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Review

Molecular reflection of the mind: Exosomes in major depressive disorder

Shayan Boozarjomehri Amnieh [a,b,1], Mohammad Yazdi [a,c,h,1], Melika Abrishami [a,d,h,2], Nazanin Zahra Keshvari [a,e,h,2], Kiarash Saleki [a,f,h], Nima Rezaei [f,g,h,*]

[a] Universal Scientific Education and Research Network (USERN), Tehran, Iran
[b] Animal Model Integrated Network (AMIN), Universal Scientific Education & Research Network (USERN), Tehran, Iran
[c] School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[d] Student Research Committee, Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran
[f] Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[g] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[h] Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

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ABSTRACT

Exosomes, nanoscale extracellular vesicles (EVs) released by neural and peripheral cells, have become essential mediators in major depressive disorder (MDD). Their diverse cargo, including MicroRNAs (miRNAs), proteins, lipids, and metabolites, impacts key biological processes involved in depression, such as neuroinflammation, synaptic plasticity, hypothalamic-pituitary-adrenal (HPA) axis activity, and mitochondrial function. Therapeutically, both natural and engineered exosomes are being researched for their ability to deliver neuroprotective and anti-inflammatory molecules across the blood-brain barrier (BBB). In this review, we carefully analyze current findings, highlighting advantages and drawbacks across different cohorts, and identify common limitations that hinder reproducibility. We also suggest a framework connecting mechanistic insights with biomarker discovery and therapeutic development. Overall, these advances underscore exosomes as versatile tools for precision psychiatry.

1. Introduction

Major depressive disorder (MDD) is one of the most significant mental health challenges, with the World Health Organization (WHO) predicting it will become the leading cause of disease burden by 2030 (Wang et al., 2025). Currently, it affects more than 250 million individuals worldwide, and its prevalence is expected to rise further by 2050 (Bains and Abdijadid, 2025). Delayed diagnosis and treatment of MDD contribute to poor outcomes, including an elevated risk of suicide (Fabrazzo et al., 2023; Colomer et al., 2021). Comorbidities, dependence on subjective diagnostic criteria, and the limited effectiveness of available treatments further worsen patient outcomes (Luciano et al., 2025; Berk et al., 2023). Although advances have been made in understanding the pathophysiology of MDD, its diagnosis and treatment remain highly challenging.

So far, researchers have looked into several biomarkers for diagnostic purposes. One area of growing interest is extracellular vesicles (EVs). EVs are particles surrounded by a lipid bilayer that are released by most cell types, and they play a crucial role in communication between cells under both normal and abnormal conditions (Abrishamdar et al., 2023). Although they lack nuclei and cannot replicate, EVs carry various molecular cargos, including proteins, lipids, and nucleic acids, which can alter the function of recipient cells by transferring these bioactive components (Li et al., 2023a).

Recent research has highlighted the distinct potential of exosomes, a type of EV, as innovative diagnostic and therapeutic tools due to their natural ability to deliver specific molecules and surface proteins to target cells (Palomar-Alonso et al., 2024a; Rahmani et al., 2020). However, several technical barriers still hinder their translation into clinical practice. These include the lack of standardized isolation

* Correspondence to: Tehran University of Medical Sciences, Children's Medical Center Hospital, Dr. Qarib St, Keshavarz Blvd., Tehran 14194, Iran.
E-mail addresses: rezaei_nima@tums.ac.ir, rezaei_nima@yahoo.com (N. Rezaei).
[1] Co-first authorship and contributed equally to the present work.
[2] Co-second authorship and contributed equally to the present work.

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protocols, issues with purity and reproducibility, insufficient characterization of vesicular subtypes, and the relatively low yield of exosomes produced by cells (Palomar-Alonso et al., 2024b; Afshar et al., 2025).

Although the molecular basis of neuropsychiatric disorders is still not fully understood, it's clear that disrupted neural networks and abnormal information processing play a key role in the onset and progression of these diseases. In this context, exosomes released by neurons, glia, and other cells associated with the brain have become crucial to understanding the underlying pathology (Si et al., 2023). Since neuronal exosome release is closely tied to synaptic plasticity, and exosomes can pass through the blood–brain barrier (BBB), circulating and plasma-derived exosomes show promise as biomarkers that could reflect central nervous system (CNS) changes linked to MDD (Shin et al., 2023; Wei et al., 2020a).

Exosomes have diagnostic value, and they also represent the principles of precision psychiatry by providing a minimally invasive way to access molecular information from the brain. Their stability in biofluids, diverse cargo, and response to environmental stressors make them dynamic messengers of disease biology. As a result, research focused on exosomes not only offers insights into how MDD works but also paves the way for personalized approaches that could improve on the limitations of current symptom-based classification systems and inconsistent treatment responses.

This review brings together the latest research on exosomes in MDD, exploring their formation, roles in disease, and the molecules they carry. We also assess their potential as biomarkers for diagnosis and as therapeutic tools, showing their potential to improve targeted treatment for depression and revolutionize its clinical management.

2. Exosome biology: a neuropsychiatric perspective

2.1. Biogenesis of exosomes

Exosomes are nano-sized vesicles (approximately 30–100 nm) originating from the endosomal membrane system. They are formed and released into the extracellular space following the fusion of multivesicular bodies (MVBs) with the plasma membrane (Arya et al., 2024). Exosome biogenesis involves release from the cells through both the endosomal sorting complexes required for transport-dependent (ESCRT-dependent) as well as ESCRT-independent mechanisms (Juan and Fürthauer, 2018). Each of these mechanisms has a vital influence on the molecular makeup formation and functionality of secreted vesicles.

2.1.1. ESCRT-dependent pathway

The ESCRT-dependent pathway is one of the first identified routes for exosome formation. It is responsible for cargo selection, primarily focusing on ubiquitinated proteins, and for facilitating membrane invagination within MVBs. This pathway contains four main complexes: ESCRT-0, which identifies and clusters ubiquitinated cargos via Hrs and STAM proteins; ESCRT-I and -II, which drive membrane deformation and budding; and ESCRT-III, which facilitates vesicle scission with the help of VPS4 ATPase for recycling. However, this complex process is further modified by accessory proteins, including ALIX (which links ESCRT-I and -III), VPS4, and deubiquitylating enzymes, assisting in membrane scission and the recycling of proteins (Elsherbini et al., 2018).

Dysregulation in ESCRT components could adjust exosome cargo, leading to pathological states, such as altered protein sorting in neuropsychiatric conditions (Ouyang et al., 2013; Plooster et al., 2022). For example, applying glucocorticoid treatment to hippocampal neurons and N2a cells of in vitro models would mimic chronic stress. Thus, it would cause accumulation and neurotoxicity due to damaged ESCRT-mediated degradation of Tau and reduced Rab35 levels. In vivo, in rat models exposed to glucocorticoids, the Rab35/ESCRT dysfunction exacerbates Tau buildup and hippocampal atrophy, which can be rescued by AAV-mediated Rab35 overexpression, highlighting its relevance to stress-related psychiatric disorders like MDD (Plooster et al., 2022; Vaz-Silva et al., 2018). Likewise, an in vitro study of autism spectrum disorders (ASD) revealed dysregulation of the endosomal system. It displays the ESCRT pathway, interrupting receptor trafficking and synaptic function. For instance, mutations in SLC9A6 (NHE6) could induce overacidification of endosomes and reduce BDNF-TrkB signaling. Additionally, knockout mouse models demonstrate axonal spheroids, reduced synaptic field potentials, and ASD-like phenotypes (Ouyang et al., 2013). In schizophrenia, endosomal trafficking dysregulation, including ESCRT components, contributes to synaptic alterations; in vitro interference of early-to-late endosomal trafficking alters AMPAR endocytosis and synaptic plasticity. As well, in vivo Drosophila models show ESCRT's role in axonal pruning, with potential implications for altered connectivity in the disorder (Plooster et al., 2022).

