MicroRNA Regulation in Oxidative Stress-Driven Mental Disorders: A Molecular Perspective

Gunjegaonkar Shivshankar M.[1], Bhalerao Aparna V[2], Chorage Trushal V.[3], Nimje Hemlata M.[4], Holam Macchindra R.[5], Chaudhari Priyankar S.[6], Joshi Amol A.[7]

[1]Department of Pharmacology, ASPM's KT Patil College of Pharmacy, Siddharth Nagar, Barshi Road, Osmanabad-413 501, Maharashtra, India.

[2]Department of Pharmaceutics, School of Pharmaceutical Sciences, JSPM University, Wagholi, Pune-412 207, Maharashtra, India.

[3]Department of Pharmacognosy, JSPM's Charak College of Pharmacy and Research, Wagholi, Pune-412 207, Maharashtra, India.

[4]Department of Pharmaceutical Chemistry, JSPM's Jayawantrao Sawant College of Pharmacy and Research, Hadapsar, Pune-411 025, Maharashtra, India.

[5]Department of Pharmaceutical Chemistry, Sant Gajanan Maharaj College of Pharmacy, Mahagaon, Kolhapur-416 503, Maharashtra, India.

[6]Department of Pharmaceutical Chemistry, Rasiklal M. Dhariwal Institute of Pharmaceutical Education and Research, Chinchwad, Pune-411 019, Maharashtra, India.

[7]Department of Pharmacognosy, ASPM's KT Patil College of Pharmacy, Siddharth Nagar, Barshi Road, Osmanabad-413 501, Maharashtra, India.

Corresponding Author:

ORCHID ID: https://orcid.org/0000-0001-7822-2859

Abstract:

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by binding to target messenger RNAs, leading to their degradation or translation inhibition. Recent research has revealed the critical role of miRNAs in oxidative stress-associated mental disorders, which include depression, schizophrenia, bipolar disorder, and Alzheimer's disease. Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, is a key contributor to neuronal damage, neuroinflammation, and mitochondrial dysfunction—hallmarks of these disorders. miRNAs such as miR-34a, miR-137, miR-132, miR-146a, and miR-9 regulate oxidative stress pathways, influencing antioxidant defense systems, mitochondrial function, and neuroinflammation. For example, miR-34a downregulates the expression of antioxidant genes, exacerbating oxidative damage, while miR-137 and miR-132 are linked to mitochondrial dysfunction, impacting cognitive function and mood regulation. Additionally, miR-146a and miR-21 modulate inflammatory cytokines, further contributing to neuroinflammation and the progression of mental disorders. Given their pivotal roles, miRNAs are promising biomarkers for early diagnosis and treatment response and targets for therapeutic interventions. miRNA-based therapies, such as miRNA mimics or inhibitors, and antioxidant compounds that modulate miRNA expression offer new avenues for treatment. However, further studies are needed to understand better the complex interactions between miRNAs and oxidative stress pathways and to explore their clinical applications in mental health care. This review highlights the emerging potential of miRNAs in the diagnosis, pathophysiology, and treatment of oxidative stress-associated mental disorders.

Key Words:

miRNA, Oxidative Stress, Mental Disorders, Depression, Neuroinflammation

Introduction:

Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, plays a pivotal role in the pathogenesis of various mental disorders[1]. Elevated ROS levels can damage cellular components, leading to neuronal dysfunction and contributing to conditions such as depression, anxiety, and schizophrenia. Recent research has highlighted miRNAs as critical regulators in this context, influencing gene expression related to oxidative stress responses and neuronal integrity. miRNAs are small, non-coding RNA molecules that modulate gene expression post-transcriptionally, thereby affecting numerous biological processes, including neuronal differentiation, survival, and activity[2]. Dysregulation of miRNA biogenesis has been linked to increased neuronal vulnerability to cellular stress, potentially contributing to the development and progression of neurodegenerative diseases. Specific miRNAs in the central nervous system have been identified as key players in maintaining neuronal health by regulating oxidative stress pathways [3]. For instance, the miR-181 family has been implicated in mitochondrial function by regulating cytochrome c oxidase subunit 1 (mt-COX1) mRNA, leading to remodeling of electron transport chain complex IV and increased ROS production. Similarly, miR-30e targets uncoupling protein 2 (UCP2), a mitochondrial proton transporter that reduces ROS production and promotes neuroprotection. These interactions underscore the role of miRNAs in modulating oxidative stress within neuronal cells. The involvement of miRNAs in mental disorders is further evidenced by their altered expression profiles in conditions such as major depressive disorder, schizophrenia, and bipolar disorder [4]. Alterations in circulating miRNA levels have been proposed as potential biomarkers for these psychiatric conditions, reflecting their role in disease pathogenesis. For example, reduced global miRNA expression in the prefrontal cortex has been associated with depression and suicidal behavior, suggesting a direct link between miRNA dysregulation and psychiatric manifestations. Moreover, miRNAs like miR-21 have been shown to influence oxidative stress-related processes by inhibiting superoxide dismutase activation, a key enzyme in the oxidative stress response [5]. This inhibition contributes to the persistence of oxidative stress, thereby playing a role in the genesis of various diseases, including Alzheimer's disease and other mental health disorders. Understanding the intricate relationship between miRNAs and oxidative stress in mental disorders offers promising avenues for therapeutic interventions. Targeting specific miRNAs to modulate oxidative stress responses could potentially ameliorate neuronal damage and improve clinical outcomes in patients with mental health conditions [6, 7]. However, further

research is necessary to elucidate the precise mechanisms by which miRNAs influence oxidative stress pathways and to develop effective miRNA-based therapeutic strategies. In conclusion, miRNAs serve as crucial regulators of oxidative stress in the brain, with significant implications for the development and progression of mental disorders. Their ability to modulate gene expression related to oxidative stress responses positions them as potential biomarkers and therapeutic targets. Advancements in miRNA research could lead to novel approaches to diagnosing and treating mental health disorders, ultimately improving patient care and outcomes.

Molecular mechanism of miRNAs

1. Regulation of Antioxidant Pathways

miRNAs are small non-coding RNA molecules that regulate gene expression by binding to complementary sequences in target mRNAs, leading to their degradation or inhibition of translation. In oxidative stress, miRNAs play a crucial role in regulating antioxidant defense pathways, essential for maintaining cell redox homeostasis [8, 9]. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the antioxidant capacity of the cell, which can lead to cellular damage and contribute to the development of various mental disorders, including neurodegenerative diseases and psychiatric conditions. Among the miRNAs that regulate antioxidant pathways, miR-34a, miR-144, and miR-155 have been identified as key players in modulating redox homeostasis by targeting genes such as Nrf2 (nuclear factor erythroid 2-related factor 2) and SOD (superoxide dismutase) [10]. Nrf2 is a central regulator of the cellular antioxidant response. Under normal conditions, Nrf2 is bound to its repressor protein Keap1 in the cytoplasm. However, under oxidative stress, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it activates the transcription of antioxidant genes, including those encoding enzymes like SOD, catalase, and glutathione peroxidase [11]. These enzymes work together to detoxify ROS and restore cellular homeostasis. Studies have shown that miR-34a, a well-known tumor suppressor, directly targets Nrf2 and suppresses its expression. By downregulating Nrf2, miR-34a exacerbates oxidative stress by impairing the antioxidant defense system. This results in increased ROS levels, contributing to cellular damage, neuroinflammation, and neurodegeneration, which are implicated in psychiatric disorders such as depression and Alzheimer's disease. MiR-144 is another miRNA that regulates the expression of antioxidant genes, particularly SOD, an enzyme that plays a pivotal role in neutralizing superoxide radicals [12]. SOD is one of the first lines of defense against oxidative damage, converting superoxide

