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Systematic Review

Therapeutic Applications of Exosomal microRNAs in Alzheimer's, Parkinson's, and Multiple Sclerosis: A Systematic Comparative Analysis (2014-2024)

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Abstract

Introduction: Neurodegenerative disorders like Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) lack effective treatments. Exosomal microRNAs (miRNAs), small vesicle-derived regulators of gene expression, have emerged as therapeutic agents for disease treatment due to their ability to cross the blood-brain barrier. To systematically review therapeutic applications of exosomal miRNAs in preclinical models of AD, PD, and MS, identifying key miRNAs, mechanisms of action, and therapeutic outcomes.

Data Sources: Literature search in PubMed, Web of Science, and Scopus (January 2014-March 2024) using combinations of exosome, microRNA, and neurodegenerative disease terms.

Study Selection: Studies investigating therapeutic applications of exosomal miRNAs in AD, PD, or MS using disease models, examining specific miRNAs and their therapeutic effects, published in English. Reviewers screened studies using predefined criteria.

Data Extraction: Data extracted using standardized forms encompassing study characteristics, exosome sources, microRNA information, and outcomes. Quality assessed using modified SYRCLE and JBI tools.

Results: Forty studies were included: AD (n = 20), PD (n = 11), and MS (n = 9). Mesenchymal stem cell-derived exosomes were predominant (55%). In AD, miR-29 and miR-124 targeted amyloidogenesis via BACE1 and NLRP3 pathways, with cognitive improvement in 55% of studies and 40-50% Aβ reduction. In PD, miR-7 and miR-100a-5p modulated autophagy and oxidative stress, providing neuroprotection in 72% of studies. In MS, miR-219 and miR-23a promoted remyelination in 67% of studies with enhanced oligodendrocyte differentiation and reduced inflammatory markers by 30-60%.

Conclusion: Exosomal miRNAs demonstrate significant therapeutic potential for neurodegenerative diseases. Their ability to target pathological pathways positions them as promising candidates for clinical translation.

Keywords: Extracellular Vesicles, Alzheimer Disease, Parkinson Disease, Multiple Sclerosis, Systematic Review, Gene Therapy

Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), represent a significant global health burden characterized by progressive neuronal dysfunction and death.[1,2] Current therapeutic approaches for these conditions remain largely symptomatic and provide limited disease-modifying effects. In AD, FDA-approved medications such as cholinesterase inhibitors and NMDA receptor antagonists offer modest cognitive benefits but do not halt disease progression.[3] For PD, dopamine replacement therapy alleviates motor symptoms but becomes less effective over time and is associated with significant side effects, including dyskinesias.[4] MS treatments, including disease-modifying therapies like interferons and immunomodulators, can reduce relapse rates but show limited efficacy in preventing progressive disability, particularly in primary progressive forms.[5] These therapeutic limitations underscore the urgent need for novel approaches that can target multiple pathological pathways simultaneously and provide disease-modifying rather than merely symptomatic relief.

Despite extensive research efforts, effective treatments for these conditions remain limited, creating an urgent need for novel therapeutic approaches. Exosomal microRNAs (miRNAs) have emerged as promising candidates for therapeutic applications in these conditions. MicroRNAs are small, non-coding RNA molecules that regulate gene expression post-transcriptionally.[2,6] In the central nervous system (CNS), miRNAs regulate critical processes including neurogenesis, synaptic plasticity, and neuronal maintenance, with their dysregulation implicated in various neurodegenerative disorders.[7] Exosomes, small extracellular vesicles (30-150 nm) secreted by most cell types, function as mediators of intercellular communication. They contain diverse molecular cargo, including miRNAs, which can be transferred to recipient cells.[7,8] Crucially, exosomes can cross the blood-brain barrier (BBB), making them ideal vehicles for delivering therapeutic agents to the CNS.[9] Despite extensive research into individual therapeutic approaches, there is a lack a comprehensive systematic analysis comparing the therapeutic applications of exosomal microRNAs across the major neurodegenerative diseases. While previous reviews have examined exosomal miRNAs in individual diseases, no study has systematically compared their mechanisms, efficacy, and therapeutic outcomes across AD, PD, and MS to identify common pathways and disease-specific targets. This gap limits our understanding of the broader therapeutic potential and optimal clinical translation strategies for exosomal miRNA therapies in neurodegeneration.

