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Role of Exosomes in Neurodegenerative Disorders: Recent Advances in Alzheimer's and Parkinson's Disease (2022–2025)

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Abstract:

Neurodegenerative disorders (NDDs) like Alzheimer's disease (AD) and Parkinson's disease (PD) involve progressive neuronal loss, synaptic dysfunction and pathological protein aggregation, which together form the basis of their diagnosis. Recent diagnostic and therapeutics approach remain limited due to invasiveness, cost and lack of disease modifying efficacy. Exosomes are micro-extracellular vesicles that are excreted by neurons, glia and peripheral cells. They have emerged as vital mediator of intracellular communication and promising tools for biomarker research and therapeutic delivery. Exosomes have capability of crossing blood brain barriers and encapsulate proteins, lipids and nucleic acids, which represents physiological state of parent cells making them one of the least invasive ways to detect and monitor neurodegeneration. Various researches done in recent years emphasise neuron derived exosomal cargo, such as, $A\beta_{42}$, phosphorylated tau, α-synuclein, and dysregulated miRNAs, as promising diagnostic biomarkers associated with cognitive impairment and dopaminergic loss. Advancement in exosome engineering has enabled precise delivery of APIs such as siRNAs, neurotropic factors and anti-inflammatory molecules in human body. Intranasal delivery of mesenchymal stem cell–derived and plant-based nanovesicles has shown strong neuroprotective effects, reducing neuroinflammation and improving cognitive and motor functions in preclinical trials, with early human trials confirming safety and tolerance. Despite these optimistic results, significant translational challenges still remain, including the need for standardized isolation methods, scalable biomanufacturing processes, and clear regulatory frameworks for clinical-grade exosome products. Integrating advancements in synthetic biology, microfluidic isolation, and AI-driven multi-omics analysis together is expected to accelerate the path toward clinical translation.

KeywordsNeurodegenerative disorder, Alzheimer's Disease, Parkinson's Disease, Exosomes, Therapeutics, Diagnostics, Non-invasive, Mesenchymal stem cells, intranasal delivery, biomarkers.

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I. INTRODUCTION

Neurodegenerative disorders (NDDs) like Alzheimer's disease (AD) and Parkinson's disease (PD) represent a growing global public health challenge. These are characterized by progressive neuronal loss, synaptic dysfunction and the accumulation of misfolded proteins. AD is marked by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyper-phosphorylated tau [1][2][3][4]. Current

diagnostic methods, such as cerebrospinal fluid analysis and neuroimaging, are usually invasive or expensive. Effective treatments for these diseases are still mostly unavailable. Therefore, new biomarker and treatment strategies are needed.

Extracellular vesicles (EVs), especially exosomes, play a crucial role in inter-cellular communication. They are promising tools for diagnosing and treating NDDs. Exosomes are nanovesicles, about 30 to 150 nanometres in diameter, generated from endosomes. They carry various cargo, including proteins, lipids, and RNAs, and can be released by many cell types, such as neurons, glia and peripheral cells [5][6][7]. Exosomes can also cross the blood-brain barrier. Their molecular makeup reflects the condition of the parent cells, making them potential vehicles for discovering biomarkers and delivering therapy.

In the context of neurodegenerative diseases, exosomes have a dual role. They can help spread disease by carrying and transmitting misfolded proteins between cells. At the same time, they may be useful as diagnostic tools or engineered carriers for treatment delivery. For example, in AD, small extracellular vesicles taken from the brains of patients were found to contain oligomeric Aβ. Blocking their formation or intake reduced the spread of pathology in lab tests [8][9]. In PD and related conditions, exosomes play a role in transfer of aggregated α-synuclein (α-syn) between neurons, which aids in promoting disease spread [10].

Recent methodological advances have improved the isolation and molecular profiling of brain or neuron-derived exosomes from peripheral biofluids, increasing their translational potential. For example, a magnetic-transferrin nanoparticle (MTN) assay was created to rapidly isolate brain-derived exosomes from serum in under 35 minutes [6]. This method used proteomics to identify potential biomarkers for neurodegenerative diseases [6]. In AD, researchers profiled serum-derived exosomes (proteomically) to find novel biomarker candidates, such as AACT and C4BPα, which bind to Aβ and were confirmed in different patient groups [3].

