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American Journal of Pharmacotherapy and Pharmaceutical Sciences

Review Article *Neurosciences and Behavioral Sciences*

Role of exosomes in nerve regeneration: Systematic review

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Received: 28 February 2024
Accepted: 29 July 2024
Published: 14 June 2025

DOI
10.25259/AJPPS_2025_009

Quick Response Code:

ABSTRACT

Exosomes, small extracellular vesicles secreted by cells, have emerged as a promising therapeutic approach for promoting neuroregeneration after neurological injury or disease. This systematic review aims to consolidate the current evidence on the role of exosomes in nerve regeneration. Electronic databases including PubMed, Ovid Medline, Cochrane Library, Embase, Psychinfo, SportDiscus, CINAHL, Proquest Health and Science, SCOPUS, and Web of Science were searched until January 2024 to identify studies investigating exosome-based therapies for nerve regeneration in animal models. Inclusion criteria were studies using exosomes derived from various cell sources and evaluating outcomes related to nerve repair and functional recovery. Data was extracted on exosome sources, transplantation methods, animal models, and quantitative measures of neuroregeneration. Study quality was assessed using the SYRCLE risk of bias tool. Sixty-one studies conducted predominantly in rodent models with sciatic nerve injury, were included in the study. Mesenchymal stem cells, Schwann cells, and induced pluripotent stem cells were the major sources of therapeutic exosomes. Exosomes were commonly delivered through local injection or incorporation into nerve conduits. Treatment improved axonal regrowth, remyelination, functional recovery, and attenuated muscle atrophy. Molecular analyses revealed enhanced neurotrophic signaling and angiogenesis. However, the risk of bias was high across most studies. Conclusion: Exosome therapy augments nerve regeneration in preclinical models through multifaceted mechanisms. Further high-quality studies in larger animal models are warranted to validate efficacy and elucidate optimal exosome sources and delivery approaches before clinical translation.

Keywords: Animal models, Exosomes, Extracellular vesicles, Mesenchymal stem cells, Nerve regeneration, Schwann cells

INTRODUCTION

Neurological disorders are a leading cause of disability and death globally. In India, these disorders are significant contributors to the neurological disorder burden.[1] Complete recovery from neurological disorders is dependent on neuroregeneration. Neuroregeneration is crucial for restoring function lost due to neurological diseases while aiming to repair or replace damaged neural tissue. Among emerging approaches, exosome-mediated therapies are notable for their potential in neuroregeneration and offering innovative ways to enhance recovery.[2-4] Exosomes facilitate communication between cells and can deliver therapeutic molecules, promoting neuronal regeneration and functional recovery. Their ability to cross biological barriers,

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biocompatibility, and capacity to carry and protect therapeutic agents are key advantages.[3]

With the evolving landscape of exosome research in neuroregeneration, there is a need for systematic reviews to show gaps in current knowledge and the potential for significant impact.[4] Given the rapid advancements and diverse methodologies in the field, a systematic review is essential to consolidate evidence, identify effective strategies, and guide future research directions.

MATERIALS AND METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed in the study design.[5] The online tool was used to generate the PRISMA diagram [Figure 1].[6]

Literature search

Up to January 2024, published articles on exosomes and nerve regeneration were selected from PubMed, Ovid Medline, Cochrane Library, Embase, Psychinfo, SportDiscus, CINAHL, Proquest Health and Science, SCOPUS, and Web of Science for inclusion in this review. The words "exosomes" and "nerve regeneration" were combined with traumatic brain injury as well as various Boolean (OR, AND) and wildcard operators to create the search equations. Full-text papers and abstracts were taken into consideration. Every title and abstract were examined by two investigators to ensure eligibility.

The inclusion and exclusion criteria for each article were applied by the same two investigators after they got the full texts of possibly eligible research. One investigator (SA) looked through the reference lists of all the included articles to find other investigations.

The web and mobile application Rayyan®,[7] which has been verified for systematic searches was used to group and sync all the studies that were found throughout the search.[7] The two investigators, SA and JPJ, conducted a double-blind search based on the title and abstract for the first bibliographic review. Following their consensus-building throughout the search phase, the two investigators SA and VCRA separately examined the entire text. In the selection stage, the studies meeting the qualifying requirements were considered.