This systematic review analyzes current evidence for therapeutic applications of exosomal miRNAs in AD, PD, and MS, identifying key miRNAs, delivery strategies, mechanisms of action, and outcomes across these conditions, while adhering to PRISMA 2020 guidelines.[10]

Materials and Methods

Search Strategy

A systematic search was conducted in PubMed, Web of Science, and Scopus for studies published between January 2014 and March 2024. Search terms included combinations of exosomes, extracellular vesicles, microRNAs, neurodegenerative diseases (Alzheimer's, Parkinson's, multiple sclerosis), and therapeutic relevance terms. Specific search phrases included: ("exosomes" OR "extracellular vesicles") AND ("microRNA" OR "miRNA") AND ("Alzheimer disease" OR "Parkinson disease" OR "multiple sclerosis") AND ("therapy" OR "treatment" OR "therapeutic"). These terms were combined using Boolean operators (AND, OR) with truncation symbols (*) to capture variant word endings.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: 1) original research investigating therapeutic applications of exosomal miRNAs in AD, PD, or MS; 2) *in vitro* and/or *in vivo* studies using established disease models; 3) studies examining specific miRNAs within exosomes and their therapeutic effects; 4) studies published in English; and 5) peer-reviewed journal articles with full text available.

Data Extraction and Quality Assessment

Data from included studies were extracted by two independent reviewers using a standardized form. For *in vivo* studies, quality was assessed using a modified version of the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) risk of bias tool, which evaluates sequence generation, baseline characteristics, allocation concealment, random housing, blinding, random outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.[11] For *in vitro* studies, the JBI (Joanna Briggs Institute) Critical Appraisal Checklist was adapted, assessing study objectives, methodology, subject characteristics, outcome measurement, statistical analysis, and results presentation.[12]

Statistical Analysis

Due to significant heterogeneity in study designs, outcome measures, and methodological approaches across the included studies, meta-analysis was not feasible. Instead, a narrative synthesis approach was adopted, with descriptive statistics used to summarize study characteristics and therapeutic outcomes. Percentage calculations were performed for categorical outcomes, and ranges were provided for continuous variables where appropriate.

Results

Study Selection and Characteristics

This systematic review synthesizes findings from 40 preclinical studies published between 2014 and 2024. The included studies focused on AD (n = 20), PD (n =

11), and MS (n = 9). The majority of studies (n = 31, 77%) employed both *in vivo* and *in vitro* methodologies. Detailed characteristics of each included study are presented in Figure 1.

