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Current Translational Medicine Approach in Schizophrenia: MicroRNA Research

Şizofrenide Güncel Translasyonel Tıp Yaklaşımı Olarak MikroRNA Araştırmaları

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ABSTRACT

Schizophrenia is a common and complex psychiatric disorder with symptoms that significantly affect public health. Candidate gene studies reported that variants in genes involved in molecular processes associated with schizophrenia such as glutamatergic, dopaminergic, and GABAergic signaling pathways increase the risk of schizophrenia. Yet, the data obtained so far are incomplete for the development of new translational medicine approaches. Although the current research has promising results, it is still insufficient for the development of early diagnosis and treatment methods for schizophrenia management. Recent studies have reported that microRNAs detected in brain tissue and body fluids are differentially expressed in schizophrenia patients and control groups may be related to the etiology of schizophrenia. Although the determination of microRNA profiles associated with schizophrenia pathophysiology is very important for the development of new molecular approaches in the early diagnosis and treatment of the disease, the literature is still lacking in this field. Studies reporting schizophrenia-associated microRNAs in the existing literature have some limitations and methodological differences. In this review, we extracted the studies investigating the relationship between schizophrenia and microRNA in the last ten years and it was revealed that sample selection and microRNA detection methods are very important in terms of obtaining consistent results. Non-invasive detection of microRNAs expressed in the brain may have promising results for schizophrenia management. In this context, after a comprehensive literature search, miR-124-3p, miR-16-5p, and miR-34a-5p, which are differentially expressed in schizophrenia patients in the brain and blood, were prioritized as potential epigenetic biomarkers for schizophrenia. Our study provides data that can be utilized for translational medicine approaches to alleviate the burden of the disease in the community.

Keywords: Schizophrenia, microRNA, epigenetic, biomarker, translational medicine

ÖZ

Şizofreni toplum sağlığını önemli ölçüde etkileyen semptomlarla seyreden yaygın ve kompleks bir psikiyatrik hastalıktır. Aday gen çalışmalarında şizofreni ile ilişkili glutamaterjik, dopaminerjik ve GABAerjik sinyal yolakları gibi moleküler yolaklarda etkin genlerde bulunan varyantların şizofreni riskini arttırdığı raporlanmıştır. Ancak, araştırmaların spesifik popülasyonlarda sınırlı sayılı örnek grupları ile sınırlı olması sebebiyle şu ana kadar elde edilen veriler translasyonel tıp alanında yeni yaklaşımların geliştirilmesi için eksik kalmaktadır. Moleküler düzeyde yapılan araştırmaların sonuçları umut verici olsa da hastalık yönetimi için gerekli erken tanı ve tedavi yöntemleri yetersizdir ve bu yönde daha fazla araştırma yapılmasına ihtiyaç duyulmaktadır. Son yıllarda yapılan çalışmalarda postmortem beyin dokusunda ve vücut sıvılarında tespit edilen bazı mikroRNA'ların şizofreni hastaları ve kontrol gruplarında farklı eksprese olarak şizofreni etiyolojisi ile ilişkili olabilecekleri raporlanmıştır. Şizofreni patofizyolojisi ile ilişkili mikroRNA profillerinin belirlenmesi hastalığın erken tanı ve tedavisinde yeni moleküler yaklaşımların geliştirilmesi açısından oldukça önemli olsa da literatürde bu alanda boşluklar vardır. Mevcut literatürde şizofreni ile ilişkili mikroRNA'ları raporlayan çalışmalar metodolojik olarak farklılıklar içermektedir. Son on yılda şizofreni ve mikroRNA ilişkisini araştıran araştırmaların incelendiği bu derleme, özellikle örnek seçiminin ve mikroRNA tespit yöntemlerinin çalışmalarda uyumlu sonuçların alınması açısından oldukça önemli olduğunu ortaya koymuştur. Postmortem beyin dokusunda eksprese olan mikroRNA'ların minimal invaziv olarak vücut sıvılarından tespiti şizofreni yönetimi için umut verici sonuçlar doğurabilir. Bu kapsamda yaptığımız kapsamlı literatür araştırması sonrası miR-124-3p, miR-16-5p ve miR-34a-5p şizofreni için potansiyel epigenetik biyobelirteç olarak önceliklendirilmiş ve mikroRNA'ların hastalığın toplumdaki yükünün hafifletilmesi için geliştirilecek translasyonel tıp yaklaşımlarında kullanım potansiyeli üzerine veri sunulmuştur.

Anahtar sözcükler: Şizofreni, mikroRNA, epigenetik, biyobelirteç, translasyonel tıp

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Introduction

Schizophrenia is a complex, chronic psychiatric disorder that affects approximately 1% of the world's population and is one of the ten diseases that impair the vital functions of individuals worldwide (Kato et al. 2023, Zhao et al. 2023). In the clinical evaluation of schizophrenia, symptoms are classified into 3 categories: negative (affective flattening, anhedonia, alogia, etc.), positive (with significant impairment in the perception of reality, typical hallucinations, delusions, disorganized behaviors, etc.), and cognitive disorders (impairment in attention, memory, and executive functions, etc.) (Sabaie et al. 2022a, Kato et al. 2023). The onset is typically adolescence, with childhood and late-onset being less common (Ayari et al. 2024). The prevalence of schizophrenia is higher in men, and the illness occurs later in life for women than for men (Ayari et al. 2024). The average age of onset is between 18 to 25 for men and 25 to 35 for women, with a second peak occurring during menopause in women (Peng et al. 2023). There are also some indications that the prognosis is worse in men.

The development of schizophrenia has been associated with some genetic and epidemiologic risk factors. Some of the epidemiologic risk factors include obstetric complications, stress, seasonal influences, infectious diseases, advanced paternal age at conception, living in an urban area, migration, cannabis, smoking, and childhood adversity (Janoutová et al. 2016, Stilo and Murray, 2019). The heritability of the disease was determined as 60-80% from genetic studies, and it has been revealed that the effect of different genes plays a role in the development of schizophrenia. (Sözen and Kartalcı, 2023, Kato et al. 2023). Furthermore, defects in molecular mechanisms involved in schizophrenia development have been associated with sequence variants in several genes. Candidate gene studies and multi-omic analyses performed with next-generation sequencing methods have shown that sequence variants in genes such as COMT, DISC1, NRG1, AKT3, DOC2A, GNL3, NRGN, SNX19, SRA1, GAD1, GRM3, ErbB4, BDNF, KMT2F, DRD2, DRD3, and DRD4 can lead to dysregulations in dopaminergic and glutamatergic systems. These findings hold promise in the molecular etiology of schizophrenia by affecting gene expression and regulation according to their functional properties (Zhang et al. 2022, Kato et al. 2023, Yao et al. 2023). However, the effect of inflammation and immune factors in the development of schizophrenia has been explained by the Knudson hypothesis. It suggests that the combination of genetic predisposition and environmental factors, such as immunological changes during neurodevelopment, may increase the vulnerability of the individual to a second stimulus, leading to the development of schizophrenia-like illness (Sotelo-Ramírez et al. 2023). Moreover, different or deficient immune structures have been reported in some schizophrenia patients (Morozova et al. 2021, Liu et al. 2022, Sotelo-Ramírez et al. 2023). The idea that immune response-related differences may be associated with schizophrenia risk by causing epigenetic changes in interaction with environmental factors has been an interesting research topic for researchers in recent years. For this reason, studies have focused on the identification of epigenetic biomarkers associated with schizophrenia. Research conducted in this direction has shown that epigenetic changes contribute to the risk of developing schizophrenia and may be considered as significant risk factors in managing the disease. Despite recent advances in biotechnology and omics technologies, the etiology of schizophrenia remains unclear. Original studies in this direction are of great importance in developing new diagnostic and therapeutic approaches.