The authors SA, AKE, SKA, VCRA, and JPJ discussed and resolved any issues until they came to a consensus. The data

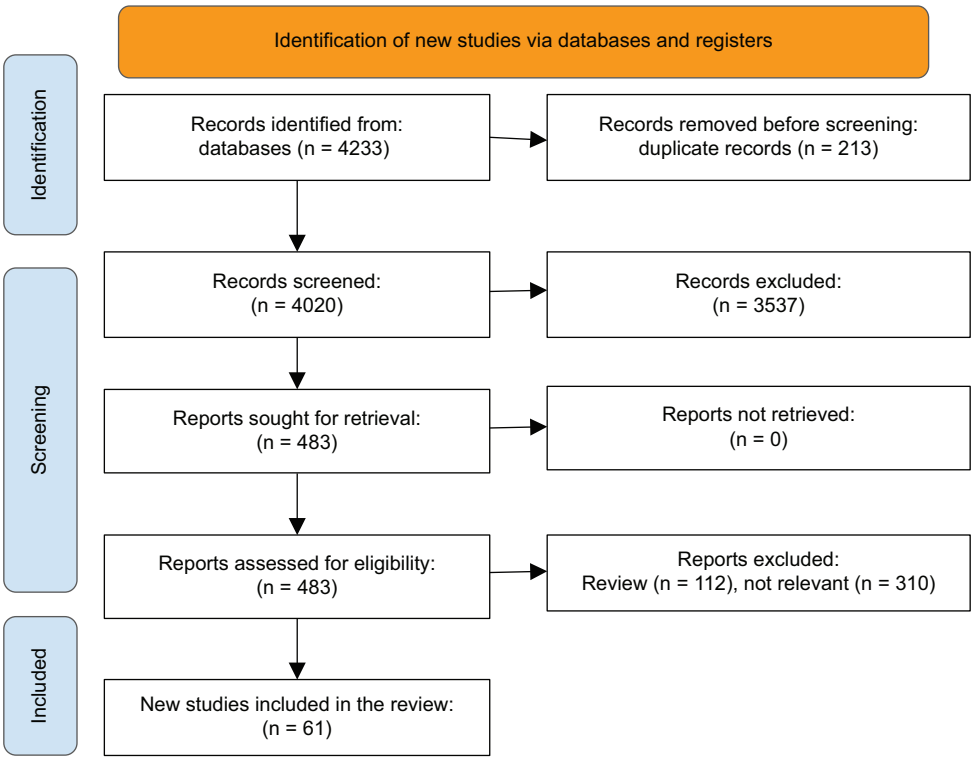

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

was then separately extracted by the two authors AKE and SKA using a database made in Microsoft Excel® software (version 2013) from the articles that were included in the eligibility phase. The third author resolved disagreements.

Data extraction and analysis methods

The characteristics and results of the investigation were extracted using an *a priori* data extraction form. One author (SA) extracted the data. We documented the author, publication year, nation, exosome source, model, animal type (species, strain, and sex), therapy (dosage, timing, and mode of administration), and results from the studies, we included the following outcomes: injury volume, functional recovery, and brain repair markers. For statistical significance, $P < 0.05$ was taken into account.

Quality assessment of included studies

The quality score estimate approach which is a checklist [Table 1] for each preclinical investigation to analyze the animal data from experimental studies was utilized. It defined ten criteria based on SYRCLE recommendations.[8]

RESULTS

Quality score

Only one out of 61 studies was rated as having a low risk of bias for random sequence generation. The rest of the studies provided insufficient data for this assessment. Only two studies were rated as having a low risk of bias for allocation concealment. The rest of the studies provided insufficient data for this assessment. None of the studies were rated as having a low risk of bias for blinding of caregivers/investigators. Most were unclear. Only two studies were rated as having a low risk of bias for blinding of outcome assessors. The rest of the studies provided insufficient data for this assessment. Only three studies were rated as having a low risk of bias for incomplete outcome data. The rest of the studies provided insufficient data for this assessment. Only four studies were rated as having a low risk of bias for selective reporting. The rest of the studies provided insufficient data for this assessment. None of the studies were rated as having a low risk of bias for other potential sources of bias. All were unclear.

Sources of exosomes

Mesenchymal stem cells (MSCs) – either from bone marrow, adipose tissue, umbilical cord, or other tissues – were the most common source of exosomes, with 25 studies using MSC-derived exosomes. Schwann cells were the source of exosomes in ten studies. Induced pluripotent stem cells (iPSCs) were the source in two studies. Other cell types such as neurons, fibroblasts, endothelial cells, and platelets were each used in 1–2 studies. Nine studies did not specify or did not have access to the source of exosomes [Figure 2].

