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Unveiling the role of exosomes as cellular messengers in neurodegenerative diseases and their potential therapeutic implications

Sumel Ashique [a,b], Nitish Kumar [c], Neeraj Mishra [d], Sathish Muthu [e,f], Ramya Lakshmi Rajendran [g], Balakumar Chandrasekaran [h], Brenya Francis Obeng [i], Chae Moon Hong [g,l], Anand Krishnan [j,*], Byeong-Cheol Ahn [g,k,l,**], Prakash Gangadaran [g,k,**]

[a] Department of Pharmaceutics, Bengal College of Pharmaceutical Sciences & Research, Durgapur, West Bengal 713212, India
[b] Research Scholar, School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab 144411, India
[c] SRM Modinagar College of Pharmacy, SRM Institute of Science and Technology (Deemed to be University), Delhi-NCR Campus, Modinagar, Ghaziabad, Uttar Pradesh 201204, India
[d] Amity Institute of Pharmacy, Amity University Madhya Pradesh (AUMP), Gwalior, Madhya Pradesh 474005, India
[e] Department of Orthopaedics, Orthopaedic Research Group, Coimbatore, Tamil Nadu 641045, India
[f] Department of Biotechnology, Faculty of Engineering, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu 641021, India
[g] Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu 41944, the Republic of Korea
[h] Faculty of Pharmacy, Philadelphia University, P.O. Box 1, Amman 19392, Jordan
[i] Faculty of Science, College of Health and Allied Sciences, School of Medical Sciences, University of Cape Coast, PMB, Cape Coast, Ghana
[j] Department of Chemical Pathology, School of Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein 9300, South Africa
[k] BK21 FOUR KNU Convergence Educational Program of Biomedical Sciences for Creative Future Talents, Department of Biomedical Science, School of Medicine, Kyungpook National University, Daegu 41944, the Republic of Korea
[l] Department of Nuclear Medicine, Kyungpook National University Hospital, Daegu 41944, the Republic of Korea

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ABSTRACT

Exosomes are a subgroup of extracellular vesicles that function as transmitters, allowing cells to communicate more effectively with each other. However, exosomes may have both beneficial and harmful impacts on central nervous system disorders. Hence, the fundamental molecular mechanisms of the origin of illness and its progression are currently being investigated. The involvement of exosomes in the origin and propagation of neurodegenerative illness has been demonstrated recently. Exosomes provide a representation of the intracellular environment since they include various essential bioactive chemicals. The latest studies have demonstrated that exosomes transport several proteins. Additionally, these physiological vesicles are important in the regeneration of nervous tissue and the healing of neuronal lesions. They also offer a microenvironment to stimulate the conformational variation of concerning proteins for aggregation, resulting in neurodegenerative diseases. The biosynthesis, composition, and significance of exosomes as extracellular biomarkers in neurodegenerative disorders are discussed in this article, with a particular emphasis on their neuroprotective effects.

1. Introduction

In recent years, the prevalence of neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS), and other neuronal complications has increased dramatically because of longer life expectancy, environmental pollution, and various other factors combined. In addition to being a category of refractory illnesses, neurodegenerative disorders have imposed a significant medical, social, and economic impact globally. Although significant attempts to understand the pathogenic causes and therapeutic strategies to manage neurodegenerative disorders were developed, only a few have been efficacious [1].

Exosomes are released by almost all cell types and contain macromolecules such as lipids, proteins, and nucleic acids, including non-coding RNA (ncRNA). Examples of non-coding RNAs are long non-coding RNA (lncRNA), microRNA (miRNA), and messenger RNA

* Corresponding author.
** Corresponding authors at:Department of Nuclear Medicine, School of Medicine, Kyungpook National University, Daegu 41944, the Republic of Korea.
E-mail addresses: Krishnana1@ufs.ac.za (A. Krishnan), abc2000@knu.ac.kr (B.-C. Ahn), prakashg@knu.ac.kr (P. Gangadaran).

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(mRNA). Following release, these exosomes target specific tissues such as the brain (central nervous system [CNS]) and blood cells (lymphocytes), causing pleiotropic impacts [2]. Exosomes are involved in a variety of physiologic and pathological functions as well as in establishing intercellular interaction between cells, making them essential in the manifestation of a variety of disorders, including immunological diseases, cancers, and neurodegenerative disorders [3]. Exosomes that play a role in neurodegenerative illnesses come from a variety of places, including human mesenchymal stem cells (MSCs), immune cells, and microglia [4,5]. Exosomes originating from various sources with various cargos seem to have a distinct influence on neurodegenerative disorders [6]. Various biologically fundamental events in neurodegenerative disorders have had several consequences. Exosomes have been linked to neurodegenerative disorders because they are thought to contain information about physiological changes in the cells from which they originate. According to various studies, exosomes may thus have therapeutic and neuroprotective functions in neurodegenerative disorders. Exosomes are implicated not just in the transmission of macromolecules and pathogens linked to neurodegenerative disorders, but also in neuroprotection by encapsulating macromolecules, which requires further investigation. Exosomes are also linked to treatment methods such as neuroinflammatory condition management and gene therapy, where they are utilized to transfer medications or therapeutic nucleic acids such as short interfering RNA (siRNA) or miRNA to target areas [7]. Hence, this review focuses on the function of exosomes in neurodegeneration and how they might be used in neuroprotective therapies.

2. Molecular composition and biogenesis of exosomes

Exosomes are microscopic endosomal-derived cup-shaped membrane vesicles with a diameter of 30–150 nm and a density of 1.13–1.19 g/cm^2. Exosomes are produced by secretion from a variety of cells (neurons, endothelial cells, epithelial cells, mast cells, platelets, and dendritic cells [DCs]). In addition, they may be found in a variety of biological fluids, including plasma, amniotic fluid, urine, breast milk, saliva, and others [8,9]. Exosomes are made up of a complicated and solitary combination of macromolecules comprising DNA, miRNAs, mRNAs, lipids, and proteins, as illustrated in Fig. 1 [10,11]. Exosomes

