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# MicroRNA-mediated regulation of BDNF in depressive disorder: a pathway to diagnosis and therapy

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**ABSTRACT:** Depressive disorder, also known as depression, represents a major global health concern. Effective diagnosis and treatment of depression are critical to moderate its impact. Current diagnostic methods for depression are time-consuming and subjective, which can lead to misdiagnosis and impact treatment effectiveness. Therefore, identifying potential biomarkers for early and accurate diagnosis is critically needed. Although the exact pathophysiology of depression remains unknown, neurotrophic factors, with brain-derived neurotrophic factor (BDNF) being the most important, have been elucidated to play a key role in the pathogenesis of depression. Alterations in functional BDNF may contribute to the pathophysiology of depression by impairing neuroplasticity, a process closely linked to antidepressant action. Meanwhile, advancements in next-generation sequencing (NGS), quantitative polymerase chain reaction (qPCR), and bioinformatics have enabled the identification of various microRNAs (miRNAs) associated with depression. This review aims to assess the role and mechanisms of microRNAs that target BDNF in depression. These microRNAs regulate the pathophysiology of depression, particularly through abnormalities in neuroplasticity and neurogenesis, as well as other mechanisms such as hypothalamic-pituitary-adrenal axis hyperactivity and inflammatory dysregulation. These microRNAs may serve as biomarkers for diagnosis and as targets for novel antidepressants. Our study identifies 16 miRNAs that target BDNF in depression, either directly or indirectly through other molecules. Among these, miR-124, miR-132, and miR-221 are promising candidates for biomarkers of depression. Meanwhile, miR-124 and miR-132 present significant promise for treatment. However, major challenges remain in translating these findings into clinical practice, underscoring the need for further research.

**Keywords:** Depression; MicroRNA; MiRNA; BDNF; Diagnosis; Treatment

## 1.0 INTRODUCTION

Depressive disorder, also known as depression, is one of the most prevalent and recurrent mental health disorders worldwide (Kennis et al., 2020). According to the World Health Organization (WHO) in 2023, approximately 280 million people worldwide suffer from depression, which represents around 3.8% of the global population (WHO, 2023). Depression is also a significant factor in approximately 700,000 suicide deaths annually.

Current diagnosis relies mainly on patient-reported symptoms collected during clinical interviews, with depressed mood or loss of interest or pleasure serving as the key criterion (Ortega et al., 2021). Because this evaluation depends on subjective self-reports and clinician interpretation, diagnostic accuracy varies widely. Moreover, depression shares symptoms with other disorders such as anxiety, bipolar disorder, and posttraumatic stress disorder (PTSD), increasing the risk of misdiagnosis. Symptom presentation also varies among individuals, making standardised diagnosis challenging.

Additionally, factors such as stigma, denial, and delayed help-seeking can contribute to late diagnosis and hinder timely treatment. As a result, the current diagnostic approach, which is both time-consuming and relatively subjective, may sometimes lead to misdiagnosis and impact treatment effectiveness. Therefore, identifying potential biomarkers associated with depression is crucial for enabling early and accurate diagnosis.

Depending on the severity of the disease, there are a variety of treatment options for depression, ranging from psychological treatment and general measures such as relaxation techniques, yoga, exercise, to using antidepressant medication, electroconvulsive therapy, or transcranial magnetic stimulation. Methods are often combined to achieve the best therapeutic outcomes (Institute for Quality and Efficiency in Health Care, 2024). Psychological therapies act gradually by reshaping cognition and behaviour, and their success depends on the severity of the illness and the patient's engagement. Psychological therapy is frequently combined with medication to show significant results.

Typical antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), work gradually over weeks by modulating neurotransmitter levels. In contrast, fast-acting antidepressants, like ketamine and its derivatives, can produce rapid symptom relief within hours or days by targeting glutamatergic pathways. Although typical antidepressants appear to be the most common clinical treatment, their onset of action can take up to 6 weeks, side effects are common, and between one-third and half of patients either do not respond or require treatment with multiple different agents for recovery (Marwaha et al., 2023). Meanwhile, the dissociative properties and abuse potential of fast-acting antidepressants limit their use for psychiatric indications. As a result, it is critical to develop more effective treatments for depression.

To date, our understanding of the pathophysiology of depression is still limited. Several theories have been proposed, including the monoamine hypothesis, the neuroendocrine mechanism, hypothalamic-pituitary-adrenal axis (HPA) dysfunction, neuroinflammation, and microbiome-gut-brain axis mechanism, among others. However, none of these can perfectly explain the nature of depression (Duman et al., 2019; Kunugi et al., 2010).

Recently, the neuroplasticity hypothesis of depression has been widely developed and has become the focus of intense research (Duman et al., 2019). According to this hypothesis, dysfunction or decrease of neurotrophic factors, of which brain-derived neurotrophic factor (BDNF) is the most representative, leads to impaired neuronal plasticity, which eventually leads to depression. This hypothesis is strongly supported by research results showing that antidepressant drugs act by increasing BDNF expression or its release, or by binding to its TrkB receptors to enhance BDNF signalling (Casarotto et al., 2021; Duman et al., 2019; Kunugi et al., 2010; Miranda et al., 2019; Moliner et al., 2023). Building on this hypothesis, it is proposed that BDNF, its receptor, and associated signalling pathways could be the target for the development of novel and promising antidepressant drugs. Especially, agents that facilitate gene expression and the release of BDNF in the brain hold significant potential.

MiRNAs have emerged as key regulators in post-transcriptional gene regulation and are expected to remain central to future studies. These small, noncoding RNAs serve as central regulators of cellular signalling, influencing nearly every biological process. To date, over 2,300 distinct miRNAs have been identified in human cells (Diener et al., 2022; Kozomara et al., 2019). They have been found to play a crucial role in the pathogenesis of numerous diseases, including depression. A growing body of evidence indicates that

BDNF expression is tightly modulated by a network of miRNAs (e.g., miR-124, miR-132, miR-221).

This review will examine the role of miRNAs in targeting the BDNF signalling pathway in depression, highlighting their potential implications for diagnostic and therapeutic strategies. Additionally, the challenges in translating these findings into clinical applications will be thoroughly discussed.

## 2.0 BDNF AND ITS INVOLVEMENT IN THE PATHOGENESIS OF DEPRESSION

BDNF is a member of the neurotrophin family. In addition to BDNF, the neurotrophic family includes other members, such as nerve growth factor (NGF), neurotrophin 3, and neurotrophin 4. Neurotrophins were initially identified as crucial regulators of cell proliferation, migration, maturation, and survival during development. Later, they are also found to maintain expression in the adult brain, where they play key roles in synaptic plasticity, neuronal function, and survival (Duman et al., 2019; Miranda et al., 2019).

BDNF stands out among neurotrophins due to its high expression levels in the brain and its significant effects on nerve synapses (Leal et al., 2017). In the brain, high levels of BDNF have been detected in the hippocampus, amygdala, cerebellum, and cerebral cortex of both rodents and humans, with the highest concentrations observed in hippocampal neurons. Lower levels of BDNF have also been detected in various organs, including the liver, heart, and lungs (Miranda et al., 2019). The transcript of the *BDNF* gene is initially translated as the precursor proBDNF, which then undergoes processing and cleavage to produce a mature BDNF protein (Lee et al., 2001; Mowla et al., 2001).

BDNF is released as a mixture of pro- and mature BDNF in an activity-dependent manner (Pang et al., 2004). Interestingly, mature BDNF and proBDNF exert opposing effects on cellular function, adding complexity to the role of BDNF (Miranda et al., 2019). Specifically, mature BDNF binds to TrkB and activates downstream signalling pathways, which in turn facilitate neural plasticity, including synaptic plasticity, long-term potentiation, synaptogenesis, neuronal differentiation, and neuronal survival.

