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REVIEW ARTICLE

Effectiveness of Mesenchymal Stem Cells and Their Derivatives in Modulating Oxidative Stress in Neurodegenerative Diseases: A Structured Narrative Review

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HIGHLIGHTS

- MSCs and their derivatives effectively reduce oxidative stress in neurodegenerative models
- MSC-derived extracellular vesicles enhance antioxidant pathways and mitochondrial function
- Cell-free MSC strategies show strong potential for safe neuroprotective therapy

ABSTRACT

Background: Oxidative stress plays a critical role in the development and progression of neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS). Mesenchymal stem cells (MSCs) and their derivatives have emerged as promising therapeutic strategies due to their antioxidant, anti-inflammatory, and neuroprotective properties. **Objective**: This review evaluated the effectiveness of MSC-based interventions in modulating oxidative stress in neurodegenerative disease models. **Methods**: A structured narrative review search was conducted following PRISMA 2020 guidelines using PubMed and Scopus databases for studies published between 2020 and 2025, with the last search in December 2025. **Results**: 33 studies met the inclusion criteria, primarily involving Parkinson's and Alzheimer's disease models. Overall, MSC-based therapies reduced oxidative stress markers, enhanced antioxidant defenses, activated the Nrf2/HO-1 pathway, improved mitochondrial function, and reduced neuroinflammation in experimental neurodegenerative disease models.

INTRODUCTION

Oxidative stress is a contributing factor to neuronal cell loss. It is closely associated with various neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). In PD, progressive degeneration of dopaminergic neurons in the substantia nigra leads to motor and non-motor symptoms (Caproni et al., 2025). AD is characterized by the accumulation of amyloid-beta plaques and tau neurofibrillary tangles, resulting in progressive cognitive decline (Zheng & Wang, 2025). ALS is marked by degeneration of upper and lower motor neurons, causing progressive weakness and loss of voluntary motor control (Mead et al., 2023). These conditions share oxidative stress and redox dysregulation as common pathogenic mechanisms contributing to neuronal dysfunction and death.

Oxidative stress may occur due to the excessive production and accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) within cells and tissues, as well as the inability of cells to eliminate ROS byproducts effectively. ROS and RNS are metabolic byproducts generated during cellular respiration. Under normal conditions, cells possess mechanisms to neutralize these compounds; however, when their accumulation exceeds the antioxidant capacity, it disrupts redox homeostasis and triggers cellular damage. The consequences of oxidative stress include alterations in cellular energy production processes and dysregulation of cellular balance, which may lead to several neurodegenerative diseases that induce cell death through multiple mechanisms, including apoptosis, necrosis, tissue scarring, and autodegradation processes (Olufunmilayo et al., 2023).

Research on therapies aimed at modulating oxidative stress in neurodegenerative diseases has become a major focus in recent years. Recent studies have investigated the potential of mesenchymal stem cell (MSC)- based interventions, as MSCs have been shown to restore redox balance and reduce neuronal damage in neurodegenerative diseases (Angeloni et al., 2020). MSCs have been widely utilized as a form of cell therapy due to their antioxidant, anti-inflammatory, and tissue-regenerative properties. Furthermore, the use of exosomes derived from mesenchymal stem cells (MSC-Exo) for the treatment of neurodegenerative diseases has been claimed to represent a safe and effective therapeutic approach (Issa et al., 2025).

Nevertheless, to date, there have been a limited number of reviews that specifically integrate evidence regarding the role of MSCs and their derivatives, such as extracellular vesicles, secretome, and mitochondrial transfer in modulating oxidative stress across various neurodegenerative diseases. Most previous reviews remain largely narrative in nature, focusing on whole-cell transplantation and positioning oxidative stress as a secondary outcome. Therefore, this study aims to conduct a literature review to comprehensively evaluate the effectiveness of MSCs and their derivatives in modulating oxidative stress as the primary pathogenic mechanism in neurodegenerative diseases.

METHOD

This study is a narrative literature review designed to analyze the effectiveness of MSCs and their derivatives in modulating oxidative stress in neurodegenerative diseases. The review employs a structured search strategy and transparent selection criteria, though it does not follow the full methodological rigor of a PRISMA-compliant systematic review. No protocol was prospectively registered.

Study design and literature search

This study was designed as a structured narrative review aimed at synthesizing current evidence regarding the role of mesenchymal stem cells (MSCs) and their derivatives in modulating oxidative stress in neurodegenerative diseases. A systematic search strategy was employed to enhance transparency and reproducibility. Literature searches were conducted in PubMed and Scopus databases covering publications from January 2020 to December 2025. The search strategy was guided by predefined keywords related to MSCs, oxidative stress, and neurodegenerative diseases. Although elements of the PRISMA 2020 framework were adopted to ensure clarity in study identification and selection, this review was not conducted as a formal systematic review. No protocol was prospectively registered, and no formal quantitative synthesis or meta-analysis was performed. The PICO framework (Population, Intervention, Comparator, Outcome) was used as a conceptual tool to guide study selection and data extraction. However, the overall objective of this review was interpretative synthesis rather than exhaustive systematic evaluation.

Table 1. Detailed Search String

Database	Search String*
PubMed:	"mesenchymal stem cell"[Title/Abstract] OR "mesenchymal stromal cell"[Title/Abstract]) AND ("oxidative stress"[Title/Abstract] OR "reactive oxygen species"[Title/Abstract]) AND ("neurodegenerative disease"[Title/Abstract] OR "neurodegenerative disorder"[Title/Abstract] OR "Parkinson"[Title/Abstract] OR "Alzheimer"[Title/Abstract] OR "amyotrophic lateral sclerosis"[Title/Abstract])
Scopus:	TITLE-ABS-KEY ("mesenchymal stem cell" OR "mesenchymal stromal cell") AND TITLE-ABS-KEY ("oxidative stress" OR "reactive oxygen species") AND TITLE-ABS-KEY ("neurodegenerative disease" OR "Parkinson" OR "Alzheimer" OR "amyotrophic lateral sclerosis")

*The search was restricted to articles published in English, available in full-text format, and published within the last five years (2020-2025).

