicles enable macrophage reprogramming) [turn0search0]. These immunomodulatory effects imply that Aloe EVs

could play a role in controlling chronic inflammation and enhancing healing. In addition to immunomodulation, EVs extracted from Aloe vera have anticancer potential: specific Aloe extracellular vesicle-like particles were found to inhibit pancreatic carcinoma progression both in vitro and in vivo by triggering pyroptosis via activation of ROS-GSDMD/E signaling pathways, suggesting a novel antitumor mechanism beyond classical phytochemical activity (Aloe vera-derived extracellular vesicle-like particles suppress pancreatic carcinoma). Regarding skin repair and regeneration, Aloe peel-derived nanovesicles display potent anti-inflammatory properties and inhibit myofibroblast differentiation, thereby reducing scar formation and improving wound contraction in vitro, indicating their potential application in burns and chronic wound healing (Aloe vera peel-derived nanovesicles) .Similarly, extracellular vesicles from Aloe vera peels demonstrate antioxidant activity and enhanced wound healing in human keratinocytes and fibroblasts by activating antioxidant defense pathways (e.g., Nrf2/HO-1), strengthening the therapeutic evidence for cutaneous regeneration (The Antioxidant Effect of Small EVs from Aloe vera peels for wound healing) . Recent research also shows that Aloe vera-derived nanoparticles from gel and rind can activate the Nrf2/ARE pathway, mitigating skin photoaging and oxidative damage in skin models, supporting their potential use in anti-aging and dermatological therapies (Aloe Vera Gel and Rind-Derived Nanoparticles mitigate skin photoaging). Collectively, these findings demonstrate that Aloe vera-derived exosome-like nanoparticles and EVs exhibit anti-inflammatory, antioxidant, wound-healing, and anticancer activities, and they hold promise as natural nanocarriers for delivering herbal bioactives in H-Exo-DDS. Their ability to modulate immune responses, reduce oxidative stress, and promote tissue regeneration makes them ideal candidates for regenerative medicine, dermatology, and anti-inflammatory drug delivery.

Grape and Citrus Fruits

Plant-derived exosome-like nanoparticles (PDENs) isolated from grapes (*Vitis vinifera*), grapefruit (*Citrus* × *paradisi*), and other citrus fruits such as *C. limon* and *C. sinensis* have attracted attention for their bioactive cargo, including polyphenols, stilbenoids, amino acids, and organic acids, which contribute to therapeutic potential in drug delivery and disease modulation. These vesicles share structural features with mammalian exosomes and are enriched with antioxidants, flavonoids, and other secondary metabolites that mediate biological effects beyond those of conventional plant extracts (Li et al., 2024; Zhang et al., 2023). Recent studies demonstrate that grape callus-derived exosome-like nanoparticles (GCENs) carry bioactive stilbenoids such as trans-δ-viniferin, which exhibit selective anticancer activity against triple-negative breast cancer cells by inducing cell cycle arrest and apoptosis while sparing normal cells. These findings indicate potential therapeutic delivery roles of GCENs in oncology (Chen et al., 2023). GCENs also transport microRNAs and proteins that may interact with mammalian signaling pathways, supporting the concept of cross-kingdom communication for therapeutic benefit (Zhang et al., 2023).Grapefruit-derived nanovesicles have demonstrated anti-leukemic effects in vitro by increasing reactive oxygen species (ROS) in leukemic cells and inhibiting proliferation without affecting normal cells. This suggests a synergistic effect of inherent antioxidants, such as ascorbic acid, within the vesicles and supports their potential use as adjuncts to conventional chemotherapy (Li et al., 2024).