On the other hand, the proBDNF preferentially binds to the p75 neurotrophin receptor (p75NTR) and activates a set of different downstream signalling pathways in the opposite direction, which are involved in the disruption of synaptic plasticity, long-term depression, reduced growth, and apoptosis (Duman et al., 2019). **Figure 1** illustrates BDNF processing, BDNF signalling pathways, and the mechanisms of antidepressant medications.

The neuroplasticity hypothesis suggests that depression, in part, arises from impaired neural plasticity, particularly in the prefrontal cortex and limbic system, including the hippocampus and amygdala. This impairment results in dysfunction in the brain's ability to adapt and rewire itself in response to stressful experiences, leading to changes in brain structure and function that manifest as depressive symptoms.

As a crucial player in neural plasticity, BDNF is significantly involved in the pathogenesis of depression. Multiple reports and meta-analyses on depressed patients have shown significantly lower BDNF levels in the blood. Animal studies further demonstrate that chronic stress reduces BDNF expression in both cortex and hippocampus, while deletion of *BDNF* increases depression-like behaviour. Additionally, the Val66Met polymorphism in the *BDNF* gene affects BDNF release, which has been linked to an increased risk of depression and varying responses to antidepressant treatments (Yang et al., 2020a). Interestingly, recent studies have revealed that low BDNF concentration is correlated with elevated proinflammatory cytokines, such as IL-6 and TNF-α (Porter & O'Connor, 2022), as well as with dysregulation of the HPA axis (Mikulska et al., 2021), suggesting that BDNF intersects with neuroinflammatory and neuroendocrine pathways.

BDNF and its receptor TrkB are central to the therapeutic action of antidepressants. Exposure to stress and depression reduces BDNF expression, while studies on adult brain tissue samples have shown that antidepressant treatment can upregulate BDNF and reverse the effects of stress. BDNF expression was found to be elevated following treatment with various classes of antidepressants, including selective serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, as well as electroconvulsive seizure (ECS) (Nibuya et al., 1995). These conventional agents gradually increase BDNF expression over several weeks, contributing to adaptive changes that reverse the effects of stress and induce an antidepressant response.

By contrast, rapid-acting drugs such as ketamine and scopolamine appear to trigger immediate BDNF release without enhancing its expression, leading to swift synaptogenesis and faster symptom relief (**Figure 1**) (Duman et al., 2019). Recently, it was discovered that

both typical and fast-acting antidepressants directly bind to TrkB, thereby facilitating synaptic localisation of TrkB and increasing BDNF signalling (Casarotto et al., 2022). Together, these observations highlight BDNF as a convergence point for multiple antidepressant modalities, underscoring its potential as a promising target for novel therapeutic development.

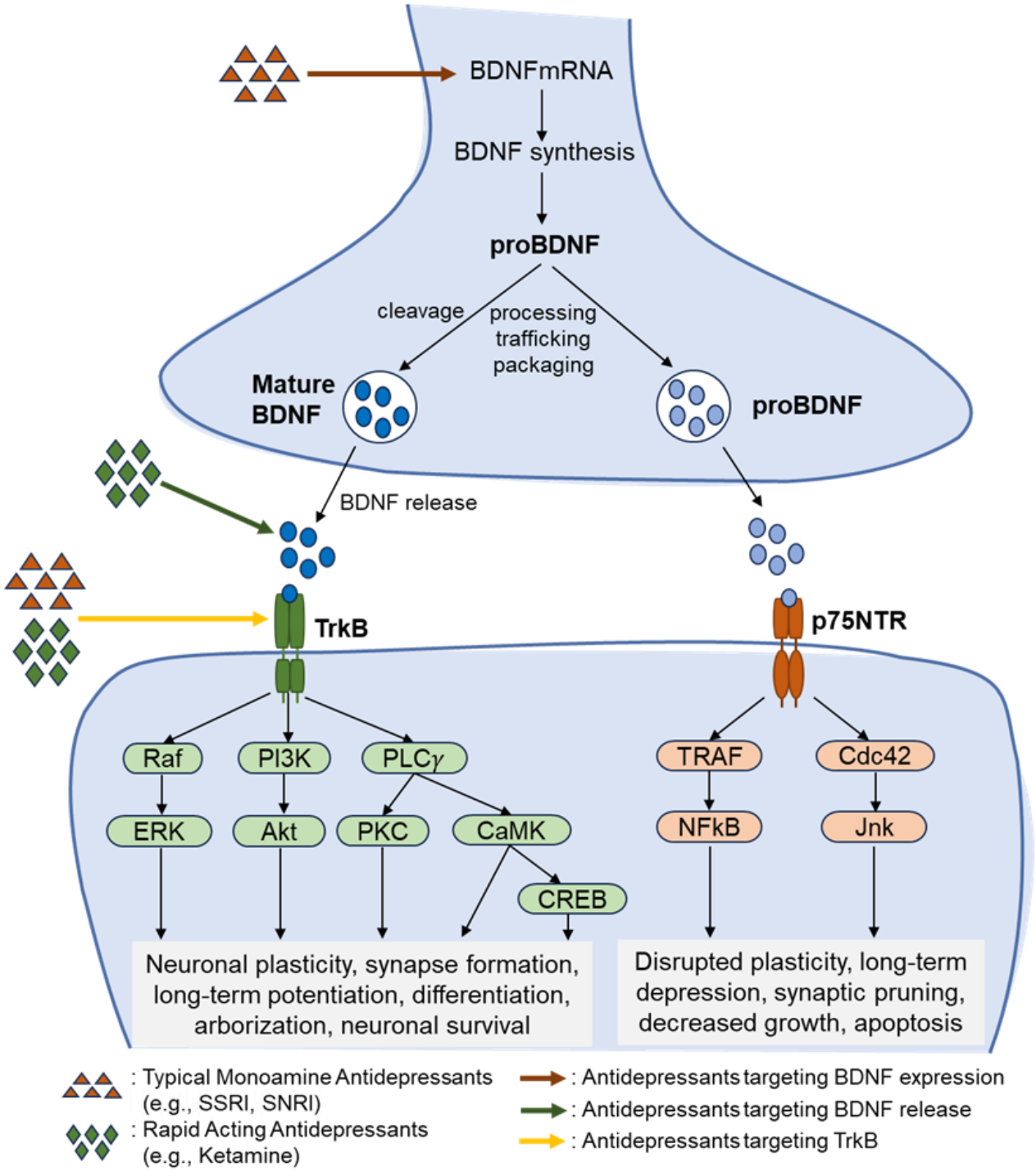


**Figure 1. BDNF processing, BDNF signalling pathways, and the mechanisms of antidepressant medications.** Akt: Serine-threonine kinase; BDNF: Brain-derived neurotrophic factor; CaMK: Calcium/calmodulin-dependent protein kinase; Cdc42: Cell division cycle 42; CREB: cAMP response element-binding protein; ERK: Extracellular signal-regulated kinase; Jnk: c-Jun N-terminal kinase; NF-κB: Nuclear factor-kappa B; p75NTR: p75 neurotrophin receptor; PI3K: Phosphatidylinositol 3-kinase; PKC: Protein kinase C; PLCγ: Phospholipase C gamma; proBDNF: Precursor brain-derived neurotrophic factor; Raf: Serine/threonine-protein kinase; SNRI: Serotonin-norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; TRAF: TNF receptor-associated factor; TrkB: Tropomyosin receptor kinase B.