Eligibility criteria and study selection

Articles included in this review met the following inclusion criteria: original research studies (experimental, *in vitro*, *in vivo*, clinical trials, observational studies, or randomized controlled trials). Studies employing neurodegenerative disease models (PD, AL, ALS, MS, HD, or other related conditions), Interventions involving MSCs or their derivatives, including extracellular vesicles (EVs), exosomes, secretome, conditioned medium, or mitochondrial transfer. Studies reporting at least one oxidative stress biomarker, and published in peer-reviewed scientific journals, with full text available in English. The selection process, conducted independently by the authors, screened the titles and abstracts of all retrieved articles. Full-text articles were then assessed for eligibility based on the PICO framework (Population: neurodegenerative disease models; Intervention: MSCs or derivatives; Comparator: control/vehicle groups; Outcomes: oxidative stress parameters). Disagreements during screening or eligibility assessment were resolved through discussion and consensus. Exclusion criteria comprised narrative reviews, case reports, editorials, articles lacking primary data, studies that didn’t clearly report oxidative stress parameters, and publications with incomplete methodological or outcome information.

Data extraction and synthesis

Data were extracted narratively from included studies, focusing on: (1) type of neurodegenerative disease and model used, (2) research model (*in vitro*, *in vivo*, or clinical), (3) MSC source and type of intervention (whole cells, EVs, secretome, mitochondria), (4) dose and route of administration, (5) methods used to measure oxidative stress (assay type, specific markers), (6) key findings related to oxidative stress modulation, and (7) secondary outcomes such as inflammation, apoptosis, functional improvement.

Data synthesis was performed descriptively and thematically, with studies grouped by disease type to facilitate interpretation and comparison.

Quality assessment

No formal risk-of-bias assessment tool (e.g., SYRCLE, RoB 2, ROBINS-I) was applied. Instead, methodological robustness was evaluated descriptively by considering the appropriateness of study design, the clarity of model description, the characterization of MSC interventions, the consistency of oxidative stress reporting, and the transparency of analytical methods. This approach was adopted to provide contextual interpretation of evidence strength while acknowledging that the review does not fulfill criteria for a full systematic review with formal bias scoring.

RESULT

Inclusion and exclusion criteria

This narrative literature review encompasses 33 articles that met the inclusion criteria and were thoroughly analyzed. These studies reported various MSC-based interventions and their derivatives in the context of neurodegenerative diseases and oxidative stress. The main characteristics of all included studies, such as type of disease, research model, form of intervention, MSC/MSC-EV dose, and reported outcomes, are presented in detail in **Table 2**. Most of the studies employed preclinical experimental models, both *in vitro* and *in vivo*, with a primary focus on neurodegenerative diseases characterized by increased oxidative stress and mitochondrial dysfunction.

Distribution of neurodegenerative disease models

Based on the analysis of the included articles, Parkinson’s disease and Alzheimer’s disease were the most frequently investigated neurodegenerative conditions in relation to MSC interventions and oxidative stress modulation. A total of 29% of the studies focused on Parkinson’s disease, while 17% examined Alzheimer’s disease. The distribution of neurodegenerative disease models utilized across all studies is presented in **Figure 2**. In addition to Parkinson’s and Alzheimer’s disease, several studies also reported models of amyotrophic lateral sclerosis (ALS), multiple sclerosis, aging-related neurodegeneration, as well as neuroinflammation and neurotoxicity induced by chemical agents.

