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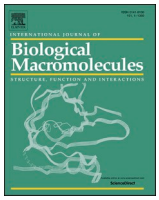

Review

Exosome-mediated delivery and regulation in neurological disease progression

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ABSTRACT

Exosomes (EXOs), membranous structures originating from diverse biological sources, have recently seized the attention of researchers due to their theranostic potential for neurological diseases. Released actively by various cells, including stem cells, adipose tissue, and immune cells, EXOs wield substantial regulatory influence over the intricate landscape of neurological complications, exhibiting both positive and negative modulatory effects. In AD, EXOs play a pivotal role in disseminating and breaking down amyloid-β protein. Moreover, EXOs derived from mesenchymal stem cells showcase a remarkable capacity to mitigate pro-inflammatory phenotypes by regulating miRNAs in neurodegenerative diseases. These vesicles possess the unique ability to traverse the blood-brain barrier, governing the aggregation of mutant huntingtin protein. Understanding the exosomal functions within the CNS holds significant promise for enhancing treatment efficacy in neurological diseases. This review intricately examines the regulatory mechanisms involving EXOs in neurological disease development, highlighting therapeutic prospects and exploring their utility in exosome-based nanomedicine for various neurological complications. Additionally, the review highlights the challenges associated with drug delivery to the brain, emphasizing the complexities inherent in this critical aspect of neurotherapeutics.

1. Introduction

Neurological diseases represent the most prevalent pathological conditions among severe diseases worldwide, affecting approximately 10 million people on average [1]. Common neurological diseases encompass Alzheimer's disease (AD), Parkinson's disease (PD), Ischemic stroke, central nervous system (CNS) injuries, and brain cancer, among others. The pathogenesis of these diseases is often characterized by immune cell-mediated reactions that promote neuroinflammation and protein aggregation (e.g. β-amyloid, α-synuclein, etc.) in the brain [2]. Developing effective therapeutic interventions for neurological diseases remains challenging due to the limited availability of drugs that can adequately cross the Blood-brain barrier (BBB) and exert the desired therapeutic effects on the brain [3]. Consequently, researchers are dedicating their efforts to drug delivery strategies targeting neurological problems. Nanotechnology holds immense promise in this regard and is poised to revolutionize neurological disease treatment in the future. Various nanotechnological approaches are being explored for drug delivery in neurological complications. These include nanoscale carriers such as nanoparticles (NPs), Exosomes (EXOs), mesosomes, and dendrimers, which are widely utilized to deliver drugs to the affected

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Abbreviations

AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
ADSc EXO	Adipose Tissue Mesenchymal Stem Cell-Derived EXO
AAD	L-amino Acid Decarboxylase
ASOs	Antisense oligonucleotides
BBB	Blood-Brain Barrier
BMSc EXO	Bone Mesenchymal Stem Cell-Derived EXO
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
EVs	Extracellular Vesicles
E-MSCs EXO	Embryonic Mesenchymal Stem Cells-derived EXO
GSH	Glutathione
hUMSCs	Human Umbilical Cord Mesenchymal Stem Cells
HD	Huntington Disease
MVBs	Multivesicular Bodies
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MHC	Major Histocompatible Complex
OXR1	Oxidation Resistance 1
PDGFR	Platelet-derived Growth Factor Receptor Alpha
PD	Parkinson's disease
SCI	Spinal cord injury
SOD1	Superoxide Dismutase 1
SEV	Small Extracellular Vesicles

regions of the brain [4]. By leveraging nanotechnology, researchers aim to enhance drug delivery efficiency, reduce off-target effects, and increase drug retention in the brain, thereby facilitating more effective treatment outcomes for individuals with neurological disorders or diseases.

EXOs are nanosized small vesicles secreted into body fluids as a result of the fusion of multivesicular bodies (MVBs) with the plasm membrane in both prokaryotic and eukaryotic cells. Unlike the broader category of extracellular vesicles (EVs), which encompasses various vesicle types with sizes ranging from nano to micro levels, EXOs specifically fall within the nm scale, typically ranging from 30 to 150 nm [5]. These vesicles play a crucial role in intercellular communication in both healthy and diseased states. Through the delivery of functional proteins, metabolites, and nucleic acids to target cells, EXOs facilitate important cellular communication processes [6–8]. The unique properties of EXOs have attracted considerable attention for clinical applications, particularly as diagnostic biomarkers and carriers for therapeutic cargo [9]. Due to their biocompatibility and bilayered lipid structure, EXOs protect the genetic payload from degradation. Additionally, their small size and membrane composition enable them to traverse key biological barriers such as BBB [10]. Researchers are actively exploring the production of modified EXOs, which opens up avenues for evaluating various therapeutic payloads, enhancing target selectivity, and optimizing the manufacturing process. Moreover, a plethora of preclinical evidence has unequivocally highlighted the remarkable immunological advantages of EXOs, propelling them to the forefront as nanocarriers with exceptional potential to mitigate drug clearance issues [11]. By their distinctive attributes, EV-based nanocarriers hold the tantalizing promise of donning an invisibility cloak, seamlessly integrating with therapeutics for unparalleled efficacy. In this comprehensive review, we embark on a captivating journey into the pivotal role of EXOs in the dynamic progression of neurological diseases. We delve deeply into their therapeutic potential, where these extraordinary EXOs emerge as potential game-changers in the landscape of neurological treatments. They hold immense promise as therapeutic agents, and EXOs also wield the power to function as non-invasive diagnostic markers for neurological diseases, ushering in a new era of precision medicine. Furthermore, our keen exploration encompasses the vexing challenges associated with drug delivery to the brain, an enigmatic fortress that has thwarted conventional therapeutic strategies. However, amidst these challenges, EXOs have emerged as a beacon of hope, adeptly navigating the BBB to deliver therapeutics accurately. Thus, EXOs provide a compelling and elegant solution for effectively treating neurological diseases, paving the way for a transformative paradigm in modern medicine.

2. Origin, composition, and release of EXOs

EXOs are nanosized EVs surrounded by a lipid bilayer membrane, that are derived from the endocytic pathway and are ubiquitously produced by various cell types under both physiological and pathological conditions [12]. The term EXOs was first coined by Trams et al. in 1981 [13]. These vesicles are part of a broader group of EVs that includes apoptotic blebs, shedding vesicles, microparticles, prostasomes, tolerosomes, and prominosomes, each exhibiting distinct characteristics based on their origin, type, and state. The initial discovery of EXOs can be traced back to their involvement in the elimination process of transferrin receptors (Tfr) during reticulocyte maturation. Reticulocytes undergo significant cellular reprogramming during early maturation stages, and as they reach the final stages, the transferrin receptors are exocytosed with the assistance of MVBs. EXOs play a crucial role in cellular homeostasis, waste removal, and mediating communication between cells and organs by transporting proteins, lipids, mRNA, long non-coding RNA (lncRNA), DNA, and other essential molecules [14].

EXOs are complex EVs containing a diverse array of biomolecules such as proteins, lipids, metabolites, mitochondrial DNA, microRNAs (miRNAs), mRNA and several other noncoding RNAs [12,13]. Notably, EXOs derived from endosomes contain specific proteins, including Tetraspanins (CD9, CD63, CD81, and CD82), heat shock proteins (HSP70, HSP 90), proteins involved in multivesicular body biogenesis (Alix, TSG1010), and lipid-related proteins and phospholipases. Exosomal cargo compositions play a significant role in maintaining homeostasis in various bodily systems, and their altered content can indicate potential abnormalities. To study the composition of EXOs, mass spectrometry is a powerful analytical technique that allows researchers to identify and quantify different biomolecules. The researcher identified proteins and EXOs containing protein using mass spectrometry in different clinical conditions and some databases also designed by the researcher for EXOs composition such as ExoCarta [14], EVpedia [15] and Vesiclepedia [16].

EXOs synthesis occurs through two distinct processes: ESCRT-dependent and ESCRT-independent pathways (Fig. 1). The release of EXOs initiates when MVBs are transported to the cell's plasma membrane. This process involves a general mechanism for vesicular docking and fusion with the cell membrane, facilitated by key components such as v-SNAREs (found on vesicles), t-SNAREs (present on target membranes), Rab GTPases, tethering proteins, and other additional factors [17]. Intracellular membrane fusion events are largely regulated by specific protein machinery, including soluble factors such as N-ethylmaleimide-sensitive factor (NSF) and soluble NSF-attachment protein (SNAP), as well as membrane complexes such as SNAP-attachment protein receptor (SNARE). Within this context, the v-SNAREs VAMP7 and VAMP8, along with the t-SNAREs SNAP23, syntaxin-3, and syntaxin-4, play significant roles in determining the specificity of intracellular membrane fusion events [9]. During the fusion process between membranes, multiple binding complexes form between one v-SNARE and three t-SNAREs. The involvement of specific tethers further aids in binding to SNARE proteins and facilitates vesicular docking at the cell membrane. Rabs, such as Rab 27a, Rab 27b, and Rab 35, ensure proper membrane targeting during this process. SNARE proteins,

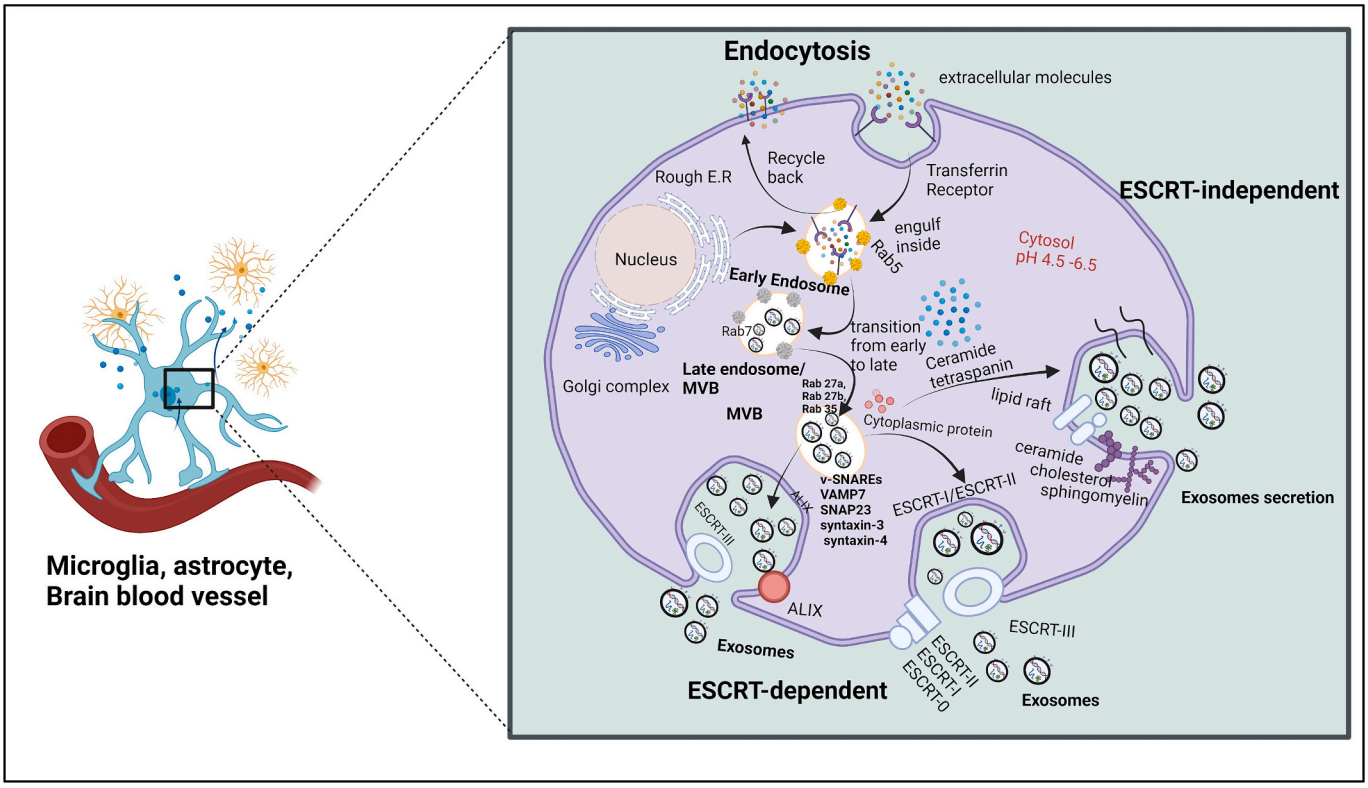

Fig. 1. EXOs biogenesis and mechanism of secretion and release in the CNS; endocytosis initiates EXOs formation, involving inward cell membrane budding and incorporation of bioactive substances to create endosomes, aided by transferrin receptors, which are later recycled to the membrane. Subsequently, smaller vesicles emerge from the endosome membrane, giving rise to late endosomes from early endosomes. EXOs are released when MVBs fuse with the lysosome for degradation or with the plasma membrane. MVBs produce EXOs through ESCRT-dependent and ESCRT-independent mechanisms involving various proteins. These released EXOs play vital roles in cellular communication, delivering functional proteins, metabolites, and nucleic acids to target cells. **Abbreviations:** MVBs - multivesicular bodies; ESCRT - endosomal sorting complex necessary for transport.

including VAMPs (v-SNAREs), syntaxins (t-SNAREs), and SNAPs (t-SNAREs), play crucial roles in the secretory process by promoting fusion between endosomal and plasma membranes. In certain hematopoietic cells such as T cells and mast cells, late endocytic vesicles fuse with the plasma membrane in a Ca^{2+}-dependent manner (Fig. 1).