## 3.0 MICRORNA AND ITS INVOLVEMENT IN THE PATHOGENESIS OF DEPRESSION

Mature microRNAs are small, noncoding, single-stranded RNA molecules, about 17 to 23 nucleotides long. They are present in virtually all mammalian tissues and post-transcriptionally regulate more than 60% of genes (Friedman et al., 2009). The interaction networks of miRNAs are intricate and extensive; a single miRNA can target multiple mRNAs, while one mRNA can be regulated by a variety of different miRNAs (Licursi et al., 2019). Genes encoding miRNAs may be monocistronic, polycistronic, or intronic (Treiber et al., 2018). They are transcribed as several hundred to a few thousand nucleotide-long primary miRNAs (pri-miRNAs) in the nucleus.

Pri-miRNAs have a typical hairpin-loop secondary structure, which is then cleaved into 60-70 bp precursor microRNAs (pre-miRNAs) by the microprocessor complex consisting of Drosha (a type of RNAse III) and DGCR8 (cofactor of the Drosha enzyme). After processing in the nucleus, pre-miRNAs are transported by the transporter protein exportin-5 from the nucleus to the cytoplasm. After leaving the nucleus, pre-miRNAs are cleaved by the enzyme Dicer, forming a double-stranded RNA chain (approximately 22 nucleotides), with one single strand being the miRNA and the other strand carrying a complementary sequence. Double-stranded RNA strands are incorporated into RNA-induced silencing complex (RISC) and processed by the Argonaute 2 (AGO2) protein to form mature microRNAs. RISC (engage with miRNAs) binds to the 3' untranslated region (3'UTR) of target mRNA, inhibiting mRNA expression or leading to mRNA degradation, thereby controlling gene expression at the post-transcriptional level (Leitão & Enguita, 2022; Żurawek & Turecki, 2021).

In the central nervous system, miRNAs play key roles in neurodevelopment, synaptic plasticity, and stress responses, establishing their involvement in various neurological and mental health disorders (Issler & Chen, 2015). In depression, distinct miRNAs modulate key pathogenic pathways, as summarised in sections below.

### 3.1 Dysregulation of monoamines

Several miRNAs, such as miR-200a, miR-30a, miR-30e (Gorinski et al., 2019), miR-135a (Issler et al., 2014), miR-1202 (Lopez et al., 2014), miR-329, miR-362 (Kim et al., 2021), and miR-124 (Rajasethupathy et al., 2009), disrupt serotonin signalling, glutamate regulation, and vesicle transport by affecting the expression of key proteins such as ZDHHC21, 5HT1AR, SERT, GRM4, and BAIAP3. These alterations contribute to neurotransmitter imbalance and may exacerbate depressive symptoms.

### 3.2 Neuroplasticity and neurogenesis abnormalities

MiR-124-3p (via the mTOR signalling pathway) (Wang et al., 2018), miR-128-3p (via the Wnt signalling pathway) (Roy et al., 2020), and miR-139-5p (via the cAMP/PKA/CREB/BDNF pathway) (Huang et al., 2021), have been shown to disrupt the regulation of key signalling pathways involved in neuroplasticity and neurogenesis (Ding et al., 2023). Dysregulation of these miRNAs leads to neuronal signalling dysfunction, which in turn impairs synaptic plasticity and reduces hippocampal neurogenesis, thereby contributing to the pathophysiology of depression. For instance, miR-128-3p was found to be elevated in the amygdala of individuals with depression and associated with the downregulation of Wnt signalling-related genes, including Wnt5b, LEF1, and DVL1 (Roy et al., 2020). This disruption of the canonical Wnt/Fz/GSK3 signalling pathway contributes to abnormal neurodevelopment associated with depressive disorder (Voleti & Duman, 2012).

### 3.3 HPA axis changes

Dysregulation of the HPA axis, characterised by sustained hypersecretion of glucocorticoids, has been implicated in hippocampal structural and functional alterations. Elevated glucocorticoid levels can impair hippocampal plasticity, reduce neurogenesis, and promote atrophic changes, thereby contributing to the pathophysiology of depression (Kronenberg et al., 2009; Schmidt et al., 2009). MiRNAs may affect the expression of glucocorticoid receptors or other pathways to modify HPA axis activity (Uchida et al., 2008; Vreugdenhil et al., 2009). For instance, increased expression of miR-124-3p in human and animal models has been confirmed to be associated with downregulation of AMPA receptor family members (GRIA3 and GRIA4) and the glucocorticoid receptor NR3C1. This miR-124-3p-mediated suppression of NR3C1 may thus be critical to the stress-related neuroendocrine response (Roy et al., 2017).

### 3.4 Inflammation

Depression and inflammation mutually contribute to each other's pathophysiology, with miRNAs playing a key role in promoting the production of inflammatory cytokines, such as TNF-α, IFN-α, IL-1β, and IL-6 (Ding et al., 2023). For instance, exosomal miR-9-5p levels were found to be elevated in the serum of depressed patients. In a cultured cell model, the transfer of miR-9-5p from neurons to microglia, mediated by exosomes,

promoted M1 polarisation and triggered the excessive release of proinflammatory cytokines (IL-1β, IL-6, TNF-α), thereby aggravating neuronal damage (Xian et al., 2022).

## 4.0 MICRORNAS TARGETING BDNF IN DEPRESSIVE DISORDER

Research over the past decade has provided significant insights into the roles of miRNAs and BDNF in depression. This review focuses on miRNAs that target the BDNF signalling pathway in depressive disorders, drawing from peer-reviewed articles published over the last decade. Systematically, miRNAs can regulate BDNF expression directly by binding to its mRNA or indirectly via upstream regulators such as CREB (cAMP Response Element-Binding Protein) and MECP2 (Methyl-CpG-Binding Protein 2), among others. The patterns, functions, and regulatory mechanisms of miRNAs targeting BDNF and being involved in depression are summarised in **Table 1** and diagrammed in **Figure 2**.

### 4.1 MiRNAs directly regulating BDNF

MiR-190b, miR-134, miR-206, miR-155, and miR-432 have each been shown to target BDNF directly in depression studies. MiR-190b has been found to bind to the 3'-UTR of BDNF mRNA directly. Chronic mild stress (CMS) or corticosterone (CORT) significantly reduces testis glucocorticoid receptor (GR) expression and simultaneously increases expression of miR-190b in testis and sperm in F0 depressive-like models. Administration of cinnamaldehyde, the principal compound in the Chinese herb cinnamon bark, reverses these changes. In the hippocampus of F1 males, miR-190b expression is elevated and accompanied by reduced BDNF and GR, which is also ameliorated by cinnamaldehyde. Together, these results suggest that cinnamaldehyde is a promising intervening agent for the intergenerational inheritance of depression, likely by regulating the GR/miR-190b/BDNF pathway (Gao et al., 2022).

Similarly, miR-134 plays a crucial role in regulating synaptic function by targeting the expression of synaptic proteins, including BDNF, PSD95 (postsynaptic density protein 95), and SYN (synapsin I), and by mediating dendritic morphogenesis in hippocampal neurons. Chronic unpredictable mild stress (CUMS) in rats has been shown to induce depression-like behaviours and decrease the expression of BDNF and other synaptic proteins in the hippocampus by downregulating the SIRT1/miR-134 pathway. An enriched environment (EE) can reverse depression-like behaviours and cognitive deficits, likely by reactivating the SIRT1/miR-134 pathway (Shen et al., 2019). Additionally, in another study, brain-specific miR-134 can directly bind to the *BDNF* 3' UTR, and ginsenoside Rb1 (Rb1) exhibits an antidepressant-like effect in CUMS-induced mice by modulating hippocampal synaptic plasticity via the miR-134-mediated BDNF signalling pathway (Wang et al., 2022).

