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Review article

Deciphering the role of miRNA-134 in the pathophysiology of depression: A comprehensive review

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ABSTRACT

This study summarizes the significance of microRNA-134 (miRNA-134) in the pathophysiology, diagnosis, and treatment of depression, a disease still under investigation due to its complexity. miRNA-134 is an endogenous short non-coding RNA that can bind to the 3′ untranslated region (3′UTR) of miRNA-134, inhibiting gene translation and showing great potential in the regulation of mood, synaptic plasticity, and neuronal function. This study included 15 articles retrieved from four English-language databases: PubMed, Embase, The Cochrane Library, and Web of Science, and three Chinese literature databases: CNKI, Wanfang, and Chinese Science and Technology Periodical Database (VIP).We evaluated each of the 15 articles using the Critical Appraisal Skills Program (CASP) tool.The standard integrates analyzes of genomic, transcriptomic, neuroimaging, and behavioral data analyses related to miRNA-134 and depression. A multidimensional framework based on standardized criteria was used for quality assessment. The main findings indicate that miRNA-134 significantly affects synaptic plasticity and neurotransmitter regulation, in particular the synthesis and release of serotonin and dopamine. miRNA-134 shows high sensitivity and specificity as a biomarker for the diagnosis of depression and has therapeutic potential for the targeted treatment of depression. miRNA-134 plays a crucial role in the pathogenesis of depression, providing valuable insights for early diagnosis and the development of targeted

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therapeutic strategies. This work highlights the potential of miRNA-134 as a focal point for advancing personalized medicine approaches for depression.

1. Introduction

With the acceleration of modern life, depression has become one of the most serious mental health disorders, leading to disability. According to the World Health Organization (WHO, 2020) [1], approximately 280 million people worldwide suffered from depression in 2019, including 23 million children and adolescents, accounting for 4.6 % of the global population. During the COVID-19 pandemic, the number of people with depression increased by 27.6 % in 2020, placing significant pressure on healthcare systems, economies, and individual well-being. As depression cases rise, so do instances of depression-induced suicide [2].

Typical symptoms of depression include persistent low mood, decreased appetite, lack of pleasure, self-loathing, weight loss, and suicidal tendencies. Despite significant advances in depression research, its etiology remains unclear [3]. Prevention is more crucial than treatment, emphasizing the importance of identifying predictive indicators for early intervention.

miRNAs are endogenously acquired non-coding short-chain RNAs, consisting of 18-24 nt single-strand molecules that regulate gene expression at the translational or transcriptional level. Within the nucleus, genes transcribed by miRNA polymerase II produce pri-miRNAs, which are cleaved by Drosha enzyme into pre-miRNAs with a single stem-loop structure. These pre-miRNAs are transported to the cytoplasm by Exportin 5, where they are further processed by the Dicer enzyme into mature miRNAs. These miRNAs then form a RISC complex with Argonaute proteins, pairing with the 3′-UTR of mRNA to inhibit gene expression [4–9] (see Fig. 1).

miRNA-134, primarily expressed in the brain, plays a key role in neuronal development and synaptic plasticity, both of which are crucial for advanced neural functions like learning and memory. It regulates genes related to synaptic plasticity, such as Limk1 and CREB, thereby influencing brain function [10,11]. Despite progress in depression research, significant gaps remain in understanding its complex pathophysiology.

In depression, miRNA-134 influences gene expression in specific brain regions, affecting synaptic plasticity and neuroplasticity by regulating BDNF, which is crucial in neuroplasticity and depression [12,13]. Abnormal BDNF expression is a key mechanism in depression, and miRNA-134's regulation of this pathway may be crucial in the disease's pathophysiology. Additionally, miRNA-134 affects neuron survival and function by regulating genes like SIRT1 and CREB, which influence mood and behavior, making it a potential target for new antidepressant strategies [14].

However, current research on miRNA-134's role in depression is limited, with most studies focusing on miRNAs in general rather than on miRNA-134 specifically. Most studies rely on animal models and in vitro experiments, with few clinical studies, limiting a comprehensive understanding of miRNA-134 in depression. These gaps underscore the need for further research.

This study aims to fill these gaps by exploring how miRNA-134 regulates synaptic function and neural plasticity through gene expression in specific brain areas. By systematically analyzing existing literature and integrating various research methods, this study seeks to provide new insights into miRNA-134's role in depression. This research could elucidate the pathophysiological basis of depression and support the development of new diagnostic methods and personalized treatment strategies. Additionally, given the elevated expression of miRNA-134 in depressed patients, this study will explore its potential as a diagnostic biomarker and its impact

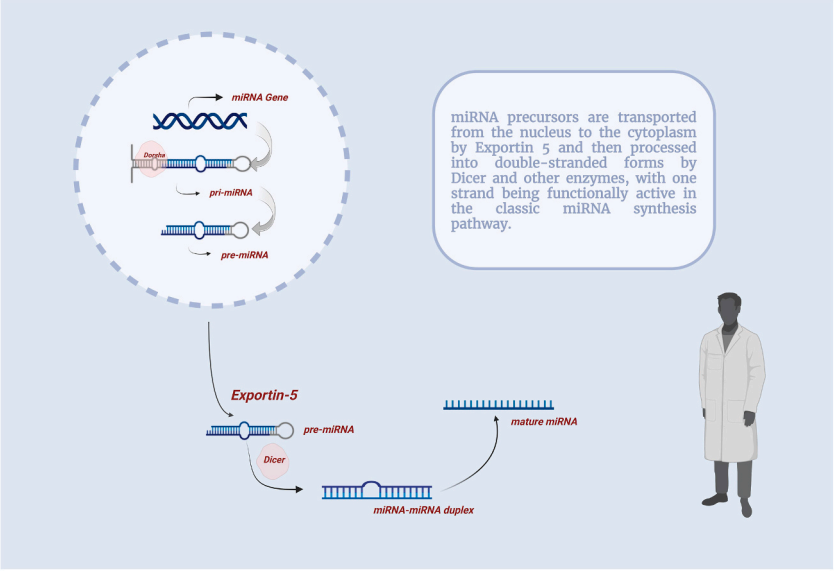

Fig. 1. miRNA Biogenesis and Mechanism of Action Diagram.

on antidepressant efficacy. Focusing on miRNA-134 may address current research shortcomings and promote further advances in depression research, potentially guiding new strategies for personalized treatment and precision medicine.

2. Materials and methods

2.1. Literature search

We searched four English databases: PubMed, Embase, The Cochrane Library, and Web of Science.three Chinese literature databases: CNKI, Wanfang, and Chinese Science and Technology Periodical Database (VIP), The PubMed search terms were as follows: ((((((((((((((((((((((((miRNA-134) OR (microRNA-134)) OR (MiR-134)) OR (microRNA-134, human)) OR (microRNA 134, human)) OR (hsa-mir-134)) OR (miR-134, human)) OR (microRNA-134, rat)) OR (rno-mir-134)) OR (miR-134, rat)) OR (miR-134, mouse)) OR (microRNA-134, mouse)) OR (mmu-mir-134)) AND (Depression)) OR ((Depressive syndrome)) or (depressive syndrome)) or (syndrome, depression)) or (syndrome, depression)) or (depression)) or (disorder, depression)) or (disorder, depression)) or (depression symptoms)) or (depression symptoms)) or (symptoms, depression)) or (mood depression)) or (depression, mood).

Web of Science search formula is as follows: ((((((((((((((((((((((((((ALL=(miRNA-134)) OR ALL=(microRNA-134)) OR ALL=(miR-134)) OR TI=(microRNA-134, human)) OR TI=(microRNA 134, human)) OR TI=(hsa-mir-134)) OR TI=(miR-134, human)) OR TI=(microRNA-134, rat)) OR TI=(rno-mir-134)) OR TI=(miR-134, rat)) OR TI=(miR-134, mouse)) OR TI=(microRNA-134, mouse)) OR TI=(mmu-mir-134)) AND ALL=(Depression)) OR TI=(Depressive Syndrome)) OR TI=(Depressive Syndromes)) OR TI=(Syndrome, Depressive)) OR TI=(Syndromes, Depressive)) OR TI=(Depressive Disorders)) OR TI=(Disorder, Depressive)) OR TI=(Disorders, Depressive)) OR TI=(Depressive Symptoms)) OR TI=(Depressive Symptom)) OR TI=(Symptom, Depressive)) OR TI=(Emotional Depression)) OR TI=(Depression, Emotional)) OR TI=(Yiyuzhangai)) OR TI=(Yiyuzheng).

The search time range is from January 2004 to January 5, 2024(see in Table 1). A total of 52,214 relevant articles were identified, of which 15 were subjected to in-depth analysis (see in Fig. 2). The framework shown in Table 1 outlines the inclusion and exclusion criteria for this study.

2.2. Inclusion and exclusion criteria

Inclusion criteria: experimental studies and observational studies on miRNA-134 and depression were included; studies involving human or animal models were included, especially studies that clearly explored the expression, mechanism and function of miRNA-134 in depression; the pathophysiological changes of miRNA-134 related to depression were reported in the studies, including but not

Table 1
Search strategies for English databases or Chinese databases.