Transplantation approaches

Direct injection of exosomes into the injury site or localized tissues was used in 15 studies. Different injection sites included major pelvic ganglion, cavernous nerve, caudal vein, and wound sites. Loading exosomes into nerve conduits or grafts for transplantation was used in 12 studies. Exosomes were incorporated into various nerve conduits such as chitosan, collagen, and silk fibroin. Systemic intravenous injection was used in ten studies. No transplantation details were provided in nine studies.

Animal models

Rodents were the most common animal model, used in 67 studies. Rats were used in 58 studies, while mice were used in nine studies. Sprague-Dawley rats were the most popular rat strain, used in 44 studies. Wistar rats were used in eight studies. The sciatic nerve injury/defect model was the most common disease model, used in 55 studies. Other models such as cavernous nerve injury, cortical injury, and skin injury were each used in —one to two studies. Nine studies did not specify the animal model used.

Cells used

Schwann cells were the most used cell type, seen in 27 studies. They were often used for *in vitro* experiments and exosome collection. MSCs were used in 19 studies for exosome collection. Bone marrow and adipose tissue were common MSC sources. Dorsal root ganglion (DRG) neurons were used in five studies. Other cell types such as fibroblasts, macrophages, and endothelial cells were each used in —one to two studies.

Diverse study groups have been utilized to assess the therapeutic potential of exosome-mediated interventions across various models of nerve injury. The groups were delineated based on the type of nerve injury, the source of exosomes, and the regenerative strategies employed. Groups bridged with autografts, acellular nerve allografts, and iPSCs-derived exosomes to assess direct regenerative effects. Exosome treatment groups were compared with control groups to evaluate the efficacy of exosomal therapy.

Studies involving different concentrations of exosome preparations were done to establish dose-dependent effects on Schwann cell proliferation and nerve repair. Comparative analyses of exosome treatments derived from various cell types such as Schwann cells, adipose-derived stem cells, and bone marrow stromal cells were performed to determine the most efficacious source.

Table 1: Quality check of the studies using SYRCLE guideline.