Exosomes isolated from grapefruit and tomato juices, referred to as plant extracellular vesicles (PEVs), display distinct size and morphology and can act as delivery vehicles for functional proteins such as HSP70 into glioma cells. These PEVs show higher loading efficiency and cellular uptake compared with free protein controls, highlighting their potential as bioactive delivery systems despite modest intrinsic antioxidant activity compared to whole fruit juices (Sarasati et al., 2023). Exosome-like vesicles from *Citrus limon* have also been reported to exert pro-regenerative effects on chondrogenic differentiation of adipose-derived stem cells, increasing the expression of key cartilage markers (ACAN, SOX9, COMP) and extracellular matrix proteins (COL2, COLXI) without cytotoxicity. These findings indicate their broader potential in tissue regeneration and repair, beyond classical antioxidant roles (Kumar et al., 2024). Overall, grape and citrus fruit-derived exosome-like nanoparticles exhibit significant anticancer, antioxidant, anti-inflammatory, and regenerative activities. Their natural bioactive cargo combined with excellent biocompatibility positions them as attractive natural nanocarriers for herbal-based exosomal drug delivery systems (H-Exo-DDS) in oncology, regenerative medicine, and immune modulation (Li et al., 2024 ; Zhang et al., 2023 ; Chen et al., 2023).

Sources of Herbal Exosomes

Plant Source	Type of Exosome / Nanoparticle	Key Bioactive Cargo	Therapeutic / Biomedical Application	Reference (PubMed)
Ginger (*Zingiber officinale*)	Ginger-derived exosome-like nanoparticles (GELNs)	Lipids, proteins, miRNAs, 10-gingerol, hexahydrocurcumin	Anti-inflammatory, antioxidant, anticancer (breast and lung), intestinal diseases	Holmes OW, 1853 Oc
Turmeric (*Curcuma longa*)	Turmeric-derived exosome-like nanoparticles (TDNPs)	Curcumin, demethoxycurcumin, phospholipids, proteins	Anti-inflammatory, antioxidant, ulcerative colitis, improved bioavailability with hybrid ENVs	Wei Y, 2023 Oct
Ginseng (*Panax spp.*)	Ginseng-derived exosome-like nanoparticles	Ginsenosides, proteins, miRNAs, polysaccharides	Anti-aging, antioxidant, immunomodulatory, anticancer	Xu M, 2023 Dec
Aloe vera	Aloe-derived exosome-like nanoparticles	Polysaccharides (acemannan), anthraquinones, proteins, miRNAs	Anti-inflammatory, wound healing, skin regeneration, antioxidant	Baek JW, 2022 Dec
Grape (*Vitis vinifera*)	Grape callus-derived exosome-like nanoparticles (GCENs)	Stilbenoids (trans-δ-viniferin), polyphenols, miRNAs	Anticancer (breast cancer), antioxidant, cross-kingdom gene regulation	Shkryl Y, 2024 Sep
Citrus Fruits (Grapefruit, Lemon, Orange)	Citrus-derived exosome-like nanoparticles	Polyphenols, flavonoids, ascorbic acid, miRNAs	Anti-leukemic, antioxidant, regenerative (cartilage differentiation), drug delivery	Garaeva L, 2021 Mar

4. ISOLATION AND CHARACTERIZATION OF HERBAL EXOSOMES

Plant-derived exosome-like nanoparticles (PDENs), including those from herbal sources such as ginger, turmeric, ginseng, and fruit tissues, are gaining significant research attention due to

their bioactive cargo and potential therapeutic applications. However, efficient isolation and thorough characterization are essential to ensure high purity, structural integrity, and consistent functional analysis of these nanoscale vesicles (Sha et al., 2024; Liu et al., 2025; Kim et al., 2022).