Number	Search terms
#1	miRNA-134 [All fields]
#2	microRNA-134 [All fields]
#3	MiR-134 [All fields]
#4	microRNA-134, human[MESH]
#5	MicroRNA 134, human [MESH]
#6	hsa-mir-134 [MESH]
#7	miR-134, human [MESH]
#8	microRNA-134, rat [MESH]
#9	rno-mir-134 [MESH]
#10	miR-134, rat [MESH]
#11	miR-134, mouse [MESH]
#12	microRNA-134, mouse [MESH]
#13	mmu-mir-134 [MESH]
#14	Depression [All fields]
#15	Depressive Syndrome [MESH]
#16	Depressive Syndromes [MESH]
#17	Syndrome, Depressive [MESH]
#18	Syndromes, Depressive [MESH]
#19	Depressive Disorders [MESH]
#20	Disorder, Depressive [MESH]
#21	Disorders, Depressive [MESH]
#22	Depressive Symptoms[MESH]
#23	Depressive Symptom[MESH]
#24	Symptom, Depressive[MESH]
#25	Emotional Depression[MESH]
#26	Depression, Emotional[MESH]
#27	Yiyuzhangai (Depressive Disorders)
#28	Yiyuzheng (depression)
#29	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#30	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#31	#29 AND #30

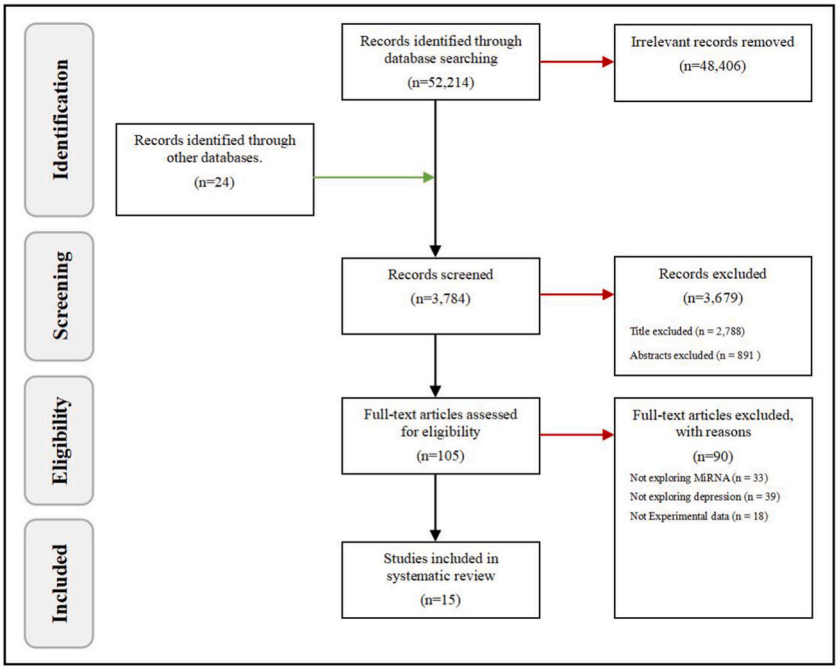

Fig. 2. Flow diagram for the included and excluded articles. *Note*. This figure follows by PRISMA-P format = Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols. Adapted from Moher et al. (2009). Copyright by 2009 Moher et al.

limited to gene expression levels, regulation of neural networks, and the association with clinical manifestations of depression; only literature published in English and Chinese was included.

Exclusion criteria: Studies that did not specifically study miRNA-134 or did not explore its role in depression were excluded; studies with serious missing data or inadequate analysis methods were excluded; reviews, commentary articles, and conference abstracts without systematic data analysis were excluded; studies that did not use depression models or had no relevant population data were excluded, such as studies involving other mental illnesses but not including depression; studies that repeated the content of the existing included literature and had no new data or analysis were excluded.

2.3. Quality assessment methods

Two independent reviewers selected and assessed articles for eligibility and inclusion in the review [15,16]. The quality of the articles was evaluated using a multidimensional framework based on standardized criteria, covering aspects such as study design, participant characteristics, research procedures, and conclusions. The framework comprises four main quality dimensions: validity,

Table 2
Record of citation score.

	Validate	Suitability	Therapeutic	Consistency	Overall score
Scientific Research					
Wang,G et al. [20]	4	4	4	4	excellent(4.0)
Gao,J et al. [24]	4	4	3	3	Moderate(3.5)
Fiore,R et al. [25]	4	3	3	4	Moderate(3.5)
Lou,J et al. [26]	4	4	4	4	excellent(4.0)
Jiang,T et al. [27]	4	4	4	4	excellent(4.0)
Schratt,G.M et al. [28]	5	4	4	4	excellent(4.25)
Yu H et al. [29]	4	5	4	4	excellent(4.25)
Zhao youying et al. [33]	3	3	2	3	poor (2.75)
Rong han et al. [34]	4	5	3	3	good(3.75)
RCT					
Zhang,H.P et al. [21]	3	4	4	4	good(3.75)
Wang,G; Liu,Y et al. [22]	4	3	4	4	good(3.75)
Fan,C et al. [23]	4	5	4	4	excellent(4.25)
Zhu xiuzhi et al. [30]	4	4	4	4	excellent(4.0)
Huang fei et al. [31]	4	5	3	3	good(3.75)
Li hong et al. [32]	3	5	4	3	Moderate(3.75)

practicality, efficacy, and consistency [17]. Each article was assessed using the Critical Appraisal Skills Program Qualitative Checklist (CASP) [18], approved by the Cochrane Qualitative Research Methods Group, focusing on validity, applicability, treatment, and consistency. Articles were scored, with scores ≤3 rated as poor, 3–3.5 as good, 3.5–4 as fair, and >4 as excellent. Discrepancies were resolved by Y.K.W. and Y.L.H., who calibrated the quality scores of a sample of 15 studies (see Table 2). The PICO(S) design was used to extract RCT data from these studies (see Table 3) [19], and a summary table was created to ensure the quality and reliability of the selected articles (see Table 4) [20–34].

3. Results

All 15 included studies used a chronic unpredictable mild stress (CUMS) model in mice (see Fig. 3) to simulate depression-like symptoms. Mice in the CUMS model were injected with miRNA-134 (see Fig. 4A), and the experimental process is depicted in Fig. 4B. Subgroup analysis categorized the studies into synaptic plasticity research (see Table 5), biological examination (see Table 6), and drug intervention experiments (see Table 7) to investigate miRNA-134's role in depression onset, diagnosis, and treatment.

3.1. miRNA-134 and the pathogenesis of depression

Depression is a complex disorder with multiple molecular and cellular mechanisms. miRNA-134, known for its role in synaptic and neural plasticity, has garnered significant research attention [35]. The 15 included articles all conducted studies on synaptic plasticity (see Table 5) and biological examinations (see Table 6), and analyzed in detail the specific mechanisms of miRNA-134 in depression. The following will review the effects on synaptic function, neuronal connectivity, signaling pathways and ion channel regulation, as well as its application prospects as a potential biomarker and therapeutic target.

As a brain-specific microRNA, miRNA-134 regulates genes involved in synaptic connectivity and signaling, affecting dendritic spine morphology and synaptic strength, which are essential for learning and memory [36]. Synaptic plasticity is often reduced in depression [37], leading to impaired neural connectivity and decreased function in emotion-regulating brain regions such as the hippocampus and prefrontal cortex [38–43]. In hippocampal neurons, miRNA-134 reduces dendritic spine volume by inhibiting Limk1 protein translation [23,26,28], impacting synaptic function and neural plasticity. This regulatory role is crucial for understanding depression's pathophysiology [44,45].

Clinical biochemical indicators, such as plasma and proteomic analysis, are also critical in detecting mood disorders like depression [46–49]. miRNA-134 influences neural development and neurotransmitter regulation, particularly through the BDNF and CREB pathways [20,24]. BDNF, a key regulator of synaptic plasticity, affects dendritic spine morphology and synaptic strength, activates the TrkB receptor [50], and promotes local protein synthesis via the mTOR pathway [51,52]. miRNA-134 inhibits Limk1 translation, interfering with CREB's function [53–56], thus affecting the brain's reward circuitry and influencing emotion and behavior [57–59].

Studies on the anterior cingulate cortex (ACC) show that miRNA-134 expression is closely linked to abnormal ACC connectivity [22]. The ACC plays a key role in emotion regulation, cognitive function, and stress response [60,61]. Imaging transcriptomics studies indicate that miRNA-134 may regulate ACC-related dysfunction, directly affecting depression symptoms [62,63]. By modulating neuronal connectivity and synchronization in the ACC, miRNA-134 may exacerbate depressive symptoms, making it a potential

Table 3
Principal characteristics of all included RCTs in this review.

References	Participant	Design	sample size (T/Z)	Outcomes measure	Treatment group		control group
					Intervention	Procedure time	
Zhang,H.P et al. [21]	Homo sapiens (200) AND 16 CUMS rats	RCT	100/100 16 rats	miRNA-134 expression in plasma; HIP; PFC; OB	CUMS AND MDD	8 weeks	HC
Wang,G; Liu,Y et al. [22]	75 CUMS rats	RCT	15/15/15/ 15/15	ACC; PLS, miRNA-134	CUMS AND GFP AND AAV-miR-134-KD AND AAV-miR-134-OE	5 weeks	HC
Fan,C et al. [23]	48 male Wistar rats	RCT	12/12/12/ 12	G-Eg1+CUMS; miRNA-134	CUMS AND CUMS + G-Eg1	5 weeks	HC
Zhu xiuzhi et al. [30]	male Wistar rats	RCT	N/A	Golgi staining; Western Blot	CUMS AND G-Rg1+CUMS AND Nac0.9 %+CUMS	6weeks	HC
Huang fei et al. [31]	mice	RCT	8/8/8	Detection of miRNA levels	CUMS AND CUMS + sertraline (10 mg/kg)	5 weeks	HC
Li hong et al. [32]	Homo sapiens (124)	RCT	62/62	SR-miRNA; SNAS; SDS	amisulpride + paroxetine	3 months	paroxetine

miR-134 expression in plasma; HIP,hippocampus; PFC,prefrontal cortex; OB,olfactory bulb; CUMS, chronic unpredictable mild stress; HC,healthy control; MDD,Major depressive disorder; ACC,anterior cingulate cortex; PLS,partial least squares.
GFP,AAV-green fluorescent protein; AAV-miR-134-KD,AAV-miR-134-knockdown; AAV-miR-134-OE.
AAV-miR-134-overexpression; G-Eg1,ginsenosides; PDE,prenatal dexamethasone exposure; NPCs: Neural Progenitor Cells; GR: Glucocorticoid Receptor; SR,synapse-related miRNAs; SDS,self-rating Depression scale; SNAS, cale for the Assessment of Negative Symptoms; PCR,Real-timePCR,QRT-PCR.

Table 4
Record of citation analyses and full texts reviewed.