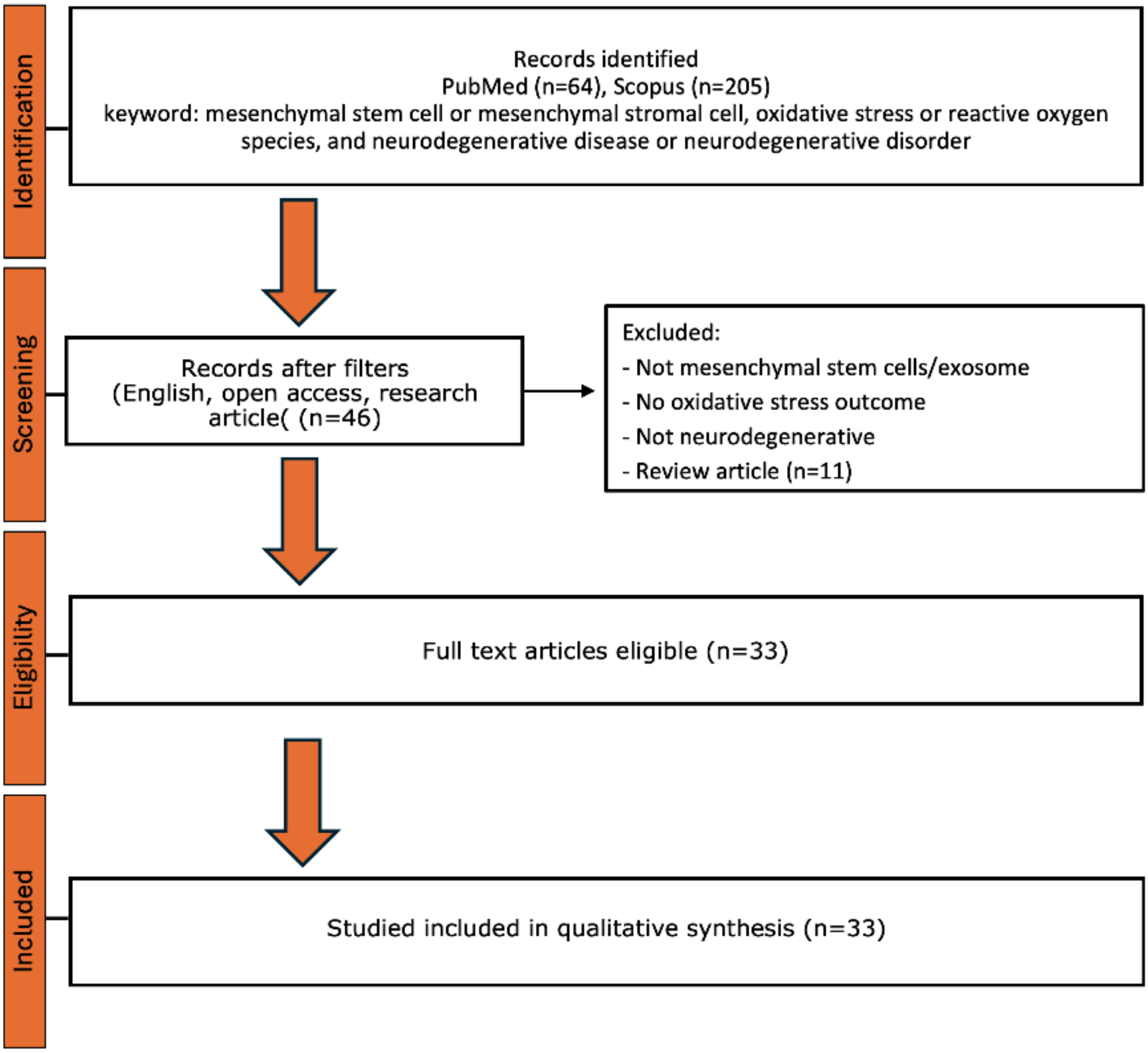

Figure 1. PRISMA flow diagram outlining search strategy for review

Types of mesenchymal stem cell-based interventions

Various forms of MSC-based interventions were employed in the included studies. A summary of the intervention types and their main reported effects is presented in **Table 9**. The most frequently used intervention was MSC-derived exosomes or extracellular vesicles (EVs), reported in 15 studies. This intervention demonstrated predominant effects such as reducing reactive oxygen species (ROS) levels, enhancing antioxidant enzyme activity, including superoxide dismutase (SOD), and modulating microglial responses. In addition, MSC-conditioned medium or secretome was utilized in six studies and was associated with the activation of antioxidant pathways such as Nrf2/HO-1, reduction of malondialdehyde (MDA), and provision of neurotrophic support. Direct MSC transplantation was reported in eight studies and was linked to improved neuronal survival, reduced apoptosis, and enhanced motor function.

Other reported interventions included the use of MSC-derived mitochondria, MSC-derived neurons or organoids, as well as engineered MSC-derived EVs or nanoparticles, although these were investigated in a more limited number of studies.

