

Unveiling the Complex Role of Exosomes in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative illness, characterized by memory loss and cognitive decline, accounting for 60–80% of dementia cases. AD is characterized by senile plaques made up of amyloid β ($A\beta$) protein, intracellular neurofibrillary tangles caused by hyperphosphorylation of tau protein linked with microtubules, and neuronal loss. Currently, therapeutic treatments and nanotechnological developments are effective in treating the symptoms of AD, but a cure for the illness has not yet been found. Recently, the increased study of extracellular vesicles (EVs) has led to a growing awareness of their significant involvement in neurodegenerative disorders, including AD. Exosomes are small extracellular vesicles that transport various components including messenger RNAs, non-coding RNAs, proteins, lipids, DNA, and other bioactive compounds from one cell to another, facilitating information transmission and material movement. There is growing evidence indicating that exosomes have complex functions in AD. Exosomes may have a dual role in Alzheimer's disease by contributing to neuronal death and also helping to alleviate the pathological progression of the disease. Therefore, the primary aim of this review is to outline the updated understandings on exosomes biogenesis and many functions of exosomes in the generation, conveyance, distribution, and elimination of hazardous proteins related to Alzheimer's disease. This review is intended to provide novel insights for understanding the development, specific treatment, and early detection of Alzheimer's disease.

Keywords: Alzheimer's disease, exosomes, pathogenesis, diagnosis, treatment

Introduction

Alzheimer's disease (AD), commonly referred to as senile dementia, is a common central neurodegenerative disorder. AD primarily manifests as a slow reduction in self-care abilities, increasing memory loss, and cognitive impairment, along with neuropsychiatric disorders, significantly impacting the quality of life of patients.¹ AD accounts for over 60% of dementia cases. Sporadic cases account for over 90% of cases. The disease progresses through memory and cognitive disabilities, causing mood swings, agitation, irritability, and reduced vital functions.^{2–4} Amyloid-beta ($A\beta$) plaques and neurofibrillary tangles (NFTs) are key factors in Alzheimer's disease (AD) pathophysiology.⁵ These plaques form when extracellular $A\beta$ monomers are handled by secretases, leading to inflammatory response and damaging neurons.⁶ Defective hyperphosphorylation as well as incorrectly folded tau also produce intracellular NFTs, impairing neuronal signal.⁷ The researchers have dedicated significant resources to investigate etiology of AD, but it remains incompletely understood, and there is now no viable medication to halt the progression of AD. Food and Drug Administration (FDA)-approved drugs do not provide a definitive therapy for the pathophysiology of AD, but they do give symptomatic relief by slowing down the course of the disease. Treatment for Alzheimer's disease often involves targeting the increase of Acetylcholine levels to avoid its degradation, hence protecting memory and cognitive abilities.⁸ Recent advancements in therapy, such as disease-modified AD medications, have been developed to overcome the limitations of traditional treatments. This technique requires a thorough understanding of metabolic pathways and utilizes several targeted tactics to provide effective medicine.⁵ As research on extracellular vesicles (EVs) advances, it has become evident that a specific kind of tiny EVs known as exosomes are significant in the pathogenic process of AD.

Exosomes are nanosized extracellular vesicles released upon the exocytosis of a MVB, characterized by a bilayer membrane structure. Exosomes may be secreted by the majority of cell types and are often found in bodily fluids.⁹ Exosomes in the central nervous system (CNS) transmit messages locally inside cells and extensively across the brain via the cerebrospinal fluid (CSF).¹⁰ Exosomes, containing proteins, lipids, and nucleic acid molecules, are transported from donor cells to distant recipient cells through mechanisms like phagocytosis, pinocytosis, endocytosis, or plasma membrane fusion, containing specific cargoes.¹¹ Additionally, exosomes are seen as carrier vehicles that may travel actively between cells, facilitating material and information exchange. Research indicates several cells within the CNS, such as neurons, astrocytes, oligodendrocytes, microglia, and endothelial cells, are capable of releasing exosomes. These exosomes may have positive or negative effects in both normal and diseased states.¹²

Exosomes are increasingly shown to play a crucial role in the formation as well as dissemination of two pathological hallmarks in AD, senile plaques and intracellular neurofibrillary tangles, which are characterized by the deposition of extracellular amyloid β protein and the hyperphosphorylation of microtubule-related tau protein.¹³ Exosomes associated with AD were first discovered while studying the buildup of APP cleavage in MVBs,^{14,15} which are considered as progenitors of exosomes. Later research discovered that A β peptides are present in exosomes,¹⁶ providing more evidence that exosomes play a role in the progression of Alzheimer's disease. Interestingly, exosomes derived from impaired nerve cells can play a dual role in AD. They can transfer APP, γ/β -secretase, A β peptide, and tau protein to healthy neurons, accelerating the death of peripheral neurons and spreading pathological features of AD.^{17,18} Additionally, exosomes can promote A β clearance, transporting A β to microglia's lysosomes and degrading in them.¹⁹ Therefore, the primary aim of our work is to outline the updated understandings on exosomes biogenesis and many functions of exosomes in the generation, conveyance, distribution, and elimination of hazardous proteins related to Alzheimer's disease. This is intended to provide novel insights for understanding the development, specific treatment, and early detection of Alzheimer's disease.

Overview of Exosomes: Biogenesis, Secretion, Sources, Isolation, and Biological Characteristics

The Biogenesis and Secretion of Exosomes

Three primary categories of EVs, exosomes, microvesicles (MVs), and apoptotic bodies, have been identified according to their size and origin. Microvesicles (MVs) are generated by budding off the plasma membrane and typically range in diameter from 100 to 1000 nm.^{20,21} Apoptotic bodies, ranging from 100 to 2000 nm in diameter, are generated by the plasma membrane of apoptotic cells. They are not often engaged in cellular communication since they are ingested by phagocytic cells.²² Exosomes are the smallest extracellular vesicles formed during endocytosis, typically ranging in size from 40 to 160 nm in diameter.^{9,23} Exosome development starts in the endosomal system and is linked to the processing of membrane organelles such as the transGolgi network, endoplasmic reticulum, lysosomes, and autophagosomes.²⁴ Endosomes are formed during endocytosis, aiding cells in absorbing substances (such as proteins, lipids, and molecules) through engulfing.^{25,26} Intracellular endocytosis occurs from an early endosome involving the plasma membrane and external cargos. The trans-Golgi network and endoplasmic reticulum play a role in the formation of early endosomes. The early endosome transitions into the late endosome as it matures. Endosomes undergo further invagination to create intraluminal vesicles (ILVs),^{7,27} leading to the formation of multivesicular bodies (MVBs). Multi-vesicular bodies (MVBs) may merge with the plasma membrane to expel intraluminal vesicles (ILVs) as exosomes.^{28,29} Alternatively, multivesicular bodies (MVBs) may merge directly with lysosomes or autophagosomes (Figure 1).

The Sources of Exosomes

Exosomes are prevalent in several bodily fluids including bronchioalveolar lavage, synovium, saliva, urine, bile, cerebrospinal fluid (CSF), breast milk, and plasma. They have distinct cell-derived components on their surfaces and are secreted by different cell types such as nerve cells, mesenchymal cells, reticulocytes, fibrin, epithelium, endothelium, thrombocytes, allophycocyanins, and cancer cells. It is currently understood that the majority of cell types, including brain cells, produce exosomes. Dendritic cells and β -lymphocytes were also found to produce similar vesicles. Exosomes from multiple cell types contain identical