3. Regulatory role of EXOs in neurological diseases

3.1. EXOs in neurodegenerative diseases

EXOs play a crucial role in the regulation of pathogenesis in a wide spectrum of neurodegenerative diseases such as AD, PD, and ALS. In AD, EXOs facilitate the transport of Aβ plaques from the extracellular space into the intracellular environment. Moreover, EXOs serve as vehicles for the intercellular transfer of Aβ, enabling its propagation from one cell to another. EXOs in AD exhibit a dual role, while they are implicated in the pathogenesis of AD, they also demonstrate protective functions by facilitating the clearance of accumulated toxins, such as Aβ and α-synuclein, thereby alleviating cellular burden [18]. In addition, EXOs have been found to serve as transport vehicles for α-synuclein, a protein associated with PD, into neuronal cells. In an in-vitro study, it was observed that EXOs released from α-synuclein-overexpressing SH-SY-5Y cells were able to transmit α-synuclein to healthy SH-SY5Y cells. These findings strongly suggest that EXOs play a crucial role in the progression of PD [19]. EXOs play a significant role in mediating neuroinflammation within the brain. Peripheral EXOs have been identified as contributors to neuroinflammation by regulating microgliosis and astrogliosis. Conversely, a study conducted by Zhang et al. demonstrated the use of IL-1β-stimulated EXOs as a targeted approach to address neuroinflammation. The researchers developed a thermosensitive supramolecular injectable HDU/SF1 hydrogel that effectively enhances the retention of IL-1β-stimulated EXOs. This retention of EXOs in the hydrogel leads to the inhibition of neuroinflammation and subsequent recovery of neurons [20]. Furthermore, EXOs have also been implicated in the progression of ALS. In an in-vitro study, it was observed that EXOs play a role in facilitating the expression of SOD1. The study revealed that EXOs released from ALS-affected cells were able to transfer SOD1 to neighbouring cells, thereby potentially contributing to the spread of pathology in ALS. These findings suggest that EXOs may have a significant impact on the pathogenesis and progression of ALS [21].

3.2. EXOs in stroke and CNS injury

Stroke and CNS injuries are leading contributors to global mortality and morbidity. Stroke is broadly classified into two categories; ischemic stroke and haemorrhagic stroke. Ischemic stroke is due to insufficient blood flow to particular area of the brain, while in haemorrhagic stroke involves bleeding inside the brain by ruptured blood vessels. EXOs play a crucial role in the pathophysiology of stroke and CNS injuries. A few preclinical studies have demonstrated their significant involvement in these conditions. Interestingly, the EXOs derived from cerebral endothelial cells promote axonal growth by modulating specific miRNAs and their target proteins [22]. EXOs harbouring miRNAs play a pivotal role in both diagnostic and therapeutic aspects. Another study provided a piece of compelling evidence for the protective function of EXOs-derived miRNA-26a in the context of ischemic brain injury, mediated through the modulation of microglial polarization [23]. Also microglia-derived exosomal miRNA-137 exhibits a neuroprotective effect by modulating the notch1 protein [24]. Wang et al. investigated the role of EXOs derived from miRNA-126-modified endothelial progenitor cells, authors

observed the neuroprotective role via increasing cerebral blood flow, promoting angiogenesis and downregulation of Caspase 3 and later upregulation of vascular endothelial growth factor receptor 2 (VEGFR2) [25]. Additionally, the neuroprotective effect of EXOs carrying miR-181c-3p was observed in the context of neuroinflammation, wherein they inhibit CXCL1 in ischemic brain injury [26].

3.3. EXOs in glioblastoma

Glioblastoma (GBM), represents the most prevalent and aggressive form of brain tumour, originating from glial cells primarily composed of astrocytes, microglia, and oligodendrocytes. In the United States alone, approximately 12,000 cases of glioblastoma are reported annually. Glioma is characterized by its highly proliferative nature, driven by the dysregulation of growth factors, including c-Met, EGFR, and PDGFR. EXOs play a pivotal role in the pathogenesis of glioblastoma, contributing to tumour development. However, their potential extends beyond that, as EXOs hold promise for targeted therapies aimed at achieving more effective treatment outcomes for GBM. Few studies have investigated the delivery of miRNAs from EXOs to investigate their biological function in glioma. The EXOs containing miR-1298-5p showed a detrimental effect in glioma via targeting SETD7 and MSH2 proteins [27] whereas EXOs expressing miRNA-146b are helpful in the inhibition of glioma growth via lowering the level of EGFR and NF-kB protein expression [28]. Furthermore, it proved in the in-vitro study that EXOs containing circRNA0001445 promote glioma progression via regulating the miRNA-127-5p/SNX5 pathway.

3.4. EXOs in CNS infection

CNS infections, encompassing conditions such as meningitis, encephalitis, and abscesses, are the most prevalent form of infectious diseases. Among these, Japanese encephalitis is a common CNS infection that predominantly affects countries in South Asia [29]. Extensive research has highlighted the regulatory role of EXOs in CNS infections, particularly in Japanese encephalitis and meningitis. The researchers observed increased CD93 expression in patients with meningitis compared to healthy individuals [30]. Moreover, serum EXOs CD93 levels and inflammatory factors such as IFN-γ, TNF-α, and IL-4 were found to contribute to HIV-associated cryptococcal meningitis. Treatment with amphotericin-B showed a protective effect by reducing the levels of CD93, IFN-γ, and IL-4 in the serum [31]. Microglia are the immune cells of CNS which play a significant role in encephalitis. EXOs secreted by infected microglia stimulate inflammatory responses in neighbouring cells [32]. However, EXOs can also have a detrimental impact on CNS infections. For instance, the exosomal secretion of let-7a/b miRNA promotes the pathogenesis of the Japanese encephalitis virus and exacerbates disease severity [33]. Furthermore, EXOs have emerged as valuable tools in target-based therapies for CNS infections associated with tuberculosis. In the treatment of tuberculosis-associated CNS infection, Angiopep-2-modified EXOs loaded with rifampicin have shown promise. These modified EXOs facilitate the targeted delivery of rifampicin, enhancing its therapeutic efficacy [34].

3.5. EXOs in spinal cord injury (SCI)

Spinal cord injury (SCI) results from severe damage to the spinal cord, typically caused by mechanical injuries or neurological dysfunction. SCI is associated with an intense and potentially exacerbated painful condition, particularly if left untreated. Addressing SCI poses a challenging task for physicians and biomedical scientists. Presently, researchers are directing their efforts toward comprehending the complete pathogenesis of SCI, investigating the regulatory roles of specific enzymes, proteins, miRNAs, and other molecular factors. Furthermore, extracellular vesicles known as EXOs play a profound role in the regulation and therapeutics of SCI. EXOs, membrane-bound vesicles, participate in cellular differentiation, proliferation, and cell survival. EXOs serve as natural drug carriers, facilitating the transportation of drugs across the BBB for the treatment of spinal cord injuries and neurodegenerative conditions [35]. A study by Shu-Qin-Ding et al. reported alterations in serum exosomal miRNAs in SCI patients, with changes observed in miR-200c-3p, miR-125b, miR-152-3p, among others [36]. The authors concluded that serum exosomal miRNAs could serve as valuable biomarkers for SCI. EXOs originating from diverse cellular sources exhibit substantial therapeutic potential in the context of SCI. Specifically, EXOs released by mesenchymal stem cells engineered with circZFHX3 are implicated in the restorative processes of SCI by modulating mir-16-5p/IGF-1 signaling within a murine model [37]. Additionally, the synergistic application of miRNAs in conjunction with EXOs derived from neurons demonstrates a protective influence in SCI through the modulation of the miR-124-3p/MYH9 axis [38]. Likewise, EXOs encapsulating miR-181c confer a protective effect against SCI-induced alterations by suppressing NF-KB signaling and inhibiting PTEN [39]. Furthermore, EXOs enriched with miR-672-5p exert a direct inhibitory effect on the AIM2/ASC/Caspase-1 signaling pathway, thereby mitigating neuronal pyroptosis and promoting functional recovery in SCI [40].

3.6. EXOs in peripheral nerve injury (PNI)

Apart from SCI, another comparable condition is peripheral nerve injury (PNI), which induces dysfunction in both sensory and motor functions of the CNS. The causative factors of PNI can vary, with major causes including trauma and iatrogenic interventions leading to the loss of structural integrity and functional impairment [41]. Additionally, Shi Guidong et al. identified the endocytosis pattern in nerve regeneration following PNI. The authors observed the upregulation of genes such as *RAB7A*, *ARF6*, *ARF1*, *VPS45*, and the downregulation of genes like *RAB11A*, *DNM3*, *NEDD4* during nerve regeneration [42]. EXOs play a crucial role in therapeutic interventions compared to their regulatory role in PNI [43]. Limited studies have reported the regulatory effects of EXOs in PNI progression, highlighting their significant role in peripheral nerve maintenance and repair. Din Yi et al. developed platelet-rich plasma-derived EXOs (PRP-EXOs) that promote nerve regeneration and repair in the context of PNI [44].

4. Therapeutic potential of different types of EXOs in neurological diseases

4.1. Adipose tissue-derived mesenchymal stem cells EXOs

Adipose tissue-derived mesenchymal stem cells EXOs (A-MSC EXOs) have been extensively investigated for their potential therapeutic applications in various neurodegenerative diseases. Clinical and preclinical studies have demonstrated their ability to modulate inflammation effectively. The anti-inflammatory effects of A-MSC-EXOs have been attributed to their ability to target the ROCK1/PTEN pathway [45]. One promising area of research involves the use of circ-Epc-1 enriched A-MSC EXOs, which has shown significant improvement in cognition and a reduction in neuronal damage in AD. These effects are believed to be mediated through the regulation of microglia polarization from the M1 to M2 stage [46]. In PD, genetic therapy utilizing A-MSC EXOs has shown great potential. Specifically, EXOs derived from adipose tissue-derived stem cells and modified with miR-188-3p demonstrated neuroprotective effects in an MPTP-induced model [47]. Additionally, A-MSC EXOs have been explored as a therapeutic option for HD. Studies by Le et al. have revealed that A-MSC EXOs exert neuroprotective effects in an in-vitro model of HD by mitigating mitochondrial dysfunction and reducing cell apoptosis [48]. Moreover, A-MSC EXOs have emerged as a promising treatment approach for stroke management. Numerous case studies have highlighted its potential efficacy, with more detailed information provided in Table 1. These findings collectively demonstrate

Table 1
Preclinical evidences of EXOs-based therapy in neurological complications.

Disease	Source of EXOs	Model	Pharmacological observation	References
AD	A-MSCs EXOs	C57BL/6J mice	Neuroprotective effect in AD by enhancing neurite growth and reduction of Aβ in neurons.	[67]
	MSCs EXOs	C57BL/6J mice	The immunomodulatory effect, reduces the plaque load in neurons.	[68]
	AD-MSCs EXOs	STZ-induced rat	Neuroprotective effect via proteolysis of Aβ peptide due to neprilysin enzyme.	[69]
	NSCs EXOs	5 × FAD mice	Prevent the BBB disruption in the AD model.	[70]
	hMSCs EXOs	Mice and Bv-2 cell line	Repair cognitive dysfunctions and help to clear Aβ deposition	[71]
	BM-MSCs EXOs	APP/PS1 mice	Inhibition of Aβ level and enhanced NeuN expression in cortex and hippocampus.	[72]
	MSCs	APP/PS1 mice	Reduced the expression of pro-inflammatory mediators TNF-α, IL-β, and IL-6	[73]
PD	MSCs	SH-SY5Y cell line	Inhibit the apoptosis via autophagy and reduce dopaminergic neuron loss	[74]
	miR-188-3p-modified adipose-derived MSCs	C57BL/6J mice	Suppress pyroptosis and protective effects on dopaminergic neurons	[47]
	MSCs EXOs	BALB/c mice	Neuroprotection via ICAM1-related angiogenesis	[75]
	BM EXOs	SH-SY5Y cell line	Neuroprotective effect due to reduction in ROS and apoptosis	[76]
	Blood EXOs	C57BL/6J mice	Neuroprotection via inhibiting neuroinflammation and apoptosis	[77]
	Human endometrial stem cell-derived EXOs	C57BL/6J mice	Improve motor symptoms, and suppress aggregation of α-syn protein.	[78]
ALS	ASC-EXOs	B6SJL mice	Improves motor symptoms, decreases glial cell activation	[79]
	ASCs-EXOs	NSC-34 Naïve cells	Restore complex-1 activity, mitochondrial potential	[80]
	ADSC-EXOs	G93A ALS mice	Reduction in SOD1 level decreases the expression of PGC-α, phospho-CREB	[81]
	Murine adipose-derived stromal cells	NSC-34 cell line	Reduction in oxidative stress	[82]
	ADSC-EXOs	C57BL/6J mice	Inhibit glial cell activation and release of pro-inflammatory mediator	[83]
Stroke	AD-MSC EXOs	SD Rat	Neuronal protection via inhibiting apoptosis and neuroinflammation	[84]
	AD-EXOs	C57BL/6J mice	Increases neuron viability and inhibits apoptosis	[85]
	LPS-stimulated Macrophages	RAW264.7	Beneficial effect in ischemic condition by skewing the microglia functional polarity from M1 to M2 phenotype.	[86]
	NSC-derived EXOs	CB57/B6	Reduction in infarct volume observed and neuroprotection via preservation of astrocyte functions.	[87]
	Bone marrow stem cells derived EXOs	Wistar rat	Lowered the size of infarct volume and downregulate genes like NLRP3, NLRP1 etc.	[88]
	Mesenchymal stromal cells	Wistar rat	Enhances neurite remodelling, neurogenesis and angiogenesis	[89]
	hNSC-derived EXOs (human neural stem cells)	SD rat	Increases cell proliferation, and cell survival and reduces apoptosis	[90]
Encephalomyelitis	MSCs derived EXOs	C57BL/6J mice	Increases IL-4, IL-10, TGF-β, and IDO-1, and decreased the levels of IL-2, IL-6, IL-17A, IFN-γ, and TNF-α	[91]
	BM-SCs EXOs	C57BL6 mice	Suppresses microglia-induced neuroinflammation and pyroptosis.	[92]
	MSCs	C57BL6 mice	Inhibition of microglia ferroptosis.	[93]
Glioblastoma	GBM-derived EXOs (glioblastoma derived)	Balb/c nude mice	Antitumor activity observed in animal models and cell line	[94]
	MSCs EXOs	C57BL/6	Suppressed glioma cell growth, spread, and movement through the inhibition of EZH2 and the Wnt/β-catenin signaling pathway	[95]
	MSCs EXOs	Balb/c nude mice	Inhibited glioma cell proliferation, invasion, and migration	[96]

the promising therapeutic potential of A-MSC EXOs in various neurological conditions.