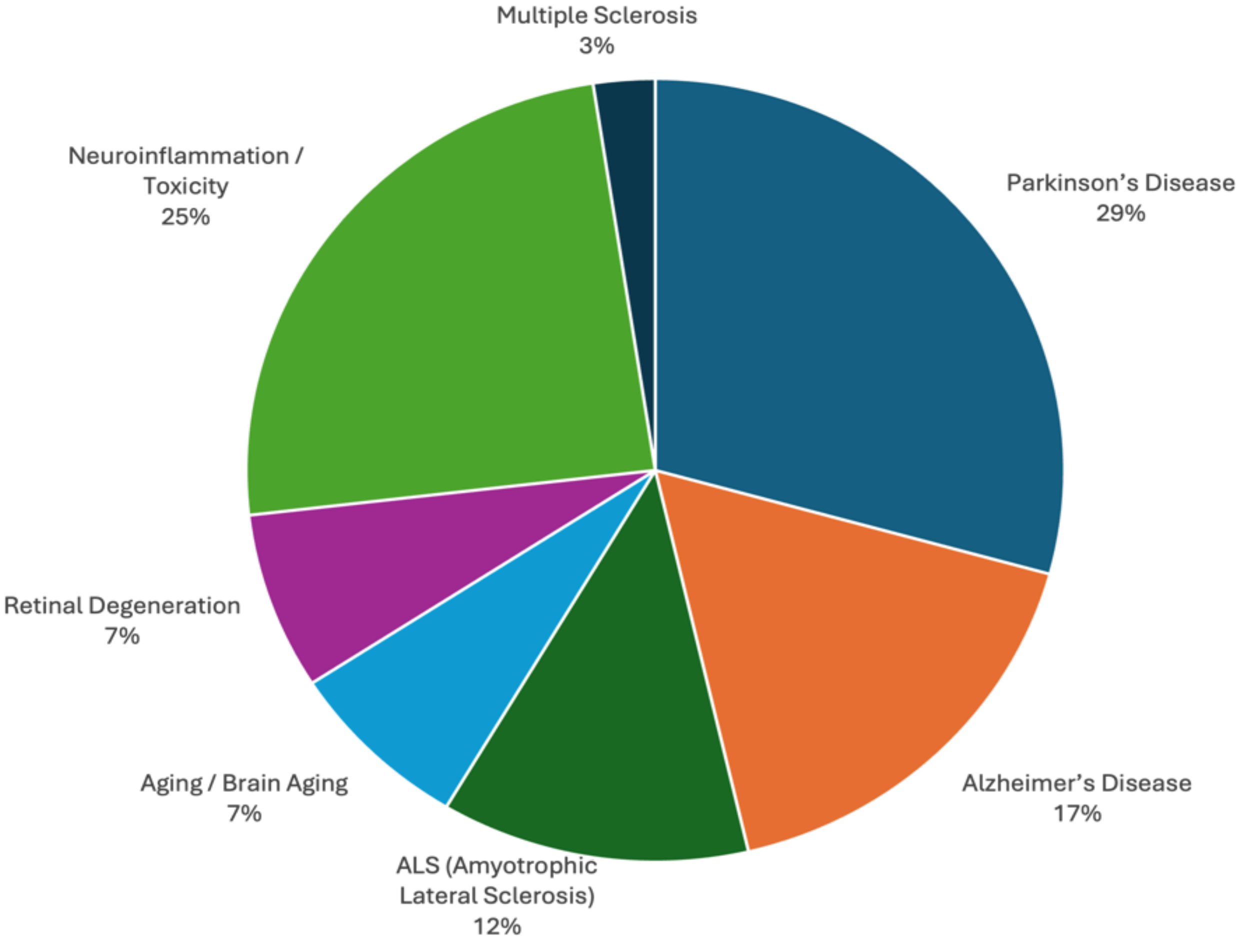

Figure 2. Distribution of neurodegenerative disease models among included studies

Oxidative stress outcomes and related parameters

Most of the included studies reported at least one oxidative stress parameter as a primary or secondary outcome. Oxidative stress and ROS levels were measured using various methods across the included studies, including: DCFDA for general cellular ROS, DHE for superoxide detection, MitoSOX for mitochondrial superoxide, DPPH for antioxidant capacity, JC-1 or TMRM for mitochondrial membrane potential. Biochemical assays such as: Lipid peroxidation markers (MDA), protein oxidation markers (protein carbonyl content), antioxidant enzymes (SOD, CAT, GPx), glutathione system (GSH, GSSG, GSG/GSSG ratio), and total antioxidant capacity assays. Molecular markers such as Nrf2 nuclear translocation (WB, immunofluorescence, HO-1 expression (qPCR, WB), Antioxidant gene expression (SOD1, SOD2, CAT, GPx), 8-OhdG (oxidative damage marker).

The most frequently reported parameters included reductions in ROS levels, decreases in lipid peroxidation biomarkers such as MDA, and increases in antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). Several studies also documented the activation of antioxidant molecular pathways, such as Nrf2 and HO-1, as well as improvements in mitochondrial function, indicated by enhanced mitochondrial membrane potential and ATP production.

In addition to oxidative stress modulation, a number of studies reported secondary outcomes, including reductions in inflammatory mediators (TNF-α, IL-6, NF-κB), inhibition of apoptosis, increases in neurotrophic factors (BDNF, NGF, GDNF), and improvements in cognitive and motor functions in *in vivo* models.

Table 2. Characteristics of all studies organized by Parkinson's disease

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
El Mahdy et al., 2023	***In vitro:*** MSC culture ***In vivo:*** mice induced rotenone 1.5 mg/kg over 2 weeks	EPO-activated vs laser-activated bone marrow MSCs	ELISA	5 × 10^5 BM-MSC	Laser-activated BM-MSCs showed best ROS reduction, neuroprotection, and homing
Minoia et al., 2025	***In vitro:*** human bone marrow MSCs ***In vivo:*** Zebrafish	Homotaurine + MSCs	Flowcytometry	MSCs: 100uM homotaurine Zebrafish: 0.5 mM homotaurine	decrease ROS MSC aging, p21, increase viability and sestrin 1, marker osteogenesis, VEGFR1 in Zebrafish aging, RUNX2, and restoring β-catenin,
Ramalingam et al., 2022	***In vitro:*** rotenone-induced in SH-SY5Y human neuroblastoma cells	Neuro-induced ADSC-conditioned medium	H2DCFDA ROS assay read with fluorescence microplate reader	NI-hADSC-CM 50% (in DMEM + 1% FBS) against ROT 0.5 µM	Restored autophagy markers, ↓ ROS, ↑ p62, normalized lysosomal proteins
Ji et al., 2023	***In vitro:*** Human iPSCs	Cerebral organoid vs MSC-derived exosomes	DHE-based fluorescence imaging	100 µg/mL exosome for 48 hours or 14 – 28 days for iPSCs	Decrease ROS and lipid peroxidase, ↑ dopaminergic differentiation via LMX1A pathway
Labunets et al., 2025	***In vivo:*** mice	hUC-MSCs vs EVs	SOD, CAT, GPx, GR, and MDA (TBARS) in brain, read with spectrophotometer	5×10^5 cells/mice	hUC-MMSCs and their EVs improve CNS function in Parkinsonism by suppressing neuroinflammation and oxidative stress. EVs are superior in modulating macrophages and antioxidant enzymes and do not impair cognition.

