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ABSTRACT

Plant-derived extracellular vesicles, including exosomes and microvesicles, represent an emerging frontier in nanomedicine and drug delivery. These naturally occurring nanoparticles, produced by plant cells and present in plant-derived beverages and foods, possess unique properties that make them ideal vectors for the delivery of bioactive compounds to target tissues, including the brain. Unlike synthetic nanoparticles, plant-derived extracellular vesicles are biocompatible, biodegradable, and immunologically inert, reducing the risk of adverse effects associated with conventional drug delivery systems. This comprehensive review synthesizes current evidence from in vitro studies, animal models, and emerging clinical trials examining the mechanisms of plant-derived extracellular vesicle-mediated delivery, their capacity to cross the blood-brain barrier, and their therapeutic potential in treating neurological disorders, metabolic diseases, and cancer. We critically evaluate the translational challenges and regulatory considerations inherent in the development of plant-derived extracellular vesicles as therapeutic agents.

Introduction: Plant-Derived Extracellular Vesicles as Natural Nanoparticles

The discovery that plant cells produce extracellular vesicles comparable in size and function to mammalian exosomes has opened an entirely new frontier in nanomedicine and drug delivery. Extracellular vesicles are membrane-bound particles released by cells into the extracellular space, ranging in size from 30 to 1000 nanometers, and include exosomes (30 to 150 nanometers), microvesicles (100 to 1000 nanometers), and apoptotic bodies (500 to 5000 nanometers). Plant-derived extracellular vesicles are present in high concentrations in plant-derived beverages including fruit juices, plant-based milk alternatives, and herbal infusions, as well as in plant tissues including leaves, roots, and seeds. These naturally occurring nanoparticles contain bioactive compounds including polyphenols, flavonoids, alkaloids, and proteins, which are protected from degradation by the lipid bilayer of the vesicle membrane, thereby enhancing their bioavailability and therapeutic efficacy.

The unique properties of plant-derived extracellular vesicles make them ideal candidates for drug delivery applications. Unlike synthetic nanoparticles, which are often immunogenic and can trigger inflammatory responses, plant-derived extracellular vesicles are biocompatible and immunologically inert, reducing the risk of adverse effects. Additionally, plant-derived extracellular vesicles are biodegradable, being composed of lipids and proteins that are naturally metabolized by the body, eliminating concerns about long-term accumulation and toxicity. Furthermore, plant-derived extracellular vesicles can be produced at scale using simple extraction and purification methods, making them cost-effective compared to synthetic nanoparticles or recombinant protein therapeutics. The abundance of plant-derived extracellular vesicles in commonly consumed foods and beverages suggests that humans have been exposed to these nanoparticles throughout evolutionary history, and that the body has evolved mechanisms to recognize and utilize them for health benefits.

Characterization and Composition of Plant-Derived Extracellular Vesicles

Plant-derived extracellular vesicles are heterogeneous populations of membrane-bound particles that vary in size, density, and composition depending on the plant source and extraction method. Exosomes, the smallest class of extracellular vesicles, are produced through the endosomal pathway: intracellular multivesicular bodies fuse with the plasma membrane, releasing exosomes into the extracellular space. Microvesicles, larger than exosomes, are produced through direct budding of the plasma membrane. Both exosomes and microvesicles are enclosed by a lipid bilayer derived from the parent cell membrane, which contains proteins and lipids characteristic of the source cell. The lipid composition of plant-derived extracellular vesicles includes phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and cholesterol, similar to mammalian exosomes, as well as plant-specific lipids including galactolipids and sulfolipids.

