Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

Role of microRNAs in major brain diseases, focusing on neuroinflammation and neuronal apoptosis

Nimra Aziz [1]*, Ghulam Hussain [2], Qammar Abbas [1]

[1] Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The University of Lahore, Lahore, Pakistan
[2] Department of Physiology, Faculty of Life Sciences, Government College University Faisalabad, Faisalabad, Pakistan

ARTICLE INFO

Article type:
Review

Article history:
Received: May 12, 2025
Accepted: Feb 7, 2026

Keywords:
Apoptosis
Brain diseases
Health and-
disease MicroRNA
Molecular pathways
Neuroinflammation

ABSTRACT

MicroRNAs are non-coding small RNA molecules that play a significant role in regulating gene expression. Increasing lines of evidence have highlighted the microRNA dysregulation and neuroinflammation-associated apoptosis in common brain diseases, including Parkinson's disease, Alzheimer's disease, epilepsy, traumatic brain injury, depression, and migraine. In fact, microRNAs regulate multiple physiological and pathological processes, thus implicating them in both health and disease. Though studies have suggested that the alterations or modifications in microRNA-associated regulatory pathways might contribute to the disease pathogenesis, the underlying molecular mechanisms and the targeted genes remain exclusively unknown. We hope that the idea of using microRNAs as therapeutic targets for brain disorders is not far from reality, but important issues must be addressed before moving into clinical practice. The aim of this review is to enlighten the molecular mechanisms and targeted genes of microRNAs implicated in the multifaceted brain disorders. Moreover, several microRNAs have been reported to be up-regulated following disease, but their targeted pathways have not been elucidated yet. This review also highlighted microRNAs that are expected to warrant further exploration of their mechanism of action. This comprehensive overview of the prediction of microRNAs' functions might be helpful in providing more efficient insight for the development of microRNA-based therapeutic interventions for neuropsychiatric and neurodegenerative diseases.

▶Please cite this article as:
Aziz N, Hussain Gh, Abbas Q. Role of microRNAs in major brain disease, focusing on neuroinflammation and neuronal apoptosis. Iran J Basic Med Sci 2026; 29:

Introduction to miRNA

MicroRNAs (miRNAs) are small (about 22 nucleotides) non-coding RNA molecules that play a significant role in regulating gene expression. The 1st miRNA named lin-4 was discovered in 1993 in the *Caenorhabditis elegans* by Ambros and colleagues, which was a revolution in molecular biology. The miRNAs biogenesis encompasses several steps and defines cellular machinery that facilitate the miRNA transcription as the short stem loops, comprising 70 base pairs (bp) long. RNA polymerase II is responsible for the formation of exons and introns of both the non-coding and protein-coding transcripts from which the miRNAs are produced. Firstly, primary miRNAs (pri-miRNA) are formed (inside the nucleus) as the transcriptional products of the DNA sequences, which are then processed into pre-miRNAs (the precursor). Finally, the mature miRNAs are produced by the endonuclease named Dicer RNase III (1). The pri-miRNA might be relatively longer, and it is characterized by the synthesis of a stem-loop structure. Inside the nucleus, macromolecular machinery (microprocessor) then cuts the precursor (pri-miRNA) by an enzyme known as Drosha. This leads to the formation of pre-miRNA, which is typically b/w 60 and 100 nucleotides in length. The pre-miRNA shifts from the nucleus to the cytoplasm via the RanGTP-dependent exportin-5 pathway. The pre-miRNA is further cut to the 22-nucleotide length in the cytoplasm by an enzyme named Dicer RNase III to produce mature miRNA (2).

To date, about 3 thousand miRNAs have been reported in the genomes of mammals, and more than 2000 of them belong to the human genome. It is speculated that each miRNA may have the capability of repressing the expression of hundreds of targeted genes. The reported data have revealed that each miRNA can target multiple mRNAs, and several miRNAs can target a single mRNA. They execute their function by binding directly with the 3' untranslated region (UTR) of the targeted mRNA, which ultimately suppresses the protein expression as well as promotes the degradation of that particular mRNA (3). The miRNAs regulate several physiological as well as pathological processes, thus endorse both the health promoting as well as disease promoting effects. A plethora of work has been done to explore the connection of miRNA with brain disorders and traumatic brain injuries. In our review, we have highlighted the recently published data regarding the implications of miRNA in the development of neuropsychiatric and neurodegenerative diseases (NDDs). This can facilitate the researchers to understand the several molecular pathways and numerous

***Corresponding author:** Nimra Aziz. Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The University of Lahore, Lahore, Pakistan. Email: nimra.aziz@deaht.uol.edu.pk

factors that are being regulated by miRNAs in disease progression or prevention. A comprehensive literature search was conducted using multiple electronic databases, including PubMed, ScienceDirect, and SpringerLink. The search covered peer-reviewed original research articles and review papers published in English. Relevant keywords and their combinations were used, including microRNA, neuroinflammation, Parkinson's disease, epilepsy, oxidative stress, and neurodegeneration. The reference lists of selected studies were also screened to identify additional relevant publications.

Introduction to neuroinflammation

Neuroinflammation is a well-orchestrated and complex process involving glial cells, particularly astrocytes and microglia (4). It is a defensive mechanism that initially aids in inhibiting or removing diverse pathogens. This neuroinflammatory response elicits beneficial effects via the removal of cellular debris, thus promoting neural tissue repair. However, sustained and persistent inflammation is detrimental and inhibits tissue regeneration (5). Neuroinflammation can be initiated by various endogenous and exogenous factors, including infection, toxic metabolites, injury, aging, autoimmune diseases, passive smoke, and air pollution. These factors stimulate the pro-inflammatory chemokines and cytokines that activate microglial cells, elicit primary immune responses in the CNS. Sustained microglial activation allows the recruitment of B or T lymphocytes and macrophages that can cross the compromised blood-brain barrier (BBB), amplifying the chronic inflammation and ultimately neurodegeneration. Excessive and prolonged neuroinflammation acts as a pivotal driver of various neurological disorders, including traumatic brain injury, cerebrovascular disease (CVD), multiple sclerosis (MS), Alzheimer's disease (AD), psychological disorders, epilepsy, and chronic pain. It is a common mechanism connecting the ischemic, traumatic, epileptic, psychiatric, demyelinating, and degenerative pathologies (6).

Physiological role of miRNA

The role of miRNA in biological functions is gradually widening. They are implicated in the physiology and normal development of both plants and animals. In plants, they regulate the floral timing and development, leaf shape and patterning, fertility and vascular development, environmental stress response, and seed biology. In animals and humans, the diversity of miRNAs has been involved in several cellular activities, including apoptosis, cellular proliferation, cell differentiation, renewal of stem cells, metabolism, and embryonic development. They are anticipated to have the capability to regulate almost 60% protein-encoding genes. The miRNAs act by fine-tuning the expression of genes during the development and the maintenance of tissue homeostasis. Under the pathological conditions and/or cellular stress, the cells undergo a condition of alleviated translation and transcription. During these circumstances, the miRNA offers a rapid, potent, and effective source of gene regulation that could allow the cells to recover or become adapted to the abnormal state (7). The experimental evidence indicated that approximately 70% of miRNAs are expressed within the brain and play a crucial role in neural development and functions.

They are primarily enriched in pre- and postsynaptic compartments and implicated in synaptic plasticity during memory formation by coordinating genetic circuitry. In the mature brain, miRNA also modulates the functions and morphology and thereby tightly regulates the neuronal activity. They also modulate the number of behavioral and neuronal phenotypes, such as synapse number, dendrite complexity, synaptic efficiency, and short-term memory, dependent on context. Moreover, miRNAs also control the glial cells differentiation as well as their maintenance in developing and the mature brain (8).

Implications of miRNA in brain diseases

Besides the physiological functions, the miRNAs are also incorporated in the development and progression of numerous pathological conditions, including brain disorders such as AD, Parkinson's disease (PD), psychiatric and behavioral disorders, and many others. MiRNAs have both disease-promoting and disease-modifying roles, and a list of these miRNAs is illustrated in Figure 1.

Alzheimer's disease (AD)

AD is one of the NDDs, and it is characterized by the synaptic functional loss, disorientation, atrophy of certain brain areas, cognitive impairment, and psychiatric symptoms. The neuritic/ amyloid-beta (Aβ) plaques and the neurofibrillary tangles (NFTs) are considered hallmarks in the development and aggravation of AD. The Aβ plaques are generated by the cleavage of amyloid precursor proteins (APP) and β-secretase (beta-site amyloid precursor protein cleaving enzyme, BACE 1), which is mediated by the gamma secretase enzyme (9).

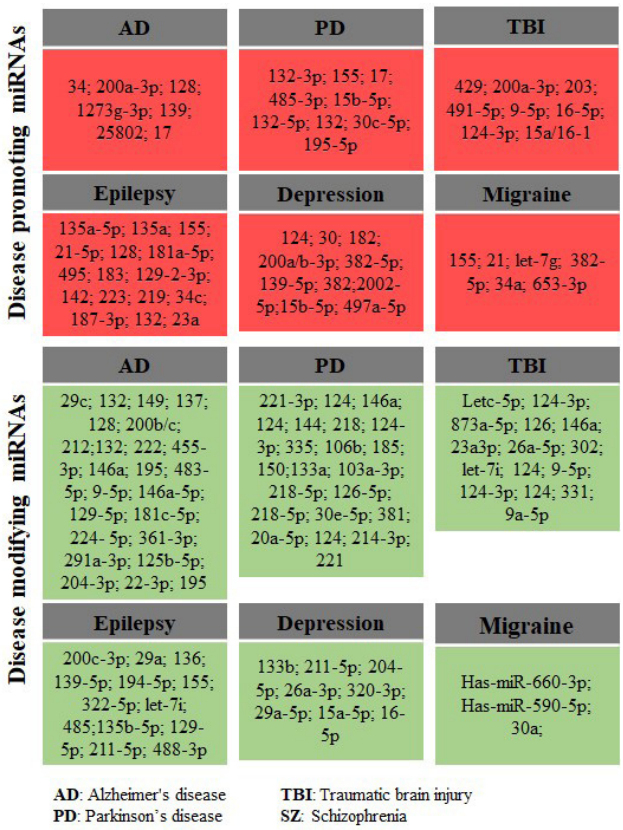

Figure 1. MicroRNA in health and disease

Disease-promoting role in AD

The association of aberrant expression of miR-200a-3p with Sirtuin 1 (SIRT1)(anti-apoptotic protein) in the hippocampus was explored by using a mouse model of AD (APPswe/PSDE9). The enhanced level of miR-200a-3p with the reduced SIRT1 level was observed in the hippocampus of the mouse model. Additionally, the PC12 cells were used for *in vitro* investigation to analyze the apoptotic rate when exposed to $A\beta_{25-35}$. The overexpression of miR-200a-3p could alleviate the SIRT1 expression, which then promotes the neuronal apoptosis by $A\beta_{25-35}$ (10). Being the most crucial hallmark in the pathogenesis of AD, Aβ, and tau hyperphosphorylation-related studies have been performed most frequently by researchers. MiR-1273g-3p plays a crucial role in the pathogenesis and progression of AD by increasing Aβ production through oxidative stress-induced mitochondrial impairments. It was shown that miR-1273g-3p principally integrated with the mitochondrial genes and, thus, down-regulates their expression. In particular, the target gene of miR-1273g-3p is translocase of inner-mitochondrial membrane-13 (TIMM13), which imports as well as inserts the precise proteins into inner-membrane mitochondria (11).

As AD advances, glial cells, such as microglia and astrocytes, become activated and release inflammatory cytokines, which contribute to neurotoxicity and worsen Aβ and tau protein pathologies, ultimately leading to neurodegeneration. Krüppel-like factor 4 (KLF4) likely acts as a transcription factor influencing the expression of genes involved in the inflammatory response mediated by microglia in AD. Specifically, it may regulate the expression of pro-inflammatory cytokines and other molecules that contribute to neuroinflammation, thereby influencing disease progression (12). By using two mouse models of AD, including age-matched wild-type (WT) mice and 5× familial AD (5× FAD) mice, as well as AD patients, a study investigated the role of miR-25802 in AD pathogenesis. Through bioinformatics and experimental validation, miR-25802 was found to be up-regulated in AD patients and AD mouse models, correlating with cognitive impairment, Aβ deposition, and microglial activation towards a pro-inflammatory phenotype. Mechanistically, miR-25802 regulates microglial polarization by targeting KLF4, thereby enhancing NF-κB-mediated inflammation. Modulating miR-25802 levels altered microglial phenotype and inflammatory responses (13), implicating the miR-25802/KLF4/NF-κB axis as a potential therapeutic target for AD treatment. In addition, a study explored the therapeutic potential of targeting microglial miR-17 using mannose-coated lipid nanoparticles in C57BL/6 WT and 5xFAD AD mouse models. MiR-17, implicated in neuroinflammation and AD pathology, was selectively inhibited using the nanoparticles. The intervention effectively mitigated AD-related pathology and improved behavioral outcomes in the mice. In addition to reducing AD pathology and improving behavior, the targeted inhibition of miR-17 through mannose-coated lipid nanoparticles led to a notable decrease in neuroinflammation markers associated with microglial activation (14). The study underscores the potential of nanoparticle-mediated miRNA modulation as a precise therapeutic approach to address neuroinflammatory mechanisms in AD, suggesting avenues for further clinical exploration and development.

Disease-modifying role in AD

It is notable that a variety of miRNAs are deregulated in AD and are involved in BACE1/APP or neuronal functions. Extensive studies have been done to identify the alterations or mutations in the particular miRNAs that could be considered as the therapeutic targets in the treatment of AD. MiR-132 is implicated in the anti-inflammatory, cognition-promoting, and pro-survival functions in NS. Increasing the expression of miR-132 may have a protective and therapeutic role against AD pathogenesis. The expression of miR-132 could be increased by melatonin treatment and thereby prevent neurotoxicity induced by Aβ. MiR-132 also improved the cognitive deficits by suppressing FOXA1 in a rat model of AD (15). BACE1 is also the target for miR-149 that inhibits the accumulation of Aβ and improves the neuronal functions by targeting BACE1 (16). MiR-23b has also been reported to improve cognitive impairment and attenuate Aβ and tau pathology through activation of the Akt/GSK-3β pathway (17).

The voltage-gated Ca^{2+} channels, encoded by the *CACNA1C* gene, also play a crucial role in the pathogenesis of AD. The association of this gene with miR-137 was confirmed in APP/PS1 transgenic mice of AD and SH-SY5Y. The results showed that spatial memory and learning were reduced with the reduction in miR-137 expression, whereas CACNA1C gene and Aβ1-42 expression were elevated in the cerebral cortex and hippocampus of APP/PS1 AD transgenic mice. Moreover, miR-137 mimics in SH-SY5Y cells significantly repressed CACNA1C expression, leading to decreased Aβ1-42 levels and instigated tau hyperphosphorylation (18). The peroxisome proliferator-activated receptor gamma (PPARγ) is involved in the processes of inflammation, morphogenesis, and metabolism, and it is involved in the progression of several NDDs, such as AD. PPARγ is a target for miR-128, and its level was reported to be down-regulated in AD, with increased expression of miR-128 in the cerebral cortex of mice with AD. This resulted in the formation of amyloid plaques, Aβ generation, inflammatory responses, and APP processing, whereas the overexpression of miR-128 could counteract these effects (19).

Insulin signaling, due to Aβ oligomers, is also thought to be compromised in the pathology of AD with cognitive impairment. *In vitro* and *in vivo* studies have shown that MiR-200b and miR-200c can reduce Aβ secretion and associated memory impairment by stimulating insulin signaling (20). The reduced expression of miR-101a-3p could lead to the APP processing and ultimately aggravate AD. Osthole (bioactive compound in traditional Chinese medicines) can mediate the expression of this miRNA, resulting in protection against AD. In APP/PS1 AD mice, osthole up-regulated the expression of miR-101a-3p, which ameliorated the memory and learning and inhibited the APP processing (21).

MiR-455-3p has recently been identified as one of the circulating biomarkers for early AD, with its increased expression in the brain tissue of patients with AD. It directly targets APP and down-regulates its expression as well as suppresses its toxic effects. MiR-455-3p is also associated with weight gain, indicating a metabolic disturbance. Angiotensin-II converting enzyme-1 (ACE1) is overactive in AD brains and is concomitant with cognitive debility and disease pathophysiology. Overexpression of miR-

455-3p resulted in the reduction in tau, BACE1, and APP expression, as well as modulating the ACE1 activity and improving the cognitive performance in AD mice (22). Recently, high levels of miR-455-3p have been reported in the serum of patients with AD. This elevated expression was also confirmed in AD-associated postmortem brains, B-lymphocytes, fibroblasts, mouse models, and cerebrospinal fluid. This miRNA attenuated the Aβ-induced neurotoxicity, ameliorated synaptic activity and biogenesis of mitochondria, and sustained the mitochondrial dynamics. This miRNA also improved cognitive performance by targeting APP, tau, and BACE1 (23).

miR-146a is particularly considered a microglia-specific miRNA as being involved in opposing the pathological processes, mainly by neuroinflammation-associated pathways. It can switch the microglial phenotypes, attenuate pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6), Interleukin-1beta (IL-1β), and increase the phagocytic functions to protect neuronal cells, as confirmed by both *in vivo* and *in vitro* experiments. MiR-146a also improved the cognitive functions, decreased Aβ levels, and ameliorated plaque-related neuritic pathology. In addition, miR-146a could also down-regulate the levels of caspase-1, Apoptosis-Associated Speck-Like Protein Containing a CARD (ASC), and NOD-like receptor pyrin domain-containing 3 (NLRP3), thus inhibiting the activation of NLRP3 inflammasome (24). Apoptosis-Associated Speck-Like Protein Containing a CARD (ASC) is an adaptor protein that links NLRP receptors (like NLRP3) to caspase-1, facilitating inflammasome assembly and triggering inflammation and pyroptotic cell death. Another study employed a rat model (APPswe/PS1dE9) in which AD pathology was induced by direct intra-hippocampal administration of the Aβ1-42 peptide. Through this model, miR-146a-5p was identified as a promising candidate biomarker detectable in blood samples. Importantly, microRNA-146a-5p was found to exert anti-inflammatory effects specifically within astrocytes, which are pivotal in neuroinflammatory responses implicated in AD progression (25). These findings underscore the potential of miR-146a-5p not only as a diagnostic marker but also as a therapeutic target for mitigating neuroinflammation associated with AD. Enhancing phagocytosis may promote the Aβ clearance, reduce neuroinflammation, and slow cognitive decline. A study have shown that miRNA-129-5p mediates translational repression of microglial, leading to enhanced phagocytosis (26). These results imply therapeutic opportunities for addressing miR-129-5p in neuroinflammatory conditions, such as AD. Regarding microglia, enhancing microglial Aβ phagocytosis is beneficial in AD as it reduces amyloid plaque burden and associated neuroinflammation (27), identifying miR-181c-5p as a potential therapeutic target. Using both *in vitro* models, such as SH-SY5Y and BV2 cells, as well as APP/PS1 transgenic mice, the study demonstrated that the down-regulation of miR-181c-5p in AD impairs microglial Aβ phagocytosis. This diminished capacity to clear Aβ plaques exacerbates AD pathology (28). Thus, the study suggests that miR-181c-5p enhances the phagocytosis of Aβ by microglial cells in AD patients, thereby reducing neuroinflammation.

In Aβ1-42-stimulated cells and APP/PS1 mice, miR-224-5p was shown to inhibit the expression of NLRP3. Diminazene (DIZE) treatment significantly up-regulated miR-224-5p in the astrocytes of APP/PS1 mice, with NLRP3 identified as a direct target of this miRNA. The increased expression of miR-224-5p suppressed NLRP3, whereas its down-regulation abrogated this inhibitory effect. Notably, inhibiting miR-224-5p reversed the suppression of the astrocytic NLRP3 inflammasome induced by DIZE. Furthermore, DIZE alleviated cognitive impairment and neuronal and synaptic damage in APP/PS1 mice (29).