Title	Year	1) Was the allocation sequence adequately generated and applied? (*)	2) Were the groups similar at baseline or were they adjusted for confounders in the analysis?	3) Was the allocation to the different groups adequately concealed during?	4) Were the animals randomly housed during the experiment?	5) Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	6) Were animals selected at random for outcome assessment?	7) Was the outcome assessor blinded?	8) Were incomplete outcome data adequately addressed? (*)	9) Are reports of the study free of selective outcome reporting? (*)	10) Was the study apparently free of other problems that could result in high risk of bias? (*)
Endothelial cell-derived exosomes boost and maintain repair-related phenotypes of Schwann cells through miR199-5p to promote nerve regeneration.	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes combined with biosynthesized cellulose conduits improve peripheral nerve regeneration.	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
LIPUS-SCs-Exo promotes peripheral nerve regeneration in cavernous nerve crush injury-induced ED rats through PI3K/Akt/FoxO signaling pathway.	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Doseâ€"response analysis after administration of a human platelet-derived exosome product on neurite outgrowth in vitro	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Controlled extracellular vesicles release from aminoguanidine nanoparticle-loaded polylysine hydrogel for synergistic treatment of spinal cord injury	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Low-temperature 3D-printed collagen/chitosan scaffolds loaded with exosomes derived from neural stem cells pretreated with insulin growth factor-1 enhance neural regeneration after traumatic brain injury	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Neuron-derived exosomes promote the recovery of spinal cord injury by modulating nerve cells in the cellular microenvironment of the lesion area	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes-loaded electroconductive nerve dressing for nerve regeneration and pain relief against diabetic peripheral nerve injury	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Fibroblast exosomal TFAP2C induced by chitosan oligosaccharides promotes peripheral axon regeneration through the miR-132-5p/CAMKK1 axis	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Human platelet-rich plasma-derived exosomes promote the proliferation of Schwann cells cultured in vitro	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Tissue-engineered core-shell silk-fibroin/poly-l-lactic acid nerve guidance conduit containing encapsulated exosomes of human endometrial stem cells promotes peripheral nerve regeneration	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
extracellular vesicles in peripheral nerve regeneration: extracellular vesicles derived from adipose stem cells increase Schwann cell proliferation following internalization	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Impact of mesenchymal stem cells derived laminin-binding extracellular vesicles on Schwann cells and in peripheral nerve regeneration processes	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Spatiotemporally deciphering peripheral nerve regeneration *in vivo* after extracellular vesicle therapy under NIR-II fluorescence imaging	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Chitosan nerve grafts incorporated with SKP-SC-EVs induce peripheral nerve regeneration	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Enhancing functional recovery after segmental nerve defect using nerve allograft treated with plasma-derived exosome	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
The effects of adipose-derived mesenchymal stem cells and adipose-derived mesenchymal stem cell-originating exosomes on nerve allograft regeneration: An experimental study in rats	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Sciatic nerve derived exosomes in promotion of axon regeneration and functional recovery following peripheral nerve injury in rat	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Muscle-derived stem cell exosomes with overexpressed miR-214 promote the regeneration and repair of rat sciatic nerve after crush injury to activate the JAK2/STAT3 pathway by targeting PTEN	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Neural grafts containing exosomes derived from Schwann cell-like cells promote peripheral nerve regeneration in rats	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Reduced graphene oxide-embedded nerve conduits loaded with bone marrow mesenchymal stem cell-derived extracellular vesicles promote peripheral nerve regeneration	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schwann cell exosomes as possible therapeutic intervention to enhance axonal regeneration after peripheral nerve injury	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Hypoxic culture of umbilical cord mesenchymal stem cell-derived sEVs prompts peripheral nerve injury repair	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Repair of peripheral nerve defects by nerve grafts incorporated with extracellular vesicles from skin-derived precursor Schwann cells	2021	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Acellular nerve grafts supplemented with induced pluripotent stem cell-derived exosomes promote peripheral nerve reconstruction and motor function recovery	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Biomimetic nerve guidance conduit containing engineered exosomes of adipose-derived stem cells promotes peripheral nerve regeneration	2021	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Human umbilical cord mesenchymal stem cell-derived extracellular vesicles promote the proliferation of Schwann cells by regulating the PI3K/AKT signaling pathway through transferring miR-21	2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Extracellular vesicles from skin precursor-derived Schwann cells promote axonal outgrowth and regeneration of motoneurons through Akt/mTOR/p70S6K pathway	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Efficacy of exosomes in peripheral nerve injury	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes derived from Schwann cells ameliorate peripheral neuropathy in type 2 diabetic mice	2020	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear
Mesenchymal stem cell derived extracellular vesicles enhance myelin plasticity in rhesus monkeys	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Therapeutic advances of stem cell-derived extracellular vesicles in regenerative medicine	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Adipose stem cell-derived extracellular vesicles induce proliferation of schwann cells through internalization	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes from LPS-preconditioned bone marrow MSCs accelerated peripheral nerve regeneration through M2 macrophage polarization: Involvement of TSG-6/NF-Î²B/NLRP3 signaling pathway	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes derived from umbilical cord mesenchymal stem cells treat cutaneous nerve damage and promote wound healing	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Combination of olfactory ensheathing cells and human umbilical cord mesenchymal stem cell-derived exosomes promotes sciatic nerve regeneration	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Dose-effect relationship and molecular mechanism by which BMSC-derived exosomes promote peripheral nerve regeneration after crush injury	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Mechanical stimulation of Schwann cells promote peripheral nerve regeneration through extracellular vesicle-mediated transfer of microRNA 23b-3p	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Extracellular vesicles derived from olfactory ensheathing cells promote peripheral nerve regeneration in rats	2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gingiva-derived mesenchymal stem cell-extracellular vesicles activate Schwann cell repair phenotype and promote nerve regeneration	2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes produced by adipose-derived stem cells inhibit Schwann cells autophagy and promote the regeneration of the myelin sheath	2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Mesenchymal stem cell-derived exosomes promote recovery of the facial nerve injury through regulating macrophage M1 and M2 polarization by targeting the P38 MAPK/NF-Kb pathway	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes from human gingiva-derived mesenchymal stem cells combined with biodegradable chitin conduits promote rat sciatic nerve regeneration	2019	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Stem cell-derived exosomes as therapeutic agents for nerve repair	2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Endocytosis-associated patterns in nerve regeneration after peripheral nerve injury	2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schwann cellâ€like cells derived from human amniotic mesenchymal stem cells promote sciatic nerve repair through an exosomeâ€induced SOX2/FN1 pathway inÂ vitro	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Muscle-derived extracellular vesicles influence motor neuron regeneration accuracy	2019	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Unclear
Low-stiffness hydrogels promote peripheral nerve regeneration through the rapid release of exosomes	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes from hair follicle epidermal neural crest stem cells promote acellular nerve allografts to bridge rat facial nerve defects	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Ultrasound-targeted microbubble destruction assisted delivery of platelet-rich plasma-derived exosomes promoting peripheral nerve regeneration	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes from human adipose-derived stem cells promote sciatic nerve regeneration through optimizing Schwann cell function	2019	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Effect of exosomes from adipose-derived stem cells on peripheral nerve regeneration	2018	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Upregulated lncARAT in Schwann cells promotes axonal regeneration by recruiting and activating proregenerative macrophages	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Enhanced nerve regeneration by exosomes secreted by adipose-derived stem cells with or without FK506 stimulation	2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schwann cellâ€derived exosomes induce bone marrowâ€derived mesenchymal stem cells to express Schwann cell markers inÂ vitro.	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Xenogenic neural stem cell-derived extracellular nanovesicles modulate human mesenchymal stem cell fate and reconstruct metabolomic structure	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schwann cell reprogramming into repair cells increases micro RNA-21 expression in exosomes promoting axonal growth	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Human umbilical cord mesenchymal stem cell-derived exosomes loaded into a composite conduit promote functional recovery after peripheral nerve injury in rats	2024	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomal miR-673-5p from fibroblasts promotes Schwann cell-mediated peripheral neuron myelination by targeting the TSC2/mTORC1/SREBP2 axis	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Administration of purified exosome product in a rat sciatic serve reverse autograft model	2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Additive manufacturing of Schwann cell-laden collagen/alginate nerve guidance conduits by freeform reversible embedding regulate neurogenesis through exosomes secretion towards peripheral nerve regeneration	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Effect of exosomes from adiposeâ€derived stem cells on the apoptosis of Schwann cells in peripheral nerve injury:' Corrigendum	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schwann cell exosomes mediate neuronâ€"glia communication and enhance axonal regeneration	2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Schwann cell-derived exosomes enhance axonal regeneration in the peripheral nervous system	2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
SHED-derived exosomes ameliorate hyposalivation caused by Sjögren's syndrome through Akt/GSK-3Î²/Slug-mediated ZO-1 expression	2023	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Human multipotent mesenchymal stromal cellâ€"derived extracellular vesicles enhance neuroregeneration in a rat model of sciatic nerve crush injury	2022	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Subventricular zone-derived extracellular vesicles promote functional recovery in rat model of spinal cord injury by inhibition of NLRP3 inflammasome complex formation	2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Modulating pro-inflammatory cytokines, tissue damage magnitude, and motor deficit in spinal cord injury with subventricular zone-derived extracellular vesicles	2020	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Electrical stimulation enhances neuronal cell activity mediated by Schwann cell derived exosomes	2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Extracellular vesicles from human umbilical cord mesenchymal stem cells improve nerve regeneration after sciatic nerve transection in rats	2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Effect of exosomes from rat adipose-derived mesenchymal stem cells on neurite outgrowth and sciatic nerve regeneration after crush injury	2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Neuromuscular regeneration: Perspective on the application of mesenchymal stem cells and their secretion products	2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Exosomes in neurological disease, neuroprotection, repair and therapeutics: problems and perspectives	2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