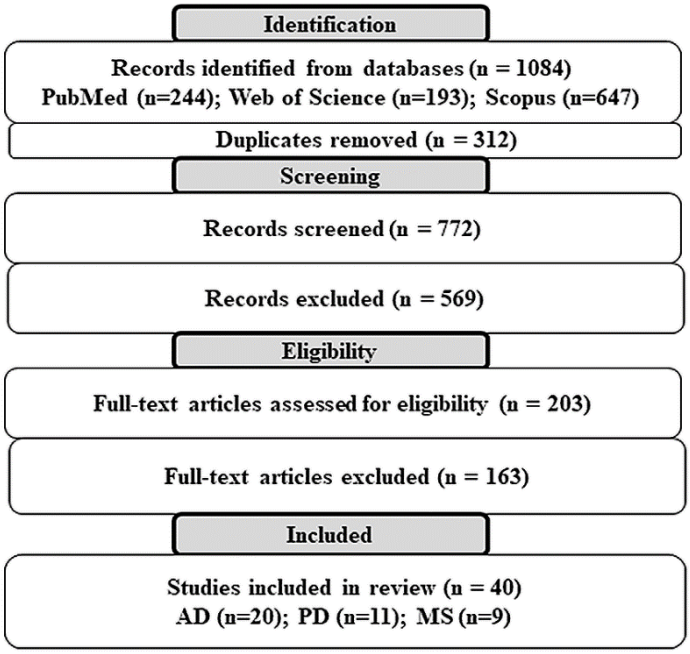

Figure 1. PRISMA 2020 Flow Diagram Illustrating the Study Selection Process.

Quality Assessment

Of the 40 studies, 45% (n = 18) were rated as high quality, 30% (n = 12) as moderate-to-high quality, and 25% (n = 10) as moderate quality. No studies were assessed as low quality overall.

Exosome Sources

Mesenchymal stem cells (MSCs) from various origins were the most common source of therapeutic exosomes, utilized in 55% (n = 22) of all included studies. Specifically, MSCs were the source in 40% of AD studies, 72% of PD studies, and 67% of MS studies.

Therapeutic Effects by Disease

Alzheimer's Disease (AD)

In the 20 AD-focused studies, exosomal miRNAs showed promise in targeting key pathological features. Therapeutic strategies frequently aimed at reducing amyloid-beta (Aβ) pathology, with 45% (n = 9) of studies reporting decreased Aβ levels. The miR-29 family (miR-29b, -29b-2, -29c-3p) was prominent and investigated in 15% (n = 3) of AD studies for its role in regulating BACE1. Modulating neuroinflammation was another major focus, implicated in 25% (n = 5) of AD studies, including inhibiting pyroptosis via the NLRP3 inflammasome. Cognitive improvement was reported in 55% (n = 11) of AD studies. A comprehensive summary of exosomal miRNA studies in AD is presented in Table 1.

Parkinson's Disease (PD)

The 11 PD studies primarily aimed to protect dopaminergic neurons, modulate neuroinflammation, and reduce α-synuclein pathology. Protection of dopaminergic neurons was explicitly mentioned in 27% (n = 3) of studies. Regulation of neuroinflammation was targeted in 27% (n = 3) of studies, often involving NLRP3 or NF-κB pathways. Enhancement or regulation of autophagy was investigated in 36% (n = 4) of PD studies, involving miRNAs like miR-188-3p, miR-106b, miR-23b-3p, and miR-7. Table 2 summarizes studies examining exosomal miRNA applications in PD.

Multiple Sclerosis (MS)

The 9 studies focusing on MS/EAE models primarily addressed neuroinflammation and demyelination. Modulation of immune response and reduction of inflammation were central therapeutic mechanisms,

Table 1. Comprehensive Table of Exosomal microRNA Studies in Alzheimer's Disease (2014-2024)