4.2. Bone mesenchymal stem cells derived EXOs

Bone mesenchymal stem cell-derived EXOs (B-MSC EXOs) are a prevalent type of EXOs utilized for advanced drug delivery. These EXOs have extensive applications in the treatment of neurological diseases such as AD, PD and stroke. The exosomal miR-146a secreted from BM-MSCs exerts a protective effect on astrocytes by reducing NF-kB expression, leading to improved cognitive function in AD [49]. The underlying mechanism behind the neuroprotective properties of BM-MSCs involves the regulation of neuroinflammation through the modulation of immune cell activation, apoptosis, and proliferation in the pathogenesis of neurological diseases. Moreover, human MSCs derived from bone marrow (h-BMSCs) have shown a neuroprotective effect in a rat model of PD induced by 6-hydroxydopamine (6-OHDA) [50]. Similarly, BMSCs have been found to inhibit the Sp1 signaling pathway, leading to a decrease in neuron loss and inflammatory response in a model of PD induced by MPTP [51]. Furthermore, BMSCs carrying noncoding ZFAS1 have been shown to reduce oxidative stress, and apoptosis, and increase proliferation in the context of ischemic stroke. This effect is attributed to the inhibition of miR-15a-5p, resulting in a reduction of neuroinflammation [52]. Wang et al. explored the neuroprotective effect of BMSCs exosomal miR-193b-5p, which inhibits the AIM2 pathway-mediated pyroptosis in ischemic stroke [53]. Moreover, BMSCs have shown therapeutic potential in the treatment of glioma. BMSC-derived EXOs facilitate the transportation of miR-512-5p, which targets JAG1 and thus reduces the progression of glioblastoma [54]. The studies mentioned above collectively demonstrate the extensive therapeutic potential of BMSCs in the treatment of neurological diseases. Their EXOs play a crucial role in delivering miRNAs and regulating various pathways, leading to neuroprotection and attenuation of neuroinflammation.

4.3. EXOs from embryonic mesenchymal stem cells

Embryonic cells are pluripotent cells that differentiate into any tissue of the body. EXOs derived from embryonic stem cells have low immunogenicity and wide therapeutic potential in the treatment of diseases such as cancer, neurodegenerative diseases etc. Chen et al. conducted a preclinical study utilizing embryonic mesenchymal stem cell-derived EXOs (E-MSCs EXOs) in a neurological disease model. They compared the performance of transgenic (Tg) mice treated with MSC-EXOs to those treated with phosphate-buffered saline (PBS). The cognitive function was assessed using the Novel Object Recognition (NOR) test, and the discrimination index served as a measure of cognitive improvement, results showed that the Tg mice treated with MSC EXOs exhibited

significantly better performance in the NOR test [55]. Additionally, Cui et al. carried out a related study where they explored the effects of MSC EXOs conjugated with the RVG peptide (MSC-RVG-EXO) in a similar neurological disease model. They revealed that the group treated with RVG-conjugated MSC EXOs (MSC-RVG-EXO) exhibited a significant reduction in plaque deposition and Aβ levels compared to the control group. Moreover, astrocyte activation was dramatically reduced, suggesting a potential anti-inflammatory effect of the MSC-RVG-EXO treatment [56]. The above case study indicates the therapeutic benefits of using embryonic mesenchymal stem cell-derived EXOs in neurological diseases.

4.4. Immune cells derived EXOs

EXOs derived from immune cells, particularly microglia and astrocytes, play a significant role in the management of neurological diseases. These tiny vesicles are involved in controlling neurodegeneration, reducing neuronal inflammation, and facilitating communication between the innate and adaptive immune systems [57]. In a study by Nan Le et al., the neuroprotective effects of microglia-derived EXOs (M-EXOs) were observed. These EXOs were found to decrease the accumulation of Aβ, improve the PINK1/Parkin pathway-mediated autophagy, and ultimately restore mitochondrial function in a mouse model of AD (APP/PS1 mice) [58]. Furthermore, M2 microglia-derived EXOs were shown to attenuate brain injury caused by ischemia and increase neuronal survival. This effect was attributed to the expression of miR-124 in these EXOs [59]. Wang et al., recently observed alterations in MCP-1 (monocyte chemoattractant protein-1) levels in astrocyte-derived EXOs in the context of AD [60]. Moreover, astrocyte-derived EXOs (AD-EXOs) were found to reduce neuronal death in a cell culture model of PD. This protective effect was attributed to the release of miR-200a-3p from the AD-EXOs, which inhibited MKK4 [61]. These findings highlight the crucial role of immune cell-derived EXOs, particularly those from microglia and astrocytes, in modulating various aspects of neurological diseases.

4.5. Bacterial extracellular vesicles (BEVs)

Bacterial Extracellular Vesicles (BEVs) released from prokaryotic cells play a pivotal functional role within bacterial cells, particularly in their communication with host cells. These vesicles contain various bioactive components such as lipoglycans, quorum sensing peptides, nucleic acids, and proteins enclosed within membrane vesicles [62]. BEVs are produced by both gram-positive and gram-negative bacteria, with distinct pathways for their formation. In gram-negative bacteria, BEV production initiates with the blebbing of the outer membrane, leading to the generation of outer membrane vesicles (OMVs), followed by explosive cell lysis resulting in outer membrane vesicles (OIMVs). Conversely, in gram-positive bacteria, cytoplasmic membrane vesicles (CMVs) are produced through endocytosis. Moreover, BEVs exhibit broad applications in cancer treatment and neurological diseases, representing a current focus of research. Researchers have endeavored to develop BEV-mediated drug delivery for CNS diseases, showcasing therapeutic potential in treating neurological disorders [63]. Notably, Pan Jingmei et al. reported the neuroprotective activity of bacteria-derived OMVs, demonstrating a reduction in NLRP3 inflammasome and ferroptosis during ischemic brain stroke [64]. Additionally, microbiota-derived extracellular vesicles in the intestine play a crucial role in communication through the gut-brain axis, highlighting the therapeutic potential of BEVs in neurodegenerative diseases, particularly AD and PD [65,66].

5. Role of EXOs in diagnosis of neurological diseases

Early diagnosis of neurological diseases presents significant challenges due to the lack of specific markers detectable in the peripheral blood of patients. To address this issue, researchers have explored EXOs, tiny vesicles with biomolecule-carrying capabilities, as potential biomarkers for the diagnosis of neurological conditions. Notably, EXOs-derived miRNAs have shown promise as diagnostic biomarkers for neurodegenerative diseases. A study by Yang et al., identified exosomal miRNAs, such as miR-135a, miR-193b, and miR-385, in serum as potential biomarkers for AD [97]. Similarly, in the case of PD, various clinical investigations have provided evidence supporting EXOs as biomarkers, with serum α-synuclein in neuronal EXOs serving as a diagnostic marker for PD [98]. Moreover, exosomal miRNAs have demonstrated potential as biomarkers for diagnosing strokes. For instance, miRNAs like miR-21-5p and miR-30a-5p have shown promise as early diagnostic markers for strokes [50]. These findings, along with others detailed in Table 2, underscore the potential of EXOs as biomarkers for various neurological diseases [99]. In short, EXOs hold promise as potential biomarkers for neurological diseases. The detection of exosomal miRNAs in peripheral blood could provide valuable insights for early diagnosis, enabling timely interventions and improved patient outcomes.

6. EXOs isolation for targeting neurological diseases and overcoming BBB challenges

6.1. EXOs isolation for treatment of neurological diseases

Various exosome subtypes can be isolated from biological sources, including bone marrow, blood, and adipose tissue. EXOs are extracted using diverse methods, such as ultracentrifugation, ultrafiltration, PEG-based precipitation, immunoaffinity capture, microfluidics, and size exclusion chromatography. Among these techniques, ultracentrifugation (dUC) stands out as the common and gold standard method for EXOs isolation. The dUC process involves multiple centrifugation steps to eliminate cellular debris and apoptotic bodies. In this method, the pellet and supernatant are separated based on the density gradient principle. Initially, centrifugation at 300 $\times g$ for 10 min is performed, followed by subsequent steps at 2000 $\times g$ and a final step at 10,000 $\times g$. The ultimate separation of EXOs is achieved by centrifuging at 100,000–300,000 $\times g$ for 2–3 h. The entire protocol is depicted in a graphical format for better comprehension (Fig. 2). The isolated EXOs undergo further characterization and are subsequently utilized for drug loading. These EXOs find application in delivering drugs or biomolecules for addressing neurological diseases.

6.2. EXOs-based nanomedicine in neurological diseases

Efficient drug delivery to the brain faces formidable challenges due to the BBB and other biological barriers. Overcoming these obstacles is crucial for effective therapeutic interventions in neurological diseases. The BBB, a highly selective barrier, limits the entry of many drugs into the brain. Additionally, the diverse array of diseases affecting the CNS further complicates drug delivery strategies. In addition to the major challenge of BBB, several other challenges are also shown in Fig. 3. for delivering drug molecules to the brain. This background sets the stage for understanding the significance of innovative approaches like exosome-based nanomedicine in addressing these challenges. EXOs are microvesicles that are typically enclosed in a lipid bilayer membrane that is used for transport and serves to protect the luminal cargo against damage from severe extracellular environments [110]. The lipid bilayer contains proteins, some of which have been identified as relatively specific exosomal markers, including CD9, Alix, CD63, and TSG [111]. All of these markers, together with CD81, can be used to identify EXOs; otherwise, they could be mistaken for other forms of EVs [112]. Moreover, the lipids in EXOs can regulate the exosomal sorting of small RNAs and proteins [113]. In addition to proteins and lipids, there are a number of other genetic materials found in EXOs, including DNA, mRNA, miRNA, ribosomal RNA (rRNA), circular RNA, and long noncoding RNA

Table 2
Evidence for EXOs as potential diagnostic marker in neurological diseases.

Disease	Exosome sources	Level of expression	Observation Findings	References
Transient ischemic attack	Blood	rno-miR-122-5p downregulated, rno-miR-300-3p upregulated.	The levels of miRNAs in plasma or serum have been found as novel biomarkers.	[100]
AD	Blood	Exosomal HSP-70 decrease in mild stages (CDR) but a substantial increase in moderate, advanced stage	Exosomal HSP70 levels vary with AD neurodegeneration, suggesting HSP70 as a potential biomarker.	[101]
	Blood	ADE levels of C1q, C4b, C3d, factor B, factor D, Bb, C3b, and C5b-C9 terminal complement complex were significantly higher for AD patients	levels of IL-6, TNF-a, and IL-1b were higher in AD patients.	[102]
PD	Blood	Downregulation of miR-19b, upregulation of miR-195 and miR-24	MiR-19b, miR-195, and miR-24 blood levels could serve as noninvasive PD biomarkers.	[103]
	Blood	The ratio of α-syn oligomer/total α-syn and p-α-syn oligomer/ total p-α-syn in plasma EXOs is significantly higher.	Differential α-syn species expression in plasma EXOs of PD patients and healthy controls reveals potential PD biomarkers.	[104]
ALS	Blood & Serum	miR-27a-3p expression was down-regulated	miR-27a-3p has the potential to be a novel biomarker for ALS	[105]
HTLV-1 Infection	CSF	High level of HTLV-1 TAX protein	Infected cell EXOs contained relatively high quantities of Tax.	[106]
Down Syndrome	Blood	Elevated Levels of CD8, CD63	CD63 and CD81 in EXOs aid biomarker analysis normalization	[107]
Multiple sclerosis (MS)	Blood	Progressive MS - (miR-370-3p, miR-409-3p, miR-432-5p) dysregulated. RRMS - (miR-15b-5p, miR-23a-3p, miR-223-3p, miR-374a-5p, miR-30b-5p, miR-433-3p, miR-485-3p, miR-342-3p, miR-432-5p)	Exosomal microRNAs are precise MS diagnostic and subtype predictors.	[108]
Neuroinflammation	Neuronal cells	Release of miR-144-3p and miR-30d was found to be significantly increased within the EXOs of IL-1β stimulated astrocytes	MiR-30d upregulates IL-1β and controls autophagy and apoptosis, while miR-141-3p is abundant in inflammatory stress EXOs.	[109]

(lncRNA) [114]. EXOs can carry and transmit these genetic materials to play a part in normal physiological processes and neurological diseases. In addition to this, a diverse range of nanocarriers such as liposomes, polymeric, lipids, carbon nanotubes, dendrimers, metal nanoparticles, and hybrid nanoparticles [115], including EXOs, has emerged as promising vehicles for drug delivery to the brain. A plethora of nanocarriers, each with distinct sizes, compositions, loaded drugs, and biochemical properties, have emerged. This section explores the potential of EXOs in treating neurological diseases, such as AD, PD, MS, ALS, neuropathic pain, and stroke.