2.1.2. ESCRT-independent pathway

The ESCRT-independent mechanisms rely on lipid-driven membrane remodeling rather than protein complexes. Having this in mind, ceramide production through the activation of neutral sphingomyelinase 2 (nSMase2) promotes intraluminal vesicle creation independent of ESCRT machinery (Juan and Fürthauer, 2018). Among all these lipids, ceramide plays a particular role. Ceramide endorses exosome formation by inducing endosomal membrane budding and assisting the development of sphingomyelin-enriched lipid raft microdomains on the endosomal membrane (Elsherbini et al., 2018; Brunkhorst-Kanaan et al., 2019). Other lipids, such as cholesterol and phosphatidic acid, also contribute by facilitating membrane curvature and vesicle budding, often in conjunction with tetraspanin proteins like CD63 and CD81, which organize membrane domains for cargo enrichment. The role of lipid in exosomes would not just be limited to exosome structure; lipid would also serve as a biosynthetic, release, and cell-to-cell interaction modulator. Of note, increased plasma levels of ceramide have been found in both MDD patients and mouse models, emphasizing the significant roles of these bioactive lipids in the pathophysiology of MDD (Brunkhorst-Kanaan et al., 2019; Schumacher et al., 2022; Skotland et al., 2019).

2.2. Functional relevance in the brain

In the CNS, exosomes have a variety of critical roles. They are released from neurons, glial cells, and stem cells to regulate essential functions such as synaptic plasticity, neuroinflammation, and neuroregeneration. These functions are highly influential for MDD, due to the link of these vesicles alteration to impaired neurotrophic signaling.

2.2.1. Neuron-derived exosomes

Neuron-derived exosomes (NDEs) can be released from both developing and mature neurons. Meanwhile, they have a crucial effect on neuronal communication within the CNS. These SSRI30–150 nm with a membrane enriched in cholesterol, sphingomyelin, and tetraspanins. NDEs contain diverse cargo, including synaptic proteins such as synaptophysin and PSD-95, miRNAs, neurotrophic factors like BDNF, and mitochondrial components. All of these factors could promote synaptic plasticity, neuroprotection, and intercellular signaling. Moreover, synaptic activity modulates NDEs secretion. By synaptic activity, depolarization, and calcium influx, MVB fusion with the plasma membrane could be addressed (Liu et al., 2024a; Wei et al., 2020b). Growth factors, such as basic fibroblast growth factor (bFGF), can further enhance exosome release. In fact, NDEs display selective uptake by neurons over glial cells, emphasizing a specific influence on neuron-to-neuron signaling. Notably, recipient neurons are able to re-release some internalized NDEs. This process might amplify their signaling effect and extend their signaling reach in both physiological and pathological conditions (Huo et al., 2021; Spinelli et al., 2025).

Beyond NDEs' role as a biomarker, new in vitro and in vivo studies propose promising therapeutic applications. In vitro Alzheimer's models

underline reduced neurotoxicity. Following NDEs' ability to modulate amyloid-beta (Aβ) conformation into nontoxic forms and boost its internalization by microglia (Brown et al., 2020; Wang et al., 2023; Yassaghi et al., 2024). Neural stem cell-derived exosomes, which share properties with NDEs, support cell proliferation, survival, and reduce apoptosis in neuronal cultures under stress conditions (Nogueras-Ortiz et al., 2024). In vivo, these exosomes alleviate neurodegeneration in animal models of CNS disorders, such as improving cognitive function and reducing Aβ aggregation in Alzheimer's mice, highlighting their neuroprotective roles (Du et al., 2022). As an example of NDE cargo in pathology, patients with MDD showed reduced levels of key mitochondrial proteins in NDEs, indicating mitochondrial dysfunction. After SSRI treatment, these protein levels normalized in treatment responders but not in non-responders (Goetzl et al., 2021).

2.2.2. *Microglia-derived exosomes*

Microglia are the brain's resident immune cells that maintain neural balance. However, it has a dual nature; based on its activation state, it could harm or repair. Their pivotal communication tool is the microglia-derived exosomes (MGEs). With this in mind, in normal conditions, MGEs support CNS health. In contrast, when it is dysregulated, they may promote neurodegenerative diseases such as Alzheimer's, Parkinson's, MS, and traumatic brain injuries (Guo et al., 2021a). For instance, in Alzheimer's disease, pro-inflammatory MGEs exacerbate amyloid plaque formation and neuronal loss, while in Parkinson's, they propagate alpha-synuclein aggregates; in MS, they modulate demyelination and remyelination processes; and in TBI, they influence post-injury inflammation and repair (Guo et al., 2021a; Ghosh and Pearse, 2024). The effects of MGEs depend on whether they originate from pro-inflammatory or anti-inflammatory microglia, with the former worsening inflammation and neuronal damage, and the latter supporting repair through neuroprotective and anti-inflammatory cargo.

Understanding how to shift MGE signaling toward beneficial outcomes is crucial for future CNS treatments (Ghosh and Pearse, 2024). Microglia might help reduce brain inflammation by releasing exosomes that carry miR-146a-5p. In addition, this process has been deeply investigated in diseases like Alzheimer's. It might have a protective role in depression by helping neurons recover from stress and inflammation. That indicates microglia-neuron communication is an emerging factor affecting how depression develops or heals (Fig. 2) (Xian et al., 2022a).

2.2.3. *Mesenchymal stem cell-derived exosomes*

MSCs could be obtained from several tissues, such as bone marrow, umbilical cord, and adipose tissue. They can self-renewal and turn into multiple cell types. However, current studies reveal that the major part of their therapeutic impact comes from EVs that they release. These MSC-derived EVs, which have low immunogenicity, can be extracted from body fluids and cell cultures. This means that they could be a more suitable option than using cell therapy. MSC-EVs retain many functional properties of their origin cells and have demonstrated efficiency in immune modulation, tissue repair, and particularly in treating fibrotic conditions (Kou et al., 2022). For instance, several preclinical studies examined MSC-EVs in MDD for therapeutic purposes. They detected reduced depressive symptoms even in the treatment-resistant depression model, and also increased serotonin and dopamine synthesis (Costa-Ferro et al., 2025a; Yang et al., 2021; Jiang and Xu, 2020; Kin et al., 2020). These indicate that MSC-EVs are capable of changing CNS neurochemistry in MDD models by secreting neurotrophic factors. Consequently, neuronal plasticity and survival would be promoted especially by MSC-EVs that transfer miR-26a (Yang et al., 2021).

3. The pathophysiological roles of exosomes in MDD

Exosomes play an active role in the development of MDD by affecting neuroimmune signaling, synaptic function, stress regulation, and mitochondrial balance. Instead of being mere byproducts, they function as dynamic mediators that influence vulnerability, symptom expression, and treatment response.

