

## The potential use of miRNAs in forensic science

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### ABSTRACT

The use of molecular genetic approaches to identification of tissues and biological fluids of the body, which often provide important information for reconstruction of a potential crime, is relevant for forensic studies. MicroRNAs (miRNAs) are short, single-stranded noncoding RNAs (containing on average 18–22 nucleotides) that regulate gene expression at the post-transcriptional level by binding to the 3'-untranslated region (3'-UTR) of specific mRNA targets, which results in a decrease in protein expression by blocking translation and / or promotes degradation of target mRNAs. MiRNAs are involved in virtually all biological processes, including cell proliferation, apoptosis, and differentiation. By acting on target genes, miRNAs are involved in regulation of many pathological processes. In addition, numerous miRNAs called circulating miRNAs were found in many biological fluids of the human body, for example, in blood. Molecular genetic approaches undoubtedly outperform histological and immunological tests in tissue characterization, and miRNAs, due to their characteristic tissue specificity and stability in biological fluids, have potential for application in forensic practice and are of great interest for experts.

**Key words:** microRNA, biological fluids, forensic science, expression, circulating.

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## Потенциал использования микроРНК в судебно-медицинской экспертизе

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### РЕЗЮМЕ

Применение молекулярно-генетических подходов для идентификации тканей и биологических жидкостей организма, которые часто дают важную информацию для реконструкции потенциального преступления.

ния, является актуальной темой судебно-медицинских исследований. МикроРНК – это короткие, в среднем 18–22 нуклеотида, одноцепочечные некодирующие РНК, которые регулируют экспрессию генов на посттранскрипционном уровне путем связывания с 3'-нетранслируемой областью (3'-НТО) специфических мРНК-мишеней, что приводит к уменьшению экспрессии белка посредством блокады трансляции и (или) способствуя деградации мРНК-мишеней. МикроРНК участвуют практически во всех биологических процессах, включая клеточную пролиферацию, апоптоз и дифференцировку клеток. Через воздействие на гены-мишени микроРНК участвуют в регуляции многих патологических процессов. Кроме того, во многих биологических жидкостях организма человека, таких как кровь, были обнаружены многочисленные микроРНК, называемые циркулирующими микроРНК. Молекулярно-генетические подходы, несомненно, превосходят гистологические и иммунологические анализы в характеристике тканей, и микроРНК, благодаря характерной для них тканеспецифичности и стабильности в биологических жидкостях, несомненно, имеют потенциал в применении в судебно-медицинской практике и заслуживают внимания экспертов.

**Ключевые слова:** микроРНК, биологические жидкости, судебно-медицинская экспертиза, экспрессия, циркулирующие.

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## INTRODUCTION

MicroRNAs (miRNAs) are short (containing on average 18–22 nucleotides), single-stranded non-coding RNAs that regulate gene expression at the post-transcriptional level by binding to the 3'-untranslated region (3'-UTR) of specific messenger RNA (mRNA) targets, which results in a decrease in protein expression by blocking translation and / or promotes degradation of target mRNA [1]. There are many studies proving the importance of miRNA in the regulation of many biological processes, such as neurogenesis, cell proliferation and differentiation, apoptosis, regulation of immune processes, fat metabolism, glucose homeostasis, etc. [1, 2].

It was shown that dysregulation or aberrant expression of miRNAs associated with these processes leads to development of various human diseases, such as cancer, cardiovascular, autoimmune, and neurodegenerative diseases [3]. In addition, in many biological fluids of the human body, such as blood, urine, cerebrospinal fluid, saliva, etc., numerous miRNAs, called circulating miRNAs, were found [4]. Due to an association with various carriers, these extracellular or circulating miRNAs turned out to be extremely stable: resistant to the effects of ribonucleases (RNases), freeze – thaw cycles, and significant pH fluctua-

tions [5]. Additionally, the content of circulating miRNAs did not significantly change during prolonged incubation of plasma at room temperature [6, 7].

It was initially shown that various extracellular vesicles (EVs) serve as carriers of circulating miRNAs. Indeed, almost all types of cells form and secrete several types of EVs, including microvesicles and exosomes [4, 8]. Microvesicles form by protrusion of the plasma membrane from the cell with subsequent separation of the formed vesicle from the membrane and have a size of 100–1000 nm. Exosomes, on the other hand, are much smaller (40–100 nm) and are released after fusion of the multivesicular body fraction with the plasma membrane [9]. Consequently, the sizes of some microvesicles and exosomes can be very similar.

