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Systematic Review

Neuroprotective effects of exosome therapy in Parkinson's disease: a systematic review

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons. Current treatments primarily address symptoms but fail to halt disease progression. Exosome-based therapies have emerged as a promising neuroprotective strategy due to their ability to cross the blood-brain barrier and deliver bioactive molecules. This systematic review and meta-analysis aim to evaluate the neuroprotective potential of exosome therapy in PD by synthesizing data from preclinical studies. A systematic literature search was conducted in PubMed, Embase, Web of Science and Scopus. Studies were included if they examined exosome therapy in PD models, evaluated neuroprotective effects and provided clear methodological details. Data extraction focused on exosome sources, experimental models, therapeutic mechanisms and outcomes. Risk of bias was assessed using the SYRCLE tool. Twelve preclinical studies met the inclusion criteria. Exosomes derived from mesenchymal stem cells demonstrated significant neuroprotective effects, including reduced neuronal apoptosis, restoration of autophagy, inhibition of neuroinflammation and enhanced dopaminergic neuron survival. Key mechanisms involved the modulation of signalling pathways (PI3K/AKT, NOX4-ROS-Nrf2 and TLR4/NF-κB/NLRP3). Despite these promising findings, variability in exosome isolation, administration routes and study designs was noted. Exosome therapy exhibits strong neuroprotective potential in preclinical PD models. However, standardized protocols, dose optimization and rigorous clinical trials are essential for translating these findings into viable treatments.

Keywords: Exosome therapy, Mesenchymal stem cells, Neuroprotection, Neuroinflammation, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta.[1] This neuronal loss results in a range of motor symptoms, including bradykinesia, rigidity, tremors and postural instability, as well as non-motor manifestations such as cognitive decline, depression and autonomic dysfunction.[1] Current therapeutic approaches, including pharmacological treatments like levodopa and deep brain stimulation, primarily provide symptomatic relief but fail to halt or reverse disease progression. The limited efficacy of existing treatments highlights the urgent need for disease-modifying strategies targeting the underlying neurodegenerative processes.

Exosome-based therapy has emerged as a promising avenue for neuroprotection and regenerative medicine in PD. Exosomes are nanoscale extracellular vesicles secreted by various cell types, including mesenchymal stem cells (MSCs) and are known to facilitate intercellular communication through the transfer of bioactive molecules such as proteins, lipids and nucleic acids. Their ability to cross the blood-brain barrier and modulate

cellular processes, including apoptosis, autophagy, neuroinflammation and oxidative stress, has generated significant interest in their therapeutic potential for neurodegenerative disorders.[2]

Preclinical studies suggest that exosome therapy may mitigate neuronal loss, reduce inflammation and enhance cellular repair mechanisms in the diseased brain. Preclinical studies have demonstrated that exosome therapy may mitigate neuronal loss and enhance neuroprotection in PD models through mechanisms such as modulation of inflammatory pathways (e.g., TLR4/NF-κB/NLRP3), regulation of oxidative stress (e.g., NOX4-ROS-Nrf2 axis) and promotion of dopaminergic neuron survival.[3]

However, despite these promising findings, variability in exosome sources, isolation methods, dosing regimens and administration routes remains a challenge in standardizing their therapeutic application. Furthermore, clinical translation of exosome-based therapies is hindered by the need for rigorous validation of safety, efficacy and optimal delivery methods.

This systematic review and meta-analysis aim to comprehensively evaluate the neuroprotective effects of exosome therapy in PD. By synthesizing data from preclinical studies, we seek to elucidate the mechanisms underlying exosome-mediated neuroprotection, assess therapeutic outcomes and identify critical gaps in current research. Our findings will contribute to guiding future experimental and clinical investigations toward the development of standardized and effective exosome-based interventions for PD.

METHODS

Search strategy and study selection

A systematic literature search was conducted at Healthway Hospitals, Goa, using PubMed, Embase, Web of Science and Scopus to identify relevant preclinical studies on exosome therapy in Parkinson's disease (PD). The search strategy included the following terms: "Exosome therapy" OR "exosome-based therapy" OR "stem cell-derived exosomes" AND "Parkinson's disease" OR "PD" OR "Parkinsonism" AND "neuroprotection" OR "neuroprotective effects."