MiR-206 is also a significant regulator in depression through its direct target gene, *BDNF*. Hippocampal miR-206-3p participates in the pathogenesis of depression by regulating BDNF biosynthesis (Guan et al., 2021). In models of depression, such as post-weaning social isolation (SI) and chronic social defeat stress (CSDS) in mice, increased hippocampal miR-206 levels are associated with decreased BDNF signalling and neurogenesis (Chang et al., 2020; Guan et al., 2021). Another study also indicates that treatment with ketamine increases BDNF expression and decreases miR-206 levels and that *BDNF* is a direct target gene of miR-206 (Yang et al., 2014). In pregnant stressed (PS) mice, BDNF expression declines in both the hippocampus and medial prefrontal cortex (mPFC) with enhanced miR-206-3p levels, whereas BDNF levels increase and miR-206-3p expression decreases in the amygdala. Therefore, although miR-206 and BDNF expression are clearly correlated, their levels vary across different brain regions (Miao et al., 2018).

Long noncoding RNA (lncRNA) MIR155HG was found to directly bind to and negatively modulate the expression of miR-155, which in turn directly binds to *BDNF* mRNA and regulates BDNF expression. In CUMS mice, decreased MIR155HG led to increased miR-155 expression and inhibited BDNF expression, resulting in the development of depression-like behaviours. It was concluded that lncRNA MIR155HG could protect CUMS mice by regulating the miR-155/BDNF axis (Huan et al., 2021). Additionally, another study found that blueberry phenolics reduced gastrointestinal infections in patients with cerebral venous thrombosis by enhancing antidepressant activity through the upregulation of miR-155-mediated BDNF (Xu et al., 2017).

Adenosine deaminase acting on RNA1 (ADAR1) is a newly discovered epigenetic molecule marker that is sensitive to environmental stressors. An ADAR1 inducer restores brain- and serum-BDNF levels and reduces depressive-like behaviour in chronic unpredictable stress (CUS) animals. *In vitro* experiments demonstrate that overexpression of ADAR1 reduces miR-432 levels, whereas low ADAR1 expression increases miR-432 levels, and miR-432 might link to *the BDNF 3 ' UTR to*

*decrease* BDNF expression. These findings suggest that ADAR1 contributes to antidepressant effects by regulating BDNF via miR-432 (Zhang et al., 2021a). Additionally, another study in mice demonstrates that ADAR1 influences CUS-induced depressive-like behaviour and BDNF expression by modulating miR-432 and circ_0000418, further strengthening the role of ADAR1 as a potential antidepressant (Zhang et al., 2021b).

### 4.2 MiRNAs indirectly regulating BDNF

While the miRNAs discussed above directly target BDNF, many others indirectly influence BDNF levels by targeting other proteins essential for BDNF transcription, such as cAMP response element-binding protein (CREB) and methyl-CpG-binding protein 2 (MECP2).

#### 4.2.1 MiRNA regulating BDNF via CREB

In the nervous system, CREB supports neuronal survival, regulates neuronal migration, modulates synaptogenesis, and contributes to the formation of long-term potentiation and long-term memory. CREB, which forms a transcriptional complex with its coactivators CREB-binding protein (CBP) and p300, is the major mediator of BDNF transcriptional autoregulation in cortical neurons (Esvald et al., 2020). CREB-BDNF signalling plays a crucial role in various neuronal functions, including synaptic structure, synaptic plasticity, and cell survival (Karege et al., 2005). In rodents, deletion of *CREB* or mutation of *BDNF* disrupts the CREB/BDNF signalling cascade in the hippocampus, producing depression-like behaviour, while activating this pathway elicits consequent antidepressant-like effects (Tan et al., 2022). The miRNAs below target CREB directly and consequently modulate the expression of BDNF.

Although miR-134 has been known to regulate BDNF directly, it also influences BDNF through CREB. In rats, chronic stress lowers the expression of miR-134 in the basolateral amygdala (BLA), accompanied by decreased phosphorylation of CREB and decreased expression of BDNF. Ginsenoside Rg1 suppresses miR-134, leading to increased CREB and BDNF levels, which improve synaptic plasticity and potentially alleviate depression-like behaviours (Yu et al., 2018). In a cocaine-induced conditioned place preference (CPP) mouse model, during the cocaine extinction (CE) period, elevated miR-134 correlates with anxiety-like and depression-like behaviours and decreased expression of genes associated with synaptic plasticity in the ventral hippocampus (vHP).

MiR-134 was found to target *Creb-1*, regulating CREB and BDNF expression post-transcriptionally, and knocking down miR-134 in the vHP reverses these gene expression changes, mitigating anxiety-like and depression-like behaviours (Li et al., 2020c). Additionally, research by Jun Shen et al. in 2018 demonstrated that resveratrol treatment prevents CUMS-induced spatial learning and memory impairments by activating the Sirt1/miR-134 pathway (increasing Sirt1 and decreasing miR-134) and upregulating CREB/BDNF expression in the hippocampus both *in vivo* and in *vitro* (Shen et al., 2018).

In patients with major depressive disorder and the hippocampus of CUMS mice, miR-221 expression was elevated, while Wnt2, p-CREB, and BDNF levels were reduced. Silencing miR-221 enhances Wnt2, p-CREB, and BDNF protein expression. MiR-221 directly targets and negatively regulates *Wnt2*, and knockdown of *Wnt2* reverses the effects of miR-221 inhibitor on hippocampal neuron proliferation and apoptosis. These findings suggest that miR-221 promotes the development of depression by regulating the Wnt2/CREB/BDNF axis (Lian et al., 2018).

Experiments with miR-199a-5p followed the same design as those for miR-221, using cerebrospinal fluid and serum samples from depressed patients, as well as hippocampal tissue from CUMS mice. The results also demonstrated that miR-199a-5p could directly target *Wnt2* to enhance the development of depression by regulating the CREB/BDNF signalling pathway in hippocampal neurons (Liu et al., 2021).

MiR-182 is linked to depression-like behaviours. In the CUMS model, miR-182 expression was upregulated, resulting in decreased BDNF expression in the hippocampus, and silencing miR-182 has an antidepressant-like effect (Li et al., 2016). In rat models of post-stroke depression (PSD), stimulation of the fastigial nucleus (FN) can be used to treat PSD by increasing the expression of BDNF through down-regulation of miR-182 (Zhang et al., 2022). A study by Yuxiao Tang et al. in 2022 found that the activation of NF-κB led to an increase in miR-182, which inhibited GPR39 expression and, consequently, resulted in a decrease in BDNF expression. This study suggests that the NF-κB/miR-182/GPR39/CREB/BDNF pathway is important for chronic stress-induced depression-like behaviours in mice (Tang et al., 2022).

