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Plant-derived Extracellular Vesicles in the Central Nervous System: Emerging Mechanisms and Therapeutic Opportunities

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Abstract: Exosomes are nanoscale extracellular vesicles secreted by cells that transport proteins, nucleic acids and lipids, thereby mediating intercellular communication and regulating a wide range of physiological and pathological processes. In recent years, plant-derived extracellular vesicles have emerged as promising therapeutic agents, particularly for neurological disorders. This Review summarizes current knowledge of the biogenesis of plant exosomes, highlights their similarities and differences with animal-derived exosomes, and discusses the mechanisms governing their intercellular transfer. We further outline the molecular mechanisms underlying major neurological diseases and examine the signaling pathways through which plant-derived extracellular vesicles may exert neuroprotective and therapeutic effects. Together, these insights underscore the potential of plant-derived exosomes as a novel and versatile platform for the treatment of neurological disorders.

Keywords: plant-derived extracellular vesicles; neurological disorders; Alzheimer's disease Parkinson's disease; molecular mechanisms

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1. Introduction

Exosomes are nanoscale extracellular vesicles (typically ~40–150 nm in diameter) that have been identified across diverse biological systems, including animals, plants and bacteria[1]. Once regarded as cellular debris, exosomes are now recognized as integral mediators of intercellular communication, capable of transferring proteins, nucleic acids and lipids to modulate recipient-cell phenotypes[2]. Eukaryotic cell–derived exosomes have attracted substantial interest as delivery vehicles for neurological disorders, owing to their biocompatibility and amenability to engineering [3]. Plant-derived exosome-like nanovesicles (ELNs) have recently emerged as an appealing complement to animal-derived vesicles. Compared with their mammalian counterparts, ELNs are generally associated with low immunogenicity, favourable biocompatibility and an abundant repertoire of bioactive cargos, including antioxidants and nucleic acids. Notably, ELNs can be administered via non-invasive routes such as oral or intranasal delivery, and their production benefits from readily

accessible sources, lower cost and scalability. In addition, the relatively robust lipid architecture of plant ELNs may confer enhanced physicochemical stability, which could be advantageous for systemic delivery and for traversing biological barriers such as the blood–brain barrier (BBB) [4].

Neurological disorders are broadly classified into diseases of the central nervous system (CNS) and those of the peripheral nervous system (PNS). Here, we focus on recent advances in CNS disorders, including Alzheimer's disease, ischaemic stroke and Parkinson's disease. The onset and progression of these conditions typically reflect the interplay of environmental exposures, genetic susceptibility and immune dysregulation. Their pathophysiology converges on several core processes, including neurodegeneration, aberrant glial activation and disrupted neurotransmission. Despite substantial clinical heterogeneity, many CNS disorders share conserved molecular hallmarks, most notably neuroinflammation, oxidative stress, mitochondrial dysfunction and synaptic impairment[5]. Current therapeutic strategies span multiple modalities, including nanogel-based delivery systems, liposomal formulations and gene regulation approaches targeting long non-coding RNAs (lncRNAs). However, nanogels remain limited by concerns over biocompatibility and potential neurotoxicity, as well as suboptimal penetration and delivery efficiency within brain tissue, which complicates access to deep parenchymal regions [6]. Liposomes, although widely used, can exhibit insufficient targeting specificity, constrained drug loading and release kinetics, and reduced bioavailability, thereby diminishing therapeutic benefit. Moreover, translation of lncRNA-based interventions is still hindered by a central challenge—achieving safe, specific and durable in vivo delivery—often necessitating sequence optimization and chemical modification to improve stability while minimizing immunogenicity[7]. Against this backdrop, plant-derived exosome-like nanovesicles (ELNs) have attracted growing interest as delivery vehicles because of their favourable delivery performance and reported potential to traverse the blood–brain barrier, positioning them as a promising platform for CNS therapeutics.