Studies were included if they met the following criteria: 1 preclinical in vitro or in vivo studies evaluating the effects of exosome therapy in PD models, assessment of neuroprotective mechanisms or functional outcomes and 3 clear methodologies for exosome isolation, characterization and administration.[2] Studies were excluded if they were clinical trials, reviews, editorials or conference abstracts with insufficient data. Two independent reviewers screened titles and abstracts, followed by full-text assessment of eligible studies. Discrepancies were resolved by discussion or consultation with a third reviewer. The PRISMA flow diagram (Figure 1) summarizes the study selection process.

Data extraction

Data were independently extracted over two months from February 2025 to April 2025 by two reviewers using a data extraction form. The following variables were recorded: 1 study characteristics (authors, publication year), 2 exosome source (e.g., bone marrow-derived mesenchymal stem cells (BM-MSCs), Wharton's Jelly-derived MSCs, human umbilical cord MSCs (hUCMSCs), tonsil-derived MSCs (T-MSCs),3 experimental model (in vitro and in vivo), 4 PD induction method (6-hydroxydopamine (6-OHDA), 1-methyl-4-phenylpyridinium (MPP+), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 5 therapeutic mechanisms and 6 key findings.

A total of 1,925 records were identified from databases. After removal of duplicates and other exclusions, 1,708 records were screened. Of these, 20 reports were sought for retrieval, 13 were assessed for eligibility and finally, 12 studies met the inclusion criteria and were included in the review.

Risk bias assessment

The methodological quality of animal studies was assessed using the risk of bias (RoB) tool developed by the systematic review centre for laboratory animal experimentation (SYRCLE), which is adapted from the Cochrane RoB tool for animal experiments.4 The assessment included ten criteria. Sequence generation evaluated whether subjects were randomly assigned to case or control groups using an appropriately generated allocation sequence.

Baseline characteristics examined whether the groups were comparable at the start of the study. Allocation concealment assessed whether the assignment of subjects was adequately concealed. Random housing determined if all subjects were randomly housed under similar environmental conditions. Researcher blinding ensured that researchers were unaware of treatment allocations, such as exosome therapy. Random outcome assessment was performed to check if animals were selected in a random order for outcome evaluation.

Blinding of outcome assessors examined whether assessors were unaware of group assignments. Incomplete outcome data assessed whether missing data or dropouts were properly addressed. Selective outcome reporting determined if the study was free from biased reporting of significant results. Lastly, other sources of bias are considered potential risks, such as errors in unit analysis or design-specific biases. Each criterion was rated as "yes" (low risk of bias), "no" (high risk of bias) or "unclear" (insufficient information to assess bias). Any disagreements were resolved through consensus-based discussion.

RESULTS

Study selection and characteristics

A total of 12 preclinical studies investigating the neuroprotective effects of exosome therapy in Parkinson's disease (PD) were included in this systematic review and meta-analysis. Figure 1 presents the PRISMA flow diagram outlining the study selection process.

The included studies examined exosomes derived from various mesenchymal stem cell (MSC) sources, including bone marrow-derived MSCs (BM-MSCs), Wharton's Jelly-derived MSCs, human umbilical cord MSCs (hUCMSCs) and tonsil-derived MSCs (T-MSCs). Experimental models included in vitro studies using SH-SY5Y, MN9D, BV2 and olfactory bulb neurons, as well as in vivo studies involving MPTP- and 6-OHDA-induced PD models in rodents. The key characteristics of these studies, including exosome sources, experimental models, PD induction methods, therapeutic mechanisms and major findings, are summarized in Table 1.

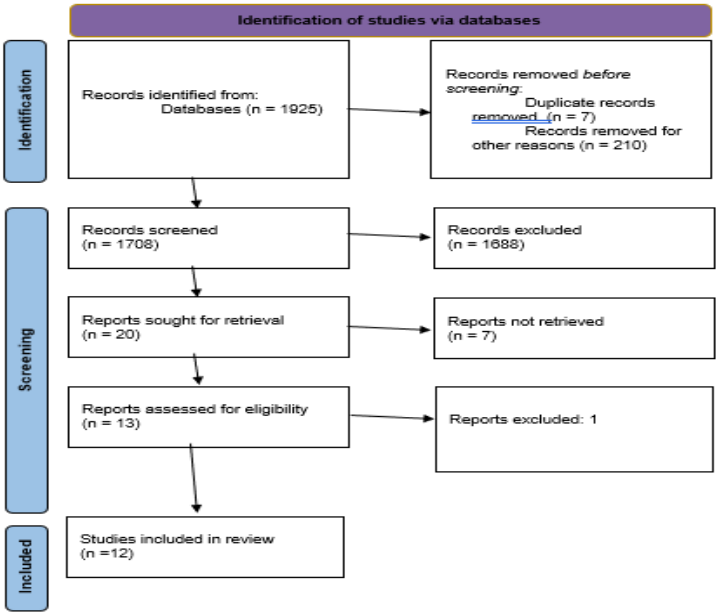

Figure 1: PRISMA flow diagram.