The nuclear factor kappa B (NF-κB) signaling pathway is a key factor involved in the activation of the neuroinflammatory process and the subsequent production of neuroinflammatory mediators, which contributes to the progression of AD. TRAF2 (TNF Receptor Associated Factor 2) plays a pivotal role as a mediator in the NF-κB signaling pathway, which is crucial for inflammatory responses. In an *in vitro* HMC3 cell model mimicking an AD environment, miR-361-3p targeted TRAF2, whose expression was regulated by miR-361-3p. Triptolide influenced miR-361-3p levels through its interaction with long non-coding RNA (lncRNA) nuclear paraspeckle assembly transcript 1 (NEAT1), subsequently modulating TRAF2 expression. This regulatory cascade led to the suppression of the NF-κB signaling pathway (30). lncRNA NEAT1 also targets miR-291a-3p, one of the key miRNAs in ameliorating AD, and was found to be down-regulated in both the *in vivo* (mice) and *in vitro* (neural stem cells; NSCs) models of AD. Moreover, Rab22a is implicated in neuroinflammation and Aβ accumulation, and the NF-κB pathway affects apoptotic proteins like Bcl-2, highlighting its role in AD pathology, which is crucial for understanding Rab22a's impact. In both *in vivo* and *in vitro* models of AD, Rab22a was identified as a direct target of miR-291a-3p, validated through dual-luciferase assays and modulation experiments using tanshinone IIA (Tan-IIA). Tan-IIA mitigated oxidative stress and neuroinflammation induced by Aβ1-42 via activation of AKT/Nrf2 signaling mediated by the NEAT1/miR-291a-3p/Rab22a axis, as evidenced by changes in cellular viability, apoptosis markers, and inflammatory cytokine levels (31). Additional studies further elucidate the role of lncRNAs in AD pathology. For instance, a study on the lncRNA brain-derived neurotrophic factor antisense (BDNF-AS) investigates its role in inducing neuronal cell apoptosis in AD models by targeting miR-125b-5p. The research demonstrates that BDNF-AS negatively regulates miR-125b-5p, a microRNA involved in neuronal survival and function. Down-regulation of miR-125b-5p by BDNF-AS leads to increased neuronal apoptosis, contributing to the progression of AD (32). Using both *in vitro* models, such as primary cerebral cortex neuronal culture and PC12 cell culture, as well as Sprague-Dawley rat models, the study highlighted the potential of targeting the BDNF-AS/miR-125b-5p axis as a therapeutic approach to mitigate neuronal loss in AD.

In addition to the treatments discussed earlier, another promising approach involves Dexmedetomidine (Dex), which is an agonist of the α2-adrenergic receptor and is commonly utilized in neurosurgical settings owing to its sedative, anesthetic, and neuroprotective properties. Notably, there is observed overexpression of F-box/LRR-repeat protein 7 (FBXL7) in a transgenic mouse model of AD. Researchers found that Dex reduces neuroinflammation in the C57BL/6 mouse model of AD through modulation of the miR-204-3p/FBXL7 signaling pathway via up-regulation

of miR-204-3p and inhibition of FBXL7 (33), making it a potential therapeutic agent targeting neuroinflammation in this context.

Crucial determinants for maintaining the homeostasis of phosphoinositol biphosphate (PIP2) in the brain are apoE proteins, and the dysfunctional apoE4 isoform contributes to the enhanced susceptibility of memory deficits in AD. In the brain, a reduction in PIP2 levels is related to ApoE4, which increases the expression of synaptojanin 1 (synj1), a PIP2-degrading enzyme. miR-195 targets synj1 and its overexpression ameliorated the cognitive function, decreased Aβ burdens, and hyper-phosphorylation of tau in a mouse model of apoE4$^{+/+}$ (34). Employing various functional assays, miR-483-5p has been found to regulate ERK1/2 at both protein and mRNA levels, thereby reducing phosphorylated ERK1/2 levels. Hence, miR-483-5p-mediated ERK1/2 suppression resulted in tau hypo-phosphorylation at epitopes related to tau neurofibrillary pathophysiology in AD (35). It indicates that miR-483-5p up-regulation can repress tau phosphorylation by targeting the ERK signaling pathway, representing a neuroprotective mechanism in AD pathology. Xenopus kinesin-like protein-2 (TPX2) has been confirmed to be concomitant with the astrocytoma development, and its up-regulation is associated with the pathology of AD. In AD mice, overexpressed miR-9-5p improved the behavioral alterations and neuronal damage as well as repressed the oxidative stress and plaque deposition in the hippocampus via targeting TPX2 (36).

Circular RNAs (circRNAs) are single-stranded non-coding RNA molecules known for their stable circular structures and ability to regulate the expression of protein-coding genes by acting as miRNA sponges, thus contributing to the competing endogenous RNA (ceRNA) network. The oncogene zinc finger protein 217 (ZNF217) is often amplified in cancer and represses genes that control cell proliferation, survival, and invasiveness. A study using Aβ-stimulated SK-N-SH cells demonstrated that inhibiting circ_0049472 and up-regulating miR-22-3p alleviated Aβ-induced neuronal toxicity, apoptosis, and inflammation by regulating ZNF217 through the activation of the PI3K-AKT signaling pathway (37). Consequently, targeting the circ_0049472/miR-22-3p/ZNF217 axis may represent a promising therapeutic strategy for alleviating AD symptoms. Interestingly, a study on miR-195 liposomes for AD therapy highlighted miR-195's potential in reducing Aβ levels and alleviating neuroinflammation, thereby mitigating the cognitive deficits associated with AD. Employing liposomal delivery systems to enhance the stability and targeting efficiency of miR-195, the research demonstrated significant therapeutic effects in AD models, including neuronal cell cultures and APP/PS1 mice. The liposome-encapsulated miR-195 efficiently crossed the blood-brain barrier and specifically targeted neuronal cells, resulting in reduced Aβ production and deposition (38). This approach illustrates the innovative use of liposomes as a promising delivery mechanism for miRNA-based therapies, offering a new avenue for AD treatment by leveraging the regulatory potential of miR-195.

The implications of miRNAs in AD, along with their targets, have been summarized in Table 1.

Parkinson's disease (PD)

PD is one of the common neurodegenerative diseases

Table 1. Implications of miRNA in Alzheimer's disease (AD)

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-200a-3p	SIRT1	↑Neuronal apoptosis	APPswe/PSΔE9 mice, PC12 cells (*in vitro*)	(10)
	miR-1273g-3p	TIMM13	↑Aβ generation and oxidative stress	AD patients, H4-APPswe^{mut} cell line (*in vitro*)	(11)
	miR-25802	KLF4	Cognitive impairment, Aβ deposition, and microglial activation	Age-matched WT, 5xFAD, and AD patients	(13)
	miR-17	-	Defective autophagy, ↑Aβ accumulation, and pro-inflammatory cytokines production	C57BL/6 WT, 5xFAD	(14)
	miR-132	ITPKB, FOXA1	↓Aβ aggregation improves cognition	AD rats	(15)
	miR-23b	Akt/GSK-3β pathway	↓Aβ aggregation improves cognition and neuronal functions	AD patients, SH-SY5Y and HEK293 cell line	(17)
	miR-137	*CACNA1C* gene	↓tau hyperphosphorylation	APP/PS1 AD transgenic mice, SH-SY5Y cell line	(18)
	miR-128	PPARγ	↓Aβ generation and inflammatory responses	3×Tg-AD mice, N2a cell line	(19)
	MiR-200b and miR-200c	Insulin signaling	↓Aβ secretion, improve cognition	C57BL/6J and Tg2576 mice, primary neuronal culture	(20)
	MiR-455-3p	APP, ACE1	↓tau hyperphosphorylation, ↓APP expression, improve cognition,	Null MiR-455 mice	(22)
	miR-146a	NLRP3 inflammasome	↓Neuroinflammation	APP/PS1 (B6/JNju-Tg) and C57BL/6J (WT) mice	(24)
	miR-146a-5p	IRAK1, TRAF-6	↓IL-6, IL-1_, and CXCL1 production	APPswe/PS1$_{dE9}$ rats	(25)

Continued Table 1.

Disease-modifying role	miR-181c-5p	P38 activity	↓TNF-α, IL-6, IL-1β, apoptosis, and Aβ plaques	SH-SY5Y, BV2 cells, and APP/PS1 transgenic mice	(28)
	miR-224-5p	Astrocytic NLRP3	↓TNF-α, IL-6, IL-1β, cognitive impairment, and neuronal and synaptic damage	Aβ1–42-stimulated cells and APP/PS1 mice	(29)
	miR-361-3p	TRAF2	Suppress NF-κB signaling pathway	HMC3 cells	(30)
	miR-291a-3p	Rab22a	↓Neuroinflammatory cytokines, apoptosis, oxidative stress, and Aβ accumulation	Neural stem cells, AD mice model	(31)
	miR-204-3p	FBXL7	↓TNF-α, IL-6, IL-1β	C57BL/6 mice	(33)
	miR-195	synj1	↓Aβ aggregation, ↓tau hyperphosphorylation, improve cognition	AD patients, *apoE3*$^{+/+}$ or *apoE4*$^{+/+}$ (KI) mice	(34)
	miR-483-5p	ERK1/2	↓tau hyperphosphorylation	Neuroblastoma SK-N-MC, HEK293 cells, and human dermal fibroblasts (neonatal)	(35)
	miR-9-5p	TPX2	↓Oxidative stress and neuronal damage	APPswe/PSE9 transgenic and C57BL/6 (WT) mice	(36)
	miR-22-3p	ZBF217	↓Neuronal toxicity, apoptosis, and neuroinflammation	Aβ stimulated SK-N-SH cells	(37)

in the elderly, which is caused by dopaminergic neuronal degeneration, particularly in the substantia nigra (SN) pars compacta. It is characterized by severe locomotor deficits, such as gait problems resulting in intermittent walking disturbances during turning and walk initiation. Multiple molecular mechanisms contribute to neuronal cell apoptosis, such as α-synuclein accumulation, oxidative stress, and mitochondrial dysfunction (39). Its etiology is certainly multifactorial, but a permanent treatment to attenuate disease progression is still lacking. In this scenario, a clear mechanistic understanding would be favorable for proposing therapeutic interventions. The implications of miRNAs in PD are illustrated in Figure 2.

Disease-promoting role in PD

Neuroinflammation plays a significant role in the progression of PD and may prompt the dopaminergic

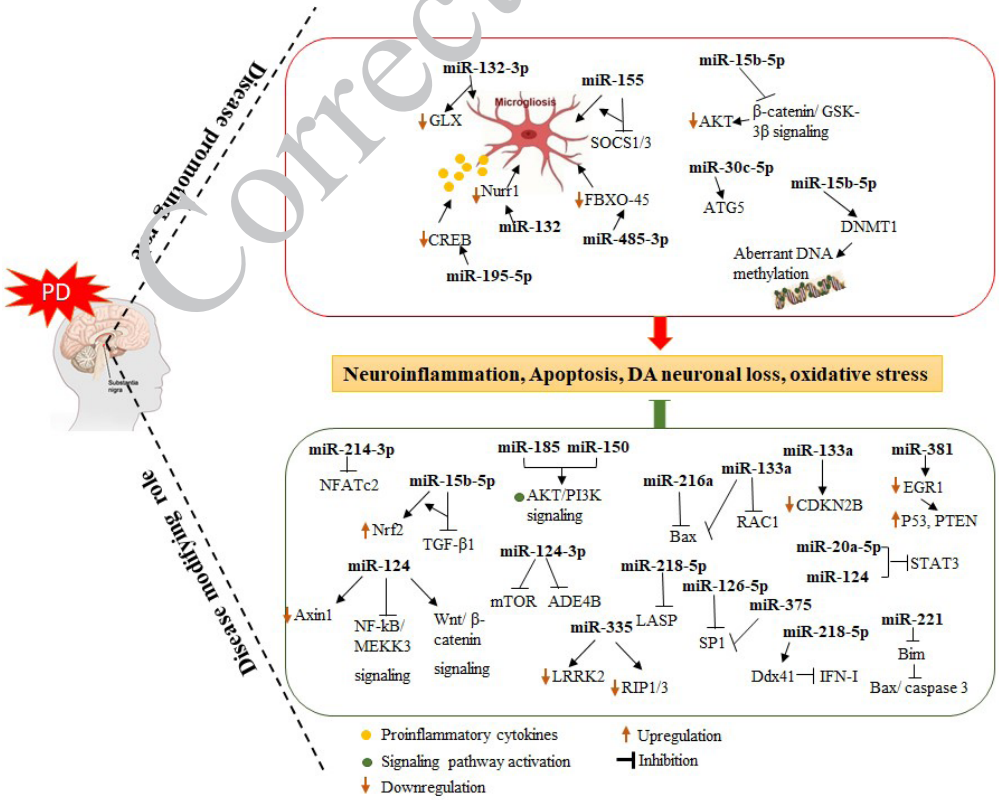

Figure 2. Role of microRNA as disease-promoting and disease-modifying in Parkinson's disease

neuronal degeneration. It leads to the activation of microglial cells that trigger the release of multiple pro-inflammatory factors, including TNF-α, IL-1β, and IL-6. MiR-132-3p overexpression in PD aggravates the microglial cells activation and ultimately prompts the secretion of cytokines by suppressing GLRX (a glutathione-dependent disulfide oxidation reduction reaction catalyzing protein). Studies in both mouse and cell models have shown that the stimulation of GLRX may overpower the miR-132-3p toxic effects and hence may suppress the dopaminergic neuronal damage and microglial activation in PD (40). A close association of abnormal DNA methylation in the pathogenesis of PD is quite evident. The patterns of DNA methylation are established and maintained by enzymes known as DNA methyltransferases (DNMTs). Down-regulation of DNMT1 in PD is mediated by miR-17 and subsequently results in abnormal DNA methylation (41). miR-485-3p also prompts the neuroinflammation, which is supposed to be executed by targeting FBXO protein-45 (FBXO45), whereas its inhibition halts the pro-inflammatory cytokines release. Its higher expression has also been confirmed in the serum of patients with PD (42).

In patients with PD, the serum expression level of miR-15b-5p and Akt3 has been found to be markedly up-regulated and down-regulated, respectively. Moreover, miR-15b-5p mimic and silenced Akt3 enhanced the caspase-3 activity and apoptosis rate, while miR-15b-5p inhibition and Akt3 overexpression suppressed the apoptotic activity in both animals and cellular models of PD. Additionally, it is noteworthy that miR-15b-5p targets the β-catenin/ GSK-3β signaling pathway mediated by Akt3 (43). The alterations in the level of miR-132 are widely associated with the worsening of PD. Particularly, overexpression of miR-132-5p increases apoptosis and reduces cell survival, while its inhibition can restrain autophagy by suppressing Beclin-1 and LC3 protein expression levels in PD (44).

Several therapeutic techniques can also regulate miRNA expression to counteract the pathogenesis of PD, including Repetitive Transcranial Magnetic Stimulation (rTMS). In fact, miR-195-5p is associated with the development of PD by directly targeting cyclic AMP-response element-binding protein (CREB), a transcription factor that promotes neuronal survival and neuroprotection and has anti-inflammatory actions. Sun and colleagues explored that rTMS treatment down-regulates the expression of miR-195-5p and up-regulates the subsequent CREB expression, thereby attenuating the neuronal apoptosis and neuroinflammation (45). Autophagy is a very conserved process to maintain homeostasis, which is about the elimination of damaged organelles and the cellular dysfunction of unfolded proteins. Defects in autophagy, particularly in SN, are closely associated with the stimulation of apoptosis in PD, while their restoration could aid in PD treatment. miR-30c-5p directly targets ATG5, a gene related to autophagy, resulting in dopaminergic neuronal loss, aggravating motor functions, increased apoptosis, and oxidative stress (46).

Disease-modifying role in PD

A redox-sensitive transcriptional factor, nuclear factor erythroid 2-related factor2 (Nrf2), facilitates cells to adapt to inflammation and oxidative stress, while TGF-β1 overexpression is linked with dyskinesia in PD (47). Lately, it has been reported that miR-221-3p has the capability to suppress TGF-β1 expression and elevate Nrf2 expression by targeting TGFBR1, making it a novel candidate to prevent and treat PD (48). Up-regulation of miR-124 in a mouse model of PD has the potential to ameliorate motor deficits, attenuate oxidative stress, and improve the dopaminergic neuronal loss. It is one of the most abundant miRNAs in the brain parenchyma compared to other tissues. A direct target of miR-124 is Axin1, which actually suppresses Axin1 and activates the Wnt/ β-catenin signaling pathway, thereby attenuating the progression of PD. Basically, this targeted pathway plays a significant role in the regulation of inflammation and oxidant stress response during neuronal repair and neurogenesis (49).

In PD, the level of microglial activation correlates with the motor impairment and dopaminergic degeneration, suggesting that the resident microglia-induced neuroinflammation contributes to the progressive pathogenesis of PD. Prolonged and excessive activation of type I interferon (IFN-I) response can be the leading cause of microglia-mediated neuroinflammation and ultimately neuronal death. Overexpression of miR-218-5p can alleviate the levels of pro-inflammatory cytokines (IL-6 and IL-1β) and, thereby, neuroinflammation in microglia by down-regulating the IFN-I pathways in MPTP-induced C57BL/6J mice. Moreover, *Ddx41* was verified as a target gene of miR-218-5p in BV2 cells *in vitro*. Hence, miR-218-5p inhibited microglia IFN-I responses and inflammation by targeting *Ddx41* (50).

Li and colleagues showed that Nurr1 deficiency results in the down-regulation of miR-30e-5p that exacerbates NLRP3 inflammasome, microglial activation, and pro-inflammatory responses both *in vivo* and *in vitro*. Moreover, reduced expressions of miR-30e-5p and Nurr1 have also been observed in PD patients' plasma samples. On the other hand, overexpression of Nurr1 leads to the up-regulation of miR30e-5p that directly regulates the expression of the NLRP3 gene and thereby alleviates the pro-inflammatory cytokines and neuroinflammation (51). This data suggests the significance of the Nurr1-miR-30e-5p-NLRP3 axis in the regulation of neuronal survival and neuroinflammation in PD.

Another negative regulator of pro-inflammatory pathways is miR-146a. It mediates its effects by regulating NF-kB, thereby suppressing inflammation and promoting cell survival and immunity (52). A member of mitogen-activated protein 3 kinase (MAP3K) is MEKK3, which is also implicated in the process of inflammation, and it prompts its effect by inducing the activation of NF-κB. miR-124 inhibits the progression of neuroinflammation by targeting NF-κB/MEKK3 signaling pathway, thereby regulating the inflammatory process in PD (53). Additionally, down-regulation of miR-144 and miR-218 is also associated with the activation of the NF-κB pathway, and it was confirmed by a postmortem study of PD brain samples (54). PDE4B is a negative regulator of the inflammatory process, and it is a direct target of miR124-3p. In PD, overexpression of miR-124-3p could inhibit the expression of PDE4B and prevent the phosphorylation of the mTOR signaling pathway, which in turn ameliorates neuronal death and neuroinflammation. In addition, NEAT1 promoted the down-regulation of miR-124-3p in PD experimental models while its knockdown suppressed the PDE4B expression and promoted the miR-

124-3p expression, thereby improving the PD-associated damage (55). Pathogenic mutation in LRRK2, a leucine-rich-repeat kinase-2 gene, is one of the known causes of the monogenic PD (56), and LRRK2 mRNA is the direct target of miR-335. It could significantly reduce the expression of proinflammatory gene triggered by both LRRK2-Wt and α-synuclein. Moreover, miR-335 also has the potential to suppress the other players of inflammatory and necroptotic pathways, named as receptor-interacting protein-1 (RIP1) and RIP3, thereby mitigating the chronic neuroinflammation (57). Mesenchymal stem cells (MSCs) derivative extracellular vesicles (EV) are an effective therapeutic tool that acts as biological nanoparticles associated with beneficial outcomes in PD. Dysfunctional autophagy is involved in the pathogenesis and progression of PD. MiR-106b transported by MSC-derivative EVs ameliorated the autophagy, neuronal survival, Bcl-2 expression, and LC3I/LC3II ratio. It also alleviated the Bax expression and neuronal apoptosis in the mouse model of PD via down-regulating CDKN2B (58). Growing evidence showed that lower levels of IGF-1 are associated with the progression and aggravation of PD (59). miR-185 overexpression could ameliorate the dopaminergic neuron apoptosis in SN by targeting IGF1 and, in turn, activating the AKT/PI3K signaling pathway in PD. It can also improve the behavioral functions and reduce oxidative stress (60). Bcl-2 and Bax are involved in multifaceted cellular activation as anti-apoptotic and apoptotic regulators. If the amount of Bcl-2 is higher than that of Bax, it suppresses apoptosis, while a higher amount of Bax relative to Bcl-2 promotes apoptosis, and Bax is highly expressed in dopaminergic neurons in PD. miR216a attenuates neuronal apoptosis by restraining Bax (61), unraveling a new therapeutic chapter for PD treatment. A study has revealed that overexpression of miR-150 could also suppress the neuroinflammatory response by regulating the AKT3 signaling (62).