References	Types	Nation	Method	Study aims	Participants	Analysis	Results
Wang,G et al. [20]	Scientific Research	China	CUMS mouse model, electron microscopy, electrophysiological recording and other techniques.	To explore the antidepressant mechanism of ginsenoside Rb1 in a chronic stress-induced depression model.	16 CUMS rats	To analyze how ginsenoside Rb1 regulates hippocampal synaptic plasticity through the miRNA-134-mediated BDNF signaling pathway.	Rb1 regulates hippocampal synaptic plasticity through the miRNA-134-mediated BDNF signaling pathway.
Zhang,H.P et al. [21]	RCT	China	PCR measurement of plasma miR-134 levels in patients with depression and validation in CUMS rat model.	Investigating the potential of plasma miR-134 as a biomarker for the diagnosis of major depressive disorder (MDD).	100(MDD)/100 (HC) and 16 CUMS rats	Analyze how plasma miRNA-134 is downregulated in MDD, regulating synaptic plasticity and the CREB-BDNF pathway.	Plasma miR-134 is significantly down-regulated in patients with depression and can effectively distinguish depression from other mental illnesses.
Wang,G; Liu,Y et al. [22]	RCT	China	CUMS mouse model, genetic manipulation, protein analysis technology.	To explore the effects of miR-134-5p knockout on hippocampal dendritic ridge morphology and mitophagy in CUMS mice.	75 CUMS rats	Analyze how knocking out miR-134-5p promotes AMPK-mediated mitophagy.	Knocking out miR-134-5p significantly improved depressive behavior, promoted mitophagy, and restored hippocampal dendritic ridge density in CUMS mice.
Fan,C et al. [23]	RCT	China	CUMS model, protein analysis technology.	To explore the role of miR-134 in chronic stress-induced depression and the antidepressant potential of Rg1.	48 male Wistar rats	Analyzing CUMS rats, how miR-134 affects the brain and how Rg1 fights depression.	CUMS significantly increases the expression of miR-134 in the ventromedial vmPFC, and ginsenoside Rg1 can protect nerves and resist depression.
Gao,J et al. [24]	Scientific Research	United States	Behavioral tests, LTP measurements, qPCR and Western blot.	To investigate the role of SIRT1 in synaptic plasticity and memory formation through miR-134-mediated mechanisms.	SIRT1D mice	To analyze how SIRT1-deficient mice inhibit miR-134 to regulate the expression of CREB and BDNF.	SIRT1 upregulates the expression of CREB and BDNF by inhibiting miR-134.
Fiore,R et al. [25]	Scientific Research	Germany	qPCR, confocal microscopy and immunofluorescence staining.	To explore how miR-134 regulates gene expression in synaptic plasticity and synaptic downregulation.	Mature hippocampal neurons	Analyze target genes such as Plk2 and Pum2 to affect synaptic density and function.	Downregulation of Pum2 is limited to the synaptic-dendritic compartment, and the Pum2/Plk2 interaction is functionally involved in the downregulation of chronic activity by the GluA2 surface receptor.
Lou,J et al. [26]	Scientific Research	China and United States	Analysis of blood genomics, neuroimaging, transcriptomics and behavioral data.	How miRNA-134 affects the pathophysiology of depression by regulating gene expression and brain functional connectivity.	56(MDD)/51 (HC) 57(MDD)/52 (HC)	Analysis of miRNA-134 expression levels, brain imaging data, gene function and mediating effects.	Downregulation of miRNA-134 is closely associated with changes in synaptic plasticity and functional connectivity of brain regions in patients with depression.
Jiang,T et al. [27]	Scientific Research	China	PDE rats and their offspring were subjected to behavioral tests, molecular and tissue analyses, and combined with in vitro experiments.	To explore how gestational dexamethasone exposure regulates miR-134-5p and affects the	Rats exposed to gestational dexamethasone (PDE) and their offspring	Analysis of miR-134 regulation of GR/SIRT1 signaling pathway and inhibition of SOX2, leading to neural	PDE miR-134-5p through the GR/SIRT1 pathway, inhibits SOX2, leads to neural precursor cell proliferation disorder, and increases the susceptibility of offspring to depression.

(*continued on next page*)

Table 4 (*continued*)

References	Types	Nation	Method	Study aims	Participants	Analysis	Results
				susceptibility of offspring to depression.		precursor cell proliferation disorder	
Schratt,G.M et al. [28]	Scientific Research	United States	Electrophoretic mobility shift assay, fluorescent labeling, luciferase reporter gene assay, confocal microscopy and Western blot.	To explore how miR-134 regulates the translation of Limk1 mRNA and affects the size of neuronal dendritic spines and synaptic plasticity.	Primary cerebral cortex and hippocampal neurons	To analyze the interaction between miR-134 and Limk1 mRNA, the mechanism of translation inhibition and its regulatory effect on the structure of neuronal dendritic spines and synaptic plasticity.	miR-134 inhibits the translation of Limk1 mRNA by binding to its 3′ UTR, resulting in the reduction of dendritic spines and affecting synaptic plasticity.
Yu H et al. [29]	Scientific Research	China	Behavioral testing, real-time quantitative PCR, Western blot and electron microscopy, etc.	How Rg1 regulates the miR-134-CREB-BDNF signaling pathway.	48 Wistar male rats	Analysis of the regulation of ginsenoside Rg1 on the miR-134-CREB-BDNF signaling pathway.	Rg1 significantly improved the depressive-like behavior of CUMS rats and protected the synaptic structure and function of rat amygdala neurons by regulating the miR-134-CREB-BDNF signaling pathway.
Zhu xiuzhi et al. [30]	RCT	China	Golgi staining, transmission electron microscopy, Western Blot, immunofluorescence, RT-PCR and qPCR	To study the role of miRNA-134-Limk1-Cofilin signaling pathway in the pathogenesis of depression.	Male Wistar rats	To analyze the effects of CUMS on depressive-like behavior and neural structural plasticity in rats.	Ginsenosides reduce miRNA-134 expression and improve depressive behavior.
Huang fei et al. [31]	RCT	China	Body weight measurement, sugar water preference, and PCR detection of mouse hippocampal miRNA levels.	To explore how sertraline affects the levels of miRNA in the hippocampus of depression model mice.	24 mice	Analyze the changes in the levels of miRNA in the hippocampus of mice and evaluate the antidepressant effect of sertraline.	Sertraline can reverse the abnormal levels of miRNA in the hippocampus of depressed mice and exert an antidepressant effect by regulating the levels of miRNA in the hippocampus.
Li hong et al. [32]	RCT	China	Synapse-related miRNAs expression, SANS score, SDS score and adverse reaction incidence.	To explore the effect of amisulpride combined with paroxetine in the treatment of major depression and its effect on the expression of synapse-related miRNAs.	124 patients with major depression.	Detection of synapse-related miRNAs expression and evaluation of depression and negative symptoms.	Amisulpride combined with paroxetine can effectively improve depression and negative symptoms in patients with major depression.
Zhao youying et al. [33]	Scientific Research	China	Detect the expression levels of vitamin D, acylated ghrelin, and miR-134 in peripheral blood.	Explore the relationship between vitamin D, acylated ghrelin, and miR-134 and depression.	176 Homo sapeins	Analyze the mechanism of how vitamin D, acylated ghrelin, and miR-134 act in depression.	The expression levels of 25-(OH) D3, acylated ghrelin, and miR-134 in patients with depression are negatively correlated with the degree of depression.
Rong han et al. [34]	Scientific Research	China	Depression model, detection of plasma miRNA expression.	Study the relationship between plasma miR-34a, miR-134, and miR-143 expression levels and depression.	40 male Sprague-Dawley rats.	Analyze mouse plasma miRNA expression data to explore how miRNA is related to depressive behavior.	The expression of miR-134 is reduced in depressed mice

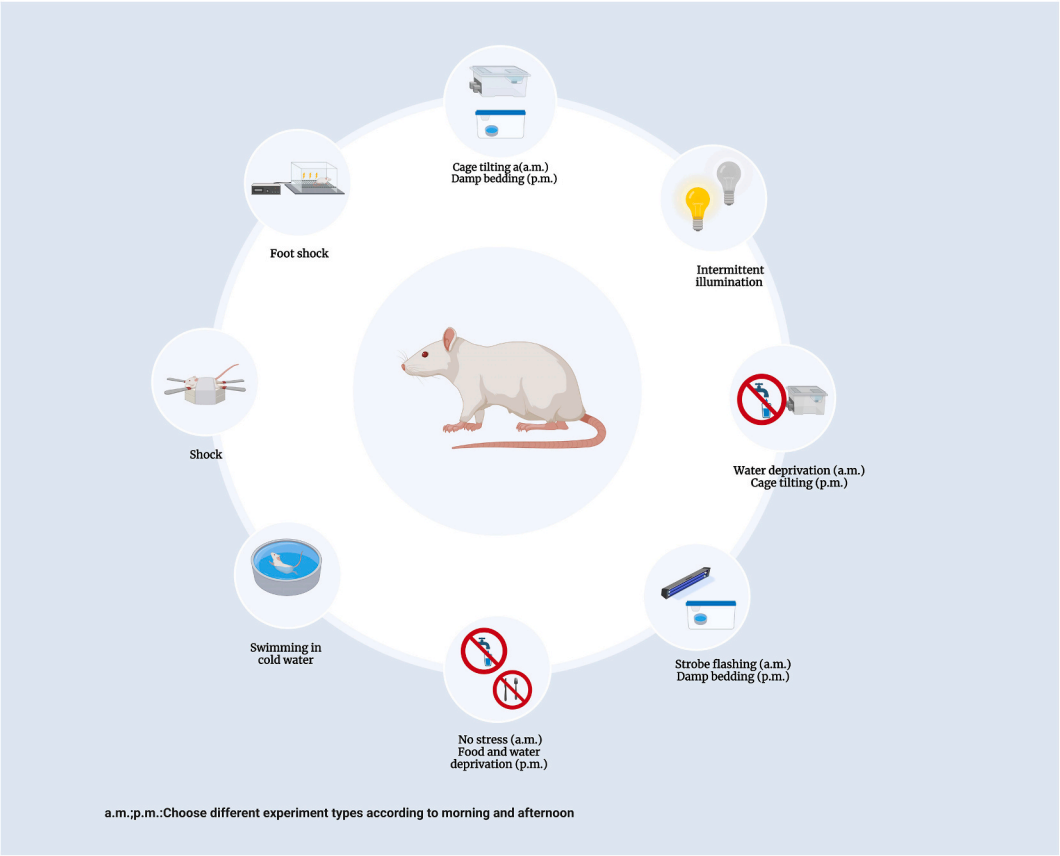

Fig. 3. Mouse-specific locus miRNA-134 injection.

biomarker for depression and a target for personalized treatment [64].

Regarding ion channel regulation and synaptic transmission, miRNA-134 affects neuronal excitability and balance through various mechanisms. It regulates sodium-potassium ion channels and ion pumps, impacting membrane potential and action potential generation [65–67]. Gene ontology (GO) analysis reveals that miRNA-134 targets genes involved in ion transport and synaptic transmission, particularly G protein-coupled receptors (GPCRs), which play a significant role in neuronal signaling and synaptic plasticity [68–75]. miRNA-134's structural differences result in functional variability; for example, miRNA-134-5p significantly affects synaptic morphology in hippocampal neurons [76–78], and its knockdown can ameliorate depressive-like behavior in the CUMS mouse model [79–81]. By influencing the AMPK pathway, miRNA-134-5p regulates mitochondrial autophagy, protecting neuronal cells. The potential of miRNA-134 in diagnosing, monitoring, and treating depression underscores its importance in personalized medicine.