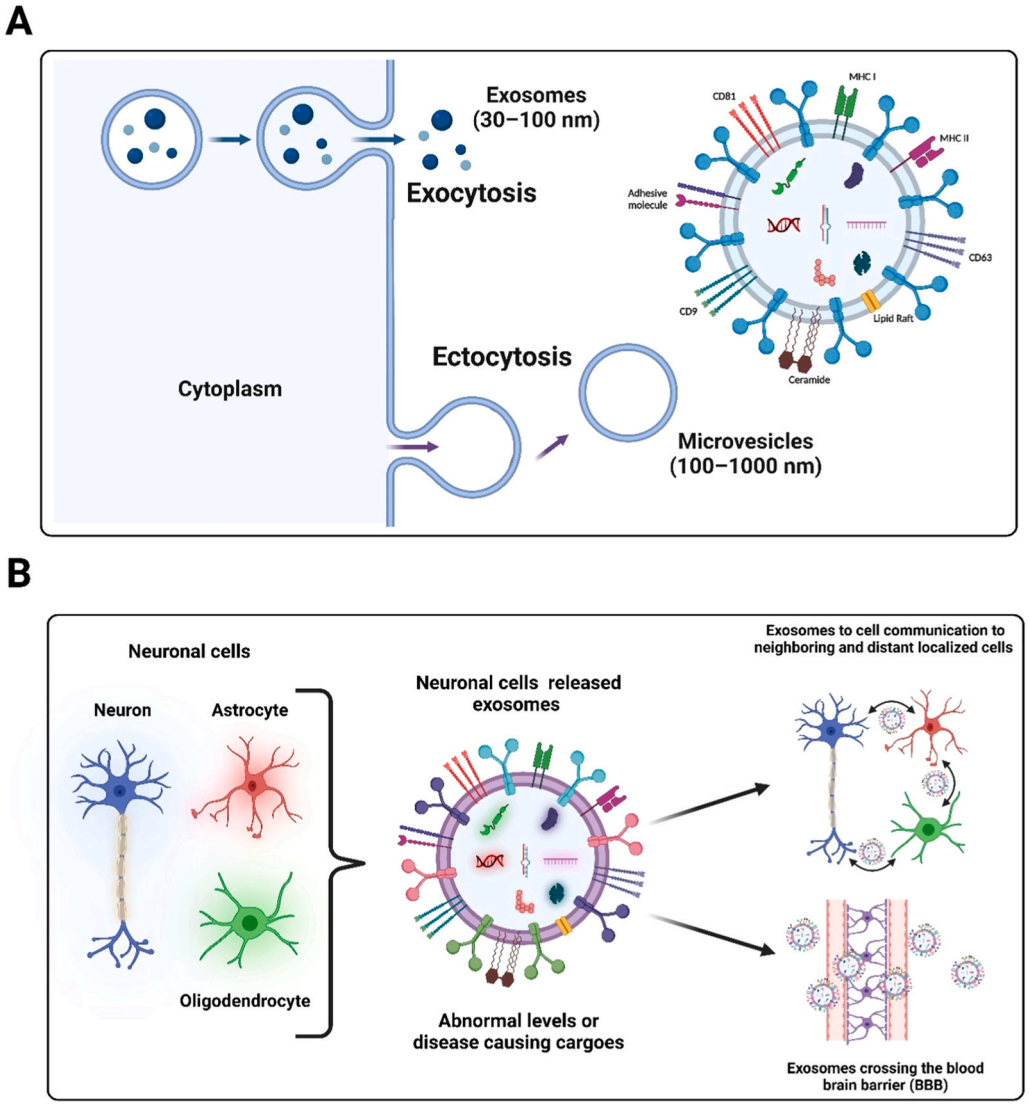


Fig. 1. : Exosome Structure, Origin, and Role in Neurological Diseases. (A) Exosomes have a lipid bilayer structure and carry various biomolecules such as proteins, lipids, and nucleic acids. Exosomes originate from the endosomal secretory pathway, where early endosomes mature into late endosomes and multivesicular bodies (MVBs), which then fuse with the plasma membrane to release exosomes. (B) Exosome production in neuronal cells can worsen neurological diseases by carrying disease-causing cargoes to nearby and distant cells. However, their ability to cross the blood-brain barrier (BBB) can also help prevent various neurological diseases. Created with BioRender.com.

from various creatures have been shown to include a diversity of nearly 1639 mRNAs, 194 lipids, 764 miRNAs, and 4563 proteins, as per the "ExoCarta" database [12]. Cargo and constitutive molecules are the two types of components found in exosomes. Constitutive molecules have a critical impact on the functional and structural features of exosomes, and they are specific to the exosome depending on the originating cell type. Exosomes carry a variety of cargo molecules, including proteins, lipids, and genetic elements, all of which are encapsulated, sorted, and carried by the exosome transport system. These cargo molecules are exceedingly varied, depending on the cell of origin and the pathological or physiological circumstances under which they form. Protein cargoes like heat shock proteins (Hsc70 and Hsp90), several forms of tetraspanins (CD82, CD81, CD63, and CD9), Tsg101, Alix, GTPases, Rab, and flotillin lipid cargoes are important in controlling the exosomal sorting of small RNAs and protein molecules (Fig. 1A). DNA and other forms of RNA (lncRNA, circular RNA, rRNA, mRNA, and miRNA), make up the genetic material cargoes [6]. Cell membrane anchoring sheddases (e.g., ADAM, a disintegrin, and metalloproteinase), as well as the cell membrane and soluble matrix metalloproteinases (MMPs), were also discovered during the proteomic study of exosomes [13]. Exosomes are also produced through the endosomal route, which involves the invagination of biological membranes and the entrapment of cytosolic constituents to create "early endosomes." Such early endosomes go through a developmental phase that results in the creation of "late endosomes" due to changes in their biomolecular makeup. The endosomal layer invaginates throughout this development phase, forming intraluminal vesicles (ILVs) in the organelle lumen. The microvesicular structures are then fused to the lysosome membrane and degraded, or they are discharged into the extracellular area by fusion with the plasma membrane [14]. Investigating exosome synthesis and trafficking might help researchers to better understand how cells use exosomes for cell-to-cell interactions and microenvironment changes [15]. Exosome synthesis and subsequent release were shown to be highly dependent on the physiological state and circumstances of both the producing and destination cells, resulting in variable compositions of nucleic acids, lipids, and proteins in various exosomes [3,16–18]. According to previous investigations, exosome production and secretion are thought to include both endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent mechanisms [14]. The ESCRT unit is composed of four primary protein compounds: ESCRT0, ESCRT-I, ESCRT-II, and ESCRTIII, and the AAA ATPase Vps4 Complex. Seven ESCRT proteins were discovered to participate in the production of exosomes in an investigation using an RNA interference screening targeting elements of ESCRT and related proteins [19]. ESCRT and numerous other proteins are engaged in the sorting and packaging of proteins throughout exosome maturation. Numerous scientific investigations [20,21] have detailed the molecular processes underlying the synthesis of exosomes and protein complexes that participate in cargo sorting and packaging.

3. Types of aggregated proteins in neurodegenerative diseases

Most neurodegenerative disorders are assumed to follow a similar progression paradigm. An unusually folded disease-related protein forms an organized association with the capacity to spread within a cell by self-associating into a sheet structure. Nevertheless, the language used to characterize these complexes, as well as their potential to transmit disease within and across the cells and individuals, is debatable. For almost a century, the word "amyloid" has been used to characterize extracellular protein clumps, seen in diseased organs and tissue, which are insoluble and resistant to breakdown. Perhaps the most well-known of these aggregations is the β-amyloid (Aβ) (A) peptide, which creates amyloids in Alzheimer's disease [15]. A distinct intracellular aggregation occurs in neurodegeneration, consisting mostly of synuclein, which is implicated in a variety of synucleinopathies, including Parkinson's disease and dementia with Lewy bodies (DLB) [22]. The term "prion" (proteinaceous infectious molecule) was developed to define a contagious protein aggregation with the potential for propagation between people [23]. Moreover, the infectious agent in prion pathology has been identified as the PrP^{Sc} protein, which is implicated in Creutzfeldt-Jakob Disease (CJD) in humans (Scrapie in sheep). Additional terminology such as "paranoid" or "prion-like" has been coined based on this concept and the latest investigation findings in various neurodegenerative disorders concerning pathological transmission, which does not include PrP proteins [24]

4. Role of exosomal proteins in neurodegenerative disorders

Exosomes have various roles in cell-to-cell interaction. Cells of the CNS including Schwann cells, microglia, astrocytes, and oligodendrocytes, generate cell-type-specific exosomes that may operate as cargo transport systems for facilitating interactions across distinct cell types [25]. Exosome release is controlled by several neurotransmitters, which have been shown to aid in the interaction between oligodendrocytes and neuronal cells, as well as play important functions in neuronal integrity and myelination, as explained in Fig. 1A–B [26]. Exosomes are involved in transmitting hazardous protein molecules from neurons to glia or neurons to neurons [27]. Protein misfolding and agglomeration, and cell-cell transfer of particular disease-related proteins all contribute to the propagation of pathogenic protein aggregates [28]. A few instances regarding the analysis of proteins implicated in neurodegeneration will be presented briefly.

5. Exosome-mediated intercellular communication in the nervous system

In 1980, exosomes were thought to dispose of cell debris [29]. Meanwhile, they have been shown to perform a variety of functions in biological processes such as cell-cell interaction through tight junctions, receptors/ligands, or electrical and chemical impulses [30]. In one study, exosome production was increased in neural cells after therapy using a GABA-receptor antagonist (bicuculline). Nevertheless, this enhancement was prevented by N-methyl-D-aspartate (NMDA) or alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) antagonists (CNQX) [31]. Exosomes released by oligodendrocytes into the extracellular environment may suppress architectural differentiation and myelin production in oligodendrocytes, and this action can be inhibited by antagonists of actomyosin contractility [32]. As per the recent investigation, microglia may ingest exosomes secreted by oligodendroglia through macropinocytosis, and these exosomes are subsequently transported to late endosomes and lysosomes [33,34]. Nerve cells also use exosomes to communicate with other cells and regulate homeostatic functions such as neurogenesis and synaptic function. Exosomes were shown to be released from the somatodendritic regions of mature cortical neurons in investigations utilizing electron microscopy, indicating that neurons produce exosomes [31]. Exosomes produced from primary cortical neurons included a variety of functional proteins that may influence synaptic function, and their release was regulated by cellular depolarization [35]. Numerous investigations have shown that microglia can crosstalk with neurons and attenuate neurological function via exosomes that control neurotransmitter discharge from glial cells. This promotes neuronal outgrowth in hippocampal neurons and the survival of cortical neurons [36]. The extracellular vesicles secreted by microglia include a variety of miRNAs (i.e., miR-146a-5p) that modulate synaptic protein production [37]. Exosomes exhibit a potential impact on intercellular interactions because of their connection/communication between receptors on target tissue/-cells and proteins, proteolysis of their payloads, and ingestion of their components through endocytosis. Furthermore, they facilitate interactions through the transfer of nucleic acids in both normal and disease conditions, suggesting that they are engaged in cellular formation, functionality, and pathogenesis.