radicals into hydrogen peroxide, which is then further detoxified by other antioxidant enzymes. Downregulation of SOD expression results in a decreased capacity to neutralize ROS, leading to an increase in oxidative damage and cellular dysfunction. MiR-144 has been shown to target the 3' UTR of SOD1 mRNA, leading to its degradation and reduced enzyme activity. This modulation of SOD levels by miR-144 contributes to the oxidative imbalance observed in various neurological disorders, including Alzheimer's and Parkinson's diseases [13]. MiR-155, an inflammation-associated miRNA, also plays a significant role in regulating antioxidant pathways. It has been implicated in the pathophysiology of several neuroinflammatory and neurodegenerative diseases [14]. MiR-155 targets multiple genes involved in oxidative stress responses, including Nrf2. Elevated levels of miR-155 have been shown to reduce the expression of Nrf2 and its downstream antioxidant targets, contributing to increased oxidative damage and neuroinflammation. Furthermore, miR-155 is associated with increased levels of pro-inflammatory cytokines, further exacerbating oxidative stress and promoting neuronal injury [15, 16]. This mechanism is particularly relevant in psychiatric disorders like schizophrenia, where oxidative stress and inflammation play key roles in disease progression [17]. In summary, miRNAs such as miR-34a, miR-144, and miR-155 play crucial roles in regulating antioxidant defense mechanisms by targeting key genes like Nrf2 and SOD. Dysregulation of these miRNAs can lead to impaired antioxidant responses, resulting in elevated oxidative stress and contributing to the pathogenesis of neurodegenerative and psychiatric disorders. The understanding of miRNA-mediated regulation of redox homeostasis provides valuable insights into potential therapeutic strategies for treating oxidative stress-associated mental disorders. Targeting specific miRNAs to restore the balance of oxidative stress could be a promising approach to mitigating neurodegeneration and psychiatric symptoms.

2. Mitochondrial Dysfunction

Mitochondria are essential organelles responsible for cellular energy production, metabolism regulation, and cell survival control. In the context of mental disorders such as schizophrenia and bipolar disorder, mitochondrial dysfunction has emerged as a critical factor contributing to disease pathophysiology [18]. Recent studies have highlighted the role of miRNAs in regulating mitochondrial function, with miRNAs such as miR-137, miR-210, and miR-34a playing key roles in mitochondrial biogenesis, dynamics, and energy metabolism [19, 20]. Dysregulation of these miRNAs contributes to mitochondrial dysfunction, which in turn leads to neuronal deficits and mental health disorders. MiR-137 is a well-known regulator of neuronal function and has been linked to psychiatric disorders such as schizophrenia [21]. One of the key targets of

miR-137 is the gene encoding the mitochondrial protein, mitochondrial fission 1 (Fis1). Fis1 is a crucial regulator of mitochondrial fission, a process that involves the division of mitochondria to maintain their size and function. Dysregulation of miR-137 leads to increased expression of Fis1, which results in excessive mitochondrial fission, disrupting the balance between mitochondrial fusion and fission [22]. This imbalance causes mitochondrial fragmentation and dysfunction, associated with neuronal damage and impaired synaptic plasticity. Furthermore, miR-137 has been shown to regulate other mitochondrial-related genes, including those involved in oxidative phosphorylation, further implicating this miRNA in mitochondrial dysfunction in psychiatric conditions like schizophrenia [23, 24]. MiR-210 is another miRNA implicated in mitochondrial function, particularly under hypoxic conditions. During hypoxia, miR-210 is upregulated to help cells adapt to low oxygen levels. One of the key targets of miR-210 is the transcription factor hypoxia-inducible factor 1-alpha (HIF-1α), which plays a pivotal role in regulating mitochondrial biogenesis and energy metabolism. Under hypoxic stress, miR-210 modulates mitochondrial dynamics by promoting mitochondrial biogenesis and adjusting energy metabolism to enhance cellular survival [25]. However, in the context of neuropsychiatric disorders, such as bipolar disorder, dysregulation of miR-210 can lead to maladaptive mitochondrial responses. Elevated levels of miR-210 in these disorders have been linked to impaired mitochondrial function, contributing to oxidative stress, reduced ATP production, and neuronal dysfunction. The altered expression of miR-210 in patients with bipolar disorder underscores its potential as a biomarker for mitochondrial dysfunction and neurodegenerative changes in the brain [26]. MiR-34a, a well-established regulator of cellular stress responses, is another miRNA that plays a significant role in mitochondrial function. MiR-34a targets various mitochondrial genes, including those involved in mitochondrial dynamics, apoptosis, and energy metabolism. MiR-34a is upregulated in response to oxidative stress and promotes mitochondrial dysfunction by inhibiting genes such as Sirt1, which is involved in mitochondrial biogenesis and cellular stress resistance [27]. MiR-34a has also been shown to target mitochondrial dynamics-related genes such as Drp1, a key protein involved in mitochondrial fission. The overexpression of miR-34a disrupts the balance of mitochondrial fusion and fission, leading to fragmented mitochondria and impaired energy metabolism. In mental disorders such as schizophrenia, elevated levels of miR-34a exacerbate mitochondrial dysfunction, contributing to neurodegeneration and cognitive deficits [28]. The involvement of miR-34a in mitochondrial regulation makes it a promising therapeutic target for alleviating mitochondrial-related pathologies in psychiatric

disorders [29]. In conclusion, miRNAs such as miR-137, miR-210, and miR-34a play crucial roles in regulating mitochondrial function by targeting genes involved in mitochondrial biogenesis, dynamics, and energy metabolism. Dysregulation of these miRNAs leads to mitochondrial dysfunction, which is associated with neuronal damage and the pathophysiology of mental disorders, including schizophrenia and bipolar disorder. Understanding the mechanisms by which miRNAs regulate mitochondrial function offers new insights into the molecular basis of psychiatric disorders and may open up novel therapeutic avenues for mitigating mitochondrial dysfunction and improving cognitive and neuronal health.

3. Neuroinflammation and Oxidative Stress

Oxidative stress and neuroinflammation are closely intertwined processes that play significant roles in the pathophysiology of various neurodegenerative diseases and psychiatric disorders, including depression and Alzheimer's disease [30]. Oxidative stress occurs when there is an imbalance between the production of ROS and the body's antioxidant defenses, leading to cellular damage. This cellular damage activates various inflammatory pathways, including the upregulation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [31]. Emerging evidence has revealed that miRNAs such as miR-146a and miR-21 are key regulators of these inflammatory pathways, modulating the expression of inflammatory cytokines and contributing to the neuroinflammatory response associated with oxidative stress [32]. MiR-146a is a well-characterized miRNA that plays a crucial role in regulating the innate immune response. It is upregulated in response to inflammatory stimuli, including oxidative stress, and acts by targeting key signaling molecules involved in the inflammatory cascade. MiR-146a targets various genes in the NF-κB (nuclear factor-kappa B) signaling pathway, such as IRAK1 (interleukin-1 receptor-associated kinase 1) and TRAF6 (TNF receptor-associated factor 6), both of which are involved in the activation of pro-inflammatory cytokines like TNF-α and IL-6 [33]. By downregulating these signaling molecules, miR-146a helps to attenuate excessive inflammation and oxidative damage. However, in chronic inflammatory conditions such as depression and Alzheimer's disease, elevated levels of miR-146a contribute to sustained neuroinflammation, exacerbating neuronal damage and cognitive decline. In depression, miR-146a has been shown to regulate the inflammatory response in the brain, and its dysregulation has been associated with altered cytokine levels and impaired neuroplasticity [34]. MiR-21 is another miRNA that plays a central role in inflammation and oxidative stress. It is known to be upregulated in response to various stressors, including oxidative damage, and acts as an important modulator of the inflammatory response [35]. MiR-

21 targets several genes involved in inflammatory signaling, including the phosphatase and tensin homolog (PTEN), which regulates the PI3K/AKT pathway, a critical pathway in the control of inflammation and cell survival. Elevated miR-21 levels have been observed in both depression and Alzheimer's disease, where it contributes to the amplification of the inflammatory response [36]. In Alzheimer's disease, miR-21 modulates the expression of pro-inflammatory cytokines such as TNF-α and IL-6, contributing to the chronic neuroinflammation that is characteristic of the disease. Similarly, in depression, miR-21 has been linked to the regulation of inflammation and oxidative stress, with increased miR-21 levels being associated with altered immune responses and neuronal damage [37]. The upregulation of miR-146a and miR-21 in neuroinflammatory conditions highlights their potential as biomarkers for inflammatory diseases of the brain, as well as potential therapeutic targets. Given that oxidative stress and neuroinflammation are implicated in the pathophysiology of depression, Alzheimer's disease, and other psychiatric and neurodegenerative disorders, miRNAs may offer novel avenues for therapeutic intervention [38]. By targeting the pathways regulated by miR-146a and miR-21, it may be possible to mitigate the neuroinflammatory response and reduce the associated neuronal damage, potentially improving clinical outcomes in these conditions [35]. In conclusion, miR-146a and miR-21 are crucial modulators of oxidative stress and inflammation in the brain. Their upregulation in response to oxidative damage and their ability to regulate key inflammatory cytokines like TNF-α and IL-6 makes them central players in the neuroinflammatory processes underlying depression and Alzheimer's disease. Understanding the precise mechanisms by which these miRNAs regulate inflammatory pathways will provide valuable insights into the molecular basis of these disorders and could inform the development of novel therapeutic strategies targeting miRNAs to alleviate neuroinflammation and oxidative stress.