Pathophysiological differences occur in the brains of schizophrenia patients. However, sampling and processing brain tissue to detect these differences is challenging. Therefore, there is a need for biomarkers that can be used for early and sensitive detection of these differences in the brain. Although molecular changes in brain tissue associated with the development of schizophrenia can be investigated by analyzing cerebrospinal fluid (CSF), this method is invasive and complicated. On this basis, recent research has focused on identifying reliable and sensitive molecular biomarkers that can be used routinely in the clinic and be detected by minimally invasive or non-invasive methods from body fluids such as blood and saliva. Although the biomarkers identified in the literature reveal promising results about the genetic etiology of schizophrenia, further research is needed in this field due to clinical heterogeneity, variations in sample selection methods, and limitations in research design. Thus, accumulating research continues to discover microRNA (miRNA) profiles with biomarker potential for schizophrenia. This study aims to review the role of miRNAs in the etiology of schizophrenia, a significant research topic in recent years, and to present miRNAs with high biomarker potential to researchers by comparing the methodologies in the studies conducted in the last ten years (2014-2023). In this review, research published in the PubMed database from 2014 until December 2023 was extracted using the keywords "schizophrenia" and "miRNA." The sample types used in the studies were divided into postmortem brain tissue and body fluid, and the miRNAs validated in multiple studies were prioritized by including the results of in silico studies. Our review, carried out to emphasize the importance of sample selection in miRNA research, aims to provide a new

perspective on prioritizing miRNA profiles reflecting molecular level changes in brain tissue in schizophrenia pathology, , offering hope for the future of schizophrenia research.

MiRNAs and Schizophrenia

MiRNAs are small, non-coding RNA sequences that contain 20-24 nucleotides and are involved in post-transcriptional regulation of gene expression. RNA polymerase II forms hairpins containing pri-miRNAs from miRNA genes in the nucleus, which are then converted into pre-miRNA by the enzyme Drosha and transported to the cytoplasm. The pre-miRNA passing into the cytoplasm is converted into short RNA molecules by the endonuclease function of the Dicer enzyme, which interacts with RNA-induced silencing complexes (RISC) (Figure 1).

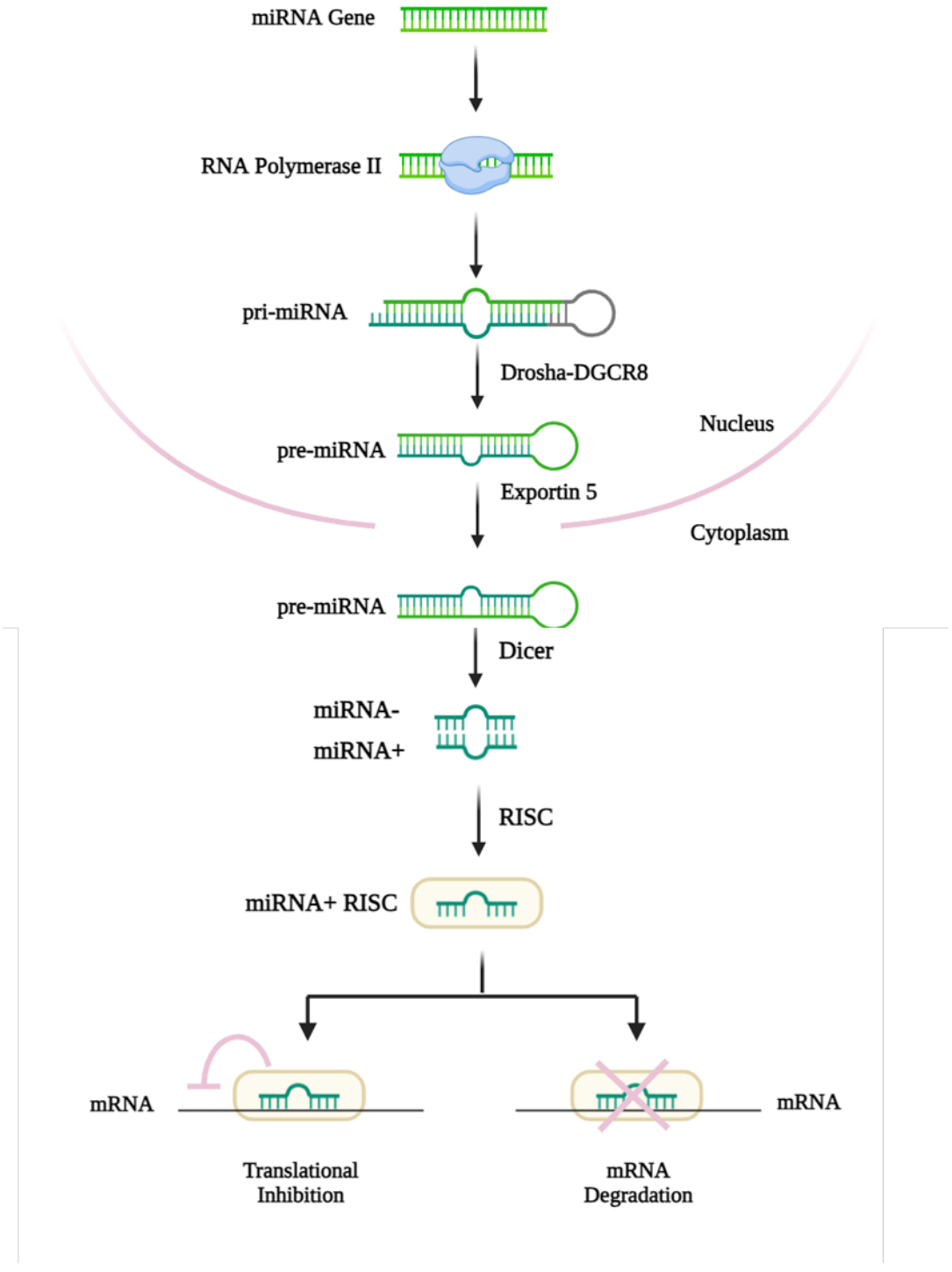

Figure 1. miRNA Biogenesis (Jafri et al. 2019)