Reduction of apoptosis and promotion of cell survival

Several studies demonstrated that exosome therapy reduced apoptosis-related proteins and increased cell viability in PD models. Wharton's Jelly-derived MSC exosomes reduced apoptosis, restored mitochondrial function and decreased alpha-synuclein aggregation in SH-SY5Y cells exposed to 6-OHDA.[5] Similarly, bone marrow-derived MSC (BM-MSC) exosomes in MPTP-induced mice inhibited Sp1-mediated LRRK2 activation, leading to decreased apoptosis, improved motor coordination and enhanced neuronal survival.[8]

Regulation of autophagy and proteostasis

MSC-derived exosomes restored autophagy mechanisms in experimental PD models. In vitro studies using SH-SY5Y cells demonstrated that Wharton's Jelly-derived MSC exosomes played a role in maintaining proteostasis, reducing protein aggregation and improving cell viability.5 Additionally, BM-MSC exosomes exhibited secretome-based neuroprotection by regulating oxidative stress and proteostasis, ultimately leading to the rescue of dopaminergic neurons and behavioral improvements 10 Anti-Inflammatory and Immunomodulatory Effects

Exosome therapy significantly attenuated neuroinflammation in multiple PD models. Studies using umbilical cord MSCs (hUCMSCs) demonstrated inhibited microglial activation, reduced IL-1β and IL-18 secretion and prevention of pyroptosis in BV2 microglia and SH-SY5Y cell models.[16] Another study indicated that hUCMSC-derived exosomes crossed the blood-brain barrier (BBB) and reduced astrocyte activation and inflammation, resulting in improved motor and non-motor functions in MPTP-induced PD mice.[15]

Enhancement of dopaminergic neuron survival and dopamine levels

Multiple studies reported enhanced dopaminergic neuron survival and increased dopamine levels following exosome therapy. BM-MSC exosomes in 6-OHDA rat models increased dopamine levels via modulation of the PI3K/AKT signaling pathway while reducing TNF-α and caspase-3 expression.[7] Furthermore, MSC-derived

exosomes promoted angiogenesis in MPTP-induced PD models by restoring ICAM1 expression and activating the SMAD3/p38 MAPK signaling pathway, leading to increased dopaminergic neuron survival and dopamine restoration in the striatum.[6]

Oxidative stress regulation and antioxidant effects

Several studies identified the antioxidative properties of exosomes in PD models. T-MSC-derived exosomes enriched with miE-100-5p targeted the NOX4-ROS-Nrf2 axis and the Keap-Nrf2-SOD pathway, reducing oxidative stress and ameliorating motor deficits in MPTP-induced mice.[13] Additionally, BM-MSC exosomes, in combination with hydrogen sulfide (H_2S), demonstrated potent antioxidant effects, reducing neurodegenerative changes and improving histopathology in PD rat models.[7]

Gene expression modulation and neurogenesis

Exosome therapy was also found to influence gene expression pathways associated with PD pathogenesis. hUCMSCs-derived exosomes inhibited the hyperphosphorylation of MAPK p38 and ERK1/2 signaling pathways, which contributed to improvements in motor dysfunction, cognitive decline and pathological damage to the substantia nigra.[11] Additionally, MSC-derived exosomes facilitated neurogenesis and neuronal differentiation, further supporting their therapeutic potential.

Risk of bias assessment

The methodological quality of the included studies was assessed using key risk-of-bias indicators (Table 2). Only a minority of studies reported adequate randomization procedures, allocation concealment and investigator blinding.

The most common sources of bias were the lack of blinding of outcome assessors and incomplete reporting of data. Despite these limitations, several studies provided robust evidence supporting the neuroprotective potential of exosome therapy in PD. Studies with lower bias scores tended to report more significant therapeutic effects, underscoring the need for rigorous experimental design in future research.

Table 1: Characteristics of the studies.