4. Synaptic Plasticity and Neurotransmitter Regulation

Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses, adversely affects synaptic function and plasticity. Synaptic plasticity is the capacity of synapses to strengthen or weaken over time, which is essential for learning, memory, and mood regulation [39]. miRNAs, particularly miR-132 and miR-134, have emerged as critical regulators of synaptic plasticity by modulating the expression of key proteins such as brain-derived neurotrophic factor (BDNF). Dysregulation of these miRNAs is associated with neuropsychiatric conditions, including depression and cognitive deficits [40]. MiR-132 and Synaptic Plasticity, miR-132 is highly expressed in neuronal cells and is known to promote

neuronal outgrowth and sprouting by decreasing the levels of p250GAP, a GTPase-activating protein linked to neuronal differentiation. This miRNA is regulated by the cAMP response element-binding (CREB) protein pathway and is activated by neuronal activity and BDNF. By enhancing dendritic growth, miR-132 contributes to the brain's plasticity and helps establish stronger connections between neurons. Additionally, miR-132 has been implicated in regulating MeCP2, a protein that increases BDNF levels in the brain [41]. MiR-132 may be involved in a homeostatic mechanism that regulates MeCP2 levels, thereby influencing BDNF expression and synaptic function. Failure to regulate MeCP2 levels is connected to neurological disorders, including Rett syndrome. Mir-134 is known to regulate the size of dendritic spines, which are small protrusions on neurons essential for synaptic transmission (Synaptic Plasticity). By modulating the expression of proteins involved in spine morphology, miR-134 influences synaptic strength and plasticity. Dysregulation of miR-134 has been linked to impaired synaptic development and cognitive deficits. Dysregulation of miR-132 and miR-134 has been associated with various neuropsychiatric conditions [42]. Altered levels of miR-132 have been observed in individuals with depression, suggesting its role in mood regulation. Similarly, aberrant expression of miR-134 has been linked to cognitive impairments, highlighting its importance in maintaining normal cognitive function. MiR-132 and miR-134 are pivotal regulators of synaptic plasticity, influencing neuronal connectivity and function by modulating key proteins such as BDNF [43]. Their dysregulation under conditions of oxidative stress can impair synaptic function, contributing to the pathophysiology of depression and cognitive deficits. Understanding the roles of these miRNAs in synaptic regulation offers potential avenues for therapeutic interventions aimed at restoring normal synaptic function in neuropsychiatric disorders.

miRNAs in Specific Mental Disorders:

a. Depression:

Major Depressive Disorder (MDD) is a complex psychiatric condition influenced by various molecular mechanisms, including the dysregulation of miRNAs. Among these, miR-9, miR-16, and miR-34a have garnered attention for their roles in modulating oxidative stress-induced neuroinflammation, impaired neurogenesis, and serotonin metabolism—all critical factors in the pathophysiology of depression [44].

miR-9 and Dendritic Morphology

MiR-9-5p has been implicated in the structural integrity of neurons, particularly in the hippocampus—a brain region essential for mood regulation and cognitive function. Stress-induced dendritic shortening of hippocampal pyramidal neurons is a hallmark of depressive states. Notably, acute antidepressant treatment with ketamine has been shown to rescue this dendritic atrophy, a process in which miR-9-5p plays a crucial role. Studies demonstrated that miR-9-5p is involved in reversing stress-dependent dendritic shortening, highlighting its potential as a therapeutic target in MDD [45].

miR-16 and Serotonin Transporter Regulation

miR-16 is another miRNA integral to the brain's response to stress and the regulation of serotonin levels. Serotonin, a neurotransmitter pivotal in mood regulation, is transported by the serotonin transporter (SERT). MiR-16 has been shown to downregulate SERT expression, thereby influencing serotonin availability in the synaptic cleft. In vivo models have demonstrated that alterations in miR-16 levels can affect the brain's response to stress, suggesting its involvement in the development of depressive symptoms [46].

miR-34a and Neuroinflammation

Neuroinflammation is a significant contributor to the pathogenesis of MDD, and miR-34a has been associated with the regulation of inflammatory responses in the brain. Elevated levels of miR-34a have been observed in individuals with depression, correlating with increased expression of pro-inflammatory cytokines. This upregulation of miR-34a can exacerbate neuroinflammatory processes, leading to neuronal damage and the manifestation of depressive behaviors [8].

Interplay Between miRNAs and Serotonin Metabolism

The dysregulation of miR-9, miR-16, and miR-34a not only affects neuronal structure and inflammatory responses but also has profound implications for serotonin metabolism. By modulating the expression of genes involved in serotonin synthesis, transport, and receptor activity, these miRNAs influence serotonin availability and signaling. For instance, miR-16's regulation of SERT directly impacts serotonin reuptake, affecting mood and emotional regulation. Similarly, miR-9 and miR-34a can alter the expression of serotonin receptors and related signaling molecules, further influencing serotonergic neurotransmission [47].

Therapeutic Implications

Understanding the roles of miR-9, miR-16, and miR-34a in MDD opens avenues for novel therapeutic strategies. Targeting these miRNAs to normalize their expression levels could

potentially alleviate depressive symptoms by restoring neuronal integrity, reducing neuroinflammation, and optimizing serotonin metabolism. For example, miRNA-based therapies aimed at modulating miR-16 levels could enhance serotonin availability, offering a complementary approach to traditional antidepressants. Additionally, interventions that adjust miR-9 and miR-34a expression may promote neurogenesis and mitigate inflammatory responses, contributing to overall neural health and resilience against depression [48]. The dysregulation of miR-9, miR-16, and miR-34a plays a significant role in the development and progression of Major Depressive Disorder. By influencing oxidative stress-induced neuroinflammation, impairing neurogenesis, and modulating serotonin metabolism, these miRNAs contribute to the complex molecular landscape of depression. Ongoing research into their specific mechanisms and interactions holds promise for the development of targeted miRNA-based therapies, potentially offering more effective and personalized treatment options for individuals suffering from this debilitating condition.

b. Schizophrenia:

Schizophrenia is a complex psychiatric disorder characterized by disruptions in thought processes, perceptions, emotional responsiveness, and social interactions. Emerging evidence implicates miRNAs, particularly miR-137 and miR-132, in the pathophysiology of schizophrenia through their influence on oxidative stress, mitochondrial function, cognitive processes, and neurotransmission [49].

miR-137 and Schizophrenia

MiR-137 has been identified as a significant genetic risk factor for schizophrenia. Genome-wide association studies have linked variations in the MIR137 gene locus to an increased susceptibility to the disorder. MiR-137 is known to regulate neuronal development and synaptic plasticity by targeting multiple genes involved in these processes [50]. Dysregulation of miR-137 can lead to aberrant neuronal differentiation and connectivity, contributing to the cognitive deficits observed in schizophrenia. Moreover, miR-137 has been associated with mitochondrial dysfunction, a condition characterized by compromised brain metabolism and increased oxidative stress. Mitochondria are essential for energy production and cellular homeostasis, and their dysfunction can lead to neuronal damage and impaired cognitive function. By regulating genes involved in mitochondrial function, miR-137 plays a role in maintaining neuronal health, and its dysregulation may contribute to the pathogenesis of schizophrenia [51].

miR-132 and Schizophrenia

MiR-132 is another miRNA implicated in schizophrenia, particularly concerning its role in synaptic plasticity and neuronal connectivity. It is highly expressed in the brain and is involved in the regulation of dendritic spine morphology, which is crucial for effective neurotransmission and cognitive function. Alterations in miR-132 expression have been linked to the synaptic deficits observed in schizophrenia. Additionally, miR-132 has been associated with the regulation of oxidative stress responses [52]. Oxidative stress, resulting from an imbalance between the production of reactive oxygen species and the body's ability to detoxify them, has been implicated in the etiology of schizophrenia. By modulating the expression of genes involved in antioxidant defense mechanisms, miR-132 helps maintain oxidative balance within neurons. Dysregulation of miR-132 can therefore exacerbate oxidative stress, leading to neuronal damage and contributing to the cognitive impairments characteristic of schizophrenia [53].