Disease	Study Type	microRNA	Exosome Source	Disease Model	Administration Method	Main Mechanism of Action	Main Findings	Refrences
AD	*In vitro & in vivo*	miR-22	Adipose-derived MSCs	APP/PS1 mice	Tail vein injection	Inhibiting pyroptosis	Reduced inflammatory factors and improved cognition	[13]
AD	*In vitro & in vivo*	miR-711	BV2 microglial cells	rmTBI mouse model	Tail vein injection	Decreased Tau phosphorylation	Improved cognitive function and increased M2/M1 ratio	[14]
AD	*In vitro & in vivo*	miR-21	Bone marrow MSCs	APP/PS1 mice	Intravenous injection	Regulating inflammatory responses	Decreased Aβ levels and increased synaptic proteins.	[15]
AD	*In vitro & in vivo*	miR-29b-2	Dendritic cells	3xTg-AD mice	Intravenous injection	Reduced PSEN1 expression	Reduced PSEN1 and reduced Aβ1-42 oligomers	[16]
AD	*In vivo*	miR-29b	Rat bone marrow MSCs	Aβ1-42 injected rats	Intracerebroventricular	Downregulation of BACE1 and BIM	Improved spatial learning and memory	[17]
AD	*In vitro & in vivo*	miR-223-3p	iPSC-derived MSCs	STZ-induced mouse model	Intracisternal injection	Inhibition of pyroptosis	Reduced neuroinflammation and improved cognition	[18]
AD	*In vivo*	miR-124-3p, miR-125b-5p	Human neural stem cells	5xFAD mice	Intravenous injection	Mitigation of hallmarks	Reduced Aβ plaque accumulation	[19]
AD	*In vitro & in vivo*	miR-342-5p	Human serum	APP transgenic mice	*In vitro* culture	Targeting BACE1	Reduced BACE1, APP, and Aβ42 levels	[20]
AD	*In vitro & in vivo*	miR-223	M2-like microglia	APP/PS1 mice	Intravenous injection	Reduced PTEN	Improved spatial learning, reduced inflammation	[21]
AD	*In vitro & in vivo*	miR-29c-3p	Rat bone marrow MSCs	Aβ1-42 injected rats	Intracerebroventricular	Regulation of BACE1	Reduced Aβ deposition and improved memory	[22]
AD	*In vitro & in vivo*	miR-7670-3p	M2 microglial cells	5xFAD mice	Intranasal administration	Modulation by 1070-nm light	Reduced Aβ burden and enhanced synaptic proteins	[23]
AD	*In vitro & in vivo*	circ-Epc1, miR-770-3p	Adipose-derived stem cells	APP/PS1 mice	Intravenous injection	Shifting microglial polarization	Improved spatial learning and memory	[24]
AD	*In vitro*	ata-miR156c-3p	Lyciumruthenicum Murray	Aβ-induced PC12 cells	Direct addition to culture	Inhibiting apoptosis	Increased cell viability from 63.3% to 90.7%	[25]
AD	*In vitro*	miR-124-3p	SH-SY5Y cells	APP695 Swedish mutation	*In vitro* co-culture	Reduced inflammatory markers	Improved mitochondrial function	[26]
AD	*In vivo*	miR-146a	Choroid plexus cells	5xFAD mice	Environmental enrichment	Enhanced secretion from choroid plexus	Reduced neuroinflammation and increased synapses	[27]
AD	*In vitro*	miR-211-5p inhibitor	Human umbilical cord MSCs	Aβ1-40-induced cells	Direct addition to culture	Increasing NEP expression	Decreased apoptosis and enhanced cell migration	[28]
AD	*In vitro & in vivo*	miR-138-5p	Neural stem cells	APP/PS1 mice	Intravenous injection	Decreased Tau expression	Reduced neuronal apoptosis and improved cognition	[29]
AD	*In vitro & in vivo*	miR-206-3p	Rat cortical astrocytes	APP/PS1 mice	Intranasal administration	Upregulation of Brain-Derived Neurotrophic Factor	Improved synaptic plasticity	[30]
AD	*In vitro & in vivo*	miR-322, miR-17, miR-485	Rat hippocampal NSCs	Aβ oligomer-induced	Intracerebroventricular	Preserved memory function	Protected against Aβo-induced suppression	[31]
AD	*In vitro & in vivo*	Multiple miRNAs	Human umbilical cord MSCs	APP/PS1 mice	Direct hippocampal injection	Regulated secretase expression	Reduced Aβ42 deposition and improved cognition	[32]

AD: Alzheimer's disease; MSCs: Mesenchymal stem cells; Aβ: Amyloid β protein; BACE1: Beta-site amyloid precursor protein cleaving enzyme 1; iPSC: Induced pluripotent stem cell; NSCs: Neural Stem Cells.