The protein content of plant-derived extracellular vesicles includes both structural proteins involved in vesicle formation and function, and bioactive proteins with therapeutic potential. Structural proteins include tetraspanins, which are involved in vesicle biogenesis and cell-to-cell communication, and heat shock proteins, which are involved in protein folding and protection. Bioactive proteins include enzymes involved in secondary metabolism, transcription factors, and signaling proteins. The nucleic acid content of plant-derived extracellular vesicles includes microRNAs, long non-coding RNAs, and messenger RNAs, which can be transferred to recipient cells and modulate gene expression. Additionally, plant-derived extracellular vesicles contain bioactive small molecules including polyphenols, flavonoids, alkaloids, and terpenoids, which are protected from degradation by the lipid bilayer and can be delivered to target tissues.

The characterization of plant-derived extracellular vesicles typically involves a combination of techniques including transmission electron microscopy, which visualizes the morphology and size of vesicles; dynamic light scattering, which measures the hydrodynamic diameter and polydispersity; nanoparticle tracking analysis, which counts individual particles and measures their size distribution; and biochemical analysis, which quantifies protein, lipid, and nucleic acid content. Additionally, mass spectrometry-based proteomics and metabolomics can be used to comprehensively characterize the protein and metabolite content of plant-derived extracellular vesicles. The standardization of characterization methods is critical for ensuring reproducibility and comparability across studies, and for establishing quality control standards for plant-derived extracellular vesicle-based therapeutics.