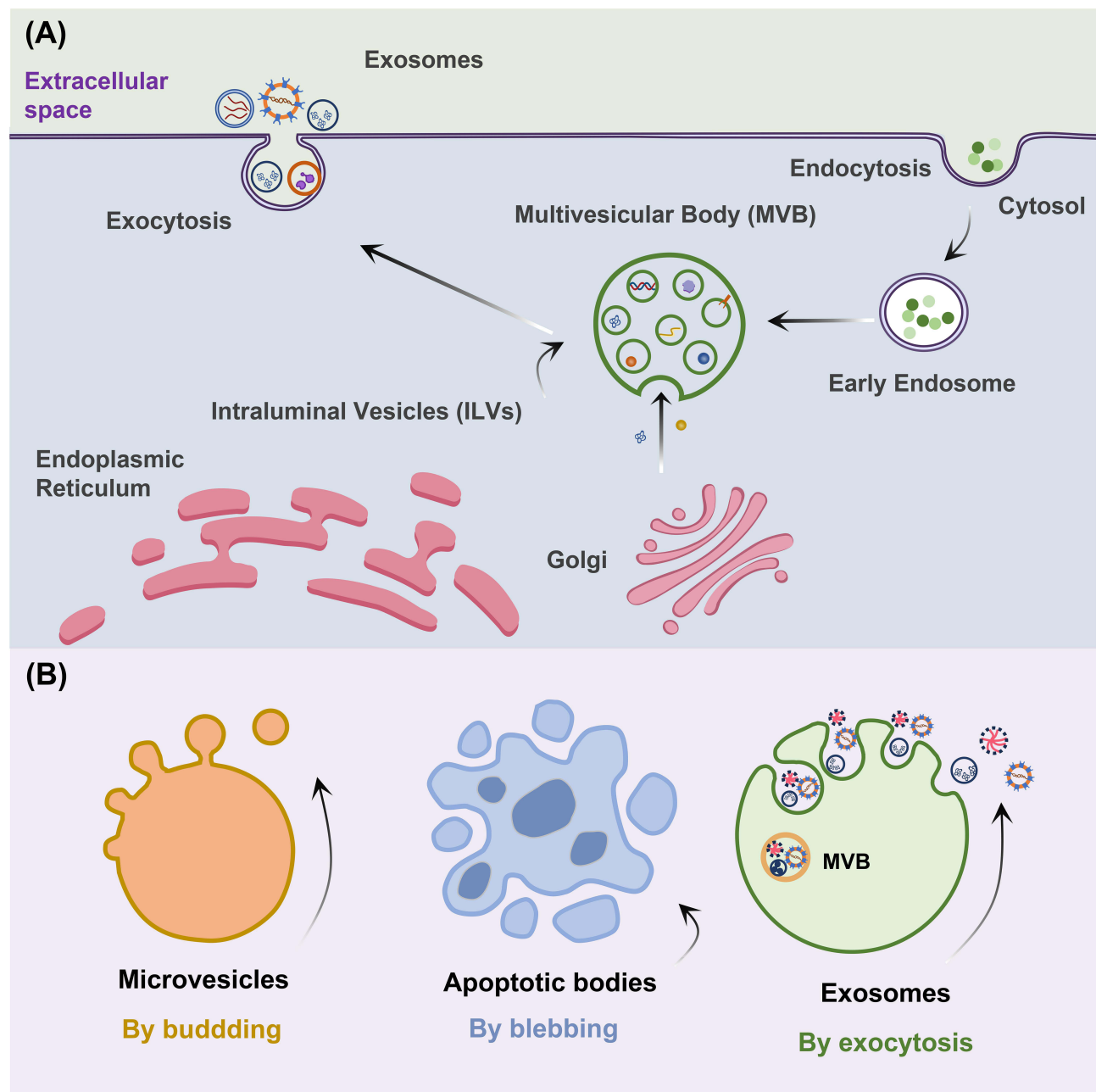


Figure 1 Three categories of extracellular vesicles and exosome biogenesis. **(A)** Endocytosis creates an early endosome via the plasma membrane's invagination to internalize cargo from the extracellular space. The early endosome is situated near the endoplasmic reticulum (ER) and the trans-Golgi network to assist in the internalization and modification of intracellular cargo. The early endosome transitions into a multivesicular body (MVB) or multivesicular endosome (MVE). Cytosolic molecules like as proteins and RNA are taken up by the multivesicular body (MVB) by membrane invagination, resulting in the creation of intra luminal vesicles (ILVs) inside the MVB. The multivesicular body combines with the plasma membrane and releases intraluminal vesicles known as exosomes into the extracellular matrix by exocytosis. **(B)** Three kinds of extracellular vesicles (EVs) are differentiated by their production and size. 1) Apoptotic bodies, ranging from 1000 to 5000 nm in diameter, are generated by the process of "blebbing" from the cellular membrane of a cell undergoing apoptosis. 2) Microvesicles are created by protruding from the plasma membrane and have a diameter ranging from 100 to 1000 nm. 3) Exosomes, with a diameter between 30 and 150 nm, come from the endosomal system.

substances. The structure usually comprises a lipid bilayer with transmembrane proteins and distinct protein markers, encircling a core comprising enzymes, extracellular matrix proteins, lipids, nucleic acids (DNA and RNA), and transcription factors.³⁰

The Isolation of Exosomes

Various techniques have been used to extract exosomes and vesicles that resemble them from both plants and animal, and detailed procedures for isolating exosomes have been recently reviewed by Kandimalla et al.³⁰ Exosomes are isolated

using methods such as ultracentrifugation, isoelectric precipitation, ultrafiltration, polymer-based precipitation, size-exclusion chromatography, and microfluidic technologies.³¹

Since it is both simple and inexpensive, ultracentrifugation (UC) has become the method of choice for separating and purifying exosomes and particles that resemble them. While the process does increase purity, it reduces the amount of isolated exosomes.³² An attempt was made to rectify this shortcoming by increasing the efficiency of the exosomes separation method while preserving a higher level of purity and yield. To enhance the exosomes yield, UC was slowed down by the use of ultrafiltration, which separates biomolecules according to their sizes. The extra stage in this process, however, makes it more susceptible to contamination and drives up manufacturing costs.^{32,33} To separate exosomes according to their sizes, size-exclusion liquid chromatography (SEC) is useful. It gets rid of the need to pellet exosomes at high speeds, yields a very pure product, and works well with serum or plasma purification.³⁴ Nevertheless, additional procedures are required when using SEC to prevent sample-lipoprotein interference and protein aggregation.³⁵ To guarantee very pure separation, the immuno-isolation method employs magnetic beads coated with antibodies to target proteins on the exosomes surface. Problems with this approach persist, however, due to our incomplete understanding of exosomal architecture, surface components, and systemic problems.³⁶ A chemical conjugation approach may be used to modify the surface of paper in order to generate an immunoaffinity system that is based on paper. Antibody with strong affinity for particular EV is selected as the capture molecule. Consequently, this method requires a small sample size and is easy to implement.^{35–37} Because of its many benefits, including high-purity separation, economy, and reduced processing time, microfluidics has recently emerged as a cutting-edge method for isolating exosomes. These benefits are based on the device's architecture that has a high surface-to-volume ratio. This reduces the volume required for important samples, and speeds up the response time by performing many phases at once.^{32,35} According to the Minimal information for studies of extracellular vesicles 2018 guidelines, it is recommended to use a combined approach for isolating exosomes.³⁸

The Biological Characteristics of Exosomes

Exosomes were first reported in the early 1980s to analyse vesicles released by various cultured cells, with a size range of 40 to 1000 nm. In the next years, this phrase may describe endosomal vesicles with diameters between 30 and 100 nanometers.^{39,40} Exosome membranes are mostly phospholipids and proteins, with flag molecules including CD9, CD63, CD81, CD82, adhesion proteins, integrins, and glycoproteins on the surface. They can transport microRNAs, mRNA, DNA, heat shock proteins, lipid-associated proteins, sphingolipids, and phospholipids.⁴¹ Exosomes have comparable cargoes, but also exhibit cell specificity determined by the chemicals in their source cells and the physiological or pathological circumstances during exosome synthesis. Exosome contents may vary under diverse stimuli and can be identified via proteomics, lipidomics, sequencing, and PCR.¹² Thorough investigation and comprehension of exosomes have improved the knowledge of their roles in three areas: 1) Exosomes carry unique contents that facilitate cell-cell communication as well as cellular processes. 2) Exosomes are present in cerebrospinal fluid, blood, urine, and other bodily fluids, making them useful as diagnostic markers. 3) Exosomes also play a role in delivering drugs.

Exosomes as a Player in AD Pathogenesis

Alzheimer's disease (AD) is the predominant cause of dementia and the most prevalent neurodegenerative disorder that worsens with time. Symptoms include memory loss, mobility difficulties, learning impairment, speech and motor deficiencies, psychological disruption, etc. Alzheimer's disease has a complex pathogenesis, which is characterized by the accumulation of insoluble A β -amyloid deposits outside cells, the presence of tau fibrils forming NFTs within cells, and neuronal death.^{42,43} The release of amyloid- β protein from cultured cells and the accumulation of exosomal proteins like Alix and Flotillin-1 surrounding amyloid plaques in AD patients demonstrate the link between exosomes and the illness.⁴⁴ Extracellular deposits seen in the brains of Alzheimer's disease patients, known as amyloid plaques, mostly consist of A β . Amyloid fibrils and A β oligomers are entangled to form aggregates in a regular pattern in the plaques.⁴⁵ The evolution of AD may include soluble A β oligomeric forms.⁴⁶ A β peptides are APP's proteolytic derivatives. The endosomal pathway controls this process, which may occur at various parts of the cell and is also important for making exosomes.⁴⁷

Despite the fact that our knowledge of exosome activity in AD is still limited, there is mounting evidence from both new and existing studies indicating exosomes have diverse functions in the disease.⁴⁸ Research shows that exosomes

have many roles in AD pathogenesis. Exosomes may remove and oligomerize A β , contributing to plaque formation. Exosomes carry both harmful and beneficial payloads throughout the brain, including A β , tau, inflammatory compounds, and enkephalins, insulin-degrading enzymes. Glial cells and neurons may also take up exosomes. Due to their capacity to communicate and control neuron-glial cell interactions, exosomes contribute to Alzheimer's disease (AD).

The exact function of exosomes in the degenerative process of Alzheimer's disease is still unclear, despite the fact that their involvement in the disease is well-established. According to several researchers, exosomes in AD enhance the spread of A β as well as p-tau, leading to neurotoxicity.^{18,49–51} Contrarily, there is evidence that exosome production may ameliorate the pathogenic phenotype of AD, according to some studies (Figure 2).^{19,52–55}