Table 2. Comprehensive Table of Exosomal microRNA Studies in Parkinson's Disease (2014-2024)

Disease	Study Type	microRNA	Exosome Source	Disease Model	Administration Method	Main Mechanism of Action	Main Findings	Refrences
PD	*In vitro*	miR-200a-3p	Primary mouse astrocytes	MPP+-induced cell death	Co-culture with exosomes	Inhibition of MKK4-JNK apoptotic pathway	Prevented MPP+-induced apoptotic cell death	[33]
PD	*In vitro & in vivo*	miR-124-3p	Human UCB-MNCs	6-OHDA model	Intracerebroventricular	Previous targets include STAT3, AMPK/mTOR	Protected dopaminergic neurons	[34]
PD	*In vivo & in vitro*	miR-188-3p	Adipose-derived MSCs	MPTP-induced PD mouse	Intravenous injection	Inhibition of autophagy and inflammasome	Reduced neuroinflammation	[35]
PD	*In vitro & in vivo*	miR-100-5p	Trophoblast-derived MSCs	MPTP-induced PD mouse	Intravenous injection	Nox4-ROS-Nrf2 axis	Enhanced antioxidant effects	[36]
PD	*In vitro & in vivo*	Multiple miRNAs	Human neural stem cells	6-OHDA-induced PD	Intracerebral injection	Neurotrophic factor signaling	Reduced ROS and neuroinflammation	[37]
PD	*In vivo & in vitro*	miR-106b	Human umbilical cord MSCs	MPTP-induced PD mouse	Intracranial injection	Enhancement of neuronal autophagy	Alleviated neuronal apoptosis	[38]
PD	*In vitro & in vivo*	Multiple miRNAs	Human umbilical cord MSCs	6-OHDA-induced rat	Tail vein injection	Inhibition of microglial activation	Protected dopaminergic neurons	[39]
PD	*In vivo & in vitro*	miR-23b-3p	Adipose-derived MSCs	6-OHDA-induced PD rats	Intravenous injection	Regulation of Wnt signaling	Reduced α-synuclein	[40]
PD	*In vitro & in vivo*	miR-494-3p	Human nasal mucosal MSCs	$MnCl_2$-induced PD-like	Intranasal delivery	Reducing neuroinflammation	Decreased neuroinflammation	[41]
PD	*In vivo & in vitro*	miR-7, miR-21	Adipose tissue stem cells	Rotenone-induced rat	Intravenous injection	Modulation of autophagy	Reduced α-synuclein	[42]
PD	*In vitro*	miR-17-5p, circZNRF1	Mouse microglial cells	Paraquat-induced toxicity	Direct addition to culture	CircZNRF1 sponging miR-17-5p	Reduced apoptosis; decreased ROS levels	[43]

PD: Parkinson's Disease; MSCs: Mesenchymal Stem Cells; 6-OHDA: 6-hydroxydopamine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive Oxygen Species.

Table 3. Comprehensive Table of Exosomal microRNA Studies in Multiple Sclerosis (2014-2024)