Ras-related-C3 botulinum toxin-substrate 1 (RAC1) is linked with the reactive oxygen species (ROS) production associated with the apoptotic pathway. miR-133a increases the cellular proliferation while inhibiting the autophagy and apoptosis (increases Bcl-2 and decreases Bax) via inhibiting the expression of RAC1 (63). Parkin is a vital protein that regulates the clearance of damaged mitochondria via mitophagy and sustains cellular homeostasis, and its mutation leads to autosomal-recessive PD (AR-PD). Mechanistically, Parkin mediates mitophagy by recruiting and interacting with activating molecules in Beclin-1-regulated autophagy (Ambra1). Up-regulated miR-103a-3p in PD suppresses the expression of Parkin, while its inhibition promotes neuroprotection in PD that might be involved in the regulation via Parkin/Ambra1 signaling pathway (64). LIM and SH3 protein 1 (LASP1) is involved in the oxidative stress and apoptosis process in dopaminergic neurons with PD. It is a direct target of miR-218-5p, and overexpression of miR-218-5p can counteract the negative effects of LASP1. It inhibits the LASP1 mediated oxidative stress and improved dopaminergic neuronal cells damage in SN of PD brain by repressing the LASP1 expression (65).

Early growth response 1 (EGR1) has been reported to effectively promote dopaminergic neurodegeneration and neuroinflammation in the MPTP-induced mice model of PD. Overexpression of miR-381 has been shown to alleviate oxidative stress and the associated dopaminergic neuronal apoptosis. Mechanistically, miR-381 binds to EGR1 to counteract its expression, which then elevates the expression of p53 and PTEN (66), providing a novel insight for neuroprotection in PD. Signal transductors and transcriptional activator 3 (STAT3) are one of the factors associated with the pathology of PD (67). Both in *vitro* and *in vivo* models of PD confirmed that STAT3 is the target of miR-20a-5p. Overexpression of miR-20a-5p enhances the viability of BV2 cells as well as reduces the rate of apoptosis. In addition, its overexpression in MPTP-induced PD mice model inhibited STAT3, resulting in the reduction of neuroinflammation-associated markers, microglia activation, and α-synuclein levels (68). Like miR-20a-5p, STAT3 is also a target gene of miR-124 that inhibits the microglial activation and expression of proinflammatory cytokines, including IL-1β. TNF-α e IL-6 (69). Another transcription factor, nuclear factor of activated T cells, cytoplasmic 2 (NFATc2), is associated with the PD that regulates chemokines and cytokines to build a neurotoxic neuro-inflammatory environment. It has been reported that the overexpression of miR-23a-3p in a mouse model of PD suppressed the microglial activation, neuroinflammation, and reduced the dopaminergic neuronal loss by inhibiting the transcription of NFATc2 (70). Furthermore, overexpression of miR-221 has been shown to improve motor behavior and reduce the dopaminergic neuronal loss in SN via promoting their antiapoptotic and antioxidative capacities in 6-OHDA-induced PD mice model. Mechanistically, miR-221 inhibits the Apaf-1/caspase-3 signaling pathways activation via restricting Bim, a proapoptotic member of the Bcl-2 protein family. This alleviates the dopaminergic neuronal apoptosis (71), suggesting a potential target for the treatment of PD.

Higher levels of transcription factor specificity protein 1 (SP1) could trigger neuronal cell death in NDDs. miR-126-5p and miR-375 are the negative regulators of SP1, and both can ameliorate the dopaminergic neuronal loss, attenuate oxidative stress, and neuroinflammatory responses mediated by PD via inhibiting SP1 (72). The implications of miRNAs in PD, along with their targets, have been summarized in Table 2.

Epilepsy

Epilepsy is one of the serious, debilitating, and long-term neurological and neurobehavioral disorders that are characterized by susceptibility to recurring seizure episodes and abnormal, unsynchronized neuronal discharge. It affects over 50 million people globally (73), and about 60% of them have the most common site for epilepsy, the temporal lobe epilepsy (TLE). It is characterized by the unpredictable and spontaneous recurrent seizure episodes (SRS), such as status epilepticus (SE)(74).

3.3.1 Disease-promoting role in epilepsy

Various studies have demonstrated the implications of miRNA and the associated pathways in the development and progression of TLE in humans as well as animal models. They are gradually recognized as the targets for the disruption of epilepsy and also act as biomarkers for the diagnosis of epileptogenesis. It is evident that neuroinflammation plays a critical role in the pathophysiology of TLE, and the CFH-miR-146a-IL-1β loop circuit is found to be the cause of inflammation, perpetuating inflammation, in the case of TLE. The up-regulation of miR-146a resulted in increased

Table 2. Implications of miRNA in parkinson's disease (PD)

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	MiR-132-3p	GLRX	↑Neuroinflammation and DA neuronal damage	PD patients, BV-2 cells, SH-SY5Y, and (HEK)293T cell line	(40)
	miR-17	DNMT1	Abnormal DNA methylation	PD mice model and C57BL/6 mice (WT), HeLa and SH-SY5Y cell lines	(41)
	miR-485-3p	FBXO45	↑Neuroinflammation	PD patients, BV2 microglial cells	(42)
	miR-15b-5p	β-catenin/ GSK-3β signaling	↑Neuronal apoptosis	PD patients, SH-SY5Y cells	(43)
	miR-132-5p	Beclin-1 and LC3	↑DA neuronal apoptosis, restrain autophagy	MPTP PD mice model, SH-SY5Y cells	(44)
	MiR 195-5p	CREB	↑Neuroinflammation	MPTP-induced PD mice model and primary cortical neurons	(45)
	miR-30c-5p	ATG5	↑DA neuronal apoptosis and oxidative stress	MPTP PD mice model, SH-SY5Y cells	(46)
Disease-modifying role	miR-221-3p	TGFBR1	Improve PD symptoms	MPTP PD mice model, SH-SY5Y cells	(48)
	miR-124	Axin1, Wnt/ β-catenin signaling	↓DA neuronal apoptosis and oxidative stress, Promote neurogenesis	PD patients and mice	(49)
	MiR-218-5p	Ddx41	↓Neuroinflammation and neuronal damage	MPTP PD mice model and BV2 cells	(50)
	MiR-30e-5p	NLRP3	↓Neuroinflammation	PD patients, PD mice model, and primary microglia culture	(51)
	miR-146a	NF-kB	↓Neuroinflammation, improves cell survival	PD patients	(52)
	miR-124	NF-κB/MEKK3 signaling	↓Neuroinflammation	MPTP-HCl PD mice, SH-SY5Y, and BV-2 cells	(53)
	miR-144 and miR-218	NF-kB	↓Neuroinflammation	PD patients, SH-SY5Y cells	(54)
	miR124-3p	PDE4B, mTOR signaling	↓Neuronal apoptosis and neuroinflammation	SH-SY5Y and HEK-293 T cell lines	(55)
	miR-335	LRRK2, RIP1, RIP3	↓Neuroinflammation	MPTP PD mice model, BV-2, and N9 microglial cells	(57)
	MiR-106b	CDKN2B	↓Improve autophagy, Neuronal apoptosis	MPTP PD mice model, primary mouse hippocampus neuronal cells	(58)
	miR-185	IGF1, AKT/PI3K signaling	↓DA neuronal apoptosis and oxidative stress	PD mice	(60)
	miR-150	AKT3 signaling	↓Neuroinflammation	PD patients, BV-2 cell line	(62)
	miR-133a	RAC1	↓DA neuronal apoptosis and oxidative stress	PD patients, SH-SY5Y cell line	(63)
	miR-103a-3p	Parkin/Ambra1 signaling	↓DA neuronal apoptosis	MPTP-HCl PD mice, SH-SY5Y cell line	(64)
	miR-218-5p	LASP1	↓DA neuronal apoptosis	6-OHDA-induced PD rats	(65)
	MiR-[illegible]	EGR1	↓Neuronal apoptosis and oxidative stress	MPTP PD mice model	(66)
	MiR-20a-5p	STAT3	↓Neuroinflammation and apoptosis	MPTP PD mice model and BV2 cells	(68)
	MiR-124	STAT3	↓Proinflammatory cytokines and microglial activation	PD patients, SH-SY5Y and BV2 cells	(69)
	MiR-314-3p	NFATc2	↓Microglial activation and neuroinflammation	MPTP PD mice model	(70)
	MiR-221	Bim	↓Neuronal apoptosis	PD patients and 6OHDA PD mice model	(71)
	miR-126-5p	SP1	↓Neuroinflammation and oxidative stress	SK-N-SH and SH-SY5Y cells	(72)

IL-1β expression by down-regulating the complement factor-H (CFH) expression in the hippocampus of rat models of chronic TLE. In turn, the upsurge in IL-1β also elevated miR-146a levels via a positive feedback loop and reduced CFH expression. This mechanism is somehow twisted with the fact that knockdown of CFH did not allow the enhanced miR-146a to up-regulate IL-1β expression level (75).

It is the fact that TLE in children is different from that observed in adults, but miR-135a-5p is found to be up-regulated in both children and adults. In order to evaluate the role of this miRNA in children with TLE, primary hippocampus neurons were used, mimicking the TLE in children. The results clearly depicted the up-regulated expression of miR-135a-5p with the suppressed expression of Caap1, leading to the TLE-mediated apoptosis in hippocampal cells (76). The expression of miR-135 in the hippocampus is significantly increased with the enhanced TNF-α expression level in both the rats with SE and children with mTLE. Deregulated miR-135a also alters

Mef2a protein expression, thereby affecting plasticity and synaptic function. Fascinatingly, seizure activity at the chronic stage (SRS stage) can be reduced by silencing miR-135a and thereby amending the *Mef2a* protein expression (77). Additionally, the correlation of TNF-α with another miRNA, miR-155, was evaluated in both rats and patients with TLE. The level of both miR-155 and TNF-α was found to be up-regulated in hippocampal tissues of rats with SE at the chronic phase. Moreover, TNF-α expression was also significantly up-regulated in patients with TLE (78), which indicated the implementation of miR-155 and TNF-α in neuroinflammatory responses during TLE pathogenesis. Another study in patients with TLE explored that miR-155 leads to the development and progression of epilepsy via Akt/PI3K/mTOR signaling pathways (79). Moreover, the overexpression of miR-155 also regulates the increased matrix metalloproteinase 3 (MMP3), which promotes epileptogenesis, induced by the stimulation of IL-1β in astrocytes. These increased expressions were also marked in the TLE rat model as well as patients with TLE hippocampal sclerosis (TLE-HS)(80).

MiR-21-5p is linked with apoptosis-induced cell death and cellular proliferation by regulating the cell cycle via directing phosphatase and tensin homolog (PTEN). PTEN inhibits the mTOR pathway in protection from the diseased condition. In the KA-induced rat model of SE, the expression level of MiR-21-5p and mTOR was reported as up-regulated, while PTEN was down-regulated. Additionally, the knockdown of this miRNA resulted in down-regulation of mTOR and up-regulation of PTEN. It also contributed to the memory and cognitive improvement and alleviation of neuronal damage (81). miR-199a is also associated with apoptosis-induced damage in several disease conditions. SIRT1 acts as a significant endogenous apoptosis suppressor in NDDs and also supports axonal regeneration and promotes neurite outgrowth. In the pilocarpine-induced SE rat model, miR-128 was found to be up-regulated with the reduced expression of SIRT1, which led to apoptosis and neuronal loss (81). This concept was also supported by the *in vitro* epilepsy model, where overexpressed miR-128 suppressed the SIRT1 expression and elevated the activity of caspase 3/9, also with enhanced expression of disease-promoting factors (tumor protein p53, Cytochrome c, and Bcl-2-linked X), and stimulated neuronal apoptosis (82). Another report also supported the role of SIRT1 in neuroprotection against apoptosis-induced neuronal damage in a lithium-pilocarpine immature rat model. The expression of miR-181a-5p enhances seizure susceptibility, so its inhibition suppresses seizures through the regulation of SIRT1. Additionally, its inhibition also prevented the hippocampal insult, activation of microglia and astrocytes, neuroinflammation, mitochondrial dysfunction, neuronal apoptosis, and oxidative stress (83).

The Nrf2 has the ability to bind with antioxidant response element (ARE), and the activation of this (Nrf2-ARE) signaling pathway can protect the brain from damage, followed by the epileptic seizure. It was found that elevated levels of miR-495 reduced the NRf2 expression level (84), indicating the role of the Nrf2-ARE pathway in protection from epilepsy. The Janus Kinase (JAK) and signal transducer and activator of transcription (STAT) signal pathway also play a critical role in the development of epilepsy. The overexpressed miR-183 also activated the JAK/STAT pathway, which suppressed the Foxp1 in hippocampal neurons, resulting in apoptosis and hippocampal neuronal injury, which aggravated the epilepsy in rats (85). Its expression is negatively regulated by miR-146a following SE, mediating the synaptic plasticity in neurons of the hippocampus via activating the STAT3 pathway, while its suppression could lessen the synaptic connections and shorten the neurite length (86). Moreover, miR146a is also associated with seizure frequency.

PTEN-induced kinase (PINK) is a protective kinase, regulated by healthy microglia, which protects the cells from mitochondrial dysfunction induced by stress. Its deficiency leads to oxidative stress, mitochondrial fragmentation, and suppression of mitophagy. PINK is a direct target of miR-142, which results in a reduction of PINK expression, while its inhibition in epileptic rats resulted in alleviation of oxidative stress and hippocampal damage, as well as stimulation of mitochondrial autophagy (87). MiR-223 is closely associated with the aggravation of epilepsy-linked abnormalities by targeting ATG16L1 and thus inhibiting microglial autophagy (88). The miR-181b and miR-219 also regulate the expression of excitatory neurotransmitter receptor AMPA-GluR2 and NMDA-R1, respectively, in the amygdala and hippocampus of patients with mTLE, contributing to the pathogenesis of epilepsy. Surprisingly, the association between miR-219 and NMDA-NR1 expression was different in the hippocampus and amygdala of mTLE patients. The expression of NMDA-NR1 was reported to have increased in the amygdala and decreased in the hippocampus, while miR-129 was alleviated in the amygdala and overexpressed in the hippocampus (89). The increased level of NMDA-NR1 may contribute to the generation of seizures and neuronal hyperexcitability, giving a new direction to researchers in the field of epilepsy. MiR-34c exerted negative impacts on cognition (memory and learning functions) via dysregulation of N-methyl-D-aspartate (NMDA) receptors in pentylenetetrazol (PTZ) induced TLE rats (90).

The brain-derived neurotrophic factor (BDNF) and tropomyosin-related kinase type B (TrkB) also aggravate the pathogenesis of epilepsy. It has been reported that miR-132 up-regulation resulted in the down-regulation of BDNF expression level, promoting the epileptogenesis in hippocampus neuron culture of SE (91). The shreds of evidence have indicated that oxidative stress is prompted by the seizure insult, leading to epileptogenesis. Recently, Zhu and co-workers have shown that miR-23a contributes to the generation of oxidative stress damage as well as neuronal injuries with spatial memory deficits in the hippocampus of TLE by targeting ADAM10. They observed that the up-regulation of miR-23a by its agomir aggravated the neuronal injuries, impairment of spatial memory, and oxidative stress in the hippocampus, while the miR-23a antagomirs alleviated these adverse effects (92).

Disease-modifying role in epilepsy

As mentioned above, the increased level of matrix MMP3 could promote the epileptogenesis induced by the stimulation of IL-1β in astrocytes. A protein, reversion-inducing cysteine-rich protein with kazal motifs (RECK), suppresses the MMPs' activity, and it acts as neuroprotective against epilepsy. It was shown that miR-200c-3p decreased the RECK expression in hippocampal tissues of rats with

epilepsy. Conversely, alleviation of miR-200c-3p elevated the expression of RECK, which reduced the apoptosis in the hippocampus. It also decreased the expression of IL-1β, IL-6, and TNF-α, as well as inactivated the Akt signaling pathway (93). In the epilepsy-associated neuroinflammatory process, high mobility group box-1 (HMGB-1) accompanies the process of neurodegeneration and reactive gliosis. Overexpressed HMGB-1 can lead to the activation of monocytes and macrophages that contribute to the neuronal damage, aggravating the progression of SE (94). The miR-29a inhibits the TLE-induced release of inflammatory cytokines (TNF-α and IL-6) and neuronal apoptosis through targeting HMGB1 (95). Being enriched in miRNAs, exosomes are considered a significant communication tool b/w the cells and have been proven as a potential therapeutic technique for the treatment of neurological diseases. Systemic injection of exo-miR129-5p in the SE mice model suppressed the neuroinflammatory factors (TNF-α, IL-6, and IL-1β) and neuronal damage in the CA3 region of the hippocampus. It did so by inhibiting the proinflammatory encoding HMGB1 and the downstream TLR4 gene signaling axis, hence protecting the neurons against degeneration mediated by SE (96). These data provide evidence that exosomes loaded with miR129-5p may be a potential therapeutic strategy to relieve the pathological damage in an epileptic brain.

Ferroptosis is an iron-dependent mechanism of cellular death characterized by lipid peroxide accumulation. P2RX7, a nonselective ligand-gated homotrimeric cation channel, mostly enhances neuronal activity during epileptic episodes. It is particularly activated in pathological conditions, such as neuroinflammation (97). It has been shown that the up-regulation of P2RX7 in epilepsy is associated with the reduction of miR-211-5p expression levels, resulting in hypersynchronization as well as both convulsive and non-convulsive seizures. Li and coworkers have demonstrated that the genetic silencing of P2RX7 or the induction of miR-211-5p expression attenuated the oxidative stress and ferroptosis *in vivo* (98). These results indicate that the miR-211-5p/P2RX7 axis is a unique target for regulating ferroptosis and epilepsy.

Forkhead box D3 (FOXD3), a transcription factor, is confirmed to be involved in the progression of epilepsy by inducing neuron damage via suppressing the expression of sodium voltage-gated channel alpha subunit 2 (SCN2A) (99). Using an epilepsy cell model, researchers confirmed that miR-488-3p inhibits neuronal apoptosis and neuroinflammation by down-regulating FOXD3 and up-regulating SCN2A (100).

The β-catenin/Wnt pathway can affect several cellular processes, including differentiation, proliferation, cell motility, and apoptosis. Its abnormality can result in the development and progression of multiple diseases. The activation of β-catenin/Wnt signaling can be inhibited by up-regulation of miR-136, resulting in reduced neuroinflammatory cytokine levels (TNF-α, IL-6, and IL-1β), inhibition of apoptosis, and thus reducing the duration and frequency of seizures (101).

Insulin-like growth factor 1 receptor (IGF1R) is found in the cytomembranes of microglia, astrocytes, and neurons. In pentylenetetrazole and pilocarpine rat models of epilepsy, IGF1R inhibition has been reported to improve the epileptiform activities, suggesting it is a target for epilepsy therapy (102). Overexpression of miR-194-5-p alleviated the TLE development and the hippocampal cell apoptosis induced by TLE. As IGF1R is the direct target of miR-194-5p, this protective effect was speculated to be executed via targeting IGF1R, but further research is still needed in this field (103). Reduced or dysregulated expression of miR-15a-5 in children with TLE has been confirmed by researchers, but reports on its mechanism of action and molecular targets remain lacking. However, its overexpression can inhibit the hippocampus cellular apoptosis and promote the cell viability (104).