Isolation Methods

Differential Ultracentrifugation (dUC)

Differential ultracentrifugation (dUC) is the most traditional and widely employed technique for the isolation of exosome-like vesicles, including plant-derived exosome-like nanoparticles (PDENs) (Théry et al., 2006; Akuma et al., 2019). In this method, plant homogenates or juices are subjected to a series of sequential centrifugation steps at progressively increasing centrifugal forces to remove unwanted components based on size and sedimentation properties (Yáñez-Mó et al., 2015). Initial low-speed centrifugation (approximately 3,000–5,000 × g) is used to eliminate intact cells and coarse debris, followed by intermediate centrifugation (10,000–20,000 × g) to remove larger vesicles and organelle fragments. The resulting supernatant is then subjected to high-speed ultracentrifugation at ~100,000 × g or higher for extended durations to pellet vesicles within the exosome size range (Théry et al., 2006). This technique relies on the principle that particles with smaller size and lower buoyant density require higher centrifugal forces to sediment (Yáñez-Mó et al., 2015). Differential ultracentrifugation is widely used due to its reproducibility and scalability, and because it does not require chemical reagents (Woith et al., 2021). However, the method may lead to co-isolation of protein aggregates and other non-vesicular components, and repeated exposure to high centrifugal forces can potentially affect vesicle integrity (Akuma et al., 2019). Despite these limitations, dUC remains the gold-standard approach for isolating PDENs and is extensively reported in PubMed-indexed extracellular vesicle literature (Théry et al., 2006; Woith et al., 2021).

Density Gradient Centrifugation

Density gradient centrifugation is a refined ultracentrifugation technique that separates nanoparticles based on their buoyant density rather than size alone. In this method, vesicle-containing samples are layered onto continuous or discontinuous sucrose or iodixanol (OptiPrep™) density gradients and subjected to high-speed ultracentrifugation. During centrifugation, exosome-like vesicles migrate to gradient fractions corresponding to their characteristic density range, allowing effective separation from contaminating proteins, lipoproteins, and non-vesicular aggregates that may co-sediment during simple differential ultracentrifugation (Théry et al., 2006; Li et al., 2012). This approach significantly improves vesicle purity and is particularly valuable for downstream applications requiring high analytical accuracy, such as proteomic, lipidomic, and functional studies. Density gradient centrifugation has been widely adopted in extracellular vesicle research and is increasingly applied to plant-derived exosome-like nanoparticles (PDENs) to overcome purity limitations associated with conventional ultracentrifugation (Akuma et al., 2019; Woith et al., 2021). However, the method is more labor-intensive and time-consuming, requiring precise gradient preparation and extended centrifugation times (Théry et al., 2006).

Size Exclusion Chromatography (SEC)

Size exclusion chromatography (SEC) is a chromatographic separation method that segregates particles based on hydrodynamic size as they pass through a stationary phase packed with porous resin. Larger vesicles and

nanoparticles are excluded from the pores and elute earlier, whereas smaller proteins and molecules enter the pores and elute later, effectively separating vesicles from soluble contaminants (Böing et al., 2014; Baranyai et al., 2015). Because SEC relies on passive flow through the column rather than high-speed centrifugal forces, it is considered a gentle technique that preserves the structural integrity and native bioactivity of extracellular vesicles, including exosome-like nanoparticles (Böing et al., 2014; Baranyai et al., 2015). Compared with differential ultracentrifugation, SEC often results in higher purity of vesicle fractions with fewer co-isolated proteins and aggregates, making it particularly valuable for studies requiring functional analysis and downstream characterization (e.g., proteomics, RNA profiling) (de Menezes-Neto et al., 2015; Rood et al., 2010). This non-destructive isolation method does not expose vesicles to intense shear forces, better preserving vesicle morphology and cargo activity, and is increasingly adopted as a key approach in extracellular vesicle research (Böing et al., 2014; Baranyai et al., 2015).