EXOs, showed promise as a nanomedicine strategy due to their molecular-specific characteristics and carrying properties. These entities demonstrate the capacity to traverse biological barriers, such as the challenging BBB, and reach organs devoid of a direct blood supply. EXOs are also excellent candidates for delivering drug payloads, either independently or as vehicles, because of their biocompatibility, stability, low toxicity, and ability to cross blood vessels. Exhibiting an exceptional cell tropism, EXOs boast a remarkable drug delivery specificity, rendering them highly suitable for the transportation of biological drugs. This encompasses an array of substances, including but not limited to proteins or nucleic acids. In certain cases, the EXOs are endowed with the ability to be adorned with specific ligands on their surface, thereby enabling receptor-mediated tissue targeting [116]. However, neurological diseases pose a significant challenge to neurological health due to dysregulated immune responses and inflammatory processes within the CNS [116]. In recent years, EXOs-based nanomedicines have emerged as promising candidates for therapeutic intervention in neurological diseases. EXOs, small EVs secreted by various cell types, can traverse the BBB and deliver bioactive drugs, including proteins, nucleic acids, and lipids, to target cells. This unique capability makes EXOs potential vehicles for the targeted delivery of therapeutic agents to the inflamed neural microenvironment. By harnessing the intrinsic properties of EXOs, a new frontier in neuroinflammation therapeutics is unfolding, offering innovative strategies to mitigate the debilitating effects of these complex disorders [117,118]. Numerous inquiries have delved into the curative capabilities of EXOs in the realm of neuroinflammatory ailments, encompassing the likes of PD, AD, and MS among others as elaborated and displayed in Fig. 4.

6.2.1. *EXOs based nanomedicines in AD*

In recent times, there has been a significant surge in the exploration of novel therapeutic strategies for AD, with a particular emphasis on utilizing nanotechnology and the unique properties of EXOs [119]. The cerebral state predominantly impacts cognitive faculties and remembrance within the cranial matter and is distinguished by the assemblage of anomalous antecedent protein conglomerations such as Aβ deposits and tau entanglements within neural tissue. These aggregates disrupt communication between neurons, leading to synaptic dysfunction and neuronal death, triggering inflammation [120]. At the molecular level, APP undergoes aberrant processing, generating insoluble Aβ fragments that aggregate and form plaques. Meanwhile, tau protein undergoes hyperphosphorylation, leading to the formation of twisted tangles that disrupt cellular transport systems [121]. Numerous studies have been conducted to uncover the multifaceted and somewhat controversial role of EXOs in AD, which is the most prevalent degenerative neurological condition. EXOs have exhibited their ability to transmit hazardous Aβ and hyperphosphorylated tau among cells, potentially provoking apoptosis and causing neuronal decay. On the other hand, EXOs also possess the potential to alleviate brain Aβ through microglial absorption and are renowned for transporting neuroprotective components amidst cells. These characteristics, in addition to various other qualities, make EXOs remarkably fascinating with regard to formulating novel therapeutic approaches.

Raised levels of Aβ in the human brain have been associated with the pathogenesis of AD. Yang et al. aimed to demonstrate the impact of the culture substrate on the content of EXOs, miRNAs, and proteins. To accomplish this feat, the authors employed a 3D graphene scaffold and 2D graphene film as a foundation for the cultivation of human umbilical cord mesenchymal stem cells (hUMSCs). The byproducts obtained from this cultivation were utilized to isolate EXOs [122]. The composition of 195 distinct types of miRNAs and proteins, which included insulin-degrading enzyme and heat shock protein 70, neprilysin, in 3D cultured EXOs (3D EXOs) were notably distinct from those obtained from 2D cultivation. Additionally, through their unique drug-loading techniques, 3D EXOs exhibited the ability to elevate the expression of α-secretase while simultaneously diminishing the expression of β-secretase in both AD pathology cells and transgenic mice, in vivo,

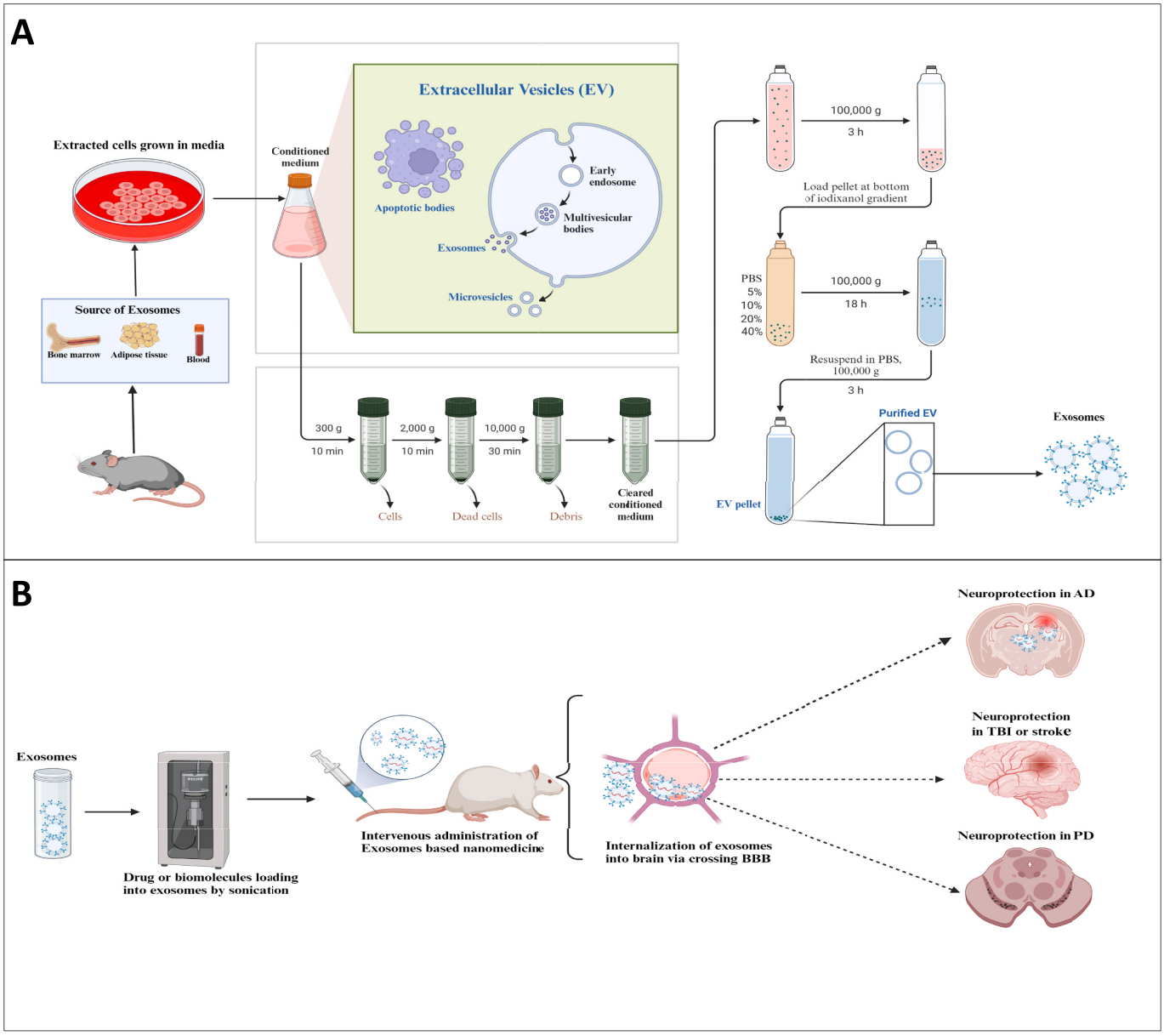

Fig. 2. Isolation of EXOs from Various Biological Sources Using Density Gradient Centrifugation and Intravenous Delivery for the Treatment of Neurological Disorders. A) EXOs derived from murine bone marrow, blood, and adipose tissues were cultivated in respective specialized culture media and isolated via the ultracentrifugation technique. B) The isolated EXOs were subsequently loaded with therapeutic agents and administered intravenously to address neurodegenerative conditions, including AD, PD, TBI etc.

ultimately reducing Aβ production. Furthermore, 3D EXOs were superior in mitigating inflammation, oxidative stress, and suppressing microglia activity. The results of this study suggest the prospective clinical usage of EXOs acquired from hUMSCs which were cultivated on a 3D scaffold in the treatment of AD and other associated ailments. Furthermore, this study established the efficacy and safety of this methodology [55].

Chen and his colleagues embarked on a study to appraise the efficacy of mesenchymal stem-cell-derived EXOs (MSC EXOs) in managing AD. MSC EXOs are membranous entities that secrete and encapsulate various MSC factors. In order to accomplish their objective, the authors utilized a human neural cell culture model, which exhibited familial AD mutations, and co-cultured it with MSC EXOs. To gauge the therapeutic effect in vivo, the 2-[18F] fluoro-2-deoxy-D-glucose ([18F] FDG) and novel object recognition testing were performed pre- and post-treatment. Furthermore, AD-related pathology and the expression of neuronal memory/synaptic plasticity-related genes were also evaluated. The study findings revealed that MSC EXOs reduced Aβ expression and restored the expression of neuronal memory/synaptic plasticity-related genes in the human neural cell culture model. In addition, a significant enhancement in brain glucose metabolism and cognitive function was observed in AD transgenic 9-month-old Tg mice and WT mice through ([18F] FDG)-PET imaging and cognitive assessment. Furthermore, the phase of neurons and astrocytes in the brain of AD mice was also found to be regulated after treatment with MSC EXOs. Overall, Chen et al. provided a conclusion on the therapeutic mechanism of MSC EXOs and proposed an alternative therapeutic strategy based on cell-free MSC EXOs for the treatment of AD [56]. In a separate study, researchers demonstrated that modifying MSC EXOs with the CNS-specific peptide rabies viral glycoprotein (RVG) improved learning and memory function in intravenously administered APP/PS1 transgenic mice. The MSC EXOs underwent a mesmerizing conjugation with RVG, accomplished through

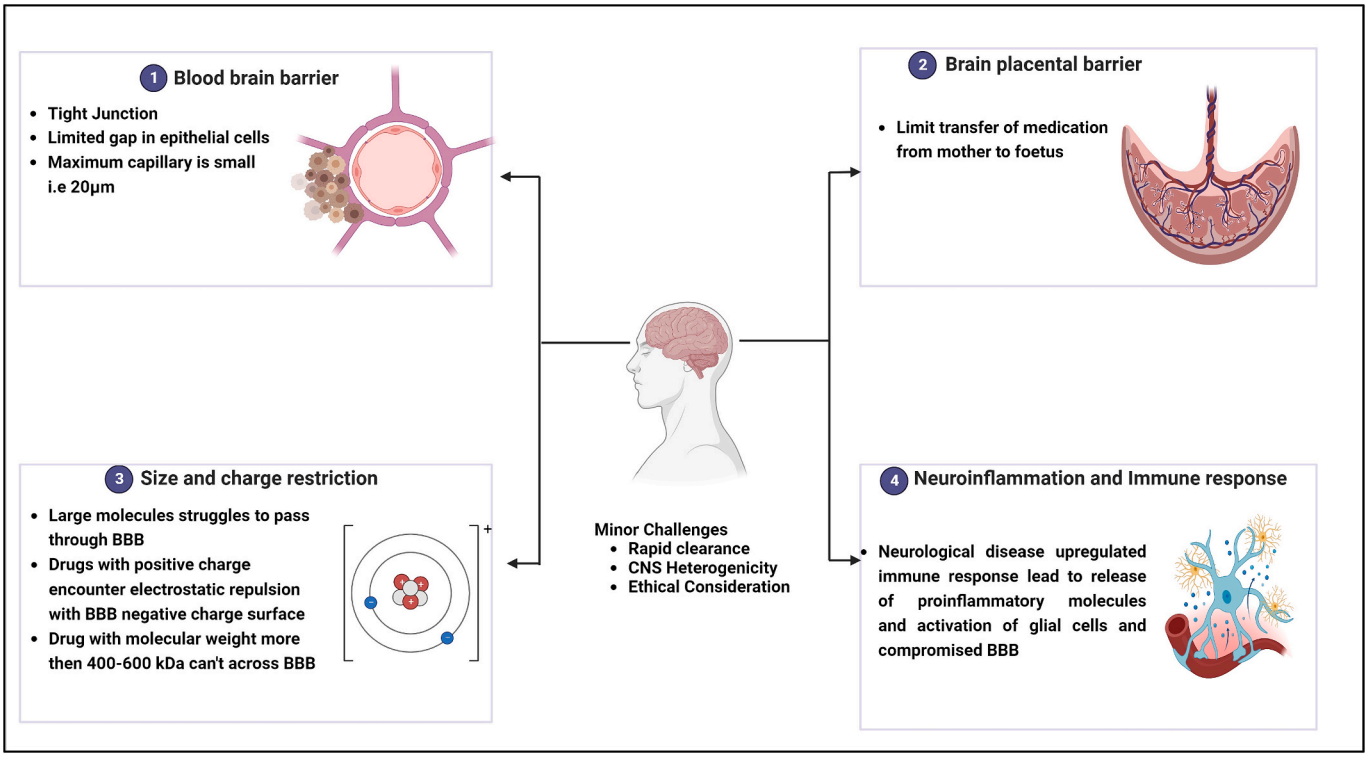

Fig. 3. Major and minor challenges associated with brain drug delivery for treatment of Neurological diseases.