miRNAs binding to target sequences in messenger RNA (mRNA) can modulate gene expression and have the potential to repress transcription. Given that, the ongoing research on miRNA-mediated gene regulations has been associated with many pathological conditions, including schizophrenia. The identification of disease-associated miRNA profiles has significantly contributed to our understanding of critical molecular networks for disease etiology. Recent studies have revealed the essential role of miRNAs in the pathophysiology of schizophrenia. However, the field is challenging, as methodological and material differences pose limitations. As a result, well-established miRNA profiles for use as a biomarker in the diagnosis and treatment of schizophrenia are yet to be determined. To date, many miRNAs expressed in the brain have been identified, and these are shown to regulate neuronal development and synaptic plasticity (Zhang et al. 2023). Studies in this field show that miRNA-related changes in the brain often translate into behavioral changes (Roy et al. 2020, Han et al. 2023). The role of the DiGeorge syndrome critical region gene 8 (DGCR8) 22q11.2 deletion is considered an excellent example of miRNA dysregulations in schizophrenia, which is often linked to a higher likelihood of developing schizophrenia (Lim et al. 2023). Moreover, miRNAs detected by minimally invasive methods and expressed in peripheral blood have been reported to have important roles in the diagnosis and progression of schizophrenia (Grosu et al. 2023). Recent studies have found that changes in circulating miRNA expression levels correlate with changes in neuronal tissues in patients with neuropsychiatric diseases. This indicates the importance of miRNAs as a biomarker for both prognosis and diagnosis of mental diseases. For this reason, miRNAs have recently gained significant attention due to their role in epigenetic regulations of brain functioning. MiRNAs are considered functional elements of exosomes that can affect cells through negative regulation of gene expression and by interactions with cell receptors as ligands (Figure 2).

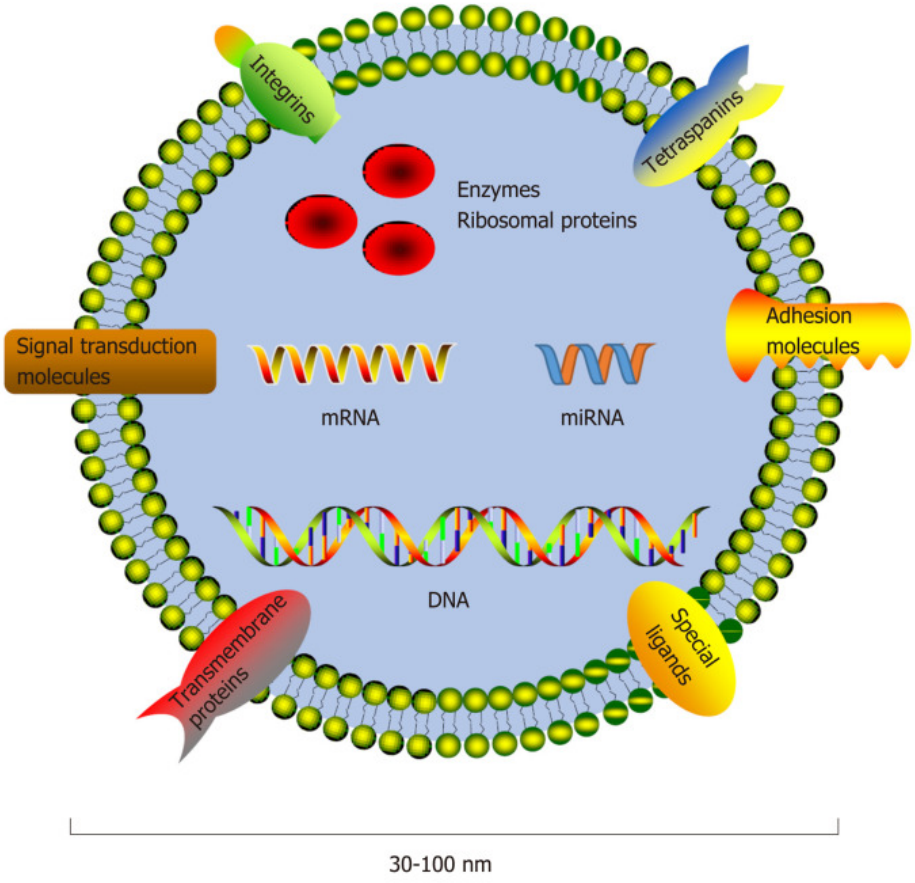

Figure 2. Exosome structure (Lv et al. 2020)

Goldie et al.'s (2014) research showed that different miRNA profiles have been observed in the cellular and subcellular structures of cultured human neurons by potassium ion-induced depolarization. They showed that depolarization-associated changes were mediated by exosomes secreted by neurons, encompassing miRNAs and a synaptic protein, MAP1b. These findings suggest that miRNA release and function may be impaired in neuropsychiatric disorders, as neuropsychiatric disorders is typically characterize synaptic dysfunction. Heterogeneity in miRNA dysregulation may contribute to the heterogeneity of schizophrenia symptoms.

However, the exact mechanisms by which miRNA dysregulation contributes to the disease onset are not fully understood. On the other hand, research shows that miRNAs are highly dynamic at all stages of brain maturation and are essential for developmental processes involved in the onset of schizophrenia (Thomas and Zakharenko, 2021). Despite some limitations and challenges, the foundation of miRNA research is strong and has significant potential for developing biomarkers in neuropsychiatric disorders. The most important ones are their ability to cross the blood-brain barrier due to their small size and to remain stable in a biological fluid, especially in the blood. Furthermore, detecting miRNAs from body fluids by minimally invasive methods, sample collection, processing, and storage is relatively easy under standard laboratory conditions (Roy et al. 2020). This review summarizes the miRNAs examined in the literature studies and groups the studies according to the type of sample used (body fluids, postmortem brain tissue, and in silico). Afterward, group intersections were analyzed; 1 miRNA (miR-223) at the intersection of body fluids and postmortem brain tissue, 6 miRNAs (miR-22-3p, miR-423-5p, miR-9-5p, miR-137, miR-181b-5p, miR-21) at the intersection of body fluids and in silico studies, 1 miRNA (miR-132-3p) at the intersection of brain tissue and in silico studies, and 3 miRNAs common to all three groups (miR-124-3p, miR-34a-5p, and miR-16-5p) were determined (Figure 3). The following sections explain the miRNAs at the intersection of the three groups in detail.