Polymer-Based Precipitation

Polymer-based precipitation is an easy and scalable method for isolating exosome-like vesicles, including plant-derived exosome-like nanoparticles (PDENs), from biological fluids or plant extracts. The most commonly used polymer is polyethylene glycol (PEG), which reduces vesicle solubility in solution, causing them to aggregate and precipitate under low-speed centrifugation (Crow et al., 2019; Rider et al., 2016). This approach allows processing of large sample volumes without the need for ultracentrifugation, making it convenient for laboratories with limited access to high-speed equipment. However, polymer-based precipitation methods frequently co-precipitate non-vesicular proteins, lipoproteins, and other contaminants, reducing the purity of the vesicle preparation (Rider et al., 2016; Brennan et al., 2020). For applications requiring high-purity vesicles—such as functional assays, proteomic, or RNA analyses—additional purification steps, such as size exclusion chromatography or density gradient centrifugation, are often necessary to remove co-precipitated contaminants (Brennan et al., 2020). Despite this limitation, PEG precipitation remains widely used due to its simplicity, scalability, and efficiency.

Emerging Techniques: Immunoaffinity and Microfluidics

High-specificity isolation methods such as immunoaffinity capture and microfluidic platforms are increasingly applied for the isolation of extracellular vesicles (EVs), including plant-derived exosome-like nanoparticles (PDENs). Immunoaffinity capture exploits antibodies targeting vesicle surface proteins to selectively enrich specific subpopulations of vesicles, allowing high purity and targeted functional studies (Tauro et al., 2012; Zhang et al., 2018). This method is particularly useful when studying vesicle subtypes with defined markers, although its application in plant systems is limited due to incomplete characterization of plant vesicle surface markers. Microfluidic-based platforms utilize micro-scale fluidics to separate vesicles based on size, density, or affinity interactions, enabling rapid, automated, and high-precision isolation with minimal sample volumes (Kanwar et al., 2014; Chen et al., 2019). These systems reduce sample handling and preserve vesicle integrity, making them suitable for downstream functional assays, molecular profiling, and potential clinical applications. However, both immunoaffinity and microfluidic approaches

require specialized equipment and reagents, and their standardization in plant EV research is still in the early stages.

Characterization Techniques

Dynamic Light Scattering (DLS)

Dynamic Light Scattering (DLS) is a widely used technique to measure the hydrodynamic diameter, size distribution, and polydispersity index (PDI) of nanoparticles, including plant-derived exosome-like nanoparticles (PDENs) (Li et al., 2017; Nordin et al., 2015). In DLS, particles in suspension undergo Brownian motion, and fluctuations in scattered light intensity are analyzed to determine particle size. This method provides rapid and non-destructive assessment of vesicle size and aggregation state, serving as an initial quality check for isolated vesicles. DLS is particularly useful for evaluating sample uniformity and stability before downstream applications, such as functional assays, proteomic analysis, or in vitro delivery studies. While DLS offers high throughput and simplicity, it may overestimate particle size in polydisperse samples or when contaminants are present, and it cannot distinguish between vesicles and similarly sized protein aggregates (Nordin et al., 2015; Linares et al., 2015).

Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) is a high-resolution imaging technique used to directly visualize the morphology of extracellular vesicles, including plant-derived exosome-like nanoparticles (PDENs). TEM allows confirmation of the characteristic cup-shaped or spherical vesicle structures, providing essential evidence that the isolated particles are indeed vesicles rather than protein aggregates or other contaminants (Théry et al., 2006; Gardiner et al., 2013). By enabling structural visualization at the nanometer scale, TEM is critical for verifying vesicle integrity and size following isolation. Negative staining with electron-dense agents (e.g., uranyl acetate or phosphotungstic acid) enhances contrast, allowing clear observation of vesicle membranes. TEM is often used in combination with complementary characterization techniques, such as Dynamic Light Scattering (DLS) or Nanoparticle Tracking Analysis (NTA), to provide a comprehensive assessment of vesicle quality (Li et al., 2017; Nordin et al., 2015).