Given the strong scientific basis and the emerging potential of exosomes, this review will focus on their roles in the diagnosis and therapeutic application in neurodegenerative disorders, mainly Alzheimer's disease and Parkinson's disease. We will summarize key developments in using exosomes for diagnostics, such as their molecular cargo, isolation methods, and sources from bodily fluids. We will also look at treatment strategies involving natural and engineered exosomes, discussing future directions for clinical applications.

II. EXOSOMES OVERVIEW

To understand how exosomes can act as diagnostic biomarkers and therapeutic tools in neurodegenerative disorders, it is essential to explore their basic biology, including their biogenesis, composition and uptake mechanisms.

A. Biogenesis and Release

Exosomes are a type of extracellular vesicle (EV) defined by their small size (approximately 30-150 nm) and their endosomal origin [11][12][13]. The standard pathway for exosome production starts when the plasma membrane invaginates to form early sorting endosomes (ESEs). These then develop into late sorting endosomes (LSEs), leading to the creation of multivesicular bodies (MVBs) that contain intraluminal vesicles (ILVs). When MVBs fuse with the plasma membrane, they release the ILVs into the extracellular space as exosomes [11][13][14]. Alternatively, MVBs can fuse with lysosomes and be degraded without releasing exosomes [13][15].

The regulation of this process involves both ESCRT-dependent and independent mechanisms, along with small GTPases, SNARE proteins, and microdomains rich in tetraspanins [15][16].

In neural cells, the release of exosomes can be activity dependent. For instance, neuronal depolarization or synaptic activity may trigger increased secretion of exosomes [9][17].

B. Molecular Composition

Exosomes have a lipid bilayer membrane that encases a core of aqueous cytosolic material. Their cargo is heterogenous but typically includes important types of biomolecules: proteins, lipids, and nucleic acids [12][18].

Proteins: Common markers found on/in exosomes include tetraspanins CD9, CD63, CD81; ESCRT-associated proteins like ALIX and TSG101; Rab GTPases; heat-shock proteins such as HSP70 and HSP90; and cytoskeletal proteins like annexins and flotillins [19][20].

Lipids: The membrane of exosomes is rich in sphingomyelin, cholesterol, ceramides, phosphatidylserine, and glycerophospholipids, which often differ from the composition of the parent cell membrane [11][20].

Nucleic Acids: Exosomes contain mRNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and occasionally DNA of mitochondrial or nuclear origin [18].

Since their cargo reflects the physiological or pathological condition of the originating cell, exosomes are sometimes seen as molecular snapshots of these cells [11].

C. Uptake and Targeting Mechanisms

After exosomes are released, they can interact with recipient cells in several ways:

- Ligand-receptor interactions on the exosome's surface can trigger signalling pathways in target cells [21].

- Fusion of the exosome membrane with the recipient cell's membrane can directly release cargo into the cytosol [21].

- The recipient cell can take in the exosome through endocytosis or micropinocytosis, followed by the release of cargo within endosomal compartments [21].

In the central nervous system (CNS), exosomes from neurons, astrocytes, oligodendrocytes, microglia, and neural stem cells contribute in intercellular communication between cells. They influence synaptic plasticity, myelin maintenance, manage neuroinflammation, and support neuronal survival [17][22].

D. Unique Features Relevant to Neurobiology

Several characteristics of exosomes are especially significant in neuroscience:

- **Crossing the blood-brain barrier (BBB):** Not all exosomes can cross the BBB, but those from neural cells or engineered to target neural tissue may facilitate communication between the brain and peripheral systems [12].
- **Activity dependence:** Neuronal activity, such as synaptic firing, increases exosome release, linking the dynamics of exosomes to the functional state of neurons [9][17].
- **Cargo variation with cell state:** Under pathological conditions like oxidative stress or inflammation, the content and release rate of exosomes can change significantly [16][22].

E. Isolation and Characterization

Exosome research often uses techniques like ultracentrifugation, size-exclusion chromatography, immunoaffinity capture, and nanoparticle tracking analysis (NTA) to separate and quantify them. Characterizing their size (30–150 nm), density (approximately 1.08-1.22 g/mL), and marker proteins is crucial for ensuring accuracy [11].