Therefore, many authors use the term “extracellular vesicles” to refer to a mixed population of microvesicles and exosomes. In addition to EVs, biological fluids also contain apoptotic bodies of 1–4 μm, which also consist of miRNAs. Circulating miRNAs were also found in high-density lipoproteins (HDL), which range in size from 9 to 12 nm. Finally, a large proportion of circulating miRNAs was found in the form of complexes with argonaute-2 proteins (Ago2-miRNAs) [4, 10].

An ideal biomarker should be accessible by non-invasive methods, cheap to quantify, specific to a disease

or physiological condition, and, in case of pathological conditions, it should be a reliable predictor of the disease even before clinical symptoms appear. Since circulating miRNAs have these characteristics, they are very promising for development of new non-invasive biomarkers. In addition, compared with DNA and mRNA, the small size of miRNAs makes them more stable and, therefore, less prone to degradation, which makes them a good option for biomarker development [5].

Another factor that plays a key role in their stability is Ago2 proteins, which are a catalytic component of the RNA-induced silencing complex (RISC). Interaction of Ago2 proteins with mature miRNAs makes them much more resistant to degradation [10]. For these reasons, and taking into account the fact that miRNAs exhibit different expression profiles depending on the tissue or the studied fluid, this characteristic was studied not only for diagnosing various pathological conditions, but also as a method for identifying tissues or biological fluids in a forensic medical examination [11].

During a forensic medical examination, correct identification of possible detected tissues or biological fluids is crucial for detecting possible sources of DNA that will be subsequently used for identifying a donor of biological material. Over the years, several methods have been developed to identify biological material, such as serological tests [11]. However, these methods show low levels of sensitivity and specificity. Therefore, due to the characteristics of miRNAs, they have recently been studied as an alternative to traditional methods of identifying biological material in forensic medical examinations.

## CIRCULATING miRNAs AND BIOLOGICAL FLUIDS

In 2009, E.K. Hanson et al. were the first to present results on expression profiling of circulating miRNAs in the field of forensic medicine [12]. In a well-designed and comprehensive study, they demonstrated that circulating miRNAs could be extracted from a variety of human biological fluids and studied. They ultimately examined 452 circulating miRNAs using real-time polymerase chain reaction (qRT-PCR). For blood, saliva, semen, vaginal discharge, and menstrual blood, the authors developed a specific assay consisting of two differentially expressed circulating miRNAs, used to successfully identify and distinguish between a particular biological body fluid.

In a recent study, C. Courts et al. analyzed altered expression of 800 circulating miRNAs in venous blood and saliva using microarrays and identified six

differentially expressed circulating miRNAs (miR-126, miR-150, miR-451, miR-200c, miR-203, and miR-205) for potential identification of a specific biological body fluid [13]. Subsequently, the authors investigated the change in the expression of these six circulating miRNAs using qRT-PCR. The results demonstrated that even taking into account the fact that the panel of the analyzed circulating miRNAs in the study by E.K. Hanson et al. contained approximately half the amount of miRNAs, one of six candidate miRNAs for blood (miR-451) and saliva (miR-205) was also identified for the corresponding biological fluid.

In another study, seven circulating microRNAs were identified as potentially specific miRNAs for a particular biological fluid of the body, which can be used as significant markers in forensic science: miR-16 and miR-486 for venous blood, miR-888 and miR-891a for semen, miR-214 for menstrual blood, miR-124a for vaginal discharge, and miR-138-2 for saliva [14]. According to the results of the study by Z. Wang et al., the authors proposed five specific circulating miRNAs for biological body fluids (miR-16 and miR-486 for venous blood, miR-888 and miR-891a for semen and miR-214 for menstrual blood). Although current research confirms the potential use of these miRNAs to determine the origin of a particular body fluid for subsequent examinations, the authors were unable to identify circulating miRNAs specific to saliva and vaginal discharge.

E. Sauer et al. proved that miR-891a-5p was a semen-specific circulating miRNA among the five studied body fluids (venous blood, saliva, semen, vaginal discharge, and menstrual blood) [15]. In addition, circulating miR-10a-5p, miR-10b-5p, and miR-135-5p were overexpressed in semen samples compared with venous and menstrual blood, saliva, and vaginal discharge, which makes them additionally suitable markers. Besides, circulating miR-144-3p exhibited a specific expression profile for separating blood samples from non-blood samples.