Sex-determining region Y box 7 (SOX-7) has been recognized to prevent apoptosis in hippocampal neuronal cells of epilepsy (105). CircRNA Ubiquilin-1 (circUBQLN-1) serves as a sponge of miR-155. Interestingly, circUBQLN1 has the capability to suppress the process of epileptogenesis by stimulating the expression of SOX-7 by serving as a miR-155 sponge (106). This miR-155/circUBQLN-1/SOX-7 signaling network contributes to the widespread understanding of the unique mechanisms involved in epilepsy. Hence, opening a new avenue to find a novel treatment for epileptogenesis. Acquired functional modifications or genetic mutations lead to a GABAergic neurotransmission dysfunction. A strong relationship b/w inflammatory networks and reduced inhibitory neurotransmitter activity, Gamma Aminobutyric acid (GABA) activity has already been reported in the process of epileptogenesis. Notably, the GABA levels are being regulated by an enzyme known as glutamate decarboxylase-1 (GAD-1). Altogether, these enzymes and signaling circuits play a crucial role in the occurrence of epileptogenesis. The overexpression of miR-322-5p plays a significant role in counteracting the inflammation-associated circuits by targeting NF-kB and toll-like receptor 4 (TLR4), thereby increasing the expression of GABA (107). It also participates in improving the neuronal apoptosis process induced by epileptic insult (108).

The miR-let-7i elicits its effects by mediating the TLR4 signaling network, providing insight into SE pathogenesis. In particular, this miRNA could significantly attenuate the SE degree and prolong the SE latent period, which could be reversed by its antagomir. It might also reduce the action potential frequency and cellular apoptosis following SE (109). A downstream regulator of histone deacetylase-5 (HDAC-5) is a proinflammatory factor, which is known as Hypoxia-inducible-factor-1α (HIF1α), where the downstream target of HIF1α is the PFKFB3 enzyme that may promote neuronal damage in epilepsy. Overexpression of miR-485 can alleviate neuronal apoptosis and neuroinflammatory cytokine production via inhibition of HIF1α, HDAC5, and PFKFB3 in epilepsy (110). It has been reported that the overexpression of miR-135b-5p has attenuated the seizure-induced cellular apoptosis and improved the cell viability by targeting SIRT1 (111). The implications of miRNAs in epilepsy, along with their targets, have been summarized in Table 3. Graphical representation of disease-promoting and disease-modifying miRNAs is shown in Figure 3.

Traumatic brain injury

Traumatic brain injury (TBI) is defined as the modifications in brain functionality, or other pathological alterations, following external force, such as accidents, etc. Globally, it is a cause of serious injuries leading to neurological disability and even death. Every year, around 69 million individuals suffer from TBI, and approximately

Table 3. Implications of miRNA in epilepsy

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-146a	CFH, NF-kB	↑Neuroinflammation	KA-IH rat model, U251 cells, TLE patients	(75)
		STAT3 pathway	↑Abnormal synaptic connections	PTZ mouse model, Primary hippocampus neuronal cells	(86)
	miR-135a-5p	Caap1	↑Neuronal apoptosis	Children with TLE	(76)
	miR-135a	*Mef2a*	↑Abnormal plasticity and synaptic functions	KA-IAK mouse model	(77)
	miR-155	Akt/PI3K/mTOR signaling	↑Neuroinflammation	HT22 mouse hippocampal cells	(79)
		MMP3	↑Epileptogenesis	TLE patients, primary astrocyte culture	(80)
	MiR-21-5p	PTEN	↑Cognitive impairment and neuronal damage	KA-IH rat model	(81)
	miR-128	SIRT1	↑Neuronal apoptosis	Pilocarpine-induced TLE rat model	(81)
	miR-181a-5p	SIRT1	↑Neuronal apoptosis and seizure susceptibility	Lithium-pilocarpine rat model	(83)
	miR-495	Nrf2-ARE signaling	↑Neuronal damage and oxidative stress	Lithium-pilocarpine rat model, hippocampal neuronal cell culture	(84)
	miR-183	JAK/STAT signaling	↑Neuronal apoptosis	Lithium-pilocarpine rat model, hippocampal neuronal cell culture	(85)
	miR142	PINK	↑Oxidative stress and hippocampal damage, restrain mitophagy	Lithium-pilocarpine rat model	(87)
	MiR-223	ATG16L1	Restrain microglial autophagy	TLE patients, KA-ICV mice model	(88)
	miR-219	NMDA-NR1	↑Neuronal hyper-excitability	TLE patients	(89)
	MiR-34c	NMDA receptor	Cognitive impairment	PTZ rat model	(90)
	miR-132	BDNF	↑Epileptogenesis	Children with TLE	(91)
	miR-23a	ADAM10	↑Oxidative stress and neuronal damage, cognitive decline	Primary hippocampal neuronal cell culture	(92)
Disease-modifying role	miR-200c-3p	RECK	↓Neuronal apoptosis and neuroinflammation	Lithium-pilocarpine rat model	(93)
	miR-29a	HMGB1	↓Neuronal apoptosis and neuroinflammation	TLE patients, primary hippocampal neuronal cell culture	(95)
	MiR-129-5p	HMGB1	↓Neuronal apoptosis and neuroinflammation	KA-IP mice model	(96)
	MiR-211-5p	P2RX7	↓Neuronal apoptosis and oxidative stress	Epileptic patients, KA-IH mice models	(98)
	MiR-488-3p	FOXD3	↓Neuronal apoptosis and neuroinflammation	SH-SY5Y cells, Pilocarpine rat model	(100)
	miR-136	β-catenin/Wnt	↓Neuronal apoptosis, neuroinflammation, and seizure frequency and duration	Lithium-pilocarpine rat model	(101)
	miR-194-5p	IGF1R	↓Neuronal apoptosis	Children with TLE	(103)
	miR-155	circUBQLN-1/SOX-7 signaling network	↓Neuronal apoptosis and epileptogenesis	TLE patients, human hippocampus neuronal cell line	(106)
	miR-322-5p	NF-kB, TLR4	↓Neuroinflammation and neuronal apoptosis	Lithium-pilocarpine rat model	(108)
	miR-485	HIF1α, HDAC5, and PFKFB3 signaling	↓Neuronal apoptosis and neuroinflammation,	Huh7 and $HepG_2$ human HCC cell line	(110)
	miR-135b-5p	SIRT1	↓Neuronal apoptosis, ↑Cell viability	Children with TLE	(111)

80–90% of such cases account for mild TBI (mTBI)(112). Instead of progress in the pathophysiological understandings of TBI, people are still suffering from lifelong neurological deficits with mild to severe TBI.

Disease-promoting role in TBI

Among the multifaceted pathological alterations in TBI, neuroinflammation plays a significant role as a secondary injury process, exerting either beneficial or detrimental effects in the process of CNS damage following TBI. Dual specificity phosphatase-1 (DUSP1), a MAPK phosphatase-1 (MKP-1), can modulate the MAPK signaling pathway, thus regulating cellular proliferation and cell death. miR-429 targets the DUSP1 signaling pathway in activated microglia and stimulates increased expression of pro-inflammatory factors following TBI. Hence, its inhibition can impede the NF-κB and MAPK-p38 pathways regulated by DUSP1, thereby inhibiting the microglia activation (113). Persistent and robust neuroinflammatory responses after TBI are also associated with elevated expression of miR-155 in

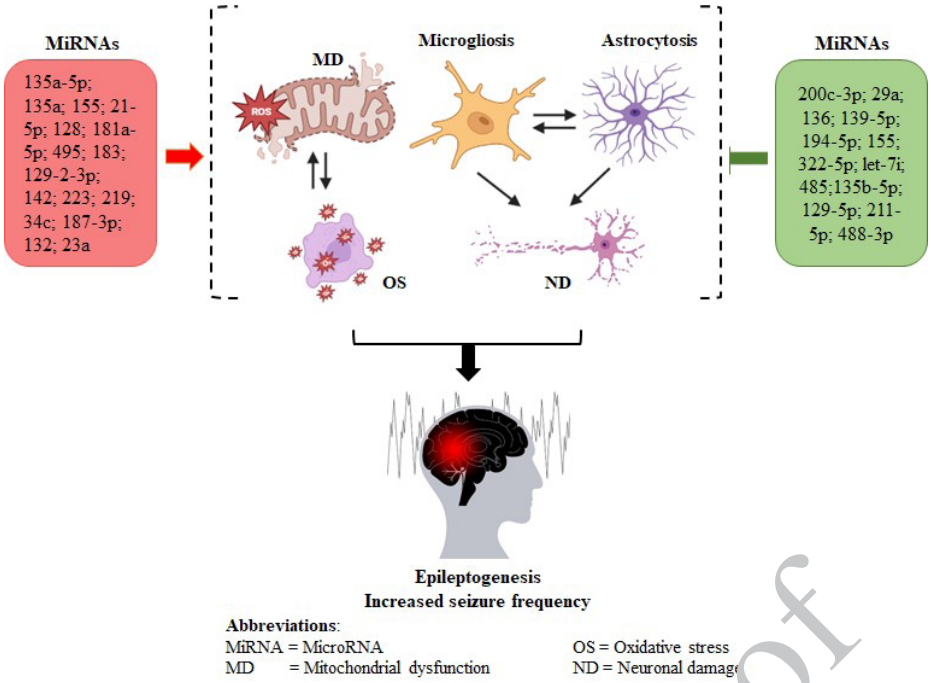

Figure 3. Role of microRNA as disease-promoting and disease-modifying in epilepsy

macrophages/microglia, while its inhibition can alleviate the post-traumatic inflammatory response and improve the neurological recovery (114).

NLRP3 inflammasome is a cytoplasmic protein that is a main component of inflammation regulators in response to injury. Its assembly promotes the IL-1β maturation leading to neuroinflammation in neurodegenerative diseases. Higher expressions of miR-200a-3p associated with NLRP3 have been reported in sepsis-prompted brain injury. It promotes sepsis via Keap1/HO-1/ROS/Nef2 induced NLRP3 (115). The BBB is crucial for the maintenance of cerebral homeostasis and to protect the brain from pathogenic attack. TBI damages the BBB, leading to local inflammatory responses, brain edema, and neuronal excitability that lasts for days to years if left untreated. Overexpression of miR-21-3p has been reported be associated with BBB damage aggravation after TBI by promoting inflammation and cellular apoptosis. Hence, its down-regulation may restore the BBB damage following TBI (116). Another miRNA, named miR-423-3p, has been reported to be significantly associated with TBI, which is highly overexpressed in early trauma. It is highly correlated with the consciousness impairment and severity of injury after TBI (117). Thus, it could be a promising biomarker for the identification of the severity of injury. Higher expressions of miR-203 after injury are the leading cause of dementia markers such as **tau** hyperphosphorylation and apoE4 expression. One study has claimed that miR-203 inhibition can suppress these TBI-induced expressions as well as inhibit the neuronal damage. It also improved the memory deficits and hippocampus-associated learning. Additionally, it prevents neuronal apoptosis via elevation of Bcl-2 expression and inhibition of caspase-3 activity (118). miR-9-3p and miR-136-3p have also been reported, both in humans and experimental models of mTBI, to be associated with disease severity. Increased levels of these miRNAs were found in the plasma of mTBI patients, in correlation with elevated plasma S100B levels (119).

Microvessels in the neurovascular unit become damaged after a TBI, disrupting the blood supply and exacerbating neuronal loss around or at the site of injury. Neovascularization is supposed to lessen the functional neurological loss and partly reverse the pathological state following TBI. Evidence has suggested that the down-regulation of miR-491-5p can promote the neovascularization, improve the neurological functions, and restore the cerebral blood supply after TBI. It is thought to be mediated by the elevation of metallothionein-2 (MT2) expression that regulates the HIF-1α/ vascular endothelial growth factor (VEGF) signaling pathway and reduces oxidative stress (120). The miR-9-5p level has been reported to be elevated in brain tissue after TBI, but its effects depend solely on the phase of injury. The down-regulation of miR-9-5p during the chronic phase could improve the recovery of neurological function by enhancing the release of astrocyte-derived neurotrophic factors and endorsing astrocyte proliferation around injured tissues following TBI. Its down-regulation leads to the activation of the Notch/TAK1/CYLD pathway in neurons of the neurovascular unit (NVU) and allows synapse remodeling by promoting the Thbs-2 expression in astrocytes (121).

Bcl-2 is particularly associated with the augmented marker genes for osteoblast and reduced osteoblast apoptosis, and cyclin D1 is a significant regulator of the progression of the cell cycle. Reduction in miR-16-5p in TBI can accelerate the bone formation by suppressing apoptosis and endorsing osteoblast proliferation through induction of cyclin-D1 and Bcl-2. Hence, its inhibition accelerated the fracture healing in the mouse model of fracture. A flow cytometry investigation has shown that miR-16-5p overexpression halts the cell cycle progression and induces apoptosis (122). Downstream activation pathways of BDNF, MAPK/Ras, and PI3K/Akt signaling pathways play a significant role in cell survival, development, and differentiation, as

well as cognitive function, such as learning and memory (123). These pathways are being targeted by miR-124-3p, resulting in disease aggravation and cognitive decline after TBI. Disruption or down-regulation of miR-124-3p has intensified the activation of Ras and PI3K/Akt signaling pathways, and thus improved the neuronal survival and cognitive performance in a mouse model of TBI (124).

Research on ischemic stroke indicated that both pharmacological inhibition and genetic silencing of miR-15a/16-1 in murine models led to a notable reduction in brain infarction and neuronal apoptosis. These interventions were associated with enhanced short-term sensorimotor function following ischemic stroke (125). Then, a study investigates the role of miR-15a/16-1 in experimental TBI models. The research used various experimental models to demonstrate that inhibiting miR-15a/16-1 reduced neuroinflammation, neuronal apoptosis, and enhanced neurogenesis. The recovery was also linked with the improved motor and cognitive functions in TBI models (126).

Disease-modifying role in TBI

Nevertheless, excessive and sustained neuroinflammation can aggravate the neuronal apoptosis post-TBI. It is principally propagated by microglia in the injured brain, and the altered ratio of M2/M1 has been reported to be involved in the exacerbation of brain damage after TBI. It has been reported that the overexpression of let-7c-5p can attenuate the TBI-mediated brain edema as well as neurological dysfunction. It inhibits the neuroinflammation and alleviates microglial activation, both by elevating M2 polarization and reducing or halting M1 polarization. Moreover, it also inhibits the expression of caspase-3 by targeting PKC-d, as it mediates the effects of caspase-3 (127). Likewise, miR-124-3p also promotes the M2 polarization in microglial cells, and exosomal miR-124-3p inhibits the neuronal inflammation by suppressing the mammalian target of rapamycin (mTOR) signaling activity mainly via inhibiting the PDE4B gene expression (128). It is noteworthy to mention that exosomes (Exos) are a type of bioactive nanomaterial with the potential to regulate cellular functions. They achieve this by releasing active cargo, including miRNAs, which can bind to target mRNAs to control their expression and degradation, with minimal impact from internal and external environmental factors. In addition to promoting M2 polarization in microglial cells and inhibiting neuronal inflammation, miR-124-3p also exhibits neuroprotective effects against Endoplasmic reticulum (ER) stress. ER stress contributes to neuronal damage following repetitive mild TBI that can trigger apoptotic pathways, inflammation, and oxidative stress (129). Wang and colleagues explored that microglia-derived exosomes enriched with miR-124-3p effectively reduce apoptosis and ER stress.

The miR-124-30 alleviates the IRE1α expression, which was confirmed by the specific binding of miR-124-3p to an ER stress-related protein, inositol-requiring enzyme 1α (IRE1α), thereby mitigating ER stress in injured neurons. microglia-derived exosomes containing miR-124-3p were intranasally delivered in a mouse model of repetitive mild TBI, which significantly reduced apoptosis and ER stress in hippocampal neurons (130). Hence, this suggests that the miR-124-3p transferred via microglia-derived exosomes may offer neuroprotection by reducing ER stress, indicating a promising therapeutic approach for repetitive mild TBI.

It is also speculated that activated microglia may suppress synapse recovery and neurite outgrowth after TBI, partially by down-regulating exosomal miR-5121. Both *in vitro* and *in vivo* studies have confirmed that miR-5121 overexpression in microglia-derived exosomes can somewhat reverse the suppression of synapse recovery and neurite outgrowth following TBI (131). Hence, microglial exosomes manipulated by miRNAs can be a novel therapeutic strategy for TBI and other neurological diseases as well. One of the significant components of astrocyte-derived exosomes is miR-873a-5p, which allows microglia-astrocyte interaction. These miR-873a-5p-enriched astrocyte-derived exosomes promote M2 microglial polarization through inhibition of NF-κB p65 and ERK phosphorylation, thereby improving cerebral injury and ameliorating neurological function following TBI (132). MiR-124 is also implicated in microglia M2 polarization. Using the C57BL/6 TBI mouse model and BV2 microglia culture, the research demonstrates that miR-124 inhibits TNF receptor-associated factor 6 (TRAF6) expression, thereby attenuating activation of neuroinflammatory pathways, including the toll-like receptor (TLR4) pathway, and promoting M2 microglial polarization. Apart from its function of inhibiting TRAF6-induced neuroinflammation, miR-124 has also been related to the enhancement of neuronal survival and promotion of neuroprotection after traumatic brain injury. It increased the expression of anti-inflammatory factors (IL-4, IL-10, and TGF-β) and decreased the expression of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6)(133). The research highlights the therapeutic potential of miR-124 regulation as a potentially effective approach to alleviate the deleterious consequences of neuroinflammation in traumatic brain injury.

Interestingly, MiR-126 also executes its neuroprotective effects against sepsis-induced injury by inhibiting the activity of the NF-κB signaling pathway, thereby impeding the neuroinflammatory responses and oxidative stress post-TBI (134). miR-146a mimics also ameliorate the severity of TBI by inhibiting the NF-κB signaling pathway, followed by a relative reduction of phosphorylated IκBα and JNK. It rescued the NVU dysfunction and improved the memory and learning ability as well as alleviated the level of IL-1β, TNF-α, and IL-6 both in serum and brains of TBI mice model (135). It has been well demonstrated that the activation of the mTOR/AKT signaling pathway mediates the neuroprotective effects after TBI by suppressing neuronal apoptosis. Whereas PTEN acts as a negative regulator of this signaling pathway, and its inhibition could also improve the TBI-associated neuronal damage. Li and colleagues have reported that miR-23a up-regulation can inhibit neuronal apoptosis and neuroinflammatory responses by preventing activation of the PTEN/mTOR/AKT signaling pathway (136).

Significantly, miR-331 shows substantial down-regulation in brain tissue within 12 hours of TBI (137). Research demonstrated that intranasal delivery of miR-331 mimics can suppress the reactive gliosis, reduce neuroinflammation, and enhance cognitive function in a mouse model of hippocampal stab injury (HSI). Mechanistically, IL-1β is directly targeted by miR-331 following HIS (138).

In TBI patients with fractures, it has been speculated that sustainers of TBI have faster healing times as compared

to individuals with isolated fractures. It has been shown that miRNA-26a-5p overexpression has improved fracture healing by down-regulating PI3K/AKT and PTEN signaling (139). So, it could be a novel therapeutic strategy to improve fracture healing. It has been thought that elevated connexin43 phosphorylation by ERK1/2 is linked with the early cerebral ischemia-induced brain damage (140). In the shear stress-induced cell model of TBI, augmented miR-302 expression repressed the connexin43 phosphorylation and ERK1/2. It has also significantly ameliorated the cognitive impairment and improved TBI-associated brain damage in rats by suppressing edema (141).

Stimulator of interferon genes (STING) plays a significant role in neuroinflammatory response after brain injury (142). A downstream target of let-7i is STING after traumatic brain injury, making it a novel candidate for neuroinflammation-related injury. Let-7i agomir significantly reduced the neuroinflammatory response, glial scars, and neuronal apoptosis and improved the cognitive deficits following brain injury via targeting STING (143). Death-associated protein kinase-1 (DAPK-1) stimulates neuronal apoptosis during ischemic stroke and other NDDs via phosphorylation of NR2B (p-NR2B). It is a subunit of the NMDA receptor that regulates calcium influx, which is important for the maintenance of neuronal plasticity and normal cellular function (144). Evidence has shown that inhibition of NR2B phosphorylation can reverse the neurological impairments induced by TBI (145). Overexpression of miR-124 could inhibit the expression of DAPK-1 and thereby reduce the phosphorylation of NR2B, improve motor and behavioral functions, and attenuate apoptosis associated with TBI (146).