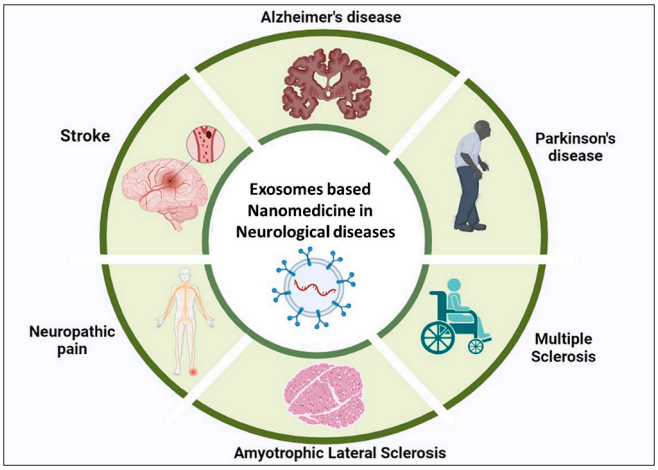

Fig. 4. Role of exosome-based nanomedicine in treatment of neurological diseases.

the utilization of a DOPE-NHS linker. The authors noted that compared to the MSC EXOs group, the administration of MSC-RVG EXOs led to a significant reduction in plaque deposition, Aβ levels, and astrocyte activation. In the Morris water maze test, the behavioral study showed that the brain-targeted MSC EXOs were superior to unmodified EXOs in enhancing cognitive function in APP/PS1 transgenic mice. Furthermore, the researchers stumbled upon a discovery that MSC EXOs displayed a remarkable decrease in the manifestation of pro-inflammatory agents, namely TNF-α, IL-6, and IL-β, while detecting no alterations in the anti-inflammatory markers of IL-10 and IL-13. Additionally, the administration of MSC-RVG EXOs resulted in a significant downregulation of TNF-α, IL-6, and IL-β, levels, while significantly upregulating the levels of IL-4, IL-10, and IL-13. In summary, the authors of this study have presented a novel approach to increase EXOs delivery for the treatment of AD [123]. Qi and collaborators have ingeniously crafted plasma EXOs that are infused with quercetin (Que), thus called as Que. EXOs, to amplify the accessibility of cargo and optimize brain targeting. This breakthrough innovation holds immense potential for mitigating cognitive dysfunction in okadaic acid-induced AD in SD rats. The researchers compared Que. EXOs with free Que. and found that Que. EXOs more effectively relieved symptoms of AD by inhibiting cyclin-dependent kinase 5-mediated phosphorylation of Tau and reducing the formation of insoluble neurofibrillary tangles. This suggests that Que. EXOs has therapeutic potential for the management of AD [124]. Interestingly, experts have exhibited that hypoxia conditions and personalized Exo from MSCs can remarkably enhance learning and memory functions in APP/PS1 transgenic mice. Additionally, the MSC EXOs was revealed to be highly effective in diminishing Aβ accumulation and boosting the expression of synaptic proteins in the brain of mice. Furthermore, it was discovered that personalized MSC EXOs under hypoxia conditions regulate glial cell activation and decrease the levels of inflammatory factors, with STAT3 and NF-κB pathways taking part. Moreover, the miR-21 levels in the brains of AD mice were observed to be upregulated, and the restoration of miR-21 rescued memory deficits and prevented pathological features. These findings highlight the potential therapeutic benefits and clinical applications of hypoxia MSC EXOs in treating AD (Table 3).

The research conducted by Yuama et al. has revealed that EXOs play a significant role in the metabolism of Aβ within the brain. In a fascinating display, the authors demonstrated that EXOs derived from neuroblastoma had the ability to trap Aβ and internalize it into the brain-resident phagocyte microglia after being injected into mouse brains. This resulted in a profound reduction in Aβ levels, amyloid deposition, and Aβ-mediated synaptoxicity in the hippocampus. The authors also noted that glycosphingolipids, a unique type of glycolipid, were highly embedded in EXOs, and the enriched glycans of these glycosphingolipids played a crucial role in binding Aβ and assembling it on EXOs both in vitro and in vivo. The study also revealed that intracerebrally administered EXOs can act as potent scavengers for Aβ by carrying it on the EXOs surface glycosphingolipids. These findings suggest that EXOs play an

Table 3
Recent findings of EXOs-based nanomedicine-based treatments for neurological diseases.

Pathological condition	Source of EXOs	Methods of isolation	Outcome	References
AD	Human umbilical cord mesenchymal stem cell culture (hUMSCs)	Ultracentrifugation	3D-cultured hUMSC EXOs reduced Aβ, and improved memory in APP/PS1 mice, offering AD treatment promise.	[184]
	MSCs	Exo-Prep kit (Lonza) + Ultracentrifugation	MSC EXOs reduced HDAC4, enhanced cell phases, and improved cognition in both cell models and transgenic mice by decreasing Aβ.	[56]
	MSCs	Ultracentrifugation	RVG-tagged MSC EXOs targeted cortex/hippocampus, reduced Aβ, and improve learning/memory by downregulating TNF-α, IL-1β, and IL-6.	[123]
AD	Rat plasma	Ultracentrifugation	Quercetin-loaded EXOs improved brain targeting, reduced Tau phosphorylation, and suppressed NFT formation, promising AD therapy.	[124]
	Hypoxia-preconditioned MSCs	Exo Quick Kit + Centrifugation	Hypoxia-preconditioned MSC EXOs boosted memory, lowered Aβ, activated glial cells, and raised miR-21 in AD mice.	[125]
	Murine neuroblastoma Neuro2a (N2a) cells	Ultracentrifugation	Neuroblastoma EXOs reduced Aβ, amyloid, and synaptoxicity, showing promise for Aβ-related disorders.	[126]
PD	Immature dendritic cell (imDC) with modified RVG peptide	Ultracentrifugation	The REXO-C/ANP/S platform effectively treats PD, improving motor behavior and clearing immune activation.	[128]
	Human bone marrow (BMSCs)	Ultracentrifugation	Exo-ASO4 reduced α-syn aggregation, improved neuron health, and enhanced locomotor function in α-syn A53T mice when injected intracerebroventricularly.	[129]
	Mice serum	ExoQuick-TC kit	The amelioration of oxidative stress injury in PD is facilitated by the up-regulation of OXR1 via the down-regulation of exosomal miR-137.	[130]
MS	AMCs	Exocib EXOs isolation kit	The intranasal delivery of MSC-SEV exhibited a remarkable effectiveness in mitigating clinical scores and histological damages of the central nervous system tissue in EAE mice, surpassing that of administering MSC alone.	[136]
	RAW264.7 murine macrophage cells	Ultracentrifugation	EXOs were able to inhibited inflammatory responses in the CNS and efficiently enhanced clinical evolution of MS in vivo.	[79]
ALS	ASCs	EXOs isolation kit	EXOs from adipose-derived stem cells targeted ALS lesions, protecting muscles, motoneurons, and neuromuscular junctions	[139]
	ASCs	PureExo EXOs isolation kit	The EXOs have exhibited their remarkable ability to provide a protective shield to the NSC-34 cells against any oxidative damage. EXOs have also been found to augment the overall cellular viability to a significant extent.	[141]
Neuropathic Pain	DRG neuron cell bodies	Ultracentrifugation	miR-21-5p upregulation in DRG neurons increased. Inhibiting miR-21-5p reduced neuropathic hypersensitivity and inflammation in DRG.	[142]
Stroke	MSCs	EXO-FBS-250 A-1 + Ultracentrifugation	EXOs improved axon density, synaptophysin, neurite modelling, neurogenesis, and angiogenesis in rats with cerebral artery occlusion.	[144]
	MSCs	Ultracentrifugation	Personalized miR-17-92 EXOs enhance stroke recovery through the PI3K/Akt/mTOR/GSK-3β pathway.	[145]

integral role in Aβ clearance in the CNS, which presents a promising therapeutic intervention for AD [125].

6.2.2. *Exosome-based nanomedicines in PD*

In PD, the loss of dopaminergic neurons and neuroinflammation contribute to motor dysfunction. However, small vesicles called EXOs, which are secreted by cells can offer a natural delivery system for therapeutic neuroprotective factors aimed at preserving dopaminergic neurons, such as growth factors or antioxidants. These factors can also help mitigate oxidative stress and apoptosis, which are crucial contributors to neuron loss in PD [126]. Furthermore, EXOs have surface markers that facilitate their interaction with specific cells, including neurons, making them molecularly tailored to effectively cross the BBB, a challenge in PD treatment. Additionally, EXOs can carry genetic material, like microRNAs, that regulate gene expression and signaling pathways implicated in PD pathology [127]. Addressing the most critical issue in the treatment of neurological diseases involves protecting brain neurons. Traditional drug delivery systems have been inadequate for this purpose. Liu and colleagues, in their innovative research, have created a remarkable core-shell hybrid system named REXO-C/ANP/S. This system has been ingeniously modified with the RVG peptide and is composed of EXOs curcumin/phenylboronic acid-poly(2-(dimethylamino)ethyl acrylate) nanoparticles/small interfering RNA targeting SNCA. The system has been shown to function as a nano scavenger, effectively clearing α-synuclein aggregates and reducing their cytotoxicity in PD neurons. Notably, administering REXO-C/ANP/S has substantially improved motor behavior in 6- to 8-week-old (C57BL/6) mice with PD. Furthermore, REXO-C/ANP/S has been found to be efficacious in clearing immune activation due to its natural immature dendritic cell Exo coating [128]. PD is distinguished by the emergence of Lewy bodies in the brain, which are primarily composed of aggregated α-synuclein and are believed to play a pivotal role in the pathogenesis of PD. Although antisense oligonucleotides (ASOs) can diminish the expression of α-synuclein, the challenge lies in securely and effectively delivering them into the neurons. However, in a recent study conducted by Yang et al., a secure and highly effective ASO delivery method was devised using Exo. The authors discovered that Exo-ASO4 displayed superior cellular uptake and minimal toxicity in primary neuronal cultures. In Vitro, Exo-ASO4 notably reduced α-synuclein aggregation instigated by preformed α-synuclein fibrils. Moreover, intracerebroventricular injection of Exo-ASO4 into the brains of α-synuclein A53T transgenic mice of the PD model considerably reduced the expression of α-synuclein and attenuated its expression. Additionally, Exo-ASO4 alleviated the degradation of dopaminergic neurons in the A53T mice. Overall, these compelling findings suggest that EXOs-mediated ASO4 delivery could be a promising treatment option for PD [129]. Recent research has indicated that microRNA-137 plays a pivotal role in the induction of oxidative stress in neurons in PD. To delve deeper into this phenomenon, Jiang and his colleagues embarked on a study to explore the impact of serum exosomal microRNA-137 on oxidative stress injury in neurons in PD. The study employed microarray analysis to screen PD-related differentially expressed genes and anticipate the interaction between oxidation resistance 1 (OXR1) and microRNA-137 in PD. The findings revealed a downregulation in OXR1 and an upregulation in microRNA-137 in PD. Furthermore, microRNA-137 targeted OXR1 and negatively regulated its expression. To determine the significance of microRNA-137 and OXR1 in oxidative stress injury, a neuron model of PD was created, using both gain and loss of function approaches. The results showed a decrease in pole-climbing time and an increase in the score for the traction test. Additionally,

the study found an increase in neuronal viability and a decrease in apoptosis in the PD model, accompanied by a reduction in MDA content and ROS levels, and an enhancement in SOD levels. The study confirmed that a decrease in exosomal microRNA-137 alleviates oxidative stress injury in PD by increasing oxidative stress [130]. Moreover, here, we report another study where a series of synthetic biology-inspired control devices that we call Exosomal Transfer into Cells (EXOtic) devices, which serve to enhance these steps, enabling efficient exosomal mRNA delivery without the need to concentrate EXOs [131]. Since EXOs can cross the blood-brain barrier, researchers assessed whether our designer EXOs bearing catalase mRNA produced by exosome producer cells equipped with the EXOtic devices could rescue neuronal cell death induced by 6-hydroxydopamine (6-OHDA). 6-OHDA is widely used to trigger experimental PD, as it damages neurons in part, though not exclusively, by producing cytotoxic levels of reactive oxygen species (ROS) [132]. In another study HEK293 cells have been transduced with designed plasmids to generate catalase mRNA-loaded EXs that target the brain to treat PD [131]. One interesting approach to target EXOs to the brain has been to genetically modify EXO-producing cells by transfecting genes expressing a targeting moiety (e.g., peptides, receptors) with exosomal membrane components, such as tetraspanins, lysosomal membrane associated protein 2B (LAMP2B), or the C1C2 domain [133]. For example, cells were transfected with a fusion protein comprised of LAMP2B and RVG, and the cells generated EXs with RVG embedded in the exosomal membrane. These RVG-expressing EXs more readily localized to the brain due to the cell surface expression of receptors for RVG by neurons and glia [134]. In another interesting study researchers provide a suite of devices for Exosomal transfer into cells that allow for the efficient and customisable synthesis of designer exosomes in mammalian cells that have been modified. Effective cell-to-cell communication is made possible by these genetically encoded devices in EXO producer cells, which improve EXO synthesis, targeted mRNA packing, and mRNA delivery into the cytoplasm of target cells without the need to concentrate EXOs. Furthermore, cargo mRNA may be reliably delivered to the brain by modified producer cells implanted in living animals. In vitro and in vivo models of PD, therapeutic catalase mRNA administration via designer EXOs reduced neurotoxicity and neuroinflammation, suggesting the potential use of the EXOtic devices for RNA delivery-based therapeutic applications [131].