Implications for Cognitive Function and Neurotransmission

The dysregulation of miR-137 and miR-132 impacts cognitive function and neurotransmission in schizophrenia through several mechanisms:

Synaptic Plasticity

Both miR-137 and miR-132 are involved in the regulation of synaptic strength and plasticity. Altered expression of these miRNAs can lead to impaired synaptic connectivity, which is associated with the cognitive deficits observed in schizophrenia [54].

Neurotransmitter Regulation

MiR-137 and miR-132 influence the expression of genes involved in neurotransmitter synthesis, release, and receptor function. Dysregulation of these miRNAs can disrupt neurotransmitter systems, such as the dopaminergic and glutamatergic pathways, which are implicated in the pathophysiology of schizophrenia [55].

Oxidative Stress and Mitochondrial Function

By modulating genes related to mitochondrial function and oxidative stress responses, miR-137 and miR-132 help maintain neuronal integrity. Their dysregulation can lead to increased oxidative damage and mitochondrial dysfunction, further impairing cognitive function and neurotransmission. MiR-137 and miR-132 play critical roles in the molecular mechanisms underlying schizophrenia. Their involvement in regulating oxidative stress, mitochondrial function, synaptic plasticity, and neurotransmission highlights their significance in maintaining cognitive health. Dysregulation of these miRNAs can contribute to the development and

progression of schizophrenia, making them potential targets for therapeutic interventions aimed at restoring normal miRNA expression and ameliorating cognitive deficits associated with the disorder [56].

Bipolar Disorder

Bipolar Disorder (BD) is a chronic psychiatric condition marked by alternating episodes of mania and depression. Recent research has highlighted the role of miRNAs in the pathophysiology of BD, particularly miR-499 and miR-221, which are implicated in oxidative stress-related mood dysregulation.

miR-499 and Neuroplasticity

MiR-499-5p has been associated with neuroplasticity, a critical factor in mood regulation. Studies demonstrated that miR-499-5p regulates dendritogenesis and cognitive function by downregulating the BD risk gene CACNB2, which encodes the β2 subunit of voltage-gated calcium channels. This regulation affects calcium influx in neurons, influencing neuronal excitability and synaptic strength, thereby impacting mood stability [57].

miR-221 and Oxidative Stress Response

MiR-221 plays a role in the neuronal response to oxidative stress. Research indicates that miR-221 modulates pathways that promote neuronal survival under oxidative conditions. For instance, studies have shown that miR-221 can influence the expression of genes involved in antioxidant defenses, thereby mitigating oxidative damage in neuronal cells [58].

Implications for Mood Dysregulation in BD

The dysregulation of miR-499 and miR-221 contributes to mood instability in BD through several mechanisms:

Neuroplasticity Impairment: Abnormal miR-499 expression can disrupt dendritic architecture and synaptic connectivity, leading to cognitive deficits and emotional dysregulation characteristic of BD [57].

Inadequate Oxidative Stress Response: Altered miR-221 levels may impair the neuronal antioxidant response, increasing oxidative stress. Elevated oxidative stress has been linked to the pathophysiology of mood disorders, including BD [59].

Therapeutic Potential

Understanding the roles of miR-499 and miR-221 in BD opens avenues for novel therapeutic strategies. Targeting these miRNAs to normalize their expression could potentially stabilize mood by enhancing neuroplasticity and bolstering antioxidant defenses. For example, miRNA-based therapies aimed at modulating miR-499 levels could improve synaptic connectivity, while adjusting miR-221 expression may strengthen the neuronal response to oxidative stress [60]. The abnormal expression of miR-499 and miR-221 is intricately linked to oxidative stress-related mood dysregulation in Bipolar Disorder. By affecting neuroplasticity and the oxidative stress response, these miRNAs contribute to the complex molecular landscape of BD. Ongoing research into their specific mechanisms holds promise for the development of targeted miRNA-based therapies, potentially offering more effective and personalized treatment options for individuals suffering from this debilitating condition.

Alzheimer's Disease:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss. Central to its pathology is the accumulation of amyloid-beta (Aβ) plaques and increased oxidative stress, both contributing to neuronal damage. miRNAs, particularly miR-29 and miR-146a, have been identified as key regulators in these processes, influencing Aβ production and the neuronal response to oxidative stress [61].

miR-29 and Amyloid-Beta Accumulation

The miR-29 family, including miR-29a, miR-29b, and miR-29c, plays a significant role in modulating Aβ levels. Research has demonstrated that decreased expression of miR-29a/b-1 correlates with elevated levels of BACE1 (β-site amyloid precursor protein cleaving enzyme 1), the enzyme responsible for initiating Aβ production. Studies found that reduced miR-29a/b-1 expression leads to increased BACE1 levels, thereby promoting Aβ accumulation and contributing to AD pathogenesis. Further studies have confirmed these findings, indicating that downregulation of miR-29 not only elevates BACE1 expression but also accelerates Aβ deposition. This suggests that maintaining normal miR-29 levels is crucial for regulating BACE1 activity and preventing excessive Aβ accumulation, a hallmark of AD pathology [62].

miR-146a and Oxidative Stress

MiR-146a is another miRNA implicated in AD, particularly concerning the brain's response to oxidative stress. Oxidative stress results from an imbalance between the production of ROS and the body's ability to detoxify them, leading to neuronal damage. MiR-146a modulates inflammatory responses and has been shown to influence pathways associated with oxidative

stress. For instance, miR-146a can reduce Aβ deposition and tau protein hyperphosphorylation through the TLR/IRAK1/TRAF6 pathway, thereby mitigating oxidative damage in neuronal cells. Elevated levels of miR-146a have been observed in the brains of AD patients, suggesting a compensatory response to increased oxidative stress and inflammation. However, chronic upregulation of miR-146a may disrupt normal neuronal function, indicating a complex role in AD progression [63].

Interplay Between miR-29 and miR-146a

The interactions between miR-29 and miR-146a are critical in maintaining neuronal health. While miR-29 primarily regulates Aβ production by targeting BACE1, miR-146a modulates inflammatory and oxidative stress responses. Dysregulation of either miRNA can exacerbate AD pathology: reduced miR-29 levels lead to increased Aβ accumulation, and altered miR-146a expression affects the neuronal response to oxidative stress [62].

Therapeutic Implications

Understanding the roles of miR-29 and miR-146a in AD opens avenues for potential therapeutic strategies. Restoring normal levels of miR-29 could help regulate BACE1 expression, thereby reducing Aβ production. Similarly, modulating miR-146a expression may enhance the neuronal response to oxidative stress and inflammation, protecting against neuronal damage [64]. Developing miRNA-based therapies offers a promising approach to addressing the complex molecular mechanisms underlying AD. MiR-29 and miR-146a are integral to regulating amyloid-beta accumulation and oxidative stress in Alzheimer's disease. Their dysregulation contributes to the neurodegenerative processes characteristic of AD. Ongoing research into these miRNAs not only enhances our understanding of AD pathology but also paves the way for innovative therapeutic interventions aimed at mitigating the progression of this debilitating disorder.