**Table 1.** Expression, roles, and regulatory mechanisms of miRNAs that target BDNF and are implicated in depression.

| MiRNAs | Study model; sample source | Expression of miRNAs | Regulation mechanism | Regulation to BDNF | Expression of BDNF | Treatment | Result after treatment | References |
|---|---|---|---|---|---|---|---|---|
| **MiR-190b** | CORT- and CMS-induced mouse; testis and sperm/ hippocampus | Increase | GR/miR-190b/BDNF pathway | Negative | Decrease | Cinnamaldehyde | Downregulate miR-190b and increase BDNF expression | Gao et al., 2022 |
| **MiR-134** | CUMS-induced rat; the basolateral amygdala | Increase | CREB/BDNF | Negative | Decrease | Ginsenoside Rg1 | Downregulate miR-134 Upregulate BDNF | Yu et al., 2018 |
| | CUMS-induced rat; hippocampus and primary cultured hippocampal neurons | | SIRT1/miR-134/BDNF | | | Enriched environment (EE) | | Shen et al., 2019 |
| | CPP mice model; the ventral hippocampus | | CREB/BDNF | | | Knockdown of miR-134 | | Li et al., 2020c |
| | CUMS-induced mice; hippocampus | | BDNF | | | Ginsenoside Rb1 | | Wang et al., 2022 |
| | CUMS-induced rat; hippocampus | | Sirt1/miR-134/CREB/BDNF | | | Resveratrol | Increase Sirt1, p-CREB, CREB, BDNF expression Decrease miR-134 levels | Shen et al., 2018 |
| **MiR-206-3p** | Rat; hippocampus/ cultured hippocampal neurons | Increase | BDNF | N/A | N/A | Ketamine | Downregulate miR-206 Upregulate BDNF | Yang et al., 2014 |
| | PS mice; hippocampus/mPFC/ amygdala Hippocampal HT22 cells | Increase (in the hippocampus, mPFC) Decrease (in amygdala) | BDNF | Negative | Decrease (in the hippocampus, mPFC) Increase (in amygdala) | N/A | N/A | Miao et al., 2018 |
| | SI mice; hippocampus | Increase | BDNF | Negative | Decrease | AM206 (an antagomir of miR-206) | Increase BDNF expression | Chang et al., 2020 |
| | CSDS mice; hippocampus | Increase | BDNF-TrkB | Negative | Decrease | N/A | N/A | Guan et al., 2021 |

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|---|---|---|---|---|---|---|---|---|
| **MiR-155** | CUMS mice, hippocampus/293T cells | Increase | lncRNA MIR155HG /miR-155/BDNF | Negative | Decrease | N/A | N/A | Huan et al., 2021 |
| | Patients, serum/HT22 hippocampal cells | N/A | N/A | N/A | N/A | Blueberry (Phenolics) | Increase BDNF expression and miR-155 | Xu et al., 2017 |
| **MiR-432** | CUS mice, frontal cortex/SH-SY5Y cells | Decrease | BDNF | Positive | Decrease (adar1: decrease, circ_0000418: increase) | ADAR1 inducer (IFN-γ) | adar1, circ_0000418, BDNF: return to the control levels; miR-432 expression was partially recovered | Zhang et al., 2021a, 2021b |
| **MiR-221** | CUMS mice, hippocampus | Increase | Wnt2/CREB/BDNF | Negative | Decrease | Inhibition of miR-221 | Increase the expression of Wnt2, p-CREB and BDNF | Lian et al., 2018 |
| **MiR-199a-5p** | Patients; cerebrospinal fluid and serum. CUMS mice; hippocampal tissue | Increase | Wnt2/CREB/BDNF | Negative | WNT2, p-CREB và BDNF: decrease | MiR-199a-5p-inhibitor | Increase the expression of Wnt2, p-CREB and BDNF | Liu et al., 2021 |
| **MiR-182** | CUMS rat, hippocampus | Increase | BDNF | Negative | Decrease | LV-si-miR-182 or LV-BDNF | Upregulate BDNF | Li et al., 2016 |
| | CUMS mice and CRS mice; hippocampus cells | Increase | NF-κB/miR-182/ GPR39/CREB/BDNF | Negative | Decrease | N/A | N/A | Tang et al., 2022 |
| | CSDS mice; hippocampus | Increase | MiR-182-5p/Akt/GSK3β/CREB | N/A | N/A | Adeno-associated virus (AAV)-siR-182-5p | Increase Akt/GSK3β/CREB expression | Zheng et al., 2024 |
| | Patients; serum/SH-SY5Y cells; | Increase | N/A | Negative | Decrease | N/A | N/A | Li et al., 2013 |
| | Post-stroke depression rat/SH-SY5Y and SK-N-MC cells | Increase | BDNF | Negative | Decrease | Fastigial nucleus stimulation | Downregulate miR-182, partly recover BDNF level | Zhang et al., 2022 |

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|---|---|---|---|---|---|---|---|---|
| **MiR-139-5p** | CUMS mice; hippocampal cells/HT-22 cells | Decrease | PDE4D/cAMP/PKA/CREB/BDNF | Negative | PDE4D: increase cAMP, p-CREB, BDNF: decrease | AAV-miR-139-5p | Suppress PDE4D increasing cAMP, p-CREB, and BDNF expression | Huang et al., 2021 |
| | Chronic CORT mice; hippocampus | Increase | NR3C1/BDNF-TrkB | Negative | Decrease | Antago-miR-139-5p | Decrease miR-139-5p level | Su et al., 2022 |
| **MiR-124** | Patients; plasma | Increase | N/A | No significant correlation | Increase | Citalopram (8 weeks) | Upregulate miR-124<br>Increase BDNF | Fang et al., 2018 |
| | Chronic CORT-treated mice; hippocampus | Increase | GR/<br>BDNF-TrkB signaling | Negative | Decrease | MiR-124 antagomir | Downregulate miR-124<br>Upregulate BDNF | Wang et al., 2017 |
| | CUMS -induced rat; hippocampus | Increase | CREB1 and BDNF | Negative | Decrease | MiR-124 antagomir | Increase CREB1 and BDNF | Yang et al., 2020b |
| | CSDS mice; hippocampus | Increase | N/A | N/A | N/A | Knockdown of hippocampal miR-124 | Increase BDNF-TrkB | Shi et al., 2022 |
| | Patients; blood | Increase | N/A | Negative | Decrease | Sertraline | Decrease miR-124, BDNF | Ahmadimanesh et al., 2023 |
| **MiR-132** | Patients; peripheral blood/A rat model of chronic stress-induced depression; hippocampi/ primary hippocampal neurons | Increase | MECP2/BDNF | Negative | Decrease | MiR-132 inhibitors | Upregulate MECP2, BDNF | Su et al., 2015 |
| | SPS rat; PFC | Increase | MECP2/BDNF | Negative | Decrease | anti-miR-132 | Upregulate MeCP2, BDNF level | Tong et al., 2021 |
| | Patients; plasma | Increase | N/A | No significant correlation | Increase | Citalopram (8 weeks) | Downregulate miR-132<br>Increase BDNF | Fang et al., 2018 |
| | Patients; blood | Increase | N/A | Negative | Decrease | Sertraline | Decrease miR-132, BDNF | Ahmadimanesh et al., 2023 |

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| **MiR-144** | CUMS rat; hippocampus/primary hippocampus neurons | Decrease | PTP1B/TrkB/BDNF | Positive | Decrease (PTP1B: upregulated, pTrkB: down-regulated) | LV-miR-144 | Inhibit PTP1B expression Upregulated the expression of downstream pTrkB and BDNF. | Li et al., 2021 |
| **MiR-138** | CUMS mice; hippocampus/cultured primary neuronal cells | Increase | Sirt1/PGC-1α/FNDC5/BDNF | Negative | Decrease SIRT1, BDNF expression | LV-si-miR-138 lentivirus | Decrease the mRNA level of Sirt1, PGC-1α, FNDC5 and BDNF | Li et al., 2020a |
| **MiR-101** | CUMS rat; ventrolateral orbital cortex (VLO) | Decrease | DUSP1/ ERK/BDNF | Positive | Decrease (Increase DUSP1) | miR-101 mimic | Enhance miR-101 expression, promote downstream ERK/BDNF signaling | Zhao et al., 2017 |
| **MiR-142** | SPS rats; amygdala | Increase | Npas4/BDNF | Negative | Decrease (Npas4: decrease) | LV-anti-miR-142 | Increase expression of Npas4 and BDNF | Ji et al., 2019 |
| **MiR-382-5p** | CUMS rats; hippocampus | Increase | NR3C1/BDNF and p-TrkB | Negative | (NR3C1: decrease) | LV-si-miR-382-5p | Elevate NR3C1, BDNF and p-TrkB | Li et al., 2020b |
| | Post-stroke depression rat/SH-SY5Y and SK-N-MC cells | Increase | BDNF | Negative | Decrease | Fastigial nucleus stimulation | Downregulate miR-382-5p, partly recover BDNF level | Zhang et al., 2022 |