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Essawy et al., 2024	***In vivo:*** rat	IV vs intracranial MSCs	TBARS assay, Nitric oxide (NO), GSH, SOD, and CAT.	BM-MSC 1×10^4 cells/5 µL CCM (intrastriatal), 1×10^6 cells/1 mL CCM (intravenous)	Both routes ↓ ROS, ↑ TH, restored DA; IV safer
Gonmanee et al., 2025	***In vitro:*** SH-SY5Y cells	Mitochondria isolated from human dental pulp stem cells (hDPSCs) to SH-SY5Y cells that have been exposed to MPP	DCFDA/H_2DCFDA ROS assay read with fluorescence microplate reader	100 µg mitochondria per 10^5 cells for 24 hours	Restored Complex I, decreased ROS, increased GAP43, TH, and DAT
Asemi-Rad et al., 2022	***In vivo:*** rats	ADSC-derived dopaminergic neurons + melatonin	GSH as marker of ROS	Combination of ADSC dopaminergic neuron transplantation + melatonin 20 mg/kg/day	↑ GSH, ↓ caspase-3, ↑ neuron survival, improved PD symptoms
Zhang et al., 2023	***In vitro:*** BV2 (microglia) and SH-SY5Y (neuron) ***In vivo:*** rats induced with MPTP 30 mg/kg	Exosome-AK76, Exosome-AK76 +Quercetin	DCFH-DA using flow cytometry	***In vitro:*** Exosome + Quercetin 25 ug/mL ***In vivo:*** Exosome + Quercetin 2 mg/kg	↓ ROS, ↑ autophagy (LC3-II), ↑ motor function, ↓ depression-like symptoms
Lei et al., 2024	***In vitro:*** SH-SY5Y and BV2 ***In vivo:*** SH-SY5Y	MSC-derived neuron-like membrane NPs	DCFH-DA fluorescence microscope	***In vitro:*** 4mM for 24 days ***In vivo:*** 100 mg/kg for 2 days	Decrease of ROS and apoptosis, increase of dopamine and mitochondrial potential

Table 3. Characteristics of all studies organized by Parkinson's disease

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Soto-Mercado et al., 2020	***In vitro:*** MSC from patient with PSEN1 E280A mutations	MSC-derived cholinergic-like neurons	H2O2 by flow cytometry	100 mg/kg for 2 days	↑ ROS, TAU phosphorylation; JNK inhibitor blocked damage
Gomez-Sequeda et al., 2024	***In vitro:*** cholinergic-like neurons (ChLNs) with mutation of PSEN1 I416T	Tramiprosate + Curcumin + SP600125	DCFH$_2$-DA, by flow cytometry	10–20 µM	↓ ROS, ↓ TAU, restored Ca^{2+} influx; multitarget synergy
Li et al., 2023	***In vitro:*** SH-SY5Y ***In vivo:*** mice	PDMAEMA-berbasis BAP polymer, MSC-derived exosomes, siRNA-loaded MSC-exosomes	DCFDA by flow cytometry	N/A	↓ BACE1 & caspase-3, ↓ ROS, restored memory in 3xTg-AD mice
Zavatti et al., 2022	***In vitro:*** SH-SY5Y neuroblastoma cells treated with Aβ	hAFSC-derived exosomes	DCFH-DA	0,5×10^9 exosome/10^6 cells	↓ ROS, ↓ apoptosis, preserved microglia & neurons
Ma et al., 2025	***In vitro:*** AD organoid from human iPSCs	3D bioreactor MSC-EVs	DCFH-DA	1×10^8 EV/mL	↑ EV yield, ↓ ROS, ↓ NF-κB, suppressed cytokines
Zhang et al., 2023	***In vitro:*** BV2 ***In vivo:*** rat	MSC-exosomes	DCFH-DA	MSC-Exos 50 µg/mL	↑ SIRT1, ↓ ROS, ↓ apoptosis, restored cognition in SAMP8 mice

Table 4. Characteristics of all studies organized by Amyotrophic Lateral Sclerosis (ALS) models

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Dabrowska et al., 2024	***In vitro:*** SIM-A9 microglia expressing hSOD1(G93A) mutation	Adipose MSC-derived EVs	DCFDA assay	EVs 50 µg/mL for 24h	Reduced ROS and NO production, shifted microglia from M1 to M2 anti-inflammatory phenotype

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Provenzano et al., 2022	***In vitro:*** astrocytes from ALS rats ***In vivo:*** SOD1-G93A transgenic ALS rats	MSC-EVs engineered with miRNA mimics (miR-466i-5p)	EVs 10^9 particles intrathecal injection	DHE, Nrf2 nuclear translocation (immunofluorescence)	↓ ROS in astrocytes, ↑ Nrf2 activation, ↓ neuroinflammation, ↑ motor neuron survival
Kook et al., 2020	***In vivo:*** SOD1-G93A transgenic ALS mice	Repeated intramuscular human umbilical cord blood MSCs (hUCB-MSCs)	DHE staining, iNOS expression	1×10^6 cells IM every 2 weeks from 8 weeks of age	↑ HO-1 & Nrf2; ↓ IL1β, IL6, TNFα; ↑ BDNF & GDNF; neuroprotective effect on PC-12 and HMC3 cells

Table 5. Characteristics of all studies organized by aging & brain aging models

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Barilani et al., 2022	***In vivo:*** Human bone marrow-derived MSCs from young vs aged donors	Comparison study (no treatment, observational)	MitoSOX, MitoTracker, Seahorse XF analyzer for mitochondrial respiration, GSH/GSSG ratio	N/A	Aged MSCs showed ↓ mitochondrial membrane potential, ↑ basal ROS, but compensated by ↑ glutathione system; maintained immunomodulatory capacity

Table 6. Characteristics of all studies organized by multiple sclerosis & demyelination models

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Barkat et al., 2019	***In vivo:*** rat	Adipose MSCs	SOD, MDA	1×10^6 AD-MSC intravenously in 500 µL medium, once, after 6 weeks of 0.2% cuprizone	↑ remyelination; ↓ oxidative stress; ↑ motor and cognitive function
Soumya et al., 2025	***In vitro:*** MSC	Adipose MSCs	DCFH-DA	N/A	↑ remyelination, ↓ oxidative stress, ↑ motor/cognitive function

Table 7. Characteristics of all studies organized by neurotoxicity & neuroinflammation models