miR-124-3p

Our literature review revealed that miR-124-3p is expressed in body fluids and brain tissue and has potential as a candidate biomarker in diagnosing and treating schizophrenia (Table 1-3). In a study examining the co-regulation of miRNAs and transcription factors in pathways with crucial role in the pathophysiology of schizophrenia, miR-124-3p was reported to affect the expression of early growth response protein 1 (EGR1) and SKI Like Proto-Oncogene (SKIL) gene indirectly (Xu et al. 2016). In the aforementioned study, the expression levels of EDR1 and SKIL were found to be downregulated, while miR-124-3p was upregulated in schizophrenia patients before treatment (Xu et al. 2016). All patients were treated with oral second-generation or atypical antipsychotic (SGA) drugs and followed up for 12 weeks (Xu et al. 2016). When the Positive and Negative Syndrome Scale (PANSS) was compared before and after treatment, above 25% clinical improvement, a decrease in miR-124-3p, and an increase in EGR1 and SKIL expressions were observed (Xu et al. 2016). In another study, the Brain-derived neurotrophic factor (BDNF) gene, which plays a role in cell maturation, survival, diffusion, and synaptic functions, was examined in untreated schizophrenia patients (Fu et al. 2022). While BDNF showed low expression in schizophrenia patients compared to controls, the expression of miR-124-3p was 2-fold higher than controls (Fu et al. 2022). Expression analyses performed on blood samples taken 12 weeks after the beginning of treatment showed that BDNF expression increased 3.5-fold and miR-124-3p levels decreased in the post-treatment compared to the pre-treatment period (Fu et al. 2022). In a bioinformatics study conducted by Sabaie et al. (2022b), competing endogenous RNA (ceRNA) groups associated with schizophrenia were aimed at determining using a microarray data set (GSE17612) including samples taken from the Brodman's Area 10 (BA10) region of the postmortem brains of schizophrenia patients and controls. As a result of the study, eight mRNAs (EGR1, ETV1, DUSP6, PLOD2, CD93, SERPINB9, ANGPTL4, TGFB2), two long non-coding RNAs (lncRNAs) (PEG3-AS1, MIR570HG) and seven miRNAs (hsa-miR-124-3p, hsa-miR-17-5p, hsa-miR-181a-5p, hsa-miR-191-5p, hsa-miR-26a-5p, hsa-miR-29a-3p, hsa-miR-29b-3p) were observed to expressed differently in schizophrenia patients compared to healthy controls (Sabaie et al. 2022b).

MiR-124-3p is a significant regulator of miRNA-mediated neuroplasticity and is abundantly expressed in the brain, affecting neuronal differentiation and functions in neurogenesis (Martins et al. 2021, Cheng et al. 2009, Zhang et al. 2023, Namkung et al. 2023). Besides our literature review, recent studies have suggested miR-124 as a potential therapeutic target in clinical applications of central nervous system and brain diseases due to its involvement in cellular processes related to neuronal migration, neural stem cell differentiation, proliferation, and cell apoptosis (Zhang et al. 2023). In addition, a recent study reported that it regulates tyrosine-protein phosphatase non-receptor type 1 (PTPN1) expression in mice via tyrosine and affects on testicular development in male mice (Luo et al. 2024).

miR-34a-5p

According to our literature review, miR-34a-5p is one of the crucial miRNAs associated with schizophrenia in studies using body fluids, tissue samples, and in silico tools (Figure 3, Table 1, and Table 3). Lai et al. (2016) examined the expression levels of 7 miRNAs, including miR-34a-5p, and 2 miRNAs (miR-34a-5p and miR-548d) using blood samples of 48 schizophrenia patients and 37 healthy controls, and postmortem brain tissues from Brodmann area 46 (BA46) and caudate putamen regions of the brain of 25 schizophrenia patients and 27 healthy controls. As a result of the study, approximately 2-fold higher levels of miR-34a-5p expression were detected in

the blood of schizophrenia patients compared to controls (Lai et al. 2016). Also, upregulation of miR-34a-5p was observed in BA46 tissue samples of schizophrenia patients with long symptom duration when compared with short symptom duration (Lai et al. 2016). However, no statistical significance was observed in BA46 and caudate putamen tissues compared to healthy controls (Lai et al. 2016). In another study, a meta-analysis was conducted to assess the diagnostic value of miRNAs for schizophrenia (Liu et al. 2017b). Following the meta-analysis, validation was carried out using 39 patients and 50 healthy individuals to confirm the findings (Liu et al. 2017b). The study reported significant differences in the expression levels of 6 miRNAs, including miR-34a-5p, between patients and controls (Liu et al. 2017b). He et al. (2019) examined the potential of 14 candidate miRNAs, including miR-34a-5p, for diagnosing schizophrenia. The study analyzed the miRNA expression in serum samples from 40 schizophrenia patients and 40 healthy controls using the qRT-PCR method (He et al. 2019). Three miRNAs (miR-34a-5p, miR-432-5p, and miR-449a) were suggested to have significant expression changes in schizophrenia patients (He et al. 2019). Sabaie et al. (2021) reanalyzed microarray datasets, including postmortem tissue and blood samples of schizophrenia patients, and identified common differentially expressed mRNAs (DEmRNA) and lncRNAs (DElncRNA) in the data sets. miRNA interactions were determined by constructing a ceRNA network using the identified DEmRNAs and DElncRNAs. As a result of the analysis, it was reported that miR-34a-5p may interact with multiple ceRNA axes with upregulation observed in different brain regions (Brodman's area, hippocampus, and striatum) (Sabaie et al. 2021b). In another study by Sabaie et al. (2021a), in silico analyses were performed to define the role of ceRNA groups in olfactory epithelium samples of schizophrenia patients to understand better the molecular processes involved in schizophrenia. The study reported two different ceRNA networks in which miR-34a-5p plays a role in the pathogenesis of schizophrenia (Sabaie et al. 2021a). Furthermore, another study examined the expression levels of nine different miRNAs (hsa-miR-7, hsa-miR-30e, hsa-miR-34a, hsa-miR-132, hsa-miR-195, hsa-miR-212, hsa-miR-346, hsa-miR-432 and hsa-miR-181b) in plasma and peripheral blood mononuclear cells of 25 schizophrenia patients and 13 healthy controls (Sun et al. 2015). Among the nine miRNAs analyzed, four miRNAs (miR-132, miR-195, miR-30e, miR-7) and three miRNAs (miR-212, miR-30e, miR-34a) showed significantly different expression between the healthy group and schizophrenia patients in plasma and peripheral blood mononuclear cells, respectively (Sun et al. 2015). miR-132, miR-195, miR-30e, and miR-7 were found to be statistically higher in the plasma of schizophrenia patients compared to healthy controls, while miR-212, miR-34a, and miR-30e were reported to be upregulated in peripheral blood mononuclear cells (Sun et al. 2015). In addition, miR-34a-5p has recently been indicated to play an active role in diseases such as Huntington's disease, cervical cancer, and prostate cancer (Jiang et al. 2021, Wen et al. 2022b, Hart et al. 2023).

miR-16-5p

In recent years, miR-16-5p has been proposed as a potential biomarker candidate for different types of cancer. Based on our literature review, it also might have an essential role in the development of schizophrenia (Wang et al. 2021, Peng et al. 2022, Zanjirband et al. 2023) (Table 1, Table 2, and Table 3). In a study by Kimoto et al. (2016), the relationship between miR-16 and the regulator of G protein Signaling 4 (RGS4) was examined using postmortem brain tissue of 62 schizophrenia patients and 62 healthy controls. After analysis, it was found that miR-16 levels were 14.7% higher in schizophrenia patients compared to healthy controls. Furthermore, RGS4 expression and protein levels were lower in schizophrenia patients compared to healthy controls (Kimoto et al. 2016). In a recent study, RNA sequencing was performed using ten schizophrenia patients and eight healthy controls (Huang et al. 2023). The study groups included patients with early-onset schizophrenia who were younger than 13 years of age and did not have any other psychological and developmental disorders (autism spectrum disorders, intellectual disability, etc.) and healthy individuals who were age and gender-matched with these patients (Huang et al. 2023). It was reported that there was an increase in the blood miR-16-5p levels in schizophrenia patients compared to healthy controls, and this is negatively correlated with the expressions of 4 different circular RNAs (Huang et al. 2023). In a recent in silico study, potential biomarker candidates associated with schizophrenia were investigated using four microarray data sets (GSE18312, GSE27383, GSE54913, and GSE38485), including 192 schizophrenia patients and 170 normal controls (Xie et al. 2022). They identified four miRNAs, including miR-16-5p, which showed statistically significant different expression levels in schizophrenia patients and controls and could be used as biomarkers in diagnosing schizophrenia (Xie et al. 2022). In a study by Asadi et al. (2022), the relationship between TTP (tristetraprolin) protein, a key regulator of BDNF, and miR-16-5p levels in the context of schizophrenia was examined using 50 schizophrenia patients and 50 healthy control samples who did not use drugs and did not have 22q11.2 deletion syndrome, a known risk factor for schizophrenia.