MiRNA-Based Therapeutics

Targeting specific miRNAs that are dysregulated in depression presents a potential therapeutic strategy. For instance, miR-16 has been implicated in the modulation of serotonin transmission, a neurotransmitter system often disrupted in depressive disorders. Modulating miR-16 levels could, therefore, influence serotonin availability and alleviate depressive symptoms [47]. The delivery of miRNA-based therapeutics poses significant challenges, including stability, specificity, and efficient delivery to target tissues. Nanoparticle-based carriers and viral vectors have been explored as potential delivery systems to overcome these obstacles. These methods

aim to protect miRNAs from degradation, enhance their uptake by target cells, and ensure controlled release, thereby improving therapeutic efficacy.

Antioxidant Therapy

Oxidative stress has been implicated in the pathophysiology of depression, and miRNAs play a role in regulating oxidative stress responses. Compounds with antioxidant properties, such as N-acetylcysteine (NAC), curcumin, and polyphenols, have been studied for their potential to modulate miRNA expression. By influencing miRNA profiles, these antioxidants may enhance the brain's resilience to oxidative damage, thereby contributing to the alleviation of depressive symptoms [65].

Biomarker Development

The identification of reliable biomarkers for depression is crucial for early diagnosis and monitoring of treatment responses. Circulating miRNAs in blood or cerebrospinal fluid (CSF) have emerged as potential biomarkers due to their stability and accessibility. Studies have demonstrated that specific miRNA expression profiles correlate with depression severity and therapeutic outcomes. For example, changes in peripheral miR-1202 levels have been associated with responses to antidepressant treatment, suggesting its potential as a biomarker for monitoring therapeutic efficacy [44].

Pharmacological Interventions

Traditional antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), have been shown to influence miRNA expression. This interaction suggests that miRNAs could serve as predictors of treatment outcomes. Understanding how antidepressants modulate miRNA profiles can provide insights into their mechanisms of action and help in tailoring personalized treatment strategies [66]. Moreover, targeting specific miRNAs may enhance the efficacy of existing pharmacotherapies or lead to the development of novel antidepressant agents.

The exploration of miRNAs in the context of depression offers promising therapeutic and diagnostic possibilities. miRNA-based therapeutics, antioxidant modulation of miRNA expression, the development of miRNA biomarkers, and the influence of pharmacological interventions on miRNA profiles represent multifaceted approaches to addressing the complexities of depressive disorders. Continued research in this field is essential to translate these findings into clinical applications, ultimately improving outcomes for individuals affected by depression.

DISCUSSION

miRNAs are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level by binding to the 3' untranslated regions of target mRNAs, leading to their degradation or inhibition of translation [2]. These miRNAs have been increasingly implicated in various mental disorders, including those associated with oxidative stress, a key factor in the pathophysiology of many neuropsychiatric conditions [1]. Oxidative stress results from an imbalance between the production of ROS and the body's ability to detoxify these harmful byproducts. Chronic oxidative stress is known to contribute to neuronal damage, inflammation, mitochondrial dysfunction, and apoptosis, which underlie several mental disorders such as depression, schizophrenia, bipolar disorder, and Alzheimer's disease [3, 9]. miRNAs have emerged as crucial regulators in oxidative stress-associated mental disorders by modulating key pathways involved in the cellular response to oxidative damage. For instance, miR-34a has been identified as a significant player in oxidative stress-induced neurodegeneration [8]. It targets various genes that are involved in antioxidant defense mechanisms, including those encoding the antioxidant enzyme superoxide dismutase (SOD). By downregulating these genes, miR-34a exacerbates oxidative damage, leading to neuronal dysfunction and contributing to neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease [67]. Furthermore, miR-155, another miRNA, has been shown to regulate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which is critical for the cellular antioxidant response. Reduced Nrf2 activity, due to miR-155 upregulation, impairs the antioxidant defense mechanisms and increases the vulnerability to oxidative damage, thus promoting the development of neuroinflammation and neurodegeneration [15, 16]. In addition to its role in regulating antioxidant pathways, miRNAs are involved in mitochondrial dysfunction, a hallmark of several mental disorders. Mitochondria are essential for energy production, and oxidative stress can cause mitochondrial damage, resulting in reduced energy production and the generation of ROS, further perpetuating the cycle of oxidative damage [19]. miRNAs such as miR-137 and miR-132 have been linked to mitochondrial dysfunction in mental disorders like schizophrenia and bipolar disorder. These miRNAs influence mitochondrial biogenesis, dynamics, and energy metabolism by targeting key genes involved in these processes. Dysregulation of these miRNAs can lead to impaired mitochondrial function, contributing to cognitive deficits, mood dysregulation, and other symptoms characteristic of these disorders [54]. Furthermore, miRNAs have been shown to modulate neuroinflammation, a critical aspect of oxidative stress-related mental disorders. Chronic inflammation in the brain is often driven by oxidative stress and contributes to the pathogenesis of depression and neurodegenerative

diseases. miRNAs such as miR-146a and miR-21 regulate the expression of pro-inflammatory cytokines, including TNF-α and IL-6, which are elevated in response to oxidative stress [32]. By modulating the levels of these cytokines, miRNAs can influence the inflammatory response in the brain, thereby affecting the progression of mental disorders. In conditions like depression, where neuroinflammation plays a crucial role, miRNAs may serve as potential therapeutic targets for modulating the inflammatory response [9]. In conclusion, miRNAs play a central role in the pathophysiology of oxidative stress-associated mental disorders by regulating antioxidant defense mechanisms, mitochondrial function, and neuroinflammation. Their ability to influence key cellular pathways makes them attractive candidates for therapeutic intervention in these conditions. Targeting dysregulated miRNAs with miRNA-based therapies or using antioxidant compounds to modulate miRNA expression holds great potential for developing novel treatments for oxidative stress-associated mental disorders. Further research is needed to better understand the complex relationship between miRNAs and oxidative stress and to explore their potential as biomarkers and therapeutic targets in clinical settings.

Table 1. miRNA Role in Oxidative Stress and Mental Disorders

miRNA	Associated Mental Disorder(s)	Role in Oxidative Stress and Mental Disorders	Source
miR-132	Schizophrenia, Major Depressive Disorder	Upregulated in both disorders, suggesting involvement in pathophysiology.	68
miR-34a	Schizophrenia, Major Depressive Disorder	Upregulated in both conditions, indicating a role in disease mechanisms.	38
miR-206	Alzheimer's Disease	Implicated in regulating β-amyloid accumulation, contributing to disease progression.	38
miR-155	Post-Traumatic Stress Disorder, Traumatic Brain Injury	Involved in neuroinflammation and oxidative stress responses.	65
miR-124	Various Psychiatric Disorders	Regulates neuroinflammation and oxidative stress pathways.	69

Table 2. miRNA as Therapeutic Target in Mental Disorders

Therapeutic Target	miRNA Involved	Mental Disorder	Clinical Trial Phase	Findings/Comments	Source
miR-34a	miR-34a	Depression, Schizophrenia, Bipolar Disorder	Preclinical to Phase I/II	miR-34a has been shown to regulate oxidative stress and neurodegeneration. Initial trials focus on	70

				targeting miR-34a to reduce neuroinflammation and improve cognitive function.	
miR-137	miR-137	Schizophrenia, Bipolar Disorder	Preclinical	Dysregulation of miR-137 is associated with mitochondrial dysfunction and cognitive deficits in schizophrenia and bipolar disorder. Clinical trials are investigating its therapeutic potential.	71
miR-132	miR-132	Depression, Alzheimer's Disease	Preclinical	miR-132 regulates synaptic plasticity and neurogenesis. Trials are exploring its role in alleviating mood disorders and cognitive deficits associated with Alzheimer's.	72
miR-9	miR-9	Depression	Preclinical to Phase I	Altered miR-9 levels are linked to stress-induced dendritic changes in depression. Trials aim to restore miR-9 levels to improve neuroplasticity.	73
miR-146a	miR-146a	Alzheimer's Disease, Depression	Preclinical	miR-146a regulates inflammation and oxidative stress. Clinical trials are evaluating its potential to modulate neuroinflammation in Alzheimer's and depression.	34
miR-221	miR-221	Bipolar Disorder	Preclinical to Phase I	miR-221 is implicated in oxidative stress-related mood dysregulation in bipolar disorder. Research focuses on its therapeutic potential to restore normal mood regulation.	44

miR-499	miR-499	Bipolar Disorder	Preclinical	Dysregulated miR-499 has been linked to mitochondrial dysfunction in mood disorders, with clinical investigations into its role in restoring mitochondrial health.	74