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Hernández-Pérez et al., 2022	***In vitro:*** MSC	MSC + RSV + CoQ10	ROS intracellular with Fluorometric Intracellular ROS Kit	Resveratrol 2.5 µM + CoQ10 10 µM	↑ viability, ↓ LDH & ROS, ↑ neural differentiation
Ibrahim et al., 2025	***In vivo:*** rat	MSC-Exo + Olea leaf hydrogel	ELISA	Lipo-OLE-Hydrogel 50 mg/kg/day orally + MSC-Exo 50 µg i.p. weekly for the last 4 weeks of HFD	↓ ROS, ↓ TNF-α, ↑ Bcl-2, restored memory & neurotransmitters
Mateo et al., 2025	***In vitro:*** PC12 cell	hUCESC secretome	mRNA expression of Nrf2 and HO-1	H_2O_2 400 µM as a stress inducer + full hUCESC-CM on PC-12; LPS 5 µg/mL + hUCESC-CM on PC-12; IL-1β 10 ng/mL + IFN-γ 10 ng/mL + hUCESC-CM on HMC3	↑ HO-1 & Nrf2; ↓ IL1β, IL6, TNFα; ↑ BDNF & GDNF; neuroprotective effect on PC-12 and HMC3 cells
Zaazaa et al., 2022	***In vivo:*** neurodegenerative disorders induced by cadmium in rats	MSC-derived exosomes + CuSNPs	ROS Assay Kit	combination of MSCs-exosomes (100 µL, single intravenous injection) and CuSNPs 6.5 mg/kg orally for 30 days after cadmium exposure	↑ TAC, BDNF, NGF; ↓ ROS, NF-κB, TNF-α; improved histology and behavior
Abdel Halim et al., 2025	***In vitro:*** bmMSC ***In vivo:*** rats	BM-MSCs	SOD, GSH, and MDA	a single intraperitoneal injection of 1×10^7 MSCs in 0.2 mL physiological NaCl, given after acrylamide 50 mg/kg/day i.p. for 2 weeks	↑ IGF-1, BDNF, NGF; ↓ ROS, ↓ IL-6, TNF-α
Khushi et al., 2025	***In vitro:*** hucMSCs	Engineered hucMSC-derived EVs + CHPG	DCFH-DA	N/A	↑ macrophage migration & proliferation; ↓ cell death; mitigated oxidative stress via mGluR5 agonist

Table 8. Characteristics of all studies organized by other oxidative stress models

Author	Research Model	Treatment	ROS Measurement Method	Dose	Key Result
Puig-Pijuan et al., 2020	***In vitro:*** Primary hippocampal culture	Wharton's jelly MSCs vs EVs	CM-H_2DCFDA	2,1×10^4 cell	↓ ROS; MSCs > EVs in viability protection
Monroe et al., 2025	***In vitro:*** hB-MSC	hBM-MSCs + EZH2 inhibitor	H_2O_2	GSK126 20 µM	↓ chromatin compaction, ↓ DNA damage, modulated epigenetics
Usategui-Martín et al., 2022	***In vitro:*** bmMSC	Bone marrow MSC secretome	Gene expression of COX2, CYBA, CYBB, GPX6, SOD1, TXN2, TXNRD1 by qRT-PCR	bmMSC secretome medium (0.75 mL secretome + 0.75 mL fresh medium per 1.5 mL total) for 72 hours in neuroretinal culture	Preserved retinal morphology, ↓ apoptosis & necroptosis markers, ↑ antioxidant gene expression, modulated autophagy
Teli et al., 2022	***In vitro:*** neuro 2-a cell	MSC-secretome	DCFH-DA/H_2DCFDA	N/A	Restored neurite outgrowth, ↑ neuronal markers, ↓ ROS
Lin et al., 2024	***In vitro:*** Wharton's jelly mesenchymal stem cells	Miro1-overexpressed WJ-MSC mitochondria	DCFH-DA/H_2DCFDA	N/A	↑ ATP, ↓ ROS, ↑ proliferation; did not alter mtDNA mutation

Table 9. Intervention of MSC

Intervention	Studies	Effect
MSC-derived exosomes/EVs	15	↓ ROS, ↑ SOD, modulate microglia, deliver miRNA
Conditioned medium/secretome	6	↑ Nrf2, ↓ MDA, anti-inflammatory, neurotrophic support
MSC direct transplantation	8	↑ TH neurons, ↓ apoptosis, ↑ motor function
MSC-derived mitochondria	2	↑ ATP, ↓ ROS, restore mitochondrial function

Intervention	Studies	Effect
MSC-derived neurons/organoids	3	Disease model, TAU phosphorylation, cholinergic markers
Engineered MSC-EVs/nanoparticle	3	Targeted delivery, ↑ uptake, ↓ glutamate toxicity

DISCUSSION

This narrative review of 33 included articles demonstrated that mesenchymal stem cells (MSCs) and their derivatives, including extracellular vesicles (EVs), secretome, and mitochondrial transfer, consistently play a role in reducing oxidative stress across various neurodegenerative disease models. The findings are organized thematically by disease to facilitate comparison and to highlight disease-specific mechanisms and methodological approaches.

MSC-based interventions in Parkinson's disease

The most frequently studied diseases were Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (ALS), all of which are pathogenetically characterized by oxidative stress and mitochondrial dysfunction as central mechanisms. The predominance of EV- and secretome-based approaches indicates a paradigm shift from whole-cell therapies toward secretory product-based strategies, which are considered safer and potentially more translatable due to lower risks of immunogenicity and tumorigenesis (Issa et al., 2025).