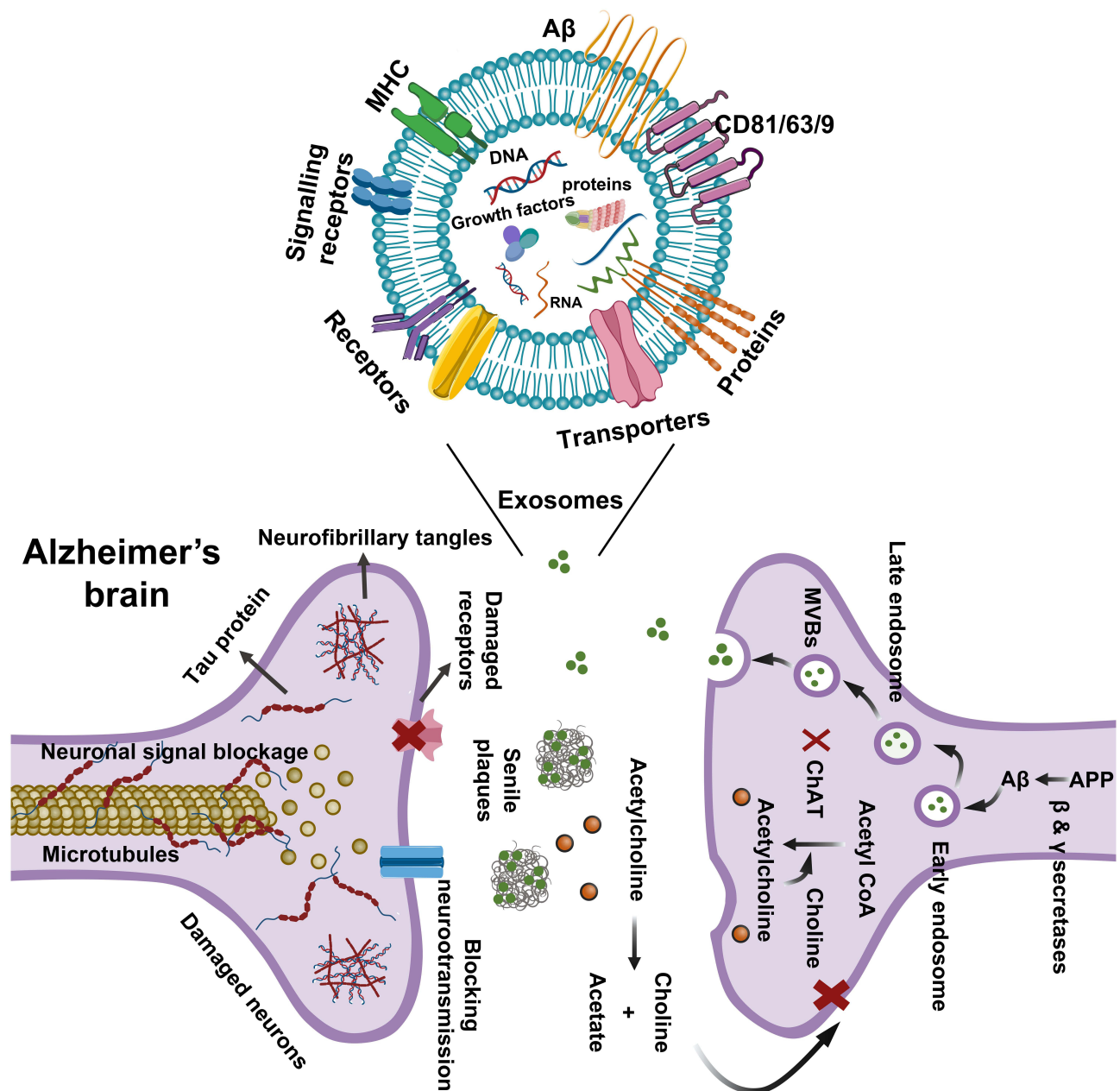


Figure 2 Alzheimer's disease pathophysiology and the involvement of exosomes. The breakdown of amyloid precursor protein creates amyloid beta (A β), which is deposited on the exosome surface by early endosomes. Exosomes with A β in the synaptic cleft cause AD by inducing senile plaque development and inhibiting neurotransmission. Unstable micro tubules in recipient neurons release tau and form neurofibrillary tangles, which harm neurons and receptors. Choline acetyltransferase (ChAT) synthesis is inhibited by damaged neurons, which limit acetyl-CoA and choline interaction. A β and neurofibrillary tangles destroy neuronal cells and hinder neurotransmission, producing brain dysfunction and advancing AD.

Exosomes are Involved in the APP Metabolic Process, A β Aggregation and Plaque Formation, the Spread of A β and Tau

Intracellular A β is typically destroyed via the endosomal-lysosomal route. Inhibition of the A β degradation pathway, particularly key molecules like metalloproteinase endothelin-converting enzyme, can cause intracellular A β accumulation, facilitating exosome encapsulation and release of A β and APP metabolites.⁵⁴ Exosomes regularly contain APP, CTFs-APP, and various proteases involved in APP processing.⁵⁶ APP cleavage by β - and γ -secretase in early endosomes releases A β to MVBs. The export of A β to exosomes was produced by a small fraction of the peptide being sorted into intraluminal vesicles in MVBs.⁵⁷ Numerous studies reveal APP-associated proteins and metabolites in exosomes of AD cell models and patients during A β production. Rajendran et al noticed APP in exosomes and β -secretase cleavage in early endosomes. APP-transfected cells may leak a tiny quantity of A β into the culture medium via exosomes. Brain slices from all AD patients show exosome marker Alix enrichment around small neuritic plaques, indicating exosome deposition around amyloid plaques.¹⁶ Vingtdeux et al found that MVBs are necessary for APP metabolism and can secrete all APP metabolites.⁵⁸ Exosomes may also house critical members of the secretase family, including β -site APP cleaving enzyme 1, presenilin 1, and disintegrin.⁵⁶ Zheng et al stereotactically injected HEK293-APP Swe/Ind cell conditioned media exosomes into the hippocampus dentate gyrus. Exosomes harboring pathogenic proteins were more neurotoxic and impaired hippocampal neurogenesis.⁵⁹ In addition to direct engagement in APP metabolism, exosomes may also participate indirectly. Recent research found that exosome-mediated miR-185-5p distribution regulates APP expression in various cells. Exosomes from AD mice and APP-overexpressed N2a cell cultures dramatically boosted recipient cell APP expression. Exosomes do not directly transport APP gene products to destination cells, which is surprising. Instead, exosome miR-185-5p expression decreases.⁶⁰ More data is needed to establish that indirect regulation has expanded the complexity of APP metabolism exosomes.

Research indicates that exosomes may expedite the production of amyloid plaques by promoting A β aggregation. Exosomes are linked to A β fibrosis, since Yuyama et al demonstrated that exosomes from PC12 cells given chloroquine and KCl increase A β assembly. Cholera toxin B subunit blocking and endoglycoceramidase-treated glycolysis in vitro investigations revealed that exosome glycosphingolipids (GSLs) glycochains significantly influence A β fibril formation.¹⁹ On the outer layer of exosomal membranes, glycochain membrane lipids (GSLs) expose their glycans to the environment. After traversing the cell membrane, GSLs form dense clusters that monomeric A β can detect and attach to.⁶¹ Research suggests that GM1 ganglioside, found in GSLs, may bind to A β and enhance aggregation.^{62,63} Especially NDE exosomes enrich GSLs. Exosomes may serve seeds for A β aggregation, and plaque development. GSLs and cellular prion protein (PrP(C)) are significantly loaded in exosomes. Glycosylphosphatidylinositol-anchored surface glycoprotein PrP(C) is found on neuron and exosome outer leaflets. Research suggests that exosomes attach to A β via PrP(C), which has the strongest affinity for dimeric, pentameric, and oligomeric A β species, accelerating fibrosis and lowering neurotoxic effects.⁶⁴ Results indicate that NDEs may capture A β via GSLs and PrP(C) in a single or synergistic way, promoting A β aggregation and amyloid plaque formation.

With more and more proof A β and tau spread in the brain, the idea that exosomes might be the means by which A β and tau are transmitted is becoming more popular.^{65–67} Normal mouse brains are subjected to AD-like neuropathology when exosomes produced from plasma neuronal cells of AD patients seed tau aggregation.⁵¹ Results from some investigations show that tau clumps may multiply and spread throughout the brain by exosomes, much like prion diseases. Pathological tau “seeds” transported by exosomes cause tau misfolding into a harmful conformation in cells that take them up.⁶⁸ Only exosomes and tau seeds devoid of vesicles have been shown to transmit across synapses in neuronal networks, according to recent literatures.⁶⁹ A β enhances the seeding activity of the majority of the exosomal tau produced by AD synapses, which is oligomeric and has its C-terminal truncated form.⁷⁰ Additionally, studies have shown that exosomes enriched with tau or isolated from tau transgenic rTg4510 mice brains can promote tau aggregation in recipient cells, as well as increase tau phosphorylation and soluble oligomer formation.^{49,50,71} Release of tau-containing exosomes is another way in which microglia aid in the spread of tau. By encouraging microglia production of tau-enriched exosomes, BIN1 (another gene associated with AD) contributes to advancement of tau pathology in AD.⁷² In mice, exosomes derived from cerebrospinal fluid (CSF) of Alzheimer’s disease (AD) patients that include

BIN1-associated genetic variations that cause AD expedite the spread of tau.⁷³ Inhibiting exosome formation or reducing microglia numbers considerably slows tau propagation in both laboratory and living organism studies.⁷⁴ Glial cell-derived exosomes have the potential to promote A β aggregation in the brains of 5XFAD mice, along with spreading tau. The cognitive deficits in the 5XFAD mouse model can be alleviated by reducing A β 1–42 and amyloid plaques in the brain. Even more crucially, exosomes retrieved from AD patients, such as blood and cerebrospinal fluid, display an abnormally high level of soluble A β 1–42, A β oligomer, p-T181-tau, and p-S396-tau. What's more, these abnormalities could be identified prior to a clinical diagnosis, suggesting that exosomes could be used as a way to diagnose AD. Also, neurons in culture may be exposed to these harmful substances via exosomes produced by Alzheimer's disease patients, which have elevated quantities of A β oligomer. Crucially, oligomer spread and associated toxicity were reduced when two ESCRT proteins, TSG101 and VPS4A, were knocked down, which inhibited exosome production, secretion, or absorption.¹⁸ These evidences suggest that exosomes have a role in the dissemination of tau and A β , which in turn leads to pathological damage in AD, when considered collectively.

Exosomes are Involved in Neuroinflammation, Oxidative Stress, Angiogenesis, and Neuronal Dysfunction in AD

An inflammatory response including free radicals, cytokines released by microglia and astrocytes, and other factors is associated with the development of Alzheimer's disease.⁷⁵ Exosomes play a large role in neuroinflammation as a natural nanocarrier of harmful inflammatory chemicals. Furthermore, they aid in the advancement of inflammation in brain cells and speed up the production of amyloid plaques by releasing A β .^{75,76} The prevailing belief is that A β plaques cause cellular-level downstream consequences such oxidative stress, microglial activation, local inflammation, and tau protein hyperphosphorylation, which ultimately result in cell death and dysfunctional synaptic transmission.^{77–79} The levels of complement, which include C1q, C4b, and C3d, as well as pro-inflammatory markers (IL-1, TNF- α , and IL-1 β), were noticeably greater in AD patients compared to matched controls.⁸⁰ Patients in the CE 2 stage had lower levels of regulatory proteins and greater levels of complement proteins compared to those in the CE 1 preclinical stage, adding to the mounting evidence linking inflammatory chemicals in exosomes to AD by showing that levels of complement proteins in exosomes produced from astrocytes are correlated with disease stage.⁸⁰ In neuroinflammatory illnesses like AD, synaptic dysfunction may be one of the first mechanisms impacted.^{81,82} A study found that EV produced by A β 1–42 activates microglia, which in turn causes a significant reduction in the density of dendritic spines in hippocampal neurons both in living organisms and in laboratory settings. One possible explanation is that EV contains a large number of miRNAs that control the expression of important synaptic proteins.⁸³ A β treatment in astrocytes leads to the production of the proapoptotic PAR-4 protein, leading to increased cell death in cultured astrocytes.⁸⁴ Both serum and brain tissue from 5XFAD mice and Alzheimer's patients contain ceramide-enriched and astrocyte-derived exosomes connected to A β pathology. These exosomes were transferred to mitochondria by bypassing neurones in vitro or in vivo, causing mitochondria to cluster and increase DRP1 levels. A β -linked exosomes promoted the binding of A β to VDAC1. After binding, caspase triggered neurite breakdown and neuronal cell death.^{85,86}