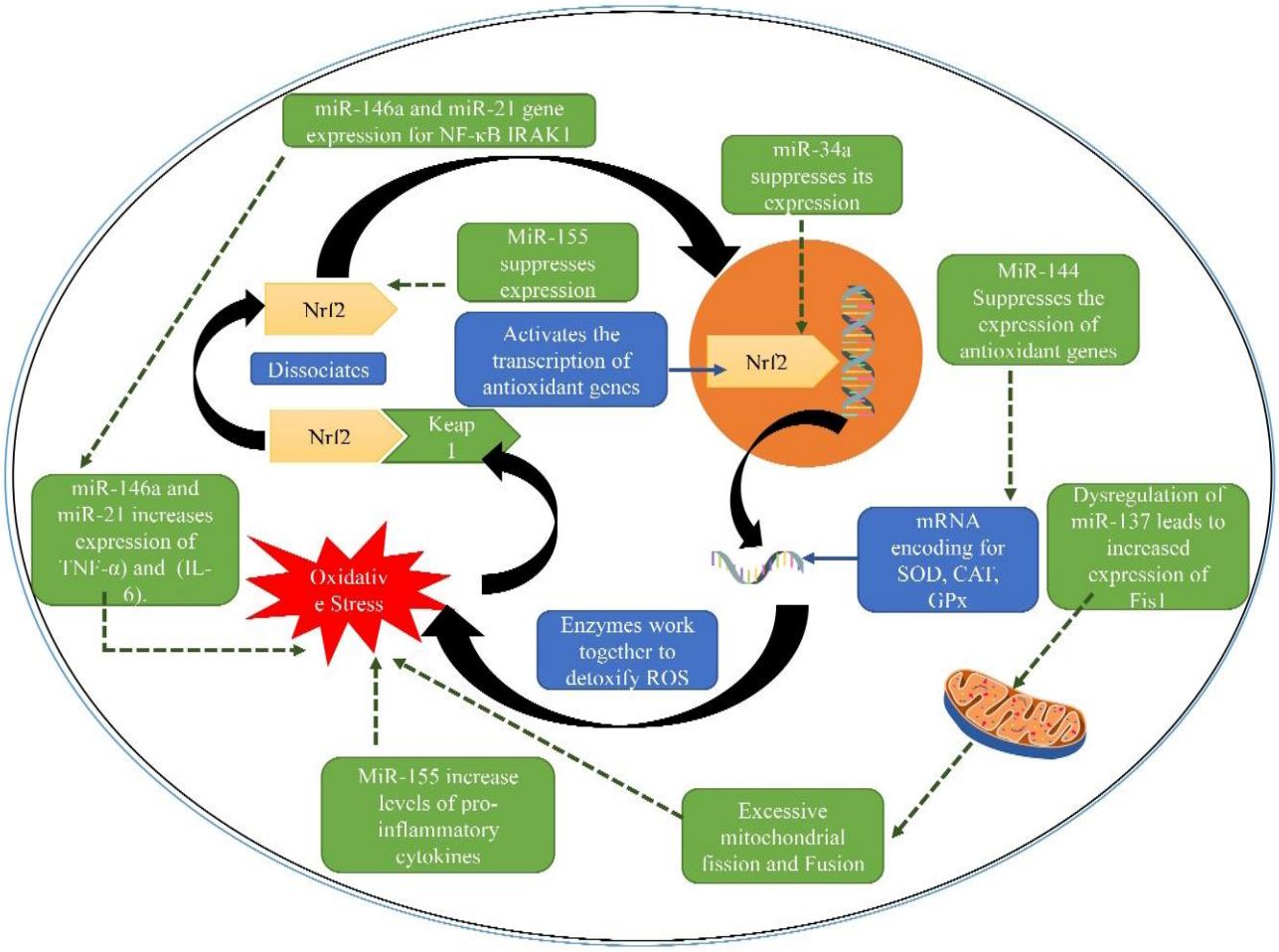

Figure 1. Signalling mechanism and role of miRNAs in oxidative stress

CONCLUSION

In conclusion, miRNAs play a pivotal role in regulating oxidative stress-associated mental disorders by modulating key cellular pathways involved in antioxidant defense, mitochondrial function, and neuroinflammation. Their ability to influence gene expression in response to oxidative damage highlights their potential as both biomarkers and therapeutic targets for disorders such as depression, schizophrenia, bipolar disorder, and Alzheimer's disease.

Dysregulation of miRNAs, such as miR-34a, miR-137, and miR-146a, can exacerbate oxidative damage, impair neurogenesis, and promote neuroinflammation, leading to the progression of these disorders. Targeting specific miRNAs with therapeutic strategies, such as miRNA mimics or inhibitors, and using antioxidant compounds to modulate miRNA expression, could offer novel avenues for treatment. Additionally, miRNAs may serve as biomarkers for early diagnosis and treatment response, facilitating personalized medicine approaches in mental health care. However, further research is required to fully elucidate the complex interactions between miRNAs and oxidative stress pathways, as well as to explore the clinical applicability of miRNA-based therapies. Ultimately, miRNAs hold significant promise in advancing our understanding and treatment of oxidative stress-related mental disorders.

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Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Author Contributions

SMG: concept, designed; BAV and CTV: reviewed the manuscript; NHM and HMR: manuscript preparation, editing and designing the manuscript; CPS and JAA: all image works. Finally, all authors had approved for manuscript publication.

REFERENCES

1. Steckert AV, Valvassori SS, Moretti M, Dal-Pizzol F, Quevedo J. Role of oxidative stress in the pathophysiology of bipolar disorder. Neurochemical research. 2010; 35:1295-301.
2. Réus GZ, Fries GR, Stertz L, Badawy M, Passos IC, Barichello T, Kapczinski F, Quevedo J. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. Neuroscience. 2015; 6; 300:141-54.
3. Kapczinski F, Dal-Pizzol F, Teixeira AL, Magalhaes PV, Kauer-Sant'Anna M, Klamt F, Moreira JC, de Bittencourt Pasquali MA, Fries GR, Quevedo J, Gama CS. Peripheral biomarkers and illness activity in bipolar disorder. Journal of psychiatric research. 2011; 45(2):156-61.
4. Pedrini M, Massuda R, Fries GR, de Bittencourt Pasquali MA, Schnorr CE, Moreira JC, Teixeira AL, Lobato MI, Walz JC, Belmonte-de-Abreu PS, Kauer-Sant'Anna M. Similarities in serum oxidative stress markers and inflammatory cytokines in patients with overt schizophrenia at early and late stages of chronicity. Journal of psychiatric research. 2012; 46(6):819-24.
5. Barbé-Tuana FM, Parisi MM, Panizzutti BS, Fries GR, Grun LK, Guma FT, Kapczinski F, Berk M, Gama CS, Rosa AR. Shortened telomere length in bipolar disorder: a comparison of the early and late stages of disease. Revista Brasileira de Psiquiatria. 2016; 38(04):281-6.
6. Konovalova J, Gerasymchuk D, Parkkinen I, Chmielarz P, Domanskyi A. Interplay between MicroRNAs and oxidative stress in neurodegenerative diseases. International journal of molecular sciences. 2019;20(23):6055
7. N Prasad K. Oxidative stress, pro-inflammatory cytokines, and antioxidants regulate expression levels of microRNAs in Parkinson's disease. Current Aging Science. 2017;10(3):177-84.
8. Chua CE, Tang BL. miR-34a in neurophysiology and neuropathology. Journal of Molecular Neuroscience. 2019;67:235-46.