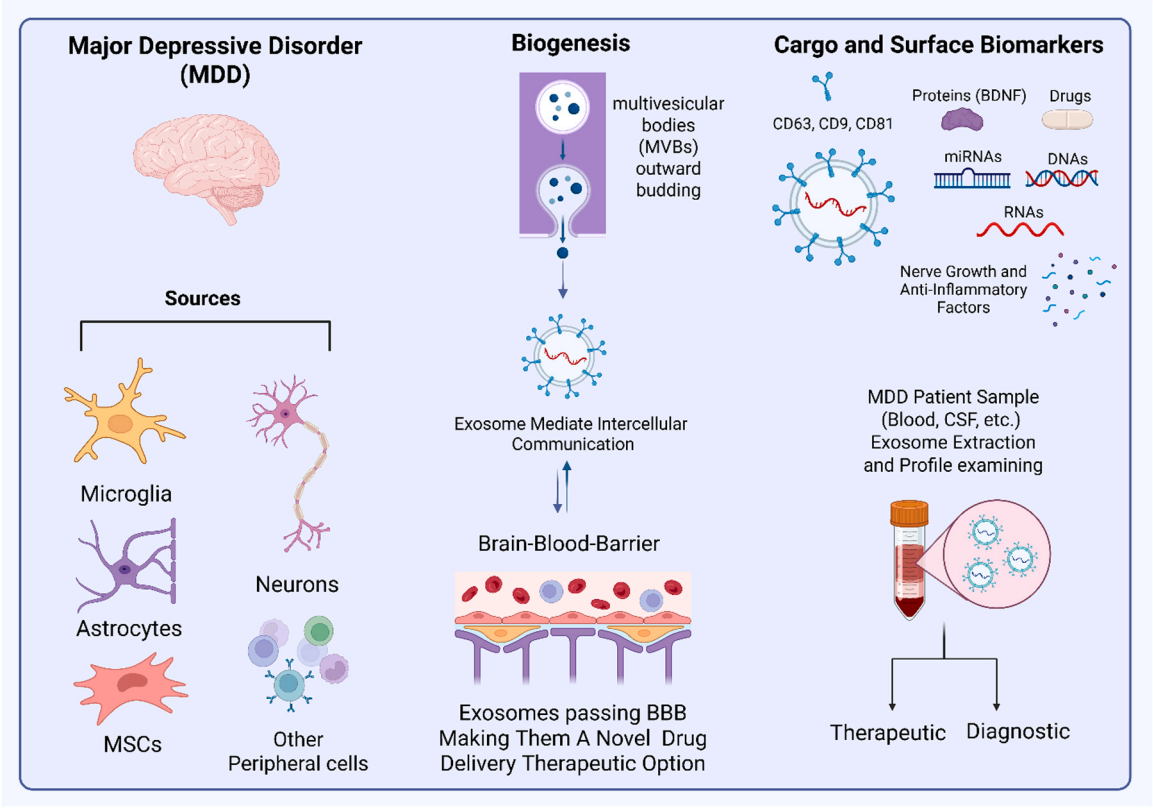

Fig. 1. Overview of the role of exosomes in MDD.

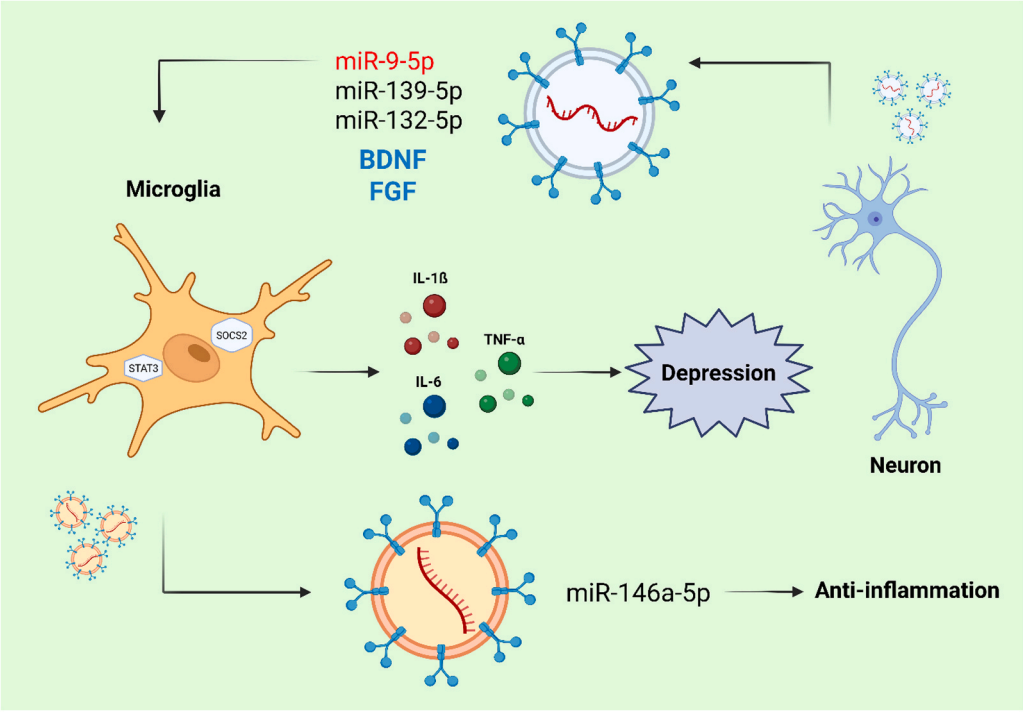

Fig. 2. Neuron–Microglia Exosome Crosstalk in MDD. In MDD, neurons release exosomes carrying miRNAs (e.g., miR-9–5p, miR-139–5p, miR-132–5p) and growth factors like BDNF and FGF, which influence microglia toward either protective or inflammatory roles. Activated microglia, in turn, release pro-inflammatory signals (IL-1β, IL-6, TNF-α) that can impair synaptic function. Regulators like STAT3 and SOCS2 shape this immune response. On the flip side, microglia can also release anti-inflammatory exosomes containing miR-146a-5p to help restore balance.

3.1. Neuroinflammation and cytokine signaling

Neuroinflammation is the continuous activation of CNS immune cells such as microglia and astrocytes, which activates extreme release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Miller and Raison, 2016; Najjar et al., 2013). Cytokine signaling has vital role in synaptic plasticity, neurotransmitter metabolism, and stress regulation that are the processes that are interrupted in MDD. Peripheral and central cytokines have had consistent elevation in depressed patients. These studies introduce inflammation as a mechanistic component in mood dysregulation (Miller and Raison, 2016; Felger and Lotrich, 2013; Liu et al., 2019; Kiecolt-Glaser et al., 2015). Within this framework, exosomes purpose as crucial messengers that shuttle cytokines, miRNAs, and regulatory proteins across neural circuits, strengthening or reducing neuroimmune responses (Li et al., 2023a; Colombo et al., 2014; Yáñez-Mó et al., 2015; Guo et al., 2021b).

Neuroinflammation has long been implicated in MDD, and exosomes play a critical role in transmitting inflammatory signals across neural circuits. Several studies demonstrate that microglia-derived exosomes regulate cytokine release and neuroimmune activity. For instance, reduced expression of the epigenetic regulator PCGF1 in both MDD patients and animal models promotes microglial activation via MMP10 signaling, linking inflammation to nucleosome remodeling and depressive behaviors (Li et al., 2025). Similarly, progranulin (PGRN) has been shown to exert dual effects: while neuroprotective in frontotemporal dementia, in MDD, it enhances microglia-driven inflammation within the nucleus accumbens, underscoring region-specific inflammatory vulnerability (Wang et al., 2022). Exosomal pathways also intersect with metabolic stress, as glycolysis inhibition with 2-deoxy-D-glucose (2-DG) reduces hippocampal microglial activation under chronic stress (Liu et al., 2024a). Finally, genetic modulation of microglial Pdcd4 influences resilience to inflammation-driven depressive phenotypes via the Pdcd4-PPARγ-IL-10 axis, establishing a strong immunoregulatory pathway relevant to MDD (Zhu et al., 2025a). Collectively, these findings indicate that exosome-mediated neuroinflammation is a key mechanism in MDD, particularly through microglial activation and altered cytokine signaling. Converging evidence supports the notion of inflammatory modulation across both patient samples and animal models; however, discrepancies persist, particularly regarding region-specific effects, such as those in the nucleus accumbens. These inconsistencies are likely attributable to differences in sample size, disease stage, and exosome isolation techniques. Despite such challenges, exosomes consistently emerge as regulators of neuroimmune crosstalk and hold promise as both mechanistic mediators and therapeutic targets in depression.