3.2. Research progress of miRNA-134 targeted drugs

The 15 included papers found that the combination of antidepressant drugs (ginsenosides, sertraline, etc.) [20,29,29,32,34](see in Table 7) and miRNA-134 through drug intervention experiments revealed differences in patients' responses to drugs and promoted personalized treatment plans.

Experimental results confirmed that microRNA has a therapeutic effect on mental illness [82–86]. miRNA-134 has attracted attention as a target for the treatment of depression [87–89]. miRNA-134 is widely expressed in the brain, especially in the regulation of mood and cognitive function [90–92], and abnormal expression is closely related to depressive symptoms, especially in the hippocampus and prefrontal cortex [93,94].

Drug development targeting miRNA-134 has mainly focused on two strategies: the use of small molecule inhibitors such as dexamethasone to reduce miRNA-134 levels [29], and the synthesis of anti-miRNA molecules (antimiRs) to disrupt the binding of miRNA-134 to its target RNA. These approaches aim to restore the imbalance in gene regulatory networks caused by aberrant expression of miRNA-134, particularly genes that regulate neuronal plasticity and cell survival, such as brain-derived neurotrophic factor (BDNF) [20,29,30,95,96] and serotonin reuptake inhibitors (SSRIs) such as sertraline and fluoxetine [31,34]. Other microRNAs, such as miRNA-146a/b-5, miRNA-335, miRNA-139-5p, and miRNA-124, also regulate depression [97–100]. Although these treatments have shown promise in laboratory and animal studies, clinical application remains challenging, including effective drug delivery to the brain, long-term safety, and potential side effects [101].

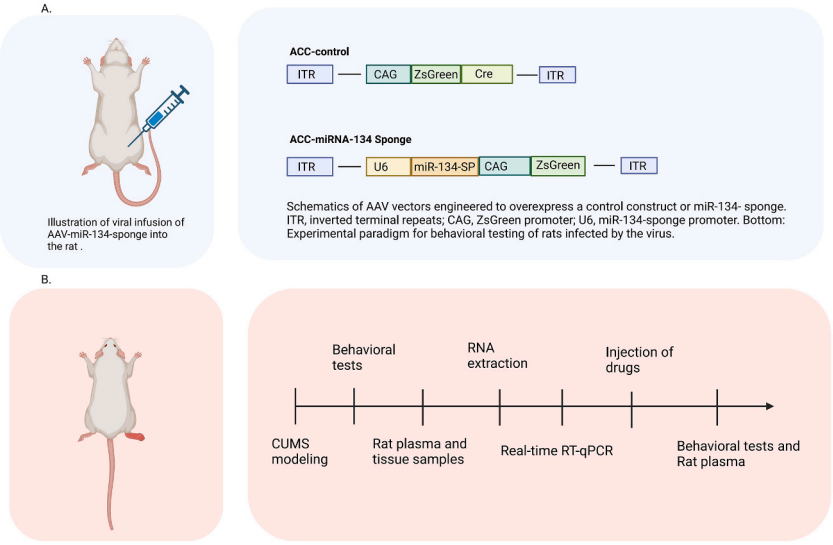

Fig. 4. Chronic unpredictable mild stress (CUMS) in mice.

Table 5
Synaptic function analysis table.

Method	References	Types	Results
Synaptic Plasticity	Wang,G et al. [20]	Scientific Research	miRNA-134 affects synaptic plasticity of BDNF in the hippocampus by regulating BDNF expression.
	Zhang,H.P et al. [21]	RCT	In the CUMS rat model, miR-134 levels were altered in the peripheral and central nervous systems.
	Wang,G; Liu,Y et al. [22]	RCT	Knockdown of miR-134-5p improved the morphology and number of dendritic spines in hippocampal neurons of CUMS mice.
	Fan,C et al. [23]	RCT	miR-134 downregulates the expression and phosphorylation of synaptic proteins Limk1 and cofilin, resulting in a decrease in dendritic spines and synaptic density.
	Gao,J et al. [24]	Scientific Research	SIRT1 limits miR-134 expression, promotes CREB and BDNF expression, and enhances and maintains dendritic spine formation.
	Fiore,R et al. [25]	Scientific Research	Plk2 and Pum2 genes, promote synapse elimination and synaptic downregulation, ultimately reducing synaptic density and AMPA receptor expression.
	Lou,J et al. [26]	Scientific Research	miRNA-134 affects the structure and function of synapses by downregulating the expression of Limk1.
	Jiang,T et al. [27]	Scientific Research	PDE leads to a significant reduction in neuronal structural complexity and dendritic spine density.
	Schratt,G.M et al. [28]	Scientific Research	Overexpression of miR-134 reduced the volume and width of dendritic spines, while 2′-O-Me-134, which inhibits miR-134, increased the volume and width of dendritic spines.
	Yu H et al. [29]	Scientific Research	CUMS treatment resulted in a significant decrease in synaptic density in rat BLA neurons.
	Zhu xiuzhi et al. [30]	RCT	Rats in the CUMS group showed depressive-like behaviors, decreased synapse numbers, and thinning of pre- and post-synaptic active zones.
	Li hong et al. [32]	RCT	Amisulpride combined with paroxetine improves the expression of synapse-related miRNAs in major depressive disorder.
	Zhao youying et al. [33]	Scientific Research	Peripheral blood vitamin D, acylated ghrelin and microRNA-134 expression levels are associated with synapses.

miRNA-134 interacts with existing antidepressants such as SSRIs, altering its expression and affecting downstream gene regulation [102,103]. This interaction may explain the variable response of patients to antidepressants and suggests that miRNA-134-targeted drugs could be combined with traditional antidepressants to improve efficacy and reduce side effects [31,34].

4. Discussion

The association of miRNA-134 downregulation with the BDNF (brain-derived neurotrophic factor) and CREB (CAMP response element binding protein) signaling pathways makes it specific in the mechanism of depression [104]. Inhibition of BDNF and CREB translation through the interaction of the 3′ untranslated region (3′UTR) of BDNF and CREB microRNA promotes neuronal survival and adaptation. Synaptic plasticity is key to the adaptation of neural networks, and the downregulation of miRNA-134 may enhance the activity of the BDNF-CREB signaling pathway with specific effects on synaptic plasticity. It affects synapse formation and function.

Table 6
Biological examination Subgroup Analysis.

Method	References	Types	Results
protein	Wang,G et al. [20]	Scientific Research	Ginsenoside Rb1 increased the expression of TrkB, AKT, ERK1/2, GSK-3b, b-catenin and CREB downstream proteins.
	Wang,G; Liu,Y et al. [22]	RCT	The expression of proteins related to autophagy and mitochondrial function was different between depression patients and healthy groups.
	Fan,C et al. [23]	RCT	The expression level of Limk1 protein and the level of phosphorylated cofilin in the vmPFC of CUMS rats were significantly decreased.
	Gao,J et al. [24]	Scientific Research	CREB protein levels are significantly reduced in the hippocampus of SIRT1D mice.
	Fiore,R et al. [25]	Scientific Research	Pentylenetetrazol (Ptx) significantly upregulated the expression of miR-134 in neuronal networks
	Jiang,T et al. [27]	Scientific Research	PDE upregulates GR and downregulates SIRT1 expression, causing neural precursor cell proliferation disorders and increasing the susceptibility of offspring to depression.
	Schratt,G.M et al. [28]	Scientific Research	Overexpression of miR-134 leads to a significant decrease in endogenous Limk1 protein levels.
	Yu H et al. [29]	Scientific Research	Ginsenoside Rg1 improves molecular abnormalities in CUMS rats by upregulating the expression of BDNF and phosphorylated CREB
	Zhu xiuzhi et al. [30]	RCT	The expression of Limk1, p-Limk1, Cofilin, p-Cofilin and Spinophilin proteins in the prefrontal cortex of rats in the CUMS group was decreased.
plasma	Zhang,H.P et al. [21]	RCT	Plasma miRNA-134 expression is downregulated in MDD patients.
	Lou,J et al. [26]	Scientific Research	The expression level of exosomal miRNA-134 in the plasma of patients with depression was significantly lower than that in the healthy control group.
	Li hong et al. [32]	RCT	The expression level of plasma miR-134 in the observation group after treatment was lower than that in the control group.
	Zhao youying et al. [33]	Scientific Research	The expression levels of plasma 25-(OH)D3, acylated ghrelin and miRNA-134 in patients with depression were lower than those in healthy subjects.
	Rong han et al. [34]	Scientific Research	The expression level of miR-134 in plasma is associated with depressive behavior.

Table 7
Pharmacological intervention experiment.

Method	References	Types	Results
Ginsenosides	Wang,G et al. [20]	Scientific Research	Ginsenoside Rb1 reduces the expression of miRNA-134 in CUMS mice, and overexpression of miRNA-134 reduces the positive effects of Rb1 on dendritic spine density and synapse-related proteins in CUMS mice.
	Fan,C et al. [23]	RCT	Ginsenoside Rg1 can protect nerves and fight depression.
	Yu H et al. [29]	Scientific Research	Ginsenoside Rg1 relieves the inhibitory effect of miR-134 on CREB and BDNF by downregulating miR-134 expression.
	Zhu xiuzhi et al. [30]	RCT	In the ginsenoside pretreatment group, the expression of miRNA-134 was decreased, and the expression of Limk1, p-Limk1, Cofilin, p-Cofilin and BDNF proteins was increased.
Sertraline	Huang fei et al. [31]	RCT	Sertraline exerts antidepressant effects by regulating the expression level of miRNA-134 in the hippocampus.
Amisulpride AND Paroxetine	Li hong et al. [32]	RCT	Amisulpride combined with paroxetine treatment can improve patients' depressive symptoms.

Thus, providing biomarkers for the diagnosis and treatment of depression.

In the diagnosis of depression, miRNA-134 combined with synaptic plasticity test, molecular biology experiments, gene manipulation experiments, and pharmacological intervention experiments in depression patients provide target diagnostic treatment for diagnosing depression. miRNA-134 cannot predict depression in a single patient or separate it from other psychiatric disorders very clearly due to the different concentrations of miRNA-134 in human skin tissues, cerebrospinal fluid, and blood plasma. Future studies need to determine cutoff values for plasma miRNA-134 levels that can be used to separate depression from other psychiatric disorders to improve accuracy.miRNA-134 is also associated with several other signaling pathways. For example, miRNA-134 affects neuronal survival and function by regulating the expression of SIRT1 and CREB; it participates in the regulation of synaptic structural remodeling and functional transmission by regulating the MAPK/ERK and PI3K/AKT pathways. Abnormalities in these pathways may lead to the onset and development of depression.