With important consequences for the development of ischemic injury, ELAVL1 regulates ischemia/reperfusion injury, cancer, and cellular iron death. According to earlier studies, autophagy regulation via ELAVL1 activation by FOXC1 increases iron death in myocardial ischemia/reperfusion injury. TBI is also associated with vascular endothelial growth factor (VEGF), with higher levels of VEGF and MMP-9 following a TBI leading to the disruption of the blood-brain barrier and subsequent neurological impairment. By inhibiting ELAVL1 and down-regulating VEGF expression, MiR-9a-5p reduces brain tissue injury in TBI rats by targeting the ELAVL1/VEGF signaling system (147), indicating that these molecules may have therapeutic promise in the treatment of brain tissue injury. Because of its proven neuroprotective, anti-inflammatory, and antioxidant qualities, ursolic acid (UA) is a viable treatment option for a number of neurological conditions. Numerous studies have shown that UA is neuroprotective against brain damage. It dramatically lowers oxidative stress, neuroinflammation, neuronal death, and cerebral edema. It has been demonstrated that UA enhances TBI outcomes in mice by up-regulating the PDCD4/PI3K/AKT signaling pathway, which is mediated by miR-141. Furthermore, in neurons injured by TBI, miR-141-3p specifically targets PDCD4, a regulator of the PI3K/AKT pathway. These results lend credence to UA's possible therapeutic use in the management of traumatic brain injury (148).

The implications of miRNAs in TBI, along with their targets, have been summarized in Table 4. Graphical representation of disease-promoting and disease-modifying miRNAs is shown in Figure 4.

Depression

Depression is a prevalent psychiatric disorder characterized by loss of self-confidence and anhedonia, driven by public health issues. Almost 17% of the global population is affected by depression and other stress-associated mood disorders, which are associated with an

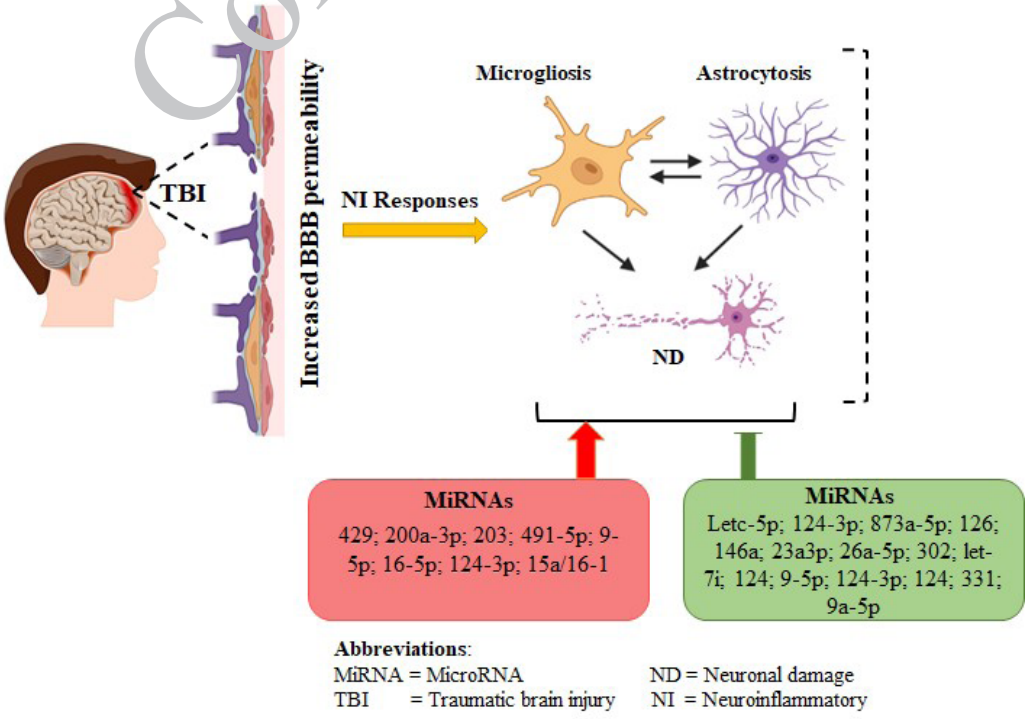

Figure 4. Role of microRNA as disease-promoting and disease-modifying in traumatic brain injury

Table 4. Implications of miRNA in traumatic brain injury (TBI)

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-429	DUSP1	↑Neuroinflammation	TBI patients, TBI mice model	(113)
	miR-200a-3p	Keap1/HO-1/ROS/Nef2 pathway	Promote sepsis	TBI mouse model, HBMEC cell line	(115)
	miR-203	Bcl-2, caspase-3	↑Neuronal apoptosis, cognitive decline	TBI mouse model	(118)
	miR-491-5p	HIF-1α/VEGF	↓Neovascularization, ↑oxidative stress	TBI mouse model, BMEC cell line	(120)
	miR-16-5p	cyclin-D1 and Bcl-2	↑Apoptosis, halts the cell cycle	Fracture and TBI patients and a mouse model, MC3T3-E1 cells	(122)
	miR-124-3p	Ras and PI3K/Akt	↑Neuronal apoptosis, cognitive decline	TBI rat model	(124)
	miR-15a-161	-	↑Neuronal apoptosis, neuroinflammation, and ↓neurogenesis	miR-15a/16-1–KO and WT mice, C57BL/6J mice	(126)
Disease-modifying role	let-7c-5p	PKC-d	↓Neuroinflammation	TBI mouse model, primary mouse microglia	(127)
	Exosomal miR- 124-3p	PDE4B	↓Neuroinflammation	TBI mouse model, microglial BV-2 cells, primary cortical neuronal cells	(128)
	MiR-124-3p	IRE1α	↓ER stress and apoptosis	rmTBI mouse model and HT22 neuronal cells	(130)
	miR-873a-5p	NF-κB and ERK phosphorhylation	Improve neuronal functions and cerebral injury, ↓neuroinflammation	TBI patients, TBI mouse model, primary astrocytes, and microglial cells	(132)
	MiR-124	TRAF6	↓IL-1β, IL-6, and TNF-α ↑IL-4, IL-10, and TGF-β	C57BL/6 TBI mice model and BV2 microglia culture	(133)
	MiR-126	NF-κB	↓Neuroinflammation and oxidative stress	Sepsis rat model	(134)
	miR-146a	NF-κB	↓Neuroinflammation, NVU recovery,	TBI mice model	(135)
	miR-23a-3p	PTEN/mTOR/AKT	↓Neuroinflammation and neuronal apoptosis	TBI mice model	(136)
	MiR-331	IL-1β gene	↓Neuroinflammation, reactive gliosis, improve cognitive functions	C57BL/6J TBI mice model, Astrocyte and microglia culture	(138)
	miR-302	connexin43, ERK1/2	Improve cognition	TBI rat model, SH-SY5Y cells	(141)
	let-7i	STING	↓Neuroinflammation and neuronal apoptosis	TBI mice model	(143)
	miR-124	DAPK1	Improve motor and behavioral functions, neuronal apoptosis	TBI patients, TBI mice model	(146)
	MiR-9a-5p	ELAVL1	Improve brain tissue injury	TBI rat model	(147)
	miR-141-3p	PDCD4	↓Neuroinflammation, oxidative stress, and neuronal apoptosis	TBI mice model	(148)

elevated suicide rate. The pathophysiology of depression includes aberrant processing of information in brain circuits and disruption of cellular networks that regulate cognition and mood. This can lead to altered structural and synaptic plasticity, which can be critical in the development and progression of major depressive disorder (MDD)(149).

Disease-promoting role in depression

Dysregulated expression of miRNA has been observed in both the human brain tissues (post-mortem) and animal models suffering from depression. MiR-124 is abundantly found in the brain and has the potential to regulate adult neurogenesis, synaptic plasticity, and neuronal differentiation. The expression of miR-124 can be dysregulated by the elevated corticosterone (CORT) and cortisol levels. Stress exposure leads to increased corticosterone (CORT) levels in rodents, which in turn up-regulate miR-124 expression in the prefrontal cortex. In humans, elevated cortisol levels have been similarly associated with higher miR-124 expression in the serum of patients with MDD (150). Moreover, the higher level of CORT also altered the brain-derived neurotropic factor (BDNF). Alternatively, miR-124 inhibition ameliorated the changes in BDNF induced by CORT and produced the antidepressant-like actions via activation of the BDNF/TrkB signaling pathway (151). From these reports, one can postulate that miR-124 is strongly associated with depression pathophysiology, and it could be a great target for antidepressant treatments and drug development as well.

Chronic stress exposure can also negatively impact synaptic plasticity by stimulating alterations in the trophic factors production, neurogenesis in adult hippocampus, and neuronal morphology, leading to impairment in memory and learning processes. MiR-30 family's miRNAs mediate the depression like phenotypes by modifying the hippocampal neuroplasticity and neurogenesis via modulating the transcription and epigenetic regulators like *Runx1* and *Mll3,* as well as cell signaling mediators such as *Nrp1*, *Gpr125*, *Ppp3r1*, and *Socs3* (152).

Up-regulation of miR-200a and 200b-3p (miR-200a/b-3p) is associated with the chronic unpredictable mild stress (CUMS) that promotes anxiolytic behavior and apoptosis via targeting nuclear receptor sub-family-3 group C-member-1 (NR3C1). It executes its effects by down-regulating the expression of NR3C1, elevating the expression of Bax and cleaved caspase-3, and alleviating Bcl-2 (anti-apoptotic protein), thereby promoting neuronal death and stress-related behaviors (153). miR-382-5p also modulates the

expression of NR3C1 following stress and depression. In the rat model of depression, it reduced the expression of p-TrkB and NR3C1, downstream targets of BDNF, in hippocampal tissues, highlighting its role in depression. It was also confirmed by using lentivirus miR-382-5p and lentivirus si- miR-382-5p. BDNF, p-TrkB, and NR3C1 were up-regulated by si-miR-382-5p, while opposite effects were observed by using si-miR-382-5p (154). As it is known that a single protein can be targeted by several miRNAs, here is another target of NR3C1, named miR-139-5p. In an animal model of depression, its inhibition significantly elevated the sucrose-preference index, alleviated neuronal damage, increased NR3C1, BDNF, p-TrkB/TrkB, p-CREB/CREB, and p-ERK/ERK. On the other hand, up-regulated miR-139-5p expression reduced its novel target NR3C1 (155). The miR-182 and miR-382 directly target the BDNF and reduce its expression in post-stroke depression (PSD), indicating the involvement of miR-382 and miR-182/BDNF signaling pathways in PSD (156). Another BDNF-targeting miRNA is MiR-202-3p, which is associated with the aggravated depression-like behavior and reduced BDNF levels in the hippocampus (157).

The miR-345-5p induces the inflammation-associated damage in neuronal cells of the hippocampus via activation of microglia. The SOCS-1 can potentially inhibit the TLR and cytokines signaling pathway, thus terminating the signal cascade in time (158). The miR-345-5p directly targets the SOCS-1, resulting in a reduction in Bcl-2 and SOCS-1 expression and an increase in Bax level, hence aggravating the neuronal apoptosis in the hippocampus (159). Epigenetic regulator miR-15b inhibits the proliferation of neuronal progenitor cells (NPCs) and is reported to be up-regulated in the medial prefrontal cortex, suggesting a role in major depression. The miR-15b-5p could critically attenuate the excitatory synaptic transmission, VAMP-1/STXBP3A (synaptic proteins) expression, and activities in the nucleus accumbens following CUMS (160).

A study showed that the knockdown of miR-497a-5p could alleviate the depression-like behavior in rats as well as repress the microglial activation, thereby inhibiting neuroinflammation (161). Elevation of HECT domain E3 ubiquitin protein ligase 1 (HECTD1) could restore the neuronal functions and improve the BBB injury. Moreover, it could also regulate the activation of astrocytes (162). Another study claimed that the up-regulated HECTD1 expression might inhibit the activation of microglial cells, thereby alleviating the symptoms of depression (163). Consistent with these studies, Chen and Cao (2023 confirmed that miR-497a-5p targets the HECTD1 to promote neuroinflammation and neuronal apoptosis in depression, while its inhibition can restrain these effects in BV2 cells and hippocampal neuron cells (HT22). Interestingly, Circular RNA (circRNA) circ-Bnc2 can inhibit neuronal apoptosis and neuroinflammation by positively regulating HECTD1 expression via miR-497a-5p sponging (164), suggesting a potential therapeutic target for depression treatment.

Disease-modifying role in depression

Some studies have indicated the health-promoting role of miR-132 (brain-enriched miRNA) during adult neurogenesis, such as differentiation and proliferation of neural stem cells, synaptic plasticity, and dendritic morphogenesis regulation (165, 166). It is also predicted to be involved in the regulation of multiple neuronal membranes and biological pathways, and dysregulation of miR-132 may contribute to the pathogenesis of MDD (167). Dysregulation of MiR-132 in MDD is also linked with lower volume of grey matter and fractional amplitude of low frequency fluctuations (fALFF) in amygdala and hippocampal nuclei, thus resulting in cognitive impairment associated with the relevant brain region (168). Connective tissue-growth factor (CTGF) plays a significant part in both the pathological and physiological activities. Implications of CTGF in the pathogenesis and progression of depression have already been confirmed. miR-133b is poorly expressed in the hippocampus, whereas CTGF is highly expressed following depression. Conversely, up-regulation of miR-133b and inhibition of CTGF in rats could control neuronal apoptosis in the hippocampus, suppress the inflammatory response, and enhance BDNF expression in hippocampal tissues, highlighting the protective efficacy of miR-133b against neuronal injury and subsequent depression (169). It is noteworthy that overexpressed miR-133b could repress the CTGF expression, providing protection against hippocampal neuronal apoptosis and inflammatory reactions in depression.

CUMS results in the activation of ASK1/Dyrk1A/JNK signaling pathway leading to neuronal apoptosis and stress-like behaviors, particularly in the cornu Ammonis (CA1) of the hippocampus. miR-211-5p promotes anti-depressant effects by targeting ASK1/Dyrk1A/JNK signaling pathway, resulting in restrained neuronal apoptosis in CA1 (170). Therefore, the Dyrk1A/miR-211-5p pathway could critically be involved in the depression pathogenesis and may serve as a novel therapeutic candidate to treat depression.

Lately, it has been found that the miR-204-5p expression within the dentate gyrus (DG) of the hippocampus is considerably down-regulated after chronic unpredictable stress (CUS), in association with the deterioration of neurons induced by oxidative stress in the rat model of CUS. In contrast, miR-204-5p overexpression in DG alleviated the neuroinflammation and oxidative stress via directly targeting a G-protein signaling-12 regulator (RGS-12), concomitant with improvement in depression like behaviors. In particular, RGS-12 is a downstream targeted gene of miR-204-5p that stimulates the inflammation and oxidative stress in DG by regulating the NF-κB/Nrf2 signaling pathway (171). The miR-26a-3p could alleviate neuronal damage coupled with CUMS induced depression by suppressing, via suppression of the PI3K/Akt/ PTEN signaling pathway. The protective efficacy of this miRNA was also confirmed by knocking down miR26a-3p in a rat model of CUM induced depression. The suppression of miR-26a-3p in the DG induced depression-linked phenotypes, accompanied by PI3K/Akt/PTEN pathway activation and neuronal anomalies, including autophagy repression, synaptic plasticity impairments, and elevated neuronal apoptosis (172).

Microglial activation is associated with the development and progression of numerous neurological diseases, leading to inflammation aggravation and neuronal apoptosis. Notably, the correlation between neuroinflammation and psychiatric disorders has been reported, and the expression levels of inflammatory markers act as crucial indicators of the occurrence and development of depression (173). In a

CUMS mouse depression model, miR-29a-5p was shown to be down-regulated, which consequently promoted the microglia M1 polarization via up-regulating the TMEM33 expression. This increased inflammatory chemokines, resulting in neuronal apoptosis. On the contrary, the miR-29a-5p up-regulation in the prefrontal cortex (PFC) repressed the expression of TMEM33, facilitated the M2-polarization of microglia, and improved the depressive-like behaviors (174). The data suggest that the miR-29a-5p/TMEM33 axis may serve as a potential therapeutic target for depression treatment. However, this study has some limitations because patient samples were not included.

Another catalyst for the activation of microglia is enhancer of zeste homolog 2 (EZH2), which is a regulator of methylation in the neuroinflammatory process in the development of depression. In the mouse forebrain, it retarded the neuronal activities and induced depression-like behavior (175). Chemokine C-X-C ligand 10 (CXCL10) expression has also been reported to be up-regulated in patients with depression, which is a functional target of miR-15a (176, 177). It has been reported that elevation of miR-15a-5p or down-regulation of EZH2 attenuated the hippocampal proinflammatory cytokines, improved depressive behaviors, and inhibited the hippocampal neuronal apoptosis by inhibiting the expression of CXCL10 (178). Neural stem cells (NSCs) derived extracellular vesicles (EVs) are highly rich in proteins and miRNAs involved in anti-apoptosis, neuroprotection, anti-oxidant, anti-inflammatory, BBB repair, and neurogenic activities, as well as proteins and miRNAs that promote synaptic plasticity and synaptogenesis. The MYB family of proteins, is associated with the pro-apoptotic activity. Min *et al.* (2014) showed that NSC-EVs carry miR-16-5p, which reduces neuronal apoptosis and injury by targeting MYB, both *in vivo* and *in vitro* (179).

Bone marrow (BM) mesenchymal stem cells (BM-SCs) derivative exosomes have been widely used as disease therapeutics. In depressed rats, BM-SCs derivative exosomes increased the expression of miR-26a in hippocampal tissues, resulting in restrained apoptosis and improved neuronal damage. Moreover, BM-SCs associated up-regulation of miR-26a elevated the superoxide dismutase (SOD), whereas reduced the level of lactate dehydrogenase (LDH), IL-1β, tumor necrosis factor α (TNF-α), and malondialdehyde (MDA) in serum and hippocampal tissues (180). However, further studies need to be done for better clarification of the precise mechanism of the BM-SCs-derivative exosomes in depression. Corticotropin-releasing hormone-receptor-1 (CRHR-1) and nuclear enriched-abundant transcript-1 (NEAT-1) have been associated with the progression of depression and depression-like behaviors. NEAT-1, in particular, binds with miR-320-3p to upsurge the expression of CRHR-1, thus promoting apoptosis and neuronal injury in the hippocampus of depressed rats. Fascinatingly, up-regulating miR-320-3p and silencing NEAT-1 improve behavioral phenotypes, suppress apoptosis, and attenuate neuronal anomalies in the hippocampus (181). This study enlightens the binding relation b/w miR-320-3p and NEAT-1 and the targeting relation b/w CRHR1 and miR-320-3p. The implications of miRNAs in depression, along with their targets have been summarized in Table 5.

Migraine

Migraine is one of the extremely persistent neurological conditions, and its one-year prevalence in Western Europe and the United States is 6% in males and 15 to 18% in females (11% average). According to the World Health Organization (WHO), it is listed as the 6th leading cause of death because of its heavy social and economic burdens (182). It is awfully disabling for the suffering individuals because of high-intensity pain and the characteristics of linked symptoms during attacks, such as vomiting, nausea, photophobia, and phonophobia. The quality of life is more disturbed in the case of migraine with aura, happening in

Table 5. Implications of miRNA in depression

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-200a/b-3p	NR3C1	↑Anxiety and neuronal apoptosis	Rat depression model	(153)
	miR-382-5p	NR3C1	↑Anxiety and neuronal apoptosis	Rat depression model	(154)
	miR-139-5p	NR3C1	↑Neuronal apoptosis	Mice depression model, HT22 cells	(155)
	miR-182 and miR-382	BDNF	Aggravate depression-like behavior	Post-stroke depression rat model	(156)
	MiR-202-3p	BDNF	Aggravate depression-like behavior	SK-N-MC and SH-SY5Y cells	(157)
	miR-345-5p	SOCS-1	↑Neuroinflammation	BV-2 microglial cells	(159)
	miR-497a-5p	HECTD1	↑Neuroinflammation and neuronal apoptosis	BV2 and HT22 cells	(164)
Disease-modifying role	miR-133b	CTGF	↓Neuroinflammation and neuronal apoptosis	Rat depression model	(169)
	miR-211-5p	ASK1/Dyrk1A/JNK	↓Neuronal apoptosis	Rat depression model	(170)
	miR-204-5p	RGS-12	↓Neuroinflammation and oxidative stress	Rat depression model	(171)
	miR-26a-3p	PI3K/Akt/ PTEN	↓Neuronal damage	Rat depression model	(172)
	MiR-29a-5p	TMEM33	↓Neuroinflammation and neuronal apoptosis	CUM mice model	(174)
	MiR-15a-5p	CXCL10	↓Neuroinflammation and neuronal apoptosis	CUM mice model	(178)
	miR-16-5p	MYB	↓Apoptosis and neuronal injury	CORT mice model. PC12 cells	(179)
	miR-320-3p	CRHR1	↓Neuronal damage	Rat depression model	(181)

approximately 1/3rd of individuals, where pain is generally accompanied or preceded by a transient focal neurological symptom, recurrently involving paresthesia, language, or visual disturbance. At present, there is still a dearth of existing clinical markers for migraine, and their diagnosis is strictly dependent on the clinical symptoms, which brings substantial difficulties for clinical diagnosis (182). Indeed, patients with migraine are 2-fold more prone to ischemic stroke risk, and this risk can also be elevated by the enhancement in attack frequency, with young people and women being typically affected. Despite progress in recent years, the complete pathophysiology remains unclear, which directly reflects the limited availability of therapies and the frequent unsatisfactory medical reduction or control of symptoms (183). So, the enhanced interest has consequently been developed in researchers to hunt for the new biomarkers that could not only be helpful in early diagnosis of disease but also provide the sufferers with different therapeutic options. On the basis of this, altered miRNA expression levels in migraine patients have also been hypothesized, although insufficient preliminary work has so far been done in this respect.