Parkinson's disease, characterized by progressive dopaminergic neuronal degeneration in the substantia nigra, consistently demonstrated oxidative stress reduction following MSC-based interventions. ROS levels were measured using DCFDA, DHE, fluorescent probes, alongside biochemical assays such as MDE, SOD, and glutathione parameters. Several studies revealed that the effectiveness of MSC-based therapies is strongly influenced by the biological condition and preconditioning of cells prior to therapeutic application. Preconditioning MSCs with erythropoietin or low-level laser therapy enhanced cell viability, homing ability, and neuroprotective effects through reduced oxidative stress and modulation of neuroinflammatory responses (El Mahdy et al., 2023). Underscoring the importance of MSC preparation protocols.

In various *in vitro* Parkinson's disease models, including rotenone-induced SH-SY5Y cells and H_2O_2-based oxidative stress models, MSC-derived secretome and EVs reduced ROS production, modulated autophagy pathways, and promoted dopaminergic neuronal differentiation (Ji et al., 2023; Minoia et al., 2025; Ramalingam et al., 2022). Notably, different ROS measurement methods revealed distinct aspects of oxidative damage: DCFDA detected general cellular ROS, while MitoSOX specifically measured mitochondrial superoxide, demonstrating mitochondria-targeted protection.

In vivo studies further demonstrated that MSC transplantation via intravenous or intracranial routes improved motor function, increased dopamine levels and tyrosine hydroxylase expression, and preserved dopaminergic neuronal integrity (Essawy et al., 2024). Beyond cell and secretome-based approaches, mitochondrial support strategies such as mitochondrial transfer from dental pulp stem cells and MSC therapy combined with melatonin consistently reduced neuronal apoptosis and oxidative stress in PD models (Asemi-Rad et al., 2022; Gonmanee et al., 2025). These findings confirm that modulation of oxidative stress, inflammation, and mitochondrial function are key mechanisms underlying the neuroprotective effects of MSCs in Parkinson's disease.

MSC-based interventions in Alzheimer's disease

Alzheimer's disease, characterized by the accumulation of amyloid-beta (Aβ) plaques and tau neurofibrillary tangles leading to progressive cognitive decline, showed significant oxidative stress reduction with MSC-based interventions (Ballard et al., 2011). MSC-based approaches and their derivatives have also demonstrated significant potential to mitigate oxidative injury and neurodegeneration. Human amniotic fluid-derived MSC exosomes were reported to preserve microglial and neuronal viability, while reducing oxidative stress and apoptosis in β-amyloid-exposed *in vitro* models (Zavatti et al., 2022). This study demonstrated dose-dependent effects with 50 µg/mL exosomes providing optimal protection. Multi-target strategies, such as combining tramiprosate, curcumin, and JNK inhibitors in cholinergic-like neurons with PSEN1 I416T mutation, reduced ROS, TAU phosphorylation, and apoptosis, emphasizing the importance of oxidative stress modulation in slowing Alzheimer's pathology (Gomez-Sequeda et al., 2024). Calcium dysregulation (measured by Fluo-4 AM) was also restored, linking oxidative stress to calcium homeostasis disruption in familial AD. Furthermore, siRNA delivery using MSC-derived exosomes via the nose-to-brain route targeting BACE1 and caspase-3 improved CNS delivery efficiency (measured by fluorescent tracking) and enhanced antioxidant effects, reducing both ROS (DHE assay) and oxidative DNA damage (8-OHdG immunostaining) while improving spatial memory in 3xTg-AD mice (Li et al., 2023). The intranasal route offered non-invasive delivery with enhanced brain bioavailability compared to systemic administration.

MSC models transdifferentiated with PSEN1 E280A mutation recapitulated Alzheimer's-specific oxidative stress and mitochondrial dysfunction (decreased mitochondrial membrane potential measured by JC-1), serving as critical platforms for mechanistic studies and therapeutic evaluation (Soto-Mercado et al., 2020). These patient-derived models revealed that JNK pathway inhibition blocked oxidative damage, identifying a key therapeutic target.

MSC-based interventions in amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS) models, marked by motor neuron degeneration affecting voluntary muscle control, showed consistent neuroprotection through MSC-based modulation of oxidative stress and neuroinflammation (Duranti, 2025). In SIM-A9hSOD1(G93A) microglia, proinflammatory activation and increased oxidative stress contribute to neurodegenerative progression. Dabrowska et al. (2024) demonstrated that ASC-derived EVs reduced ROS production and promoted microglial polarization toward an anti-inflammatory phenotype, highlighting microglial polarization as a key mechanistic link between oxidative stress attenuation and reduced neuroinflammation, thereby supporting the therapeutic potential of EV-based strategies in ALS.

Similarly, engineered MSC-EVs loaded with miRNA mimics (miR-466i-5p) delivered intrathecally (10^9 particles) activated Nrf2 antioxidant pathways (nuclear translocation confirmed by immunofluorescence), reduced astrocytic ROS (DHE staining), and improved motor neuron survival in SOD1-G93A transgenic rats (Provenzano et al., 2022). Repeated intramuscular administration of human umbilical cord blood MSCs (1×10^6 cells every 2 weeks) activated AMPK signaling, reduced oxidative stress (DHE staining) and iNOS/NO signaling (Western blot), and extended survival in ALS mice (Kook et al., 2020). Notably, these protective effects are closely linked to the biological quality of MSCs as EV sources; MSCs from elderly donors exhibit bioenergetic and mitochondrial adaptations without functional decline, maintaining immunomodulatory capacity, although younger donor cells may confer greater therapeutic potency (Barilani et al., 2022).