Plant-derived extracellular vesicles have been increasingly investigated as therapeutic mediators across a range of disease contexts. Accumulating evidence suggests that they can promote neuroprotection by modulating inflammatory signalling, engaging autophagy-associated pathways and attenuating oxidative stress. Consistent with these activities, plant-derived vesicles have been reported to exert pleiotropic biological effects, including anti-inflammatory, antioxidant, antitumour and neuroprotective functions. In the context of neuroinflammation, these vesicles appear capable of dampening pro-inflammatory mediators. For example, Yan et al. showed in a model of enteritis/intestinal inflammation that ginger-derived exosome-like vesicles reduced the production or expression of TNF, IL-6 and IL-1β, thereby mitigating inflammatory responses [8].

This Review summarizes recent advances in plant-derived extracellular vesicles, with an emphasis on their distinctive features and practical advantages, cellular uptake routes, and the molecular mechanisms underlying neurological disease initiation and progression. We discuss candidate pathways through which plant-derived vesicles may modulate neural and neuroimmune circuits, highlighting opportunities for therapeutic intervention. Finally, we outline key challenges and outstanding limitations that must be addressed to facilitate clinical translation of plant-derived extracellular vesicle–based strategies for complex neurological disorders.

2. Exosome production and comparison

2.1. Production of Extracellular Vesicles

Plant-derived extracellular vesicles have attracted growing attention and share several structural and compositional features with mammalian extracellular vesicles. Although the mechanisms governing their biogenesis and release remain incompletely resolved, current evidence supports at least three major routes: secretion via multivesicular body (MVB) fusion with the plasma membrane, unconventional secretion mediated by extracellular vesicle–positive organelles (EXPOs), and plasma membrane budding to generate microvesicles [9].

In the MVB pathway, endocytosis-derived early endosomes mature into MVBs, within which the limiting membrane invaginates to form intraluminal vesicles (ILVs). During ILV formation, selected cargos—including RNAs, lipids and

proteins—are incorporated into the vesicles. Fusion of MVBs with the plasma membrane then releases ILVs into the extracellular space as exosome or exosome-like vesicles, enabling intercellular communication and signal transmission. Support for this route has been obtained in model plants such as Arabidopsis thaliana [10].

By contrast, the EXPO pathway represents a plant-specific, non-canonical secretory route that is independent of the classical ER–Golgi–endosome trafficking axis. EXPOs typically display a characteristic double-membrane architecture and show limited colocalization with canonical organelle markers, including those of the Golgi apparatus, the trans-Golgi network/early endosomes, or MVBs/late endosomes. EXPOs can fuse directly with the plasma membrane, releasing their contents into the apoplast [11]. Emerging studies further implicate EXPO-associated processes in plant adaptation to abiotic stress, potentially contributing to cellular homeostasis and stress signalling under salinity, drought, oxidative stress and metal toxicity [12].

In addition to these routes, plant immune responses have been linked to direct fusion between the vacuole and the plasma membrane, enabling rapid extracellular discharge of hydrolases and defence-related proteins. This mechanism may facilitate the prompt establishment of local defence barriers and enhance disease resistance [13].

2.2. Comparison of exosomes

Compared with mammalian extracellular vesicles, plant-derived vesicles are often reported to display greater physicochemical stability, low apparent toxicity and a relatively narrow size distribution, alongside practical advantages such as abundant source materials, reduced cost and scalability of production. Collectively, these attributes support their development as nanodelivery platforms in nanomedicine. At the molecular level, plant-derived exosome-like vesicles also differ substantially from mammalian exosomes. Their membranes are enriched in phospholipids and glycolipids as well as phytosterols, and the absence of cholesterol is expected to confer distinct bilayer organization and biophysical properties. In addition, cell wall–associated polysaccharides (including cellulose, hemicellulose and pectin) may provide an added protective interface under complex or harsh conditions, further enhancing stability and environmental resilience. Plant vesicles can also carry and enrich plant-specific bioactive metabolites—such as polyphenols, carotenoids, terpenoids and alkaloids—which may contribute to antioxidant capacity and the maintenance of cellular homeostasis [2].