3.2. Synaptic plasticity and neurotrophic factors

Synaptic plasticity and neurotrophic support are central to the neural circuitry of mood regulation, and exosomes contribute to both adaptive and maladaptive remodeling. Reduced BDNF signaling and elevated proBDNF in serum and exosomes have been observed in MDD, with patterns reversing following treatment, highlighting the dynamic involvement of exosomes in neuroplastic processes (Wu et al., 2023). Moreover, astrocyte-derived exosomes containing BDNF appear to more reliably reflect disease state and treatment response than plasma levels, suggesting a cell-specific vesicular contribution to plasticity regulation (Li et al., 2024a). Exosomal miRNAs also participate in synaptic modulation, influencing inflammatory cascades and neuronal connectivity, though associations with clinical severity remain inconsistent (Liu et al., 2025a). Together, these findings converge on the view that exosomes are active regulators of synaptic dysfunction in MDD through BDNF-related pathways and plasticity-associated miRNAs. Human and preclinical studies generally align in demonstrating reduced neurotrophic support; however, variability in cohort characteristics, treatment exposure, and the source of exosomes, plasma versus cell-type specific, complicates interpretation. Despite these limitations, the collective evidence supports a mechanistic role for exosomes as both modulators and indicators

of impaired plasticity in depression.

3.3. HPA axis regulation and stress resilience

Stress dysregulation is a hallmark of MDD, and exosomes have emerged as modulators of the hypothalamic–pituitary–adrenal (HPA) axis. Plasma-derived exosomes from MDD patients carry dysregulated miRNAs that influence stress pathways, including FKBP5 and CRHR2, leading to elevated CRF expression in the hypothalamus and impaired stress regulation when transferred into mice (Yu et al., 2025). Beyond these direct vesicular effects, exosome-related epigenetic alterations, including non-coding RNA modifications, histone regulation, and DNA methylation, link early-life stress to persistent HPA axis hyperactivity and heightened depression risk (Yuan et al., 2023). Additionally, exosomal miRNAs have been implicated in modulating neurotransmitter regulation and stress responses at synaptic sites, reinforcing their role as intermediaries between environmental stressors and molecular vulnerability (Prodan-Bărbulescu et al., 2024).

Evidence from clinical and preclinical studies consistently implicates exosomes in HPA axis dysregulation, with converging findings around FKBP5, CRHR2, and glucocorticoid-related signaling. Nevertheless, inconsistencies remain in the directionality of miRNA changes across studies, likely due to medication status, timing of sample collection, and heterogeneity of stress paradigms. Overall, exosomes appear to act as critical modulators of stress resilience and endocrine regulation in MDD, but standardized experimental designs are required to resolve discrepancies and validate these pathways.

3.4. Mitochondrial function and oxidative stress modulation

Mitochondrial dysfunction is increasingly recognized as a driver of depressive pathology, linking cellular stress to impaired bioenergetics and inflammation. Exosomal cargos, including mtDNA, proteins, and ROS regulators, have been shown to contribute to this dysfunction in both human and animal studies. For example, chronic stress induces mitochondrial injury through glucocorticoid overload, leading to abnormal protein expression, disrupted electron transport chain activity, and oxidative damage (Daniels et al., 2020; Casaril et al., 2021; Chandel, 2015). Exosomes transporting mtDNA (EX-mtDNA) can further amplify inflammatory signaling through TNF pathways, correlating with cognitive decline and neuroinflammation in older adults (Mendes-Silva et al., 2024). TSPO, a mitochondrial membrane protein associated with microglial activation, has also been implicated as an exosome-linked biomarker reflecting mitochondrial stress in MDD (Bader et al., 2019; Setiawan et al., 2015). Consistent evidence supports exosome-mediated mitochondrial dysfunction as a core mechanism in MDD, with mtDNA release, oxidative stress, and inflammatory cross-talk forming a recurrent theme across models. However, questions remain regarding whether these mitochondrial exosomal signals are causal drivers of pathology or compensatory responses to stress. Variations in tissue source, including plasma versus neuronal exosomes, age of subjects, and technical challenges in quantifying exosomal mtDNA, may account for the conflicting findings. Despite these limitations, mitochondrial signaling via exosomes represents a crucial mechanistic pathway and a potential target for future therapeutic strategies in depression.

Moreover, oxidative stress combines these mitochondrial abnormalities and demonstrate an important pathological mechanism in MDD. It is the result of the imbalance between ROS production and antioxidant responses, causing lipid peroxidation, DNA damage, and impaired synaptic plasticity (Ng et al., 2008; Black et al., 2015; Liu et al., 2015). Elevated oxidative stress markers are reported in clinical trials in MDD patients that often correlates with symptom severity and poor treatment response (Black et al., 2015; Liu et al., 2015). Exosomes are mainly participated in this oxidation-reduction imbalance by transporting both protective and harmful cargos. On one hand, they can deliver antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase to buffer local ROS levels (Kourembanas, 2015). On the other, they can proliferate damage by transferring oxidized proteins, dysfunctional mitochondrial fragments, or pro-oxidant molecules (Shah et al., 2018). Neuronal and glial exosomes developed in oxidative stress–related miRNAs are shown to either strengthen ROS cascades or activate compensatory antioxidant responses (Kourembanas, 2015; Zhang et al., 2019). These roles highlight oxidative regulation by exosomes has crucial roles as both pathology and a potential therapeutic target. Therefore, their value as biomarkers of redox imbalance in MDD is underscored.

4. Exosomes as novel diagnostic biomarkers of neuropsychiatric disorders

Early and objective diagnosis of MDD remains a major clinical challenge because current methods mainly depend on subjective symptom reports. Exosomes offer a promising solution because they circulate in biofluids, cross the BBB, and carry molecular cargo that reflects brain function. A growing body of evidence highlights exosomal miRNAs, proteins, glycoproteins, metabolites, and even physical vesicle traits as potential biomarkers for disease detection, treatment monitoring, and differential diagnosis.

Exosomal miRNAs are the most widely studied class of biomarkers in MDD. Multiple studies report distinct expression patterns in patients compared with healthy controls (Table 1). Exosomal miR-30c, miR-101, and miR-26a were significantly downregulated in plasma, while miR-494 was primarily detectable in exosome-depleted plasma, where it also showed antidepressant treatment-related changes (Homorogan et al., 2021). In a genome-wide profiling study, 30 miRNAs were dysregulated in MDD patients following escitalopram treatment, with miR-26a and miR-494 emerging as key regulators of plasticity and stress pathways (Bocchio-Chiavetto et al., 2013). Larger cohort studies have also identified panels of upregulated miRNAs, including miR-26b, miR-1972, miR-4485, miR-4498, and miR-4743, all enriched in neural signaling pathways (Fan et al., 2014). Other consistently reported candidates include miR-132 and miR-124, which normalize after citalopram treatment (Fang et al., 2018), miR-1202 and miR-335 linked to GRM4 signaling (Lopez et al., 2014), and miR-144–5p, which is downregulated during depressive episodes but restored with treatment (Wang et al., 2015; Li et al., 2021). Adolescent depression has also been linked to altered cargo in L1CAM-positive EVs, where miR-375–3p and miR-200a-3p induced depression-like behaviors when transferred into mice (Liao et al., 2025).

Collectively, these studies highlight a recurring set of miRNAs, such as miR-26a, miR-494, miR-132, miR-124, miR-1202, and miR-144–5p, as candidate biomarkers of MDD. However, directionality and specificity differ across cohorts, particularly depending on treatment status and whether plasma, serum, or neuron-derived exosomes were analyzed. This variability underscores the promise of exosomal miRNAs as diagnostic and treatment-monitoring tools but also the need for standardized methods and extensive, cross-validated studies.