E. Sauer et al. proposed a decision making algorithm to detect each of the five biological fluids, using as few combinations of circulating miRNAs as possible, in order to simplify the analysis procedure: miR-891a-5p was used to identify semen, miR-144-3p was applied for separating blood samples from non-blood samples, a combination of miR-144-3p and miR-203a-3p was used to distinguish between venous blood and menstrual blood samples, and a similar combination of miR-203a-3p and miR-124-3p was used to distinguish between saliva and vaginal discharge samples.

Table 1 presents the results of studies on differentially expressed circulating miRNAs in biological flu-

ids of the human body, which are most important for forensic research [12–20].

Table 1

Biological fluids and circulating microRNAs specific to them						
Research method	Venous blood	Menstrual blood	Vaginal discharge	Semen	Saliva	Ref.
qRT-PCR	miR-451 and miR-16	miR-451 and miR-412	miR-124a and miR-372	miR-135b, miR-10b	miR-658 and miR-205	12
Microarray; qRT-PCR	miR-126, miR-150, and miR-451	–	–	–	miR-200c, miR-203, and miR-205	13
Microarray; qRT-PCR	miR-16 and miR-486	miR-214	–	miR-888, miR-891a	–	14
qRT-PCR	miR-144-3p and miR-144-3p + miR-203a-3p	miR-144-3p	miR-124-3p	miR-891a-5p,	miR-203a-3p + miR-124-3p	15
qRT-PCR	–	–	–	–	miR-200c-3p, miR-203a, and miR-205-5p	16
qRT-PCR	miR-16 and miR-451	–	miR-1280 and miR-4286	miR-10b	–	17
qRT-PCR	miR-451	miR-412	miR-124a	miR-891a	miR-205	18
qRT-PCR	miR-451	–	–	–	miR-205	19
qRT-PCR	miR-144-3p and miR-451a-5p	–	miR-1260b	miR-888-5p and miR-891a-5p	miR-203a-3p and miR-223-3p	20

Note: miR – microRNA; qRT-PCR – real-time polymerase chain reaction (here and in Table 3,4); “–” – biological fluids that were not investigated in this work or specific circulating miRNAs to them were not found; “+” – a combination of circulating miRNAs.

## MicroRNAs AND THEIR TISSUE SPECIFICITY

It was found that some tissue- or organ-specific circulating miRNAs could be identified mainly in the bloodstream [21–23]. In particular, organs with a high degree of vascularization, such as the kidneys, liver, brain, and lungs, secrete miRNAs specific to them into the bloodstream, and their detection seems to be important in forensic medical examination.

Y. Sun et al. found five miRNAs (miR-192, miR-194, miR-204, miR-215, and miR-216) which were predominantly expressed in human kidney tissues compared with other organs / tissues, such as the heart, spleen, lungs, striated muscle tissue, and prostate [24].

Later, K. Chandrasekaran et al. also identified these five miRNAs in kidney tissues and concluded that these miRNAs are some of the few miRNAs that have been recognized as specific to the kidneys [25]. In addition, these miRNAs were found in a stable form in the plasma / serum, and since they are predominantly highly expressed in the kidneys, this organ can secrete them into the bloodstream; therefore, they are of re-

nal origin. MiR-124 and miR-128 are considered to be brain-specific; these miRNAs were also found in the plasma and serum in healthy people [26, 27].

Similar miRNAs include miR-129-5p, miR-191, and miR-342-3p, because they can be found in the plasma and exhibit high expression in the brain tissue compared with other tissues, according to miRNAmap [28]. In the lungs, according to miRNAmap, miR-21, miR-30b, miR-30c-1, and miR-146b-5p are highly expressed in comparison with other organs and tissues [29]. These miRNAs are also present in the plasma and serum, and, based on their expression profile in the bloodstream, they probably originate from the lung tissue following whole-lung lavage [30]. MiR-122 is known to be a liver-specific miRNA, which can also be found in a stable form in the plasma, and, therefore, it originates from liver cells [31]. Likewise, miR-148, which can also be found in the plasma, is overexpressed in the liver, and experimental results confirmed its specificity to the liver [32].

Table 2 shows miRNAs with their specific expression profile in relation to a particular cell, tissue, or human organ [24–38].