Antioxidants have considerable potential for mitigating oxidative stress and may help to counteract ageing and reduce the risk of cancer and neurodegenerative disease. However, their clinical translation is frequently limited by poor in vivo stability, low bioavailability and inadequate tissue targeting. Encapsulation of antioxidant bioactives within natural nanocarriers, such as extracellular vesicles, could enhance cargo protection and delivery efficiency, offering a potentially more effective therapeutic strategy—particularly for disorders of the central nervous system [3]. For example, exosome-like nanocarriers derived from saffron-enriched, engineered tomatoes (Tomafran) have been reported to confer neuroprotection in models of neuronal injury, and permeability assessments at the blood–brain barrier suggested that vesicle encapsulation may improve the utilization and efficacy of the active compounds [14].

2.3. Uptake mechanisms of plant exosomes

Plant-derived exosome-like vesicles can be internalized by recipient cells through multiple routes. In the context of neurological applications, interactions between vesicle surface components and target-cell membranes—and the ensuing uptake pathways—are likely to be major determinants of in vivo delivery efficiency and translational feasibility [15]. Broadly, cellular entry of plant vesicles can be grouped into three modes: endocytosis-dependent uptake; internalization mediated by membrane-surface interactions; and uptake or fusion behaviours shaped by the nanovesicle membrane composition, including lipid and glycan features.

Endocytosis describes the internalization of extracellular material through plasma-membrane invagination and vesicle formation. Major endocytic routes include phagocytosis, caveolin-mediated endocytosis and clathrin-mediated endocytosis. Phagocytosis is largely restricted to professional phagocytes and supports the clearance of relatively large particles. Caveolin-mediated uptake is commonly associated with lipid-raft microdomains and may promote cytosolic

delivery while limiting lysosomal trafficking, thereby reducing degradative loss of cargo. By contrast, clathrin-mediated endocytosis involves the assembly of clathrin-coated pits and vesicles and typically cooperates with specific receptors to enable comparatively selective internalization.

Beyond canonical endocytic routes, molecular interactions at the interface between the plasma membrane and plant-derived extracellular vesicles are also likely to shape uptake efficiency and cellular tropism. Plant vesicle membranes can display bioactive small molecules and surface proteins that engage cognate receptors on recipient cells, thereby promoting receptor-mediated internalization. In addition, vesicle lipids and glycan-bearing constituents, including glycoproteins, may cooperate to strengthen adhesion and facilitate entry, potentially improving targeting precision and enhancing therapeutic efficacy [16].

3. Molecular mechanisms in the nervous system

3.1. Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized clinically by cognitive decline and pathologically by extracellular amyloid-β (Aβ) deposition, intracellular neurofibrillary tangles, glial activation and neuronal loss. Aβ pathology arises from proteolytic processing of amyloid precursor protein (APP) by β- and γ-secretases, generating Aβ peptides—particularly the aggregation-prone Aβ42—that assemble into soluble oligomers and ultimately deposit as plaques [17].

Notably, substantial evidence indicates that soluble Aβ oligomers are more synaptotoxic than mature plaques, inducing synaptic dysfunction, perturbing calcium homeostasis and elevating oxidative stress, while also amplifying inflammatory signalling and promoting tau pathology. Tau pathology is driven by aberrant tau hyperphosphorylation and detachment from microtubules, which compromises microtubule stability and axonal transport; importantly, neurofibrillary tangle burden correlates closely with neuronal injury and clinical severity. In parallel, pathogenic Aβ and tau species activate microglia and astrocytes. Although these glial cells can contribute to Aβ uptake and clearance, chronic activation favours the release of pro-inflammatory cytokines and reactive oxygen/nitrogen species and, through complement-associated mechanisms, can facilitate aberrant synaptic pruning that accelerates synapse loss[18]. Together, Aβ-mediated synaptic toxicity, tau-driven cytoskeletal disruption and sustained glia-dependent neuroinflammation converge to reduce synaptic integrity and promote neuronal degeneration, thereby driving disease progression.