Study	Exosome source	Experimental model	Pd induction	Therapeutic mechanism	Key findings
Chen et al[5]	Wharton's Jelly-derived MSCs	In vitro: SH-SY5Y cells	6-OHDA	Decreased apoptosis-related proteins; restored autophagy; Reduced aggregation of alpha-synuclein	Reduced apoptosis; restored mitochondrial function; improved cell viability
Xue et al[6]	MSCs	In vitro: HBMECs In vivo: Mice	MPP+MPTP	Angiogenesis via ICAM1 & SMAD3/p38 MAPK signaling pathways	Enhanced angiogenesis by restoring ICAM1 expression, promoted dopaminergic neuron survival, increased dopamine levels in the striatum
Samir et al[7]	BM-MSCs	In vivo: Rats	6-OHDA	Modulation of PI3K/AKT signaling pathway; increased dopamine; reduced TNF-α & caspase-3	Combined H2S ameliorated neurodegenerative changes; antioxidant & anti-inflammatory effects; improved behavior and histopathology
Cai et al[8]	BM-MSCs	In vitro: SH-SY5Y cells, HMC3 In vivo: Mice	MPP^+/LPS MPTP	Inhibited Sp1-mediated LRRK2 activation	Reduced apoptosis; promoted cell survival; reduced inflammation; improved motor coordination
Zhang et al[9]	Umbilical cord MSCs	In vitro: BV2 microglia, SH-SY5Y cells In vivo: Rats	LPS+ATP 6-OHDA	Inhibited microglial activation; reduced IL-1beta & IL-18 secretion; prevented adoption of pyroptosis-associated morphology	Inhibited microglia inflammation & pyroptosis; Increased neuron survival; Repaired nigral-striatal dopamine damage
Pinheiro et al[10]	BM-MSCs	In vivo: Rats	6-OHDA	Neuroprotection via secretome action (proteostasis & oxidative stress regulation)	Rescue of dopaminergic neurons; behavioral recovery in staircase test; neuronal differentiation
Ye et al[11]	hUCMSCs	In vitro: MN9D, SH-SY5Y In vivo: Mice	MPP^+ MPTP	Inhibited hyperphosphorylation of MAPK p38 & ERK1/2 signaling pathway	Efficacy in preventing & treating motor dysfunction, cognitive decline, substantia nigra pathological damage; differential gene expression in neuroactive ligand-receptor interaction, dopaminergic

Continued.

Study	Exosome source	Experimental model	Pd induction	Therapeutic mechanism	Key findings
					synapse, MAPK signaling pathway
Geng et al[12]	MSCs	In vitro: MN9D In vivo: Mice	MPP^+ MPTP	FTO promoted ATM via m6A-dependent stabilization on ATM mRNA in dopaminergic neurons	m6A demethylase FTO promoted neuronal death; Exo-siFTO enhanced therapeutic efficacy
He et al[13]	T-MSCs	In vitro: MN9D In vivo: Mice	MPP^+ MPTP	miE-100-5p targeted 3' UTR of NOX4, Keap-Nrf2-SOD pathway, N0x4-ROS-Nrf2 axis	miE-100-5p-enriched T-MSCs-Exo could protect against loss of DA neurons; maintain nigrostriatal system function; ameliorate motor deficits; reduce oxidative stress
Chan et al[14]	hADSCs	In vivo: Mice	Transgenic DAT-cre x TfamloxP MitoPark mice	Anti-inflammatory effect; down-regulated microglial activation & neuroinflammation of midbrain	Neuroprotective; improved motor function; improved memory function
Huang et al, 2024[15]	hUCMSCs	In vitro: Olfactory bulb neurons In vivo: Mice	MPTP	Attenuated microglia & astrocyte activation; reduced inflammation in the brain	Exosomes crossed BBB; improved motor & non-motor functions; improved olfactory bulb neuronal activity; reversed loss of dopaminergic neurons
Zhang et al[16]	hUCMSCs	In vitro: BV2, SH-SY5Y In vivo: Rats	6-OHDA	Inhibited microglia activation; prevented nigralstriatal dopamine neuron damage; inhibited TLR4/NF-kB/NLRP3 inflammasome induced by LPS/ATP	Inhibited pyroptosis; reduced secretion of IL-1β & IL-18; improved survival rate of neurons

Table 2: Risk bias analysis of the studies.