Disease	Study Type	microRNA	Exosome Source	Disease Model	Administration Method	Main Mechanism of Action	Main Findings	Refrences
MS	*In vitro & in vivo*	miR-181a-5p	Bone marrow MSCs	EAE mouse model	Intrathecal injection	Inhibiting USP15/RelA/NEK7/NLRP3 axis	Reduced microglial pyroptosis and inflammation	[44]
MS	*In vivo & in vitro*	miR-23a-3p	Human umbilical cord MSCs	EAE mouse model	Intravenous injection	Targeting Tbr1/Wnt pathway	Promoted remyelination, enhanced OPC differentiation	[45]
MS	*In vitro & in vivo*	miR-219a-5p	HEK293T cells	Lysolecithin-induced demyelination; EAE	Intranasal administration	Inducing OPC differentiation	Enhanced myelination; improved clinical scores	[46]
MS	*In vitro & in vivo*	miR-23b-3p	Bone marrow MSCs	EAE mouse model	Intrathecal injection	Inhibiting NEK7/NLRP3 inflammasome pathway	Reduced microglial pyroptosis	[47]
MS	*In vitro & in vivo*	miR-367-3p	Bone marrow MSCs	EAE mouse model	Intrathecal injection	Inhibiting microglial ferroptosis via EZH2/SLC7A11/GPX4 axis	Reduced iron and MDA levels	[48]
MS	*In vivo*	miR-326	Serum from pregnant mice	EAE mouse model	Intraperitoneal injection	Modulating Th17/Treg balance	Decreased IL-17 and IFN-γ; increased Treg cells	[49]
MS	*In vitro & in vivo*	miR-219	Dendritic cells from rats	Lysolecithin-induced demyelination	Nasal administration	Enhancing OPC differentiation	Increased MBP levels; reduced oxidative stress	[50]
MS	*In vitro & in vivo*	Multiple miRNAs	Bone marrow MSCs	EAE mouse model	Intraperitoneal injection	Suppressing Th1/Th17 responses	Enhanced miR-193 and miR-146a	[51]
MS	*In vitro & in vivo*	miR-467f, miR-466q	Bone marrow MSCs	EAE mouse model	Intravenous injection	Inhibiting p38 MAPK pathway in microglia	Shifted microglia phenotype	[52]

MS: Multiple Sclerosis; MSCs: Mesenchymal Stem Cells; EAE: Experimental Autoimmune Encephalomyelitis; NLRP3: NLR Family Pyrin Domain-Containing 3; OPC: Oligodendrocyte Progenitor Cell; Wnt: Wingless/Integrated; Th17: T helper 17 cells; Treg: Regulatory T cells.

implicated in 67% (n = 6) of studies. Promoting remyelination and enhancing oligodendrocyte precursor cell differentiation was reported in 33% (n = 3) of MS studies, with the miR-219 family and miR-23a-3p being notably investigated. The therapeutic applications of exosomal miRNAs in MS are cataloged in Table 3.

Key Molecular Mechanisms

Across the three diseases, several molecular mechanisms emerged as particularly important. In AD studies, BACE1 inhibition by miR-29 family members was dominant for reducing Aβ production. In PD studies, antioxidant mechanisms were prominent, with the Nrf2 pathway being a key target. For MS studies, immunomodulatory mechanisms predominated, with several miRNAs targeting the NLRP3 inflammasome pathway.

Discussion

This systematic review synthesizes evidence from 40 preclinical studies investigating exosomal miRNAs as therapeutic agents for neurodegenerative diseases across AD, PD, and MS. MSCs emerged as the predominant source (55% of studies), with disease-specific preferences: bone marrow MSCs in MS studies (67%) and adipose-derived MSCs in AD and PD studies, reflecting attempts to leverage specific therapeutic properties.[13,15] In AD models, exosomal miRNAs effectively targeted Aβ pathology and neuroinflammation. The miR-29 family demonstrated particular efficacy through BACE1 targeting. Jahangard et al.[17] and Sha et al.[22] showed that miR-29-containing exosomes improved memory and reduced Aβ deposition by 40-50% in rodent models. Neuro-inflammation regulation was addressed through NLRP3 inflammasome inhibition. Zhai et al.[13] demonstrated that miR-22-loaded exosomes significantly decreased pyroptosis by targeting GSDMD, improving memory function in APP/PS1 mice. Lin et al.[16] reported similar results using miR-223-3p, which directly targets NLRP3 and reduces inflammatory cytokines. In PD studies, autophagy enhancement represented a distinctive focus (36% of studies). Bai et al.[38] found that miR-106b-containing exosomes enhanced neuronal autophagy by downregulating CDKN2B, improving motor coordination in rotenone models. Oxidative stress reduction emerged as another key mechanism. He et al.[36] demonstrated that miR-100a-5p-enriched exosomes enhanced antioxidant effects by targeting NOX4 and activating the Nrf2 pathway, resulting in improved motor function and dopaminergic neuron survival in MPTP models. In MS studies, therapeutic applications centered on immuno-modulation and remyelination. Wang et al.[47] showed that miR-23b-3p significantly alleviated EAE by targeting NEK7 in the NLRP3 inflammasome pathway, reducing microglial pyroptosis. Fan et al.[48] demonstrated innovative ferroptosis targeting using miR-367-3p through EZH2/SLC7A11 pathway modulation. Remyelination promotion showed promising results, with Osorio-Querejeta et al.[46] demonstrating enhanced myelination using intranasal miR-219a-5p delivery, superior to synthetic methods. Qin et al.[45] revealed that miR-23a-3p promoted oligodendrocyte differentiation by targeting the Tbr1/Wntpathway. Common mechanisms emerged across diseases, particularly neuroinflammation regulation through NLRP3 inflammasome targeting, identified in approximately one-third of the studies. This suggests inflammasome-mediated pyroptosis represents a shared pathological mechanism effectively modulated by exosomal miRNA therapy. Clinical translation faces several challenges. Methodological heterogeneity complicates comparisons and limits definitive conclusions about optimal approaches. Standardization of exosome production, characterization, and administration protocols remains essential, with MISEV guidelines[53] representing important progress. Scalability challenges exist, as most studies utilized small-scale production. Recent bioreactor-based systems offer promising solutions for large-scale, GMP-compliant production necessary for clinical trials.