Disease-promoting role in migraine

Endothelial dysfunction (ED) has been acknowledged in both patients with syncope and migraine patients. The ED is characterized by endothelial cell dysregulation, including abnormal proliferation, migration, and morphogenic capabilities. Patients with migraine have been documented with impaired function and reduced numbers of endothelial progenitor cells, as well as vascular dysfunction. Remarkably, the miRNAs have the capability to regulate the functions of vascular endothelium, and a study was also carried out to investigate the association of altered circulating levels of endothelial-specific miRNAs (miR-155, miR-21, Let-7g, and miR-126) with endothelial function in migraine sufferers. Surprisingly, the researchers found the elevated expression of miR-126, Let-7g, and miR-155. Moreover, the levels of miR-126 and miR-155 were connected with the syncope frequency in past years of migraine patients (184)miR-126, miR-21, and Let-7g. Microglia-pathic pain is thought to be stimulated by aberrant neuronal discharge by reactive microglial cells. They release pro-inflammatory factors to promote central sensitization, thereby inducing pain in chronic migraine (185, 186). MiR-155 acts as a pro-inflammatory factor during activation of microglia via down-regulating SIRT1 expression (regulates inflammation), resulting in hyperalgesia and central sensitization (187).

By considering the clinical characteristics and patient groups, a pilot study was carried out in order to identify the differential expression of circulating miRNA(s) in patients with migraine without aura (MWA) during pain-free periods. The outcomes of the study clearly demonstrated the differential expression of 4 miRNAs (miR-27b, miR-181a, miR-22, let-7b). The expression level of miR-181a, miR-22, and let-7b was down-regulated, whereas the level of miR-27b was found to be up-regulated in a significant manner. Moreover, miRNAs are not only the biomarkers for migraine in adults, but also in children with MWA. In order to confirm this, the expression level of hsa-miR-375 and hsa-miR-34a-5p was evaluated in both the saliva and serum of young subjects (4-17 years) with MWA having four attacks/month. Higher levels of both miRNAs were found in serum as well as saliva, whereas the treatment with acetaminophen significantly alleviated their level (188). So, they can be useful biomarkers of migraine disease and also of the efficacy of drugs in patients suffering from MWA. So far, no data have been reported on the molecular targets of these miRNAs.

Neurogenic inflammation has been considered to be involved in the migraine pathogenesis, and lately, it has been reported that migraine with aura is linked with neuroinflammation and neuro-immune activation (189). An endogenous pro-inflammatory inhibitor of IL-1β signaling is IL-10 receptor-α, which is negatively modulated by miR-382-5p, thus interfering with anti-inflammatory signaling (190). MiR-34a suppresses SIRT1 by elevating NF-κB subunit p65, ultimately increasing the transcription of IL-1β, TNF-α, and IL-6. GABA is predominantly an inhibitory neurotransmitter, which is also speculated be the target of miR-34a (191).

Lack of insulin-like growth factor 1 (IGF1) causes a decrease in myelinated oligodendrocytes and axons, while its overexpression promotes the neural progenitors' proliferation and decreases apoptosis. It is well known that transient receptor potential cation channel subfamily V member 1 (TRPV1) is a key protein in NO_2-induced migraine, aggravating the NO2-stimulated neurotoxicity in migraine (192). Mechanistically, NO_2 modulates the AKT/TRPV1 signaling pathway by decreasing levels of AKT phosphorylation and increasing the expression of TRPV1 protein. Moreover, NO_2 overexpresses miR-653-3p, which targets IGF1, thereby down-regulating its expression and contributing to the activation of inflammatory cells to release IL-1β and TNFα (193). This data highlights the complexities of the etiology of migraine, underscoring the need for more research into preventive and control strategies.

Disease-modifying role in migraine

The ketogenic diet (KD) is well-recognized for the treatment of neurological diseases, including migraine, by reducing neuroinflammation. In a 6-week study, it was shown that biphasic KD could also influence circulating miRNAs associated with energy metabolism, with improvements in migraine conditions. It was found that the level of has-miR-660-3p and has-miR-590–5p was strongly influenced by KD, and it was concluded that KD could counteract the neuroinflammation in order to improve migraine pain (194). Collectively, these data highlight that the investigation of miRNA patterns in migraine could absolutely enhance the understanding of migraine pathogenesis and could open up the channels for better diagnosis, origin determination, associated comorbid conditions, dietary factors, and therapeutic treatments monitoring in migraine.

Indeed, one of the key factors involved in the pathogenesis of migraine is CALCA. Various clinical studies have revealed that the CALCA concentration in plasma was raised during both the non-episodes as well as episodes, signifying the existence of constant CALCA abnormality in patients with migraine. The expression of CALCA has also been found to be linked to the level of miR-30a. Its level was significantly decreased in migraine-suffering individuals, whereas its overexpression reduced the level of CALCA (195). Its overexpression can also inhibit the Akt/PI3K/mTOR pathway, resulting in pain relief and attenuated central sensitization (196, 197). The relationship b/w

cardiovascular risk (atherosclerotic lesions) and migraine is complicated and probably encompasses multiple aspects, but one of the promising pathophysiological connections lies in the ED.

To date, there remains a scarcity of data on the mechanism of action of certain miRNAs in migraine. Research should also focus on molecular targets of migraine-associated miRNAs to find novel strategies for the treatment of migraine. The implications of miRNAs in migraine, along with their targets, have been summarized in Table 6.

Conclusion

miRNAs are small (about 22 nucleotides) non-coding RNA molecules that play a significant role in regulating gene expression. To date, about 3 thousand miRNAs have been reported in the genomes of mammals, and more than 2000 of them belong to the human genome. Interestingly, a single miRNA may have the capability of repressing the expression of hundreds of targeted genes. They elicit their function by binding directly with the 3' untranslated region (UTR) of the targeted mRNA, which ultimately suppresses the protein expression as well as promotes the degradation of that particular mRNA. The miRNAs regulate several physiological as well as pathological processes, thus implicated in both health and disease. The diversity of miRNAs is involved in multifaceted cellular activities, which include apoptosis, cellular proliferation, cell differentiation, renewal of stem cells, metabolism, embryonic development, etc. In addition, they might have the capability to regulate almost 60% protein encoding genes. Under the pathological conditions and/or cellular stress, the cells underwent a condition of alleviated translation and transcription. During these circumstances, the miRNA offers a rapid, potent, and effective source of gene regulation that could allow the cells to recover or become adapted to the abnormal state.

This review highlights the several physiological and pathological pathways being regulated by a plethora of miRNAs in the most common brain disorders globally. This comprehensive overview of the prediction of miRNAs functions might be helpful in providing more efficient insight for the modulation of brain disorders related factors. Though various molecular pathways have been involved in brain diseases, neuroinflammation and apoptotic pathways are most often being studied in miRNA-based research lately. Following brain insults, neuroinflammation plays a significant role as a secondary injury process, exerting either beneficial or detrimental effects. It is a common mechanism connecting the ischemic, traumatic, epileptic, psychiatric, demyelinating, and degenerative pathologies. In addition to neuroinflammation, microglia and astrocyte activation, mitochondrial dysfunction, neuronal apoptosis, and oxidative stress are the main pathological hallmarks in brain disorders, resulting in cognitive impairment and neuronal loss. For instance, Overexpression of miR-21-3p has been reported be associated with BBB damage aggravation after TBI by promoting inflammation and cellular apoptosis. MiR-132-3p overexpression in PD aggravates the activation of microglial cells and ultimately prompts the secretion of cytokines. The miR-30c-5p directly targets a gene related to autophagy, resulting in dopaminergic neuronal loss, aggravating motor functions, increased apoptosis, oxidative stress, and so on.

It should be noteworthy that extensive work is required to investigate both the therapeutic role and pathological mechanisms for migraine. There is also a scarcity of data regarding molecular targeted pathways of several reported miRNAs that are found up-regulated following disease development. For example, up-regulation of a few miRNAs, including miR-183-5p, miR-382-3p, miR-493-3p, miR-202-3p, and miR-3573-5p, has been reported following depression. Marked reduction of miR-29 and hsa-mir144-3p has been associated with cognitive impairment and dysregulation process, respectively, in PD patients, but the associated molecular mechanisms need to be unraveled.

In a nutshell, mounting evidence has provided compelling support for the involvement of multiple miRNAs in health and disease. Hence, the current findings offer a foundation to develop novel miRNA-targeted strategies for the prevention and treatment of NDDs and neuropsychiatric disorders, including AD, PD, epilepsy, depression, migraine, and TBI. Although this review did not cover schizophrenia in detail, it is important to note that miRNAs also play a significant role in this disorder, representing a promising avenue for future investigation.

Acknowledgment

We acknowledge the Department of Emerging Allied Health Technologies, Faculty of Allied Health Sciences, The University of Lahore, Lahore, Pakistan, and the Department of Physiology, Faculty of Life Sciences, Government College University Faisalabad, Faisalabad, Pakistan, for providing an academic environment and institutional support for the

Table 6. Six implications of miRNA in migraine

	MicroRNA	Target	Outcomes	Study model	Reference
Disease-promoting role	miR-155, miR-21, Let-7g, miR-126	-	↑Syncope frequency	Mice migraine model	(184)
	MiR-155	SIRT1	↑Neuroinflammation, hyperalgesia	Migraine patients	(187)
	MiR-34a	SIRT1, GABA	↑Neuroinflammation	Migraine patients	(191)
	MiR-653-3p	IGF1	↑Neuroinflammation and neuronal damage	NO_2-induced migraine rat model, bilateral trigeminal ganglion culture	(193)
Disease-modifying role	has-miR-660–3p and has-miR-590–5p	-	↓Neuroinflammation	Migraine patients	(194)
	miR-30a	CALCA	Promote pain relief	Migraine patients	(195)

preparation of this review article.

Authors' Contributions

N A designed, prepared, and approved the publication version. G H and Q A revised the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration

We acknowledge the use of AI for assistance with grammatical corrections and language editing during the preparation of the manuscript.

References

1. Dwivedi S, Purohit P, Sharma P. MicroRNAs and diseases: Promising biomarkers for diagnosis and therapeutics. Indian J Clin Biochem 2019; 34: 243-245.
2. Zhou H, Huang X, Cui H, Luo X, Tang Y, Chen S, *et al.* MiR-155 and its star-form partner miR-155* cooperatively regulate type I interferon production by human plasmacytoid dendritic cells. Blood 2010; 116: 5885-5994.
3. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol 2018; 9: 402.
4. Aziz N, Ruzza C, Falcicchia C, Guarino A, Soukupova M, Asth L, *et al.* Lack of direct effects of neurotrophic factors in an *in vitro* model of neuroinflammation. Int J Mol Sci 2024; 25: 4160.
5. Yang Q qiao, Zhou J wei. Neuroinflammation in the central nervous system: Symphony of glial cells. Glia 2019; 67: 1017–1035.
6. Gorji A. Neuroinflammation: The pathogenic mechanism of neurological disorders. Int J Mol Sci 2022; 23: 1-5.
7. Hata A. Functions of microRNAs in cardiovascular biology and disease. Annu Rev Physiol 2013; 75: 69-93.
8. Sakamoto K, Crowley JJ. A comprehensive review of the genetic and biological evidence supports a role for MicroRNA-137 in the etiology of schizophrenia. Am J Med Genet Part B Neuropsychiatr Genet 2018; 177: 242–256.
9. Hussain G, Anwar H, Rasul A, Imran A, Qasim M, Zafar S, *et al.* Lipids as biomarkers of brain disorders. Crit Rev Food Sci Nut 2020; 60: 351-374.
10. Zhang QS, Liu W, Lu GX. miR-200a-3p promote β-Amyloid-induced neuronal apoptosis through down-regulation of SIRT1 in Alzheimer's disease. J Biosci 2017; 42: 397–404.
11. Kim SH, Choi KY, Park Y, McLean C, Park J, Lee JH, *et al.* Enhanced expression of microrna-1273g-3p contributes to alzheimer's disease pathogenesis by regulating the expression of mitochondrial genes. Cells 2021; 10: 2697.
12. Cheng Z, Zou X, Jin Y, Gao S, Lv J, Li B, *et al.* The role of KLF4 in Alzheimer's disease. Fron Cell Neurosci 2018; 12: 325.
13. Zhao K, Liu J, Sun T, Zeng L, Cai Z, Li Z, *et al.* The miR-25802/KLF4/NF-κB signaling axis regulates microglia-mediated neuroinflammation in Alzheimer's disease. Brain Behav Immun 2024; 118: 31-48.
14. Badr A, Daily KP, Eltobgy M, Estfanous S, Tan MH, Chun-Tien Kuo J, *et al.* Microglia-targeted inhibition of miR-17 via mannose-coated lipid nanoparticles improves pathology and behavior in a mouse model of Alzheimer's disease. Brain Behav Immun 2024; 119: 919-944.
15. Cong L, Cong Y, Feng N, Liang W, Wu Y. Up-regulated microRNA-132 reduces the cognition-damaging effect of sevoflurane on Alzheimer's disease rats by inhibiting FOXA1. Genomics 2021; 113: 3644–3652.
16. Du W, Lei C, Dong Y. Microrna-149 is down-regulated in alzheimer's disease and inhibits β-amyloid accumulation and ameliorates neuronal viability through targeting bace1. Genet Mol Biol 2021; 44: 1–8.
17. Pan K, Chen S, Wang Y, Yao W, Gao X. MicroRNA-23b attenuates tau pathology and inhibits oxidative stress by targeting GnT-III in Alzheimer's disease. Neuropharmacology 2021; 196: 108671.
18. Jiang Y, Xu B, Chen J, Sui Y, Ren L, Li J, *et al.* Micro-RNA-137 inhibits tau hyperphosphorylation in alzheimer's disease and targets the CACNA1C gene in transgenic mice and human neuroblastoma SH-SY5Y cells. Med Sci Monit 2018; 24: 5635-5644.
19. Liu Y, Zhang Y, Liu P, Bai H, Li X, Xiao J, *et al.* MicroRNA-128 knockout inhibits the development of Alzheimer's disease by targeting PPARγ in mouse models. Eur J Pharmacol 2019; 843: 134-144.
20. Higaki S, Muramatsu M, Matsuda A, Matsumoto K, Satoh J ichi, Michikawa M, *et al.* Defensive effect of microRNA-200b/c against amyloid-beta peptide-induced toxicity in Alzheimer's disease models. PLoS One 2018; 13: 1-18.
21. Lin Y, Liang X, Yao Y, Xiao H, Shi Y, Yang J. Osthole attenuates APP-induced Alzheimer's disease through up-regulating miRNA-101a-3p. Life Sci 2019; 225: 117–131.
22. Swingler TE, Niu L, Pontifex MG, Vauzour D, Clark IM. The microRNA-455 null mouse has memory deficit and increased anxiety, targeting key genes involved in Alzheimer's disease. Int J Mol Sci 2022; 23: 554
23. Kumar S, Hemachandra Reddy P. A new discovery of MicroRNA-455-3p in Alzheimer's disease. J Alzheimer's Dis 2019; 72: S117-130.
24. Liang C, Zou T, Zhang M, Fan W, Zhang T, Jiang Y, *et al.* MicroRNA-146a switches microglial phenotypes to resist the pathological processes and cognitive degradation of Alzheimer's disease. Theranostics 2021; 11: 4103–4121.
25. Aquino R, de Concini V, Dhenain M, Lam S, Gosset D, Baquedano L, *et al.* Intrahippocampal inoculation of Aβ1–42 peptide in rat as a model of Alzheimer's disease identified MicroRNA-146a-5p as blood marker with anti-inflammatory function in astrocyte cells. Cells 2023; 12: 694.
26. Das PK, Kumari R, Patra R, Soni DK, Biswas R, Patnaik S, Ghosh D. MicroRNA-129-5p-mediated translational repression of microglial ROCK1 leads to enhanced phagocytosis. J Biol Chem 2025; 301: 110293.
27. Anwar S, Rivest S. Alzheimer's disease: Microglia targets and their modulation to promote amyloid phagocytosis and mitigate neuroinflammation. Expert Opin Ther Targets 2020; 24: 331-344.
28. Li R, Yao S, Wei F, Chen M, Zhong Y, Zou C, *et al.* Down-regulation of miR-181c-5p in Alzheimer's disease weakens the response of microglia to Aβ phagocytosis. Sci Rep 2024; 14: 11487.
29. Sun X, Deng Y, Ge P, Peng Q, Soufiany I, Zhu L, *et al.* Diminazene ameliorates neuroinflammation by suppression of astrocytic miRNA-224-5p/NLRP3 axis in Alzheimer's disease model. J Inflamm Res 2023; 16: 1639-1652.
30. Zhou L, Huang X, Li H, Wang J, Lu Z. Triptolide improves Alzheimer's disease by regulating the NF-κB signaling pathway through the lncRNA NEAT1/microRNA 361-3p/TRAF2 axis. Exp Ther Med 2023; 26: 1-11.
31. Yang LX, Luo M, Li SY. Tanshinone IIA improves Alzheimer's disease via RNA nuclear-enriched abundant transcript 1/microRNA-291a-3p/member RAS oncogene family Rab22a axis. World J Psychiatry 2024; 14: 563–581.
32. Ren H, Qiu W, Zhu B, Li Q, Peng C, Chen X. The long non-coding RNA BDNF-AS induces neuronal cell apoptosis by targeting miR-125b-5p in Alzheimer's disease models. Adv Clin Exp Med 2024; 33: 233-345.
33. Lian X, Zhang X, Chen W, Xue F, Wang G. Dexmedetomidine mitigates neuroinflammation in an Alzheimer's disease mouse model via the miR-204-3p/FBXL7 signaling axis. Brain Res 2024; 1822: 148612.
34. Cao J, Huang M, Guo L, Zhu L, Hou J, Zhang L, *et al.* MicroRNA-195 rescues ApoE4-induced cognitive deficits and lysosomal defects in Alzheimer's disease pathogenesis. Mol Psychiatry 2021; 26: 4687–4701.
35. Nagaraj S, Want A, Laskowska-Kaszub K, Fesiuk A, Vaz S, Logarinho E, *et al.* Candidate Alzheimer's disease biomarker mir-