Table 2

MiRNAs specific to a certain type of cell, organ, or tissue		
Cell, organ, or tissue	miRNAs	Ref.
Kidney	miR-192, miR-194, miR-204, miR-215 и miR-216 miR-10b-5p, and miR-204-5p	24, 25 33
Brain	miR-124 miR-128 miR-129-5p, miR-191, and miR-342-3p miR-9-5p, miR-124-3p, and miR-219a-5p	26 27 28 33
Lung	miR-21, miR-30b, miR-30c-1, and miR-146b-5p miR-146b-5p, and miR-233-3p	29, 30 33
Liver	miR-122 miR-148	31, 33 32
Skeletal muscle	miR-1-3p, miR-133a-3p, and miR-206	33
Skin	miR-203a-3p and miR-205-5p miR-943	33 34
Heart	miR-208b-3p and miR-499a-5p	33
Endothelial cell	miR-126	35
Vascular smooth muscle cell	miR-143/145	36
Erythrocytes	miR-16	36, 37
Platelets	miR-223	36, 38

## EXPERIMENTAL PART

Brain damage in various pathologies is a serious condition where many processes are involved [39]. For this reason, identification of specific circulating and / or tissue biomarkers that may indicate a particular process in brain damage is relevant. F. Sessa et al. studied a change in the expression profile of five miRNAs (miR-21, miR-34, miR-124, miR-132, and miR-200b) in the brain material obtained from autopsy in three selected groups: drug addicts (cocaine), deaths associated with ischemic stroke, and the elderly [40]. The results of this study were the following: higher expression of miR-132 and miR-34 can be used as a marker of brain damage caused by drug use (cocaine); overexpression of miR-200b and miR-21 may indicate cases of age-related cognitive impairment; and, finally, the consequences of ischemic stroke may be associated with changes in the expression level of miR-200b, miR-21, and miR-124, with miR-124 having a significantly higher expression level. Changes in the expression profile of these miRNAs can be very useful as available tissue biomarkers in forensic studies to establish the exact cause of death in cases of brain pathology. These results suggest that changes

in the expression profile of these circulating miRNAs in human biological fluids can be studied in living people with brain damage associated with aging, drug abuse, and stroke.

In another preliminary study, C. Lux et al. suggested that differentiation between gunshot wounds to the head and other areas of the body could be accomplished by detecting miRNAs (or their absence) specifically or preferentially expressed in the brain matter (see the section “MiRNAs and their tissue specificity”) [41]. The aim of this study was to explore the possibilities and limitations of differentiating between brain tissue and blood, muscle, and adipose tissue by analyzing differentially expressed miR-124a and miR-124 in these samples, as well as to determine whether these miRNAs were resilient enough to withstand the physical impact associated with a gunshot wound.

A comparative analysis of the expression level of these miRNAs presented in [41] made it possible to reliably determine the brain tissue and differentiate it from blood, muscle, and adipose tissue samples. At the same time, these miRNAs not only demonstrated specificity to the brain tissue, but also, as expected, were much less susceptible to degradation compared with the *Clorf61* gene. If further studies can additionally establish specificity to the brain tissue, analysis of miR-124 / miR-124a expression can be used as an additional tool for identifying the brain tissue in forensic examinations.

P. Menathung et al. found that circulating miR-133a, miR-208b, and miR-499 are detectable and stable in human blood after death from myocardial infarction (MI) for 18 hours [42]. This study was based on already detected miRNA data in the tissue samples from the infarct zone, formalin-fixed and paraffin-embedded, the expression of which persisted for a week after death. It is known that miR-133a performs the antiapoptotic function of a damaged cardiomyocyte [43]. Overexpression of this miRNA inhibits the function of proapoptotic genes, for example, caspase-9 and apoptotic protease activating factor 1 (*APAF1*), protecting damaged cells from apoptosis [43]. The authors observed suppression of miR-133a expression in cardiomyocytes during the acute phase of MI, but its expression in the bloodstream was high (possibly within the apoptotic bodies). It is known that miR-208b is located in the intron of the *MYH7* gene [44].

M.F. Corsten et al. found that in patients with MI, the expression level of circulating miR-208b was increased by 1,600 times. P. Menathung et al. noted that this expression level was rather low after 18 hours,

which may be considered as the effect of post-mortem degradation of this circulating miRNA [44]. Recent studies demonstrated that miR-499 is specific to myocardial injury, and its expression level in the circulation after acute MI was high [45]. Therefore, circulating miR-499 was also present with a high level of expression in post-mortem blood samples of patients after MI. This study highlights the stability of some miRNAs in the post-mortem tissue, advocating their use in post-mortem examination. In addition, this result was further confirmed by the use of miR-499 to diagnose or define MI as a cause of death in post-mortem blood.