Our findings align with previous individual disease reviews while providing novel comparative insights. Consistent with Wang et al.'s review on exosomal miRNAs in neurodegeneration,[1] we found that mesenchymal stem cell-derived exosomes predominate as therapeutic vehicles. However, our systematic comparison reveals disease-specific preferences: bone marrow MSCs in MS studies (67%) versus adipose-derived MSCs in AD and PD studies, suggesting differential therapeutic properties may be leveraged based on target pathology. The identification of the NLRP3 inflammasome as a common target across all three diseases extends previous single-disease observations and suggests this pathway represents a convergent

therapeutic mechanism in neurodegeneration.[54]

The therapeutic efficacy demonstrated across preclinical models suggests several promising avenues for clinical translation. The ability of exosomal miRNAs to cross the blood-brain barrier positions them as superior alternatives to traditional gene therapy approaches that struggle with CNS delivery.[9] For AD, the consistent efficacy of miR-29 family members in targeting BACE1 suggests this pathway could be prioritized for first-in-human trials.[16,17,22] In PD, the dual targeting of autophagy and oxidative stress by miRNAs like miR-106b and miR-100a-5p offers potential for disease modification rather than symptomatic treatment.[36,38] For MS, the remyelination-promoting effects of miR-219 and miR-23a could address the progressive disability that current therapies fail to prevent.[45,50]

Several limitations should be acknowledged. First, the heterogeneity in study methodologies, disease models, and outcome measures precluded meta-analysis and limited quantitative comparisons. Second, most studies utilized acute disease models that may not fully recapitulate the chronic, progressive nature of human neurodegenerative diseases. Third, potential publication bias may exist, as studies with negative results are less likely to be published. Fourth, the quality assessment revealed that 25% of studies were of moderate quality, which may affect the reliability of findings. Fifth, long-term safety profiles and potential off-target effects of exosomal miRNA therapies remain largely unexplored in the included studies. Finally, scalability and standardization challenges for clinical-grade exosome production were insufficiently addressed in most preclinical studies, representing a significant barrier to clinical translation.

Conclusion

This systematic review reveals both disease-specific mechanisms and common therapeutic pathways across AD, PD, and MS. Exosomal miRNAs demonstrated significant efficacy in addressing key pathological features, including protein aggregation, neuroinflammation, oxidative stress, and cell death mechanisms. The versatility of exosomal miRNAs as therapeutic agents, capable of modulating diverse cellular pathways with high specificity while leveraging natural intercellular communication functions, positions them as potentially transformative treatments for neurodegenerative diseases.

Conflict of Interest

The authors declare no conflicts of interest.

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