CMS: chronic mild stress; CORT: corticosterone; CPP: cocaine-induced conditioned place preference; CRS: chronic restraint stress; CSDS: chronic social defeat stress; CUMS: chronic unpredictable mild stress; CUS: chronic unpredictable stress; DUSP1: dual specificity phosphatase 1; mPFC: medial prefrontal cortex; N/A: not available; PFC: prefrontal cortex; PS: pregnant stressed; SI: post-weaning social isolation; SPS: single-prolonged stress.

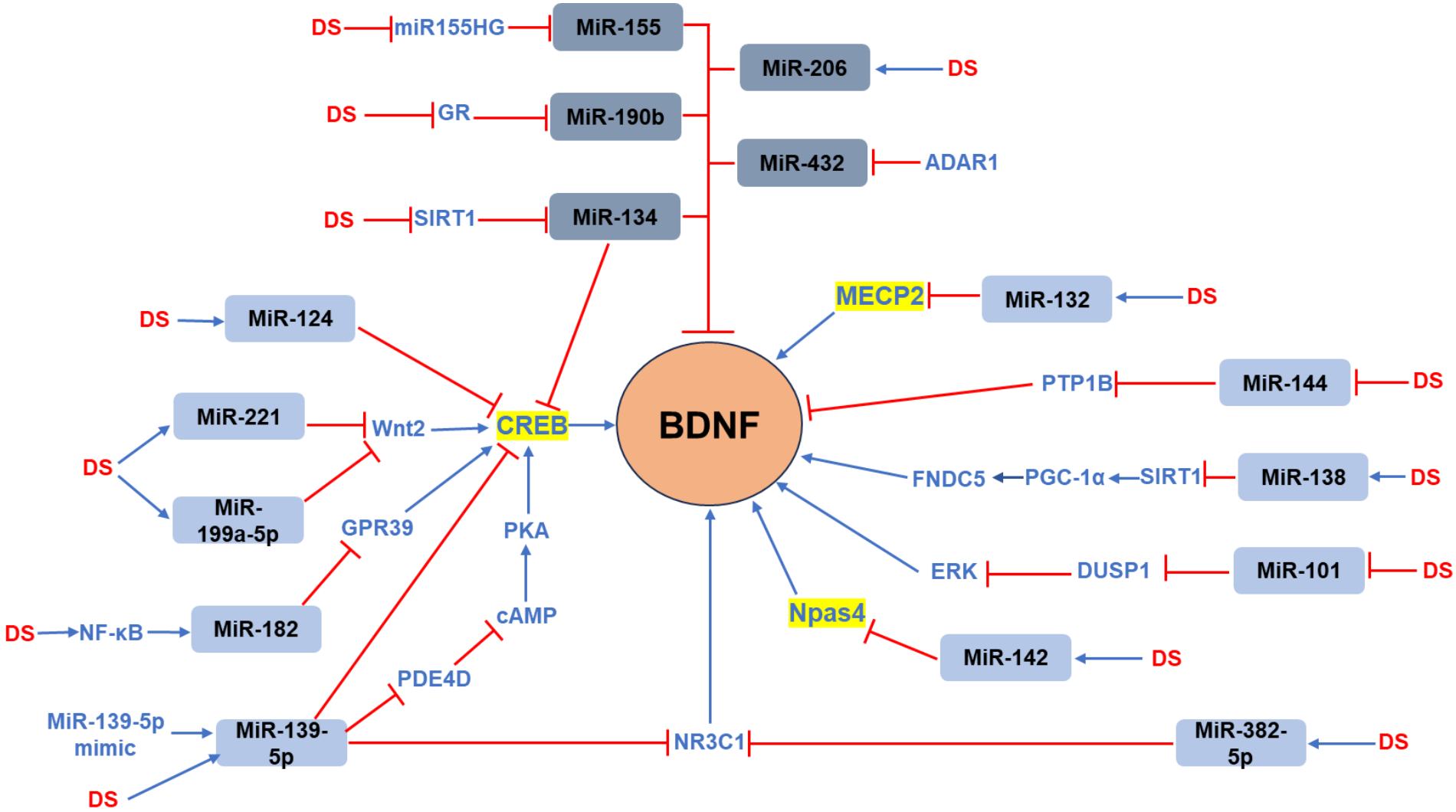


**Figure 2. Diagram summarising the miRNAs network that regulates BDNF in depression**. This diagram illustrates the regulatory network of miRNAs affecting BDNF expression in depressive disorder within the scope of this study. Three transcription factors, CREB, MECP2, and Npas4, which directly regulate BDNF expression are highlighted in yellow. Blue arrows indicate activation, while red blunt-ended lines represent inhibition. Only interactions that have been experimentally validated and discussed in this study are presented. ADAR1: Adenosine deaminase acting on RNA 1; BDNF: Brain-derived neurotrophic factor; cAMP: Cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; DS: Depressive stimuli; DUSP1: Dual specificity phosphatase 1; ERK: Extracellular signal-regulated kinase; FNDC5: Fibronectin type III domain-containing protein 5; GPR39: G protein-coupled receptor 39; GR: Glucocorticoid receptor; MECP2: Methyl-CpG-binding protein 2; NF-κB: Nuclear factor-kappa B; Npas4: Neuronal PAS domain protein 4; NR3C1: Nuclear receptor subfamily 3 group C member 1; PDE4D: Phosphodiesterase 4D; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKA: Protein kinase A; PTP1B: Protein tyrosine phosphatase 1B; SIRT1: Sirtuin 1.

Recent work with a CSDS mouse model suggests that hippocampal miR-182-5p/Akt/GSK3β/CREB signalling contributes to the pathogenesis of depression (Zheng et al., 2024). It is hypothesised that the potential mechanism by which miR-182-5p regulates depression may be mediated by targeting the CREB-BDNF signalling pathway. The serum levels of miR-182 were also observed to be higher in patients with depression compared with healthy controls (Li et al., 2013). The association between BDNF and miR-182 was consistent across different sample types.

Phosphodiesterase 4D (PDE4D) is implicated in depression primarily by inhibiting the cAMP/protein kinase A (PKA)/cAMP response element-binding protein (CREB) signalling pathway (Xu et al., 2019; Zou et al., 2017). Increasing hippocampal miR-139-5p via AAV-miR-139-5p infusion suppresses PDE4D in mouse hippocampal cells, elevates cyclic adenosine monophosphate (cAMP), p-CREB, and BDNF, stimulates hippocampal neurogenesis, and, in turn, reduces susceptibility to stress-induced depression-like behaviours (Huang et al., 2021). To summarise, miR-139-5p exhibits an antidepressant-like effect by targeting PDE4D, thereby activating the cAMP/PKA/CREB signalling pathway. In contrast, later studies using a chronic corticosterone-induced mouse model revealed that miR-139-5p expression was upregulated in the model group, and antidepressant-like effects were achieved by activating the BDNF-TrkB pathway through the inhibition of miR-139-5p (Su et al., 2022). The differences between these findings and previous studies may be attributed to the use of distinct models, which likely involve varying mechanisms, leading to inconsistencies across the studies.