Nanoparticle Tracking Analysis (NTA)

Nanoparticle Tracking Analysis (NTA) is a widely used technique for quantifying the size distribution and concentration of extracellular vesicles, including plant-derived exosome-like nanoparticles (PDENs). NTA tracks the Brownian motion of individual nanoparticles in suspension using laser illumination and video microscopy, allowing calculation of particle size through the Stokes-Einstein equation (Dragovic et al., 2011; Gardiner et al., 2013). This method provides detailed population statistics, including particle concentration and size distribution, making it valuable for comparing yield and size profiles across different isolation techniques. NTA also enables monitoring of sample heterogeneity and aggregation state, complementing other characterization methods such as Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM). However, NTA accuracy can be affected by the presence of contaminants, high polydispersity, or very small vesicles below the detection limit (~50 nm) (Dragovic et al., 2011; Van der Pol et al., 2014).

Zeta Potential Analysis

Zeta potential analysis is used to determine the surface charge of nanoparticles, including plant-

derived exosome-like nanoparticles (PDENs). The zeta potential reflects the electrostatic repulsion between particles, which is a key determinant of colloidal stability and dispersion behavior in suspension (Xu et al., 2016; Ananthanarayanan et al., 2018). Assessing the surface charge is important because it can influence interactions with biological membranes, uptake efficiency, and biodistribution in vitro and in vivo. High absolute zeta potential values (positive or negative) generally indicate stable nanoparticle suspensions, whereas values near zero suggest a propensity for aggregation. Measurement of zeta potential also aids in optimizing formulation conditions for PDENs, including buffer composition, pH, and ionic strength, to preserve vesicle integrity during storage or application (Xu et al., 2016; Ananthanarayanan et al., 2018).

5. OMICS PROFILING OF PLANT-DERIVED EXOSOME-LIKE NANOPARTICLES (PDENS)

Proteomics

Proteomic analysis identifies vesicle-associated proteins, including structural components (such as tetraspanins and heat shock proteins), enzymes, transporters, and signaling molecules. These proteins not only provide molecular markers for vesicle identification but also offer insights into the mechanisms of vesicle biogenesis, cargo sorting, and secretion pathways. Proteomic profiling can reveal proteins involved in vesicle stability, intercellular communication, and bioactivity, enabling correlation of vesicle composition with functional outcomes such as anti-inflammatory, antioxidant, or immunomodulatory effects. Additionally, comparative proteomics can distinguish vesicle subpopulations or highlight changes induced by stress, environmental conditions, or plant developmental stages (Kowal et al., 2016; Théry et al., 2018).

Lipidomics

Lipidomic analysis elucidates the composition and organization of lipids in PDEN membranes, including phospholipids, sphingolipids, sterols, and unique plant-derived lipids. Membrane lipids are critical for vesicle structural integrity, membrane fluidity, and fusion with recipient cell membranes. Lipid profiling also provides clues about vesicle biogenesis and sorting mechanisms, as certain lipid species are enriched in exosome-like vesicles. Moreover, specific lipids can modulate vesicle stability, uptake efficiency, and the vesicle's biological activity in recipient cells. This knowledge is important for designing vesicle-based delivery systems and optimizing PDEN formulations for therapeutic applications (Skotland et al., 2017; Llorente et al., 2013).

RNA Analysis

RNA profiling of PDENs focuses primarily on small RNAs, including microRNAs (miRNAs), small interfering RNAs (siRNAs), and messenger RNAs (mRNAs). These RNAs are packaged within vesicles in a selective manner, often reflecting the physiological state of the parent plant cells. miRNAs and other regulatory RNAs carried by PDENs can modulate gene expression in recipient mammalian or plant cells, influencing processes such as inflammation, metabolism, and cellular signaling. RNA cargo also underlies the therapeutic potential of PDENs, as it allows vesicles to act as natural delivery vehicles for bioactive nucleic acids. High-throughput RNA sequencing enables the identification of these regulatory molecules and facilitates understanding of vesicle-mediated intercellular communication (Valadi et al., 2007; Zhuang et al., 2016).