Drowning presents a dilemma for forensic science. There is no doubt that a significant proportion of drowning cases are associated with homicide. However, there are cases where drowning is the result of an accident. There are studies that demonstrated the relationship between changes in cellular microenvironment, especially activation of the ion channel / transport, and certain levels of miRNA expression [46]. In their study, S. Yu et al. identified 158 differentially expressed miRNAs in mouse brain tissue using microarrays in the experimental drowning model [47]. Among them, the authors classified four miRNAs (miR-6394, miR-706, miR-30c-1-3p, and miR-6238), which expression was significantly elevated in fresh water drowning models, and four miRNAs (miR-494-3p, miR-669h-3p, miR-135a-1-3p, and miR-5109) with reduced expression in salt water drowning models.

These results suggest that different drowning patterns induce changes in miRNA expression profiles in mouse brain tissue. Another question was why these miRNAs were expressed differently in different drowning models. To answer this question, the authors analyzed the target genes of differentially expressed miRNAs and studied their expression in the brain of mice. Among eight candidate miRNAs, aquaporin 4 (*AQP4*) was identified as a target for miR-30c-1-p and *HCN1* – as a target for miR-706 using *TargetScan*, *miRDB*, and *MGI* databases. However, only the change in miR-706 expression was statistically different ( $p < 0.01$ ) between the fresh water and salt water drowning models, as measured by qRT-PCR.

The expression of the *HCN1* gene was tested by qRT-PCR. It was decreased in the brain tissue of mice in the fresh water drowning model and elevated in the salt water drowning model. Hyperpolarization-activated cyclic nucleotide-gated (HCNs) channels belong to the family of pore-loop cation channels and consist of four members (HCN1–4). HCN channels

are activated by membrane hyperpolarization and are permeable to  $\text{Na}^+$  and  $\text{K}^+$ .

In the brain, *HCN1* is expressed in the neocortex, hippocampus, cerebellar cortex, and brainstem [48]. In fact, the concentration of sodium in the blood increases with drowning in salt water, and under conditions of hypernatremia, brain osmolarity and intracellular sodium concentration increase. Increased expression of *HCN1* and differences in the expression of miR-706 can be explained by the changes in the microenvironment in this drowning model. Finally, miR-706 was overexpressed in neurons in the cortex and hippocampus, which are common regions of *HCN1* expression. All of this confirms that miR-706 can contribute to crime scene investigations and help understand the pathobiological processes in a dead body.

Traumatic brain injury (TBI) is the most common cause of disability and death among people under 45 years of age worldwide [49]. Detection of TBI is becoming one of the main tasks in clinical forensic medicine. Many TBI survivors have some functional impairment of various degree of severity, especially cognitive impairment, including memory disorders. The hippocampus is critical for learning and memory, and it is quite vulnerable in TBI, showing more significant and earlier pathological changes than other areas of the brain [49]. In one of the studies, a microarray analysis showed that 205 miRNAs exhibited significant changes in the expression in the rat hippocampus in a controlled cortical impact (CCI) model [50].

This indicates that TBI dramatically alters a large number of mature miRNA transcripts, showing extremely sensitive responses to changes in miRNA expression in TBI. In addition, microarray analysis data showed that miR-142-3p and miR-221 were the only miRNAs which expression either increased or decreased in all three time intervals after TBI (1, 2, and 5 days). Specific microRNAs, such as miR-142-3p and miR-221, can be potentially used as sensitive and informative biomarkers in forensic examination of TBI and improve research on cognitive disorders associated with TBI.

Another group of researchers also used a rat CCI model to analyze changes in miRNA expression at day 1 and day 7 after TBI [51]. In this experimental work, 60-day-old rats were subjected to CCI and then sacrificed after 1 and 7 days to extract total RNA from neurons of the dorsal hippocampus. Research methods, such as next-generation sequencing (NGS) and bioinformatics analysis, were used to detect miRNA signatures altered after CCI and signaling pathways



regulated by these miRNAs. In particular, it was predicted that miRNAs (for example, miR-21 and miR-23b), which exhibited a change in expression during the acute post-trauma period (1 day after CCI), would target genes involved in apoptosis, protein folding, and aerobic glycolysis. On the contrary, it was assumed that the same miRNAs, the expression of which would be altered 7 days after injury, would target genes associated with the repair processes.