6.2.3. Exosome-based nanomedicines in MS

MS is a neurological disorder that is autoimmune and chronic. The immune system attacks the CNS, causing inflammation, demyelination, and impaired nerve communication. EXOs, when administered, can interact with immune cells and deliver therapeutic drugs, thereby dampening the pro-inflammatory response and promoting an immunotolerant environment. Moreover, EXOs have the potential to promote tissue repair and regeneration, which may aid in the recovery of damaged myelin and neurons [135]. Recently, there has been an evaluation of small extracellular vesicles (SEV), specifically EXOs derived from MSCs, which were administered intranasally to the experimental autoimmune encephalomyelitis (EAE) mouse model. The authors demonstrated that MSC-SEV was more effective in reducing clinical scores compared to MSC. Additionally, there was a decrease in clinical symptoms associated with an increase in immunomodulatory responses, which included a rise in the frequency of Foxp3+ CD25+ regulatory T cells. It was also noted that the level of TGF-β was increased by both MSC and MSC-SEV treatments, whereas interleukin-10 was increased only by the treatment with MSC. Finally, the authors found that intranasal administration of MSC-SEV to EAE mice was effective in reducing clinical scores and histological lesions of the CNS tissue for the treatment of MS [136]. EXOs that were derived from macrophages (RAW EXOs) have been found to strongly co-localize with CNS microglia. In a recent study, Zheng et al. created five sialic acid analogues with different length N-acyl side chains, drawing inspiration from previously published work. The authors have developed a resveratrol-loaded RAW EXOs nanoformulation for intranasal MS treatment. Moreover, RAW EXOs have been discovered to impede inflammatory reactions in both the central nervous system and the peripheral system within a mouse model of MS. Remarkably, this has substantially enhanced the clinical progression of MS in vivo. These remarkable findings insinuate that engineered RAW EXOs is exceedingly effective in remedying MS.

Additionally, the concept of utilizing EXOs as carriers for mRNA delivery in MS therapy holds promising potential. Researchers are exploring the design and application of EXO-based nanomedicines to address various aspects of MS pathology. For instance, EXOs engineered to carry mRNA encoding immunomodulatory proteins, aiming to regulate the immune response associated with MS. Additionally, there is interest in developing EXOs loaded mRNA encoding factors that promote remyelination, targeting the restoration of the damaged myelin sheath. Anti-inflammatory mRNA-loaded EXOs represent another avenue, seeking to mitigate the inflammatory processes lined to MS progression [137]. Neuroprotective mRNA-loaded EXOs may offer a strategy to protect neurons from damage, potentially preserving neurological function. Furthermore, advancements in EXO engineering are enabling the development of nanomedicines with cell-specific targeting capabilities, enhancing the precision of drug delivery to specific cells involved in MS pathology. However, more findings of EXO-based mRNA nanomedicines for MS were not readily available. In addition to this, EXOs offer a promising platform for the targeted delivery of therapeutic proteins to specific cells involved in the pathogenesis of MS. For example, authors of very recent study load EXOs with proteins known to regulate immune responses, such as interleukins or transforming growth factor-beta (TGF-β), to modulate the aberrant immune activity seen in MS [138]. Moreover, proteins associated with promoting the regeneration of myelin, such as growth factors or neurotrophic factors, loaded into EXOs to enhance remyelination and protect against neurodegeneration.

6.2.4. Exosome-based nanomedicines in amyotrophic lateral sclerosis (ALS)

ALS, also known by the moniker of Lou Gehrig's disease, is an insidious affliction that gradually deteriorates the function of motor neurons situated in the cerebral and spinal regions of the human anatomy. This devastating condition results in the gradual loss of muscle control and movement, leading to muscle weakness, atrophy, and eventually paralysis. EXOs have the potential to deliver therapeutic drugs directly to motor neurons and glial cells, modulate the inflammatory microenvironment, downregulate oxidative stress, and facilitate cellular communication. Furthermore, the intrinsic biocompatibility of EXOs mitigates any concerns regarding immunogenicity [79].

To this day, an effective treatment for ALS remains unavailable. However, interest in the use of stem cells for managing neurodegenerative disorders is steadily increasing. Stem cells have been found to have a beneficial paracrine effect due to the release of EXOs, which act as the main mediators of cell-to-cell communication. In a groundbreaking exploration carried out by Bonafede et al., an innovative non-cell therapeutic strategy was examined by employing EXOs sourced from murine-adipose-derived stromal cells on motoneuron-like NSC-34 cells that express ALS mutations, in vitro. Specifically, the influence of EXOs on NSC-34 unacquainted cells and NSC-34 cells that overexpress human SOD1(G937R) or SOD1(G93A) or SOD1(A4V) mutants, subjected to oxidative stress, was scrutinized. The study outcomes demonstrated that EXOs have the potential to safeguard NSC-34 cells from oxidative harm, which is the main cause of damage in ALS, by amplifying cell viability. These outcomes imply an auspicious function for EXOs obtained from stem cells in conceivable therapeutic implementations for the treatment of ALS [79].

The previous research conducted by scholars delved into the efficacy of ASC EXOs in safeguarding the nervous system against damage. This was achieved by isolating EXOs from adipose-derived stem cells and conducting in vivo experiments utilizing the human SOD1 gene with a

G93A mutation (SOD1-G93A) in C57BL/6 mice. The researchers additionally explored two approaches for EXOs administration via intravenous and intranasal methods. Moreover, motor tests were carried out, and analysis of glial cells, muscle, lumbar motoneurons, and neuromuscular junction were conducted to understand the impact of EXOs administration on disease progression. As a result, the in vivo study demonstrated the upregulation of motor performance, the neuromuscular junction, protected lumbar motoneurons and muscle, and downregulation of glial cell activation in treated SOD1-G93A mice. Lastly, it was discovered that EXOs can also be directed toward lesioned ALS regions of the mouse brain [139].

Additionally, EXO-based mRNA and protein-based nanomedicines have emerged as promising therapeutic approaches for treating ALS. In ALS, the EXOs loaded with mRNA encoding neuroprotective proteins directly can transverse the BBB, enabling efficient delivery to affected motor neurons. Moreover, this targeted approach helps mitigate the underlying pathology of ALS by promoting neuronal survival, reducing inflammation, and enhancing cellular repair mechanism. Furthermore, Abati et al. [140] conducted on a mouse model of ALS demonstrated the successful delivery of superoxide dismutase 1 (SOD1) mRNA via EXOs, resulting in improved motor function.

6.2.5. Exosome-based nanomedicines in neuropathic pain

Neuropathic pain is a multifaceted and frequently incapacitating ailment that results from damage or malfunction of the nervous system. The impaired function of ion channels and altered receptor expression increase excitability and generate spontaneous pain signals. Additionally, neuroinflammation is a contributing factor to pain sensitization by releasing pro-inflammatory mediators. Pain perception is further intensified by irregular neurotransmitter release, such as glutamate and substance P. Furthermore, maladaptive alterations in central pain processing pathways reinforce chronic neuropathic pain, resulting in a self-perpetuating cycle. As a result, EXOs possess inherent biocompatibility and reduced immunogenicity, making them suitable for clinical use [141].

Dysregulation of microRNAs that do not code for proteins (miRs) occurs in sensory neurons located in the dorsal root ganglia. According to Simeoli et al., the cell bodies of DRG neurons release EXOs containing miRs during activity. Furthermore, the erudite authors have astutely showcased that miR-21-5p is exuded into the exosomal compartment of cultured DRG subsequent to the activation of TRPV1 receptors by capsaicin. Moreover, macrophages readily phagocytose pure EXOs released by capsaicin, leading to an upregulation of miR-21-5p and the promotion of a pro-inflammatory phenotype. In vivo, studies conducted on male C57BL/6 mice after inducing nerve injury showed that miR-21-5p was enhanced in DRG neurons. The degree of recruitment of inflammatory macrophages in the DRG was diminished, alongside the alleviation of neuropathic hypersensitivity, through the intrathecal administration of a miR-21-5p antagomir coupled with the conditional removal of miR-21 in sensory neurons. This evidence implies that the heightened liberation of miR-21 instigates communication between sensory neurons and macrophages subsequent to injury to the peripheral nerve [142]. In another different study, researchers investigated the therapeutic potential of EXO delivered mRNA in the treatment of neuropathic pain. The study utilized EXOs derived from MSCs loaded with mRNA encoding an anti-inflammatory protein. Moreover, the researchers demonstrated that EXOs efficiently delivered the mRNA payload to injured nerves in a rat model of neuropathic pain. The translated protein helped modulate inflammation and promote nerve regeneration, ultimately alleviating neuropathic pain symptoms. This finding exemplifies the promising role of EXO-based mRNA delivery systems in addressing neuropathic conditions through targeted therapeutic protein expression [143].

6.2.6. Exosome-based nanomedicines in stroke

Stroke, a complex neurovascular event, arises primarily from two major mechanisms: ischemia and haemorrhage. Ischemic strokes occur due to reduced blood flow to the brain caused by arterial blockage, leading to neuronal cell death resulting from oxygen and nutrient deprivation. Haemorrhagic strokes, on the other hand, result from ruptured blood vessels, which causes blood leakage into brain tissue, creating pressure that damages surrounding cells. Furthermore, both mechanisms disrupt neurotransmission and induce neuroinflammation, contributing to a cascade of excitotoxicity, oxidative stress, and inflammation. EXOs-based nanomedicine can encapsulate neuroprotective agents and anti-inflammatory compounds, enabling precise delivery to ischemic brain regions [89]. According to a novel idea, administering EXOs obtained from multipotent MSCs to treat stroke can elevate neurovascular transformation and enhance functional rehabilitation. The authors proved that stroke rats treated with MSC EXOs showed improved recovery, with increased synaptophysin and axonal density in the ischemic boundary zone compared to the PBS group. Furthermore, EXOs treatment resulted in a substantial increase in the number of newly formed doublecortin and von Willebrand factor, both of which are markers for neuroblasts and endothelial cells, respectively. These remarkable discoveries indicate that the intravenous administration of cell-free MSC-generated EXOs has the potential to improve neurite remodelling, angiogenesis, and neurogenesis following a stroke, thereby providing a highly promising new treatment option [144].

In a similar set of findings, researchers examined EXOs enriched with the miR-17-92 cluster that were collected from MSCs transfected with a plasmid containing the miR-17-92 cluster. They found that these EXOs improved neurological recovery to a greater degree than EXOs collected from control MSCs. When compared to treatment with liposomes, the groups treated with EXOs showed a remarkable improvement in functional recovery. Treatment with miR-17-92 cluster-enriched EXOs exhibited an immensely potent effect on the amplification of neurological function and the augmentation of neurogenesis, oligodendrogenesis, and neurite remodelling in the ischemic boundary zone, exceeding the impact of MSC EXOs. Remarkably, miR-17-92 cluster-enriched EXOs administration impeded the phosphate, tensin homolog, and miR-17-92 cluster target gene. Moreover, the phosphorylation of downstream proteins, namely phosphatase and protein kinase B, the mechanistic target of rapamycin, glycogen synthase kinase 3β, and tensin homolog, was escalated in contrast to the treatment involving control MSC EXOs [145]. Another literature, where scientists explored the therapeutic potential of EXOs derived from MSCs loaded with a specific mRNA for the treatment of ischemic stroke [146]. The researchers engineered EXOs to carry anti-inflammatory mRNA, which could be delivered to the ischemic brain tissue. The study demonstrated that the EXOs effectively delivered the therapeutic mRNA to the brain, resulting in reduced inflammation, improved neural cell survival, and enhanced functional recovery in a rodent model of stroke. Recently, group of researchers create engineered EXOs (BDNF-hNSC-EXO), they loaded brain-derived neurotrophic factor (BDNF) into EXOs formed from NSCs. We next compared the effects of BDNF-hNSC-EXO on ischemic stroke both in vitro and in vivo. In a model of oxidative stress in NSCs caused by H2O2, BDNF-hNSC-EXO significantly increased cell survival. In a model of middle cerebral artery blockage in rats, BDNF-hNSC-EXO boosted the differentiation of endogenous NSCs into neurons while simultaneously inhibiting the activation of microglia. According to researchers' findings, BDNF may enhanced the ability of NSC-derived EXOs to treat ischemic stroke [147].