III. Exosomes for Disease Diagnosis

A. Alzheimer's Disease (AD)

Accurate and timely diagnosis of Alzheimer's disease (AD) is still a crucial issue: current methods like cerebrospinal fluid (CSF) Aβ/tau analysis and PET imaging are expensive and invasive. Exosomes, nanosized extracellular vesicles produced by neurons and glia, provide a minimally

invasive biomarker source, transporting molecular cargo that is indicative of the parent cells and capable of crossing the blood–brain barrier [23][24].

a. Protein Biomarkers in Exosomes

Neuron-derived exosomes (NDEs) isolated from serum or plasma carry Aβ$_{42}$, phosphorylated tau (p-tau^{181}), and total tau (T-tau) with these being markedly elevated in Alzheimer disorder (AD) and mild cognitive impairment (MCI) versus controls, providing promising early-stage diagnostic value [24]. Additionally, levels of NDE Aβ$_{42}$ correlate with cortical amyloid load and cognitive impairment [23]. These data indicate that exosomal proteins can track known AD biomarkers.

b. miRNAs and Other Nucleic -Acid Cargo

In addition to protein cargo, exosomal miRNAs, lncRNAs, and circRNAs are involved in processes related to APP metabolism, tau phosphorylation, and neuroinflammation. Dysregulated exosomal miR-193b and miR-384, for instance, are associated with amyloidogenic processing pathways and synaptic dysfunction [25]. Such molecules have diagnostic potential in early or preclinical AD when measured in blood or CSF derived exosomes.

c. Biofluid Sources and Diagnostic Performance

Diagnostic validity of exosomal biomarkers varies according to biofluid origin and isolation method. A meta-analysis revealed that the NDE core biomarkers (Aβ$_{42}$, p-tau^{181}, p-tau^{396}, T-tau) uniformly rise in plasma-derived exosomes from AD and MCI patients, paving the way for their clinical use [23]. Inter-study comparability is still reduced by ongoing differences in isolation methods (ultracentrifugation vs. immunocapture).

B. Parkinson's Disease (PD)

Diagnosis of Parkinson's disease (PD) relies heavily on clinical presentation, but molecular biomarkers are essential for early diagnosis. Exosomes containing neuron or glia derived proteins have been explored as promising diagnostic markers [26].

a. Protein Biomarkers in Exosomes

α-synuclein, the central disease-causing protein in PD, is found in high amounts in exosomes of serum, CSF and saliva. Most importantly, exosomal α-synuclein from neurons can be used to differentiate PD from multiple system atrophy (MSA) with very high sensitivity [27]. Also, plasma NDE α-synuclein is associated with disease severity and dopaminergic depletion [26].

b. **miRNAs and Molecular Signatures**

Exosomal miRNAs, including miR-19b, miR-24, and miR-195, were identified to be dysregulated in PD patients, indicating compromised mitochondrial and proteostasis pathways [28]. Aberrant upregulation of miR-34a-5p and miR-331-5p in small extracellular vesicles is also linked to disease progression.

c. Biofluid Sources and Diagnostic Potential

Exosomes purified from plasma by L1CAM enrichment (to capture neuronal vesicles) have also demonstrated early changes in α-synuclein and glucocerebrosidase (GCase) activity years prior to onset of symptoms [26]. Using these exosomal markers in panels enhances diagnostic performance (AUC ≈ 0.82) for distinguishing PD from controls.

TABLE1. EXOSOMAL BIOMARKERS IDENTIFIED IN ALZHEIMER'S AND PARKINSON'S DISEASE (2022–2025).

Disease	Biomarker Type	Key Exosomal Markers	Biofluid source	Diagnostic Relevance
Alzheimer's Disease	Proteins	Aβ$_{42}$, p-tau^{181}, p-tau^{396}, T-tau	Plasma / Serum NDEs	• Elevated levels correlate with cortical amyloid load, cognitive decline.