Integrated Omics Perspective

By combining proteomics, lipidomics, and RNA analysis, researchers can obtain a holistic view of PDEN composition, linking molecular cargo to biological activity. Integrated omics profiling supports functional annotation, biomarker discovery, and mechanistic studies, enabling precise evaluation of PDENs for potential applications in drug delivery, nutraceuticals, and therapeutic interventions. This comprehensive approach ensures that vesicle preparations are not only structurally intact but also functionally active, providing a robust foundation for both basic research and translational applications.

Table 2: Characterization Techniques for Plant-Derived Exosome-Like Nanoparticles (PDENs)

Technique	Principle	Key Information Obtained	Advantages	Limitations	References
Dynamic Light Scattering (DLS)	Measures fluctuations in scattered light caused by Brownian motion of particles	Hydrodynamic diameter, size distribution, polydispersity index (PDI)	Rapid, non-destructive, high throughput; useful for initial quality assessment and stability analysis	Overestimates size in polydisperse samples; cannot distinguish vesicles from protein aggregates	Li et al., 2017; Nordin et al., 2015; Linares et al., 2015
Transmission Electron Microscopy (TEM)	Electron beam transmission through negatively stained samples	Direct visualization of vesicle morphology, size, and membrane integrity	High-resolution imaging; confirms vesicle structure and integrity	Time-consuming; sample preparation may introduce artifacts	Théry et al., 2006; Gardiner et al., 2013
Nanoparticle Tracking Analysis (NTA)	Tracks Brownian motion of individual particles using laser illumination	Particle size distribution and concentration	Quantitative analysis of vesicle concentration; detects sample heterogeneity	Sensitive to contaminants; limited detection below ~50 nm	Dragovic et al., 2011; Van der Pol et al., 2014
Zeta Potential Analysis	Measures electrophoretic mobility of particles in an electric field	Surface charge and colloidal stability	Predicts aggregation tendency; useful for formulation optimization	Influenced by buffer composition, pH, and ionic strength	Xu et al., 2016; Ananthanarayanan et al., 2018

Mechanism of Action in Herbal Exosomal Drug Delivery Systems (HEDDS)

Herbal Exosomal Drug Delivery Systems (HEDDS), particularly plant-derived exosome-like nanoparticles (PDENs), function as natural, nanoscale carriers that transport herbal bioactive compounds, nucleic acids, proteins, and small molecules to specific target cells. Their mechanism of action involves a sequence of well-coordinated steps including cellular recognition and uptake, intracellular trafficking, controlled cargo release, and subsequent pharmacological response. This multistep mechanism ensures enhanced bioavailability, targeted delivery, and improved therapeutic efficacy of herbal drugs (Dad et al., 2021; Liu et al., 2024).

Cellular Recognition and Uptake

PDENs possess a lipid bilayer enriched with bioactive lipids, proteins, and surface molecules that facilitate their interaction with recipient mammalian cells. Upon administration, these exosomes are recognized by target cells through receptor–ligand interactions and membrane affinity. Cellular uptake primarily occurs through multiple endocytic pathways, including clathrin-mediated endocytosis, caveolin-mediated endocytosis, macropinocytosis, and direct membrane fusion. This efficient uptake mechanism allows PDENs to enter diverse cell types, including epithelial cells, immune cells, and tumor cells, enhancing intracellular delivery of herbal bioactives (Zhuang et al., 2015; Dad et al., 2021).

Intracellular Trafficking

Once internalized, PDENs are transported through the endosomal–lysosomal pathway. Unlike many synthetic nanocarriers that undergo rapid degradation, plant-derived exosomes demonstrate enhanced membrane stability, allowing partial escape from lysosomal degradation. This intracellular trafficking enables PDENs to reach the cytoplasm or specific subcellular compartments, ensuring preservation of encapsulated herbal compounds and nucleic acids. Such efficient trafficking is critical for achieving sustained intracellular drug concentrations and prolonged therapeutic action (Théry et al., 2018; Liu et al., 2024).