Beyond RNA, protein signatures in exosomes also distinguish MDD patients from controls. Astrocyte-derived EVs from patients contained reduced BDNF and elevated CD81, with ADEV-BDNF levels showing better correlation with treatment response than plasma BDNF (Li et al., 2024a). Plasma EVs from MDD patients were also found to have increased CD9 expression and altered concentration, correlating with poor antidepressant treatment response (Zadka et al., 2025). In the same study, serotonin transporter levels measured by PET in EVs correlated with amygdala activity, linking vesicular protein cargo to neural circuitry.

Protein-based exosomal biomarkers provide complementary information to miRNA signatures, with evidence pointing toward their value in monitoring disease progression and treatment response. However, validation in larger cohorts is needed to confirm their diagnostic utility.

Altered glycosylation patterns in plasma-derived EVs have also been

Table 1
Exosomal Cargo in MDD.

Reference	Specific Molecule	Expression in MDD	Associated Pathways	Exosome Origin	Biomarker Potential
(Wei et al., 2020a)	miR−139–5p	Upregulated	Neurogenesis, NSC proliferation, and differentiation	Blood-derived exosomes from MDD patients and HC subjects	Can distinguish MDD patients from healthy individuals
(Liang et al., 2025)	miR−151a−3p	Downregulated	Linked to ACC activity and multimodal MRI features; involved in mood regulation and stress response	Plasma-derived exosomes from MDD patients and HCs	High diagnostic accuracy when combined with neuroimaging; potential biomarker for MDD
(Wu et al., 2023)	miR-144-5p	Downregulated	Targeting PTEN and TLR4, modulating the PI3K/Akt/FoxO1 pathway and NF-κB (p65) signaling	Serum-derived exosomes	Potential biomarker and therapeutic target
(Huang et al., 2025)	miR−103a−3p	Upregulated	Impairs neuronal differentiation by targeting BDNF signaling	Plasma-derived exosomes from MDD patients and HCs	Potential biomarker due to its regulatory role in neurogenesis and behavioral outcomes
Zhu LL et al., 2025 (Zhu et al., 2025b)	miR−182–5p	Upregulated	Associated with synaptic plasticity and neuroinflammation; linked to altered expression of depression-related genes	Plasma-derived exosomes from MDD patients and HCs	Demonstrated high diagnostic accuracy
(Xian et al., 2022b)	miR−9–5p	Upregulated	Promotes polarization of microglia toward pro-inflammatory M1 phenotype; contributes to neuroinflammation	Serum exosomes from MDD patients and HCs, cultured cell model, and CUMS-treated mice	May serve as a mechanistic marker of neuroinflammatory activation
(Fang et al., 2020)	miR−134–5p, miR−1202, miR−124, miR−132, miR−182, miR−212, miR−218, miR−338	Several miRNAs were significantly dysregulated	Involved in synaptic plasticity, neurogenesis, inflammation, and stress response	Serum exosomes from rats subjected to CUMS	Multiple miRNAs showed potential as diagnostic markers for stress-induced depression
(Li et al., 2024b)	miR−125b−5p	Upregulated	MyD88/TRAF6/NF-κB signaling pathway	DPA-treated umbilical cord MSCs	Potential biomarker of antidepressant effect
(Li et al., 2020)	miR−207	Downregulated	Targets Tril in astrocytes; inhibits NF-κB signaling and reduces IL−1β, IL−6, TNF-α	Exosomes derived from NK cells (mouse model)	High potential as a therapeutic biomarker via anti-inflammatory effects
(Guo et al., 2020)	miR−26a	Downregulated in hippocampal neurons of rats; upregulated after exosome treatment	PI3K/Akt activation; reduced apoptosis; improved oxidative stress	Exosomes secreted by bone marrow MSCs from healthy rats	Therapeutic potential for protecting hippocampal neurons under depression-like conditions
(Gelle et al., 2021)	BDNF (Protein)	Downregulated	Involved in neuroplasticity, synaptic function, and mood regulation	Plasma-derived exosomes from MDD patients and HCs	Potential biomarker for MDD diagnosis and monitoring treatment response
(Gelle et al., 2021)	pro-BDNF (Protein)	Increased in MDD patients; imbalance with mature BDNF	Associated with neuronal apoptosis and impaired synaptic plasticity	Serum and exosomes of MDD patients and HCs	May reflect pathological state and treatment responsiveness
(Zhang et al., 2024b)	SIRT2 (Protein)	Enriched in oligodendrocyte-derived exosomes	Enhanced neurogenesis and synaptic plasticity	Exosomes derived from oligodendrocytes (mouse model)	Potential therapeutic biomarker via restoration of hippocampal neuroplasticity
(Ibrahim et al., 2025)	Multiple proteins (specific names not detailed)	Altered packaging in brain-derived EVs of MDD suicide cases	Synaptic function, vesicle-mediated transport, neurotransmission	Brain-derived EVs from post-mortem MDD patients vs. controls	Potential source of biomarkers for MDD; insights into synaptic dysfunction
(Wang et al., 2021)	Sig−1R (Protein)	Enriched	Neuroprotection, anti-inflammatory response	Plasma-derived exosomes from MDD patients and depression models	Potential therapeutic target for MDD

Abbreviations:
MDD: Major Depressive Disorder;
NSC: Neural Stem Cell;
HC: Healthy Control;
ACC: Anterior Cingulate Cortex;
BDNF: Brain-Derived Neurotrophic Factor;
CUMS: Chronic Unpredictable Mild Stress;
DPA: Docosapentaenoic Acid;
MSC: Mesenchymal Stem Cell;
IL: Interleukin;
TNF-α: Tumor Necrosis Factor-alpha;
NK: Natural Killer;
SIRT2: Sirtuin 2;
EV: Extracellular Vesicle;
Sig-1R: Sigma-1 Receptor.

linked to MDD. Concentrations of WGA-binding glycoproteins such as N-acetylglucosamine and N-acetylneuraminic acid were markedly reduced in depressed patients compared with both healthy controls and remitted cases. Proteomic analysis identified von Willebrand Factor (vWF) as a key glycoprotein marker that could differentiate depressive and remission states (Yamada et al., 2024).

These findings suggest that glycoprotein alterations in EVs may not only serve as diagnostic markers but could also monitor treatment response and disease stage.

Although less studied, lipidomic profiling has revealed distinct EV

lipid signatures in depression. Alterations in phosphatidic acid metabolism and lipid-raft-associated domains have been reported, reflecting structural changes that could influence exosome release and cargo loading (Ghossoub et al., 2014).

Lipid alterations remain an emerging but understudied domain. While they may provide valuable insights into disease biology, more systematic lipidomic analyses are required to establish clinical biomarker potential.

Metabolomic analyses of serum-derived EVs have identified 15 dysregulated sugar-related metabolites that distinguish bipolar disorder from MDD, including biopterin, glucosamine, and PAF C-16 (Du et al., 2022). Such findings suggest that exosomal metabolite signatures may be helpful in differential diagnosis across psychiatric disorders.

Exosomal metabolites hold promise for improving diagnostic specificity between overlapping mood disorders. However, replication in larger multi-site cohorts is needed to confirm reliability.

Besides molecular cargo, changes in the physical characteristics of exosomes have been detected in MDD. Plasma EVs from patients showed smaller, more uniform size distributions and lower refractive index variance, alongside increased particle concentration (Zadka et al., 2025). These biophysical properties could be allied with reduced antidepressant response. To this end, they could be beneficial as prognostic markers. In sum, exosome-based biomarkers cover a broad range of molecules and properties. Specific miRNAs have frequently stood out as potential candidates for diagnostic and treatment monitoring. As an example miR-26a, miR-494, miR-132, miR-1202, and miR-144–5p could be mentioned. Nonetheless, differences in isolation methods, biofluid sources, and treatment exposure limit the extent to which they can be replicated. Standardized protocols and large, well-studied groups will be crucial to turn these promising results into practical diagnostic tests.