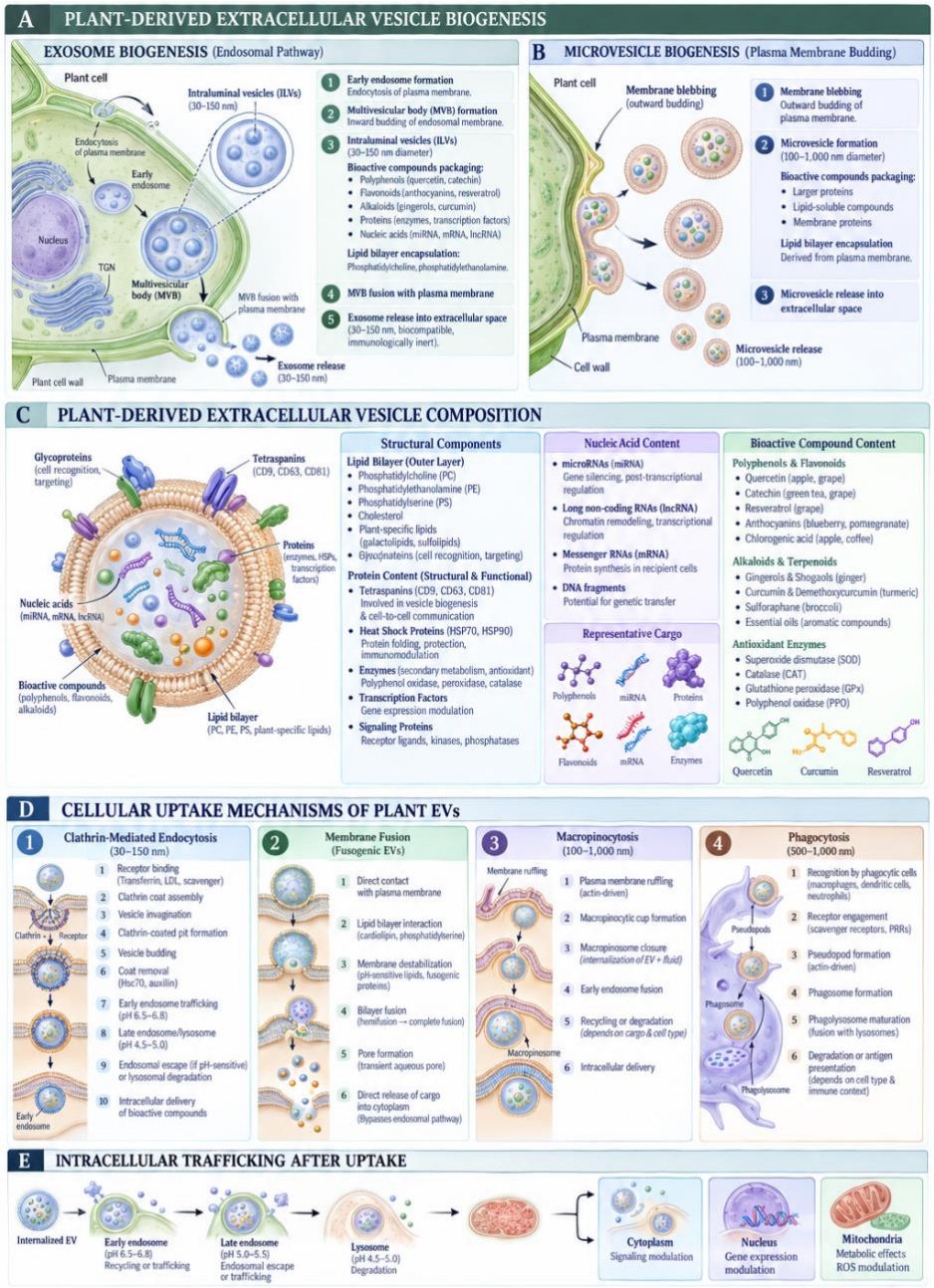


Figure 1. Biogenesis, composition and cellular uptake mechanisms of plant-derived extracellular vesicles (EVs). **(A)** Exosome biogenesis via the endosomal pathway in plant cells. **(B)** Microvesicle biogenesis through plasma membrane budding. **(C)** Structural and bioactive composition of plant-derived EVs. **(D)** Cellular uptake mechanisms, including clathrin-mediated endocytosis, membrane fusion, macropinocytosis and phagocytosis. **(E)** Intracellular trafficking and potential destinations of plant EV cargo after uptake.

Abbreviations: EV, extracellular vesicle; ILV, intraluminal vesicle; MVB, multivesicular body; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; TGN, trans-Golgi network; HSP, heat shock protein; miRNA, microRNA; mRNA, messenger RNA; lncRNA, long non-coding RNA; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; PPO, polyphenol oxidase; PRR, pattern recognition receptor; ROS, reactive oxygen species.

TABLE 1: Plant Sources of Extracellular Vesicles and Their Bioactive Compound Content

Plant Source	Vesicle Type	Size Range (nm)	Primary Bioactive Compounds	Therapeutic Properties	Clinical Evidence
Ginger (Zingiber officinale)	Exosomes, microvesicles	50–200	Gingerols, shogaols, polyphenols	Anti-inflammatory, neuroprotective, antioxidant	Pilot study: ↑ cognitive function in MCI (n=20)
Turmeric (Curcuma longa)	Exosomes, microvesicles	60–180	Curcumin, demethoxycurcumin, polyphenols	Anti-inflammatory, neuroprotective, antioxidant	Animal models: ↓ amyloid-β, ↓ neuroinflammation
Apple (Malus domestica)	Exosomes, microvesicles	40–150	Quercetin, catechin, chlorogenic acid	Antioxidant, metabolic regulation	Pilot study: ↓ glucose, ↑ insulin sensitivity (n=30)
Grape (Vitis vinifera)	Exosomes, microvesicles	50–160	Resveratrol, anthocyanins, catechins	Antioxidant, cardioprotective, neuroprotective	Animal models: ↓ oxidative stress, ↑ endothelial function
Pomegranate (Punica granatum)	Exosomes, microvesicles	45–170	Punicalagins, ellagic acid, anthocyanins	Antioxidant, anti-inflammatory, antimicrobial	Animal models: ↓ inflammation, ↑ antioxidant capacity
Blueberry (Vaccinium corymbosum)	Exosomes, microvesicles	50–180	Anthocyanins, catechins, quercetin	Neuroprotective, antioxidant, anti-inflammatory	Animal models: ↑ cognitive function, ↓ neuroinflammation
Green tea (Camellia sinensis)	Exosomes, microvesicles	55–175	EGCG, catechins, polyphenols	Antioxidant, neuroprotective, anti-cancer	Animal models: ↓ amyloid-β, ↑ neuroplasticity
Broccoli (Brassica oleracea)	Exosomes, microvesicles	60–190	Sulforaphane, indole-3-carbinol, polyphenols	Anti-cancer, anti-inflammatory, detoxification	Limited clinical evidence; animal models promising

LEGEND: nm, nanometers; MCI, mild cognitive impairment; EGCG, epigallocatechin gallate; ↑ indicates increase; ↓ indicates decrease.