As a result, no significant difference was found in miR-16-5p expression levels between patients and controls, while TTP expressions were reported to be higher in patients compared to the healthy group (Asadi et al. 2022). The literature also shows that miR-16-5p plays a role in cervical cancer, hepatocellular carcinoma, and fibrotic diseases (Ding et al. 2020, Bashir et al. 2020, Wen et al. 2022a). Although miR-16's tumor suppressor role has been extensively studied in the literature, its role in neuropsychiatric diseases has become increasingly intriguing in recent years. Recent studies suggest that miR-16 is critical in regulating neuronal differentiation (Schlichtholz 2022). While the literature shows promising results, the role of miR-16 in schizophrenia has not been fully explained. More comprehensive research on the functional importance of miR-16 in schizophrenia and its potential target genes could provide valuable data to the missing knowledge of schizophrenia molecular biology.

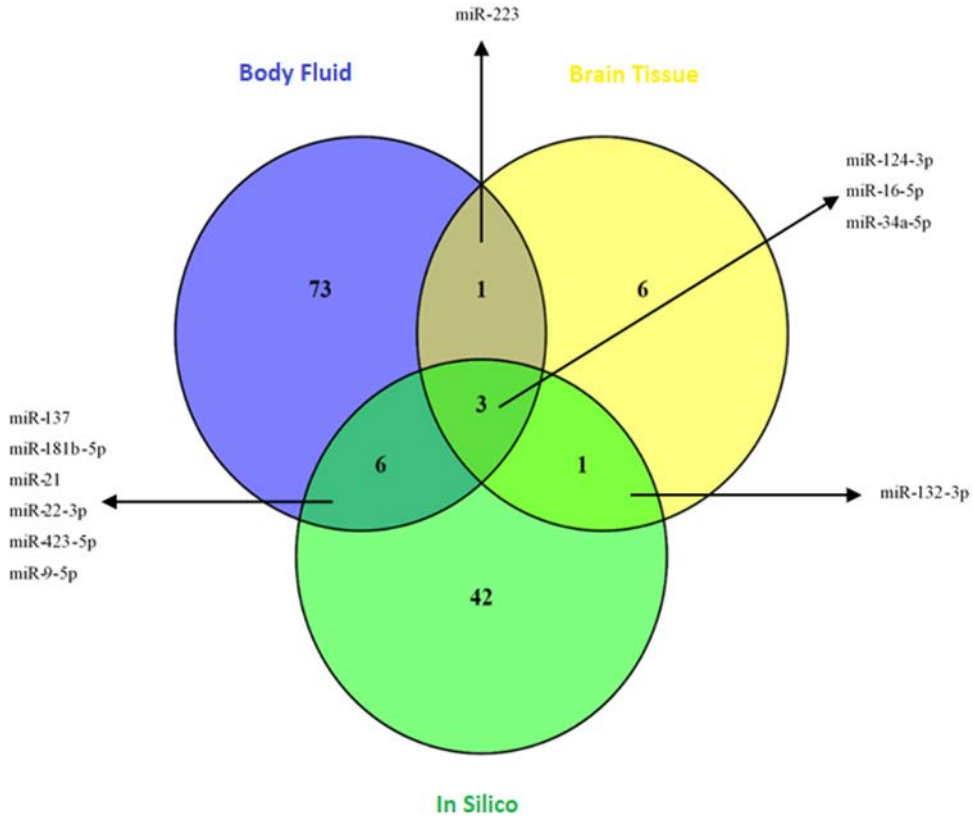

Figure 3. Venn diagram of miRNAs analysed in the review

miR-223

MiR-223 is one of the four miRNAs found to be significant in miRNA studies using body fluids and postmortem brain tissue (Figure 3, Table 1-2). In a study by Amoah et al. (2020), total RNA was isolated from postmortem brain tissue using 29 schizophrenia patients, 26 bipolar disorder patients, and 25 healthy controls, and the expression levels of 8 different miRNAs, including miR-223, were examined. The analysis revealed that miR-223 expression was increased in postmortem samples taken from the orbitofrontal cortex of patients compared to controls (Amoah et al. 2020). In the same study, it was reported that the expression of glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B) and glutamate ionotropic receptor AMPA type subunit 2 (GRIA2), which are among the targets of miR-223 were decreased (Amoah et al. 2020). In another study, miRNA microarray analysis was performed using blood samples of 21 schizophrenia patients and 21 healthy controls, and then two miRNAs were selected for validation (Zhao et al. 2019). Microarray results showed that 21 miRNAs, including miR-223, were upregulated in the patient group compared to the healthy sample group (Zhao et al. 2019). In the validation phase, the study reported a 2-fold increase in miR-223 in schizophrenia patients compared to healthy controls and targeted inositol polyphosphate-5-phosphatase B (INPP5B), SKIL and spectrin repeat containing nuclear envelope protein 1 (SYNE1) genes (Zhao et al. 2019). Other studies have also shown that mir-223 is involved in liver diseases, infectious disorders, and cardiovascular diseases (Yuan et al. 2021, Zhang et al. 2021, Gu et al. 2022).