In a recent study report, Roy et al. [105]demonstrated that miRNA-128-3p expression was enhanced in the amygdala of depressed patients, resulting in decreased expression of genes associated with the Wnt pathway, Wnt5b, LEF1, and DVL1. Wang et al. [106]found that miRNA-124-3p was significantly downregulated in depressed patients, and this downregulation eliminated its effect on the expression of DNA damage inducible transcript 4 protein (DDIT4) and SP1, and suppressed the mTOR signaling pathway. Disruption of these pathways leads to neurodevelopmental abnormalities associated with neuropsychiatric disorders. In this study, we explored the role of only one miRNA in the pathophysiology, diagnosis and treatment of depression, and considering the heterogeneity and complexity of depression, a group of microRNAs can be selected as biomarkers for the diagnosis of depression in future studies, which

can significantly improve the accuracy of diagnosis.

This study has limitations, mainly reflected in the small sample size. Only 15 papers were included, most of which focus on animal experiments, raising concerns about whether the findings can be directly applied to human clinical treatment. Additionlly, the limited sample size increases the risk of bias and restricts a comprehensive understanding of miRNA-134's function. The heterogeneity of research methods may also affect the generalizability of the results. Furthermore, there is a lack of model studies targeting different stages of depression, which hinders the development of more precise and personalized treatment plans. Addressing these issues is essential for enhancing the robustness and applicability of future research.

5. Conclusion

In conclusion, miRNA-134 is regulated at the molecular level of depression by mediating certain factors and information pathways that are key to depression to achieve a reduction in depressive states and behaviors. On the one hand, miRNA-134 also regulates several target genes, such as Limk1, Pumilio-2, Plk2, etc. through the regulation of The downstream targets of miRNA-134 are regulated to affect intracellular signaling and function. On the other hand, in combination with BDNF in the hippocampus, activation of MAPK/ERK and PI3K/AKT signaling pathways, which are involved in the regulation of synaptic structural remodeling and functional transmission, modulates depression, of which miRNA-134-5p is an important biomarker for the diagnosis of depression. Yin et al. [107]found that miRNA-137 rs1198588 and rs2660304 polymorphisms were associated with the risk of schizophrenia, and the association of carrying these polymorphisms was more significant in females, providing a precise basis for diagnosis and treatment.

In the future, researchers need to conduct further investigations to identify the specific sequence of miRNA-134-5P that may play a role in subsequent gene regulation, as well as explore other gene clusters and homologous structures in miRNA-134 associated with depression. There are large individual differences in the clinical symptoms and severity of depression [108–110]. Some studies have shown that sex hormones, which differe between male and female, may affect neurotransmitter and modulatory systems, leading to varying clinical symptoms [111–114]. A better understanding of mi RNA-134's mechanism of action could lead to new treatment strategies that improve the prognosis of patients with depression. In conclusion, research on miRNA-134 offers a promising direction for future personalized medicine and is expected to greatly enhance the diagnosis and treatment of depression.

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CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] World Health Organization. COVID-19 Weekly Epidemiological Update.[cited January 02, 2024]. Available from:https://www.who.int/publications/m/item/weeklyepidemiological-update-on-covid-19-$-$17-august-2023.

[2] Y. Dwivedi, MicroRNAs in depression and suicide: recent insights and future perspectives, J. Affect. Disord. 240 (2018) 146–154, https://doi.org/10.1016/j.jad.2018.07.075 [PMID: 30071418.

[3] M. Teymouri, et al., Investigating the mediating role of depression and anxiety in the relationship between stress management and mental health in cardiovascular patients, Health Nexus 1 (2023) 82–90.

[4] G.M. Rice, V. Shivashankar, E.J. Ma, J.L. Baryza, R. Nutiu, Functional atlas of primary miRNA maturation by the microprocessor, Mol Cell 80 (2020) 892–902, https://doi.org/10.1016/j.molcel.2020.10.028 [PMID: 3188727.

[5] J. Jodder, Regulation of pri-MIRNA processing: mechanistic insights into the miRNA homeostasis in plant, Plant Cell Rep. 40 (2021) 783–798, https://doi.org/10.1007/s00299-020-02660-7. PMID: 33454802.

[6] X. Fu, W. Zhu, L. Cai, B. Liao, L. Peng, Y. Chen, J. Yang, Improved pre-miRNAs identification through mutual information of pre-miRNA sequences and structures, Front. Genet. 10 (2019) 119, https://doi.org/10.3389/fgene.2019.00119] [PMID: 30858864.

[7] A.E. Pasquinelli, MicroRNAs and their targets: recognition, regulation and an emerging reciprocal relationship, Nat. Rev. Genet. 13 (2012) 271–282, https://doi.org/10.1038/nrg3162 [PMID: 22411466.

[8] E.C. Lai, Micro RNAs are complementary to 3' UTR sequence motifs that mediate negative post-transcriptional regulation, Nat. Genet. 30 (2002) 363–364, https://doi.org/10.1038/ng865] [PMID: 11896390.

[9] A.P. Ferragut Cardoso, M. Banerjee, A.N. Nail, A. Lykoudi, J.C. States, miRNA dysregulation is an emerging modulator of genomic instability, Semin. Cancer Biol. 76 (2021) 120–131, https://doi.org/10.1016/j.semcancer.2021.05.004] [PMID: 33979676.

[10] M. Ahmadimanesh, L. Etemad, D. Morshedi Rad, M.H. Ghahremani, A.H. Mohammadpour, R. Jafarzadeh Esfehani, P. Jowsey, F. Behdani, S.A. Moallem, M. R. Abbaszadegan, Effect of citalopram and sertraline on the expression of miRNA- 124, 132, and 16 and their protein targets in patients with depression, Iran J Basic Med Sci 26 (2023) 820–829, https://doi.org/10.22038/IJBMS.2023.66496.14595 [PMID: 37396946.

[11] M. Kasaiyan, The role of miRNA134 in pathogenesis and treatment of intractable epilepsy: a review article, Nucleosides Nucleotides Nucleic Acids 26 (2024) 1–16, https://doi.org/10.1080/15257770.2024.2331046 [PMID: 38531025.

[12] Parisa Habibi, Effect of young plasma therapy on cognition, oxidative stress, miRNA-134, BDNF, CREB, and SIRT-1 expressions and neuronal survey in the Hippocampus of aged ovariectomized rats with alzheimer's, Brain Sci. 14 (7) (2024), https://doi.org/10.3390/brainsci14070656 [PMID: 39061398.

[13] J.P. Lopez, F. Pereira, S. Richard-Devantoy, M. Berlim, E. Chachamovich, L.M. Fiori, P. Niola, G. Turecki, F. Jollant, Co-variation of peripheral levels of miR-1202 and brain activity and connectivity during antidepressant treatment, Neuropsychopharmacology 42 (2017) 2043–2051, https://doi.org/10.1038/npp.2017.9 [PMID: 28079059.

[14] D. Lou, J. Wang, X. Wang, miR-124 ameliorates depressive-like behavior by targeting STAT3 to regulate microglial activation, Mol. Cell. Probes 48 (2019) 101470, https://doi.org/10.1016/j.mcp.2019.101470 [PMID: 31626919.

[15] E. Tacconelli, Systematic reviews: CRD's guidance for undertaking reviews in health care, Lancet Infect. Dis. 10 (2010) 226, https://doi.org/10.1016/S1473-3099(10)70065-7.

[16] J.E.M. Sale, K. Brazil, A strategy to identify critical appraisal criteria for primary mixed-method studies, Qual Quant 38 (2004) 351–365, https://doi.org/10.1023/b:ququ.0000043126.25329.85 [PMID: 26526412.

[17] Mixed Methods Appraisal Tool (MMAT).A Mixed Methods Appraisal Tool for Systematic Mixed Studies Reviews.[cited January 02, 2024]. Available from: http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/84371689/MMAT%202011%20criteria%20and%20tutorial%202011-06-29updated2014.08.21.pdf.

[18] Critical Appraisal Skills Programme (CASP). Qualitative Research Checklists.[cited January 02, 2024]. Available from: http://media.wix.com/ugd/dded87_29c5b002d99342f788c6ac670e49f274.pdf.

[19] D. Moher, S. Hopewell, K.F. Schulz, V. Montori, P.C. Gøtzsche, P.J. Devereaux, D. Elbourne, M. Egger, D.G. Altman, CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials, BMJ 869 (2010) 28–55, https://doi.org/10.1136/bmj.c869 [PMID: 2033251 1.

[20] G. Wang, T. An, C. Lei, X. Zhu, L. Yang, L. Zhang, R. Zhang, Antidepressant-like effect of ginsenoside Rb1 on potentiating synaptic plasticity via the miR-134-mediated BDNF signaling pathway in a mouse model of chronic stress-induced depression, Journal of Ginseng Research 376 (2022) 376–386, https://doi.org/10.1016/j.jgr.2021.03005]. PMID: 35600767.

[21] H.-P. Zhang, X.-L. Liu, J.-J. Chen, K. Cheng, S.-J. Bai, P. Zheng, C.-J. Zhou, W. Wang, H.-Y. Wang, L.-M. Zhong, P. Xie, Circulating microRNA 134 sheds light on the diagnosis of major depressive disorder, Transl. Psychiatry 10 (2020) 95, https://doi.org/10.1038/s41398-020-0773-2 [PMID: 32179735.

[22] G. Wang, Y. Liu, X. Zhu, K. Lin, M. Li, Z. Wu, R. Zhang, Q. Zheng, D. Li, T. An, Knockdown of miRNA-134-5p rescues dendritic deficits by promoting AMPK-mediated mitophagy in a mouse model of depression, Neuropharmacology 214 (2022) 109–154, https://doi.org/10.1016/jneuropharm.2022.109154] [PMID: 35659969.

[23] C. Fan, X. Zhu, Q. Song, P. Wang, Z. Liu, S.Y. Yu, MiR-134 modulates chronic stress-induced structural plasticity and depression-like behaviors via downregulation of Limk1/cofilin signaling in rats, Neuropharmacology 214 (2018) 364–374, https://doi.org/10.1016/j.neuropharm.2018.01.009 [PMID: 29329879.

[24] J. Gao, W.-Y. Wang, Y.-W. Mao, J. Gräff, J.-S. Guan, L. Pan, G. Mak, D. Kim, S.C. Su, L.-H. Tsai, A novel pathway regulates memory and plasticity via SIRT1 and miR-134, Nature 466 (2010) 1105–1109 [PMID: 2062285610.038/nature09271].