9. Ruiz GP, Camara H, Fazolini NP, Mori MA. Extracellular miRNAs in redox signaling: Health, disease and potential therapies. Free Radical Biology and Medicine. 2021; 173:170-87.
10. Ciesielska S, Slezak-Prochazka I, Bil P, Rzeszowska-Wolny J. Micro RNAs in regulation of cellular redox homeostasis. International journal of molecular sciences. 2021;22(11):6022.
11. Bellezza I, Giambanco I, Minelli A, Donato R. Nrf2-Keap1 signaling in oxidative and reductive stress. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2018;1865(5):721-33.
12. Zhu J, Feng Y, Zhang L, Pang X, He S, Fang L. miR-144/451: A Regulatory Role in Inflammation. Current Molecular Medicine. 2024 Nov 5.
13. Elangovan A, Venkatesan D, Selvaraj P, Pasha MY, Babu HW, Iyer M, Narayanasamy A, Subramaniam MD, Valsala Gopalakrishnan A, Kumar NS, Vellingiri B. miRNA in Parkinson's disease: From pathogenesis to theranostic approaches. Journal of Cellular Physiology. 2023;238(2):329-54.
14. Onodera Y, Teramura T, Takehara T, Obora K, Mori T, Fukuda K. miR-155 induces ROS generation through downregulation of antioxidation-related genes in mesenchymal stem cells. Aging cell. 2017;16(6):1369-80.
15. Zingale VD, Gugliandolo A, Mazzon E. MiR-155: an important regulator of neuroinflammation. International Journal of Molecular Sciences. 2021;23(1):90.
16. Zhou Y, Zhang P, Zheng X, Ye C, Li M, Bian P, Fan C, Zhang Y. miR-155 regulates pro- and anti-inflammatory cytokine expression in human monocytes during chronic hepatitis C virus infection. Annals of Translational Medicine. 2021 Nov;9(21).
17. Cecerska-Heryć E, Polikowska A, Serwin N, Roszak M, Grygorcewicz B, Heryć R, Michalczyk A, Dołęgowska B. Importance of oxidative stress in the pathogenesis, diagnosis, and monitoring of patients with neuropsychiatric disorders, a review. Neurochemistry international. 2022;153:105269.
18. Clay HB, Sillivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. International Journal of Developmental Neuroscience. 2011;29(3):311-24.
19. Li P, Jiao J, Gao G, Prabhakar BS. Control of mitochondrial activity by miRNAs. Journal of cellular biochemistry. 2012;113(4):1104-10.

20. Erturk E, Onur OE, Akgun O, Tuna G, Yildiz Y, Ari F. Mitochondrial miRNAs (MitomiRs): their potential roles in breast and other cancers. Mitochondrion. 2022;66:74-81.
21. Wright C, Gupta CN, Chen J, Patel V, Calhoun VD, Ehrlich S, Wang L, Bustillo JR, Perrone-Bizzozero NI, Turner JA. Polymorphisms in MIR137HG and microRNA-137-regulated genes influence gray matter structure in schizophrenia. Translational psychiatry. 2016;6(2):e724-.
22. Ihenacho UK, Meacham KA, Harwig MC, Widlansky ME, Hill RB. Mitochondrial fission protein 1: emerging roles in organellar form and function in health and disease. Frontiers in Endocrinology. 2021;12:660095.
23. Tryphena KP, Anuradha U, Kumar R, Rajan S, Srivastava S, Singh SB, Khatri DK. Understanding the involvement of microRNAs in mitochondrial dysfunction and their role as potential biomarkers and therapeutic targets in Parkinson's disease. Journal of Alzheimer's Disease. 2023:1-6.
24. Ni P, Chung S. Mitochondrial dysfunction in schizophrenia. BioEssays. 2020;42(6):1900202.
25. Huang X, Zuo J. Emerging roles of miR-210 and other non-coding RNAs in the hypoxic response. Acta Biochim Biophys Sin. 2014;46(3):220-32.
26. Ghafouri-Fard S, Badrlou E, Taheri M, Dürsteler KM, Beatrix Brühl A, Sadeghi-Bahmani D, Brand S. A comprehensive review on the role of non-coding RNAs in the pathophysiology of bipolar disorder. International Journal of Molecular Sciences. 2021;22(10):5156.
27. Wang G, Yao J, Li Z, Zu G, Feng D, Shan W, Li Y, Hu Y, Zhao Y, Tian X. miR-34a-5p inhibition alleviates intestinal ischemia/reperfusion-induced reactive oxygen species accumulation and apoptosis via activation of SIRT1 signaling. Antioxidants & redox signaling. 2016;24(17):961-73.
28. Sun XY, Zhang J, Niu W, Guo W, Song HT, Li HY, Fan HM, Zhao L, Zhong AF, Dai YH, Guo ZM. A preliminary analysis of microRNA as potential clinical biomarker for schizophrenia. American journal of medical genetics part B: Neuropsychiatric genetics. 2015;168(3):170-8.
29. Jou SH, Chiu NY, Liu CS. Mitochondrial dysfunction and psychiatric disorders. Chang Gung Med J. 2009;32(4):370-9.

30. Rehman MU, Sehar N, Dar NJ, Khan A, Arafah A, Rashid S, Rashid SM, Ganaie MA. Mitochondrial dysfunctions, oxidative stress and neuroinflammation as therapeutic targets for neurodegenerative diseases: an update on current advances and impediments. Neuroscience & Biobehavioral Reviews. 2023;144:104961.
31. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. International journal of molecular sciences. 2019;20(23):6008.
32. Ammal Kaidery N, Ahuja M, Sharma SM, Thomas B. An emerging role of miRNAs in neurodegenerative diseases: mechanisms and perspectives on miR146a. Antioxidants & redox signaling. 2021;35(7):580-94.
33. Mortazavi-Jahromi SS, Aslani M, Mirshafiey A. A comprehensive review on miR-146a molecular mechanisms in a wide spectrum of immune and non-immune inflammatory diseases. Immunology Letters. 2020;227:8-27.
34. Zhao W, Spiers JG, Vassileff N, Khadka A, Jaehne EJ, van den Buuse M, Hill AF. microRNA-146a modulates behavioural activity, neuroinflammation, and oxidative stress in adult mice. Molecular and Cellular Neuroscience. 2023;124:103820.
35. Olivieri F, Prattichizzo F, Giuliani A, Matacchione G, Rippo MR, Sabbatinelli J, Bonafè M. miR-21 and miR-146a: the microRNAs of inflammaging and age-related diseases. Ageing research reviews. 2021;70:101374.
36. Segaran RC, Chan LY, Wang H, Sethi G, Tang FR. Neuronal development-related miRNAs as biomarkers for Alzheimer's disease, depression, schizophrenia and ionizing radiation exposure. Current medicinal chemistry. 2021;28(1):19-52.
37. Lopez MS, Dempsey RJ, Vemuganti R. The microRNA miR-21 conditions the brain to protect against ischemic and traumatic injuries. Conditioning medicine. 2017;1(1):35.
38. Li YB, Fu Q, Guo M, Du Y, Chen Y, Cheng Y. MicroRNAs: pioneering regulators in Alzheimer’s disease pathogenesis, diagnosis, and therapy. Translational Psychiatry. 2024 ;14(1):367.
39. R. Vose L, K. Stanton P. Synaptic plasticity, metaplasticity and depression. Current neuropharmacology. 2017;15(1):71-86.
40. Xu B, Hsu PK, Karayiorgou M, Gogos JA. MicroRNA dysregulation in neuropsychiatric disorders and cognitive dysfunction. Neurobiology of disease. 2012 May 1;46(2):291-301.
41. Yao ZH, Yao XL, Zhang Y, Zhang SF, Hu J. miR-132 down-regulates methyl CpG binding protein 2 (MeCP2) during cognitive dysfunction following chronic cerebral hypoperfusion. Current neurovascular research. 2017;14(4):385-96.