MiR-124, the most abundant miRNA in brain tissue, has been demonstrated to play a key role in neurogenesis and neuronal differentiation. In the hippocampus of CUMS-induced depression model rats, miR-124 expression was upregulated, while CREB1 and BDNF were downregulated. MiR-124 has been confirmed to target the 3'UTR regions of CREB1 and BDNF specifically, and it has been speculated that silencing miR-124 may exert antidepressant effects by promoting the expression of CREB1 and BDNF in hippocampal tissue (Yang et al., 2020b). Similarly, in a CSDS mouse model of depression, the level of hippocampal miR-124 robustly increased, contributing to the pathogenesis of depression by regulating BDNF biosynthesis, and genetic knockdown of hippocampal miR-124 has shown significant antidepressant-like effects (Shi et al., 2022).

In chronic corticosterone (CORT)-treated mice, inhibition of miR-124 by its antagomir can also reverse depression-like behaviours by targeting the glucocorticoid receptor (GR) and activating the BDNF-TrkB signalling pathway (Wang et al., 2017). Ahmadimanesh and colleagues (2023) reported significantly higher miR-124 in depressed patients than in controls. Among various SSRIs tested, only sertraline was able to alter miR-124 expression (Ahmadimanesh et al., 2023). In contrast to the above, Fang and colleagues (2018) found that miR-124 and BDNF in plasma increased both in depressed patients and after treatment with citalopram. No significant correlations were identified for plasma miR-124 or BDNF (Fang et al., 2018). There appeared to be differences and inconsistencies when the study was conducted in human samples.

#### 4.2.2 MiRNA regulating BDNF via other molecules

Beyond CREB, miRNAs can modulate BDNF via other molecules, including MeCP2, PTP1B, FNDC5, ERK, Npas4, and NR3C. This highlights the diverse and complex mechanisms through which miRNAs can influence BDNF expression, impacting various aspects of neuronal function and neuroplasticity.

MiR-132 indirectly regulates BDNF expression through the homeostatic control of MeCP2, a protein crucial for the modulation of neuroplasticity in post-mitotic neurons. In both an animal model of chronic stress-induced depression and the peripheral blood of patients with depression, miR-132 expression was increased while MeCP2 and BDNF expression decreased, indicating a negative correlation between miR-132 and the other two. MiR-132 may directly target MeCP2 but not BDNF, and thereby downregulate BDNF expression. The study suggested that homeostatic interactions between MeCP2 and miR-132 may regulate hippocampal BDNF levels, which may have a role in the pathogenesis of depression (Su et al., 2015).

Additionally, evidence from the other study showed that miR-132 has also been involved in the formation of anxiety-like symptoms of adult rat posttraumatic stress disorder (PTSD) models by targeting MeCP2, and this effect is related to BDNF/TrkB and its downstream ERK and Akt signalling pathways (Tong et al., 2021). In depressed patients, miR-132 expression was significantly higher compared to the healthy group. Among the various SSRIs tested, only sertraline was found to be effective in reducing miR-132 expression (Ahmadimanesh et al., 2023).

In contrast, Fang and colleagues (2018) found no significant correlation between miR-132 and BDNF in plasma from depressed patients. Both miR-132 and BDNF were increased in depressed patients, and after citalopram treatment, miR-132 expression decreased, while BDNF continued to increase in expression (Fang et al., 2018). There appeared to be differences between sample types and between animal models and human studies.

In studies on CUMS rats, the expression of miR-144 in the hippocampus was significantly lower compared to controls. Concurrently, PTP1B protein expression was significantly upregulated, while pTrkB and BDNF protein expression were significantly down-regulated. *PTP1B* was identified as a direct target of miR-144, and miR-144 could activate the downstream TrkB/BDNF signalling pathway by inhibiting the expression of PTP1B in primary hippocampus neurons. The lentiviral vector carried miR-144 (LV-miR-144) inhibited the expression of PTP1B in the CUMS rat hippocampus and upregulated the expression of downstream pTrkB and BDNF (Li et al., 2021).

In CUMS mice, hippocampal miR-138 rose, correlating with reduced SIRT1. The SIRT1/PGC-1α/FNDC5/BDNF pathway was downregulated after miR-138 overexpression and increased upon miR-138 knockdown in both the hippocampus of CUMS mice and cultured primary neuronal cells, indicating that miR-138 has a regulatory impact on this pathway (Li et al., 2020a).

MiR-101 plays a key role in the development of stress-related dysfunctions in the ventrolateral orbital cortex (VLO). In a rat model, chronic stress led to depression-like behaviours and reduced miR-101 levels in the VLO. At the same time, in CUMS rats, the levels of dual specificity phosphatase 1 (DUSP1) protein increased, accompanied by a decrease in ERK phosphorylation and BDNF levels. Treatment with a miR-101 mimic in the VLO helped reverse these effects by reducing the CUMS-induced increase in DUSP1 expression, which in turn restored ERK phosphorylation and BDNF expression. MiR-101 may directly regulate DUSP1 expression, and its antidepressant effects likely involve the negative regulation of DUSP1, thereby advancing downstream ERK/BDNF signalling (Zhao et al., 2017).

In single-prolonged stress (SPS) rats, elevated levels of miR-142 in the amygdala were associated with reduced expression of Npas4, a transcription factor involved in stress-related psychopathologies (Ji et al., 2019). Inhibition of miR-142 reduced anxiety-like behaviours and memory deficits in SPS rats while restoring Npas4 and BDNF levels. Bioinformatics analysis and a dual-luciferase reporter assay confirmed that *Npas4* is a direct target of miR-142 (Ji et al., 2019). Previous work has shown that Npas4 may promote the expression of BDNF (Bloodgood et al., 2013). Therefore, it was deduced that activation of miR-142 reduced Npas4 expression, which subsequently decreased BDNF levels, suggesting a potential miR-142-Npas4-BDNF regulatory axis in the development of PTSD.

Chronic unpredictable mild stress (CUMS) led to a dose-dependent increase in miR-382-5p expression in rats. Elevated miR-382-5p levels in the hippocampus were linked to reduced NR3C1 expression and inversely correlated with BDNF and phosphorylated TrkB (p-TrkB). The study revealed that miR-382-5p may target *NR3C1*, which in turn regulates BDNF and p-TrkB, contributing to the depression-like behaviours observed in CUMS rats (Li et al., 2020b). In rat models of post-stroke depression (PSD), BDNF mRNA and protein levels were suppressed, while miR-382 and miR-182 levels were significantly upregulated. Fastigial nucleus (FN) stimulation alleviated PSD by lowering miR-382 and restoring BDNF expression. These results support the view that FN stimulation exerts its therapeutic effect through the miR-382/BDNF signalling pathway (Zhang et al., 2022).

## 5.0 MICRORNAS TARGETING BDNF FOR DIAGNOSTIC AND THERAPEUTIC PURPOSES: PROMISING AND CHALLENGES

BDNF is recognised as a key biomarker in depression, which is closely related to the occurrence, development, and prognosis of depression (Hing et al., 2018). The intricate involvement of miRNAs in regulating the BDNF pathway offers promising avenues for both diagnosis and treatment of depressive disorder. Here, we outline the main opportunities and obstacles in leveraging miRNAs, with a focus on those that target BDNF, for both diagnostic and therapeutic purposes.