Table 1. miRNAs identified in body fluid analysis		
miRNA ID	**Reference**	**Body Fluid**
let-7	Geaghan et al. 2019	Whole blood
let-7a-5p	Long et al. 2022, Huang et al. 2023	Whole blood
let-7d-3p	Jin et al. 2023	Whole blood
let-7e	Sun et al. 2020	Whole blood
let-7g-5p	Huang et al. 2023	Whole blood
miR-107	Gallego et al. 2018	Cerebrospinal fluid
let-7i-5p	Huang et al. 2023	Whole blood
miR-124-3p	Fu et al. 2022	Whole blood
miR-125b-1-3p	Cattane et al. 2019	Whole blood
miR-1262	You et al. 2020	Whole blood
miR-1271-5p	Huang et al. 2023, Geaghan et al. 2019	Whole blood
miR-1273d	Fan et al. 2015	Whole blood
miR-1303	Fan et al. 2015	Whole blood
miR-132	Yu et al. 2015, Sun et al. 2015	Whole blood
miR-134	Yu et al. 2015	Whole blood
miR-137	Peng et al. 2023, Khadimallah et al. 2022, Chen et al. 2021a, Ma et al. 2018, Liu et al. 2017b	Whole blood, Plasma
miR-141-3p	Yao et al. 2023	Whole blood
miR-144-5p	Gallego et al. 2018	Plasma
miR-146a	Ibrahim et al. 2020	Whole blood
miR-148b-3p	Wu et al. 2020	Whole blood
miR-155-5p	Long et al. 2022	Whole blood
miR-16-5p	Huang et al. 2023, Asadi et al. 2022	Whole blood
miR-181b	Song et al. 2014, Sun et al. 2015, Ma et al. 2018	Whole blood, Plasma
miR-181b-5p	Gou et al. 2021, Liu et al. 2017b, Alacam et al. 2016	Whole blood, Plasma
miR-1827	Davarinejad et al. 2022	Whole blood
miR-185-5p	Sabaie et al. 2022a	Whole blood
miR-18a-5p	Huang et al. 2023	Whole blood
miR-195	Sun et al. 2015, Pan et al. 2021, Huang et al. 2020b	Whole blood, Plasma
miR-195–5p	Alacam et al. 2016	Plasma
miR-19b	Horai et al. 2020	Whole blood
miR-203a-3p	Tsoporis et al. 2022	Whole blood
miR-206	Du et al. 2019	Whole blood
miR-204-5p	Gallego et al. 2018	Plasma
miR-21	Chen et al. 2016, Fan et al. 2015, Liu et al. 2017b	Whole blood
miR-212	Sun et al. 2015	Whole blood
miR-218-5p	You et al. 2020	Whole blood
miR-221-5p	Geaghan et al. 2019	Whole blood
miR-223	Zhao et al. 2019	Plasma
miR-22-3p	Ma et al. 2018	Whole blood
miR-23a-3p	Jin et al. 2023	Whole blood
miR-26a	Shafiee-Tam Kandjani et al. 2023	Plasma
miR-301a-3p	Alacam et al. 2016	Plasma
miR-3064-5p	Fan et al. 2015	Whole blood
miR-30a-5p	Liu et al. 2017a	Whole blood
miR-30b-5p	Huang et al. 2023	Whole blood
miR-30e	Sun et al. 2015, Song et al. 2014	Whole blood, Plasma
miR-30e-3p	Jin et al. 2023	Whole blood
miR-3131	Fan et al. 2015	Whole blood
miR-320a-3p	Wang et al. 2019	Serum
miR-320b	Wang et al. 2019	Serum
miR-339-5p	Birdi et al. 2023	Whole blood
miR-346	Liu et al. 2017b, Sun et al. 2015	Whole blood
miR-34a-5p	He et al. 2019, Liu et al. 2017b, Lai et al. 2016, Song et al. 2014, Sun et al. 2015	Whole blood, Plasma
miR-34b	Chen et al. 2021a	Plasma
miR-34c	Chen et al. 2021a	Plasma
miR-3653-3p	Zhao et al. 2023	Whole blood
miR-375	Gallego et al. 2018	Plasma

Table 1. miRNAs identified in body fluid analysis		
miRNA ID	**Reference**	**Body Fluid**
miR-3687	Fan et al. 2015	Whole blood
miR-423-5p	Gallego et al. 2018	Plasma
miR-432-5p	He et al. 2019, Sun et al. 2015, Yu et al. 2015	Whole blood, Plasma
miR-4428	Fan et al. 2015	Whole blood
miR-4429	Davarinejad et al. 2022	Whole blood
miR-4467	Jin et al. 2022	Whole blood
miR-451a	Gallego et al. 2018	Cerebrospinal fluid
miR-449a	He et al. 2019	Plasma
miR-4725-3p	Fan et al. 2015	Whole blood
miR-4732-3p	Jin et al. 2023	Whole blood
miR-484	Bradshaw et al. 2017	Whole blood
miR-485	Guo et al. 2019	Whole blood
miR-5096	Fan et al. 2015	Whole blood
miR-574-5p	Davarinejad et al. 2022	Whole blood
miR-654-3p	Huang et al. 2023	Whole blood
miR-6734-5p	Gallego et al. 2018	Plasma
miR-675-3p	Funahashi et al. 2023	Plasma
miR-7	Song et al. 2014, Sun et al. 2015	Whole blood, Plasma
miR-769-5p	Gallego et al. 2018	Cerebrospinal fluid
miR-7110-5p	Ambrozová et al. 2023	Whole blood
miR-92a-3p	Huang et al. 2023, Ma et al. 2018	Whole blood
miR-942-5p	Gallego et al. 2018	Plasma
miR-939-5p	Jin et al. 2023	Whole blood
miR-99b-3p	Gallego et al. 2018	Cerebrospinal fluid
miR-9-5p	Jin et al. 2022	Whole blood
miR-let-7a-5p	Huang et al. 2023	Whole blood

Table 2. miRNAs identified in brain tissue analysis	
miRNA ID	**Reference**
miR-124-3p	Namkung et al. 2023
miR-132-3p	Johnstone et al. 2018
miR-16-5p	Kimoto et al. 2016
miR-219-2-3p	Smalheiser et al. 2014
miR-223	Amoah et al. 2020
miR-3162	Hu et al. 2019
miR-34a-5p	Lai et al. 2016
miR-4449	Maekawa et al. 2015
miR-508-3p	Smalheiser et al. 2014
miR-642	Smalheiser et al. 2014
miR-936	Panja et al. 2021, Hu et al. 2019

miR-9-5p

MiR-9-5p is also found in the intersection of the miRNA groups identified in studies performed with body fluids and in silico analyses (Figure 3, Table 1, and Table 2). Sabaie et al. (2021b), used microarray datasets from brain tissue (GSE53987) and lymphoblasts (LB) obtained from peripheral blood (GSE73129) of schizophrenia patients and matched controls. In the study mentioned above, researchers aimed to identify differentially expressed mRNAs (DEmRNAs) and lncRNAs (DElncRNAs) and to create a ceRNA network associated with lncRNA (Sabaie et al. 2021b). Their findings indicate that miR-9-5p supports the ceRNA hypothesis, which is considered to play an essential role in the pathophysiology of schizophrenia (Sabaie et al. 2021b). However, in a recent study, total RNA sequencing was performed on blood samples from 35 first-episode schizophrenia patients and 60 healthy controls (Jin et al. 2022). The study found lower levels of miR-9-5p in the blood of schizophrenia patients compared to healthy controls (Jin et al. 2022). Furthermore, miR-9-5p has also been found to be associated with diseases such as gastric cancer, lung adenocarcinoma, and Alzheimer's disease (Zhu et al. 2021, Chen et al. 2021b, Lv et al. 2022).

miR-137

Based on our literature review, miR-137 is one of the most extensively investigated miRNAs in schizophrenia. As previously mentioned, Liu et al. (2017b) reported that miR-137, one of the miRNAs chosen for validation after meta-analysis, was overexpressed in schizophrenia patients compared to healthy controls. Another study involved miRNA sequencing of RNAs isolated from blood samples taken from 10 adult-onset schizophrenia (AOS) patients and ten healthy controls (Ma et al. 2018). The sequencing data showed an 81% increase in miR-137 levels in schizophrenia patients compared to healthy controls (Ma et al. 2018).