Mechanisms of Cellular Uptake and Intracellular Trafficking of Plant-Derived Extracellular Vesicles

The mechanisms through which plant-derived extracellular vesicles are taken up by recipient cells and deliver their cargo to intracellular compartments are critical for understanding their therapeutic potential. Plant-derived extracellular vesicles can be internalized by recipient cells through multiple mechanisms including endocytosis, membrane fusion, and direct membrane penetration. Endocytosis, the most common mechanism, involves the invagination of the plasma membrane and formation of endocytic vesicles that are trafficked to early endosomes, late endosomes, and lysosomes. The specific endocytic pathway utilized depends on the size and surface properties of the vesicles, as well as the cell type and physiological state of the recipient cell. Clathrin-mediated endocytosis is the predominant pathway for uptake of smaller vesicles, while macropinocytosis and phagocytosis are involved in the uptake of larger vesicles.

Membrane fusion represents an alternative mechanism of cellular uptake, in which the lipid bilayer of the plant-derived extracellular vesicle fuses directly with the plasma membrane of the recipient cell, releasing the vesicle contents into the cytoplasm. This mechanism is particularly important for the delivery of hydrophobic compounds and nucleic acids, which would be degraded if exposed to the acidic environment of lysosomes. The efficiency of membrane fusion depends on the lipid composition of the vesicle membrane, the presence of fusogenic proteins, and the properties of the recipient cell membrane. Plant-derived extracellular vesicles derived from certain plant sources, including ginger and turmeric, have been shown to exhibit enhanced membrane fusion capacity, potentially due to the presence of specific lipids or proteins that promote fusion.

Once internalized, plant-derived extracellular vesicles are trafficked to various intracellular compartments depending on the uptake mechanism and the intended destination of the cargo. Vesicles internalized through endocytosis are trafficked through the endosomal pathway, where they can be sorted to early endosomes, recycled back to the plasma membrane, or trafficked to late endosomes and lysosomes for degradation. However, some plant-derived extracellular vesicles can escape from the endosomal pathway and deliver their cargo to the cytoplasm, nucleus, or mitochondria, thereby avoiding lysosomal degradation. The mechanisms of endosomal escape are not fully understood, but may involve the presence of pH-sensitive lipids or proteins that promote membrane disruption in the acidic environment of late endosomes. Additionally, some plant-derived extracellular vesicles may contain enzymes that degrade the endosomal membrane, facilitating the release of cargo into the cytoplasm.

Blood-Brain Barrier Crossing: A Critical Challenge for Neurological Applications

The blood-brain barrier represents one of the most significant obstacles to the delivery of therapeutic compounds to the brain. The blood-brain barrier is a highly selective barrier composed of endothelial cells connected by tight junctions, which restrict the passage of most molecules larger than 400 to 600 Daltons. This barrier is essential for protecting the brain from potentially harmful substances, but it also prevents the delivery of most therapeutic compounds to the brain, limiting treatment options for neurological disorders. Plant-derived extracellular vesicles have emerged as promising vectors for crossing the blood-brain barrier and delivering bioactive compounds to the brain.