### 5.1 In diagnosis

Regarding advantages, miRNAs are stable in various body fluids, including minimally invasive samples such as serum/plasma, saliva, and urine (Schwarzenbach et al., 2014). They also demonstrate high specificity and sensitivity, making them suitable for accurate diagnosis and prognosis of disease progression. To date, several miRNA-based diagnostic assays have been introduced into clinical use. These include RosettaGX Reveal panel

for distinguishing between indeterminate or benign thyroid nodules, miRviewTM Mets panel for detecting cancers of uncertain or unknown primary origin, ThyraMir for identifying thyroid cancer, OsteomiR for determining the hazard of a first fracture in type-2 diabetes and postmenopausal osteoporosis females, and ThrombomiR for assessing platelet function (Ho et al., 2022).

For depression, circulating miRNAs show considerable potential as clinical biomarkers. However, research is still in the experimental or preclinical stage, focusing on identifying individual miRNAs that may serve as diagnostic markers. For most of the 16 miRNAs discussed here, evidence comes mainly from animal studies, and concordance with human data is limited. However, three miRNAs, miR-221, miR-124, and miR-132, are emerging as the most promising for application in diagnosis.

Specifically, miR-221 expression was upregulated in cerebrospinal fluid, serum, and plasma in depressed patients compared to healthy controls (Cui et al., 2021; Enatescu et al., 2016; Kuang et al., 2018; Lian et al., 2018), with parallel findings in the hippocampus of CUMS mice (Lian et al., 2018). MiR-124 level was elevated in plasma, brain tissue, serum, and PBMCs of depressed patients (Ahmadimanesh et al., 2023; Fang et al., 2018; He et al., 2016; Roy et al., 2017), with consistent findings in the hippocampus of CORT-treated mice (Wang et al., 2017), CUMS-induced rats (Yang et al., 2020b), and CSDS mice (Shi et al., 2022). Similarly, miR-132 is elevated in the plasma, whole blood, and serum of patients with depression (Ahmadimanesh et al., 2023; Fang et al., 2018; Lin et al., 2017; Liu et al., 2016; Qi et al., 2018), as well as in rat models of depression (Su et al., 2015; Tong et al., 2021).

However, to apply these miRNAs in diagnosis, larger studies with clear and reliable data are needed. Their sensitivity and specificity in diagnosing depression should be evaluated, and the effect of noise factors, such as diet, treatments, and other accompanying health conditions, should be calculated. Furthermore, it is necessary to understand that depression is a highly heterogeneous disorder, influenced by genetic, environmental, and neurobiological factors. No single biomarker is likely to suffice, but BDNF-regulating miRNAs could be a key component.

In combination with other biomarkers, clinical data, and neuroimaging findings, these miRNAs could enhance diagnostic accuracy and help stratify patients based on biological subtypes. Additionally, due to its central role in neural plasticity and synaptic regulation, BDNF signalling, including the miRNAs that regulate it, is implicated in other neurological disorders, such as Alzheimer's disease and Parkinson's disease. But this overlap does not diminish its potential role in the diagnosis of depression if analysed within an appropriate clinical context and integrated with a comprehensive multimodal assessment.

### 5.2 In treatment

MiRNAs are promising drug targets due to several advantages: (1) a single miRNA can regulate hundreds of genes simultaneously, a capability well-suited to complex diseases that involve multiple pathways; (2) their small size (~22 nucleotides) makes them easy to design as drugs; (3) recent advances in delivery systems allow efficient *in vivo* administration; (4) As endogenous molecules, miRNAs have high biocompatibility and are less likely to provoke immune responses. (Sun et al., 2018).

Basically, two miRNA-based therapeutic approaches have been developed: (1) miRNA mimics to replicate and restore miRNA expression patterns; and (2) miRNA inhibitors (antagomirs or antimirs) to degrade or block the function of endogenous miRNAs. While preclinical and early clinical trials of miRNA therapies have shown promise for various diseases (Seyhan, 2024), none have yet reached Phase III clinical trials.

Currently, the most significant challenge related to miRNA-based therapies is their multi-target nature. Although this broad regulatory capacity makes miRNAs promising therapeutic candidates for complex diseases involving multiple genes and mechanisms, as previously mentioned, it also increases the risk of off-target effects and unpredictable outcomes.

Recent advances in bioinformatics offer powerful tools to address the challenge posed by the multi-target nature of miRNAs. A key advantage is the ability to comprehensively predict and analyse miRNA–mRNA interactions, which facilitates the identification of therapeutically relevant targets while filtering out those associated with undesirable effects. This paves the way for the development of more precise miRNA-based therapies while minimising potential side effects.

A real-world example of this approach is its application in Ewing sarcoma, where researchers aim to identify candidate microRNAs with therapeutic potential while minimising their impact on essential housekeeping

genes. They tackled the challenge by integrating multi-omics data with a developed algorithm to select the most suitable miRNAs. Their approach included assessing the "network potential" of a tumour by analysing collective transcriptomic and protein-protein interactions, ranking relevant target mRNAs, and identifying optimal miRNAs or miRNA combinations to suppress those targets (Weaver et al., 2021).

Other challenges in miRNA therapy include enhancing miRNA stability and ensuring its effective delivery to target cells. Additionally, concerns about the long-term impacts of anti-miRNA treatments need to be addressed. This includes understanding their pharmacokinetics, such as distribution, clearance, and stability, as well as their pharmacodynamics, including cytotoxicity, mechanism of action, and cell-type specificity. Ongoing research aims to unlock the potential of miRNA therapeutics and tackle the challenges associated with their clinical use.

For depression, research on miRNAs remains at the preclinical stage. Given that BDNF is the primary target of current therapies, it can be proposed that this molecule may also serve as a promising target for miRNA-based treatments. As discussed earlier, in animal models of depression, treatment with anti-miRNA, si-miRNA, or miRNA mimics can modulate miRNA expression, upregulate BDNF levels, and provide protective effects against depression-like behaviours.

Specifically, anti-miR-132/miR-132 inhibitors and miR-124 antagomir might reverse depression-like behaviours by targeting MECP2/BDNF signalling (for miR-132) (Su et al., 2015; Tong et al., 2021) and GR/BDNF-TrkB signalling (Wang et al., 2017), or CREB1/BDNF signalling (Yang et al., 2020b) for miR-124. These two miRNAs have been repeatedly studied across various studies with consistent results, suggesting their potential in treating depression. Although these miRNAs have also been explored for therapeutic applications in other brain disorders, their broad involvement does not diminish their therapeutic potential in depression, provided that critical parameters such as dosage, timing, and tissue-specific delivery are precisely controlled to ensure disease-relevant specificity.

Moreover, advancing these miRNAs toward clinical application requires further research, not only to overcome the general challenges inherent to miRNA-based therapies, but also to evaluate their effects on other key pathophysiological mechanisms of depression. Based on the well-established pathogenic pathways of depression identified to date, it is particularly important to investigate how such therapies modulate biological systems, including the HPA axis, inflammatory responses, and monoaminergic signalling.

## 6.0 CONCLUSION

In summary, BDNF is central to depression pathogenesis and remains the principal target of existing treatments. Extensive research also shows that miRNAs hold significant promise for the diagnosis, prognosis, and treatment of depression. We reviewed and analysed 16 miRNAs that target BDNF in depression, highlighting that miR-124, miR-132, and miR-221 could serve as potential biomarkers for diagnosing depression. Furthermore, utilising miR-124 and miR-132 inhibitors or mimics to upregulate BDNF expression may restore BDNF-based synaptic repair, implying their potential in depression treatment. However, substantial hurdles, including off-target effects, long-term safety concerns, and delivery, must be overcome before miRNA therapeutics can enter clinical use.

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