5. Exosome-based therapeutic strategies in MDD

Due to limitations of current antidepressants and frequent delays in beginning medications, there is an urgent need to develop novel therapeutic approaches for MDD (Malhi and Mann, 2018). Exosomes have recently emerged as promising therapeutic tools as they can cross the BBB and deliver bioactive cargo directly to target cells (Table 2 and Fig. 3) (Liu et al., 2024b).

Several agents have been examined in preclinical studies for their potential antidepressant outcomes. For instance, Agomelatine has been reported to reduce MDD symptoms through increasing BDNF levels, also decreasing inflammatory cytokines and oxidative stress (Rebai et al., 2021). Likewise, calcitriol is the active form of vitamin D that has anti-inflammatory capacity in the CNS. Although its exact function in how it regulates neuroinflammation with the P2X7 receptor is still unclear (Wang et al., 2024). Caffeine has also demonstrated anti-inflammatory effects by decreasing p-AKT and NF-κB activity and alleviating depressive symptoms in LPS-exposed rats (Zhang et al., 2024a).

Beyond small molecules, exosomes released from bone marrow mesenchymal stem cells (BMSC-exos) could modulate BDNF-related neuropathology, thus improving cognitive impairment (Liu et al., 2022a). Since mitochondrial dysfunction is a major element in MDD, interventions such as mitochondrial transplantation have been explored; however, efficacy remains limited to just preclinical models (Ciubuc-Batcu et al., 2024; Borcherding and Brestoff, 2023; Wang et al., 2019a).

Preclinical studies strongly suggest MSC-derived exosomes as therapeutic agents. For example, in rodent models, MSC-exos decreased depression-like behaviors by lowering pro-inflammatory cytokines, TNF-α, and IL-1β, and increasing anti-inflammatory signaling (Guo et al., 2020). In a rat model of chronic stress, human umbilical cord-derived MSCs (hucMSCs) and their EVs have also alleviated depressive-like behaviors. Moreover, proteomic analysis reveals enrichment of proteins associated with inflammation regulation and neural regeneration (Costa-Ferro et al., 2025a, 2025b).

Clinical evidence also supports therapeutic usage of exosomes. To delve deeper, EVs from MDD patients illustrate altered profiles, with reduced CD63, increased CD9, and lower SLC6A4, serotonin transporter expression. EV concentrations were slightly higher in patients, and both EV levels and CD9 expression correlated with better antidepressant response. To this end, EVs' dual role as both biomarkers and therapeutic modulators could be suggested (Eggerstorfer et al., 2025).

MSC-derived exosomes have been explored in other neurological conditions, such as Alzheimer's disease and Parkinson's disease (Elsharkasy et al., 2020; Lai et al., 2022). Their low immunogenicity and compatibility with the host immune system provide advantages over traditional therapies (Lou et al., 2017; Guo et al., 2023; Tew et al., 2025; Rezaie et al., 2021). Engineering exosomes to extend half-life and improve targeting even more underlines their therapeutic applications (Zhuang et al., 2011).

In terms of delivery, intranasal administration has raised attention as a noninvasive method. Due to high bioavailability and good patient compliance, yet retention and dosing difficulties would remain (Peng et al., 2022; Hao et al., 2020).

Despite these advances, several pitfalls must be addressed before the translation of these findings into clinical practice. On one hand, variability in MSC sources, isolation methods, and dosing regimens complicates reproducibility, while long-term safety remains insufficiently studied (Tew et al., 2025; Liu et al., 2022b). On the other hand, improving exosome stability during storage, adjusting delivery systems for brain targeting, and harmonizing protocols across laboratories would be the next critical steps (Sonbhadra et al., 2023). Finally, well-designed clinical trials are mandatory to confirm safety, dosing, and efficacy in MDD (Musiał-Wysocka et al., 2019).

These therapeutic approaches would raise hope for addressing current limitations in MDD treatment. In fact, their relevance may go even beyond depression. Since dysregulation of exosomal cargo is increasingly detected in various psychiatric conditions. In sum, recognizing condition-specific mechanisms could speed up translation and improve the clinical impact of exosome-based treatments. In addition to what has been discussed with regard to therapeutics, as herbal products have been used in various disorders as therapeutics (Latifi et al., 2022; Chen and Guo, 2017), investigating the effect of herbal products on exosome cargos may be a novel avenue to which more efforts (Wu et al., 2022) could be dedicated to extend their potential to MDD. Computational studies are useful in a wide range of disorders (Vaziri et al., 2023; Saleki et al., 2022a, 2024; Aram et al., 2024; Saleki et al., 2022b), including MDD (Xue et al., 2018). Particularly, Bioinformatics analyses of macromolecules using structural biology techniques as well as protein-protein interactions of effective exosome cargoes, could be useful in the context of MDD therapeutic discoveries. Targeting neuroplasticity mechanisms in MDD may also denote a valuable approach (Saleki et al., 2023; Li et al., 2024b).

6. Exosomes as transdiagnostic biomarkers in psychiatry

Exosomes also have a considerable impact on psychiatric conditions other than MDD. As research advances, evidence proposes exosomes' broad influence on psychiatric pathophysiology. Schizophrenia is a main area of attention in this part; its results offer a framework for comparing molecular signatures across diverse mental illnesses.

Exosomal metabolites have recently been implicated in schizophrenia, with the first large-scale metabolomic study analyzing serum-derived exosomes from 385 patients and 332 controls. Twenty-five dysregulated metabolites have been identified in patients. These results have been gathered from high accuracy across multiple cohorts. Moreover, these metabolites were enriched in pathways such as glycerophospholipid metabolism, supporting their role as diagnostic biomarkers (Du et al., 2021a).

Research into the miRNA profile of schizophrenia establishes a group

Table 2
Therapeutic Effects of Exosomes in MDD.