[25] R. Fiore, M. Rajman, C. Schwale, S. Bicker, A. Antoniou, C. Bruehl, A. Draguhn, G. Schratt, MiR-134-dependent regulation of Pumilio-2 is necessary for homeostatic synaptic depression, EMBO J. 33 (2014) 2231–2246, https://doi.org/10.5252/embj.2014 87921. PMID: 25097251.

[26] J. Lou, K. Liu, J. Wen, Y. He, Y. Sun, X. Tian, K. Hu, Y. Deng, B. Liu, G. Wen, Deciphering the neural mechanisms of miR-134 in major depressive disorder with population-based and person-specific imaging transcriptomic techniques, Psychiatr. Res. 329 (2023) 115551, https://doi.org/10.1016/j.psychres.2023.115551]. PMID: 37871377.

[27] T. Jiang, S. Hu, S. Dai, Y. Yi, T. Wang, X. Li, M. Luo, K. Li, L. Chen, H. Wang, D. Xu, Programming changes of hippocampal miR-134-5p/SOX2 signal mediate the susceptibility to depression in prenatal dexamethasone-exposed female offspring, Cell Biol. Toxicol. 38 (2022) 69–86, https://doi.org/10.1007/s10565-021-09590-4]. PMID: 33619658.

[28] G.M. Schratt, F. Tuebing, E.A. Nigh, C.G. Kane, M.E. Sabatini, M. Kiebler, M.E. Greenberg, A brain-specific microRNA regulates dendritic spine development, Nature 439 (2006) 283–289, https://doi.org/10.1038/nature04367]. PMID: 16421561.

[29] H. Yu, C. Fan, L. Yang, S. Yu, Q. Song, P. Wang, X. Mao, Ginsenoside Rg1 prevents chronic stress-induced depression-like behaviors and neuronal structural plasticity in rats, Cell. Physiol. Biochem. 48 (2018) 2470–2482, https://doi.org/10.1159/0004 92684]. PMID: 30121663.

[30] X.Z. Zhu, Mechanistic Study of miRNA-134 Regulation of Neural Structural Plasticity Involved in the Pathogenesis of Depression, M.Sc. Thesis, Shandong University, 2017. Available from: https://chn.oversea.cnki.net/KCMS/detail/detail.aspx?dbcode=CMFD&dbname=CMFD201702&filename=1017081300.nh&uniplatform=OVERSEA&v=mJw4D-SrJE5dM06N7Q4EHCfCC1pSIUyccC2NnERuRBn4GWxH1sRch4zAWJLbzf_z.

[31] F. Huang, X.Z. Jiang, Effects of sertraline on hippocampal MicroRNAs levels in depression model mice, Journal of Psychiatry 30 (2017) 358–360, https://doi.org/10.3969/j.2095-9346.2017.05.011].
[32] H. Li, Effect of amisulpride combined with paroxetine on the expression of synapse-associated miRNAs in patients with major depressive disorder, Int. J. Psychiatr. 47 (2020) 705–708, https://doi.org/10.13479/j.cnki.jip.2020.04.018].
[33] Y.Y. Zhao, R. Jiang, Q. Ren, Correlation of peripheral blood vitamin D, acylated Ghrelin, and MicroRNA-134 expression levels with depression severity, Journal of Psychiatry 36 (2023) 66–68, https://doi.org/10.3969/j.2095-9346.2023.01.014.].
[34] H. Rong, T.B. Liu, H.C. Yang, D. Xu, J. Zhang, G.H. Wang, Effect of fluoxetine on plasma miR-34a miR-134 miR-143 expression in rats of CUMS model group, Journal of Clinical Psychosomatic Diseases 23 (2017) 1–5, https://doi.org/10.3969/j.1672-187X.2017.03 .001-0001-05].
[35] W.N. Marsden, Synaptic plasticity in depression: molecular, cellular and functional correlates, Progress In Neuro-psychopharmacology & Biological Psychiatry 43 (2013) 168–184, https://doi.org/10.1016/j.pnpbp.2012.12.012 [PMID: 23268191.
[36] M.J.F. Levy, F. Boulle, H.W. Steinbusch, D.L.A. van den Hove, G. Kenis, L. Lanfumey, Neurot rophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression, Psychopharmacology (Berl) 235 (2018) 2195–2220, https://doi.org/10.1007/s00213-018-4950-4] [PMID: 29961124.
[37] J.G. Doench, P.A. Sharp, Specificity of microRNA target selection in translational repression, Genes Dev. 18 (2004) 504–511 [PMID: 15014042.
[38] O.F. Laterza, L. Lim, P.W. Garrett-Engele, K. Vlasakova, N. Muniappa, W.K. Tanaka, J.M. Johnson, J.F. Sina, T.L. Fare, F.D. Sistare, W.E. Glaab, Plasma MicroRNAs as sensitive and specific biomarkers of tissue injury, Clin. Chem. 55 (2009) 1977–1983, https://doi.org/10.1373/clinchem.2009.131797 [PMID: 19745058.
[39] Q. Fu, H. Jiang, Z. Wang, X. Wang, H. Chen, Z. Shen, L. Xiao, X. Guo, T. Yang, Injury factors alter miRNAs profiles of exosomes derived from islets and circulation, Aging 10 (2018) 3986–3999, https://doi.org/10.18632/aging.10689 [PMID: 30552311.
[40] Z. Zhao, Q. Zhao, J. Warrick, C.M. Lockwood, A. Woodworth, K.H. Moley, A.M. Gronowski, Circulating microRNA miR-323-3p as a biomarker of ectopic pregnancy, Clin. Chem. 58 (2012) 896–905, https://doi.org/10.1373/clinchem.2011.179283 [PMID: 22395025.
[41] S.A. Waldman, A. Terzic, MicroRNA signatures as diagnostic and therapeutic targets, Clin. Chem. 54 (2008) 943–944, https://doi.org/10.1373/clinchem.2008.105353 [PMID: 18509012.
[42] W. Wang, W. Lou, B. Ding, B. Yang, H. Lu, Q. Kong, W. Fan, A novel mRNA-miRNA-lncRNA competing endogenous RNA triple sub-network associated with prognosis of pancreatic cancer, Aging 11 (2019) 2610–2627, https://doi.org/10.18632/aging.101933 [PMID: 31061236.
[43] D. Yang, Q. Li, L. Fang, K. Cheng, R. Zhang, P. Zheng, Q. Zhan, Z. Qi, S. Zhong, P. Xie, Reduced neurogenesis and pre-synaptic dysfunction in the olfactory bulb of a rat model of depression, Neuroscience 192 (2011) 609–618, https://doi.org/10.1016/j.neuroscience.2011.06.043. PMID: 21722712.
[44] N.F. Olde Loohuis, A. Kos, G.J. Martens, H. Van Bokhoven, N. Nadif Kasri, A. Aschrafi, MicroRNA networks direct neuronal development and plasticity, Cell. Mol. Life Sci. 69 (2012) 89–102, https://doi.org/10.1007/s00018-011-0788-1 [PMID: 21833581.
[45] J.C. Madara, E.S. Levine, Presynaptic and postsynaptic NMDA receptors mediate distinct effects of brain-derived neurotrophic factor on synaptic transmission, J. Neurophysiol. 100 (2008) 3175–3184, https://doi.org/10.1152/jn.90880.2008 [PMID: 18922945.
[46] M. Fuchikami, S. Morinobu, M. Segawa, Y. Okamoto, S. Yamawaki, N. Ozaki, T. Inoue, I. Kusumi, T. Koyama, K. Tsuchiyama, T. Terao, DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potent diagnostic biomarker in major depression, PLoS One 6 (2011) e23881, https://doi.org/10.1371/journal.pone.0023881 [PMID:21912609.
[47] K. Hashimoto, Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions, Psychiatry Clin Neurosci 64 (2010) 341–357, https://doi.org/10.1111/j.1440-1819.2010.02113.x [PMID: 20653908.
[48] V.R. Enatescu, I. Papava, I. Enatescu, M. Antonescu, A. Anghel, E. Seclaman, I.O. Sirbu, C. Marian, Circulating plasma micro RNAs in patients with major depressive disorder treated with antidepressants: a pilot study, Psychiatry Investig 13 (2016) 549–557, https://doi.org/10.4306/pi.2016.13.5.549 [PMID: 27757134.
[49] S. Rahmani, S. Kadkhoda, S. Ghafouri-Fard, Synaptic plasticity and depression: the role of miRNAs dysregulation, Mol. Biol. Rep. 49 (2022) 9759–9765, https://doi.org/10.1007/s11033-022-07461-7 [PMID: 35441941.
[50] E.S. Levine, C.F. Dreyfus, I.B. Black, M.R. Plummer, Brain-derived neurotrophic factor rapidly enhances synaptic transmission in hippocampal neurons via postsynaptic tyrosine kinase receptors, Proc Natl Acad Sci U S A 92 (1995) 8074–8077, https://doi.org/10.1073/pnas.92.17.8074 [PMID: 7644540.
[51] C.P. Ferrúa, R. Giorgi, L.C. da Rosa, C.C. do Amaral, G.C. Ghisleni, R.T. Pinheiro, F. Nedel, MicroRNAs expressed in depression and their associated pathways: a systematic review and a bioinformatics analysis, J. Chem. Neuroanat. 100 (2019) 101650, https://doi.org/10.1016/j.jchemneu.2019.101650 [PMID: 31125682.
[52] Y. Dwivedi, B. Roy, G. Lugli, H. Rizavi, H. Zhang, N.R. Smalheiser, Chronic corticosterone-mediated dysregulation of microRNA network in prefrontal cortex of rats: relevance to depression pathophysiology, Transl. Psychiatry 5 (2015) e682, https://doi.org/10.1038/tp.2015.175. PMID: 26575223.
[53] L. Bocchio-Chiavetto, V. Bagnardi, R. Zanardini, R. Molteni, M.G. Nielsen, A. Placentino, C. Giovannini, L. Rillosi, M. Ventriglia, M.A. Riva, M. Gennarelli, Serum and plasma BDNF levels in major depression: a replication study and meta-analyses, World J. Biol. Psychiatr. : the Official Journal of the World Federation of Societies of Biological Psychiatry 11 (2010) 763–773, https://doi.org/10.3109/15622971003611319. PMID:20334574.
[54] C.A. Turner, H. Akil, S.J. Watson, S.J. Evans, The fibroblast growth factor system and mood disorders, Biol. Psychiatr. 59 (2006) 1128–1135. PMID: 16631131.
[55] C. Phillips, Brain-derived neurotrophic factor, depression, and physical activity: making the neuroplastic connection, Neural Plast. 2017 (2017) 7260130, https://doi.org/10.1155/2017/7260130 [PMID: 28928987.
[56] A.E. Autry, M. Adachi, P. Cheng, L.M. Monteggia, Gender-specific impact of brain-derived neurotrophic factor signaling on stress-induced depression-like behavior, Biol. Psychiatr. 66 (2009) 84–90, https://doi.org/10.1016/j.biopsych.2009.02.007 [PMID: 19358977.
[57] S. Ghosal, B. Hare, R.S. Duman, Prefrontal cortex GABAergic deficits and circuit dysfunction in the pathophysiology and treatment of chronic stress and depression, Curr Opin Behav Sci 14 (2017) 1–8, https://doi.org/10.1016/j.cobeha.2016.09.0 12] [PMID: 27812532.
[58] R.S. Duman, G.K. Aghajanian, G. Sanacora, J.H. Krystal, Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants, Nat Med 22 (2016) 238–249, https://doi.org/10.1038/nm.4050 [PMID: 26937618.
[59] E. Maffioletti, A. Cattaneo, G. Rosso, G. Maina, C. Maj, M. Gennarelli, D. Tardito, L. Bocchio-Chiavetto, Peripheral whole blood microRNA alterations in major depression and bipolar disorder, J. Affect. Disord. 8 (2016) 250–258, https://doi.org/10.1016/j.jad.2016.04.021 [PMID: 27152760.
[60] D.R. Goldsmith, M.H. Rapaport, B.J. Miller, A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression, Mol. Psychiatr. 21 (2016) 1696–1709, https://doi.org/10.1038/mp.2016.3 [PMID: 26903267.
[61] H. Sun, P.J. Kennedy, E.J. Nestler, Epigenetics of the depressed brain: role of histone acetylation and methylation, Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology 38 (2013) 124–137, https://doi.org/10.1038/npp.2012.73 [PMID: 22692567.
[62] A. Rinaldi, S. Vincenti, F. De Vito, I. Bozzoni, A. Oliverio, C. Presutti, P. Fragapane, A. Mele, Stress induces region specific alterations in microRNAs expression in mice, Behav. Brain Res. 208 (2010) 265–269, https://doi.org/10.1016/j.bbr 2009.11.012] [PMID: 19913057.
[63] Y.-Y. Xu, Q.-H. Xia, Q.-R. Xia, X.-L. Zhang, J. Liang, MicroRNA-based biomarkers in the diagnosis and monitoring of therapeutic response in patients with depression, Neuropsychiatr Dis Treat 15 (2019) 3583–3597, https://doi.org/10.2147/NDT.S237116] [PMID: 31920318.
[64] F.W. Lohoff, Overview of the genetics of major depressive disorder, Curr Psychiatry Rep 12 (2010) 539–546, https://doi.org/10.1007/s11920-010-0150-6 [PMID: 20848240.
[65] Penner-Goeke S, Binder EB. Epigenetics and depression.Dialogues Clin. Neurosci. 201; 21: 397-405 [PMID: 31949407DOI: 1031887/DCNS.2019.21.4/ebinder].
[66] R.M. O'Connor, T.G. Dinan, J.F. Cryan, Little things on which happiness depends: microRNAs as novel therapeutic targets for the treatment of anxiety and depression, Mol. Psychiatr. 17 (2012) 359–376, https://doi.org/10.1038/mp.2011.16 2. PMID: 22182940.
[67] Y. Wan, Y. Liu, X. Wang, J. Wu, K. Liu, J. Zhou, L. Liu, C. Zhang, Identification of Differential microRNAs in cerebrospinal fluid and serum of patients with major depressive disorder, PLoS One 10 (2015) e0121975 [PMID: 25763923.