6.2.7. EXO based nanomedicines in spinal cord injuries (SCI)

EXO-based nanomedicines have emerged as a promising avenue in the quest to address the challenges associated with SCI. The spinal cord, a vital component of the CNS, plays a critical role in transmitting signals between the brain and the rest of the body. Injuries to spinal cord can lead to devastating consequences, often resulting in permanent loss of motor and sensory function [148]. Traditional treatment approaches for SCI have faced limitations, prompting researchers to explore innovative

strategies such as EXO-based nanomedicines. One key advantage of EXO-based nanomedicines is their ability to cross the BBB and reach the injury site in the spinal cord. Moreover, this property allows for systemic administration, making them a less invasive and more accessible treatment option compared to traditional surgical interventions. Furthermore, EXOs exhibit inherent biocompatibility, reducing the risk of adverse reactions and improving their overall safety profile [149]. Research efforts have demonstrated the potential of EXO-based therapies in preclinical models of SCI. MSC-derived EXOs, in particular, have been extensively investigated due to their immunomodulatory properties and regenerative potential. Most EXOs are extracted from multipotent MSCs, such as those found in bone marrow, peripheral blood, umbilical cord blood, adipose tissue, and human skin. However, there are related research reports on the use of EXOs derived from macrophages, neuronal stem cells, pericytes, and other cells for SCI treatments [150,151]. Previous studies have shown that EVs, including EXOs play an important role in the development of secondary injury by transporting parent cell-specific signaling cargoes, such as signaling lipids, genetic information, cytokines, receptors, to change the function of receptor cells inside and outside the CNS [152]. As a cell-free therapeutic approach, EXOs inherit biocompatibility while reducing the uncertainty of stem cell differentiation compared to EXOs, which will be a potential for SCI therapeutic.

Bone MSCs (BMSCs) are the most commonly applied stem cell lines used to produce EXOs as well as in the treatment of SCI. Huang et al. used BMSC EXOs to treat SCI in rats intravenously and found for the first time that the systemic administration of this type of EXO effectively attenuated inflammation and apoptosis and promoted angiogenesis after SCI [153]. Similar effect also confirmed by Liu et al. in their research [154]. They also found that BMSC EXOs could inhibit scar formation and promote axon regeneration, and this process was related to the suppression of the activation of neurotoxic A1 astrocytes. In a different study by Zhao et al. [155] found that BMSC EXOs could effectively inhibit the activation of NF-κB signaling by binding to microglial cells and effectively reduce the synthesis and release of complement mRNA in SCI. In next published work, Jia et al. [156] further studied the mechanism of the inhibition of A1 astrocyte activation by BMSC EXOs in SCI and found that the inhibitory effect was related to the downregulation of the phosphorylated NF-κB P65 subunit. Cheng et al. are promoting B MSC-derived EXO-loaded hydrogel for the treatment of SCI through bioengineering techniques. Furthermore, the authors of this study discovered that cargo inside EXOs is essential for mediating the therapeutic actions of these particles. It has been demonstrated that neurotropic substances enclosed in EXOs, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), improve neuronal survival and axonal growth. Furthermore, miRNAs have the ability to alter recipient cells' gene expression, which can affect apoptosis and inflammation. These bioactive compounds work in concert to address various aspects of the intricate pathophysiology of SCI when they are combined in EXO-based nanomedicines. As a transplanted EXO delivery system, 3D gelatin methacrylate hydrogel (GeIMA) was employed (GeIMA-EXOs). The differentiation, proliferation, and viability of neural stem cells grown on GeIMA were evaluated by researchers. According to study data, hydrogel increased EXO retention, which aided in vitro neuronal expansion and differentiation. Furthermore, in the injured lesions, GeIMA-EXOs reduced glial scarring and encouraged neurogenesis. The study's findings indicated that injectable GeIMA-EXO promoted neurological and functional recovery following SCI [157].

Scholars also studied how BMSC EXOs reduced cell apoptosis to improve SCI. Gu et al. found that the inhibition of apoptosis was related to the activation of early autophagy by BMSC EXOs [158]. However, further studies by Li et al. and Fan et al. confirmed that BMSC EXOs could effectively reduce neuronal cell apoptosis in SCI by regulating the Wnt/b-catenin and TLR4/MyD88/NF-κB signaling pathways respectively [159,160]. Furthermore, Wang et al.'s study found a correlation between BMSC-EXOs anti-apoptotic activity and the NF-κBp65 signaling pathway's downregulation [161]. Following pathway downregulation, pericyte migration is successfully decreased and the BSCB's integrity is effectively preserved, both of which improve SCI. EXOs from human umbilical cord MSCs (HUCs), pericytes, NSCs, and common BMSCs can also be extracted for the purpose of treating SCI. According to Zhang et al. HPC EXOs administered to rats with SCI were able to enhance neurologic function by encouraging angiogenesis at the site of injury [162]. In similar research, Pasquale Romaneli et al. discovered that HUC EXOs have anti-inflammatory and anti-scarring properties against SCI injury [163]. Zhou et al. also discovered that this kind of EXO might stimulate neuron regeneration and reactivate endogenous neurogenesis. According to Rong et al., NSC-derived tiny EXOs were effective in lowering the incidence of nerve apoptosis by promoting the expression of the autophagy-related proteins LC3B and Beclin-1 in rats with SCI [164,165]. In the microcirculation of the spinal cord, pericytes are crucial. According to Zhong et al. NSC EXOs had high levels of VEGF-A expression, which may help spinal microvascular endothelial cells' angiogenic activity and promote the functional regeneration of the spinal cord [166,167]. Yuan et al. employed EXOs produced from pericytes to treat a rat model of SCI and discovered that endothelial cells could readily absorb them. Intravenous injections used in experiments shown significant improvements in microcirculation blood flow, BSCB protection, and decreased apoptosis.

In addition to this, EXOs derived from oligodendrocyte precursor cells have demonstrated the ability to promote the generation of myelin-forming cells, facilitating the restoration of damaged myelin sheaths [168]. Furthermore, EXOs have been implicated in enhancing vascularization at the injury site, supporting the delivery of nutrients and oxygen critical for tissue repair. In the realm of clinical translation, EXO-based therapies for SCI are still in the early stages of development. Challenges such as standardization of isolation methods, scalability, and optimization of cargo loading need to be addresses. Moreover, the heterogeneity of SCI cases demands a personalized medicine approach, tailoring EXO-based treatments to individual patient profiles for optimal outcomes. Despite of these challenges, the prospect of EXO-based nanomedicines in injured spinal cord scenarios offers a ray of hope for patients facing the debilitating consequences of SCI. The multifaceted benefits, ranging from neuroprotection and immunomodulation to tissue regeneration, position EXOs as versatile therapeutic entities.

6.2.8. EXO based nanomedicines in peripheral nerve injury (PNI)

Tiny EVs called EXOs, which are released by cells, have shown great promise in the field of PNI nanomedicine. Nanosized vesicles, which normally have a diameter of between 30 and 150 nm, are perfect for therapeutic intervention in peripheral nerve regeneration because they carry a cargo of bioactive molecules like proteins, lipids, and nucleic acid, as we have already covered in previous sections of this review article [202]. PNI pose significant challenges due to the limited regenerative capacity of the nervous system [169]. Ex vivo (EXO) produced from different cell sources has shown promise in modulating cellular processes necessary for nerve regeneration. For example, MSC-derived EXOs have demonstrated encouraging results in axonal development and remyelination, which promotes nerve regeneration. Numerous growth factors, microRNAs, and proteins found in MSC-derived EXOs have been shown in studies to work together to create a conductive milieu that promotes neuron healing [170]. The high cost of MSC-based therapy, cellular phenotypic instability, and the possibility of microinfarction from transported MSCs becoming trapped in the pulmonary microvasculature are some of its disadvantages [171]. Consequently, a novel cell-free therapy for PNI needs to be created that works just as well as MSCs. EXOs have recently been found to be the primary paracrine effectors of MSCs. They can mediate communication between cells and preserve dynamic, homeostatic microenvironments for tissue regeneration [172,173]. MSC-derived EXOs can stimulate the production of many growth factors (GFs), including NGF, insulin-like growth factor-1 (IGF-1), and stromal-derived growth factor-1 (SDF-1), via activating the

PI3k/Akt, ERK, and STAT3 signaling pathways [174]. Moreover, studies have demonstrated that exosomal miRNAs (miR-221, miR-218, miR-199b, miR-148a, and miR-135b) can promote neuronal differentiation, proliferation, and axonal outgrowth [175,176]. Also, a study has shown that via stimulating the PI3K/protein kinase B/mechanistic target of the rapamycin/glycogen synthase kinase 3-β signaling pathway, the miR-17-92 cluster can support axonal outgrowth, neurogenesis, and functional recovery. In another study, Zhang et al., also demonstrated that MSC-derived EXOs carry an elevated level of the miR-17-92 cluster, which can activate the PTEN/mTOR signaling pathway in recipient neuron cells. In PNI scenarios, research have shown that MSCs with miRNA overexpression are more responsive to functional recovery than naive MSCs [176]. Furthermore, recent studies have shown that MSC-derived EXO can upregulate miRNA and promote angiogenesis [177].

Extracellular matrix oligomers (EXOs) are a useful tool that scientists have used to encapsulate and transport specific bioactive molecules that are critical for nerve regeneration. NGF, for instance, is a well-known regulator of neuronal development and survival. By integrating NGF into EXOs, its regulated release at the site of damage creates an environment that is conducive to axon outgrowth [178]. Similarly, EXOs containing miRNAs such as miR-21 and miR-146a have been shown to regulate inflammation and enhance peripheral neuron regeneration. One prominent example of EXO-based nanomedicine in PNI is the use of EXOs made from Schwann cells. Promoting nerve regeneration requires the primary glial cells of the peripheral nervous system, also known as Schwann cells. Schwann cell-released extracellular matrix (ECM) particles contain a variety of regeneration components, including extracellular matrix proteins and neurotrophic factors. When administered at the site of damage, these extracellular sprouts (EXOs) promote functional recovery and axonal regrowth. Lopez-Leal et al., demonstrated that only the Schwann cell-derived EXOs secreted by repair Schwann cells enhanced axonal regeneration after PNI, but they did not show these promotive effects in the differentiated Schwann cells [179]. The promotion of neurite growth from dorsal root ganglia explants was in fact mediated by the repair of Schwann cell-derived EXOs, which also activated PI3K pathways, downregulated PTEN, and transferred exosomal miRNA21. The study's findings clearly show that Schwann cell-derived EXO repair shuttled particular proteins and miRNAs that improved neuron survival and axonal regeneration, whereas the EXOs from differentiated Schwann cells did not show the promotive effect to enhance axonal regeneration because of the abundance of miRNAs that inhibited cell migration, such as miRNA-21 and miRNA-92a-3p miRNAs, allowing them to concentrate on myelination, which is differentiated Schwann cells' primary function. Consequently, it may be said that different Schwann cell morphologies are capable of transferring distinct exosomal payloads that are necessary for particular tasks. However, a number of studies have shown that Schwann cells may stimulate the growth and spread of melanoma and pancreatic cancer. In these situations, Schwann cells are used by tumour cells as a means of promoting increased proliferation and inhibiting apoptosis because of their exosomal cargo [180–182].

Furthermore, EXOs derived from neural stem cells (NSCs) have demonstrated remarkable potential in the regeneration of peripheral nerves. NSC-derived EXOs are enriched with neurotropic factors and miRNAs that modulate the regeneration of peripheral nerves. NSC-derived EXOs are enriched with neurotropic factors and miRNAs that modulate the regenerative response. These EXOs not only promote the survival of injured neurons but also contribute to the differentiation of neural progenitor cells, fostering a regenerative microenvironment [183]. The use of EXO-based nanomedicine in PNS is not limited to promoting regeneration alone. EXOs have also been explored for their immunomodulatory properties, which play a crucial role in the inflammatory response associated with nerve injury. EXOs derived from immune cells, such as macrophages, carry immunomodulatory molecules that regulate the inflammatory milieu, promoting a balanced immune response that supports nerve regeneration while minimizing excessive inflammation. From the above findings, it was concluded that EXO-based nanomedicine holds tremendous promise for the treatment of PNI.