Reference	Source of Exosomes	Experimental Model	Administration Route	Therapeutic Effects	Mechanism of Action	Clinical Relevance
(Wei et al., 2020a)	Blood exosomes from MDD patients	Normal mice	Tail vein injection	Induced depressive-like behaviors	Delivery of miR−139–5p to the brain reduces hippocampal neurogenesis	Potential diagnostic and therapeutic target
(Wei et al., 2020a)	Blood exosomes from healthy donors	CUMS-treated mice	Tail vein injection	Alleviated depressive-like behaviors	Reduced miR−139–5p levels, increased hippocampal neurogenesis	Potential therapeutic intervention for MDD
(Liang et al., 2025)	Exosomes enriched with miR−151a−3p	CUMS-treated mice	Injection into the ACC	Alleviated depression-like behaviors in stressed mice	Restoration of miR−151a−3p levels in ACC modulates neural activity and emotional regulation	Supports miR−151a−3p as a therapeutic candidate for MDD
(Xian et al., 2022b)	Neuron-derived exosomes containing miR−9–5p	Mouse model of depression	Intracerebral injection and in vitro microglia culture	Induced M1 microglial activation and aggravated depressive-like behaviors	miR−9–5p promotes neuroinflammation via microglial polarization	Highlights neuron-microglia communication via exosomes as a potential therapeutic target
(Li et al., 2020)	NK cell-derived exosomes enriched in miR−207	CUMS-treated mice	Intravenous injection	Improved depression-like behaviors, increased locomotion, and reduced anxiety-like behavior	miR−207 enters astrocytes, inhibits Tril, leading to the suppression of NF-κB, hence reducing the level of IL−1β, IL−6, and TNF-α	Demonstrated efficacy in mice; BBB crossing and human translation require further study
(Li et al., 2024b)	Exosomes from DPA-treated umbilical cord MSCs	CUMS-treated mice	Intraperitoneal injection	Reduced depression-like behaviors, decreased M1 microglial neuroinflammation, improved neurotransmitter levels	miR−125b−5p modulates MyD88/TRAF6/NF-κB pathway to suppress neuroinflammation	Supports stem cell-derived exosomes as a promising therapeutic strategy for depression
(Huang et al., 2025)	Serum exosomes from healthy individuals	Male rats	Intravenous injection	Did not induce depressive behaviors; served as controls	No disruption of BDNF signaling or neuronal differentiation	Confirms pathological role of MDD-derived exosomes; supports use of healthy exosomes as baseline
(Huang et al., 2025)	Serum exosomes from MDD patients	Male rats	Intravenous injection	Induced depressive-like behaviors and impaired neuronal differentiation	miR−103a−3p suppresses BDNF signaling, reducing neurogenesis	Highlights miR−103a−3p as a mechanistic target for understanding and treating MDD
(Wang et al., 2021)	Plasma exosomes from MDD patients	LPS-induced depressive mice model	Intravenous injection	Significantly reduced depressive-like behaviors, restored BDNF levels, and decreased neuroinflammation	Delivery of Sig−1R via exosomes mediates anti-inflammatory and neuroprotective effects	Suggests a novel exosome-based therapeutic strategy targeting Sig−1R for MDD treatment
(Zhang et al., 2024b)	Oligodendrocyte-derived exosomes containing SIRT2	CUMS-treated mice	Intravenous injection	Reduced depressive-like behaviors; restored hippocampal neurogenesis; recovered synaptic plasticity	SIRT2 delivered to neurons leads to deacetylation of AKT. Hence, activation of AKT/GSK−3β signaling and improved neuronal plasticity	Preclinical evidence in mice; BBB crossing and human applicability require further investigation
(Guo et al., 2020)	Bone marrow MSC-derived exosomes	Rat model of depression induced by corticosterone injection	Intravenous	Improved hippocampal neuron morphology; reduced apoptosis; enhanced proliferation; reduced neurodegeneration	Upregulation of miR−26a leads to activation of PI3K/Akt, hence reducing oxidative stress and inflammation	Preclinical evidence in rats; further studies needed for human translation and delivery optimization
(Liu et al., 2025b)	Bone Marrow MSC-derived exosomes	LPS-induced depressive mice model	Intravenous injection	Prevented the development of depressive-like behaviors	Lowered IL−1β, IL−6, TNF-α; increased IL−10; reduced oxidative stress in CNS and periphery; promoted astrocyte proliferation and hippocampal neurogenesis	Demonstrated antidepressant-like effects in mice; BBB passage and human translation require further study
(Sun et al., 2025)	Exosomes derived from adipose MSCs	CUMS-treated mice	Intranasal administration	Amelioration of depressive-like behaviors, suppression of neuroinflammation, and enhancement of autophagy	Activation of the AMPK/mTOR pathway, inhibition of the NLRP3 inflammasome-mediated neuroinflammation	Preclinical evidence supporting adipose MSC-derived exosomes as a potential therapeutic strategy for depression

Abbreviations:
MDD: Major Depressive Disorder;
CUMS: Chronic Unpredictable Mild Stress;
ACC: Anterior Cingulate Cortex;
NK: Natural Killer;
IL: Interleukin;
TNF: Tumor Necrosis Factor;
BBB: Blood-Brain Barrier;
DPA: Docosapentaenoic Acid;
MSC: Mesenchymal Stem Cell;
BDNF: Brain-Derived Neurotrophic Factor;

LPS: Lipopolysaccharide;
Sig-1R: Sigma-1 Receptor;
SIRT2: Sirtuin 2;
CNS: Central Nervous System.

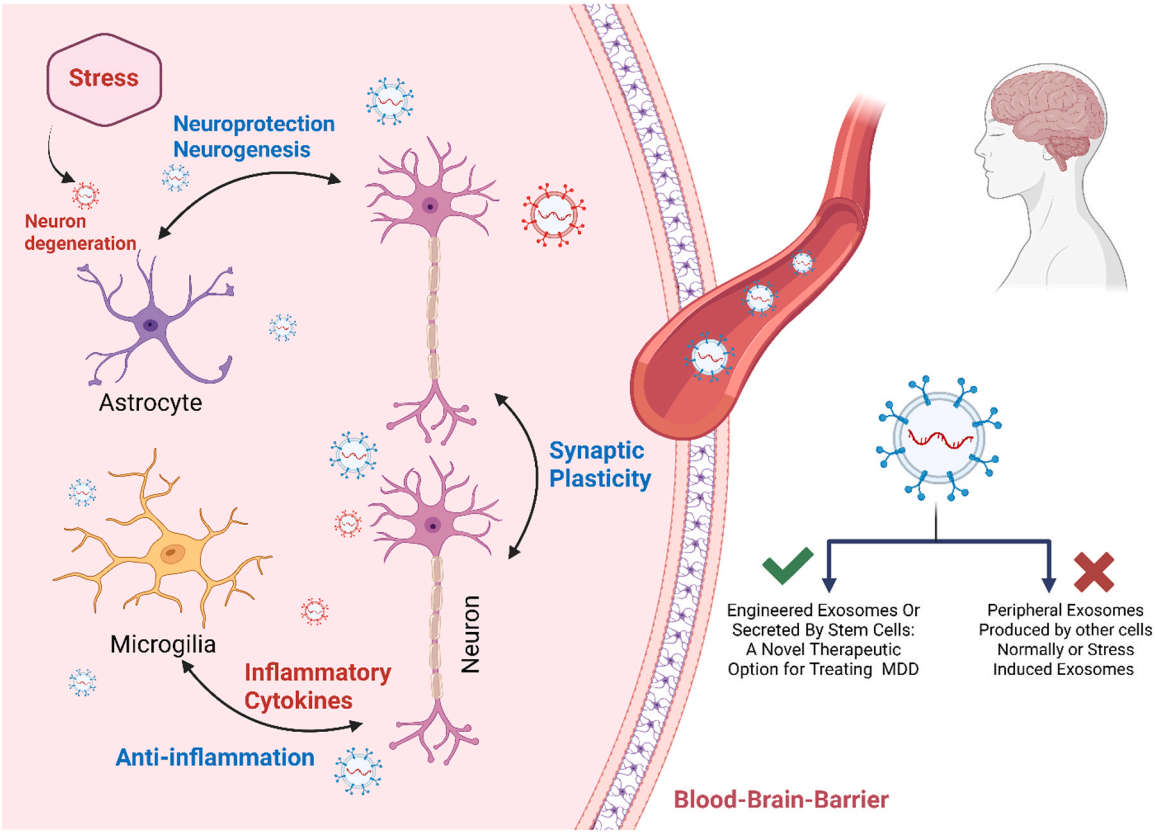

Fig. 3. Dual Role of Exosomes in Stress and Therapy. Stress triggers harmful exosomes (red) that worsen neuroinflammation. In contrast, stem cells or engineered exosomes (blue) can cross the BBB barrier to protect the CNS, reducing inflammation, supporting healing, and improving neural connections. This contrast highlights their promise for treating depression.

of dysregulated miRNAs that have an impact on synaptic and neurotrophic pathways. Among them, miR-206 was notably linked to reduced levels of BDNF. A genome-wide miRNA expression profiling of serum-derived exosomes in schizophrenia examined 49 first-episode, drug-free cases along with 46 controls, identifying several dysregulated miRNAs and co-regulated modules for which predicted targets were enriched for genes involved in protein glycosylation, neurotransmitter receptors, dendritic development and synaptic plasticity. Of note, hsa-miR-206 was the most strongly upregulated miRNA and was associated with reduced BDNF mRNA and protein levels in patients. Several differentially expressed exosomal miRNAs were independently validated by qRT-PCR in an expanded cohort (100 patients vs 100 controls), and an 11-miRNA classifier achieved ~90 % accuracy in training and ~75 % in testing samples. Together, these findings implicate exosomal miRNA dysregulation as both a mechanistic contributor to SCZ pathophysiology and a promising source of blood-based diagnostic biomarkers A validated panel of miRNAs would display high diagnostic accuracy, highlighting their role as biomarkers and contributors to disease pathophysiology (Du et al., 2019).