42. Yue J, Zhang B, Wang H, Hou X, Chen X, Cheng M, Wen S. Dysregulated plasma levels of miRNA-132 and miRNA-134 in patients with obsessive-compulsive disorder. Annals of Translational Medicine. 2020;8(16).
43. Miller BH, Wahlestedt C. MicroRNA dysregulation in psychiatric disease. Brain research. 2010;1338:89-99.
44. Ortega MA, Alvarez-Mon MA, García-Montero C, Fraile-Martinez O, Lahera G, Monserrat J, Muñoz-Merida L, Mora F, Rodríguez-Jiménez R, Fernandez-Rojo S, Quintero J. MicroRNAs as critical biomarkers of major depressive disorder: a comprehensive perspective. Biomedicines. 2021;9(11):1659.
45. Radhakrishnan B, Anand AA. Role of miRNA-9 in brain development. Journal of experimental neuroscience. 2016;10:JEN-S32843.
46. Baudry A, Mouillet-Richard S, Schneider B, Launay JM, Kellermann O. miR-16 targets the serotonin transporter: a new facet for adaptive responses to antidepressants. Science. 2010;329(5998):1537-41
47. Choudhary A, Kumar A, Jindal M, Rhuthuparna M, Munshi A. MicroRNA signatures in neuroplasticity, neuroinflammation and neurotransmission in association with depression. Journal of Physiology and Biochemistry. 2024: 19:1-3.
48. Dwivedi Y. Emerging role of microRNAs in major depressive disorder: diagnosis and therapeutic implications. Dialogues in clinical neuroscience. 2014;16(1):43-61.
49. Zhang HC, Du Y, Chen L, Yuan ZQ, Cheng Y. MicroRNA schizophrenia: etiology, biomarkers and therapeutic targets. Neuroscience & Biobehavioral Reviews. 2023;146:105064.
50. Yin J, Lin J, Luo X, Chen Y, Li Z, Ma G, Li K. miR-137: a new player in schizophrenia. International journal of molecular sciences. 2014;15(2):3262-71.
51. Siegert S, Seo J, Kwon EJ, Rudenko A, Cho S, Wang W, Flood Z, Martorell AJ, Ericsson M, Mungenast AE, Tsai LH. The schizophrenia risk gene product miR-137 alters presynaptic plasticity. Nature neuroscience. 2015;18(7):1008-16.
52. Yu HC, Wu J, Zhang HX, Zhang GL, Sui J, Tong WW, Zhang XY, Nie LL, Duan JH, Zhang LR, Lv LX. Alterations of miR-132 are novel diagnostic biomarkers in peripheral blood of schizophrenia patients. Progress in Neuro-Psychopharmacology and biological psychiatry. 2015;63:23-9.

53. Mu C, Gao M, Xu W, Sun X, Chen T, Xu H, Qiu H. Mechanisms of microRNA-132 in central neurodegenerative diseases: A comprehensive review. Biomedicine & Pharmacotherapy. 2024;170:116029.
54. Mohammadi AH, Seyedmoalemi S, Moghanlou M, Akhlagh SA, Talaei Zavareh SA, Hamblin MR, Jafari A, Mirzaei H. MicroRNAs and synaptic plasticity: from their molecular roles to response to therapy. Molecular neurobiology. 2022;59(8):5084-102.
55. Song M. miRNAs-dependent regulation of synapse formation and function. Genes & genomics. 2020;42(8):837-45.
56. Włodarski A, Strycharz J, Wróblewski A, Kasznicki J, Drzewoski J, Śliwińska A. The role of microRNAs in metabolic syndrome-related oxidative stress. International Journal of Molecular Sciences. 2020;21(18):6902.
57. Martins HC, Gilardi C, Sungur AÖ, Winterer J, Pelzl MA, Bicker S, Gross F, Kisko TM, Malikowska-Racia N, Braun MD, Brosch K. Bipolar-associated miR-499-5p controls neuroplasticity by downregulating the Cav1. 2 subunit CACNB2. EMBO reports. 2022 ;23(10):e54420.
58. Sun F, Zhang H, Huang T, Shi J, Wei T, Wang Y. [Retracted] miRNA-221 Regulates Spinal Cord Injury-Induced Inflammatory Response through Targeting TNF-α Expression. BioMed research international. 2021;2021(1):6687963.
59. Tsai KW, Yang YF, Wang LJ, Pan CC, Chang CH, Chiang YC, Wang TY, Lu RB, Lee SY. Correlation of potential diagnostic biomarkers (circulating miRNA and protein) of bipolar II disorder. Journal of Psychiatric Research. 2024;172:254-60.
60. Alural B, Genc S, Haggarty SJ. Diagnostic and therapeutic potential of microRNAs in neuropsychiatric disorders: past, present, and future. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2017;73:87-103.
61. Li S, Lei Z, Sun T. The role of microRNAs in neurodegenerative diseases: a review. Cell Biology and Toxicology. 2023;39(1):53-83.
62. Ebada MA, Mostafa A, Gadallah AH, Alkanj S, Alghamdi BS, Ashraf GM, Abuzenadah AM, Alserihi RF, Wadaa-Allah A, Salama M. Potential regulation of miRNA-29 and miRNA-9 by estrogens in neurodegenerative disorders: An insightful perspective. Brain Sciences. 2023;13(2):243.
63. Lei B, Liu J, Yao Z, Xiao Y, Zhang X, Zhang Y, Xu J. NF-κB-induced upregulation of miR-146a-5p promoted hippocampal neuronal oxidative stress and pyroptosis via TIGAR in a model of Alzheimer's disease. Frontiers in cellular neuroscience. 2021;15:653881.

64. Liang Y, Wang L. Inflamma-microRNAs in Alzheimer's disease: from disease pathogenesis to therapeutic potentials. Frontiers in cellular neuroscience. 2021;15:785433.
65. Zhu Z, Huang X, Du M, Wu C, Fu J, Tan W, Wu B, Zhang J, Liao ZB. Recent advances in the role of miRNAs in post-traumatic stress disorder and traumatic brain injury. Molecular Psychiatry. 2023;28(7):2630-44.
66. Millan MJ. MicroRNA in the regulation and expression of serotonergic transmission in the brain and other tissues. Current opinion in pharmacology. 2011;11(1):11-22.
67. Bazrgar M, Khodabakhsh P, Prudencio M, Mohagheghi F, Ahmadiani A. The role of microRNA-34 family in Alzheimer's disease: A potential molecular link between neurodegeneration and metabolic disorders. Pharmacological Research. 2021;172:105805.
68. Liu X, Dong L, Jiang Z, Song M, Yan P. Identifying the differentially expressed peripheral blood microRNAs in psychiatric disorders: a systematic review and meta-analysis. Frontiers in Psychiatry. 2024;15:1390366.
69. Saha S. Role of microRNA in Oxidative Stress. Stresses. 2024;4(2):269-81.
70. Guerci P, Claudot JL, Novy E, Settembre N, Lalot JM, Losser MR. Immediate postoperative plasma neutrophil gelatinase-associated lipocalin to predict acute kidney injury after major open abdominal aortic surgery: A prospective observational study. Anaesthesia Critical Care & Pain Medicine. 2018;37(4):327-34.
71. Sakamoto K, Crowley JJ. A comprehensive review of the genetic and biological evidence supports a role for MicroRNA-137 in the etiology of schizophrenia. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2018;177(2):242-56.
72. Ma X, Wang Y, Shi Y, Li S, Liu J, Li X, Zhong W, Pan Q. Exosomal miR-132-3p from mesenchymal stromal cells improves synaptic dysfunction and cognitive decline in vascular dementia. Stem Cell Research & Therapy. 2022;13(1):315.
73. Mingardi J, La Via L, Tornese P, Carini G, Trontti K, Seguini M, Tardito D, Bono F, Fiorentini C, Elia L, Hovatta I. miR-9-5p is involved in the rescue of stress-dependent dendritic shortening of hippocampal pyramidal neurons induced by acute antidepressant treatment with ketamine. Neurobiology of stress. 2021;15:100381.
74. Gilardi C, Martins HC, Bianco AL, Bicker S, Germain PL, Gross F, Sungur AÖ, Kisko TM, Stein F, Meinert S, Schwarting RK. Early life stress-induced miR-708-5p regulates mood disorder-associated behavioural phenotypes in mice and is a potential diagnostic biomarker for bipolar disorder. bioRxiv. 2024:2024-03.