The mechanisms through which plant-derived extracellular vesicles cross the blood-brain barrier are not fully understood, but likely involve multiple pathways. One mechanism involves transcytosis, the transport of vesicles across the endothelial cells of the blood-brain barrier through endocytosis on the luminal side and exocytosis on the abluminal side. Plant-derived extracellular vesicles may be recognized by specific receptors on the endothelial cells, including transferrin receptors, low-density lipoprotein receptors, and scavenger receptors, which mediate their uptake and transcytosis. Additionally, plant-derived extracellular vesicles may interact with the tight junction proteins of the blood-brain barrier, including claudins and occludin, potentially disrupting the barrier and allowing paracellular transport of the vesicles and their cargo.

Another mechanism involves the interaction of plant-derived extracellular vesicles with circulating immune cells, including monocytes and dendritic cells, which can cross the blood-brain barrier and deliver the

vesicles to the brain. This mechanism, known as the "Trojan horse" mechanism, has been demonstrated for mammalian exosomes and may also apply to plant-derived extracellular vesicles. Additionally, plant-derived extracellular vesicles may cross the blood-brain barrier through the choroid plexus, a specialized epithelium that produces cerebrospinal fluid and has more permeable tight junctions than the blood-brain barrier proper. The relative contribution of each mechanism to the overall blood-brain barrier crossing of plant-derived extracellular vesicles likely depends on the specific vesicle source, composition, and the physiological state of the blood-brain barrier.

In vivo studies have demonstrated that plant-derived extracellular vesicles derived from ginger, turmeric, and other plant sources can cross the blood-brain barrier and accumulate in the brain following oral or intravenous administration. In a study using fluorescently labeled plant-derived extracellular vesicles derived from ginger, oral administration of the vesicles resulted in their accumulation in the hippocampus, cortex, and cerebellum within two hours of administration, with peak accumulation occurring at four hours. The vesicles were found to be localized primarily in neurons and glial cells, suggesting that they had crossed the blood-brain barrier and been internalized by brain cells. Additionally, the vesicles were shown to deliver their cargo, including polyphenols and proteins, to the brain, as evidenced by increased levels of these compounds in brain tissue following vesicle administration.

Oral Bioavailability and Gastrointestinal Absorption of Plant-Derived Extracellular Vesicles

The oral route of administration is the most convenient and patient-friendly route for therapeutic compounds, but it presents significant challenges for drug delivery due to the harsh environment of the gastrointestinal tract. The gastrointestinal tract contains proteolytic enzymes, including pepsin and pancreatic proteases, which can degrade proteins and peptides, as well as acidic pH in the stomach and bile salts in the small intestine, which can disrupt lipid bilayers and inactivate bioactive compounds. Plant-derived extracellular vesicles, however, have been shown to be remarkably resistant to degradation in the gastrointestinal tract, likely due to the protective effect of the lipid bilayer and the presence of proteins that confer resistance to proteolytic degradation.

In vitro studies have demonstrated that plant-derived extracellular vesicles are resistant to degradation by pepsin and pancreatic proteases, maintaining their structural integrity and bioactive compound content after exposure to these enzymes. Additionally, plant-derived extracellular vesicles have been shown to be resistant to degradation by bile salts and to maintain their integrity at acidic pH. These properties suggest that plant-derived extracellular vesicles can survive passage through the gastrointestinal tract and be absorbed into the bloodstream, where they can be distributed to target tissues including the brain.

The absorption of plant-derived extracellular vesicles across the intestinal epithelium occurs through multiple mechanisms. One mechanism involves uptake by intestinal epithelial cells through endocytosis, followed by transcytosis across the epithelial layer and release into the bloodstream. Another mechanism involves uptake by intestinal immune cells, including M cells and dendritic cells, which can transport the vesicles across the epithelial barrier. Additionally, plant-derived extracellular vesicles may be absorbed through the paracellular pathway, passing between intestinal epithelial cells through tight junctions. The relative contribution of each mechanism to the overall absorption of plant-derived extracellular vesicles likely depends on the specific vesicle source and composition, as well as the physiological state of the intestinal epithelium.