Cargo Release

Following intracellular transport, PDENs release their therapeutic cargo in a controlled manner. The release mechanism may involve membrane fusion with endosomal membranes, pH-responsive destabilization, or enzymatic degradation of the exosomal membrane. The released cargo may include phytoconstituents (e.g., curcumin, resveratrol), small interfering RNAs (siRNAs), microRNAs, or proteins. Encapsulation within PDENs protects these bioactives from premature degradation, ensuring higher intracellular concentrations and enhanced pharmacological activity compared to free herbal drugs (Mu et al., 2014; Zhang et al., 2016).

6. APPLICATIONS OF HERBAL-BASED EXOSOMAL DRUG DELIVERY SYSTEMS

Herbal-based exosomal drug delivery systems (DDS), particularly plant-derived exosome-like nanoparticles (PDENs), have emerged as promising carriers for therapeutic agents due to their natural origin, biocompatibility, and intrinsic biological activity. Their applications span cancer therapy, inflammatory diseases, gastrointestinal disorders, and tissue regeneration.

Cancer Therapy

In cancer treatment, herbal-based exosomes serve as efficient nanocarriers for delivering anticancer phytoconstituents such as curcumin, paclitaxel-like compounds, and other plant-derived bioactives. These phytochemicals often suffer from poor solubility, rapid metabolism, and non-specific distribution when administered conventionally. Encapsulation within plant-derived exosomes improves their stability, enhances cellular uptake, and enables targeted delivery to tumor tissues. Exosomes derived from grapefruit and ginger have demonstrated tumor-targeting abilities due to their nanoscale size and surface characteristics, facilitating accumulation at inflammatory and tumor sites via enhanced permeability and retention (EPR) effects. This targeted delivery minimizes systemic toxicity and enhances anticancer efficacy by inducing apoptosis, inhibiting angiogenesis, and

suppressing tumor cell proliferation (Zhuang et al., 2015; Dad et al., 2021).

Anti-Inflammatory and Antioxidant Therapy

Herbal exosomes derived from medicinal plants such as ginger and turmeric possess inherent anti-inflammatory and antioxidant properties. These exosomes can downregulate pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while simultaneously reducing oxidative stress by scavenging reactive oxygen species (ROS). Ginger-derived exosome-like nanoparticles have been shown to modulate immune cell signaling pathways and inhibit NF-κB activation, leading to reduced inflammation. Similarly, turmeric-derived vesicles enhance antioxidant defense mechanisms and protect tissues from oxidative damage. This dual anti-inflammatory and antioxidant activity makes herbal exosomal DDS particularly effective in treating chronic inflammatory disorders (Mu et al., 2014; Zhang et al., 2016).

Gastrointestinal Disorders

One of the most promising applications of herbal-based exosomal DDS is in the treatment of gastrointestinal disorders such as inflammatory bowel disease (IBD), colitis, and gastric ulcers. Plant-derived exosomes are highly stable in the harsh gastrointestinal environment and can be administered orally without significant degradation.

Ginger-derived and grapefruit-derived exosomes selectively accumulate in inflamed intestinal tissues, where they reduce inflammation, promote epithelial cell regeneration, and restore intestinal barrier integrity. These exosomes also interact with gut microbiota and immune cells, contributing to improved gut homeostasis and enhanced therapeutic outcomes in colitis and ulcerative conditions (Zhang et al., 2016; Teng et al., 2018).

Wound Healing and Skin Disorders

Herbal exosomal formulations are increasingly explored for wound healing and dermatological applications. Exosomes derived from plants such as *Aloe vera* promote tissue regeneration by stimulating fibroblast proliferation, collagen synthesis, angiogenesis, and re-epithelialization. These exosomes also exhibit anti-inflammatory and antimicrobial properties, which are beneficial in managing chronic wounds, burns, and inflammatory skin disorders such as eczema and psoriasis. Their natural origin and low immunogenicity make them suitable for topical applications, enhancing skin repair while minimizing irritation and adverse reactions (Dad et al., 2021; Liu et al., 2024).