In a study by Chen et al. (2021a), miRNA expression profiling was conducted using the qRT-PCR method. Blood samples were obtained from 104 early-onset schizophrenia (EOS) patients, 111 adult-onset schizophrenia patients (AOS), 30 first-degree relatives of EOS patients (REOS), 42 first-degree relatives of AOS patients (RAOS), 31 patients with bipolar disorder, and 100 healthy individuals (Chen et al. 2021a). As a result, the study reported elevated miR-137 expression in the blood of EOS and AOS patients compared to healthy controls (Chen et al. 2021a). Additionally, in a recent study conducted by Khadimallah et al. (2022), it was reported that inhibiting miR-137 led to decreased levels of oxidative stress-related markers in mice brain tissue, and higher exosomal miR-137 levels were associated with reduced cytochrome c oxidase subunit VIa polypeptide2 (COX6A2) levels (Khadimallah et al. 2022). Furthermore, the same study investigated redox markers and exosomal miR-137 in blood samples taken from 138 patients diagnosed with early psychosis and 134 age- and gender-matched healthy controls (Khadimallah et al. 2022). The patients were divided into two groups based on mitochondrial dysfunction and exosomal COX6A2 levels (Khadimallah et al. 2022). The findings showed that both groups had higher levels of exosomal miR-137 than healthy controls and lower levels of exosomal COX6A2 (Khadimallah et al. 2022).

A recent study investigated the correlation between miR-137 and serum estradiol levels in blood samples of 1004 schizophrenia patients and 896 healthy controls (Peng et al. 2023). The findings revealed lower estradiol levels in serum samples of schizophrenia patients, which corresponded to decreased miR-137 expression (Peng et al. 2023). However, it was stated that estradiol may have a protective effect on schizophrenia in women by causing an increase in miR-137 expression (Peng et al. 2023). In addition to schizophrenia, miR-137 is also implicated in lung cancer, acute cerebral infarction, and cervical cancer (Tian et al. 2021, Gui et al. 2021, Luo et al. 2022).

miR-181b-5p

Although miR-181b-5p is a promising non-invasive biomarker that can be used in schizophrenia management, the current studies on this miRNA are insufficient (Table 1 and Table 3). In a 2017 meta-analysis by Liu et al. (2017), miRNA studies using blood samples in schizophrenia patients conducted from January 1990 to October 2016 were searched in different databases. Of the 136 articles reviewed in the study, six were included in the more detailed analysis (Liu et al. 2017b). After the literature review, six miRNAs, including miR-181b-5p, were selected for validation in 39 schizophrenia patients and 50 healthy controls (Liu et al. 2017b). After validation, miR-181b-5p was reported to be more highly expressed in schizophrenia patients compared to healthy controls (Liu et al. 2017b).

Furthermore, a study examining the associations between miRNAs and resistance to schizophrenia treatment analyzed 29 different miRNAs in blood samples from a diverse sample of 19 schizophrenia patients who responded to treatment, 18 who showed resistance, and 10 healthy controls (Alacam et al. 2016). The study found that three miRNAs, including miR-181b-5p, were associated with treatment response in schizophrenia. In another recent study, the correlation between the miR-181b-5p and its potential target, B-cell lymphoma 2 (BCL-2) gene and protein, was investigated by qPCR method using blood samples from 123 schizophrenia patients and 50 healthy controls (Gou et al. 2021). The study found an inverse correlation between miR-181b-5p and BCL-2 expression (Gou et al. 2021). Additionally, miR-181b-5p was associated with working memory function in patients with schizophrenia, while no significant associations were found between BCL-2 expression/protein levels and working memory function (Gou et al. 2021). Furthermore, miR-181b-5p has been reported to play a crucial role in diseases such as hepatoblastoma, acute myeloid leukemia, and acromegaly (Lv et al. 2023, Li et al. 2023a, Henriques et al. 2023).

miR-21

miR-21 is also one of the miRNAs examined in silico studies and studies using body fluids obtained after the literature review (Figure 3, Table 1, and Table 3). In a study conducted by Chen et al. (2016), blood samples were

taken from 82 schizophrenia patients and 43 healthy controls. Expression analysis was performed by qPCR method to examine the associations of ten miRNAs, including miR-21, with schizophrenia (Chen et al. 2016). It was reported that miR-21 levels in blood were lower in schizophrenia patients six weeks after the beginning of treatment compared to before treatment (Chen et al. 2016). Also, low expression levels of miR-21 were reported to be observed in patients treated with olanzapine compared to patients treated with other antipsychotic drugs (Chen et al. 2016).

Table 3. miRNAs identified in in silico studies

miRNA ID	**Reference**
miR-124-3p	Sabaie et al. 2022b, Sabaie et al. 2021b, Xu et al. 2016
miR-125a-5p	Ying et al. 2022
miR-125b-5p	Ying et al. 2022
miR-126-3p	Sabaie et al. 2021b
miR-126-5p	Sabaie et al. 2021b
miR-1299	Balasubramanian ve Vinod 2022
miR-132-3p	Sabaie et al. 2021b
miR-13-5a-1	Brum et al. 2021
miR-137	Brum et al. 2021, Pergola et al. 2023
miR-15a-5p	Sabaie et al. 2021b
miR-15b-5p	Sabaie et al. 2021b
miR-16-5p	Xie et al. 2022
miR-17-5p	Sabaie et al. 2022b, Sabaie et al. 2021b
miR-181a-5p	Sabaie et al. 2022b
miR-181b-5p	Han et al. 2023
miR-191-5p	Sabaie et al. 2022b
miR-195-5p	Sabaie et al. 2021b
miR-199a-3p	Pala ve Denkçeken 2020
miR-208a-3p	Cao et al. 2020
miR-208b-3p	Cao et al. 2020
miR-20b-5p	Sabiae et al. 2021b
miR-21	Xie et al. 2022
miR-22-3p	Sabaie et al. 2021b
miR-24-3p	Sabaie et al. 2021a
miR-26a-5p	Sabaie et al. 2022b
miR-296-5p	Li et al. 2021
miR-29a-3p	Sabaie et al. 2022b, Sabaie et al. 2021b
miR-29b-2	Brum et al. 2021
miR-29b-3p	Sabaie et al. 2022b, Sabaie et al. 2021b
miR-29-c	Brum et al. 2021
miR-29c-3p	Sabaie et al. 2021b
miR-3167	Balasubramanian ve Vinod 2022
miR-320e	Chen et al. 2018
miR-335-5p	Sabaie et al. 2021a
miR-340-5p	Ying et al. 2022
miR-342-3p	Ying et al. 2022
miR-34a-5p	Sabaie et al. 2021a, Sabaie et al. 2021b
miR-373-5p	Pala ve Denkçeken 2020
miR-3943	Li et al. 2021
miR-3b	Brum et al. 2021
miR-421	Balasubramanian ve Vinod 2022
miR-423-5p	Li et al. 2021
miR-425-5p	Ying et al. 2022
miR-4532	Li et al. 2021
miR-4640-3p	Li et al. 2021
miR-4705	Balasubramanian ve Vinod 2022
miR-4723-3p	Li et al. 2021
miR-593-3p	Li et al. 2021
miR-618	Li et al. 2021
miR-7-5p	Sabaie et al. 2021a, Sabaie et al. 2021b
miR-9-5p	Sabaie et al. 2021b
miR-98-5p	Sabaie et al. 2021b

In another study, a microarray analysis was performed on three schizophrenia patients and three healthy individuals selected from a cohort of 55 schizophrenia patients aged 18-30 years and age-matched 28 healthy individuals without major psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder (Fan et al. 2015). The studied identified ten miRNAs, including miR-21, with the highest expression level change between schizophrenia and healthy group from the microarray analysis, and validated them using qPCR method (Fan et al. 2015). Following the analysis, it was observed that miR-21 levels in blood samples were higher in patients with schizophrenia compared to healthy controls (Fan et al. 2015). The results of these studies were confirmed in a study by Liu et al. (2017b), which suggested miR-21 as a sensitive and specific diagnostic biomarker for schizophrenia (Liu et al. 2017b). MiR-21 has also been observed to linked to other diseases such as colorectal cancer, lung cancer, cardiorenal syndrome, and cardiovascular diseases (Huang et al. 2020a, Bai et al. 2022, Li et al. 2023c, Holland et al. 2023).