Alzheimer's Disease	Proteins	AACT, C4BPα	Serum exosomes	• Newly identified (2022–2023) • Bind Aβ • Validated as emerging biomarkers in multi-cohort analysis.
Alzheimer's Disease	miRNAs	miR-193b, miR-384	Plasma/ CSF exosomes	• Dysregulation linked to APP metabolism and synaptic dysfunction. • Potential preclinical-stage markers.
Alzheimer's Disease	circRNAs	circ-Epc1	ADSC-derived exosomes	• Associated with microglial M1/M2 shift. • Reflects inflammatory brain state. • Useful for AD pathophysiology profiling.
Parkinson's Disease	Proteins	α-synuclein	Serum/ CSF/ Saliva NDEs	• Elevated neuronal exosomal α-syn differentiates PD from MSA with high sensitivity. • Correlates with disease severity.
Parkinson's Disease	Enzymatic markers	GCase activity	Plasma NDEs (L1CAM-enriched)	• Reduced GCase activity detected years before symptom onset. • Strong predictive biomarker.
Parkinson's Disease	miRNAs	miR-19b, miR-24, miR-195	Plasma exosomes	• Reflect mitochondrial dysfunction and impaired proteostasis. • Correlates with progression.
Parkinson's Disease	miRNAs	miR-34a-5p, miR-331-5p	Small EVs	• Upregulated in PD.
			(plasma/ CSF)	• Associated with neurodegeneration rate and severity.

4.Therapeutic Applications of Exosomes

4.1. Exosome Therapy in Alzheimer's Disease

Exosomes are being developed as new delivery tools for treatments in neurodegenerative diseases. Their innate ability to cross the blood-brain barrier (BBB) and carry active substances makes engineered exosomes promising for delivering drugs, nucleic acids, and other therapies to damaged brain tissues [29][30]. In Alzheimer's disease (AD), recent studies have looked into various exosome-based methods. Exosome like nanovesicles from citrus lemon (EXO-CLs) were shown to penetrate the BBB and have strong antioxidant effects in neuronal cells [29]. Dolma et al. found that EXO-CLs (about 94 nm) had antioxidant power similar to vitamin C and maintained over 80% viability in SH-SY5Y neurons. They suggested these plant-derived exosomes as a promising treatment for neurodegenerative diseases. Additionally, nanovesicles from the medicinal fungus Ganoderma lucidum (GLENVs) have been tested in 5×FAD AD mice. Delivering GLENVs directly into the nose enabled them to enter the brain and significantly improve memory and learning. Treated mice had lower Aβ plaque buildup, reduced microglial and astrocyte activation, and lessened pro-inflammatory JAK2/STAT3 signalling [31].

Other methods modify exosomes to carry specific drugs or genes. In one study, exosomes from hippocampal neurons were altered to overexpress the Fe65 adaptor protein. This change allowed them to bind specifically to amyloid precursor protein (APP) on neurons. The Fe65-exosomes were loaded with Corynoxine-B, a natural product that induces autophagy. The Fe65-EXO-Cory-B vesicles effectively targeted the

APP–Fe65 interaction, promoting autophagy in neurons with high APP levels and reducing cognitive issues in an AD mouse model [32]. Similarly, Du et.al. created human MSC exosomes (tagged for neuronal targeting) to deliver both BACE1 siRNA and the anti-inflammatory compound berberine intranasally to 5×FAD mice. This combination improved cognitive function and helped repair the nervous system while reducing neuroinflammation. BACE1 levels and Aβ buildup dropped significantly, along with inflammatory cytokines and glial activation [33]. These cases show how exosome platforms can combine different treatment approaches, like gene silencing and drug delivery, to address AD issues.

Stem cell-derived exosomes also offer unique benefits. Liu et al. showed that exosomes from hypoxia-preconditioned adipose MSCs carry circ-Epc1 RNA, which affects microglial behaviour. In APP/PS1 AD mice, these exosomes improved cognitive function and protected hippocampal neurons by changing microglia from a pro-inflammatory M1 state to a repair-focused M2 state. High-throughput analysis identified circ-Epc1 as a crucial component: blocking its action reversed the effect of microglial polarization. Treating ADSC exosomes with hypoxia improved cognitive function by delivering circ-Epc1 and shifting microglial M1/M2 polarization [34]. Exosome therapies in AD models have included antioxidant vesicles, anti-inflammatory or drug-loaded vesicles, and miRNA/circRNA-rich vesicles, all showing improvements in memory or brain pathology in mice.