Interestingly, peripheral exosomal contents may potentiate CNS inflammation, which may play a part in explaining how a peripheral pro-inflammatory state such as depression, obesity, diabetes can be risk factors for AD. Li et al⁸⁷ investigated the involvement of serum-derived exosomes in the process of neuroinflammation by utilizing the endotoxemia model with lipopolysaccharide (LPS). The findings indicated that the mice that received exosomes derived from LPS-challenged mice experienced heightened activation of microglia and astrogliosis. Additionally, there was an increase in the production of pro-inflammatory cytokines in the body and an elevated expression of pro-inflammatory cytokine mRNA and the inflammation-associated microRNA (miR-155) in the CNS of these recipient mice. Gene expression study verified that several inflammatory microRNAs (miR-15a, miR-15b, miR-21, miR-27b, miR-125a, miR-146a, miR-155) exhibited a substantial increase in expression inside the isolated exosomes when exposed to LPS-induced conditions. Accumulated signaling within the microglia of mice that received tail-vein injections of fluorescently labeled exosomes were also observed, suggesting that peripheral exosomes may act as a neuroinflammatory mediator in systemic inflammation.⁸⁷ Another study examined whether exosomes generated during the peripheral inflammatory process have

the ability to trigger neuroinflammation.⁸⁸ It was demonstrated that proinflammatory exosomes could cross the blood–brain barrier and trigger neuroinflammation when injected intravenously. Results suggest that peripheral cholinergic signals may play a role in regulating proinflammatory exosomes-mediated signaling from the periphery to the brain.⁸⁸ Exosomes secreted during a peripheral pro-inflammatory state such as depression, obesity, and diabetes may serve as a key mechanism linking to AD.^{89–91}

More study has focused on exosomes as neuron–glial cell communication mediators. Zhu et al⁹² found that deleting the Trem2 gene in mice (Trem2 KO) can increase the spread of tau protein from the medial entorhinal cortex (MEC) to the hippocampus. This spread of tau is accompanied with a decline in synaptic function and memory behavior. Deleting Trem2 in microglia increases the spread of tau protein throughout different layers of neurons cultivated in a microfluidic chamber. Additionally, inhibiting exosomes can effectively decrease the amount of tau found in exosomes and the surrounding fluid released by microglia containing tau. While the deletion of microglial Trem2 does not impact the absorption of tau, it does improve the distribution of tau to endosomal and cellular pre-exosomal compartments once it is taken up. Trem2 deletion has been found to influence alterations in the microglial proteomic landscape in the presence of tau and LPS/ATP therapy, leading to the activation of exosomes. In addition, exosomes derived from microglia without the Trem2 gene exhibit increased amounts of tau protein and have a greater ability to induce tau aggregation in a tau FRET reporter line, as compared to exosomes from microglia with the Trem2 gene.⁹² Exosomes contain inflammation-causing payloads to cause neuroinflammation.⁹³ Research indicates that A β buildup and tau hyperphosphorylation activate microglia and astrocytes, leading to inflammation.⁹⁴ Exosomes may contain harmful proteins like A β or tau, and activated glial or neuronal cells could release them into environment, exacerbating neuroinflammatory effects.⁹⁵ MicroRNAs, an essential exosome cargo, also induce neuroinflammation. NDEs expressing miR-21-5p may be phagocytosed by microglia and promote M1 polarization. This increases neuroinflammatory factors, neurite outgrowth inhibition, P-tau accumulation, and PC12 cell apoptosis.⁹⁶ Exosomes enhance and disseminate extracellular microenvironment inflammation and may also reduce it. Due to its carrier transport, simplicity of modification, and therapeutic drug encapsulation, exosomes have been shown to treat inflammation. Related investigations have shown that AD is tightly linked to NLRP3 inflammasome activation.⁹⁷ Ginger rhizome exosomes limit NLRP3 inflammasome activation, IL-1 β and 18 release, and pyroptotic cell death by preventing NLRP3 inflammasome assembly.⁹⁸ Microglia exosomes may sometimes decrease inflammation. Upregulated miR-124-3p in microglial exosomes induces anti-inflammatory M2 polarization, reduces neuronal inflammation, and is transferred to neurons to boost neurite outgrowth after traumatic brain injury.⁹⁹ Overall, exosomes may enhance or inhibit the inflammatory response depending on the stimuli and cell types that create them. More study is required to determine the process.

A thorough investigation found a link between oxidative stress and AD growth. A self-sustaining cycle of oxidative stress and inflammatory reactions may cause persistent neuronal damage and dysfunction in AD.¹⁰⁰ Changing environmental circumstances deposit free radicals, causing oxidative stress, mitochondrial malfunction, and inflammation. Essential free radicals, reactive oxygen species, cause tissue failure and oxidative stress.¹⁰¹ To promote cell development and govern metabolism, the reactive oxygen species level must maintain signalling pathways such as the Ras/AMPK, and Protein kinase-C pathways. Oxidative stress may cause amyloid- β and neurofibrillary tangles.¹⁰² Furthermore, intracellular amyloid- β accumulation triggers oxidative and inflammatory pathways, creating a loop of oxidation and amyloid- β production.¹⁰³ Numerous studies show that neuroinflammation-induced oxidative stress increases A β production by increasing β and γ -secretase activity.¹⁰⁴ Oxidative stress triggers A β formation via p38 mitogen-stimulated protein kinase signaling, NF κ B binding, or lipid peroxidation. Several A β techniques increase oxidative stress by overexpressing reactive oxygen species in cells.¹⁰⁵ Metal ion-chelated Amyloid β may regenerate O₂ by a three-step process including reduction to superoxide and oxygen peroxide, generation of OH radical, and the release of reactive oxygen species as byproducts. Amyloid- β may induce oxidative stress via endoplasmic reticulum damage, lipid buildup, and mitochondrial malfunction.¹⁰⁶ Studies indicate that monomeric units and micro-oligomers A β are responsible for generating oxidative stress, which results in cell damage and neuronal death, rather than plaques.¹⁰⁷ Also, oxidative stress might alter the process of biogenesis, the release, and the composition of exosomes. Exosomes generated under oxidative stress contain biologically active chemicals that might potentially affect the regulation of both challenged cells and nearby cells.^{108–112} In addition, exosomes obtained from cells exposed to oxidative stress exhibited a reduction in the levels of proteins that

promote cell survival and an increase in proteins that induce cell death. These findings align with previous reports indicating that oxidative stress can modify the phosphorylation process of proteins involved in cell activity.¹¹³ Oxidative stress has been found to change the lipid content of exosomes, specifically affecting the amounts of oxidized lipids, and their transfer across cells. Exosomes have been demonstrated to have both proinflammatory and anti-inflammatory effects on nearby cells through the production or transport of oxidatively changed lipids.¹¹⁴ Establishing a two-way connection is essential for preserving cellular balance in the face of oxidative stress. Alterations in redox state stimulate an increase in the quantity of exosomes, which can be done by either enhancing their release or reducing their breakdown. Elevated autophagy conditions redirect MVBs toward lysosomes rather than the plasma membrane, impeding the secretion of exosomes.^{115,116} Conversely, inhibiting autophagic trafficking facilitates exosome secretion.¹¹⁷ Studies have demonstrated that oxidative stress can lead to an increased release of exosomes in several types of cultured cells.^{118–121} Furthermore, the presence of nanoparticles, mechanical damage, or chemicals has been shown to cause oxidative stress, leading to an increase in the quantity of exosomes, which may also be accompanied by morphological alterations.¹²¹

Regionally raised capillary concentration, vascular loop growth, glomeruloid vascular structure creation, and VEGF and TNF release are biochemical and morphological signs of angiogenesis. A study suggests that angiogenic activation of the brain endothelium in AD leads to the formation of A β plaques and neurotoxic protein that damages cortical neurons.¹²² Angiogenesis, the formation of new blood vessels from pre-existing vessels, is a complex and coordinated process that involves vascular degradation. Increasing vascular basement membrane endothelial cell and neovasculture development.^{123,124} Research indicates that microglia-produced inflammatory cytokines, regulated by Amyloid- β protein, accelerate AD development.¹²⁵ Angiopathy in cardiovascular illnesses and AD is linked to amyloid, resulting in altered artery walls and increased microcapillary thickness in A β deposits.¹²⁶ The high incidence of vascular problems in AD, A β 's regulation of endothelial inflammation, and the close link between capillaries and amyloid- β deposits lead to cerebral vasculature involvement.¹²⁷ Using DNA sequencing and proteomics to analyze gene expression levels supports the A β -inflammation-angiogenesis theory in AD.¹²⁸ Interestingly, several genetic factor translation products promote angiogenesis. This study suggests that damaged brain arteries may upregulate angiogenesis and its components and that unique DNA array information plays a role in AD pathogenesis.¹²⁹ VEGF controls brain angiogenesis and BBB integrity.¹³⁰ VEGF binds to VEGF receptor-2, activating it. VEGF exists in less active membrane-bound and inactive soluble forms, inhibiting pro-angiogenic signaling. Deficit in angiogenic response to VEGF in Alzheimer's disease may be mediated by VEGF receptor expression.¹³¹ Earlier stages of AD also show TGF-1 signalling pathway dysfunction and reduced downregulation of transforming growth factor-II receptor in neurons.¹³²

Collectively, these results suggest that exosomes may transport pathogenic proteins associated with Alzheimer's disease and lead to dysfunction in neuronal activity. Hence, pharmaceutical treatments that block exosome release might provide a novel therapeutic approach for Alzheimer's disease.

Exosomes are Involved in the A β Clearance Process, the Remission of AD Pathology, and Exert a Protective Role in AD

Despite the fact that exosomes were thought to cause AD, a substantial amount of new research suggests they may actually help prevent the disease. In particular, exosomes may carry chemicals that restore neuronal functioning or remove A β , which may have protective effects on Alzheimer's disease. Exosomes include proteins with several powerful protective roles for neurons, such as Cystatin C.^{133,134} Neprilysin (NEP) and insulin-degrading enzyme (IDE), two enzymes involved in the breakdown of A β , are also found in exosomes. New evidence from the following studies supports the idea that exosomes' protective impact is directly related to IDE.^{52,55}

Released into the extracellular environment by exosomes, metalloproteases endothelin-converting enzyme (ECE)-1 and -2 may facilitate the breakdown of A β . Increasing A β levels and facilitating the intracellular production of A β oligomers may be achieved by the inhibition of metalloproteases, which disrupts A β catabolism.⁵⁴ Exosomes produced from neuroblastoma cells/ human cerebrospinal fluid were shown to be able to inhibit A β 's ability to alter synaptic plasticity, according to another investigation. The main factor determining these effects is the ability of exosomal surface proteins, including PrP, to sequester A β oligomers.¹³⁵ Exosomes facilitate tau secretion in response to overexpression,

and this released tau does not cause cell death in contrast to cytoplasmic tau, according to one study.¹³⁶ This finding provides further evidence that tau-secreting exosomes could mitigate the harmful effects of tau overexpression in cells. Furthermore, it has been shown that neuronal cells may decrease A β oligomerization in vitro by improving microglia-mediated A β clearance via the production of exosomes. Microglia secrete mutant tau into the central nervous system via exosomes, according to a recent research.¹³⁷ Reducing microglia numbers and blocking exosomal secretory routes decreases tau growth in both in vivo and in vitro experiments. Neuronal exosomes, when injected into the brains of APP transgenic mice, reduce the buildup of A β and amyloid. A possible explanation might be neuronal exosomes capture A β via the membrane's rich glycosphingolipids, transfer it to microglia, and therefore reduce A β pathogenesis. Exosomes produced by hypoxia-preconditioned mesenchymal stromal cells may reverse the cognitive loss in APP/PS1 mice according to a newly published research.