FN1: Fibronectin 1, SREBP2: Sterol regulatory element binding protein 2, SOX2: SRY-box transcription factor 2, CAMKK1: Calcium/calmodulin-dependent protein kinase kinase 1, mTORC1: Mammalian target of rapamycin complex 1, TSC2: Tuberous sclerosis complex 2, TFAP2C: Transcription factor AP-2 gamma, STAT3: Signal transducer and activator of transcription 3, JAK2: Janus kinase 2, LIPUS-SCs-Exo: Low-intensity pulsed ultrasound-Schwann cells-exosome, ED: Erectile dysfunction, NIR: Near-infrared, SKP-SC-EVs: Extracellular vesicles obtained from skin-derived precursor Schwann cells, PTEN: Phosphatase and tensin homolog, sEVs: Small extracellular vesicles, LPS: Lipopolysaccharide, MSCs: Mesenchymal stem cells, BMSCs: Bone derived mesenchymal stem cells, SHED: Stem cells derived from human exfoliated deciduous teeth. *The relevance of the above-mentioned items depends on the experiment. Authors of the review need to judge for themselves which of the above-mentioned items could cause bias in the results when not similar.

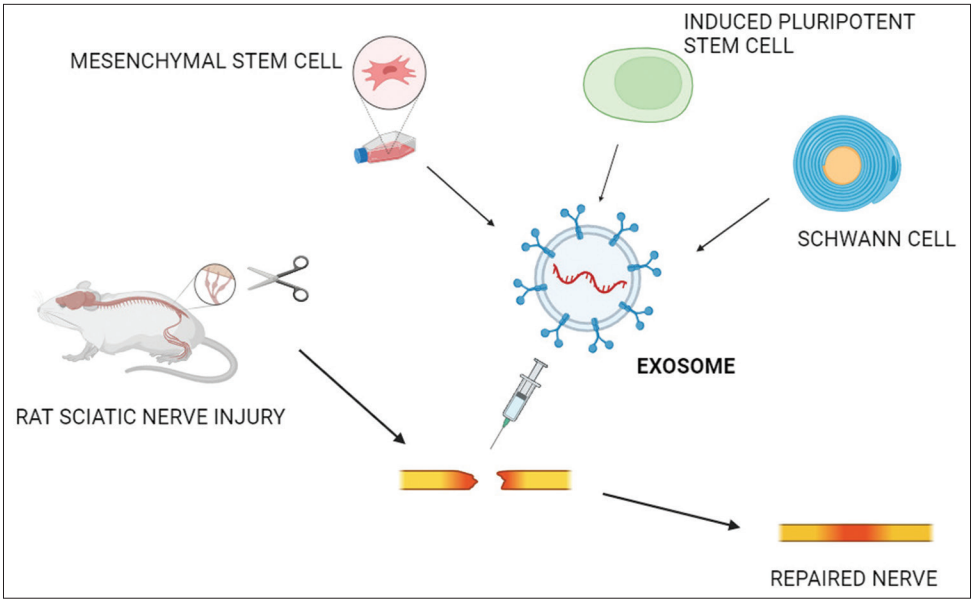

Figure 2: Exosomes in neuroregeneration.

The studies evaluating exosomes for peripheral nerve regeneration in rodent models of sciatic nerve injury demonstrate significant improvements in several quantitative measures of nerve repair. Axonal regeneration was enhanced, with exosome treatments showing increased axon count, diameter, density, and area compared to controls at 8–12 weeks post-injury ($P < 0.05$).[9] For example, one study found a two-fold increase in myelinated axon number after exosome treatment.[10] These morphological improvements translated to better functional recovery, with sciatic functional index, compound muscle action potential, and tension recovery ratios being superior in exosome groups versus controls from 4 weeks onwards ($P < 0.01$).[11] Muscle atrophy was also reduced by exosome therapy, with higher gastrocnemius muscle mass and larger muscle fiber diameter versus controls ($P < 0.05$).[12]

Nanoparticle tracking analysis revealed exosome preparations in the 100–150 nm range, consistent with reported exosome sizes.[13] Exosome uptake by Schwann cells and neurons was demonstrated by labeling techniques.[14] Proliferation assays showed 1.5–2× higher Schwann cell proliferation after exosome treatment compared to controls by 7 days ($P < 0.001$). Flow cytometry quantified increased percentages of proliferating glial cells post-exosome administration.[15] Quantitative polymerase chain reaction (qPCR) and RNA sequencing revealed exosome-mediated increases in neurotrophic, angiogenic, and myelination-related gene expression in target cells.[16] Immunofluorescence staining demonstrated up to five-fold increases in new blood vessel formation after exosome therapy ($P < 0.01$). Axonal sprouting and outgrowth were also enhanced —two to three fold based on neurofilament staining.

DISCUSSION

The most common sources of exosomes were MSCs, Schwann cells, and iPSCs. The exosomes were most often locally injected into injury sites or loaded into nerve conduits/grafts for targeted delivery. There is a diversity of exosome sources and transplantation approaches being explored for neuroregeneration. Further studies are needed to compare the efficacy of different sources and delivery methods.

Rodent models, especially rats with sciatic nerve injury, were predominantly used to study neuroregeneration. The wide utilization of rodents in the studies mirrors the broader trends in biomedical research for nerve injury models. The dominant use of Sprague-Dawley rats and the sciatic nerve injury model underscores the preference for a standardized, well-characterized animal model that allows for reproducibility and comparison across studies.[17,18] This selection reflects the ease of handling, cost-effectiveness, and extensive background knowledge available for these animals and injury models.