Name	Sequence Generation	Baseline characteristics	Allocation concealement	Randomly housing	Blinding	Random outcome assessment	Blinding (Detection bias)	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Pinheiro et al[10]	Unclear	Unclear	No	Unclear	No	No	Yes	Unclear	Unclear	Yes
Xue et al6	No	Yes	No	No	No	No	No	Unclear	Unclear	No
Cai et al[8]	Unclear	Unclear	Unclear	No	No	No	No	Unclear	Unclear	Unclear
Samir et al[7]	Yes	Yes	Unclear	Yes	No	Yes	No	No	Unclear	Unclear
Zang et al[9]	No	Yes	No	Yes	Unclear	No	Unclear	Unclear	No	No
Chan et al[14]	No	Unclear	No	Yes	No	Unclear	No	Unclear	Unclear	Unclear
Chen et al[5]	No	No	No	Unclear	No	No	No	No	No	Unclear
Geng et al[12]	No	Yes	No	Yes	Unclear	No	Unclear	Yes	Yes	Unclear
He et al[13]	No	Yes	No	Yes	Unclear	No	Unclear	Yes	Unclear	Unclear
Zhang et al[16]	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Hung et al[15]	No	Yes	No	Yes	Unclear	No	Unclear	Unclear	Unclear	No
Ye et al[11]	Unclear	Unclear	Unclear	No	No	Unclear	No	Unclear	Unclear	No

DISCUSSION

The findings from this systematic review and meta-analysis provide strong evidence supporting the potential of exosome therapy as a neuroprotective strategy in Parkinson's disease (PD). The reviewed studies demonstrate that exosome therapy contributes to neuronal survival, reduces neuroinflammation, enhances autophagy and modulates oxidative stress, offering a multifaceted approach to neuroprotection in PD. However, despite these promising results, several critical considerations and challenges must be addressed before the clinical translation of exosome-based interventions. The reviewed studies highlight multiple mechanisms by which exosomes exert their therapeutic effects. The ability of mesenchymal stem cell (MSC)-derived exosomes to cross the blood-brain barrier (BBB) and deliver bioactive molecules, such as microRNAs (miRNAs), proteins and signaling molecules, underscores their potential in neurodegenerative diseases. Notably, exosomes from different sources, including Wharton's Jelly, bone marrow and umbilical cord-derived MSCs, exhibited significant neuroprotective effects by reducing apoptosis, restoring mitochondrial function and modulating key signaling pathways such as PI3K/AKT, NOX4-ROS-Nrf2 and TLR4/NF-κB/NLRP3 inflammasome pathways.

Despite robust preclinical data, the clinical application of exosome therapy in PD remains in its infancy. Several challenges need to be addressed to ensure successful translation. Variability in exosome isolation and purification methods across studies poses a challenge in ensuring reproducibility and consistency in therapeutic efficacy. Standardized protocols for exosome characterization, including particle size, content analysis and surface markers, are necessary to define their therapeutic potential accurately.

Determining the optimal dosage and administration route for exosome therapy is crucial for maximizing therapeutic benefits while minimizing potential adverse effects. Intravenous, intranasal and intracerebral delivery methods have been explored, but further studies are needed to compare their efficacy and safety. While MSC-derived exosomes exhibit low immunogenicity, their long-term effects on immune responses and potential risks of tumorigenicity must be thoroughly investigated in clinical settings. The possibility of off-target effects and unintended biological interactions should be carefully evaluated.

Regulatory approvals for exosome-based therapies require rigorous preclinical and clinical validation. Ethical considerations regarding the source of exosomes, particularly those derived from human stem cells, must be addressed to ensure ethical compliance in research and clinical applications. To bridge the gap between preclinical research and clinical application, future studies should focus on large-scale clinical trials to evaluate the safety, efficacy and long-term outcomes of exosome therapy in PD patients.

Optimization of exosome engineering is essential to enhance their therapeutic potential by selectively loading specific neuroprotective cargoes. Developing standardized exosome formulations will ensure reproducibility and regulatory compliance for therapeutic applications. Exploring combination therapies where exosome therapy is integrated with existing PD treatments may achieve synergistic neuroprotective effects. Exosome therapy presents a promising and innovative approach to addressing the neurodegenerative processes in PD. While preclinical studies provide compelling evidence for its efficacy, significant challenges remain in translating these findings into clinical practice. Addressing these challenges through rigorous research and clinical trials will be essential for harnessing the full potential of exosome therapy as a viable treatment for PD.

CONCLUSION

This systematic review and meta-analysis suggest that exosome therapy holds significant promise as a neuroprotective intervention for Parkinson's disease. Evidence indicates that exosome-based treatments can reduce neuronal apoptosis, mitigate neuroinflammation and promote dopaminergic neuron survival, leading to improved motor and cognitive functions in preclinical models.

While findings are promising, variability in study methodologies highlights the need for standardized protocols. Further high-quality clinical trials and long-term safety studies are essential to validate efficacy and facilitate clinical translation for Parkinson's disease treatment.

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