A recent research found that microglia exosomes may secrete their contents by activating receptor expressed on myeloid cells 2 (TREM2). In order to change the inflammatory levels around A β and enhance microglia cell detection and phagocytosis of A β , pure microglia exosomes may attach to A β via TREM2, releasing chemokines.¹³⁸ Furthermore, TREM2 may influence tau pathology along with its functions in A β clearance. The enhancement of tau trafficking, dispersion, and pathogenic dissemination via microglia exosomes may be achieved by deleting Trem2, as previously mentioned.^{92,139} On the flip side, microglial overexpression of TREM2 reduces neuronal tau hyperphosphorylation pathology and the inflammatory response.¹⁴⁰ These findings lend credence to the idea that TREM2 may prevent tau pathogenesis by way of microglia exosomes. Microglial enrichment of the ATP-gated cationic channel P2X purinoceptor 7 (P2RX7) enhances exosome secretion. Giving P301S tau mice the P2RX7-specific inhibitor GSK1482160 improves their working and contextual memory by reducing the quantity of exosomes and tau.¹⁴¹ Potentially new avenues for enhancing tau pathology include inhibiting P2RX7 to decrease exosome expression.

Role of Exosomes in AD Diagnosis

AD is usually detected late in life, making treatment challenging. MRI, CT, and PET scans are the main AD diagnostic methods. Biochemical AD diagnostics are not used clinically despite their development. Reliable biochemical tests for early AD detection may enhance AD treatment throughout age.

A biomarker is a characteristic that could be reliably measured and studied as a sign for treatment-related physiological effects, pathogenic activities, or normal bioactivities.¹⁴² Possible Alzheimer's disease biomarker data comes from a wide range of places, including clinical memory impairment tests, analyses of bodily fluids or organs, imaging of neurons, and olfactory tests.¹⁴³ More and more research is focusing on exosomes as potential biomarkers to differentiate between healthy and diseased states, due to their unique biological properties. Exosomes provide several distinct benefits as a diagnostic tool for diseases. The first advantage is that exosomes may be easily and painlessly retrieved from most bodily fluids, meaning that the organism is not harmed in any way during the sampling process. Furthermore, the payloads housed inside exosomes are able to retain their biological activity and structural integrity due to the protective nature of their membranes. Plus, the exosome cargoes are process-related and change depending on the illness state. Surprisingly, exosomes may traverse the BBB via their bilayer lipid structure and end up in peripheral circulation. Researchers are focusing their efforts on searching for biomarkers from blood exosomes since blood samples are so common. More importantly, the content of patient samples may be preserved for future biomarker investigation because to the excellent stability of these exosomes. Blood, urine, CSF, saliva, synovial fluid, breast milk, semen, amniotic fluid, ascites, lymph, and as many other bodily fluids as possible contain exosomes.

Early AD diagnosis and disease progression prediction using biochemical biomarkers has been described.¹⁴⁴ A β 1–42, total tau (T-tau), and p-tau protein levels in cerebrospinal fluid (CSF) are the most commonly acknowledged AD biomarkers.^{145,146} Even in the early to mid-stages of AD, these biomarkers could provide diagnostically useful information.¹⁴⁷ The CSF sample approach has limited dissemination and applicability in clinical practice due to its invasiveness. It has been discovered that exosomes may be produced in the brain, released into the bloodstream, and identified in the peripheral circulation after crossing the blood-brain barrier.¹⁴⁸ There has been recent speculation that exosomes generated from neurons might be indications for AD. It has been discovered that exosomes secreted from the central nervous system and amyloid- β precursor protein are components of neurons in plasma.¹⁴⁹ Identified the onset of

Alzheimer's disease up to five years prior to the onset of the illness, amyloid- β , which is present in neuronal generated exosomes removed from serum. Research on exosome biomarkers is therefore driven by the requirement to diagnose AD at an earlier stage.¹⁵⁰ Exosomes are potential biomarkers for tracking the degenerative progression of Alzheimer's disease because of this quality.

Almost every biomolecule derived from the parent cells is present in exosomes. Urine is one of the physiological fluids that contains exosomes, and it is easy and non-invasive to collect this fluid. Consequently, the most typical and effective specimens for liquid biopsy are exosomes of urine. In a preliminary investigation, Sun et al¹⁵¹ assessed the concentrations of A β 1–42 and P-S396-tau in urine exosomes. According to the results of this investigation, the amounts of these pathogenic proteins in urine exosomes were much higher in people with AD as compared to healthy controls. A new, non-invasive, and inexpensive way to measure salivary exosome content was developed by Rani et al using nanoparticle tracking analysis. Patients with cognitive impairment and AD may have considerably elevated salivary exosomal levels, according to this research. Cognitively impaired people may be able to differentiate between Alzheimer's disease and other dementias using cerebrospinal fluid biomarkers. Although the absolute levels of CSF A β 40 and A β 38 are not very useful for AD diagnosis, there are a number of benefits to using the A β 42/A β 40 or A β 42/A β 38 ratios. The ratios of CSF A β 42 to A β 40 and A β 42 to A β 38 may serve as more accurate indicators of target engagement in amyloid-based therapeutic clinical trials compared to CSF A β 42 alone. As well as protein markers, exosomal nucleic acids may detect AD. APP processing, tau phosphorylation, and apoptosis activation by exosomal miRNA may impact AD progression. An AD prognostic serum miRNA signature was described by Cheng et al. Intergroup differences in miRNA modification were reported between AD and control groups.¹⁵² miR-193b may reduce APP mRNA and protein content. MiR-193b level was similar in AD patients and controls, while exosomal levels were much lower. Also, exosomal miR193b and A β 42 were adversely linked to AD, suggesting exosomal miR193b level a biomarker for AD.¹⁵³ Another AD-related biomarker is blood or CSF exosomal miR-451a. In several investigations, AD patients had lower blood and CSF exosomal miR-451a levels than controls.^{154–156} Yang et al¹⁵⁷ measured serum miR-135a, –193b, and –384 levels using qRT-PCR in 2018. MCI and AD groups had higher miR-135a and miR-384 levels than the control group. MCI and AD patients have lower serum exosomal miR-193b levels. Using Solexa sequencing and qRT-PCR, Dong et al¹⁵⁸ identified blood exosome miRNAs such as miR-31, miR-93, miR-143, and miR-146a for AD diagnosis. During the stages of AD, miR-132-3p showed the highest dysregulation of all of these. It is worth noting that nerve cells show a decline in miRNA-132-3p and a rise in P-tau as the illness progresses, suggesting that miRNA-132-3p is dysregulated and might be used as a new disease biomarker.¹⁵⁹ The AD patients had significantly lower levels of these four miRNAs than the controls.

Exosomal contents can be used as biomarkers to differentiate AD from normal controls, MCI as well as other forms of dementia such as fronto-temporal dementia. In a study by Krishna et al,¹⁶⁰ the synaptic and organellar markers in AD and frontotemporal dementia (FTD) are investigated by assessing the levels of synaptic protein, neurogranin (Ng), and organellar proteins, mitofusin-2 (MFN-2), lysosomal associated membrane protein-2 (LAMP2), and golgin A4 from neuronal exosomes. Exosomes obtained from the plasma of healthy controls (HC), AD and FTD subjects were analyzed. Neurodegenerative status was assessed by measurement of neurofilament light chain (NfL). Analyzed in this study were the pooled exosomal extracts from each group for the presence of Ng, MFN-2, LAMP-2, and golgin A4. As a result, the densitometric analysis of immunoreactive bands revealed a 65% decrease in Ng in individuals with AD and a 53% decrease in individuals with FTD. The mitochondrial protein MFN-2 shown a notable decrease of 32% in AD and 46% in FTD. The levels of Lysosomal LAMP-2 and Golgi complex related golgin A4 were significantly elevated in both AD and FTD. These findings indicate that alterations in Ng may be indicative of the progressive breakdown of synaptic connections, which is associated with cognitive impairments in AD and FTD. Crucially, alterations in the levels of synaptic protein, neurogranin (Ng) and MFN-2, LAMP2, and golgin A4 from neuronal exosomes are helpful to distinguish AD from normal controls and FTD.¹⁶⁰ The two-stage-sectional investigation by Jia et al¹⁶¹ examined the potential of exosomal synaptic proteins as a predictor of asymptomatic Alzheimer's disease. The first trial included participants with preclinical AD and controls, while the second study confirmed the findings in familial AD. As compared to controls, AD patients had reduced quantities of growth associated protein 43 (GAP43), neurogranin, synaptosome associated protein 25 (SNAP25), and synaptotagmin 1. They found a correlation between the levels of

exosomal biomarkers and those in CSF. Adverse events were recognized five to seven years before to cognitive impairment by combining exosomal biomarkers. This study revealed that exosomal GAP43, neurogranin, SNAP25, and synaptotagmin 1 act as effective biomarkers to differentiate AD from normal controls and MCI.¹⁶¹

More credible biomarkers for early diagnosis have just been proposed, namely, exosomes in the blood that are generated from neurons and astrocytes.^{162–164} In plasma neuron-derived exosome extracts, the levels of p-S396-tau, p-T181-tau, and Aβ1–42 are noticeably greater in Alzheimer’s disease (AD) patients compared to controls. This reliably predicts AD start up to 10 years before clinical manifestation and progression from MCI to AD dementia.^{51,165} It is worth noting that new studies have shown that the AD group had greater levels of neuron-derived exosomal Aβ1–42, T-tau, and p-T181-tau, which coincided with the levels in CSF. This indicates that these exosomal markers may be used for AD diagnosis much as the ones in CSF.¹⁶⁶ The APEX technology, developed by a group of researchers, analyses various populations of circulating Aβ proteins as well as exosomes that are bound or unattached to these proteins directly in the blood. When measuring Aβ linked to exosomes, as opposed to unbound or completely circulating Aβ, it is possible to more accurately represent PET imaging of brain amyloid plaques and differentiate between different groups.¹⁶⁷

It has been postulated that proteins associated with neuroinflammation found in astrocyte and stem cell derived blood exosome extracts might serve as AD biomarkers.^{168,169} Evidence suggests that these cells secreted exosomes from AD patients include much greater quantities of pro-inflammatory factors and complement factors.^{80,170} There is an association between elevated levels of GABARAP, prion proteins (PrP), and APP with the presence of damaged mitochondrial organelles in extracellular vesicles (EV) isolated from the brains of preclinical AD patients. The presence of these dysfunctional mitochondrial organelles provides further evidence that defective autophagy in the temporal lobe plays a role in the transmission of AD neuropathology via EV.¹⁷¹ And since exosomes contain a great deal of tiny miRNAs, assessing their expression is being investigated as a possible diagnostic tool in Alzheimer’s disease.^{172–174} Taken together, the aforementioned research provide credence to the idea that exosomes might be useful as biomarkers for AD (Table 1).