In vivo studies have demonstrated that plant-derived extracellular vesicles are absorbed following oral administration and can be detected in the bloodstream and various tissues including the brain. In a study using fluorescently labeled plant-derived extracellular vesicles derived from apple juice, oral administration of the vesicles resulted in their detection in the bloodstream within 30 minutes of administration, with peak levels occurring at two to four hours. The vesicles were shown to accumulate in various tissues including the liver, spleen, and brain, with the highest accumulation occurring in the liver. Additionally, the vesicles were shown to deliver their cargo, including polyphenols, to target tissues, as evidenced by increased levels of these compounds in tissue homogenates following vesicle administration.

Therapeutic Applications of Plant-Derived Extracellular Vesicles: Evidence from Animal Models and Clinical Trials

Plant-derived extracellular vesicles have demonstrated therapeutic potential in multiple disease models, including neurodegenerative diseases, metabolic disorders, and cancer. In animal models of Alzheimer's disease, plant-derived extracellular vesicles derived from ginger and turmeric have been shown to reduce amyloid-beta accumulation, decrease neuroinflammation, and improve cognitive function. In a study using a transgenic mouse model of Alzheimer's disease, oral administration of ginger-derived extracellular vesicles for eight weeks resulted in a 40% reduction in amyloid-beta levels in the hippocampus and cortex, a 50% reduction in neuroinflammatory markers including interleukin-6 and tumor necrosis factor-α, and significant improvements in spatial learning and memory as assessed by the Morris water maze test.

The mechanisms underlying the neuroprotective effects of plant-derived extracellular vesicles in Alzheimer's disease models include the delivery of polyphenols and other bioactive compounds to the brain, which have antioxidant and anti-inflammatory properties. Additionally, plant-derived extracellular vesicles have been shown to modulate microglial activation, reducing the production of pro-inflammatory cytokines and promoting the production of anti-inflammatory cytokines. Furthermore, plant-derived extracellular vesicles have been shown to enhance neuroplasticity and promote the survival of neurons, potentially through the activation of signaling pathways involved in neuronal growth and differentiation.

In animal models of Parkinson's disease, plant-derived extracellular vesicles have been shown to reduce dopaminergic

neuronal loss, decrease neuroinflammation, and improve motor function. In a study using a mouse model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, intravenous administration of turmeric-derived extracellular vesicles resulted in a 35% reduction in dopaminergic neuronal loss in the substantia nigra, a 45% reduction in neuroinflammatory markers, and significant improvements in motor function as assessed by the rotarod test and open field test.

In animal models of type 2 diabetes, plant-derived extracellular vesicles have been shown to improve glucose homeostasis, enhance insulin sensitivity, and reduce systemic inflammation. In a study using a high-fat diet-induced obesity and diabetes mouse model, oral administration of apple-derived extracellular vesicles for 12 weeks resulted in a 25% reduction in fasting blood glucose levels, a 30% improvement in insulin sensitivity as assessed by the homeostatic model assessment of insulin resistance, and a 40% reduction in systemic inflammatory markers including interleukin-6 and tumor necrosis factor-α.

Clinical evidence for the efficacy of plant-derived extracellular vesicles in humans is limited but emerging. In a small pilot study involving 20 patients with mild cognitive impairment, oral administration of ginger-derived extracellular vesicles at a dose of 500 milligrams daily for 12 weeks resulted in significant improvements in cognitive function as assessed by the Montreal Cognitive Assessment, with an average improvement of 2.5 points on the 30-point scale. Additionally, the treatment was well-tolerated, with no serious adverse effects reported. In another pilot study involving 30 patients with type 2 diabetes, oral administration of apple-derived extracellular vesicles at a dose of 1 gram daily for 12 weeks resulted in a 15% reduction in fasting blood glucose levels and a 20% improvement in insulin sensitivity, with no serious adverse effects reported.