Schwann cells and MSCs were the main cell types studied for their exosome therapeutic effects. The predominance of MSC-derived exosomes in the studies aligns with the literature, suggesting that MSCs are a versatile and rich source of therapeutic exosomes due to their accessibility and regenerative properties.[19,20] The inclusion of Schwann cells and iPSCs as sources also reflects their relevance in neuroregeneration, particularly given Schwann cells' role in peripheral nerve repair and iPSCs' pluripotency.[21] The frequent use of Schwann cells in the studies underscores their pivotal role in peripheral nervous system regeneration,

given their natural function in supporting axon regeneration after injury.[22] This aligns with current research trends emphasizing Schwann cell-derived exosomes as key mediators of nerve repair mechanisms.[23,24]

The utilization of MSCs from bone marrow and adipose tissue reflects their versatility and accessibility as sources for regenerative therapies, including their role in exosome production.[25] MSC-derived exosomes have been shown to facilitate peripheral nerve regeneration, acting as vehicles for delivering regenerative factors to injury sites.

The reliance on rats and mice highlights the need for studies in larger animal models that better replicate human physiology. Compared to other systematic reviews, our study underscores the broad spectrum of exosome sources, which may enhance understanding of their mechanisms of action and therapeutic potential in neurodegenerative diseases.[26]

The studies reviewed employed various delivery methods including local injections under the epineurium, systemic administration through caudal vein, and filling of nerve guide conduits. Direct injection into the injury site offers targeted therapy, potentially maximizing the local therapeutic effects of exosomes.[19,20] The use of nerve conduits or grafts for exosome delivery suggests a novel approach to enhance nerve regeneration, possibly by providing a sustained release of exosomes at the injury site.[21] Systemic intravenous injection indicates the exploration of a less invasive method, potentially offering a broader distribution of therapeutic effects.[27]

Comparatively, these approaches mirror the diversity of strategies found in the existing literature on stem cell-derived exosomes for various regenerative purposes. However, the specific application to neuroregeneration emphasizes the innovative use of exosomes in neural repair and functional recovery.

Dosages ranged from microgram to particle number concentrations, with treatment frequencies spanning single doses to multiple administrations over weeks. The examination of dose-dependent effects of exosome preparations on Schwann cell proliferation and nerve repair, along with the comparative analyses of exosome treatments from different sources, underscores a critical aspect of regenerative medicine: The optimization of therapeutic strategies for enhanced efficacy. The findings suggest that not only the source of exosomes but also the concentrations at which they are applied play a significant role in their regenerative capabilities. This is consistent with studies highlighting the promotive effects of Schwann cell-derived exosomes on nerve regeneration,[24,23] as well as the potential benefits of exosomes from adipose-derived stem cells and bone marrow stromal cells.[25,28]

The implications of these results are profound, indicating that tailored exosome therapies based on specific cell sources and optimal dosing could significantly enhance outcomes in nerve repair. Thus, there are certain nuanced effects of exosome therapy, advocating for a more personalized approach to treatment.

Outcome assessments were conducted from hours to weeks post-treatment, with many studies noting significant improvements in structural and neurological function recovery. Investigations into the effect of exosome pre-treatment conditions, such as hypoxia or drug treatments, on their regenerative capacity were also done. Thus, there is scope for customization of the techniques.

Quantitative methods such as the Cell Counting Kit-8 assay and flow cytometry were used to measure cell proliferation rates and effects on Schwann cells after treatment with various exosome preparations. qPCR, high-throughput sequencing, and immunofluorescence staining were utilized to assess nerve regeneration efficacy and to quantify related protein and messenger RNA expressions. Tube formation assays and immunofluorescence staining provided quantitative measures of angiogenesis and axonal outgrowth, which are crucial for nerve regeneration.

Novel techniques like nanoparticle tracking analysis were employed to assess exosome size and concentration, and established methods like the Western blot analyses were used to analyze protein expressions and the effects of treatments. The nanoparticle tracking analysis confirms the size consistency of exosome preparations, aligning with established parameters for exosomes, which facilitates their identification and characterization.[23] The enhanced uptake of exosomes by Schwann cells and neurons, along with significant proliferation observed through various assays, underscores the effectiveness of exosome therapy in promoting cellular processes critical for nerve repair.[24]

Moreover, the increase in neurotrophic, angiogenic, and myelination-related gene expression as revealed by qPCR and RNA sequencing indicates that exosome therapy not only supports the growth of nerve cells but also promotes the formation of new blood vessels and myelination, essential for the restoration of nerve function.[29] This multi-faceted impact of exosomes, evidenced by up to five-fold increases in new blood vessel formation and enhanced axonal sprouting, suggests a robust mechanism through which exosomes contribute to nerve regeneration.