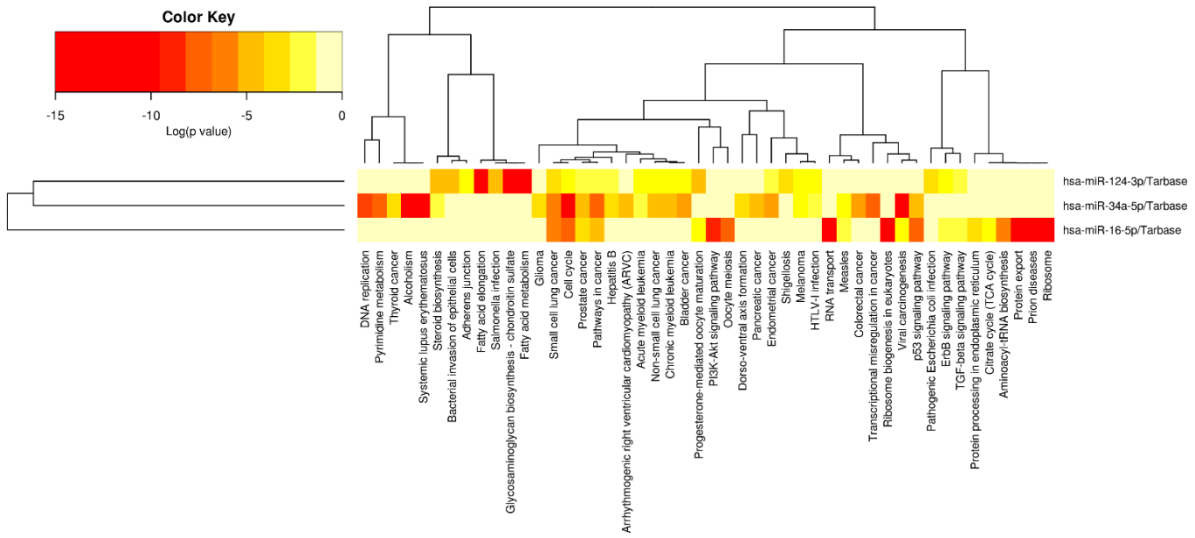

Figure 4. Results of KEGG pathway analysis (generated using DIANA-miRPath v3. database: https://diana-lab.e-ce.uth.gr/html/mirpathv3/)

miR-132-3p

As a result of our review, miR-132-3p appears to be one of the schizophrenia-associated miRNAs reported to be dysregulated in silico and brain tissue studies (Figure 3, Table 2, and Table 3). In a study examining the BA12 tissues from 12 schizophrenia patients and 11 healthy controls, miR-132-3p was found to target the Enhancer of Zeste 1 (EZH1) gene, which encodes the dominant polycomb enzyme in the human brain (Johnstone et al. 2018). Their cell culture results suggest the overexpression of miR-132-3p leads to decreased levels of the H3K27me3 histone protein (Johnstone et al. 2018). Additionally, another study examining the CeRNA hypothesis in schizophrenia patients, analyzed two different microarray data sets from brain tissue (GSE53987) and blood samples (GSE73129) of schizophrenia patients and healthy controls (Sabaie et al. 2021b). The results showed downregulation of miR-132-3p in patients with schizophrenia compared to healthy controls (Sabaie et al. 2021b). Apart from our literature, miR-132-3p was also observed to be associated with diseases such as ischemic acute kidney injury, temporomandibular joint osteoarthritis, interstitial lung disease, and epilepsy (Zhou et al. 2022, Li et al. 2023b, Fang et al. 2023, Nomair et al. 2023).

Conclusion

Schizophrenia is a complex and chronic psychiatric disorder prevalent worldwide. MiRNAs are non-coding regulatory RNA sequences involved in post-transcriptional regulation of gene expression. Recent studies have highlighted the crucial role of miRNAs in the pathophysiology of schizophrenia. However, specific miRNA biomarkers that can be used in diagnosis and treatment are yet to be identified. In our review included, we analyzed 67 studies conducted between 2014 and 2023 that investigated miRNA expression in schizophrenia. The miR-124-3p, miR-16-5p, and miR-34a-5p were identified as common miRNA biomarkers associated with schizophrenia in studies using body fluids and tissue samples. DIANA-miRPath (v3) database was used to

determine the enrichments of these miRNAs in molecular pathways, which revealed that these miRNAs involve molecular networks such as cell cycle and lipid metabolism, especially cancer (Figure 4) (Vlachos et al. 2015).

It is recommended that further research prioritizes these miRNAs to potentially establish a diagnostic/prognostic panel for schizophrenia and develop new treatment methods. However, our study also highlights several issues in the existing literature. These include variations in the sample types (tissue and fluid), differences in the experimental design and data analysis methods, and inconsistencies in the miRNA nomenclature. In addition, using postmortem samples in tissue studies makes detecting dynamic variations in disease progression difficult. On the other hand, limitations in the patient selection criteria and lack of information on antipsychotic treatment processes may have caused differences across study results. Therefore, research focusing on the first episode and treatment-resistant schizophrenia patients has the potential to provide a better understanding of the etiology of the disease and to obtain more substantial results for clinical applications. A standard methodology should be adopted to improve the quality and consistency of the literature in this direction. Furthermore, an increased number of bioinformatics studies in this field have been found, and the importance of in silico analysis has been emphasized. Several miRNAs associated with schizophrenia in bioinformatics studies also showed significance in tissue and blood studies, suggesting the potential of bioinformatics studies to generate preliminary data in this area.

This review may serve as a resource for scientists conducting research in this field, providing up-to-date information about the roles of miRNAs in schizophrenia. Notwithstanding, a limitation of our study is the lack of discussion of contradictory results, as our review only includes data from the literature with statistically significant results related to schizophrenia. Yet, current data provide promising results on miRNAs that are significant for the diagnosis, prognosis, and treatment of schizophrenia. Further research is important to develop miRNA panels for diagnosing schizophrenia, assessing risk, and evaluating prognosis in clinical settings. Additionally, miRNA-based therapeutic approaches may hold potential for treating schizophrenia in the future..

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