In the other study, transplanting serum exosomes from schizophrenia patients into mice could mimic schizophrenia like behaviors in them. This means, symptoms like impaired sociability, hyperactivity, and anxiogenesis could be detected in them. Interestingly, integrative bioinformatics discovered overlapping genetic and pathway changes between exosome-recipient mice, established SCZ models, and patient data. Key hub genes such as BDNF and NRG1 emerged, supporting a role as an exosomal cargo in disease mechanisms and underlining their importance in modeling and therapeutic exploration (Du et al., 2021b).

All of these results imply the exosomes' potential applications as transdiagnostic mediators that connect molecular dysregulation with clinical phenotypes in both depression and schizophrenia. The emerging evidence across various disorders suggests that exosomal cargo might not only revolutionize diagnostic specificity but also reveal shared therapeutic targets. Ultimately, moving closer to the broader goal of precision psychiatry.

7. Future directions for exosome therapy in MDD

Exosomes are turning to promising personalized and targeted treatment and diagnosis tool for MDD in the future research. Some of the molecular ones such as miRNAs, for example miR-146a and miR-155 implicated in inflammation regulation and they can predict antidepressant treatment response. Therefore, their potential as biomarkers is demonstrated (He et al., 2025). Moreover, plasma-derived brain EVs that contain mitochondrial proteins and insulin receptor substrate-1 (IRS-1) show central energy metabolism. Thus, normalizing utilizing them following treatment suggests as treatment indicators of depression (Li et al., 2023b). Also, exosomes are also suitable as delivery vehicles for neuroprotective molecules such as apolipoprotein D (ApoD) and fibroblast growth factor 2 (FGF-2), as a result of their ability for crossing the BBB. In future, this feature can be conducted for precision drug delivery strategies in psychiatry (Li et al., 2023b).

Exosomes therapeutic approaches are recently getting underscored in engineering methods. In a mouse model of depression, RVG-modified exosomes carrying BDNF (RVG-BDNF-Exos) successfully delivered BDNF into the hippocampus and prefrontal cortex. As a result, BDNF/TrkB/AKT signals restored, neuroinflammation reduced and neurogenesis and synaptic plasticity were promoted. Thus, exosomal BDNF can hold a role as both therapeutic approach and a biomarker for monitoring treatment outcomes and leading to precision psychiatry, again (Huang et al., 2024).

At the technological level, the field is transforming from basic discoveries to translational applications. Traditional ultracentrifugation methods are being replaced by microfluidic and nanotechnology-based isolation platforms, which give the ability for high-resolution and scalable exosomes classification (Ou et al., 2023). Exosomes which function with peptide ligands such as transferrin receptor binders have enhanced penetration across the BBB and improved targeting of neural tissues (Ou et al., 2023). In addition, hybrid exosomes in nanoparticle systems are developing as next-generation platforms for targeted delivery (Fatima et al., 2023; Mehdizadeh et al., 2025).

Future treatment strategies are more than ever regarding multimodal approaches. Theranostic exosomes are engineered to deliver therapeutic cargos and imaging agents at the same moment and have already shown promise in Alzheimer's disease by enabling both treatment and real-time monitoring of disease progression (Zhou et al., 2024). Combination therapies delivered through exosomes, such as siRNAs along with neurotrophic peptides demonstrated notable efficacy in neurodegenerative disease models and can show new paths for MDD management (Yadav et al., 2024). Additionally, vesicles designed for both treatment and diagnosis use could optimize treatment by enabling early detection and real-time assessment of treatment response (Zhao et al., 2024).

Artificial intelligence (AI) is becoming a transformative tool in exosome research, particularly in challenges of vesicle heterogeneity and optimized cargo. Machine learning and deep learning models are now being used ligand and receptor interactions prediction, which help in targeted delivery across the BBB that led to designing novel targeting peptides, and classifying vesicle subtypes with high precision. Moreover, they also support optimization of exosomal cargo loading, ensuring high efficacy in delivery of proteins, RNAs, or small molecules to neural targets (Mehdizadeh et al., 2025; Greenberg et al., 2023). By combining multiplexed molecular profiling with AI-driven prediction, exosomes treatment approaches are likely to evolve into personalized drug delivery systems.

In addition, other exosomal cargos such as circRNAs are beginning to gain attention. For instance, circDYM, which is regulated in both human patients and animal models of depression, was successfully delivered to the brain using RVG-modified vesicles (Yu et al., 2022). As a result, the ability of exosomes to connect genetic, epigenetic, and environmental factors in MDD is underscored (Wang et al., 2019b; Gruzdev et al., 2019). However, lipidomic studies in MDD and exosomes are still rare, despite their established role in other neurological disorders and represent one of the important approaches for future investigation (Li et al., 2023b).

Exosomes indicated several challenges such as standardization of isolation techniques, scalability of production, and long-term safety assessments. However, they also demonstrated unique features such as low immunogenicity, stability, biocompatibility, and BBB penetrability, which make them as one of the most promising frontiers for MDD treatments. Advances in culture systems, purification protocols, and engineered delivery strategies are gradually bringing these applications closer to clinical translation (Li et al., 2024a). To conclude, these developments underscore the potential of exosome-based therapies to transform the treatment landscape of MDD, introducing novel biomarkers and precision medicine approaches that encompass over conventional pharmacological strategies.

8. Conclusion and future perspectives

Exosomes are no longer just peripheral findings in depression research; they now hold promise as both key drivers and accessible messengers of disease. Research on neuroinflammation, neuroplasticity, stress, and mitochondria suggests that the cargo in exosomes reflects and influences the biology of MDD. Importantly, these underlying signals can be found in circulating exosomes, where they can serve as biomarkers for diagnosis or treatment monitoring. Studies on therapeutic uses of native and engineered exosomes also show their ability to cross the blood-brain barrier and deliver active molecules, making exosome-based treatments a possibility in psychiatry.

To move the field forward, several key priorities are clear. First, creating standardized methods for collecting, isolating, and characterizing EVs, especially exosomes, from various sources is crucial to reducing methodological variability and improving reproducibility. Second, prospective multi-omics studies should confirm combined exosomal signatures that include markers for miRNA, protein, and lipids. Third, translational research using animal models is essential to determine whether exosomal cargo acts as a correlate or an active mediator of depressive pathology. Finally, clinical development relies on scalable manufacturing and thorough safety evaluation of therapeutic exosomes.

By taking these steps, we can determine whether exosomes can transition from research findings to practical tools for precision psychiatry, bridging the gap between understanding and clinical application in MDD.

Authors' contributions

S.B, M.Y., M.A., and N.Z.K. conceptualized the study and drafted the manuscript. S.B. designed the figure. K.S. and N.R. supervised the research and critically appraised the manuscript. All authors confirmed the final submitted version of the manuscript to be published.

CRediT authorship contribution statement

Nima Rezaei: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation. **Shayan Boozarjomehri Amnieh:** Writing – review & editing, Writing – original draft, Conceptualization. **Kiarash Saleki:** Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Nazanin Zahra Keshvari:** Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Melika Abrishami:** Methodology, Investigation, Conceptualization. **Mohammad Yazdi:** Writing – original draft, Visualization, Investigation, Conceptualization.

Consent for publication

All authors have read and approved the final version of the manuscript.

Consent to publish

All authors provided consent to publish the manuscript.

Consent to participate

Not applicable

Ethics approval and consent to participate

Not applicable

Declaration of Competing Interest

The authors declare that they have no competing interests.

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