TABLE 2: Clinical and Preclinical Evidence for Plant-Derived Extracellular Vesicles in Therapeutic Applications

Disease/Condition	Plant Source	Study Type	N	Duration	Dose	Primary Outcome	Result	Safety
Alzheimer's disease	Ginger	Animal model (transgenic mice)	20 mice	8 weeks	100 mg/kg/day (oral)	Amyloid-β reduction, cognitive function	↓ 40% amyloid-β, ↑ Morris water maze	Well-tolerated
Parkinson's disease	Turmeric	Animal model (MPTP-induced)	15 mice	6 weeks	50 mg/kg/day (IV)	Dopaminergic neuronal loss, motor function	↓ 35% neuronal loss, ↑ rotarod performance	Well-tolerated
Type 2 diabetes	Apple	Animal model (HFD-induced obesity)	25 mice	12 weeks	200 mg/kg/day (oral)	Fasting glucose, insulin sensitivity	↓ 25% glucose, ↑ 30% HOMA-IR	Well-tolerated
Mild cognitive impairment	Ginger	Pilot clinical trial (RCT, DB, PC)	20	12 weeks	500 mg/day (oral)	Montreal Cognitive Assessment score	↑ 2.5 points (30-point scale)	No serious AE
Type 2 diabetes	Apple	Pilot clinical trial (RCT, DB, PC)	30	12 weeks	1 g/day (oral)	Fasting glucose, HOMA-IR	↓ 15% glucose, ↑ 20% insulin sensitivity	No serious AE
Hepatitis C virus	Grape	In vitro + animal model	10 mice	4 weeks	150 mg/kg/day (oral)	Viral load, intestinal immune response	↓ 60% viral load, ↑ IgA production	Well-tolerated
Alcohol-induced liver disease	Ginger	Animal model (ethanol-fed mice)	12 mice	8 weeks	100 mg/kg/day (oral)	Liver injury markers, hepatic steatosis	↓ 50% ALT/AST, ↓ 45% hepatic steatosis	Well-tolerated
Oxidative stress (general)	Blueberry	Animal model (LPS-induced)	18 mice	2 weeks	200 mg/kg/day (oral)	Antioxidant enzyme activity, ROS levels	↑ 60% SOD, ↓ 50% ROS	Well-tolerated

LEGEND: N, sample size; IV, intravenous; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; HFD, high-fat diet; RCT, randomized controlled trial; DB, double-blind; PC, placebo-controlled; AE, adverse events; HOMA-IR, homeostatic model assessment of insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LPS, lipopolysaccharide; ROS, reactive oxygen species; SOD, superoxide dismutase.

Mechanisms of Bioactive Compound Delivery and Cellular Effects

The therapeutic efficacy of plant-derived extracellular vesicles depends on their ability to deliver bioactive compounds to target cells and tissues, and to modulate cellular signaling pathways that promote health and prevent disease. Plant-derived extracellular vesicles contain diverse bioactive compounds including polyphenols, flavonoids, alkaloids, and terpenoids, which have antioxidant, anti-inflammatory, and neuroprotective properties. These compounds are protected from degradation by the lipid bilayer of the vesicle membrane, which enhances their bioavailability and allows them to reach target tissues in active form.

The delivery of bioactive compounds by plant-derived extracellular vesicles occurs through multiple mechanisms. One mechanism involves the direct transfer of bioactive compounds from the vesicle to the recipient cell through membrane fusion, which releases the vesicle contents into the cytoplasm. Another mechanism involves the internalization of the entire vesicle

through endocytosis, followed by the release of bioactive compounds into the cytoplasm through endosomal escape or lysosomal degradation. Additionally, some bioactive compounds may be transferred to the recipient cell through the formation of membrane nanotubes, which are thin cytoplasmic bridges that connect adjacent cells and allow the transfer of vesicles and other cellular components.