6. Role of exosomes in neurodevelopment

Many different types of cells in the CNS have been documented to secrete exosomes (Fig. 2A). As per recent research, exosomes have a critical role in regular neuro-progression, such as neuroplasticity, and contribute to pathological alterations in neuro-developmental illnesses [38]. Notably, exosomes generated from the embryonic cerebrospinal fluid are responsible for enhancing neural-stem cell multiplication through the rapamycin complex-1 pathway [39]. These exosomes operate as modulators of neuronal stem cell growth and cell division. Moreover, they act as a controller in the niche of mesenchymal stem cells of the brain [40]. MiR-21a in exosomes produced by neural progenitor cells was reported to boost neuronal differentiation and improve neurogenesis [41]. Additionally, *in-vitro* findings have suggested that exosomes originating from human induced pluripotent stem cells (hiPSCs) can augment the growth of neural cultures. Similarly, exosomes of DIV9 rodents (primary neuronal cultures) were injected into a P4 mouse brain (the lateral ventricle of the brain), which stimulated neurogenesis in the hippocampus (the dentate gyrus) [42]. Exosomes control synaptogenesis and neuronal circuit formation as well as neurogenesis. Neuronal exosomes contain GluR2/3 subunit receptors whereas microglial exosomes are rich in inflammatory cytokine (IL-β), cholesterol, histone proteins (astrocytes and Hsp70), lipids (myelin lipids), synapsin-1, and galactocerebrosides [43].

Protein aggregation is a clinical characteristic of neurodegenerative illnesses and protein agglomeration. The vesicles control axonal transport, synaptic transport, proteasomal activities, mitochondrial activity, and increased endoplasmic reticulum stress [44]. Exosomes' capacity to transport aggregated proteins accelerates the development of neurodegenerative disorders (Fig. 2B). Neuroinflammation is characterized by constant inflammation in CNS tissue and the over-activity of astrocytes and microglia cells. Activated microglial cells release various inflammatory factors, tissue necrosis factors (TNF-α and β), cytokines, chemokines, nuclear factor κ-B, and enzymes. Additionally, excessive reactive oxygen species (ROS) production activates microglia, resulting in an inflammatory reaction in the brain. Microglial cells are also reported to secret various enzymes such as cyclooxygenase-2 and lipoxygenases (5-LOX and 12-LOX) [45]. Because exosomes transport inflammatory chemicals, they are also inflammatory agents. The connection between neurons and glia has been linked to neuroinflammation [46]. For example, hyperphosphorylated tau protein and Aβ pathogenesis are two major pathological markers of AD. To initiate an inflammatory cascade, Aβ is encapsulated into exosomes and extended across cells. Aβ-induced microglia activation has a neuroprotective impact due to phagocytosis and Aβ degradation. Exosomes are released by microglia and activated by astrocyte-produced ATP to shield them from astrocyte signaling [47]. Astrocytes may also internalize α-synuclein (α-syn) deposits. This process is linked to the subsequent creation of inclusion bodies in the brains of PD patients, and the onset of an inflammatory reaction. Exosomes generated by active microglia are also the main modulator of α-syn-induced neurotoxicity [48].

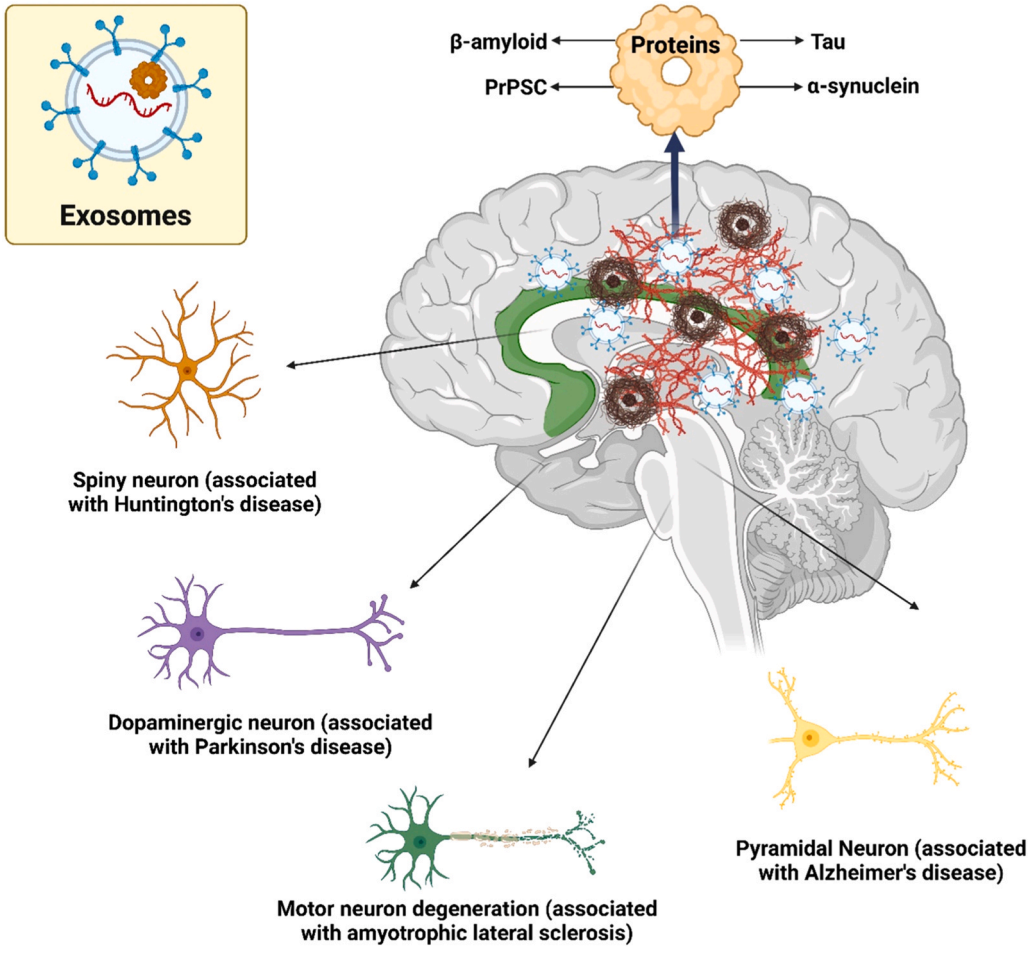


Fig. 2. : Role of Exosomes in Intercellular Communication and Neurodegenerative Disorders**.** Exosomes are essential for a variety of biological functions, including intercellular communication. They play a significant role in the pathology of various neurodegenerative diseases through the accumulation and transfer of concerned proteins such as β-amyloid, PrPSC, Tau, and α-synuclein. This accumulation leads to the progression of neurological disorders including Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. PrPSc: Scrapie prion protein. Created with BioRender.com.

7. Exosomal biomarkers in neurodegenerative disorders

PD is caused by the aggregation of the neuronal termination protein α-syn, whereas ALS is caused by an aggregation of phosphorylated TDP43 (a transcription blocker) and superoxide dismutase 1 (SOD1) (Fig. 3). Huntington's disease is caused by an accumulation of mutant Huntington's proteins [49]. Apart from the accumulation of improperly coiled proteins, these neurodegenerative disorders have diverse constituents and pathophysiologies, along with many similarities. Overloaded protein clearance mechanisms, poor protein equilibrium, and malfunction or loss of certain neuron populations are only a few examples. Neurological impairment starts with the irreversible loss of neurons and synapses, which is a hallmark of this illness [50]. In addition to serving as possible carriers, exosomes have been shown to play a significant role in the pathophysiology of neurodegenerative disorders and aid in their transmission (Table 1) [51]. On reaching systemic circulation, these exosomes serve as biomarkers for early diagnosis and prediction of various neurodegenerative diseases, which can be utilized as a non-invasive technique.

8. Impact of Exosomes on various neurodegenerative disorders

Neurodegeneration is a common feature of neurodegenerative diseases such as AD, HD, PD, Niemann–Pick disease, frontotemporal dementia, and ALS. Furthermore, protein accumulation and the creation of inclusion bodies in specific parts of the CNS are similar cellular and molecular mechanisms involved in all these illnesses. The proper sorting of proteins within cells, as well as the breakdown of cellular proteins, are vital for the functioning of neurons (Fig. 4) [60]. Exosomes are implicated in the transmission of 'toxic' proteins, which are mutant or misfolded, and act as templates for the production of oligomers in neurodegenerative disorders [61]. Neurons attempt to decrease the accumulated protein by an endosomal route that either leads to lysosome destruction or integration into multivesicular bodies (MVBs) and the formation of exosomes in the extracellular environment. Several studies have shown that normal "prion protein (PrP)" and "misfolded pathogenic prion protein (PrP^{Sc})" are both incorporated into exosomes [62]. According to Vella et al., PrP^{Sc}, which is coupled to exosomes, is transmitted to the normal cell harboring PrP. Exosomes were included by mimicking the method through which proteins seed their accumulation. Several neurodegenerative illnesses are associated with 'infectious' transport through exosomes [63].