However, certain concerns remain: 1) Exosomes as AD biomarkers may not be reliable due to the small amount of pathological proteins that cross the blood-brain barrier and the influence of various organs on blood contents. 2) Antibodies targeting proteins may immunoprecipitate plasma neuronal exosomes, but same proteins are also produced in other tissues, necessitating the development of more specific protein markers. 3) Inconsistent experimental results due

Table 1 The Expression of miRNAs in Peripheral Blood and Cerebrospinal Fluids (CSF) Derived from AD Patients

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-112, miR-161, miR-let-7d-3p, miR-5010-3p, miR-151a-3p	Blood	Upregulated	These miRNAs can discriminate AD patients from healthy controls.	[175]
miR-103a-3p, miR-107, miR-532-5p, miR-26b- 5p, miR-let-7f-5p		Downregulated		
miR-9-5p, miR-106a-5p, miR-106b-5p, miR-107	Blood	Downregulated	A reduction in whole-blood expression of these miRNAs was significantly associated with an increased risk of AD.	[176]
miR-let-7i-5p, miR-125a-5p, miR-1233-5p	Blood	Downregulated	Downregulation of miR-1233-5p as a pathologic marker for Aβ(+) MCI.	[177]
miR-98-5p, miR-885-5p, miR-483-3p, miR342-3p, miR-191-5p, miR-let-7d-5p	Serum	Downregulated	These miRNAs are downregulated in AD patients and is correlated to MMSE score.	[178]
miR-501-3p	Serum	Downregulated	The level of this miRNA is decreased in the serum of AD patients. Its lower levels are associated with lower MMSE scores.	[179]

(Continued)

Table 1 (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-210	Serum	Downregulated	The level of this miRNA is downregulated in the serum of AD patients, distinguishing AD individuals from healthy controls.	[180]
miR-519	Serum	Upregulated	The level of these miRNA in the serum of AD patients could be used to distinguish AD individuals from healthy controls.	[181]
miR-29, miR-125b, miR-223		Downregulated		
miR-125b	Serum	Downregulated	The level of this miRNA is downregulated in the serum of AD patients, distinguishing AD individuals from healthy controls and is correlated with the MMSE in AD patients.	[182]
miR-125b, miR-23a, and miR-26b	Serum	Downregulated	The levels of these miRNAs are decreased in the serum of AD patients, and serum miR-125 levels can distinguish AD individuals from healthy controls.	[183]
miR-613	Serum	Upregulated	The level of this miRNA is upregulated in the serum of AD patients and animals, and could be used to predict AD.	[184]
miR-455-3p, miR-4668-5p	Serum	Upregulated	The level of this miRNA is increased in the serum of AD individuals and can distinguish AD patients from healthy controls.	[185]
miR-195-5p, miR-146a-5p, miR-106b-3p, miR20b-5p, miR-497-5p	Serum	Upregulated	The level of these miRNAs in the serum of AD individuals and can distinguish AD patients from healthy controls.	[186]
miR-93-5p, miR-29c-3p, miR-125b-3p, miR19b-3p		Downregulated		
miR-28-3p	Serum	Upregulated	miR-28-3p level can be used as an early diagnosis and prognosis evaluation of AD patients.	[187]
miR-331-3p	Serum	Downregulated	Serum expression of miR-331-3p is decreased in AD patients, and is correlated with the MMSE scores and proinflammatory cytokine levels of AD patients.	[188]
miR-31, miR-93, miR-143, and miR-146a	Serum	Downregulated	The levels of these miRNAs are decreased in the serum of AD patients, and this panel can be used to distinguish AD individuals from healthy controls.	[158]
miR-6761-3p, miR-6747-3p, miR-6875-3p, miR-6754-3p, miR-6736-3p, miR-6762-3p, miR-6787-3p, miR-208a-5p, miR-6740-3p, miR-6778-3p, miR-6753-3p, miR-6716-3p, miR-4747-3p, miR-3646, miR-595, miR-4435	Serum	Upregulated	The level of these miRNA in the serum of AD individuals and can distinguish AD patients from healthy controls.	[189,190]
miR-125a-3p, miR-22-3p , miR-24-3p, miR-6131, miR-125b-1-3p		Downregulated		

(Continued)

Table I (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-128	Serum	Upregulated	miR-128 was significantly upregulated in the serum samples of AD patients compared with controls, and that this upregulation was negatively correlated with MMSE scores.	[191]
miR-let-7d-5p, miR-let-7g-5p, miR-15b-5p, miR-142-3p, miR-191-5p, miR-545-3p, miR-301a-3p	Plasma	Downregulated	These 7 signature miRNAs are downregulated in the plasma of AD patients and can discriminate AD individuals from healthy controls.	[192]
miR-34c	Plasma	Upregulated	The level of these miRNA in the serum of AD individuals can distinguish AD patients from healthy controls.	[193]
miR-92a-3p, miR-181c-5p, and miR-210-3p	Plasma	Upregulated	The levels of these miRNAs are increased in the plasma of AD patients and can distinguish AD individuals from healthy controls.	[194]
miR-34a-5p and miR-545-3p	Plasma	Downregulated	These miRNAs are downregulated in AD samples and show suitable diagnostic accuracy to distinguish AD patients from healthy controls.	[195]
miR-34a, miR-146a	Plasma	Downregulated	These miRNAs are downregulated in AD samples and show suitable diagnostic accuracy to distinguish AD patients from healthy controls.	[196]
miR-384	Plasma	Downregulated	The level of this miRNA in the plasma of AD individuals can distinguish AD patients from healthy controls.	[197]
miR-483-5p, miR-486-5p, miR-200a-3p, miR502-3p	Plasma	Upregulated	These miRNAs can distinguish AD patients from healthy controls.	[198]
miR-30b-5p, miR-142-3p		Downregulated		
miR-1908	Plasma	Upregulated	The level of this miRNA is increased in the plasma of AD patients and can distinguish AD patients from healthy controls.	[199]
miR-206	Plasma	Upregulated	The level of this miRNA is increased in the plasma of AD patients and can predict cognitive decline using the MMSE test.	[200]
miR-103, miR-107	Plasma	Downregulated	The level of these miRNAs are downregulated in the plasma of AD patients and can distinguish AD patients from healthy controls.	[201]
miR-135a, miR-384	Serum (Exosome)	Upregulated	These miRNAs can be used to distinguish AD patients from healthy controls.	[157]
miR-193b		Downregulated		

(Continued)

Table 1 (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-22-3p , miR-378a-3p	Serum (Exosome)	Upregulated	These miRNAs can be used to distinguish AD patients from healthy controls.	[202]
miR-30b-5p		Downregulated		
miR-342-5p	Serum (Exosome)	Downregulated	The level of this miRNA is downregulated in the plasma of AD patients and can distinguish AD patients from healthy controls.	[203]
miR-342-3p, miR-141-3p, miR-342-5p, miR-23b-3p, miR-125b-5p, miR-24-3p, miR-152-3p	Plasma (Exosome)	Downregulated	These miRNAs can predict AD status.	[204]
miR-423-5p, miR-369-5p, miR-23a-5p	Plasma (Exosome)	Upregulated	These miRNAs can be used to distinguish AD patients from healthy controls.	[205]
miR-204-5p, miR-125a-5p , miR-1468-5p, miR375, miR-let-7e-5p		Downregulated		
miR-let-7b	Cerebrospinal fluids	Upregulated	miR-let-7b can function as signaling molecules and identify TLR7 as an essential element in a pathway that contributes to the spread of CNS damage.	[206]
miR-27a-3p	Cerebrospinal fluids	Downregulated	miR-27a-3p can be used to distinguish AD patients from healthy controls.	[207]
miR-29a, miR-29b	Cerebrospinal fluids	Upregulated	These miRNAs show suitable diagnostic accuracy to distinguish AD patients from healthy controls.	[196]
miR-34a, miR-125b, miR-146a		Downregulated		
miR-384	Cerebrospinal fluids	Downregulated	The level of this miRNA in the cerebrospinal fluids of AD individuals can distinguish AD patients from healthy controls.	[197]
miR-146a , miR-100, miR-505#, miR-4467, miR-766, miR-3622b-3p, miR-296	Cerebrospinal fluids	Upregulated	The level of these miRNAs in the cerebrospinal fluids of AD individuals can distinguish AD patients from healthy controls.	[208]
miR-1274a, miR-375, miR-708, miR-219, miR-103		Downregulated		
miR-210	Cerebrospinal fluids	Downregulated	The level of this miRNA is downregulated in the cerebrospinal fluids of AD patients, distinguishing AD individuals from healthy controls.	[180]
miR-613	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients and animals, and could be used to predict AD.	[184]
miR-29a	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients and animals, and could be used to predict AD.	[209]
miR-378a-3p, miR-1291	Cerebrospinal fluids	Upregulated	The level of these miRNAs in the cerebrospinal fluids of AD individuals can distinguish AD patients from healthy controls.	[210]
miR-143-3p, miR-142-3p, miR-328-3p, miR193a-5p, miR-19b-3p, miR-30d-5p, miR-340-5p, miR-140-5p, miR-125b-5p , miR-223-3p		Downregulated		

(Continued)

Table 1 (Continued).

miRNA Profile	Sample	Expression Pattern	Utility	Reference
miR-let-7b, miR-let-7e	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients and animals, and could be used to predict AD.	[211]
miR-125-5p	Cerebrospinal fluids	Upregulated	These miRNAs represent novel targets for uncovering disease mechanisms and for biomarker development in both young-onset AD and late-onset AD.	[156]
miR-451a, miR-605-5p		Downregulated		
miR-455-3p	Cerebrospinal fluids	Upregulated	The level of this miRNA is upregulated in the cerebrospinal fluids of AD patients, and could be used to predict AD.	[212]
miR-16-5p, <i>miR-331-3p</i> , miR-409-3p, miR-454-3p	Cerebrospinal fluids	Upregulated	The miRNA cargo in cerebrospinal fluid (CSF) is associated with of sex and APOE-e4 in AD.	[213]

Note: The contradictory result is displayed in italics and bold (miRNA).
Abbreviations: MMSE, Mini-Mental State Examination; MCI, mild cognitive impairment.

to potential contamination, inconsistent extraction methods, and potential errors in the quantification of exosomes. Future studies aimed at resolving these issues should provide further evidence to aid in the diagnosis of AD.