7. Role of viral infections and EXOs in neurological disease

The intricate interplay between viral infection and EXOs in the context of neurological diseases has emerged as a captivating and complex area of research, unraveling the multifaceted mechanisms that underlie these conditions. Viruses, with their ability to take over host cells and manipulate cellular machinery, have long been implicated in various neurological disorders, ranging from acute infections to chronic, neurodegenerative conditions [185]. Notably, the impact of viral infections extends beyond the immediate consequences of the infection itself, as mounting evidence suggests a profound involvement of EXOs, small EVs secreted by cells, in both the immune response to viral pathogens and the progression of neurological diseases [186]. At the forefront of this intricate between viruses and the CNS are neurotropic viruses, capable of infecting and influencing the function of neurons and glial cells. Herpesviruses, such as herpes simplex virus (HSV) and cytomegalovirus (CMV), and RNA viruses like human immunodeficiency virus (HIV) have been extensively studied in the context of neuroinvasion and their ability to establish persistent infections within the CNS [187]. These viruses exploit a variety of strategies to breach the BBB and gain access to the brain parenchyma, where they can directly infect neurons or establish latent infections in glial cells. The ensuing immune response, involving both innate and adaptive components, is a double-edged sword. On one hand, it serves to control viral replication and spread; on the other hand, it can contribute to neuroinflammation and tissue damage. EXOs, once considered mere cellular debris, have emerged as critical players in mediating intercellular communication, particularly during viral infections. These small vesicles carry a cargo of proteins, lipids, and nucleic acids, including miRNAs and viral components, serving as vehicles for the transfer of information between cells. The authors Longatti et al. employed EXOs that were separated from an HCV sub genomic replicon cell line [188]. This cell line is incapable of producing virions due to its lack of viral structural proteins. They demonstrated that they could infect Hu7 cells following exposure to these shed EXOs without requiring direct cell-to-cell contact by employing a trans well experiment. Additionally, a sphingomyelinase inhibitor and an exosomal release inhibitor suppressed this infection. As of right moment, just one Flaviviridae member HCV is known to integrate genomic RNA into EXOs. Only hepatitis A virus (HAV), a non-enveloped picornavirus, is believed to use this mode of transmission as well [189]. It does, however, raise the prospect that other, as of yet unidentified viruses, might exploit the endosomal/exosomal mechanism to transfer their viral message to cells that are not affected. Indeed, this possibility was discussed in a review by Izquierdo et al., of HIV and EXOs [190]. According to Gould et al., there are similarities between the processes of exosome biogenesis and HIV assembly and egress, suggesting that HIV has evolved to take advantage of these processes and infect cells by packaging its viral DNA [191]. The idea that HIV virions are discharged with EXOs and have increased infectivity when these vesicles are present is backed by observations [192]. But this process was carried out by DC absorption, which then allowed HIV to be endocytosed and disseminated to nearby uninfected T cells [193].

EXOs play a pivotal role in the immune response to viral infections within the CNS. Microglia, the resident immune cells of the brain, release EXOs loaded with antiviral factors, contributing to the containment of viral spread. Astrocytes and neurons, too, release EXOs that modulate the local immune milieu, influencing the activation state of surrounding cells [194]. However, the intricate relationship between viruses and EXOs goes beyond the battlefield of the immune response. Viruses exploit EXOs as a means of intercellular communication and immune evasion. They manipulate the host cell machinery to load EXOs with viral components, facilitating their transport between cells and

potentially aiding in the establishment of persistent infections. Moreover, the immunomodulatory properties of EXOs can be harnessed by viruses to dampen host antiviral responses and promote their survival within the CNS [195]. Understanding these dynamic interactions is crucial for devising strategies to manipulate the exosomal pathway for therapeutic intervention in viral-induced neurological diseases.

As the field progresses, it becomes increasingly evident that the implications of viral infections and EXOs extend well beyond the acute phase infection. Long after the initial encounter with the virus, the host may continue to experience neurological sequelae. Persistent infections, chronic inflammation, and dysregulation of cellular processes contribute to the pathogenesis of various neurodegenerative diseases, AD, PD, ALS are among the conditions where the involvement of viral infections and EXOs is gaining recognition [195]. The concept of the "virological synapse" has been proposed, highlighting the intimate connection between viral infections and the spread of pathological proteins characteristic of neurodegenerative diseases. EXOs, once again, emerge as key players in this process, facilitating the intercellular transfer of misfolded proteins, such as β-amyloid and α-synuclein, implicated in AD and PD, respectively [196]. The ability of EXOs to transport these pathogenic proteins across the CNS, spreading pathology form cell to cell. Raises intriguing possibilities for therapeutic intervention.

In the realm of neurodegenerative diseases, EXOs derived from various cell types contribute to the propagation of pathology. Neurons release EXOs containing disease-associated proteins as a mechanism of cellular clearance. However, these EXOs can also be internalized by neighbouring cells, leading to the seeding and aggregation of misfolded proteins. Similarly, glial cells, including microglia and astrocytes, release EXOs with distinct protein signatures, influencing the neuroinflammatory milieu and contributing to disease progression [197]. The convergence of viral infections and neurodegenerative diseases is particularly evident in conditions like HIV-associated neurocognitive disorders, where the virus not only directly affects the CNS but also triggers a cascade of events involving EXOs that contribute to cognitive impairment [194]. Unraveling the intricate web of interactions between viral infections, EXOs, and neurodegenerative diseases hold promise for the development of novel therapeutic strategies aimed at disrupting these processes and halting the progression of debilitating neurological conditions.

In the pursuit of understanding the role of EXOs in viral-induced neurological disease, technological advancements have propelled the field forward. Techniques such as high-resolution imaging, single-vesicle analysis, and mass spectrometry have provided unprecedented insights into the composition and function of EXOs [161]. The ability to isolate and characterize EXOs form biological fluids, including cerebrospinal EXOs from biological fluids and blood, has facilitated the identification of specific exosomal markers associated with viral infections and neurodegenerative diseases. Liquid biopsy approaches, leveraging the information encapsulated within EXOs, hold promise for non-invasive diagnosis and monitoring of neurological conditions, providing clinicians with valuable tools for early intervention [198].

As our understanding of the intricate interplay between viral infections and EXOs in neurological diseases deepens, the prospect of targeted therapeutic interventions becomes increasingly tangible. Modulating the release, composition, or uptake of EXOs represents a novel avenue for intervention in viral-induced neurological disorders. EXO-based therapies, where engineered EXOs loaded with therapeutic cargo are administered to modulate the immune response or counteract pathological processes, hold promise for precision medicine in the realm of neurology. Similarly, strategies aimed at disrupting the viral lifecycle by targeting exosomal pathways exploited by viruses may prove effective in limiting the impact of viral infections on the CNS. However, the translation of these promising strategies forms the laboratory to the clinic requires a comprehensive understanding of the complex interplay between viruses and EXOs in the divers' landscape of neurological diseases.

8. Clinical trials on exosome-based nanomedicine for neurological disease treatment

In recent years, the field of nanomedicine has witnessed a surge in research exploring the therapeutic potential of EXOs, that play a crucial role in intercellular communication. These nanosized lipid bilayer vesicle has gained attention for their ability to transport various biomolecules, including proteins, nucleic acids, and lipids, thereby facilitating the exchange of information between cells [199]. As researchers delve into the intricacies of EXOs biology, the translational potential of harnessing EXOs for therapeutic purposes has become a focal point. Clinical trials serve as a pivotal bridge between preclinical discoveries and real-world applications, providing insights into the safety, efficacy and feasibility of exosome-based nanomedicine. This section aims to provide a comprehensive overview of both ongoing and finished clinical trials, offering readers a glimpse into the dynamic landscape of research surrounding exosome-based interventions. By summarizing key details of these trials, we aim to highlight the progress, challenges, and potential breakthroughs in the application of exosome-based nanomedicine in the clinical setting. Several ongoing trials are shedding light on the safety, efficacy, and potential applications of EXOs. The trials displayed in Table 4.

9. Discussion and future direction

Neurological diseases have undergone a significant paradigm shift in recent years with the emergence of EXOs-based theranostics. With their unique composition and intercellular communication capabilities, EXOs have illuminated new avenues for targeted interventions in neurological disorders [200]. This review provides a comprehensive exploration of the theranostic potential of EXOs in the context of neurological diseases, highlighting their role in diagnosis, therapy, and nanomedicines. EXOs have proven to be potent carriers of therapeutic cargo, including miRNAs and gene vectors, paving the way for innovative strategies to modulate neuroinflammation at a molecular level. The utility of stem cell-derived EXOs as therapeutic agents has expanded our therapeutic arsenal, offering promising avenues for treating neuroinflammatory conditions. These advancements underscore the importance of harnessing the capabilities of EXOs to address the complex and multifaceted nature of neuroinflammation. While the theranostic potential of EXOs in neurological diseases is undoubtedly promising, several challenges remain to be addressed before their clinical translation can be fully realized [201]. The journey from bench to bedside necessitates a concerted effort to overcome these hurdles and unlock the full therapeutic power of EXOs-based interventions. One of the foremost challenges lies in refining the precision of EXOs-based delivery systems [203]. Developing strategies to enhance the specificity of targeting neuroinflammatory sites within the intricate architecture of the CNS is imperative. This requires integrating advanced imaging techniques and innovative engineering approaches to ensure the efficient and targeted delivery of EXOs loaded with therapeutic cargo. Moreover, the standardization of isolation, purification, and characterization methods for EXOs is pivotal [204]. Establishing robust protocols will facilitate comparative analysis across studies and streamline the regulatory pathways for clinical applications [205]. Collaborative efforts among researchers, clinicians, and regulatory bodies will be instrumental in setting forth guidelines that ensure the safety and efficacy of EXOs-based therapies. In addition, the expanding landscape of EXOs-based diagnostics warrants further exploration. The potential of EXOs as noninvasive biomarkers holds promise for early detection and monitoring of neurological diseases, enabling timely interventions and personalized treatment strategies. Looking toward the future, the integration of EXOs-based nanomedicine into the clinical armamentarium for neurological diseases appears imminent. However, the road ahead

Table 4
Clinical trials on EXOs for the management of neurological diseases/disorders.

Clinical trial No. (CT)	Phase	Trial name	Pathological condition	Target sample size	Intervention	Current status
NCT05370105	1	EVs as Stroke Biomarkers (EXO4STROKE)	Stroke	100	blood withdrawal	Recruiting
NCT01811381	2	Curcumin and yoga therapy for those at risk for AD	AD	80	Drug: Curcumin Behavioral: aerobic yoga Behavioral: non aerobic yoga	Unknown status
NCT05490173	Not applicable	Long-term Regular Tai Chi Training for Healthy Elderly Circulating EXOs Release and Cognitive Neural Circuits/ Networks Activity Characteristics Research	Cognitive	50	Long-term Irregular exercise group	Not yet Recruiting
ChiCTR2200057303	Retrospective study	A single-center randomized controlled study of human neural stem cell-derived EXOs in the treatment of ischemic stroke	Ischemic stroke	5	Treatment group: EXOs Control group: Saline	Pending
ChiCTR2100048661	Retrospective study	Differential diagnosis of unipolar depression and bipolar depression based on neurogenic exosome miRNA	Depression	800	Gold Standard: Hamilton Depression Scale 17 items, Young's Manic Scale, DSM-5, M.I.N.I scale.; Index test: Methods: Neurogenic EXOs were isolated and miRNA sequenced; Biomarker: neurogenic exosome miRNA; Equipment: Illumina MiSeq.	Pending
ChiCTR2100044323	1	EXOs alterations following electroconvulsive therapy in depression	Depression	50	Depression cases: electroconvulsive therapy	Recruiting
ChiCTR2000039377	1	EXOs derived from Neural stem cell Induces Osteogenesis and angiogenesis following traumatic brain injury	TBI	6	normal patient group: Nil; patient with limb fracture only: Nil; patient with TBI only: Nil; patient with limb fracture following TBI: Nil	Recruiting
ChiCTR2000038262	Retrospective study	The effects on circRNAs' expression in the plasma EXOs of patients with Perioperative Neurocognitive Disorders after noncardiac surgery	Cognitive disorders	40	control group: After induction of anesthesia, 0.9%NS was injected under load, and then 0.9%NS was continuously pumped into the suture.; trial group: After anesthesia induction, 0.25 mg/kg S-ketamine was injected under load, and 0.125 mg/kg/h S-ketamine was continuously pumped until the suture.	Pending
ChiCTR2000032579	Retrospective study	The Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients with AD	AD	3	Low-dose group: 5 μg MSCs-Exos administrated for nasal drip; mid-dose group: 10 μg MSCs-Exos administrated for nasal drip; high-dose group: 20 μg MSCs-Exos administrated for nasal drip	Pending
NCT04202770	1	Focused Ultrasound and EXOs to Treat Depression, Anxiety, and Dementias	Anxiety and dementia	300	EXOs	Suspended
ChiCTR1900026776	1	Screening for early diagnosis biomarkers of mental disorders in serum EXOs	Mental disorders	615	N/A	Recruiting
NCT05886205	1	Induced Pluripotent Stem Cell Derived EXOs Nasal Drops for the Treatment of Refractory Focal Epilepsy	Epilepsy	34	Drug: iPSC-Exos	Recruiting
ChiCTR2200064447	Retrospective study	Study on the mechanism of exosome miRNA mediated autophagy in temporal lobe epilepsy	Epilepsy	20	Oxcarbazepine group: Take oxcarbazepine; Oxcarbazepine + CLMD group: Take oxcarbazepine + CLMD; Control group: None	Pending

demands unwavering dedication and innovative thinking to bridge the translational gap and usher in a new era of precision medicine for individuals grappling with neuroinflammation-associated afflictions. With continued advancements in EXOs research and collaborative interdisciplinary efforts, we are poised to revolutionize the landscape of neurological disease management, offering newfound hope and improved quality of life for countless individuals worldwide.

CRediT authorship contribution statement

Gurpreet Singh: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Ankit Mehra:** Writing – original draft, Methodology. **Sanchit Arora:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Dalapathi Gugulothu:** Writing – review & editing, Supervision, Resources, Conceptualization. **Lalitkumar Vora:** Writing – review & editing, Resources, Funding acquisition, Formal analysis, Conceptualization. **Renuka Prasad:** Writing – review & editing, Writing – original draft, Conceptualization. **Dharmendra Kumar Khatri:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Declaration of competing interest

All authors have no conflicts of interest.

Data availability

No data was used for the research described in the article.

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