9. Alzheimer's disease (AD)

MVB participation in AD sufferers was initially identified in 1970. MVBs are more abundant in forebrain cortical neurons [64]. The accumulation of aberrant proteins activates microglia and astrocytes, triggering a persistent inflammatory reaction that results in the release of several cytokines that may cause neuronal death and additional Aβ build-up in neurons. As a result, the neuroinflammation process is involved in precipitating AD. Pathologically, amyloid β42 (Aβ42) peptides slowly accumulate in MVBs and function as a prime constituent of the plaque characterizing AD [65]. Exosomes might have a crucial influence on the neuroinflammation seen in AD. Individuals with AD exhibit larger quantities of complement proteins in astrocyte-derived exosomes (ADEs), such as C1q, C46, and factor-B, as compared to healthy controls. Microglia may internalize and destroy soluble Aβ42

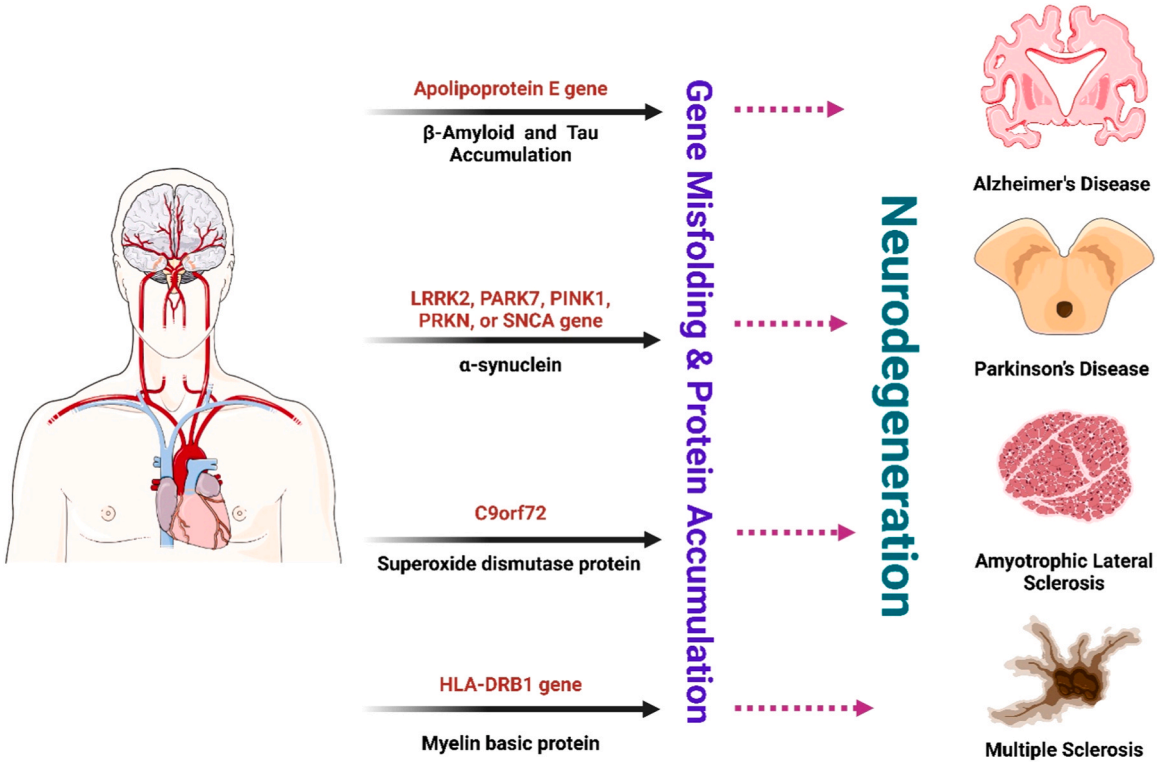


Fig. 3. : Protein Misfolding and Neuronal Dysfunction: The Role of Protein Aggregates in Neurodegenerative Disorders**.** The gradual malfunctioning of particular neuron populations characterises neurodegenerative disorders and shapes their clinical presentations. Misfolded protein accumulations within and outside of cells are associated with neuronal loss and are a common feature of many neurodegenerative proteinopathies. These buildups are frequently linked to misfolded proteins, faulty protein synthesis, and aberrant gene signalling (genetic mutations). Many neurodegenerative disorders are associated with misfolded proteins and aberrant disorder-to-order transitions in protein structures. Protein aggregates created by misfolded genes change the structural and molecular makeup of nerve cells. LRRK2: Leucine-Rich Repeat Kinase 2; PARK7: Parkinson Protein 7 (also known as DJ-1); PINK1: PTEN-Induced Kinase 1; PRKN: Parkin RBR E3 Ubiquitin Protein Ligase; SNCA: Synuclein Alpha; C9orf72: Chromosome 9 Open Reading Frame 72; HLA-DRB1: Major Histocompatibility Complex, Class II, DR Beta 1. Created with BioRender.com.

Table 1
Various biomarkers related to neurodegenerative disorders.

Neurodegenerative disorders	Sources	Biomarkers	Mechanisms	References
Alzheimer's disease	Plasma, CSF, and serum	Lamp-1, IRS, REST, Aβ, NFT, HSF-1, miR-135a, miR-384, and miR-193b	Neuron damage	[52,53]
Parkinson's disease	CSF	miR-136–3p, α -syn, miR-485–5p, DJ-1 miR-1, miR-153, 3p, miR-409, miR-433, let-7 g-3p, miR-10a-5p, miR-19b-3p, miR-132–5p, miR-873–3p, and miR-370	Neuron damage	[54,55]
Amyotrophic lateral sclerosis	CSF, plasma, and blood plasma	MiR-9–5p, TDP-43, miR-15a-5p, miR-183–5p, and miR-193a-5p	Neuron damage and inflammation	[56,57]
Huntington's disease	Blood plasma	miR-425–5p, mHtt, miR-233–3p, miR-877–5p, miR-30d-5p, miR-22–5p, miR-128, miR-223–5p, miR-338–3p, miR-222–3p, miR-628–3p, miR-130b-3p, and miR-361–5p	Neuron damage	[58,59]

NFT: Neurofibrillary tangles, CSF: Cerebrospinal fluid, α-syn: alpha-synuclein, DJ-1: oxidative stress sensor, PrP^{Sc}: misfolded prion protein, TDP-43: a protein regulating gene expression, mHtt: produces mutant Huntington protein, REST: repressor element 1-silencing transcription factor, IRS: phosphorylated type 1 insulin receptor substrate

species, but they could also secrete exosomes that enhance extracellular soluble Aβ42 species accumulation. Additionally, neuronal astrocytes or their exosomes can promote soluble Aβ42 accumulation. Exosomes released by neurons may also improve the microglia's capacity to scavenge Aβ42. Neurotoxin production is triggered by the formation of Aβ oligomeric fibrils, which act as a seeding site for AD pathogenesis in nave mice [66]. The amyloid precursor protein is proteolytically digested at the cell membrane to produce peptides that are absorbed into endosomes, digested in MVBs, and discharged as exosomes [67]. Exosomes are thought to have a role in AD because of the improper sorting and build-up of Aβ, which then spreads to other tissues through exosomes. Additionally, the oral injection of amyloid A1 (amyloidosis) into cheetahs (*Acinonyx jubatus*) implies that the disease is transmitted through exosomes seen in saliva and feces [68]. When the clearance route is overloaded, exosomes contribute to both the breakdown of toxic Aβ and the build-up of hazardous peptides [69]. Although there is an indication that exosomes are involved in the transfer of Aβ and tau proteins, their exact involvement in the AD process is unknown. In previous research, exosome transmission of these two proteins was shown to involve the degradation of neuronal microtubules, resulting in axonal transmission, whereas few of these have been reported to decrease the level of amyloid beta-protein absorbed by microglial cells [70]. Plasma or CSF-based exosomes (obtained from patients with AD) have been shown to contain the same beta-protein, suggesting that these might be employed as AD biomarkers [53]. Moreover, patients' serum samples showed changes in P-tau and Aβ levels, proving that they might be utilized as AD predictors even before symptoms appear [71]. It was also discovered that the serum of patients with AD contains various diagnostic proteins in neuronal exosomes, the level of which is altered over time (10 years). These proteins are Lamp 1, heat-shock factor-1, phosphorylated type 1 insulin receptor substrate (IRS), and repressor element 1-silencing transcription factor (REST).

Exosomes released by various brain tissue cells seem to have a variety of functions in the development and progression of AD [55]. One of the primary reasons for increased exosome formation in AD is the loss of functionality of the endosomal-lysosomal pathway owing to a heterozygous or homozygous Apo E4 genotype [72]. Proteasomal and lysosomal dysfunctions are linked to AD, which is why the Aβ precursor protein (APP)-carrying MVEs unite with the plasma wall. In general, the late endosome can either merge with a lysosome, resulting in the degradation of their intrinsic substances and the presence of hydrolases, or it can merge with MVEs made up of ILVs and the plasma membrane, resulting in the formation of the exosome [73]. Extracellular vesicles have been shown to play a role in the dispersion of Aβ and thereby exuberate Aβ pathology in AD (Table 2) [67].