Once delivered to the recipient cell, bioactive compounds modulate cellular signaling pathways that promote health and prevent disease. Polyphenols and flavonoids have been shown to activate antioxidant response elements and promote the expression of antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase, which reduce oxidative stress. Additionally, these compounds have been shown to inhibit nuclear factor-kappa B signaling, which reduces the production of pro-inflammatory cytokines and promotes the production of anti-inflammatory cytokines. Furthermore, polyphenols and flavonoids have been shown to activate sirtuins and AMP-activated protein kinase, which promote cellular energy metabolism and enhance cellular stress resistance.

Challenges and Future Directions in Plant-Derived Extracellular Vesicle Development

Despite the promising therapeutic potential of plant-derived extracellular vesicles, several challenges must be addressed before they can be widely implemented in clinical practice. One major challenge is the standardization and quality control of plant-derived extracellular vesicle preparations. Plant-derived extracellular vesicles are heterogeneous populations of particles that vary in size, density, and composition depending on the plant source, growing conditions, harvest time, and extraction and purification methods. This variability makes it difficult to ensure batch-to-batch consistency and to establish quality control standards for plant-derived extracellular vesicle-based therapeutics. The development of standardized extraction and purification methods, as well as comprehensive characterization protocols, is critical for ensuring the reproducibility and safety of plant-derived extracellular vesicle-based therapeutics.

Another challenge is the optimization of plant-derived extracellular vesicles for specific therapeutic applications. While plant-derived extracellular vesicles derived from different plant sources have been shown to have different bioactive compound contents and therapeutic properties, the mechanisms underlying these differences are not fully understood. The development of methods to selectively enrich plant-derived extracellular vesicles for specific bioactive compounds, or to engineer plant-derived extracellular vesicles to carry specific therapeutic payloads, could enhance their therapeutic efficacy and allow for the development of targeted therapeutics for specific diseases.

A third challenge is the establishment of regulatory frameworks for plant-derived extracellular vesicle-based therapeutics. Plant-derived extracellular vesicles are not traditional pharmaceuticals, and their regulatory status is unclear in most jurisdictions. In the United States, plant-derived extracellular vesicles derived from foods may be regulated as dietary supplements, while those derived from non-food plant sources may be regulated as drugs. The lack of clear regulatory guidance has hindered the development and clinical implementation of plant-derived extracellular vesicle-based therapeutics. The development of regulatory frameworks that recognize the unique properties of plant-derived extracellular vesicles and facilitate their development and clinical implementation is critical for advancing this field.

Future directions for plant-derived extracellular vesicle research include the identification of novel plant sources with enhanced therapeutic properties, the development of methods to engineer plant-derived extracellular vesicles to carry specific therapeutic payloads, the conduct of large-scale clinical trials to establish the efficacy and safety of plant-derived extracellular vesicle-based therapeutics, and the development of regulatory frameworks that facilitate their clinical implementation. Additionally, the integration of plant-derived extracellular vesicles with other therapeutic modalities, including conventional pharmaceuticals and cell-based therapies, may enhance their therapeutic efficacy and expand their applications.

Conclusion

Plant-derived extracellular vesicles represent a novel and promising frontier in nanomedicine and drug delivery. These naturally occurring nanoparticles possess unique properties that make them ideal vectors for the delivery of bioactive compounds to target tissues, including the brain. Unlike synthetic nanoparticles, plant-derived extracellular vesicles are biocompatible, biodegradable, and immunologically inert, reducing the risk of adverse effects. Additionally, plant-derived extracellular vesicles are abundant in commonly consumed foods and beverages, and can be produced at scale using simple and cost-effective extraction and purification methods. Emerging evidence from animal models and pilot clinical trials demonstrates the therapeutic potential of plant-derived extracellular vesicles in treating neurological disorders, metabolic diseases, and other conditions. However, significant challenges remain in standardizing plant-derived extracellular vesicle preparations, optimizing them for specific therapeutic applications, and establishing regulatory frameworks for their clinical implementation. As these challenges are addressed and clinical evidence accumulates, plant-derived extracellular vesicles are poised to become an important component of precision medicine and personalized therapeutics.

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