[68] K. Ma, L. Guo, A. Xu, S. Cui, J.-H. Wang, Molecular mechanism for stress-induced depression assessed by sequencing miRNA and mRNA in medial prefrontal cortex, PLoS One 11 (2016) e0159093, https://doi.org/10.1371/journal.pone.0159093 [PMID: 27427907.
[69] A. Gururajan, M.E. Naughton, K.A. Scott, R.M. O'Connor, G. Moloney, G. Clarke, J. Dowling, A. Walsh, F. Ismail, G. Shorten, L. Scott, D.M. McLoughlin, J. F. Cryan, T.G. Dinan, MicroRNAs as biomarkers for major depression: a role for let-7b and let-7c, Transl. Psychiatry 6 (2016) e862, https://doi.org/10.1038/tp.2016.131 [PMID: 27483380.
[70] N.R. Smalheiser, G. Lugli, H.S. Rizavi, V.I. Torvik, G. Turecki, Y. Dwivedi, MicroRNA expression is down-regulated and reorganized in prefrontal cortex of depressed suicide subjects, PLoS One 7 (2012) e33201 [PMID: 22427989.
[71] S.-Y. Lee, R.-B. Lu, L.-J. Wang, C.-H. Chang, T. Lu, T.-Y. Wang, K.-W. Tsai, Serum miRNA as a possible biomarker in the diagnosis of bipolar II disorder, Sci. Rep. 10 (2020) 1131, https://doi.org/10.1038/s41598-020-58195-0. PMID: 31980721.
[72] P. Zheng, H.C. Gao, Q. Li, W.H. Shao, M.L. Zhang, K. Cheng, D.Y. Yang, S.H. Fan, L. Chen, L. Fang, P. Xie, Plasma metabonomics as a novel diagnostic approach for major depressive disorder, J. Proteome Res. 11 (2012) 1741–1748. PMID: 22239730.
[73] B. Qi, L.M. Fiori, G. Turecki, Y.J. Trakadis, Machine learning analysis of blood microRNA data in major depression: a case-control study for biomarker discovery, Int. J. Neuropsychopharmacol. 23 (2020) 505–510, https://doi.org/10.1093/ijnp/pyaa029 [PMID: 32365192.
[74] K.A. Garbett, A. Vereczkei, S. Kálmán, J.A. Brown, W.D. Taylor, G. Faludi, Ž. Korade, R.C. Shelton, K. Mirnics, Coordinated messenger RNA/microRNA changes in fibroblasts of patients with major depression, Biol. Psychiatr. 77 (2015) 256–265, https://doi.org/10.1016/j.biopsych.2014.05.015 [PMID: 25016317.
[75] L. Bocchio-Chiavetto, E. Maffioletti, P. Bettinsoli, C. Giovannini, S. Bignotti, D. Tardito, D. Corrada, L. Milanesi, M. Gennarelli, Blood microRNA changes in depressed patients during antidepressant treatment, Eur. Neuropsychopharmacol : the Journal of the European College of Neuropsychopharmacology 23 (2013) 602–611, https://doi.org/10.1016/j.euroneuro.2012.06.013 [PMID: 22925464.
[76] M.A. Camkurt, Ş. Acar, S. Coşkun, M. Güneş, S. Güneş, M.F. Yılmaz, A. Görür, L. Tamer, Comparison of plasma MicroRNA levels in drug naive, first episode depressed patients and healthy controls, J. Psychiatr. Res. 69 (2015) 67–71, https://doi.org/10.1016/j.jpsychires.2015.07.023 [PMID:26343596.
[77] Z.-F. Deng, H.-L. Zheng, J.-G. Chen, Y. Luo, J.-F. Xu, G. Zhao, J.-J. Lu, H.-H. Li, S.-Q. Gao, D.-Z. Zhang, L.-Q. Zhu, Y.-H. Zhang, F. Wang, miR-214-3p targets β-catenin to regulate depressive-like behaviors induced by chronic social defeat stress in mice, Cereb Cortex 29 (2019) 1509–1519, https://doi.org/10.1093/cercor/bhy047 [PMID: 29522177.
[78] A.P. Mendes-Silva, P.T. Fujimura, JRdC. Silva, A.L. Teixeira, E.M. Vieira, P.H.G. Guedes, L.S.S. Barroso, MdS. Nicolau, J.D.R. Ferreira, L. Bertola, EdS. Nicolau, G.T. Tolentino-Araújo, C.M.S.F. Berlezzi, T.S. Rodrigues, L.D.F. Borges, MdS. Gomes, LRd Amaral, A.M. Bonetti, C. Ueira-Vieira, B.S. Diniz, Brain-enriched MicroRNA-184 is downregulated in older adults with major depressive disorder: a translational study, J. Psychiatr. Res. 111 (2019) 110–120, https://doi.org/10.1016/j.jpsychires.2019.01.019 [PMID: 30716647.
[79] W. Li, X. Li, Y. Li, Y. Chen, L. Zhu, R. Guo, Diagnostic value of MicroRNAs for depression: a systematic review and meta-analysis, J. Psychiatr. Res. 157 (2023) 132–140, https://doi.org/10.1016/j.jpsychires.2022.11.028 [PMID: 36463628.
[80] K. Ma, et al., Identification of key genes, pathways, and miRNA/mRNA regulatory networks of CUMS-induced depression in nucleus accumbens by integrated bioinformatics analysis, Neuropsychiatr Dis Treat 15 (2019) 685–700, https://doi.org/10.2147/NDT.S200264 [PMID: 30936699.
[81] K. Ma, H. Zhang, G. Wei, Z. Dong, H. Zhao, X. Han, X. Song, H. Zhang, X. Zong, Z. Baloch, S. Wang, Identification of key genes, pathways, and miRNA/mRNA regulatory networks of CUMS-induced depression in nucleus accumbens by integrated bioinformatics analysis, Neuropsychiatr Dis Treat 15 (2019) 685–700, https://doi.org/10.2147/NDT.S200264. PMID: 30936699.
[82] A. Menke, E.B. Binder, Epigenetic alterations in depression and antidepressant treatment, Dialogues Clin. Neurosci. 16 (2014) 395–404, https://doi.org/10.31887/DCNS.2014.16.3/amenke. PMID: 25364288.
[83] A. Luoni, M.A. Riva, MicroRNAs and psychiatric disorders: from aetiology to treatment, Pharmacology & Therapeutics 167 (2016) 13–27, https://doi.org/10.1016/j.pharmthera.2016.07.006] [PMID: 27452338.
[84] Y. Shi, Q. Wang, R. Song, Y. Kong, Z. Zhang, Non-coding RNAs in depression: promising diagnostic and therapeutic biomarkers, EBioMedicine 71 (2021) 103569, https://doi.org/10.1016/j.ebiom.2021.103569 [PMID: 345210 53.
[85] V. Krishnan, E.J. Nestler, The molecular neurobiology of depression, Nature 455 (2008) 894–902, https://doi.org/10.1038/nature07455 [PMID: 18923511.
[86] H.K. Manji, W.C. Drevets, D.S. Charney, The cellular neurobiology of depression, Nat Med 7 (2001) 541–547, https://doi.org/10.1038/87865 [PMID: 11329053.
[87] C. Homorogan, D. Nitusca, E. Seclaman, V. Enatescu, C. Marian, Uncovering the roles of MicroRNAs in major depressive disorder: from candidate diagnostic biomarkers to treatment response indicators, Life 11 (2021) 1073, https://doi.org/10.3390/life11101073 [PMID: 34685444.
[88] R. Petri, J. Malmevik, L. Fasching, M. Åkerblom, J. Jakobsson, miRNAs in brain development, Exp. Cell Res. 321 (2014) 84–89, https://doi.org/10.1016/j.yexcr.2013.09.022] [PMID: 24099990.
[89] A.W. Kuss, W. Chen, MicroRNAs in brain function and disease, Curr. Neurol. Neurosci. Rep. 8 (2008) 190–197, https://doi.org/10.1007/s11910-008-0031-0 [PMID: 18541114.
[90] Z. Wu, Z. Cai, H. Shi, X. Huang, M. Cai, K. Yuan, P. Huang, G. Shi, T. Yan, Z. Li, Effective biomarkers and therapeutic targets of nerve-immunity interaction in the treatment of depression: an integrated investigation of the miRNA-mRNA regulatory networks, Aging (Albany NY) 14 (2022) 3569–3596, https://doi.org/10.18632/aging.204030] [PMID: 35468096.
[91] S. Peng, Y. Zhou, L. Xiong, Q. Wang, Identification of novel targets and pathways to distinguish suicide dependent or independent on depression diagnosis, Sci. Rep. 13 (2023) 2488, https://doi.org/10.1038/s41598-023-29101-1 [PMID: 36781900.
[92] Y. Dwivedi, Emerging role of microRNAs in major depressive disorder: diagnosis and therapeutic implications, Dialogues Clin. Neurosci. 16 (2014) 43–61, https://doi.org/10.31887/DCNS.2014.16.1/ydwivedi [PMID: 2473397 0.
[93] J.P. Lopez, A. Kos, G. Turecki, Major depression and its treatment: microRNAs as peripheral biomarkers of diagnosis and treatment response, Curr Opin Psychiatry 31 (2018) 7–16, https://doi.org/10.1097/YCO.0000000000000379 [PMID: 29076893.
[94] Y. Yoshino, B. Roy, Y. Dwivedi, Differential and unique patterns of synaptic miRNA expression in dorsolateral prefrontal cortex of depressed subjects, Neuropsychopharmacology 46 (2021) 900–910, https://doi.org/10.1038/s41386-020-00861-y] [PMID: 32919404.
[95] G.-L. Wang, Y.-P. Wang, J.-Y. Zheng, L.-X. Zhang, Monoaminergic and aminoacidergic receptors are involved in the antidepressant-like effect of ginsenoside Rb1 in mouse hippocampus (CA3) and prefrontal cortex, Brain Res. 1699 (2018) 44–53, https://doi.org/10.1016/j.brainres.2018.05.035 [PMID: 29802841.
[96] S.-J. Yang, J.-J. Wang, P. Cheng, L.-X. Chen, J.-M. Hu, G.-Q. Zhu, Ginsenoside Rg1 in neurological diseases: from bench to bedside, Acta Pharmacol. Sin. 44 (2023) 913–930, https://doi.org/10.1038/s41401-022-01022-1 [PMID: 36380226.
[97] J.P. Lopez, L.M. Fiori, C. Cruceanu, R. Lin, B. Labonte, H.M. Cates, E.A. Heller, V. Vialou, S.M. Ku, C. Gerald, M.-H. Han, J. Foster, B.N. Frey, C.N. Soares, D. J. Müller, F. Farzan, F. Leri, G.M. MacQueen, H. Feilotter, K. Tyryshkin, K.R. Evans, P. Giacobbe, P. Blier, R.W. Lam, R. Milev, S.V. Parikh, S. Rotzinger, S. C. Strother, C.M. Lewis, K.J. Aitchison, G.M. Wittenberg, N. Mechawar, E.J. Nestler, R. Uher, S.H. Kennedy, G. Turecki, MicroRNAs 146a/b-5 and 425-3p and 24-3p are markers of antidepressant response and regulate MAPK/Wnt-system genes, Nat. Commun. 8 (2017) 15497, https://doi.org/10.1038/ncomms15497 [PMID: 28530238.
[98] J. Li, H. Meng, W. Cao, T. Qiu, MiR-335 is involved in major depression disorder and antidepressant treatment through targeting GRM4, Neurosci. Lett. 606 (2015) 167–172, https://doi.org/10.1016/j.neulet.2015.08.038. PMID: 26314506.
[99] Z.-X. Wei, G.-J. Xie, X. Mao, X.-P. Zou, Y.-J. Liao, Q.-S. Liu, H. Wang, Y. Cheng, Exosomes from patients with major depression cause depressive-like behaviors in mice with involvement of miR-139-5p-regulated neurogenesis, Neuropsychopharmacology 45 (2020) 1050–1058, https://doi.org/10.1038/s41386-020-0622-2] [PMID: 31986519.
[100] S. He, X. Liu, K. Jiang, D. Peng, W. Hong, Y. Fang, Y. Qian, S. Yu, H. Li, Alterations of microRNA-124 expression in peripheral blood mononuclear cells in pre- and post-treatment patients with major depressive disorder, J. Psychiatr. Res. 78 (2016) 65–71, https://doi.org/10.1016/j.jpsychires.2016.03.015 [PMID: 27078210.
[101] S. Zhang, Z. Cheng, Y. Wang, T. Han, The risks of miRNA therapeutics: in a drug target perspective, Drug Des Devel Ther 15 (2021) 721–733, https://doi.org/10.2147/DDDT.S288859 [PMID: 33654378.