3.2. Ischemic stroke

Ischaemic stroke (ischaemic cerebrovascular accident) results from occlusion of a cerebral vessel, leading to a focal reduction in blood flow and subsequent hypoxia–ischaemia that precipitates neuronal injury and infarction. The underlying pathophysiology is often conceptualized as a stereotyped ischaemic cascade encompassing energetic failure, excitotoxicity, calcium dysregulation with mitochondrial injury, oxidative stress, neuroinflammation and disruption of the blood–brain barrier (BBB). Energetic failure constitutes an early initiating event. Abrupt interruption of oxygen and glucose delivery compromises mitochondrial oxidative phosphorylation, rapidly depleting ATP and disabling energy-dependent ion pumps. The ensuing membrane depolarization and loss of ionic homeostasis promote glutamate accumulation in the extracellular space through increased release and impaired reuptake, driving excitotoxic signalling via sustained activation of NMDA and AMPA receptors and a large influx of Ca^2+. Calcium overload then propagates mitochondrial dysfunction by increasing mitochondrial membrane permeability and further suppressing ATP generation, while also promoting cytochrome c release and caspase-dependent apoptotic programmes. During ischaemia–reperfusion, mitochondrial impairment together with activation of oxidative enzymes, including NADPH oxidases, results in excessive production of reactive oxygen and nitrogen species (ROS/RNS). These species damage lipids, proteins and nucleic acids, trigger lipid peroxidation and accelerate cell death[19]. In parallel, neuroinflammation is rapidly engaged: microglia are activated early, followed by recruitment and infiltration of peripheral immune cells. Through pathways such as NF-κB

signalling and inflammasome activation, these cells drive the production of inflammatory mediators including TNF, IL-1β and IL-6, thereby amplifying tissue injury. BBB breakdown represents another central component of the cascade and is closely coupled to oxidative and inflammatory stress, involving endothelial injury, degradation of tight-junction proteins and increased protease activity (for example, MMP-2 and MMP-9), ultimately increasing permeability and promoting vasogenic oedema [20].

3.3. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder defined pathologically by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and clinically by consequent dysfunction of nigrostriatal circuitry. The resulting loss of SNpc neurons leads to a marked reduction in striatal dopamine, which underlies key motor manifestations of the disease[21]. PD pathogenesis is multifactorial and involves convergent processes, including α-synuclein misfolding and aggregation, mitochondrial and bioenergetic impairment, oxidative stress, neuroinflammation and defective proteostasis. A central molecular hallmark is the accumulation of misfolded α-synuclein into Lewy bodies and Lewy neurites. These assemblies can disrupt synaptic function, vesicular trafficking and neurotransmitter release, thereby exacerbating network-level dysfunction.

Mitochondrial dysfunction is also prominent, with reduced complex I activity reported in PD, contributing to impaired ATP production and increased generation of reactive oxygen species (ROS). In parallel, disruption of mitochondrial quality control pathways—most notably those governed by PINK1 and Parkin—can compromise mitophagy, allowing damaged mitochondria to accumulate and further amplifying bioenergetic failure and oxidative injury[22]. Oxidative stress is reinforced by the intrinsic chemistry of dopamine metabolism and is further shaped by iron dyshomeostasis and weakened antioxidant capacity within the substantia nigra, collectively accelerating neuronal vulnerability. Neuroinflammation represents an additional driver: chronic microglial activation, through signalling axes such as TLR–NF-κB and the NLRP3 inflammasome, promotes the production of cytokines including IL-1β and IL-6 and sustains injurious inflammatory cascades[23]. Finally, impairment of protein degradation pathways—including the ubiquitin–proteasome system and the autophagy–lysosome network—limits clearance of misfolded and aggregated proteins (including α-synuclein), destabilizes proteostasis and further promotes pathological protein accumulation and neurodegeneration.