483-5p lowers tau phosphorylation by direct erk1/2 repression. Int J Mol Sci 2021; 22: 3653.
36. Zhang YY, Dong LX, Bao HL, Liu Y, An FM, Zhang GW. Inhibition of interleukin-1β plays a protective role in Alzheimer's disease by promoting microRNA-9-5p and down-regulating targeting protein for xenopus kinesin-like protein 2. Int Immunopharmacol 2021; 97: 107578.
37. Xie Y, Xie D, Chen C. Hsa_circ_0049472 contributed to amyloid-beta peptide-induced neurotoxicity, apoptosis and inflammation via regulating PI3K-AKT signaling pathway by interacting with miR-22–3p/ZNF217 axis. Brain Res Bull 2024; 215: 111004.
38. Su D, Chen Z, An X, Yang J, Yang J, Wang X, *et al.* MicroRNA-195 liposomes for therapy of Alzheimer's disease. J Control Release 2024; 365: 583–601.
39. Milanese C, Gabriels S, Barnhoorn S, Cerri S, Ulusoy A, Gornati SV, *et al.* Gender biased neuroprotective effect of Transferrin Receptor 2 deletion in multiple models of Parkinson's disease. Cell Death Differ 2021; 28: 1720-1732
40. Gong X, Huang M, Chen L. Mechanism of miR-132-3p promoting neuroinflammation and dopaminergic neurodegeneration in Parkinson's disease. eNeuro 2022; 9: 1-17.
41. Zhang HQ, Wang JY, Li ZF, Cui L, Huang SS, Zhu LB, *et al.* DNA methyltransferase 1 is dysregulated in Parkinson's disease via mediation of miR-17. Mol Neurobiol 2021; 58: 2620–2633.
42. Lin X, Wang R, Li R, Tao T, Zhang D, Qi Y. Diagnostic performance of miR-485-3p in patients with Parkinson's disease and its relationship with neuroinflammation. NeuroMolecular Med 2022; 24: 195-201.
43. Zhu J, Xu X, Liang Y, Zhu R. Down-regulation of microRNA-15b-5p targeting the Akt3-mediated GSK-3 β/β -catenin signaling pathway inhibits cell apoptosis in Parkinson's disease. Biomed Res Int 2021; 2021: 8814862.
44. Zhao J, Yang M, Li Q, Pei X, Zhu X. MiR-132-5p regulates apoptosis and autophagy in MPTP model of Parkinson's disease by targeting ULK1. Neuroreport 2020; 31: 959-965.
45. Sun L, Wang F, Han J, Bai L, DU J. Repetitive transcranial magnetic stimulation reduces neuronal loss and neuroinflammation in parkinson's disease through the miR-195a-5p/CREB axis. Turk Neurosurg 2023; 33: 229-237.
46. Zhang L, Chen X, Chang M, Jiao B. MiR-30c-5p/ATG5 axis regulates the progression of Parkinson's disease. Front Cell Neurosci 2021; 15: 644507.
47. Ammal Kaidery N, Ahuja M, Thomas B. Crosstalk between Nrf2 signaling and mitochondrial function in Parkinson's disease. Mol Cell Neurosci 2019; 101: 103413
48. Lang Y, Zhang H, Yu H, Li Y, Liu X, Li L. Long non-coding RNA myocardial infarction-associated transcript promotes 1-Methyl-4-phenylpyridinium ion-induced neuronal inflammation and oxidative stress in Parkinson's disease through regulating microRNA-221-3p/ transforming growth factor /nuclear fact. Bioengineered 2022; 13: 930–940.
49. Zhang F, Yao Y, Miao N, Wang N, Xu X, Yang C. Neuroprotective effects of microRNA 124 in Parkinson's disease mice. Arch Gerontol Geriatr 2022; 99: 104588.
50. Wang D, Gao H, Qin Q, Li J, Zhao J, Qu Y, *et al.* MicroRNA-218-5p-Ddx41 axis restrains microglia-mediated neuroinflammation through down-regulating type I interferon response in a mouse model of Parkinson's disease. J Transl Med 2024; 22: 1-14.
51. Li T, Tan X, Tian L, Jia C, Cheng C, Chen X, *et al.* The role of Nurr1-miR-30e-5p-NLRP3 axis in inflammation-mediated neurodegeneration: insights from mouse models and patients' studies in Parkinson's disease. J Neuroinflammation 2023; 20: 1-19.
52. Caggiu E, Paulus K, Mameli G, Arru G, Sechi G Pietro, Sechi LA. Differential expression of miRNA 155 and miRNA 146a in Parkinson's disease patients. eNeurologicalSci 2018; 13: 1–4.
53. Yao L, Ye Y, Mao H, Lu F, He X, Lu G, *et al.* MicroRNA-124 regulates the expression of MEKK3 in the inflammatory pathogenesis of Parkinson's disease. J Neuroinflammation 2018; 15: 1-19.
54. Xing RX, Li LG, Liu XW, Tian BX, Cheng Y. Down regulation of miR-218, miR-124, and miR-144 relates to Parkinson's disease via activating NF-κB signaling. Kaohsiung J Med Sci 2020; 36: 786-792.
55. Chen MY, Fan K, Zhao LJ, Wei JM, Gao JX, Li ZF. Long non-coding RNA nuclear enriched abundant transcript 1 (NEAT1) sponges microRNA-124-3p to up-regulate phosphodiesterase 4B (PDE4B) to accelerate the progression of Parkinson's disease. Bioengineered 2021; 12: 708-719.
56. Watanabe R, Buschauer R, Böhning J, Audagnotto M, Lasker K, Lu TW, *et al.* The *in situ* structure of Parkinson's disease-linked LRRK2. Cell 2020; 182: 1508-1518.
57. Oliveira SR, Dionísio PA, Gaspar MM, Correia Guedes L, Coelho M, Rosa MM, *et al.* miR-335 targets LRRK2 and mitigates inflammation in Parkinson's disease. Front Cell Dev Biol 2021; 9: 661461.
58. Bai X, Dong Q, Zhao L, Yao Y, Wang B. microRNA-106b-containing extracellular vesicles affect autophagy of neurons by regulating CDKN2B in Parkinson's disease. Neurosci Lett 2021; 760: 136094.
59. Sherbaf FG, Mohajer B, Ashraf-Ganjouei A, Zadeh MM, Javinani A, Moghaddam HS, *et al.* Serum insulin-like growth factor-1 in Parkinson's disease: study of cerebrospinal fluid biomarkers and white matter microstructure. Front Endocrinol 2018; 9: 608.
60. Qin X, Zhang X, Li P, Wang M, Yan L, Pan P, *et al.* MicroRNA-185 activates PI3K/AKT signaling pathway to alleviate dopaminergic neuron damage via targeting IGF1 in Parkinson's disease. J Drug Target 2021; 29: 877–883.
61. Yang J, Zhang M, Wei M, Wang A, Deng Y, Cao H. MicroRNA-216a inhibits neuronal apoptosis in a cellular Parkinson's disease model by targeting Bax. Metab Brain Dis 2020; 35: 627-635.
62. Li J, Yu L, Li M, Chen X, Tian Q, Jiang Y, *et al.* MicroRNA-150 serves as a diagnostic biomarker and is involved in the inflammatory pathogenesis of Parkinson's disease. Mol Genet Genomic Med 2020; 8: e1189.
63. Baghi M, Rostamian Delavar M, Yadegari E, Peymani M, Pozo D, Hossein Nasr-Esfahani M, *et al.* Modified level of miR-376a is associated with Parkinson's disease. J Cell Mol Med 2020; 24: 2622–2634.
64. Zhou J, Zhao Y, Li Z, Zhu M, Wang Z, Li Y, *et al.* miR-103a-3p regulates mitophagy in Parkinson's disease through Parkin/Ambra1 signaling. Pharmacol Res 2020; 160: 105197.
65. Ma X, Zhang H, Yin H, Geng S, Liu Y, Liu C, *et al.* Up-regulated microRNA-218-5p ameliorates the damage of dopaminergic neurons in rats with Parkinson's disease via suppression of LASP1. Brain Res Bull 2021; 166: 92–101.
66. Guo S, Gao Y, Zhao Y. Neuroprotective microRNA-381 binds to repressed early growth response 1 (EGR1) and alleviates oxidative stress injury in Parkinson's disease. ACS Chem Neurosci 2023; 14: 1981–1991.
67. Wang X, Liu Z, Wang F. MicroRNA-93 blocks signal transducers and activator of transcription 3 to reduce neuronal damage in Parkinson's disease. Neurochem Res 2021; 46: 1859–1868.
68. Gao Y, Sheng D, Chen W. Regulatory mechanism of miR-20a-5p in neuronal damage and inflammation in lipopolysaccharide-induced BV2 cells and MPTP-HCl-induced Parkinson's disease mice. Psychogeriatrics 2024; 24: 752-764.
69. Zhang YJ, Zhu WK, Qi FY, Che FY. CircHIPK3 promotes neuroinflammation through regulation of the miR-124-3p/STAT3/NLRP3 signaling pathway in Parkinson's disease. Adv Clin Exp Med 2023; 32: 315-329.
70. Liao Y, Gu Y, Wang J, Tian Y, Ni X, Zhou L, *et al.* HSF1 inhibits microglia activation to attenuate neuroinflammation via regulating miR-214-3p and NFATc2 in Parkinson's disease. Folia Neuropathol 2023; 61: 53-67.
71. Yao Y, Zhao Z, Zhang F, Miao N, Wang N, Xu X, *et al.* microRNA-221 rescues the loss of dopaminergic neurons in a mouse model of Parkinson's disease. Brain Behav 2023; 13: e2921.
72. Han YP, Liu ZJ, Bao HH, Wang Q, Su LL. MiR-126-5p targets

SP1 to inhibit the progression of Parkinson's disease. Eur Neurol 2022; 85: 235-244.
73. Kong H, Wang H, Zhuo Z, Li Z, Tian P, Wu J, *et al.* Inhibition of miR-181a-5p reduces astrocyte and microglia activation and oxidative stress by activating SIRT1 in immature rats with epilepsy. Lab Investig 2020; 100: 1223-1237.
74. Zhu X, Zhang A, Dong J, Yao Y, Zhu M, Xu K, *et al.* MicroRNA-23a contributes to hippocampal neuronal injuries and spatial memory impairment in an experimental model of temporal lobe epilepsy. Brain Res Bull 2019; 152: 175-183.
75. Li TR, Jia YJ, Ma C, Qiu WY, Wang Q, Shao XQ, *et al.* The role of the microRNA-146a/complement factor H/interleukin-1?-mediated inflammatory loop circuit in the perpetuate inflammation of chronic temporal lobe epilepsy. DMM Dis Model Mech 2018; 11: 1-11.
76. Wu X, Wang Y, Sun Z, Ren S, Yang W, Deng Y, *et al.* Molecular expression and functional analysis of genes in children with temporal lobe epilepsy. J Integr Neurosci 2019; 18: 71–77.
77. Vangoor VR, Reschke CR, Senthilkumar K, Van De Haar LL, De Wit M, Giuliani G, *et al.* Antagonizing increased miR-135a levels at the chronic stage of experimental TLE reduces spontaneous recurrent seizures. J Neurosci 2019; 39: 5064–5079.
78. Li TR, Jia YJ, Wang Q, Shao XQ, Zhang P, Lv RJ. Correlation between tumor necrosis factor alpha mRNA and microRNA-155 expression in rat models and patients with temporal lobe epilepsy. Brain Res 2018; 1700: 56–65.
79. Duan W, Chen Y, Wang XR. MicroRNA-155 contributes to the occurrence of epilepsy through the PI3K/Akt/mTOR signaling pathway. Int J Mol Med 2018; 42: 1577–1584.
80. Korotkov A, Broekaart DWM, van Scheppingen J, Anink JJ, Baayen JC, Idema S, *et al.* Increased expression of matrix metalloproteinase 3 can be attenuated by inhibition of microRNA-155 in cultured human astrocytes. J Neuroinflammation 2018; 15: 211.
81. Tang C, Gu Y, Wang H, Wu H, Wang Y, Meng Y, *et al.* Targeting of microRNA-21-5p protects against seizure damage in a kainic acid-induced status epilepticus model via PTEN-mTOR. Epilepsy Res 2018; 144: 34–42.
82. Chen DZ, Wang WW, Chen YL, Yang XF, Zhao M, Yang YY. MiR-128 is up-regulated in epilepsy and promotes apoptosis through the SIRT1 cascade. Int J Mol Med 2019; 44: 694–704.
83. Kong H, Wang H, Zhuo Z, Li Z, Tian P, Wu J, *et al.* Inhibition of miR-181a-5p reduces astrocyte and microglia activation and oxidative stress by activating SIRT1 in immature rats with epilepsy. Lab Invest 2020; 100: 1223–1237.
84. Geng J feng, Liu X, Zhao H biao, Fan W fei, Geng J jie, Liu X zhi. LncRNA UCA1 inhibits epilepsy and seizure-induced brain injury by regulating miR-495/Nrf2-ARE signal pathway. Int J Biochem Cell Biol 2018; 99: 133–140.
85. Feng X, Xiong W, Yuan M, Zhan J, Zhu X, Wei Z, *et al.* Down-regulated microRNA-183 mediates the Jak/Stat signaling pathway to attenuate hippocampal neuron injury in epilepsy rats by targeting Foxp1. Cell Cycle 2019; 18: 3206–3222.
86. Chen Y, Chen J, Chen Y, Li Y. miR-146a/KLF4 axis in epileptic mice: A novel regulator of synaptic plasticity involving STAT3 signaling. Brain Res 2022; 1790: 147988.
87. Xiao D, Lv J, Zheng Z, Liu Y, Zhang Y, Luo C, *et al.* Mechanisms of microRNA-142 in mitochondrial autophagy and hippocampal damage in a rat model of epilepsy. Int J Mol Med 2021; 47: 98.
88. He Z, Chen H, Zhong Y, Yang Q, Wang X, Chen R, *et al.* MicroRNA 223 Targeting ATG16L1 Affects Microglial Autophagy in the Kainic Acid Model of Temporal Lobe Epilepsy. Front Neurol 2021; 12: 1–13.
89. Hamamoto O, Tirapelli DP da C, Lizarte Neto FS, Freitas-Lima P, Saggioro FP, Cirino ML de A, *et al.* Modulation of NMDA receptor by miR-219 in the amygdala and hippocampus of patients with mesial temporal lobe epilepsy. J Clin Neurosci 2020; 74: 180-186.
90. Huang Y, Liu X, Liao Y, Liao Y, Zou D, Wei X, *et al.* Role of miR-34c in the cognitive function of epileptic rats induced by pentylenetetrazol. Mol Med Rep 2018; 17: 4173–4180.
91. Xiang L, Ren Y, Cai H, Zhao W, Song Y. MicroRNA-132 aggravates epileptiform discharges via suppression of BDNF/TrkB signaling in cultured hippocampal neurons. Brain Res 2015; 1622: 484–495.
92. Zhu X, Zhang A, Dong J, Yao Y, Zhu M, Xu K, *et al.* MicroRNA-23a contributes to hippocampal neuronal injuries and spatial memory impairment in an experimental model of temporal lobe epilepsy. Brain Res Bull 2019; 152: 175–183.
93. Du Y, Chi X, An W. Down-regulation of microRNA-200c-3p reduces damage of hippocampal neurons in epileptic rats by up-regulating expression of RECK and inactivating the AKT signaling pathway. Chem Biol Interact 2019; 307: 223–233.
94. Rosciszewski G, Cadena V, Auzmendi J, Cieri MB, Lukin J, Rossi AR, *et al.* Detrimental effects of HMGB-1 require microglial-astroglial interaction: Implications for the status epilepticus -induced neuroinflammation. Front Cell Neurosci 2019; 13: 1-19.
95. Wu Y, Zhang Y, Zhu S, Tian C, Zhang Y. MiRNA- 29a serves as a promising diagnostic biomarker in children with temporal lobe. Epileptic Disord 2022; 23: 8230832.
96. Liu T, Liu H, Xue S, Xiao L, Xu J, Tong S, *et al.* MiR129-5p-loaded exosomes suppress seizure-associated neurodegeneration in status epilepticus model mice by inhibiting HMGB1/TLR4-mediated neuroinflammation. Mol Biol Rep 2024; 51: 292.
97. Alves VS, da Silva JP, Rodrigues FC, Araújo SMB, Gouvêa AL, Leite-Aguiar R, *et al.* P2X7 receptor contributes to long-term neuroinflammation and cognitive impairment in sepsis-surviving mice. Front Pharmacol 2023; 14: 1179723.
98. Li X, Quan S, Liu F, Fan Y, Ding F, *et al.* The microRNA-211-5p/P2X7/ERK/GSDMD/NLRP3/IL-1β/NLRP3/CASP1/GSDMD/P2X4 axis regulates epilepsy-associated neuronal ferroptosis and oxidative stress. J Neuroinflammation 2023; 20: 13.
99. Xiang J, Wen F, Zhang L, Zhou Y. FOXD3 inhibits SCN2A gene transcription in intractable epilepsy cell models. Exp Neurol 2018; 302: 14–21.
100. Wen F, Tan Z, Huang D, Jiang Y, Xiang J. LncRNA PVT1 promotes neuronal cell apoptosis and neuroinflammation by regulating miR-488-3p/FOXD3/SCN2A axis in epilepsy. Neurochem Res 2023; 48: 895-908.
101. Cui H, Zhang W, Khalaf OI. The neuroprotective effect of miR-136 on pilocarpine-induced temporal lobe epilepsy rats by inhibiting Wnt/β-catenin signaling pathway. Comput Math Methods Med 2022; 2022: 1938205
102. Fu P, Yuan Q, Sun Y, Wu X, Du Z, Li Z, *et al.* Baicalein ameliorates epilepsy symptoms in a pilocarpine-induced rat model by regulation of IGF1R. Neurochem Res 2020; 45: 3021-3033.
103. Niu X, Zhu HL, Liu Q, Yan JF, Li ML. MiR-194-5p serves as a potential biomarker and regulates the proliferation and apoptosis of hippocampus neuron in children with temporal lobe epilepsy. J Chinese Med Assoc 2021; 84: 510-516.
104. Li N, Pan J, Liu W, Li Y, Li F, Liu M. MicroRNA-15a-5p serves as a potential biomarker and regulates the viability and apoptosis of hippocampus neuron in children with temporal lobe epilepsy. Diagn Pathol 2020; 15: 46.
105. Li X, Giri vikash, Cui Y, Yin M, Xian Z, Li J. LncRNA FTX inhibits hippocampal neuron apoptosis by regulating miR-21-5p/SOX7 axis in a rat model of temporal lobe epilepsy. Biochem Biophys Res Commun 2019; 512: 79-86.
106. Zhu Z, Wang S, Cao Q, Li G. CircUBQLN1 promotes proliferation but inhibits apoptosis and oxidative stress of hippocampal neurons in epilepsy via the miR-155-mediated SOX7 up-regulation. J Mol Neurosci 2021; 71: 1933–1943.
107. Zhou Q, Wang Q, He B, Kong H, Luo H, Wang X, *et al.* MicroRNA 322-5p reduced neuronal inflammation via the TLR4/TRAF6/NF-κB axis in a rat epilepsy model. Open Med (Wars) 2022; 17: 907-914.
108. Zhou Q, Wang Q, He B, Kong H, Luo H, Wang X, *et al.* MicroRNA 322-5p reduced neuronal inflammation via the TLR4/TRAF6/NF-κB axis in a rat epilepsy model. Open Med 2022; 17: 907–914.