Role of Exosomes in AD Treatment

Exosomes can carry miRNA and siRNA for AD therapy due to their RNA transport capacity, stability in bodily fluids, and BBB crossing.²¹⁴ Neuron-derived exosomes influence extracellular Aβ structure, resulting in non-toxic fibrils that promote microglia absorption.¹⁹ Exosomes may cure AD in many ways (Figure 3 and 4) (Table 2).

Exosomes as a Drug Delivery Vehicle

Numerous benefits may be achieved by delivering APs via exosomes. In comparison to liposomes or polymeric nanoparticles, exosomes are superior because to their desirable properties, such as a prolonged half-life, the ability to target, biocompatibility, and almost non-immunogenicity.²³⁴ Moreover, exosomes have the ability to enter tissues, spread throughout the circulation, and traverse the blood-brain barrier (BBB) in a specific way, which makes them ideal vectors for delivering genetic and medicinal components to treat neurological diseases.^{235,236} Because exosomes mediate the transfer of foreign substances and cargo, including proteins, mRNAs, miRNAs, and lipids, from one cell to another, the idea of using them to transport drugs has evolved from their function as a mediator of intercellular communication.²³⁷ It's possible that exosomes serve many purposes in the therapy of AD. Neuroprotective effects of extracellular elastin-rich oligosaccharides (exosomes) generated from mesenchymal stem cells (MSC-EXOs) include promoting functional recovery after traumatic brain injury (TBI) and neurodegenerative diseases (NDDs) by preventing cell death and inflammation in the brain.^{75,238} Previous research has effectively reduced total Aβ1–42 levels, a key component of the amyloid plaque in AD pathogenesis, by engineering exosomes laden with siRNAs to target central nervous system cells and suppress BACE1 expression.²¹⁴ To boost Que bioavailability and brain targeting and potentially enhance cognitive performance, Qi et al²³⁹ produced exosomes loaded with Que (EXO-Que). They then used them to rats with okadaic acid-induced AD. EXO-Que reduced insoluble NFT formation and limited tau phosphorylation by cyclin-dependent kinase 5, indicating its therapeutic potential for the treatment of Alzheimer's disease, in comparison to free Que. However, there are still several unanswered questions, such as how to make exosomes correctly recognise target cells, how to load exosomes with medications, etc.

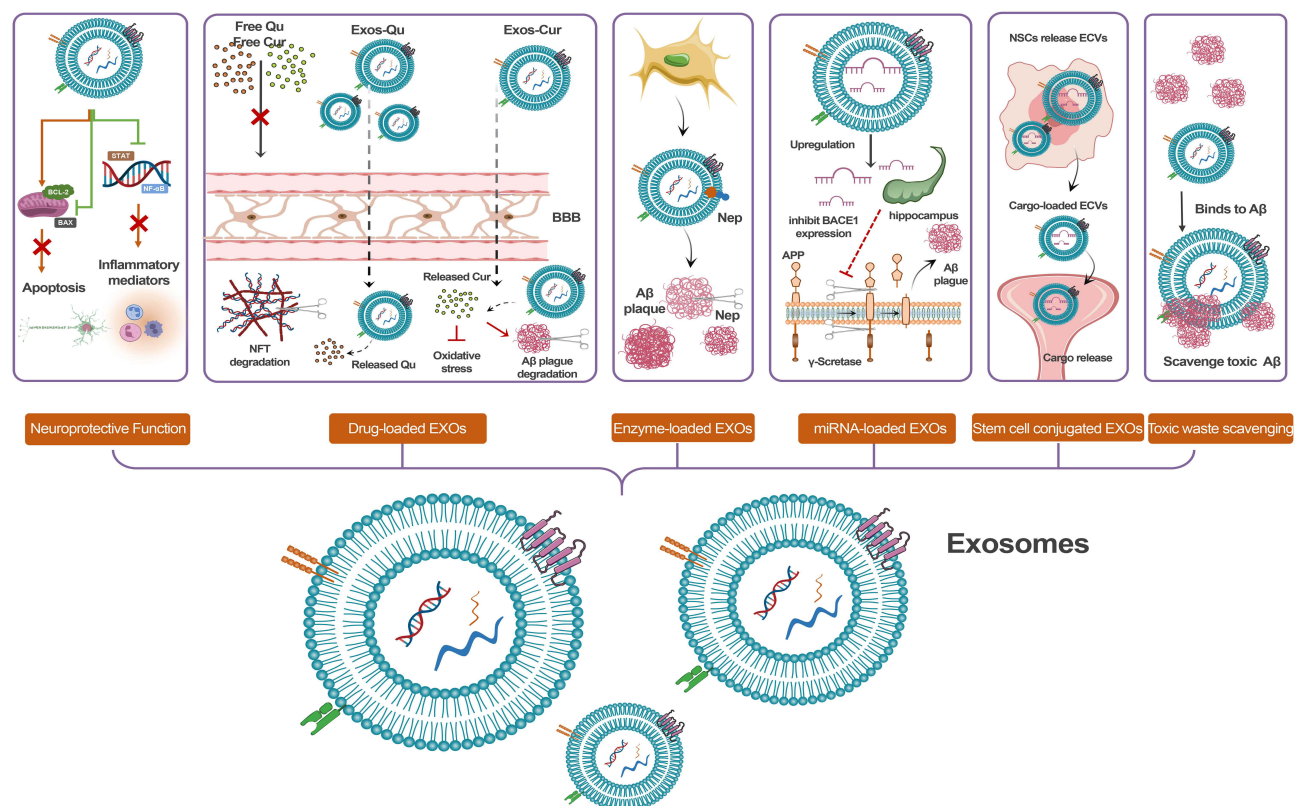


Figure 3 Role of exosomes in AD treatment.

Abbreviations: APP, amyloid precursor protein; Aβ, amyloid-beta; BCL2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; BBB, blood-brain barrier; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; Cur, curcumin; ECVs, extracellular vesicles; MP-MSCs, multipotent mesenchymal stem cells; NEP, neprilysin; NSCs, neural stem cells; NF-κB, nuclear factor kappa-light-chain enhancer of activated B-cells; NFT, neurofibrillary tangles; QU, quercetin; STAT, signal transduction and activator of transcription protein.

Bioactive Substances Delivery

Exosomes are a type of stem cell secretome. Recent scientific discoveries have shown that exosomes derived from dental pulp stem cells (DPSCs),²¹⁶ bone marrow stromal cells (BMSCs),^{217,240} and adipose-derived stem cells (ADSCs) contain neprilysin and an insulin-degrading enzyme, the roles of which are to break down Aβ.⁵² The quantity of neprilysin in the extracellular matrix (ECM) components released by DPSCs was comparatively greater than that of BMSCs and ADSCs. Furthermore, these exosomes may degrade Aβ1–42 and reduce their neurotoxic effects in laboratory-grown SH-SY5Y neuroblastoma cells.²⁴⁰ In another study, through electroporation, exogenous siRNA was loaded into purified exosomes that were targeted to the RVG. In these conditions, exosome-based gene therapy was shown to be effective in treating Alzheimer's disease (AD) by significantly lowering protein expression and reducing Aβ plaques in mice. A different study found that when miR-124a was delivered from neurons to glia through endothelial vesicles, it increased the surface expression of the excitatory amino acid transporter 2. This increased glutamate uptake is important for maintaining cognitive function in this situation.^{241,242}

Toxic Waste Scavenging and Neuroprotective Effects

Exosomes have the ability to attach to Aβ via glycosphingolipids on the surface of the cell membrane, making them excellent Aβ scavengers. This indicates that exosomes may play a role in clearing Aβ from the central nervous system. A novel therapeutic pathway for AD may be opened up by enhancing Aβ clearance with the injection of exosome.²³² N2a cells, a neuronal genetically engineered neuroblastoma cell line, produces exosomes that may inhibit neuronal death and Aβ-induced alterations in synaptic plasticity.^{135,164} In 2014, Yuyama et al found that exosomes scavenge Aβ via Aβ-glycan and exosome-glycosphingolipid attachment. This mechanism significantly reduces Aβ count, alleviating AD pathogenesis.²³² Transplantation of stem cells is