4. New advances in plant extracellular vesicles for treating neurological diseases

Neurological disorders such as Alzheimer's disease, ischaemic stroke and Parkinson's disease exhibit convergent molecular pathologies, including impaired mitochondrial function and energy metabolism, redox imbalance with oxidative stress, dysregulated calcium signalling and excitotoxicity, and sustained neuroinflammation driven by innate and adaptive immune pathways. Emerging evidence suggests that plant-derived extracellular vesicles can influence several of these processes and may therefore represent a promising strategy for modulating neuroinflammation and related neuropathology.

4.1. Mitochondrial function and energy metabolic pathways

Mitochondria are central hubs of cellular bioenergetics, generating ATP primarily through oxidative phosphorylation. Disruption of the electron transport chain—particularly at complex I—reduces ATP output and precipitates energetic failure, which compromises energy-dependent ion pumps and perturbs intracellular homeostasis. Mitochondrial dysfunction is also tightly coupled to oxidative stress and can promote cytochrome c release, thereby engaging caspase-dependent apoptotic programmes that culminate in neuronal injury and cell death[24]. Recent work suggests that plant-derived extracellular vesicles can modulate mitochondrial quality control.

For example, exosome-like vesicles isolated from kudzu root (Pueraria lobata) (Pu-Exos) have been reported to exhibit efficient transmembrane and barrier-crossing delivery properties and to activate PINK1–Parkin-dependent mitophagy, facilitating the clearance of damaged mitochondria. In parallel, Pu-Exos were associated with preservation

of respiratory chain complex I and V activities and improved ATP availability, ultimately protecting dopaminergic neurons and ameliorating Parkinson's disease–related phenotypes[25]. More broadly, extracellular vesicles have also been explored as nanocarriers to enhance delivery of mitochondrial-acting bioactives. In one study, milk-derived exosomes loaded with curcumin and resveratrol increased tissue accumulation and potentiated antiproliferative and mitochondria-dependent pro-apoptotic effects in breast cancer models. Alzheimer's disease (AD): If plant-derived extracellular vesicles (pEVs) can attenuate reactive oxygen species (ROS) and reverse metabolic reprogramming (for example, compensatory upregulation of glycolysis), they may restore cellular bioenergetic homeostasis and alleviate mitochondrial stress, thereby indirectly dampening the downstream amplification of Aβ/Tau-driven neurotoxic cascades[26]. Ischaemic stroke: During the secondary-injury window following ischaemia–reperfusion, pEVs are more likely to confer neuroprotection by suppressing oxidative stress and lipid peroxidation (including ferroptosis-related processes) while engaging pro-survival signalling axes, thus limiting further mitochondrial destabilization, reducing neuronal loss and mitigating blood–brain barrier (BBB) disruption[27]. Parkinson's disease (PD): Relative to other indications, pEVs appear to align more closely with the mitochondrial–bioenergetic pathology central to PD. A plausible mechanism is the enhancement of mitophagy coupled with restoration of respiratory-chain capacity, which could more directly support the survival and functional maintenance of substantia nigra pars compacta (SNpc) dopaminergic neurons[25].

4.2. Oxidative stress and antioxidant pathways

Oxidative stress arises from an imbalance between the production and clearance of reactive oxygen and nitrogen species (ROS/RNS), resulting in a sustained elevation of cellular oxidative burden. Excess ROS/RNS can drive lipid peroxidation, oxidative protein modifications and DNA damage, thereby compromising cellular integrity and function[28]. A major endogenous antioxidant defence axis is mediated by the Nrf2–ARE pathway: under stress, Nrf2 accumulates in the nucleus and binds antioxidant response elements (AREs), inducing a transcriptional programme that upregulates detoxification and antioxidant systems, including glutathione metabolism and superoxide dismutases, to reinforce radical scavenging and redox homeostasis.