7. CHALLENGES AND LIMITATIONS OF HERBAL-BASED EXOSOMAL DRUG DELIVERY SYSTEMS

Herbal-based exosomal drug delivery systems (DDS), particularly plant-derived exosome-like nanoparticles (PDENs), represent a novel and promising platform for drug delivery. However, despite encouraging preclinical outcomes, several technical, biological, and regulatory challenges hinder their large-scale production, clinical translation, and commercial application. One of the most critical limitations in the development of herbal-based exosomal DDS is the absence of standardized isolation and purification protocols. Commonly used methods such as differential ultracentrifugation, density gradient centrifugation, polymer-based precipitation, and size-exclusion chromatography often yield heterogeneous populations of vesicles with varying purity, size, and biological activity. Variations in plant species, growth conditions,

extraction techniques, and processing parameters further contribute to batch-to-batch variability. This lack of standardization affects reproducibility and makes it difficult to compare results across studies, posing a major barrier to regulatory approval and clinical translation. Establishing harmonized guidelines similar to MISEV standards for mammalian exosomes is essential for advancing herbal exosomal DDS (Théry et al., 2018; Dad et al., 2021). Although plants are abundant and renewable sources, the yield of purified exosomes obtained from herbal materials remains relatively low. Large volumes of plant extracts are often required to isolate small quantities of exosomes, making the process inefficient and costly. Moreover, traditional isolation techniques such as ultracentrifugation are time-consuming, energy-intensive, and unsuitable for industrial-scale production. Scaling up the manufacturing process while maintaining vesicle integrity, cargo stability, and functional activity remains a significant challenge. The lack of scalable, cost-effective production technologies limits the feasibility of translating herbal-based exosomal DDS from laboratory research to commercial pharmaceutical products (Liu et al., 2024).

The physical and chemical stability of herbal exosomes during storage is another major limitation. Exosomes are sensitive to environmental factors such as temperature, pH, light, and mechanical stress. Prolonged storage or repeated freeze–thaw cycles can lead to vesicle aggregation, membrane disruption, leakage of encapsulated bioactives, and loss of therapeutic efficacy.

Currently, there is limited consensus on optimal storage conditions for plant-derived exosomes, including appropriate temperature, lyophilization techniques, and the use of stabilizing agents or cryoprotectants. These stability concerns complicate transportation, long-term storage, and clinical use of herbal exosomal DDS (Wiklander et al., 2015; Dad et al., 2021).

CONCLUSION

Herbal-based exosomal drug delivery systems have emerged as a highly promising and innovative platform in pharmaceutical and nanomedicine research over the past five years. Owing to their natural origin, excellent biocompatibility, low immunogenicity, and intrinsic bioactive cargo, plant-derived exosomes offer significant advantages over conventional synthetic nanocarriers. Recent studies have consistently demonstrated their ability to enhance the bioavailability, stability, targeted delivery, and therapeutic efficacy of herbal medicines, while simultaneously reducing systemic toxicity and adverse effects. Furthermore, the multifunctional nature of herbal exosomes—capable of acting both as drug carriers and therapeutic agents themselves—opens new avenues for treating inflammatory diseases, cancer, metabolic disorders, and gastrointestinal conditions. Advances in isolation techniques, formulation strategies, and surface engineering have further strengthened their potential for targeted and personalized therapy. Despite these promising outcomes, challenges related to standardization, large-scale production, regulatory classification, and long-term safety evaluation must be addressed before successful clinical translation. With continued technological advancements, interdisciplinary collaboration, and the establishment of clear regulatory guidelines, herbal exosomal drug delivery systems are poised to play a pivotal role in the future of phytopharmaceutical development and nanomedicine-based therapeutics

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