Other neurodegenerative and neuroinflammatory models

More broadly, studies in neurodegenerative and neuroinflammatory models consistently demonstrated the protective effects of MSCs and their derivatives through oxidative stress reduction and modulation of inflammatory responses. *In vivo* models of cognitive impairment induced by high-fat diets and *in vitro* models of microglia and neurons exposed to oxidative stress showed that MSC-derived EVs and secretome reduced ROS production, improved mitochondrial function, and suppressed proinflammatory microglial activation (Ibrahim et al., 2025; Mateo et al., 2025; Zhang et al., 2023). Nrf2/HO-1 pathway activation was consistently observed across multiple studies, measured by nuclear translocation (immunofluorescence), mRNA expression (qPCR), and protein levels (Western blot), confirming this as a central mechanism of MSC-mediated antioxidant protection. 3D bioreactor culture increased EV production by approximately 10-fold while maintaining or enhancing functional properties. Combination approaches using bioactive agents or biomaterials such as MSC exosomes combined with copper sulfide nanoparticles, olive leaf extract hydrogels, or quercetin-loaded dendrimers further enhanced stability, delivery efficiency, and therapeutic efficacy of MSC-based interventions (Ibrahim et al., 2025; Zaazaa et al., 2022).

At the molecular level, the most frequently reported mechanisms included activation of antioxidant pathways (Nrf2/HO-1), increased endogenous antioxidant enzymes (SOD, CAT, GPx), and reductions in oxidative damage biomarkers such as ROS, MDA, and 8-OhdG (Angeloni et al., 2020). The diversity of measurement methods employed across studies—ranging from fluorescent probes (DCFDA, DHE, MitoSOX) to biochemical enzyme assays (SOD, CAT, GPx) to molecular markers (Nrf2 translocation, HO-1 expression)—provides comprehensive evidence for multi-level antioxidant effects. These molecular effects were accompanied by functional improvements, including increased dopaminergic neurons (TH+), enhanced cognitive and motor functions, and reduced apoptosis and inflammation. Several studies also emphasized the role of neurotrophic factors such as BDNF, IGF-1, and MSC-derived microRNAs as additional mediators reinforcing neuroprotective effects (Issa et al., 2025).

Translational perspectives and future directions

Despite convergent evidence for antioxidant and neuroprotective actions, several factors limit the generalizability and translational readiness of MSC-based strategies. First, MSCs were derived from diverse tissue sources (bone marrow, adipose, umbilical cord, Wharton's jelly, dental pulp, amniotic fluid), with donor age, health status, and culture conditions introducing further heterogeneity (Mushahary et al., 2018; Pittenger et al., 2019). These variables affect proliferation, secretome composition, and immunomodulatory capacity, complicating cross-study comparisons and standardization.

Second, exosome and EV characterization was often incomplete relative to MISEV2018 recommendations, with inconsistent reporting of particle counts, marker profiles (CD9, CD63, CD81, TSG101), contaminant exclusion, and morphology. This limits the assessment of purity and comparability across preparations and highlights the need for ISEV-compliant characterization in future work. Third, dosing and routes of administration varied widely, and pharmacokinetic data were scarce. Few studies systematically explored dose-response relationships or optimal timing, and routes ranged from intravenous and intracranial to intranasal, intrathecal, and intramuscular, each with distinct biodistribution and safety implications.

Finally, preclinical safety data remain limited. Potential concerns include unwanted differentiation, immunogenicity (particularly with allogeneic cells), pro-tumorigenic effects, thromboembolic events for MSCs, and off-target or cargo-related risks for EVs (Lalu et al., 2012). Regulatory translation will require

GMP-compliant production of cells and EVs, rigorous quality control, and well-designed clinical trials to establish safety, dosing, and efficacy.

Limitations of this review

This work is a narrative rather than a PRISMA-compliant systematic review. No protocol was prospectively registered, no formal risk-of-bias tool (e.g., SYRCLE, RoB2, ROBINS-I) was applied, and data extraction was not performed in duplicate using systematic review procedures. The included studies are highly heterogeneous with respect to disease models (*in vitro*, *in vivo*, limited human data), species, MSC sources, intervention types, doses, and routes, oxidative stress assays, and follow-up duration. Most evidence is preclinical and short-term, and the durability of effects and long-term safety are largely unknown. These limitations preclude meta-analysis and require cautious interpretation when extrapolating to human disease.

CONCLUSION

This narrative review indicates that MSCs and their derivatives, particularly EVs, secretome, and mitochondrial transfer approaches consistently modulate oxidative stress in diverse neurodegenerative disease models. Across studies, MSC-based interventions were associated with reductions in ROS and oxidative damage markers, activation of endogenous antioxidant pathways such as Nrf2/HO-1, improvements in mitochondrial function, and attenuation of inflammation and apoptosis, which together support neuroprotective and regenerative effects in preclinical settings. At the same time, substantial heterogeneity in MSC sources, EV characterization, dosing regimens, routes of administration, and outcome measures, combined with the predominance of animal and *in vitro* studies, limits the strength of conclusions regarding clinical effectiveness. Future research should prioritize standardized MSC and EV characterization (in line with ISEV/MISEV guidelines), systematic exploration of dose–response and pharmacokinetics, long-term safety assessments, and rigorously designed clinical trials. Addressing these methodological and translational gaps will be essential to determine whether MSC-based, cell-free therapies can be safely and effectively applied to human neurodegenerative diseases.

AUTHOR CONTRIBUTIONS

NRG: Conceptualization, Methodology, Software, Writing – Original draft, Formal analysis, Investigation, Supervision. **PEP**: Methodology, Software, Writing – Original draft, Formal analysis, Investigation, Data curation. **AS**: Methodology, Software, Writing – Original draft, Formal analysis, Investigation, Data curation. **HR**: Formal analysis, Investigation, Data curation, Writing – Review & editing. **AR**: Formal analysis, Investigation, Data curation, Writing – Review & editing. **BAS**: Formal analysis, Investigation, Data curation, Writing – Review & editing. **IB**: Formal analysis, Investigation, Data curation, Writing – Review & editing.

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COMPETING INTERESTS

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