10. Parkinson's disease (PD)

PD is the 2nd most common neurodegenerative disorder after AD, and it is defined by motion abnormalities in those over the age of 65 years. The worldwide incidence frequency of PD ranges from 5 to > 35 new cases per 0.1 million people [80,81]. The destruction of dopaminergic neurons in the substantia nigra of the midbrain is the primary pathological characteristic of PD. Another significant molecular and neurophysiological mechanism of PD pathogenesis is the intraneuronal agglomeration of misfolded α-syn and the appearance of Lewy bodies owing to oligomeric α-syn accumulation (Fig. 4) [82]. Most PD cases (around 90 %) are sporadic, but marital instances have been related to genes like α-syn and leucine-rich receptor kinase 2 (LRRK2). Unfortunately, the actual mechanism underlying the onset and course of the illness is still unclear [83]. Exosomes play a key role in PD by transferring the toxic form of α-syn to other cells and eventually releasing them [84,85]. Inflammatory responses, mitochondrial abnormalities, proteasomal consequences, and endoplasmic reticulum stress are all promoted by the neurotoxic effects of accumulated α-syn. Endocytosis is used by astrocytes and microglia to remove the accumulated α-syn. On the other hand, increased neuronal absorption of α-syn might cause glial inclusions, which can promote inflammatory reactions [86]. α-syn is usually found in a monomeric state, but after attaining neurotoxic characteristics, it undergoes oligomerization and accumulates further to produce protofibrils.

LRRK2 has been shown to co-localize with MVBs and play a significant role in exosome secretion and MVB fusion with the plasma membrane [87]. According to Shin et al., LRRK2 binds with Rab5b, which is an enzyme that regulates vesicle trafficking in the cytoplasm. Skein-like abnormal MVBs may form if a mutation arises in the LRRK2 gene R1441C. Because of the pathological LRRK2 activity, these excessively massive MVBs produce a significant number of exosomes, which may comprise the toxic form of α-syn, causing the illness to spread. Furthermore, the tau protein interacts with α-syn, boosting oligomerization and cytotoxicity of these proteins, which may accelerate the exosome-mediated production of the α-syn toxin from damaged neurons [88]. The retromer complex requires the vacuolar sorting protein 35 (VPS35), which is involved in parkinsonism. Sullivan et al. suggested that APP cells' increased exosomal production might be attributable to faulty retromer function [89]. The exosomal apparatus serves as a backup strategy for spreading early molecular changes associated with Parkinson's disease to other cells [90,91]. In a recent study, α-syn was shown to stimulate the formation of exosomes by mouse microglial BV-2 cells [92]. Additionally, exosomes may preserve neurons by inhibiting the LAS pathway, as shown by enhanced exosomal payload production

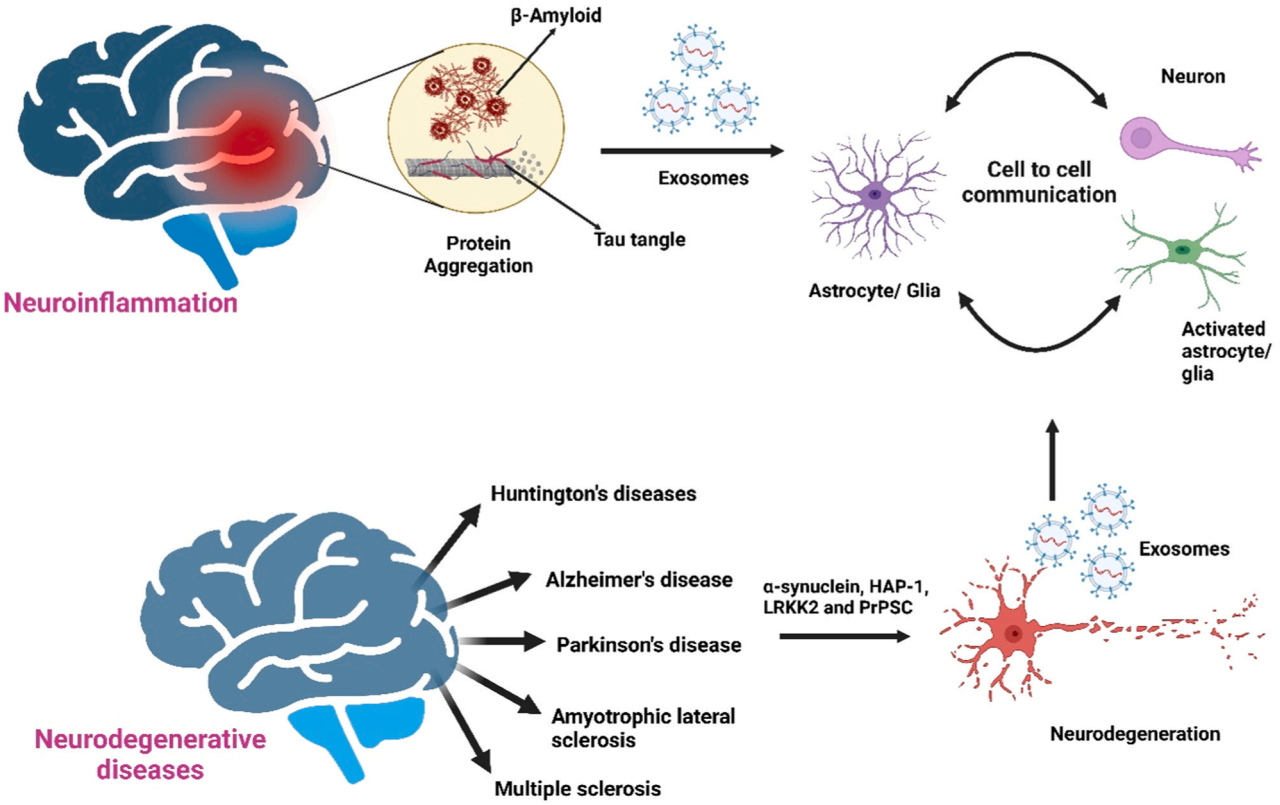


Fig. 4. Exosome-mediated Misfolded Protein Transfer in Neurodegenerative Disease Progression: Mechanisms and Therapeutic Targets. Neurodegenerative diseases are partly caused by the interaction of various functional molecules (α-synuclein, HAP-1, LRKK2 and PrPSC) produced by damaged neurons' exosomes. These misfolded proteins cause native proteins in the receiving cells to aggregate by spreading across the cell in a manner akin to prion propagation. It is thought that exosomes aid in the transfer of these misfolded molecules, contributing to progression of the diseases. The toxic neurological proteins derived from exosomes prevent neurons from functioning normally. The intricacy of neurodegenerative diseases is highlighted by this intercellular communication, which also identifies possible treatment targets. Developing solutions to stop the course of disease requires an understanding of the mechanisms behind exosome-mediated protein transfer. HAP-1: Huntingtin-associated protein 1; LRRK2: Leucine-rich repeat kinase 2 and PrPSC: Prion protein scrapie. Created with BioRender.com.

Table 2
The role of neuronal exosomes in the pathogenesis of Alzheimer's disease.

	Functions	Origins	Activation and expression	Cargos	Mechanisms	References
Neurons	Propagated and cleared toxic proteins	Brain of AD patient, embryo of rats (cortical neurons), neuroblastomas, N2a cells	Vps34 kinase inhibition (VPS34IN1). Induced lysosomal dysfunctioning	Aβ tau protein, Glycosphingolipid. Undigested lysosome substrate	Mediates the propagation of Aβ between neurons, causes cytotoxicity, and is involved in the trans-synaptic transmission of tau-protein. Promoted degradation of transformed Aβ (non-toxic) and reduced deposition of amyloid fibrils for homeostasis.	[5,27,69, 74–76]
Microglia	Propagation of toxic proteins, transmission of neuroinflammation	Cultured murine microglial cells (mouse)	Aggregated tau-proteins 1–441 (human), ATP, and LPS. IL-10, IL-4, and LPS	Tau protein down-regulated anti-inflammatory miRNAs and up-regulated pro-inflammatory miRNAs	Promoted neuroinflammatory transmission. Tau protein spreads in the brain.	[5,77]
Astrocyte	Propagation of toxic proteins, transmission of neuroinflammation, apoptosis of astrocytes	Untransformed cortical adult human astrocytes, ADEs obtained from the plasma of patients with AD	Aβ25 – 35 Aβ	Tau and p-tau proteins, L-6, TNF-α, IL-1β, complement proteins, ceramide, and PAR-4 (prostate apoptosis response 4)	Influences the spread of tau protein in the brain. Mediates neuroinflammation and neuronal damage in late AD. Induced apoptosis by caspase-3 activation.	[78,79]

with α-syn and reduced intra-neuronal α-syn agglomeration [47]. These observations suggest that the activation of large MVBs by the R1441C-LRRK2 mutation might be related to the production of exosomes (Table 3).