These results are in harmony with other systematic reviews that have highlighted the regenerative effects of exosomes in peripheral nerve injuries, indicating their role in enhancing neuronal survival, growth, and plasticity.[30] Recommendations for future research include further elucidation of the molecular mechanisms underlying exosome-mediated regeneration and exploration of

optimized dosing and administration routes to maximize therapeutic outcomes.

Sciatic nerve injury model studies demonstrated improved axonal growth, reinnervation, and motor function recovery, assessed through the sciatic functional index, nerve conduction velocity, and compound muscle action potential recovery indices. Measures included cross-sectional area, diameter, and number of myelinated axons, with evaluations conducted at 8 and 12 weeks postoperatively. This holds huge promise for neurological disease cure. The focus on the sciatic nerve injury model, used in a majority of the studies, highlights its importance in peripheral nerve repair research, given its relevance to human peripheral nerve injuries. However, the limited variety in animal models and injury types could pose a risk of narrow research outcomes that might not fully translate to human conditions.[31] In comparison with other systematic reviews, our findings likely align with the emphasis on rodents for preclinical models in nerve repair.

The DRG neurons in our review highlight the importance of neuronal components in studying nerve regeneration, given their direct involvement in transmitting signals from the peripheral to the central nervous system.

Exosome treatments enhanced functional recovery and axon outgrowth, and reduced muscle atrophy, which were quantified through muscle strength tests, tension recovery ratios, and muscle fiber analysis. And thus, they establish a strong role for exosomes in neuroregenerative medicine. The results from studies evaluating exosomes for peripheral nerve regeneration in rodent models, particularly sciatic nerve injury, indicate a significant therapeutic potential of exosome treatments. These findings are consistent with current research that highlights the role of exosomes in promoting nerve regeneration and functional recovery after injury. For instance, studies have shown that exosomes derived from various cell sources can enhance axonal regeneration, improve functional recovery, and reduce muscle atrophy following peripheral nerve injury.[2,32]

These improvements in axon count, diameter, density, area, and functional recovery metrics such as the sciatic functional index and compound muscle action potential underscore the efficacy of exosome treatments in nerve repair processes. The reduction in muscle atrophy further supports the multifaceted benefits of exosome therapy in the context of peripheral nerve injuries.

Comparatively, these results align with other systematic reviews, suggesting exosomes as a promising therapeutic strategy for peripheral nerve injuries, showcasing their regenerative effects across various models and species.[33]

The study emphasizes the dose-dependent and source-specific effects of exosome treatments. Recommendations include the need for further research to optimize exosome therapy protocols, such as identifying the most efficacious exosome sources and concentrations. In addition, translational studies to evaluate the clinical applicability of these findings in human nerve regeneration would be pertinent. We advocate for more high-quality, low risk of bias studies to be conducted in this field to strengthen the evidence base going forward.

The studies support the efficacy of exosome therapy in rodent nerve injury models across morphological, functional, proliferative, and genetic measures. Translation to humans and large animals is now required to further validate these findings.

Limitation of the study

Example: unclear risks of bias of the studies utilized

CONCLUSION

Evidence for the possibility of exosome-based treatments to promote nerve regeneration is included in this systematic review. In preclinical models of nerve injury, exosomes produced from different cell sources, including Schwann cells and mesenchymal stem cells, have diverse restorative effects. These outcomes include reduced muscle atrophy, improved axonal regeneration, remyelination, and functional recovery. The regulation of neurotrophic signaling and angiogenesis are the basic processes that underlie these advantages. But the majority of studies have a high risk of bias, which emphasizes the need for more thorough, well-thought-out research. Subsequent investigations ought to concentrate on enhancing exosome supplies, transport techniques, and dosage schedules. Furthermore, larger animal model research and potential clinical trials are essential to confirm the safety and effectiveness of exosome therapy for human neuron regeneration. Notwithstanding the drawbacks, exosomes have a promising future as a cutting-edge treatment strategy in neuroregenerative medicine, as evidenced by the consistently favorable results across a range of investigations.

Ethical approval: The Institutional Review Board approval is not required.
Declaration of patient consent: Patient's consent was not required as there are no patients in this study.
Financial support and sponsorship: None.
Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Amalakanti S, Eppalapally A, Attuluri S, *et al*. Role of exosomes in nerve regeneration: Systematic review. *Am J Pharmacother Pharm Sci* 2025:009.