Importantly, exosome-based therapies are starting to be used for Alzheimer's disease (AD). The first human trial of MSC-derived exosomes in AD (phase I/II) recently reported that giving allogeneic adipose MSC exosomes through the nose was safe and well tolerated [35]. In this open-label study, patients with mild-to-moderate AD received nasal MSC-exosomes twice a week for 12 weeks, with a total of about 4×10^8 particles per dose. No side effects were observed. The medium-dose group showed modest cognitive improvements. The ADAS-Cog score improved by about 2.3 points at 12 weeks and by around 4 points at 36 weeks after treatment. Hippocampal volume loss was also reduced in this group. These early clinical findings support the potential of exosome therapies. Engineered and cell-derived exosomes can safely reach the brain and may slow cognitive decline in AD [35].

4.2. Exosome Therapy in Parkinson's Disease

In Parkinson's disease (PD), preclinical studies have also used exosomes to deliver neuroprotective agents. Huang et al. administered human umbilical cord MSC exosomes through the nose to 6-OHDA PD mice. They saw significant functional recovery [36]. The treated PD mice showed better motor coordination and sense of smell, a reversal of dopaminergic neuron loss in the substantia nigra, and less glial activation and inflammation in brain tissue [36]. These results showed that MSC exosomes can travel through the nasal route into the brain and provide both neuroregenerative and anti-inflammatory effects in PD models. Similarly, Esteves et al. used small extracellular vesicles (sEVs) from umbilical cord blood that were infused with microRNA-124-3p. When these were injected into the brain ventricles of 6-OHDA-lesioned mice, the miR-124-3p exosomes were absorbed by subventricular zone cells and striatal neurons. They ultimately protected dopaminergic neurons in the substantia nigra and striatal fibres, completely reversing motor behaviour symptoms [37]. This shows that targeted miRNA delivery via exosomes can improve neuronal survival and reduce PD motor deficits.

Another approach used immune cell-derived exosomes for gene therapy. Zhao et al. transfected macrophages with plasmid DNA that encoded glial cell line-derived neurotrophic factor (GDNF) and collected their secreted EVs (EV-GDNF).

Intranasal EV-GDNF given to transgenic Parkin-mutant PD mice produced long-lasting benefits. Treated mice showed improved mobility, increased neuronal survival, and decreased neuroinflammation over the course of a year, with no observed toxicity [38]. Thus, exosomes can serve as "Trojan horses" to deliver neurotrophic factor genes or proteins to the brain.

Preclinical studies have also shown that exosomes from neural stem cells or other cell types have neuroprotective effects in PD models. For instance, NSC-derived EVs restored the viability of dopaminergic SH-SY5Y neurons that overexpressed mutant α-synuclein and reduced their oxidative stress levels to baseline [39]. While that work was in vitro, it highlights the general idea that exosome cargo (miRNAs, antioxidants, growth factors) can influence cell death pathways relevant to PD.

TABLE 2. EXOSOME-BASED THERAPEUTIC STRATEGIES FOR ALZHEIMER'S AND PARKINSON'S DISEASE (2022–2025).