11. Amyotrophic lateral sclerosis (ALS)

An inflammatory cascade reaction is responsible for the fundamental pathological characteristic of ALS, which is caused by an instability of protein-homeostasis in the brain region, prion-like dissemination of aberrant proteins, and mitochondrial malfunctioning. Pathologically, the mutation in the SOD1 gene causes aberrant assembling of the SOD1

Table 3
Mechanistic summary of various exosomes originating from the neuron and their pathological role in PD.

	Roles	Cells	Expressions	Responsible cargos	Mechanisms	References
Neurons	Release of toxic proteins Protein aggregation and inflammation	Differentiated SH-SY5Y cell line MN9D cell model	Over-expressed α-syn (wild type) Neurotoxic Mn (heavy metal from the environment)	α-syn miR-16–5p, miR-325–5p, miR-210–5p, miR-128–1–5	Propagation (α-syn) and neuron apoptosis triggering. Expressed miRNA for protein synthesis and cell autophagy, and responsible for hypoxia and inflammation in PD precipitation.	[85,93,94]
Microglia	Propagation of toxic proteins Transmission of neuroinflammation	BV-2 microglial cell line Microglial cell-lines (BV-2)	Exosomes originating from the plasma of a human suffering from PD α-syn-based fibrils α-syn	α-syn MHC II, TNF-α	Propagation of α-syn and subsequent aggregation in post-synaptic nerves. Induced neuronal inflammatory responses and apoptosis.	[95,96]
Astrocyte	Nerve defence	Primary mouse astrocytes		miR-200A-3p	Inhibited an apoptotic signaling pathway and decreased MPP^+-induced apoptosis in hippocampus area	[92,97]

mutant (in-vivo) and the production of toxic complexes (Figs. 3 and 4). TAR DNA-binding protein-43 (TDP-43) is the major diagnostic protein involved in the development of ALS, causing mature motor nerve cells to re-enter the cell cycle, thus promoting death [98]. The IL-6 level (plasma exosomes) is high in ALS, which has been linked to illness development within 12 months [99]. In addition, exosomes harboring inflammatory miR-124 may be produced by motor neurons transfected with SOD1 [100]. Exosomes derived from MSCs, however, suppress the pro-inflammatory behavior of microglial cells in "ALS mice" through miR467f and miR466q [101]. Numerous biomarkers have been discovered in the exosomes of individuals with ALS in recent investigations [56]. TDP-43, a crucial element of the "ubiquitinated and hyperphosphorylated cytoplasmic aggregate" discovered in post-mortem cells of participants with ALS, is widely distributed in the CNS and is a key player in the disease's pathophysiology [102]. In individuals with ALS, the ratio of TDP-43 in plasma exosomes improves with an increasing follow-up period [103]. Exosomes (spinal cord tissue) from ALS mice and humans are rich in ubiquitinated and non-native disulfide-cross-linked clusters of SOD1. Additionally, CNS-derived exosomes in ALS mice are liberated by astrocytes and neurons, but not through microglia [104]. A high amount of the novel INHAT repressor (NIR) is found in CSF exosomes from ALS sufferers, although NIR is decreased in the nucleus of motor neurons [105], as shown in Table 4.

Table 4
Various down-regulated miRNAs that control Amyotrophic Lateral Sclerosis (ALS).

MiRNAs	Up/down-regulation	Tissues	References
miR-132–5p, Let −7b, miR −124*, miR −574–5 P, miR-132–3p, and miR-143–3p	Both	Human CSF and serum; murine brain/spinal cord	[106]
miR-9	Both	Human-derived iPSC neurons and murine spinal cord	[107,108]
miR 219, mir-19a and b	Up	Murine brains	[109]
mir-125b, miR-22, and miR-146b	Up	Murine microglial cells	[110]
miR-455, miR-23a, and miR-29b	Up	Human skeletal muscles	[111]
mir-29a	Up	Spinal cord (murine)	[112]
miR-124 a*	Both	Serum and CSF	[113]
miR −155	Up	Human serum and skeletal muscles; murine plasma, serum, brain, and muscles	[114,115]
miR 206	Down	Serum, muscles, and plasma, human serum and skeletal muscles; murine brain	[116–118]
miR −338–3p	Up	CSF, spinal cord, and leucocytes	[119]
mir-665, mir-638, mir-506, mir-373, mir-518–5p, mir-551a, mir-618e, and mir-890	Up	Spinal cord (human)	[120]
Mir-665, mir-328, mir-451, mir1275, mir-149, and mir-638	Down	Leucocytes	[121]

12. Huntington's disease (HD)

The involvement of MVBs in HD, a burgeoning neurological disorder, was originally discovered in 1997. MVBs [122] accumulate mutant huntingtin protein, which is also seen in many biomembranes of the endoplasmic reticulum and surface lipid rafts [123]. HD-associated protein-1 (HAP-1) interplays with ESCRT-O, and its amplification has been linked to epidermal growth factor (EGF) receptor translocation via MVBs and lysosomes [124]. The pathogenesis of HD is linked to the regeneration and clearing of cellular proteins via MVBs, as well as the maintenance of effective endosomal–lysosomal trafficking [125]. In diverse species, non-cellular forms of exosomes transport pathogenic proteins and miRNA and activate or prevent the pathology of HD-related behavior [126]. Investigators discovered mHtt (specialized exosomes) from the fibroblast tissue of patients with HD and activated pluripotent stem cells possessing CAG-repeat sequence were implanted into the ventricles of a mouse model [127]. Exon-1 of the HTT gene was over-expressed in mouse embryonic fibroblasts (MEFs), revealing that mHtt was present in glutaminase-2-mediated exosomes (Alix and TSG101) [128]. Exosomes release various miRNAs (miR-125b, miR-214, miR1461, and miR-150) in HD. Mouse serum exosomes can cross the blood-brain barrier (BBB) and act on the CNS to control mHtt agglomeration, induce apoptosis, and influence mitochondrial disruption and cell viability in HD. Hence, these exosomes are critical for alleviating HD phenotypes and generating non-apoptotic protein content and low mHtt accumulation in R6/2 mice [129,130]. As a result, exosome-mediated mHtt propagation provides a unique strategy for HD pathogenesis, providing therapeutic potential for neurodegeneration prevention [131].

13. Multiple sclerosis (MS)

The participation of exosomes in the immunological regulatory mechanism has been demonstrated to be significant in autoimmune illnesses such as MS. According to research on participants with MS, the levels of exosomes in their blood and CSF increases with relapsing-remitting MS, as opposed to that of healthy individuals and those with chronic illness [32]. Several neurobiological studies show that exosomes

play an important role in the production of myelin sheets in the CNS. The synthesis of myelin sheaths is slowed by exosomes secreted by oligodendrocytes throughout the formation of the CNS. The discharge of autoinhibitory oligodendroglial-derived exosomes and coordinated myelin synthesis are therefore thought to be regulated by neurons [132]. Exosomes generated from mature oligodendrocytes contain myelin proteins and RNAs that promote myelination by stimulating glutamate through NMDA and AMPA receptors [36]. Moreover, exosomes, which are prevalent in synapsin-I and shed by astrocytes, may aid in the proliferation, survivability, and development of brain cells throughout maturation [133]. As a result, exosomes generated in the CNS may promote the formation and functionality of myelin, oligodendrocytes, and neurons. Furthermore, exosomes comprising metalloproteinases and caspase 1 have been revealed in epithelial cells, leukocytes, microglia, astrocytes, and platelets in response to the increased activity of proinflammatory cytokines such as TNF, IFN-gamma, and IL-1, which may stimulate BBB destruction and promote lymphocyte and myeloid cell movement towards the CNS [134]. Exosomes are also diminished by stimulated T-lymphocyte cells, which comprise a large quantity of the chemokine CCL5. This chemokine may increase T cell adherence to the mammalian brain's microvessel endothelial. [135]. Exosomes may also be capable of transferring lymphocytes and myeloid cells across the BBB, rendering this critical pathogenic activity in MS easier [136]. In lymphocytes, exosomes produced from the platelets of patients with MS exhibited P-selectin, PS, GL-1 receptors, and PECAM-1 (Fig. 5). When P-selectin signals to lymphocytes, integrin alpha-4-beta 1 is activated.

Table 5
Various sources of exosomes and their cargo.