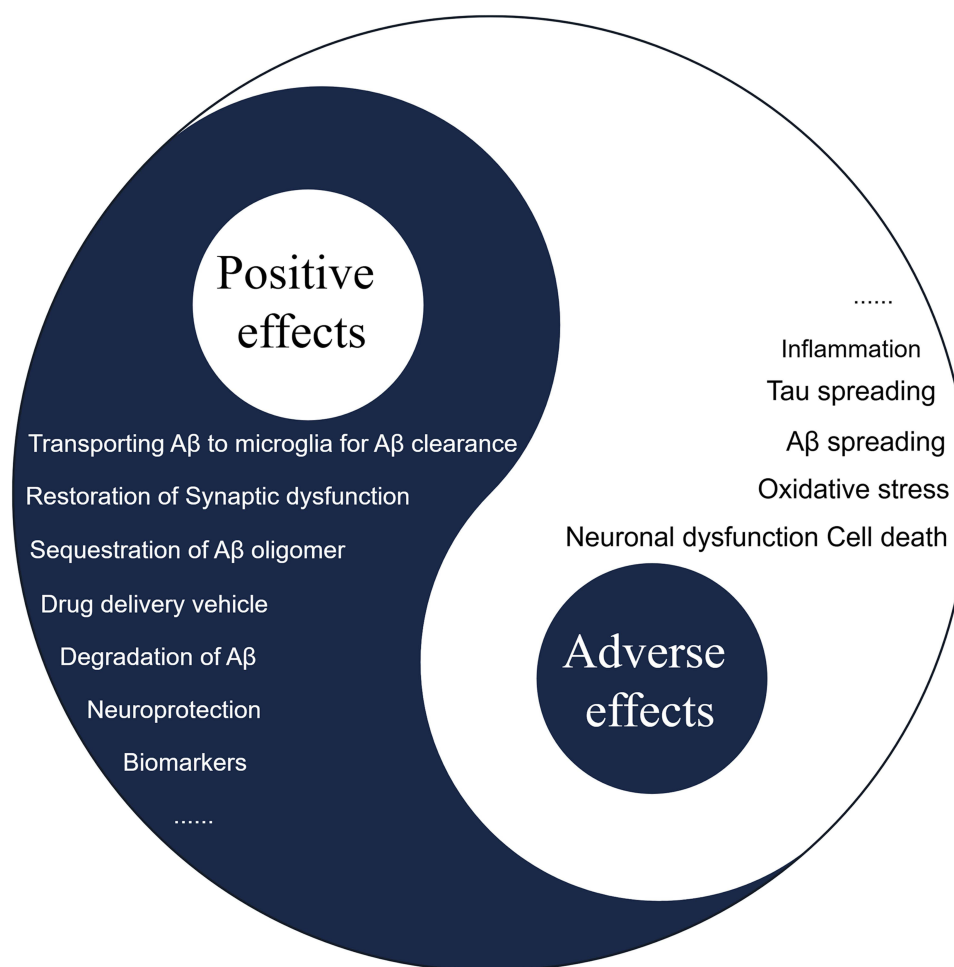


Figure 4 The dual role of exosomes in the pathogenesis of AD. By Figdraw.

now showing promise as a treatment for neurological diseases. Restoring the biomolecules required for non-functional cells, exosomes produced from MSCs when administered might alleviate a range of neurologic disorders. In order to restore bioenergy after depletion caused by glutamate excitotoxicity, MSCs generated from human adipose tissue released exosomes that had direct neuroprotective effects by avoiding neuronal apoptosis. This helped with central nervous system regeneration and repair.²⁴³ There is evidence that changes in NF- κ B are associated with cancer, inflammatory and autoimmune disorders, septic shock, viral infections, and the development of synaptic plasticity and memory.²⁴⁴ Research has shown that glial cell control and reduction of inflammatory mediator levels controlling NF- κ B pathways may be achieved with treatment with exosomes produced from MSCs.²⁴⁵ Additionally, Past research has shown that when microglia consume exosomes, they may be able to lower brain A β -protein levels. Neuroprotective substances may also be transmitted across cells by these mechanisms.²⁴⁶

Numerous studies suggest that stem cell-derived exosomes may improve AD pathology. According to Lee et al, exosomes from ADSCs may decrease β -amyloidosis and neuronal death in AD transgenic mice models and improve axon development in AD patients' brains.²¹⁵ Mesenchymal stromal cells (MSCs) have a high in-vitro multiplicity, are abundant in many tissues, and are easy to separate, making them a promising potential source of exosomes.^{247,248} Further research shows that MSC-derived exosomes may help enhance AD pathology and cognition.²¹⁸ By correcting BDNF-associated neuropathology, bone-MSC exosomes slow cognitive decline in AD-like mice.²²⁴ Furthermore, bone-MSC injection in double transgenic APP/PS1 mice may activate the sphingosine kinase-1/sphingosine-1-phosphate signaling pathway, reducing A β accumulation and promoting cognitive performance in AD animals.²²⁵ Many inflammation-related disorders may be treated using hucMSC exosomes. HucMSC-exosome injection reduces A β

Table 2 Role of Exosomes in AD Treatment

Source of Exosomes	Models	Outcomes	References
ADSC	NSCs from the brains of TG2576 AD mice	Decreasing A β 42 and A β 40 levels, AD neuronal cell death, and stimulating neurite development.	[215]
ADSC	N2a cell line	Decrease the levels of A β .	[216,217]
MSCs	Human neural cell culture model with FAD mutations and AD transgenic mice	Lowering A β levels, boosting brain glucose metabolism and cognitive performance in AD animals, and restoring the expression of genes linked to neuronal memory and synaptic plasticity in the cell model.	[218]
MSCs	5 \times FAD mice	Diminish persistent inflammation and expedite the elimination of A β .	[219]
MSCs	C57BL/6 mice	Encourage neurogenesis and the restoration of cognitive function.	[220]
MSCs	APP/PS1 mice	Reduce the neurological deficit of CA1 synaptic transmission in an AD animal model by inhibiting the inducible nitric oxide synthase (iNOS) in cultured primary neurons.	[221]
MSCs	A β -treated SH-SY5Y cells	Reduce apoptosis in neural cells and promote cell migration.	[222]
MSCs	APP/PS1 mice	Reduce A β levels and plaque accumulation while restoring normal inflammatory cytokine levels to enhance learning and memory.	[223]
BMSCs	A sporadic AD mouse model	Enhancing AD-like behaviors, preventing astrocyte and microglia hyperactivation, and enhancing BDNF-related neuropathology.	[224]
BMSCs	APP/PS1 mice	APP/PS1 mice's capacity for spatial learning and memory is improved, and SphK1 and SIP expression is increased. Amyloid levels are lowered, and NeuN expression is encouraged.	[225]
BMSCs	APP/PS1 mice	Diminish the quantity of dystrophic neurites and the A β plaque burden in the hippocampus and cortex.	[226]
BMSCs	APP/PS1 mice	The hippocampus will express more microRNA-146a, and astrocytes' levels of nuclear factor kappa B (NF- κ B) will drop. This will result in synaptogenesis and the improvement of cognitive impairment.	[227]
HucMSCs	APP/PS1 mice	Restore cognitive deficits and remove A β deposits.	[228]
HBMVECs	A β -induced AD mice model	Promoting the removal of A β from the brain and improving cognitive impairment.	[229]
M2 microglia	Neuronal HT-22 cells and APP/PS1 mice	Improving PINK1/Parkin-mediated mitophagy.	[230]
MExo-Gem	BV2 cells and A β 1-42-induced AD mice	Binding with A β and preferentially targeting microglia, which encourages lysosome-mediated A β clearance and enhances AD mice's capacity for learning and memory.	[231]
Neuroblastoma	APP transgenic mice	Reduce amyloid buildup, A β -mediated synaptotoxicity, and A β levels in the hippocampal tissues.	[232]
Neuronal	APP transgenic mice	Reduce amyloid deposition and A β .	[233]
Dendritic cells	C57BL/6 mice	Reduce A β and BACE1.	[214]

Abbreviations: AD, Alzheimer's disease; A β , amyloid beta; ADSC, adipose-derived stem cells; NSCs, neuronal stem cells; MSCs, mesenchymal stem cells; FAD, familial AD; BMSCs, bone-marrow mesenchymal stem cells, BDNF, brain-derived neurotrophic factor; SphK1, sphingosine kinase-1; SIP, sphingosine-1-phosphate; HucMSCs, human umbilical cord mesenchymal stem cells; HBMVECs, human brain microvascular endothelial cells, PINK1, PTEN-induced putative kinase1; MExo-Gem, mannose-modified exosomes laden with Gem; N2a cells, Mouse neuroblastoma Neuro-2a cells.

accumulation, improves cognitive performance in AD mice, and modulates microglia cell activation, reducing neuroinflammation.²²⁸ Transfer of ADSCs-derived exosomes into N2a cells reduces intracellular A β levels.^{216,217} In AD, stem cells and other cell-derived or bioengineered exosomes are useful. In a study, exosomes from human brain microvascular endothelial cells with p-glycoprotein were used to remove A β peptides from the brain. This was achieved through capture of p-glycoprotein and A β , resulting in improved cognitive function in AD mice.²²⁹ By enhancing PINK1/Parkin-mediated mitophagy, M2 microglia-derived exosomes also protect against AD.²³⁰ It is also necessary to use synthetic liposomes consisting of glycosphingolipids to collect A β and presenilin instead of natural exosomes. This would provide several advantages, such as consistent and contamination-free collection.²⁴⁹ Bioengineering can create microglia-targeting exosomes and tailored medication delivery. Mannose-modified exosomes with gemfibrozil interact with A β and target microglia, boosting A β entrance, stimulating lysosome activity, and speeding A β clearance in microglia.²³¹

Conclusions, Limitations and Future Perspectives

This review primarily discusses on the generation and functions of exosomes along with their complex role in the pathology, diagnosis, and treatment of Alzheimer's disease. Exosomes have attracted considerable interest due to their small size, important function in intercellular communication, biocompatibility, safety, and potential use as diagnostic and therapeutic tools in multiple brain disorders, such as AD. Exosomes seem to have a dual function in AD, being implicated in both the development of the disease and perhaps in its improvement. Exosomes may expedite the diseased process by facilitating the dissemination of disease-related proteins, triggering inflammation and oxidative stress, angiogenesis, or initiating cell death. Conversely, exosomes have been shown to slow down the disease progression by facilitating the clearance of A β and tau proteins.

However, the potential mechanisms by which exosomes exert these varying functions are still not clear enough, and further in-depth research is needed to investigate the mechanism of exosomes participating in AD and validate their potential as candidate drugs. Additional data is required to uncover the functions of exosomes in AD, particularly with advanced imaging labeling methods that provide real-time viewing of exosome interactions in cells or animals. Besides, collecting exosomes from certain cells is difficult, especially human cells. The absence of standard techniques for isolating and purifying exosomes is another primary barrier to effectively incorporating them into the translational clinical application, and thus practical and dependable exosome separation technologies require additional improvement. Moreover, exosomes function as promising diagnostic markers for AD are still in the infancy stage of development despite of their distinctive molecular traits. In future study, more clinical samples and data will be required to validate the postulated potential significance of exosomes in the diagnosis of AD. Furthermore, although a series of clinical trials have found the efficacy of exosomes in AD, there are some differences in data from different teams, and the metabolic process of exosomes in the human body and the specific process of their effects still need further investigation. With the appropriate combination of technological advancement and scientific understanding, the potential offered by exosomes could be fully realized.

Data Sharing Statement

The current study was based on the results of relevant published studies. Data is available from the corresponding author upon request.

Acknowledgments

We are grateful to the editors and reviewers for giving valuable advice and important comments in the review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This review was funded by the Scientific Research Project of Health Commission of Changzhou (No. ZD202019).

Disclosure

The authors declare no conflict of interest.

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