Consistent with these mechanisms, vesicle-based interventions have been reported to attenuate oxidative injury. For example, ginseng-derived exosome-like vesicles reduced cisplatin-induced cardiomyocyte damage, at least in part by dampening MAPK-associated oxidative stress and apoptotic signalling[29]. More generally, extracellular vesicles have been proposed to deliver Nrf2 or to potentiate downstream antioxidant signalling, thereby enhancing ARE-dependent gene expression and restoring redox balance—effects that may support tissue repair and potentially ameliorate aspects of ageing and age-associated diseases. Alzheimer's disease (AD): Plant-derived extracellular vesicles (pEVs) may reduce the Aβ/Tau-associated ROS burden and engage the Nrf2–ARE-driven endogenous antioxidant programme, thereby alleviating synaptic injury and neuronal toxicity and, at a functional level, slowing the trajectory of cognitive decline[30]. Ischaemic stroke (ischaemia–reperfusion): In the acute phase, pEVs could blunt the reperfusion-triggered oxidative burst and lipid peroxidation (including ferroptosis-related chain reactions) while preserving blood–brain barrier integrity, ultimately limiting secondary neuronal loss and cerebral oedema[26]. Parkinson's disease (PD): pEVs may counteract the sustained oxidative pressure arising from aberrant dopamine metabolism and mitochondrial dysfunction, and reinforce Nrf2-associated antioxidant defences, thereby safeguarding nigral dopaminergic neurons and improving motor phenotypes [31].

4.3. Calcium ion signaling and excitotoxicity pathways

Ca2+ is a central intracellular second messenger that orchestrates diverse physiological processes, including synaptic transmission, neuronal plasticity and cell-survival signalling. Under pathological conditions, excessive glutamate release and sustained activation of NMDA and AMPA receptors can drive a large Ca2+ influx, precipitating excitotoxicity. The ensuing Ca2+ overload activates multiple Ca2+ dependent effectors—including proteases, phospholipases and nitric oxide synthases—thereby aggravating mitochondrial dysfunction and oxidative stress and ultimately promoting neuronal injury and cell death [32]. Beyond its role in excitotoxic signalling, Ca2+ dynamics can also influence extracellular vesicle

biogenesis and cargo. For example, DETD-35 was reported to induce ROS-associated mitochondrial structural and functional damage while elevating cytosolic Ca2+ levels, leading to Ca2+ dependent exosome release from tumour cells. Notably, this process was accompanied by a reshaping of exosomal protein composition and biological activity, endowing the vesicles with the capacity to suppress proliferation of triple-negative breast cancer cells and to attenuate malignant behaviours such as migration and invasion [33]. Alzheimer's disease (AD): If plant-derived extracellular vesicles (pEVs) can curb Aβ-driven overactivation of glutamate receptors and limit Ca^{2+} influx, they may alleviate Ca^{2+} dyshomeostasis–induced synaptic dysfunction and mitochondrial injury, thereby weakening neurotoxic cascade amplification and slowing cognitive decline[34]. Ischaemic stroke (ischaemia–reperfusion): By reducing post-ischaemic glutamate accumulation and the ensuing NMDA/AMPA receptor–mediated Ca^{2+} overload, pEVs could suppress the escalation of excitotoxicity and cell-death programmes, ultimately constraining infarct expansion and promoting neurological recovery. Parkinson's disease (PD): If pEVs stabilize Ca^{2+} homeostasis in dopaminergic neurons and attenuate Ca^{2+}-dependent mitochondrial stress and oxidative burden, they may lower excitotoxic pressure and the degeneration risk of vulnerable neuronal populations, thereby improving motor phenotypes[35].