Sources of exosome	Cargos analyzed	References
T cell cultures	miRNA	[138]
Plasma	miRNA	[139]
CSF	Lipid	[140]
T cell culture	Functional assay	[141]
Urine	miRNA	[142]
Serum	miRNA	[143]
Serum	Equivalent vesicle radius, number of the equivalent vesicles, lipids, total RNA concentration	[144]
Plasma	miRNA	[145]
Serum, CSF	Protein	[146]
Human periodontal ligament stem cell culture	Functional assay	[147]
Serum	Total transcriptome, miRNA	[148]
Serum	miRNA	[149]
Urine	miRNA	[150]
Plasma	Lipids	[151]
CSF	Proteomic profile	[152]
Plasma urine	miRNA	[153]

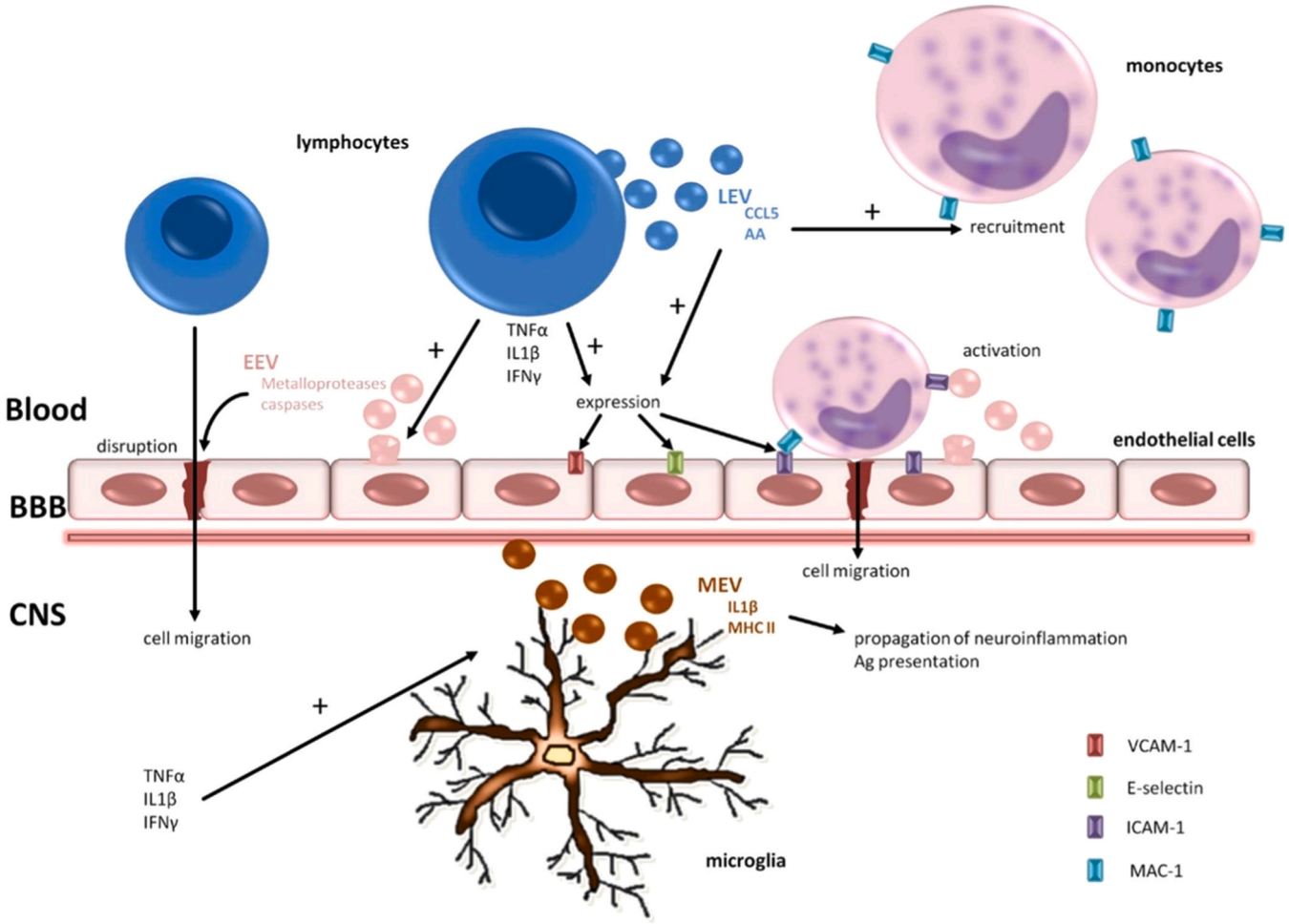


Fig. 5. : Exosomes in MS: Exosomes initiate the trans-endothelial cell migration of lymphocytes and monocytes and leads neuroinflammation. Metalloproteases which are conveyed by endothelial-derived extracellular vesicle results in blood–brain barrier (BBB) breakdown. Various proinflammatory cytokines are released from lymphocytes augments adhesion molecules on endothelial cells facilitating cell adhesion. Microglia has a significant key role in circulation of MS associated neuroinflammation due to the presence of microglia-derived extracellular vesicle containing IL1-b and MHC-II (137). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).

This makes it easier for lymphocytes to attach to endothelial cells, which improves transmission [137] (Table 5).

14. Possible therapeutic strategies based on exosomes to treat neurodegenerative disorders

The exploitation of exosomes in the management of neurodegenerative disorders is divided into three main categories: a diagnostic tool, a therapeutic tool, and a drug delivery vehicle. Exosomes, which are generated by brain cells, play a key function in dispersing harmful proteins and boosting the inflammatory response, all of which contribute to the onset and progression of neurodegenerative disorders. As a result, preventing the formation of neural exosomes or their absorption by target cells might be a promising therapeutic target for neurodegenerative disorders. For instance, recent research found that blocking P2RX7 may suppress ATP-induced production of tau-including MDEs, thereby lowering tau protein agglomeration and improving functional performance in AD animals. According to this study, P2RX7 could be a new treatment that addresses AD by reducing exosome production [154]. Nonetheless, studies on exosome-related molecular treatment approaches are still lacking. Additional research into the mechanisms of neuronal exosomal presence, composition modification, generation, and benefit cell localization can help identify novel treatment targets of neurodegenerative disorders. Using this knowledge to eventually expand the number of medications that block exosomes' pathogenic effects might be a game-changing strategy. Recently, exosome-mediated therapy has gained prominence in the usage of exosomes produced by stem cells. Exosomes generated from stem cells contain undifferentiated bioactive constituents and functional features similar to stem cells, are immunogenic, and have no potential for malignant transformation. As a result, stem cell exosomes are thought to be a healthier and more efficient treatment for neurodegenerative disorders. Numerous investigations have shown that stem cell exosomes have significant potential for treating neurodegenerative disorders. For example, exosomes secreted/produced by human mesenchymal stem cells (MSCs) produce a variety of pharmacological nucleic acids, proteins, and lipids that lower pro-inflammatory cytokines and hence, suppress neuroinflammation and ameliorate the clinical symptoms of AD and PD [155,156]. Additionally, exosomes secreted by adipose stem cells have been shown to secrete several proteins that possess a neuroprotective effect in ALS by preventing cell death [157]. Furthermore, a few studies have shown the involvement of exosomes produced by brain stem cells in lowering the incidence of neurodegenerative disorders. In addition, exosomes produced by hippocampus neural stem cells contain particular miRNAs that may boost synaptic susceptibility to the Aβ oligomer (Aβo) and prevent Aβo-induced long-term potentiation suppression and cognitive impairments. [158]. Regarding AD, a deficiency in the BBB has been linked to this disorder. According to an *in vitro* BBB AD model, the expression produced by AD might be recovered by neural stem cell-derived exosomes [159]. There is a considerable possibility that exosomes might be used to transport drugs. Depending on how transferrin receptors interact with each other, exosomes in the bloodstream appear to have significant targeting potential, allowing medications to penetrate the BBB and carry out their pharmacological properties more effectively [160]. According to Wang et al., exosomes may also be used as therapeutic vectors for AD. In a previous study, curcumin-loaded exosomes were administered intravenously to AD rats. Curcumin transportation via exosome was studied to elucidate whether it could penetrate the BBB and be deposited in the brains of AD rats. It was shown to lessen disease symptoms by decreasing tau hyperphosphorylation [161]. Curcumin's bioavailability and solubility were also lowered by the exosomes. In another study, dopamine substitution therapy was shown to improve the symptoms of PD rats and therapeutic effectiveness, and lower toxicities when compared to free dopamine. According to these results, exosomes might serve as a new delivery system for neurodegenerative disorder-targeted therapies in the future.