[102] R. Zhou, P. Yuan, Y. Wang, J.G. Hunsberger, A. Elkahloun, Y. Wei, P. Damschroder-Williams, J. Du, G. Chen, H.K. Manji, Evidence for selective microRNAs and their effectors as common long-term targets for the actions of mood stabilizers, Neuropsychopharmacology 34 (2009) 1395–1405. PMID: 18704095.
[103] O. Issler, S. Haramati, E.D. Paul, H. Maeno, I. Navon, R. Zwang, S. Gil, H.S. Mayberg, B.W. Dunlop, A. Menke, R. Awatramani, E.B. Binder, E.S. Deneris, C. A. Lowry, A. Chen, MicroRNA 135 is essential for chronic stress resiliency, antidepressant efficacy, and intact serotonergic activity, Neuron 83 (2014) 344–360, https://doi.org/10.1016/j.neuron.2014.05.042 [PMID: 24952960.
[104] L. Colucci-D'Amato, L. Speranza, F. Volpicelli, Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer, Int. J. Mol. Sci. 21 (2020) 7777, https://doi.org/10.3390/ijms21207777 [PMID: 33096634.
[105] B. Roy, M. Dunbar, J. Agrawal, L. Allen, Y. Dwivedi, Amygdala-based altered miRNome and epigenetic contribution of miR-128-3p in conferring susceptibility to depression-like behavior via Wnt signaling, Int. J. Neuropsychopharmacol. 23 (2020) 165–177, https://doi.org/10.1093/ijnp/pyz071 [PMID: 32173733.
[106] Q. Wang, G. Zhao, Z. Yang, X. Liu, P. Xie, Downregulation of microRNA-124-3p suppresses the mTOR signaling pathway by targeting DDIT4 in males with major depressive disorder, Int. J. Mol. Med. 41 (2018) 493–500, https://doi.org/10.3892/ijmm.2017.3235 [PMID: 29115444.
[107] J. Yin, X. Luo, Q. Peng, S. Xiong, D. Lv, Z. Dai, J. Fu, Y. Wang, Y. Wei, C. Liang, X. Xu, D. Zhang, L. Wang, D. Zhu, X. Wen, X. Ye, Z. Lin, J. Lin, Y. Li, J. Wang, G. Ma, K. Li, Y. Wang, Sex-specific associations of MIR137 polymorphisms with schizophrenia in a han Chinese cohort, Front. Genet. 12 (2021) 627874, https://doi.org/10.3389/fgene.2021.627874. PMID: 33708240.
[108] M. Maj, D.J. Stein, G. Parker, M. Zimmerman, G.A. Fava, M. De Hert, K. Demyttenaere, R.S. McIntyre, T. Widiger, H.-U. Wittchen, The clinical characterization of the adult patient with depression aimed at personalization of management, World Psychiatr. 19 (2020) 269–293, https://doi.org/10.1002/wps.20771 [PMID: 32931110.
[109] S.M. Monroe, K.L. Harkness, Major depression and its recurrences: life course matters, Annu. Rev. Clin. Psychol. 18 (2022) 329–357, https://doi.org/10.1146/annurev-clinpsy-072220-021440 [PMID: 35216520.
[110] G. Sampogna, C. Toni, P. Catapano, B.D. Rocca, M. Di Vincenzo, M. Luciano, A. Fiorillo, New trends in personalized treatment of depression, Curr Opin Psychiatry 37 (2024) 3–8, https://doi.org/10.1097/YCO.0000000000000903 [PMID: 37865845.
[111] M. Kundakovic, D. Rocks, Sex hormone fluctuation and increased female risk for depression and anxiety disorders: from clinical evidence to molecular mechanisms, Front. Neuroendocrinol. 66 (2022) 101010 [PMID: 35716803.
[112] J.J. Sramek, M.F. Murphy, N.R. Cutler, Sex differences in the psychopharmacological treatment of depression, Dialogues Clin. Neurosci. 18 (2016) 447–457, https://doi.org/10.31887/DCNS.2016.18.4/ncutler [PMID: 28179816.
[113] F. Rice, L. Riglin, T. Lomax, E. Souter, R. Potter, D.J. Smith, A.K. Thapar, A. Thapar, Adolescent and adult differences in major depression symptom profiles, J. Affect. Disord. 243 (2019) 175–181, https://doi.org/10.1016/j.jad.2018.09.015 [PMID: 30243197.
[114] P. Gaughwin, M. Ciesla, H. Yang, B. Lim, P. Brundin, Stage-specific modulation of cortical neuronal development by Mmu-miR-134, Cereb Cortex 21 (2011) 1857–1869, https://doi.org/10.1093/cercor/bhq262 [PMID: 21228099.