4.4. Neuroinflammation and immune signaling pathways

Neuroinflammation is largely orchestrated by microglia and astrocytes and is underpinned by signalling modules such as NF-κB and MAPK pathways and activation of the NLRP3 inflammasome, which together drive the induction and release of pro-inflammatory cytokines including TNF, IL-1β and IL-6 [36]. Although acute inflammatory responses can support debris clearance and restoration of tissue homeostasis, sustained or excessive activation promotes neuronal injury and can engage reinforcing feedback with oxidative stress and cell-death programmes, thereby accelerating disease progression. Plant-derived nanovesicles have been reported to modulate neuroinflammatory signalling in vivo. For example, oral administration of oat-derived nanoparticles (oatN) attenuated alcohol-induced pro-inflammatory signalling by altering intracellular trafficking and subcellular localization of the dectin-1–associated complex in microglia, resulting in reduced neuroinflammation and improved cognitive performance[37]. In addition, exosome-like nanovesicles isolated from Allium tuberosum (A-ELNs) were shown to mitigate microglia-driven inflammation by activating the HO-1 antioxidant axis and suppressing iNOS/NO production and inflammatory mediator expression through miRNA-dependent regulation of anti-inflammatory gene programmes. Notably, A-ELNs were also proposed as efficient carriers for anti-inflammatory therapeutics. Alzheimer's disease (AD): If plant-derived extracellular vesicles (pEVs) can restrain chronic reactive activation of microglia and astrocytes and downregulate pro-inflammatory signalling axes such as NF-κB, MAPK and the NLRP3 inflammasome, they may reduce cytokine- and complement-driven aberrant synaptic pruning, thereby mitigating synapse loss and slowing cognitive decline. Ischaemic stroke (ischaemia–reperfusion): In the acute phase, pEVs may attenuate the amplified innate-immune response (for example, via inhibition of NF-κB/NLRP3 and reduced TNF-α/IL-1β) and bias the immune milieu from a damage-amplifying state towards a reparative programme, thus limiting cerebral oedema and blood–brain barrier disruption, reducing secondary neuronal death and promoting functional recovery. Parkinson's disease (PD): By potentially intercepting α-synuclein–linked microglial TLR–inflammasome pathways and lowering chronic neuroinflammation and its accompanying oxidative burden, pEVs could enhance the resilience of nigral dopaminergic neurons, decelerate neurodegeneration and improve motor phenotypes[35].

5. Challenges and limitations

Despite rapidly expanding interest in plant-derived extracellular vesicles (PDEVs), also referred to as exosome-like nanoparticles (ELNs), several conceptual and practical barriers continue to impede mechanistic understanding and clinical translation. A central challenge is the absence of a unified definition and a definitive assignment of biogenic origin. In contrast to mammalian exosomes—which are canonically derived from multivesicular bodies—plant vesicle secretion is less well resolved, raising uncertainty as to whether isolated preparations represent bona fide exosomes or a heterogeneous

mixture of membrane-derived nanostructures. This ambiguity complicates comparisons across studies and can confound interpretation of reported biological activities. A second major limitation is the incomplete understanding of in vivo behaviour, including biodistribution, cellular tropism and long-term safety. Although PDEVs are frequently described as biocompatible and weakly immunogenic, rigorous and standardized toxicological and immunological assessments remain sparse, and an aligned regulatory framework for evaluation is still emerging. Addressing these gaps will be essential to move PDEVs from experimental systems toward robust and clinically deployable therapeutic platforms.

6. Conclusion

Plant-derived extracellular vesicles are emerging as a potentially versatile therapeutic modality for neurological disorders, bridging naturally derived nanostructures with drug-delivery strategies. Their reported biocompatibility, low apparent toxicity and capacity to traverse the blood–brain barrier support their exploration as platforms for CNS therapeutics. Moreover, chemical or biomolecular surface engineering of plant vesicles can be used to tune biodistribution, cellular tropism and cargo delivery, potentially enhancing targeting specificity and therapeutic efficacy and enabling new intervention strategies for neurological disease.

At present, plant-derived extracellular vesicles remain at an early stage of translational development. Robust preclinical and clinical evidence is still required to establish therapeutic efficacy, long-term biological effects, safety and potential immunological consequences in the context of neurological disorders. To date, most work has been confined to proof-of-concept and mechanistic studies, and systematic clinical evaluation has yet to be initiated.

In summary, plant-derived extracellular vesicles hold considerable promise as therapeutic platforms for neurological disorders. Nevertheless, rigorous validation—particularly through well-designed human studies—will be essential before these approaches can be translated into routine clinical application.

Disclosure statement

The author declares no conflict of interest.

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