Disease	**Exosome/ Vesicle Source**	**Cargo/ Engineering**	**Delivery Route**	**Key Therapeutic Outcomes (2022–2025)**
Alzheimer's Disease	Citrus lemon–derived nanovesicles (EXO-CLs)	Natural antioxidant vesicles	(in vitro)	• Strong antioxidant activity. • >80% neuronal viability. • Potential neuroprotective effects.
Alzheimer's Disease	*Ganoderma lucidum*–derived nanovesicles (GLENVs)	Natural vesicles	Intranasal	• Improved memory/learning. • Reduced Aβ plaques. • Reduced microglial/astrocyte activation. • Decreased JAK2/STAT3 signaling.
Alzheimer's Disease	Neuron-derived exosomes overexpressing Fe65	Loaded with Corynoxine-B	(mouse model)	• Targeted APP–Fe65 interaction. • Induced autophagy. • Improved cognition. • Reduced AD pathology.
Alzheimer's Disease	MSC-derived exosomes engineered for neuronal targeting	BACE1 siRNA + Berberine	Intranasal	• Reduced Aβ accumulation. • Lowered BACE. • Decreased inflammatory cytokines. • Improved cognition and neural repair.
Alzheimer's Disease	Hypoxia-preconditioned adipose MSC exosomes	circ-Epc1 RNA	(mouse model)	• Shifted microglia M1→M2. • Protected hippocampal neurons. • Improved cognitive function.
Alzheimer's Disease	Phase I/II Clinical Trial - Adipose MSC exosomes	Natural MSC cargo	Intranasal	• Safe, well-tolerated • modest cognitive improvement • Reduced hippocampal atrophy.
Parkinson's Disease	Umbilical cord MSC-derived exosomes	Natural exosome cargo	Intranasal	• Reversed dopaminergic neuron loss. • Improved motor function and olfaction • Reduced neuroinflammation.
Parkinson's Disease	Umbilical cord blood small EVs	Enriched miR-124-3p	Intra-Cerebroventricular	• Protected dopaminergic neurons • rescued striatal fibers • Fully reversed motor deficits.
Parkinson's Disease	Macrophage-derived EVs (GDNF-transfected)	GDNF gene/protein cargo	Intranasal	• Long-lasting motor improvement • Increased neuronal survival • Reduced neuroinflammation • No toxicity.
Parkinson's Disease	Neural stem cell-derived EVs	Natural Neuro-protective cargo	(in vitro PD model)	• Restored dopaminergic neuron viability. • Reduce oxidative stress.

5. Conclusion

Exosomes have become an emerging platform for biomarker discovery and therapeutic delivery in neurodegenerative disorders. Several studies from previous four years have strengthened three main concepts-

- Exosomal cargo, which may contain proteins, miRNAs/circRNAs and lipids, reflects the parent-cell pathology and can be detected in easily accessible biofluids such as blood, saliva, semen, amniotic fluid, cerebrospinal fluid and urine.
- Both naturally derived exosome-like nanovesicles as well as engineered exosomes can cross the Blood-Brain Barrier and deliver APIs made from siRNA, miRNA, small molecules, proteins to the affected neural tissue.
- Recent preclinical and clinical studies show their satisfactory efficacy, which includes proteinopathy, neuroinflammation and functional improvement in animal models and preclinical samples, supporting the therapeutic potential of exosome-based approaches.

In conclusion, exosomes provide a powerful translational link between cellular mechanisms and clinical application. Continued methodological refinement and collaborative research may soon enable their integration into the diagnostic and therapeutics for various diseases including Alzheimer's and Parkinson's disease.

6. Challenges

Despite such progress several barriers in research are highlighted before clinical translation. Key problems include standardization of isolation and characterization methods, biological heterogeneity of vesicle populations, less understanding of in-vivo distribution and long-term safety, variable cargo loading and targeting efficiencies, scalable GMP-compatible manufacturing and regulatory pathways for complex biologic-nanoparticle hybrids. Additionally, to establish the clinical utility of exosome biomarkers, we need robust validation in large, well-phenotype longitudinal cohorts to define their sensitivity, specificity, and prognostic value across disease stages and related disorders (for example, to reliably distinguish Parkinson's disease from MSA).

7. Future Prospects

To accelerate clinical translation, the field should prioritize coordinated reporting and quality standard for EV preparation and analysis. Performing comparative studies that link single vesicle and bulk-omics readouts to imaging findings and clinically relevant endpoints, thorough dose-finding and safety trials for therapeutic exosomes, development of scalable, GMP-compatible manufacturing R&D pipelines with defined in-process controls are necessary for large scale adoption. Formation of interdisciplinary consortia that integrate neurology, bioengineering, regulatory science and data analytics, including AI for multi-omics integration can provide huge assistance. Validating exosome biomarkers alongside established imaging and fluid markers, and evaluating exosome therapeutics as components of multimodal treatment strategies, offers the fastest route to clinical translation.

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Conflict Of Interest

The authors declare that there is no conflict of interest associated with this review article.

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