15. Exosomes as potential therapeutic tools

Exosomes' ability to interconnect other cells has led to their evaluation as treatment transporters for a wide range of disorders, including myocardiopathy [162,163], malignancy [164,165], and neurodegenerative disorders [166,167]. Exosomes, which have been re-engineered to carry a specific payload (medicine, bioactive molecules, and many others), can transport cargo over the BBB and deliver it to the CNS [168], which might help reduce neuropathologies. According to recent research, exosomes contain a large amount of molecular cargo that reflects the physiological health or pathological condition of their founding cellular origin [169]. Exosomes, as membrane-bound particles generated from cells that can penetrate the BBB and act as payload carriers, have several properties that make them viable therapeutic options for neurodegenerative disorders. They are especially useful therapeutic carriers due to their bioavailability and inherent physiological characteristics, which make them very potent therapeutic carriers. For instance, catalase is often employed in the treatment of PD, but it is difficult to permeate across the BBB in drug-loaded mice. This presents two main problems: nanotoxicity of the composition and the stimulation and rapid clearance of the nanoparticles by the phagocytosis phenomenon. In a PD mouse model, a formulation of catalase, "exoCAT," derived from drug-loading exosomes reached the targeted neurons and aggregated in the cells [170].

Exosomes: targeted therapeutic approaches toward neurodegeneration

Exosomes carry different payloads and travel between brain locations in a pattern that corresponds to complicated brain activities. The payload of exosomes aids in neuron protection, proliferation, repair, and synapse flexibility [171]. Exosomes also provide regulatory elements to neurological damage regions, aiding in protein biosynthesis and cell rebuilding [172]. Exosomes are often used to treat dementia, PD, ALS, and AD, among other neurodegenerative disorders, and have been proven in recent research to be a feasible treatment for AD. Neuronal death, neurofibrillary tangle development, and an oversupply (and lack of degradation) of Aβ in the brain in the form of amyloid plaques are the fundamental reasons for AD [173]. In one study, the BBB was effectively crossed by using a dendritic cell-derived exosome with siRNA for transport to the neuronal system [174]. When siRNA was delivered by exosomes, the mRNA and proteins for BACE1, a protease that discharges N-terminal fragmentation of amyloid precursor proteins and causes Aβ buildup, were dose-dependently knocked down. These results reveal that the focused distribution of siRNA-loaded exosomes has broad medicinal potential for crossing the BBB to approach the brain and precisely suppress targets to slow the progression of AD. Exosome-centered treatment methods are effective in treating PD because they have an additional pathogenic target. The absence of dopaminergic neurons in the substantia nigra of the midbrain causes PD, as does the accumulation of Lewy bodies, most of which are composed of α-syn. Inherited PD has indeed been related to mutations in the LRRK2 gene [86,175]. Furthermore, research suggests that RNA, exosome-based therapeutic applications, and protein distribution may be advantageous in PD, which is defined by a decrease in SOD1 and catalase levels [176]. Existing investigation of PD suggests that exosomes have a variety of functions involving neurotoxicity, neuroprotective effects, diagnostic biomarkers, and therapeutic delivery [177]. Because medication distribution through the BBB is thought to be dependent on functional transportation, methods such as nano-formulations and PEGylated medicines have been extensively used [178]. In independent research, Gui et al. and Cao et al. looked at the presence of miRNAs in exosomes from the CSF and serum of patients with PD. In contrast to healthy subjects, a dramatically increased or decreased frequency of the SS of miRNAs in the exosomes of PD sufferers was discovered. Most of these miRNAs can control all of the genes associated with the various PD

mechanisms [179]. Whereas nano-formulation administration was discontinued due to cytotoxicity and quick elimination by the mononuclear phagocyte system (MPS), PEGylated medications were discontinued because they reduced the target-drug relationship and hence, affected the drug's brain distribution. Although the MPS reducing momentum is tiny for nanodevices, the introduction of exosomes improves small molecule transportation through the BBB. In addition, the study discovered that exosomes may be used as nanoparticles to deliver pharmaceuticals, peptides, miRs, and siRNAs (Table 6) [126,180–185].

Challenges of therapeutic exosomes

There are significant problems associated with the CNS distribution of exosomes. Tailored synthesized payloads for therapies need extensive information on the exosome loading capabilities and payload half-life. When delivered systemically, there is an essential requirement for the pharmacological knowledge of exosome-like bioavailability. Further investigation is needed to transport engineered exosomes to particular destinations in the CNS. Immune cells can detect exosomes that have been applied topically and it has been shown that exosomes can transmit pharmacological components that may trigger an immunologic reaction in patients. Despite the paucity of human trials, contemporary investigations are based on in vitro and in vivo animal investigations; hence, additional research is needed to address these problems. Further research is required to improve exosomes' capabilities in neurodegenerative illness and to determine if they have a potential benefit in new treatment methods. Finally, the mechanism of exosome interaction at the target tissue must be understood, as well as whether the medicinal distribution of the exosome payload requires bio-engineered ligands on the particles' external surfaces to increase delivery performance to specific destinations. Furthermore, the continued advancement of exosome treatment procedures will require an ongoing study of exosome biology.

Table 6
Human mesenchymal stem cell-derived exosomes used for neurodegenerative disorders.

Diseases	Animal Models	Dose/ Route	Outcomes	References
AD	Aβ-inoculated mouse. APP/ PS1 mouse	10 μg, i.h. 30 μg, i.v.	Enhanced neurogenesis and restored cognitive function. Repaired cognitive dysfunctions by clearing Aβ deposition, and modulated microglia activation in the brain.	[180,186]
MS	EAE mouse	150 μg, i.v.	Decreased inflammation, severity, and demyelination, and upregulated regulatory T cells.	[187]
PD	Mice (C57BL/ 6)	30 mg/kg, i.p.	Reduced α-synuclein aggregation and related cytotoxicity in PD neurons.	[188]
HD	GFP transgenic mice	10 mg/kg every 2 days for 2 weeks, i.v.	siRNA carrying RVG exosomes substantially decreased HuHtt mRNA (46 %) and proteins (54 %) in transgenic mice (N171–82Q mice).	[183]
HD	Mice	100 μL, i.v.	hsiRNA-loaded exosomes targeted Huntingtin mRNA and efficiently internalized cortical neurons of the mouse by promoting dose-dependent silencing.	[189]
ALS	In-vitro study	0.2 mg/mL	Protected NSC-34 cells from oxidative damage.	[184]
ALS	Mice (B6SJL)	i.v. and i.n.	ASC-exosomes enhanced motor performance, lumbar motor neurons, and the neuromuscular junction in muscle, and reduced glial activation in treated SOD1(G93A) mice as compared to controls (PBS-treated mice).	[190]

PD; Parkinson's disease, AD; Alzheimer's disease, MS; multiple sclerosis, HD; Huntington's disease, ALS; Amyotrophic lateral sclerosis, i.h.; intrahippocampal, i.v.; intravenous, i.p.; intraperitoneal, i.n.; intranasal

Conclusion and future perspective

The progression of neurodegenerative illness is intrinsically linked to exosomes. Many pathogenic proteins and peptides, including the tau protein, α-syn, and Aβ, may play a role in disease development. Additionally, exosomes contribute to the self-release of neurotransmitters and may minimize harmful chemicals by exosome discharge. The usage of exosomes for diagnostic treatment and prognostic purposes has necessitated the development of new standardized purifying methods. According to previous studies, exosomes are important in controlling pathological processes in the CNS. They transport macromolecules such as nucleic acids, lipids, and proteins to facilitate cell-to-cell communications and their evacuation shows much promise as a diagnostic agent or a drug delivery vehicle for neurodegenerative disorders. In addition, exosomes' exterior modifications increase their targeting capability, which may lead to better medication uptake compared to that of traditional delivery methods. However, the utilization of exosomes in brain disorders requires a thorough knowledge of exosome physiology and the subsequent phases of signaling pathways. Furthermore, the mechanism of exosome surface functionalization determines their targeting ability, and the development of an improved exosome refinement and separation mechanism has recently piqued the attention of researchers.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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Authors' statement

AK, B-CA and PG contributed to the conception, writing, and discussion of this manuscript. SA wrote the initial draft of the manuscript. All authors wrote and contributed to the initial draft and critical conclusion of the manuscript. All authors contributed to the article and approved the submitted version.

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CRediT authorship contribution statement

Sumel Ashique: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nitish Kumar:** Writing – original draft, Investigation, Data curation, Conceptualization. **Neeraj Mishra:** Writing – review &

editing, Investigation, Data curation, Conceptualization. **Sathish Muthu:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Ramya Lakshmi Rajendran:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Chandrasekaran Balakumar:** Writing – review & editing, Investigation, Data curation. **Brenya Francis Obeng:** Writing – review & editing, Investigation, Data curation. **Chae Moon Hong:** Writing – review & editing, Funding acquisition, Formal analysis. **Anand Krishnan:** Writing – review & editing, Supervision, Resources, Investigation, Formal analysis, Data curation, Conceptualization. **Byeong-Cheol Ahn:** Writing – review & editing, Supervision, Resources, Project administration, Formal analysis, Data curation, Conceptualization. **Prakash Gangadaran:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare no conflict of interest

Data availability

This published article includes all the data generated or analyzed during this study.

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