109. Ou S, Liu X, Xu T, Yu X, Wang T, Chen Y, *et al.* miRNA-let-7i modulates status epilepticus via the TLR4 pathway. Acta Epileptol 2022; 4: 1–11.
110. Hu L, Zeng Z, Xia Q, Liu Z, Feng X, Chen J, *et al.* Metformin attenuates hepatoma cell proliferation by decreasing glycolytic flux through the HIF-1α/PFKFB3/PFK1 pathway. Life Sci 2019; 239: 116966.
111. Li R, Hu J, Cao S. The clinical significance of miR-135b-5p and its role in the proliferation and apoptosis of hippocampus neurons in children with temporal lobe epilepsy. Dev Neurosci 2021; 42: 187–194.
112. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, *et al.* Estimating the global incidence of traumatic brain injury J Neurosurg 2019; 130: 1080-97.
113. Qi R, Wang X. Inhibition of miR-429 improves neurological recovery of traumatic brain injury mice and attenuates microglial neuroinflammation. Int Immunopharmacol 2020; 79: 106091.
114. Henry RJ, Doran SJ, Barrett JP, Meadows VE, Sabirzhanov B, Stoica BA, *et al.* Inhibition of miR-155 limits neuroinflammation and improves functional recovery after experimental traumatic brain injury in mice. Neurotherapeutics 2019; 16: 216-230.
115. Yu J, Chen J, Yang H, Chen S, Wang Z. Overexpression of MIR-200a-3p promoted inflammation in sepsis-induced brain injury through ROS-induced NLRP3. Int J Mol Med 2019; 44: 1811–1823.
116. Ge X, Li W, Huang S, Yin Z, Yang M, Han Z, *et al.* Increased miR-21-3p in injured brain microvascular endothelial cells after traumatic brain injury aggravates blood-brain barrier damage by promoting cellular apoptosis and inflammation through targeting MAT2B. J Neurotrauma 2019; 36: 1291–1305.
117. Schindler CR, Woschek M, Vollrath JT, Kontradowitz K, Lustenberger T, Störmann P, *et al.* MiR-142-3p expression is predictive for severe traumatic brain injury (TBI) in trauma patients. Int J Mol Sci 2020; 21: 1–16.
118. Zhao L, Zhang L, Zhu W, Chen H, Ding Y, Cui G. Inhibition of microRNA-203 protects against traumatic brain injury induced neural damages via suppressing neuronal apoptosis and dementia related molecues. Physiol Behav 2021; 228: 113190.
119. Gupta S Das, Ciszek R, Heiskanen M, Lapinlampi N, Kukkonen J, Leinonen V, *et al.* Plasma miR-9-3p and miR-136-3p as potential novel diagnostic biomarkers for experimental and human mild traumatic brain injury. Int J Mol Sci 2021; 22: 1–27.
120. Tang W, Guo ZD, Chai WN, Du DL, Yang XM, Cao L, *et al.* Down-regulation of miR-491-5p promotes neovascularization after traumatic brain injury. Neural Regen Res 2022; 17: 577-586.
121. Wu J, Li H, He J, Tian X, Luo S, Li *et al.* Down-regulation of microRNA-9-5p promotes synaptic remodeling in the chronic phase after traumatic brain injury. Cell Death Dis 2021; 12: 9.
122. Sun Y, Xiong Y, Yan C, Chen L, Chen D, Mi B, *et al.* Down-regulation of microRNA-16-5p accelerates fracture healing by promoting proliferation and inhibiting apoptosis of osteoblasts in patients with traumatic brain injury. Am J Transl Res 2019; 11: 4746-4760.
123. Kowiański P, Lietzau G, Czuba E, Waśkow M, Steliga A, Moryś J. BDNF: A key factor with multipotent impact on brain signaling and synaptic plasticity. Cell Mol Neurobiol 2018; 38: 579-593.
124. Kang EM, Jia Y Bin, Wang JY, Wang GY, Chen HJ, Chen XY, *et al.* Down-regulation of microRNA-124-3p promotes subventricular zone neural stem cell activation by enhancing the function of BDNF downstream pathways after traumatic brain injury in adult rats. CNS Neurosci Ther 2022; 28: 1081–1092.
125. Yang X, Tang X, Sun P, Shi Y, Liu K, Hassan SH, *et al.* MicroRNA-15a/16-1 antagomir ameliorates ischemic brain injury in experimental stroke. Stroke 2017; 48: 1941-1947.
126. Zhou C, Li S, Qiu N, Sun P, Hamblin MH, Dixon CE, *et al.* Loss of microRNA-15a/16-1 function promotes neuropathological and functional recovery in experimental traumatic brain injury. JCI Insight 2024; 9: e178650.
127. Lv J, Zeng Y, Qian Y, Dong J, Zhang Z, Zhang J. MicroRNA let-7c-5p improves neurological outcomes in a murine model of traumatic brain injury by suppressing neuroinflammation and regulating microglial activation. Brain Res 2018; 1685: 91-104.
128. Huang S, Ge X, Yu J, Han Z, Yin Z, Li Y, *et al.* Increased miR-124-3p in microglial exosomes following traumatic brain injury inhibits neuronal inflammation and contributes to neurite outgrowth via their transfer into neurons. FASEB J 2018; 32: 512-528.
129. Shi M, Chai Y, Zhang J, Chen X. Endoplasmic reticulum stress-associated neuronal death and innate immune response in neurological diseases. Front Immunol 2022; 12: 1-26.
130. Wang Y, Li D, Zhang L, Yin Z, Han Z, Ge X, *et al.* Exosomes derived from microglia overexpressing miR-124-3p alleviate neuronal endoplasmic reticulum stress damage after repetitive mild traumatic brain injury. Neural Regen Res 2024; 19: 2010-2018.
131. Zhao C, Deng Y, He Y, Huang X, Wang C, Li W. Decreased level of exosomal miR-5121 released from microglia suppresses neurite outgrowth and synapse recovery of neurons following traumatic brain injury. Neurotherapeutics 2021; 18: 1273–1294.
132. Long X, Yao X, Jiang Q, Yang Y, He X, Tian W, *et al.* Astrocyte-derived exosomes enriched with miR-873a-5p inhibit neuroinflammation via microglia phenotype modulation after traumatic brain injury. J Neuroinflammation 2020; 17: 1-15.
133. Yang Y, Ye Y, Fan K, Luo J, Yang Y, Ma Y. MiR-124 reduced neuroinflammation after traumatic brain injury by inhibiting TRAF6. Neuroimmunomodulation 2023; 30: 55–68.
134. Nong A, Li C, Huang Z, Xu Y, He K, Jia Y, *et al.* MicroRNA miR-126 attenuates brain injury in septic rats via NF-κB signaling pathway. Bioengineered 2021; 12: 2639–2648.
135. Zhang L, Zhao L, Zhu W, Ding Y, Chen H, Chi N. miR-146a mimics ameliorates traumatic brain injury involving JNK and NF-κB signaling pathway. NeuroMolecular Med 2020; 22: 484-492.
136. Li Z, Xu R, Zhu X, Li Y, Wang Y, Xu W. MicroRNA-23a-3p improves traumatic brain injury through modulating the neurological apoptosis and inflammation response in mice. Cell Cycle 2020; 19: 24-38.
137. Meissner L, Gallozzi M, Balbi M, Schwarzmaier S, Tiedt S, Terpolilli NA, *et al.* Temporal profile of microRNA expression in contused cortex after traumatic brain injury in mice. J Neurotrauma 2015; 33: 713–720.
138. Wang JX, Xiao X, He XC, He BD, Liu CM, Teng ZQ. Agomir-331 suppresses reactive gliosis and neuroinflammation after traumatic brain injury. Cells 2023; 12: 1–17.
139. Xiong Y, Cao F, Hu L, Yan C, Chen L, Panayi AC, *et al.* miRNA-26a-5p accelerates healing via down-regulation of PTEN in fracture patients with traumatic brain injury. Mol Ther Nucleic Acids 2019; 17: 223–234.
140. Chen W, Feng J, Tong W. Phosphorylation of astrocytic connexin43 by ERK1/2 impairs blood-brain barrier in acute cerebral ischemia. Cell Biosci 2017; 7: 43.
141. Chen W, Zhao L, Zhang J, Wang B, Xu G, Lin C, *et al.* Elevated expression of miR-302 cluster improves traumatic brain injury by inhibiting phosphorylation of connexin43 via ERK signaling. J Chem Neuroanat 2019; 99: 1–8.
142. Chin AC. Neuroinflammation and the cGAS-STING pathway. J Neurophysiol 2019; 121: 1087-1091.
143. He XC, Wang J, Du HZ, Liu CM, Teng ZQ. Intranasal administration of agomir-let-7i improves cognitive function in mice with traumatic brain injury. Cells 2022; 11: 1348.
144. Wang D, Jacobs SA, Tsien JZ. Targeting the NMDA receptor subunit NR2B for treating or preventing age-related memory decline. Expert Opinion on Therapeutic Targets 2014; 18: 1121-1130.
145. Schumann J, Alexandrovich GA, Biegon A, Yaka R. Inhibition of NR2B phosphorylation restores alterations in NMDA receptor expression and improves functional recovery following traumatic brain injury in mice. J Neurotrauma 2008; 25: 945-957.
146. Shi Y, Cui W, Wang Q, Zhou J, Wu X, Wang J, *et al.* MicroRNA-124/death-associated protein kinase 1 signaling regulates neuronal apoptosis in traumatic brain injury via

phosphorylating NR2B. Front Cell Neurosci 2022; 16: 1-13.
147. Feng C, Tian Q, Tang X, Yu J, Li H, Geng C, *et al.* microRNA-9a-5p disrupts the ELAVL1/VEGF axis to alleviate traumatic brain injury. Exp Neurol 2024; 375: 114721.
148. Zhang H, Xing Z, Zheng J, Shi J, Cui C. Ursolic acid ameliorates traumatic brain injury in mice by regulating microRNA-141-mediated PDCD4/PI3K/AKT signaling pathway. Int Immunopharmacol 2023; 120: 110258.
149. Malki K, Pain O, Tosto MG, Du Rietz E, Carboni L, Schalkwyk LC. Identification of genes and gene pathways associated with major depressive disorder by integrative brain analysis of rat and human prefrontal cortex transcriptomes. Transl Psychiatry 2015; 5: e519.
150. Roy B, Dunbar M, Shelton RC, Dwivedi Y. Identification of microRNA-124-3p as a putative epigenetic signature of major depressive disorder. Neuropsychopharmacology 2017; 42: 864-875.
151. Wang SS, Mu RH, Li CF, Dong SQ, Geng D, Liu Q, *et al.* microRNA-124 targets glucocorticoid receptor and is involved in depression-like behaviors. Prog Neuro-Psychopharmacology Biol Psychiatry 2017; 79: 417–425.
152. Khandelwal N, Dey SK, Chakravarty S, Kumar A. miR-30 family miRNAs mediate the effect of chronic social defeat stress on hippocampal neurogenesis in mouse depression model. Front Mol Neurosci 2019; 12: 1–19.
153. Yuan N, Li X, Tang K, Gan H, Da X, Hao W, *et al.* Xiaoyaosan inhibits neuronal apoptosis by regulating the miR-200/NR3C1 signaling in the prefrontal cortex of chronically stressed rats. Phytomedicine 2022; 103: 154239.
154. Li S, Ma H, Yuan X, Zhou X, Wan Y, Chen S. Microrna-382-5p targets nuclear receptor subfamily 3 group c member 1 to regulate depressive-like behaviors induced by chronic unpredictable mild stress in rats. Neuropsychiatr Dis Treat 2020; 16: 2053–2061.
155. Su B, Cheng S, Wang L, Wang B. MicroRNA-139-5p acts as a suppressor gene for depression by targeting nuclear receptor subfamily 3, group C, member 1. Bioengineered 2022; 13: 11856-11866.
156. Zhang Z, Xia D jian, Xu A ding. Therapeutic effect of fastigial nucleus stimulation is mediated by the microRNA-132 & microRNA-382/BDNF signaling pathways in the treatment of post-stroke depression. Biochem Biophys Res Commun 2022; 627: 137–145.
157. Xin C, Xia J, Liu Y, Zhang Y. MicroRNA-202-3p targets brain-derived neurotrophic factor and is involved in depression-like behaviors. Neuropsychiatr Dis Treat 2020; 16: 1077–1083.
158. Yu CF, Peng WM, Schlee M, Barchet W, Eis-Hubinger AM, Kolanus W, *et al.* SOCS1 and SOCS3 target IRF7 degradation to suppress TLR7-mediated type I IFN production of human plasmacytoid dendritic cells. J Immunol 2018; 200: 4024-4035.
159. Liu Y, Yu J, Wang X, Dong J. MicroRNA-345-5p regulates depression by targeting suppressor of cytokine signaling 1. Brain Behav 2020; 10: 1–10.
160. Guo L, Zhu Z, Wang G, Cui S, Shen M, Song Z, *et al.* MicroRNA-15b contributes to depression-like behavior in mice by affecting synaptic protein levels and function in the nucleus accumbens. J Biol Chem 2020; 295: 6831–6848.
161. Zhai X, Liu J, Ni A, Ye J. MiR-497 promotes microglia activation and proinflammatory cytokines production in chronic unpredictable stress-induced depression via targeting FGF2. J Chem Neuroanat 2020; 110: 101872.
162. Tang Y, Zhou M, Huang R, Shen L, Yang L, Zhou Z, *et al.* Involvement of HECTD1 in LPS-induced astrocyte activation via σ-1R-JNK/p38-FOXJ2 axis. Cell Biosci 2021; 11: 62.
163. Zhang Y, Du L, Bai Y, Han B, He C, Gong L, *et al.* CircDYM ameliorates depressive-like behavior by targeting miR-9 to regulate microglial activation via HSP90 ubiquitination. Mol Psychiatry 2020; 25: 1175–1190.
164. Chen Y, Cao P. Circ-Bnc2 alleviates neuroinflammation in LPS-stimulated microglial cells to inhibit neuron cell apoptosis through regulating miR-497a-5p/HECTD1 axis. Brain Behav 2023; 13: e2935.
165. Magill ST, Cambronne XA, Luikart BW, Lioy DT, Leighton BH, Westbrook GL, *et al.* MicroRNA-132 regulates dendritic growth and arborization of newborn neurons in the adult hippocampus. Proc Natl Acad Sci U S A 2010; 107: 20382–20387.
166. Im HI, Kenny PJ. MicroRNAs in neuronal function and dysfunction. Trends Neurosci 2012; 35: 325-334.
167. Su M, Hong J, Zhao Y, Liu S, Xue X. MeCP2 controls hippocampal brain-derived neurotrophic factor expression via homeostatic interactions with microRNA-132 in rats with depression. Mol Med Rep 2015; 12: 5399–5406.
168. Qi S, Yang X, Zhao L, Calhoun VD, Perrone-Bizzozero N, Liu S, *et al.* MicroRNA132 associated multimodal neuroimaging patterns in unmedicated major depressive disorder. Brain 2018; 141: 916–926.
169. Pei G, Xu L, Huang W, Yin J. The protective role of microRNA-133b in restricting hippocampal neurons apoptosis and inflammatory injury in rats with depression by suppressing CTGF. Int Immunopharmacol 2020; 78: 106076.
170. Shen J, Zhang P, Li Y, Fan C, Lan T, Wang W, *et al.* Neuroprotective effects of microRNA-211-5p on chronic stress-induced neuronal apoptosis and depression-like behaviours. J Cell Mol Med 2021; 25: 7028–7038.
171. Lan T, Li Y, Fan C, Wang L, Wang W, Chen S, *et al.* MicroRNA-204-5p reduction in rat hippocampus contributes to stress-induced pathology via targeting RGS12 signaling pathway. J Neuroinflammation 2021; 18: 1–20.
172. Li Y, Fan C, Wang L, Lan T, Gao R, Wang W, *et al.* MicroRNA-26a-3p rescues depression-like behaviors in male rats via preventing hippocampal neuronal anomalies. J Clin Invest 2021; 131: e149...
173. Rossetti AC, Paladini MS, Brüning CA, Spero V, Cattaneo MG, Racagni G, *et al.* Involvement of the IL-6 signaling pathway in the anti-anhedonic effect of the antidepressant agomelatine in the chronic mild stress model of depression. Int J Mol Sci 2022; 23: 12...53.
174. Yang JC, Zhao J, Chen YH, Wang R, Rong Z, Wang SY, *et al.* miR-29a-5p rescues depressive-like behaviors in a CUMS-induced mouse model by facilitating microglia M2-polarization in the prefrontal cortex via TMEM33 suppression. J Affect Disord 2024; 360: 188–197.
175. Wang W, Qin X, Wang R, Xu J, Wu H, Khalid A, *et al.* EZH2 is involved in vulnerability to neuroinflammation and depression-like behaviors induced by chronic stress in different aged mice. J Affect Disord 2020; 272: 452–464.
176. Fanelli G, Benedetti F, Wang SM, Lee SJ, Jun TY, Masand PS, *et al.* Reduced CXCL1/GRO chemokine plasma levels are a possible biomarker of elderly depression. J Affect Disord 2019; 249: 410–417.
177. Liu XF, Wang RQ, Hu B, Luo MC, Zeng QM, Zhou H, *et al.* MiR-15a contributes abnormal immune response in myasthenia gravis by targeting CXCL10. Clin Immunol 2016; 164: 106–113.
178. Huang X, Yang C, Huang M. Protective mechanism of the EZH2/microRNA-15a-5p/CXCL10 axis in rats with depressive-like behaviors. J Chem Neuroanat 2023; 132: 102283.
179. Min XL, Liu HJ, Dou XK, Chen FX, Zhao Q, Zhao XH, *et al.* Extracellular vesicles from neural stem cells carry microRNA-16-5p to reduce corticosterone-induced neuronal injury in depression rats. Neuroscience 2024; 538: 95–109.
180. Guo H, Huang B, Wang Y, Zhang Y, Ma Q, Ren Y. Bone marrow mesenchymal stem cells-derived exosomes improve injury of hippocampal neurons in rats with depression by up-regulating microRNA-26a expression. Int Immunopharmacol 2020; 82: 106285.
181. Huang Y, Jin Y, Yao S, Nan G, Mao Y. LncRNA NEAT1 inhibits neuronal apoptosis and induces neuronal viability of depressed rats via microRNA-320-3p/CRHR1 axis. Neurochem Res 2024; 49: 2352-2363.
182. Zhai Y, Zhu YY. MiR-30a relieves migraine by degrading CALCA. Eur Rev Med Pharmacol Sci 2018; 22: 2022–2028.

183. Giamberardino MA, Martelletti P. Emerging drugs for migraine treatment. Expert Opin Emerg Drugs 2015; 20: 137-147.
184. Cheng CY, Chen SP, Liao YC, Fuh JL, Wang YF, Wang SJ. Elevated circulating endothelial-specific microRNAs in migraine patients: A pilot study. Cephalalgia 2018; 38: 1585–1591.
185. Jiang L, Zhang Y, Jing F, Long T, Qin G, Zhang D, *et al*. P2X7R-mediated autophagic impairment contributes to central sensitization in a chronic migraine model with recurrent nitroglycerin stimulation in mice. J Neuroinflammation 2021; 18: 5.
186. Long T, He W, Pan Q, Zhang S, Zhang D, Qin G, *et al*. Microglia P2X4R-BDNF signalling contributes to central sensitization in a recurrent nitroglycerin-induced chronic migraine model. J Headache Pain 2020; 21: 4.
187. Wen Q, Wang Y, Pan Q, Tian R, Zhang D, Qin G, *et al*. MicroRNA-155-5p promotes neuroinflammation and central sensitization via inhibiting SIRT1 in a nitroglycerin-induced chronic migraine mouse model. J Neuroinflammation 2021; 18: 287.
188. Gallelli L, Cione E, Peltrone F, Siviglia S, Verano A, Chirchiglia D, *et al*. Hsa-miR-34a-5p and hsa-miR-375 as biomarkers for monitoring the effects of drug treatment for migraine pain in children and adolescents: A pilot study. J Clin Med 2019; 8: 928.
189. Gazerani P. Current evidence on potential uses of microRNA biomarkers for migraine: From diagnosis to treatment. Mol Diagnosis Ther 2019; 23: 681–694.
190. Tana C, Giamberardino MA, Cipollone F. microRNA profiling in atherosclerosis, diabetes, and migraine. Ann Med 2017; 49: 93-105.
191. Ahmad L, Demartini C, Corrado M, Vaghi G, Piella EM, Allena M, *et al*. Expression of selected microRNAs in migraine: A new class of possible biomarkers of disease? Processes 202; 19: 2199.
192. Ye S, Li S, Ma Y, Wei L, Zeng Y, Hu D, *et al*. Ambient NO(2) exposure induces migraine in rats: Evidence, mechanisms and interventions. Sci Total Environ 2022; 844: 157102.
193. Ye S, Wei L, Jiang Y, Yuan Y, Zeng Y, Zhu L, *et al*. Mechanism of NO(2)-induced migraine in rats: The exploration of the role of miR-653-3p/IGF1 axis. J Hazard Mater 2024; 465: 133362.
194. Cannataro R, Perri M, Caroleo MC, Gallelli L, Sarro G De, Cione E. Modulation of microRNAs linked to pain-migraine by ketogenic diet (P14-007-19). Curr Dev Nutr 2019; 3: nzz052-P14.
195. Zhai Y, Zhu YY. MiR-30a relieves migraine by degrading CALCA. Eur Rev Med Pharmacol Sci 2018; 22: 2022–2028.
196. Liu W, Lv Y, Ren F. PI3K/Akt pathway is required for spinal central sensitization in neuropathic pain. Cell Mol Neurobiol 2018; 38: 747-755.
197. Guo JR, Wang H, Jin XJ, [illegible] DL, Zhou X, Tao Q. Effect and mechanism of inhibition of PI3K/Akt/mTOR signal pathway on chronic neuropathic pain [illegible] spinal microglia in a rat model of chronic constriction injury. Oncotarget 2017; 8: 52923.