Forensic medical examination of spontaneous abortions is complex and insufficiently studied and, therefore, poses significant difficulties for experts in resolving a number of specific issues. The etiology of spontaneous abortion is complex and multifactorial. Although researchers identified several causes of this phenomenon, including chromosomal abnormalities in the fetus, maternal immune response, endocrine factors, reproductive tract abnormalities and infections, and environmental risk, approximately half of these cases remain unexplained [52]. The emergence and development of spontaneous abortions also include epigenetic disorders, namely, dysregulation of miRNAs [53].

H. Chen et al. identified several genes and miRNAs that could potentially be involved in the development and progression of spontaneous abortion, including *FCGR1A*, *FCGR3A*, *CXCL8*, *HCK*, *PLEK*, *IL10*, *EVI2A*, *GMFG*, *ESR1*, *MMP10*, miR-498, and miR-4530 [54]. Although further studies *in vivo* and *in vitro* are required, these results provide important information for elucidating the pathological process of spontaneous abortion and may provide a theoretical basis for future research in forensic medicine.

In the field of biomedicine, human aging is of great interest, in particular, in terms of identifying diagnostic predictors of age-related diseases, such as cancer. There is potential for translating biomedical research results into forensic medicine to estimate the age of a donor of a specific biological sample using miRNA analysis. H. Noren Hooten et al. profiled the expression of 800 miRNAs in the peripheral blood using microarray analysis and qRT-PCR in both young (~30 years old) and old (~64 years old) cohorts and reported that the expression of most miRNAs decreased with age [55]. This suggests that changes in circulating miRNA expression may have potential as an indicator of donor age.

In another study, changes in the expression of miRNAs (miR-122 and miR-133a in heart tissues; miR-122 in liver tissues; and miR-133a in striated muscle tissues) *in vivo* were studied to determine post-mortem intervals (PMIs). [56]. PMI is defined as the time elapsed since an individual's death. Currently, various methods are being used to estimate PMI (e.g. physical, physicochemical, biochemical, microbiological, and entomological); however, they all have their limitations.

As mentioned, miRNAs are highly stable in various types of tissues, including post-mortem ones. This suggests that miRNAs are less sensitive to environmental conditions and, therefore, are suitable as stable markers. While the results of this study are promising, there are many variables to consider when estimating PMI, which are much more complex in real-world scenarios with humans than in laboratory settings using animal models.

A summary of the main experimental studies is presented in Table 3.

Table 3

Research devoted to the study of miRNA in forensic medical examination						
Authors	Research direction	Research methods	Research model	miRNAs	Sample type	Expression
Sessa et al. [40]	Brain damage	qRT-PCR	Humans	miR-132, miR-34, miR-124, miR-200b, and miR-21	Autopsy brain material	Increased
Lux et al. [41]	Identifying headshots by detecting miRNAs predominantly expressed in the brain tissue	qRT-PCR	Humans	miR-124a and miR-124	Autopsy material: peripheral blood, muscle and adipose tissue from the maxillofacial region, brain tissue	Increased
Menathung et al. [42]	Myocardial infarction	qRT-PCR	Humans	miR-133a, miR-208b, and miR-499	Post-mortem peripheral blood	Increased
Yu et al. [47]	Drowning	Microarray; qRT-PCR	<i>In vivo</i>	miR-6394, miR-706, miR-30c-1-3p, and miR-6238  miR-494-3p, miR-669h-3p, miR-135a-1-3p, and miR-5109	Brain tissue	Increased Increased

Table 3 (continued)

Authors	Research direction	Research methods	Research model	miRNAs	Sample type	Expression
Sun et al. [50]	TBI	Microarray; qRT-PCR	<i>In vivo</i>	miR-142-3p miR-221	Brain tissue (hippocampus)	Decreased (1 <sup>st</sup> and 3 <sup>rd</sup> day) and increased (5 <sup>th</sup> day) Increased (1 <sup>st</sup> , 3 <sup>rd</sup> , and 5 <sup>th</sup> day)
Martinez et al. [51]	TBI	Microarray; qRT-PCR	<i>In vivo</i>	miR-21 miR-23b	Brain tissue (hippocampus)	Increased (1 <sup>st</sup> and 7 <sup>th</sup> day) Decreased (1 <sup>st</sup> and 7 <sup>th</sup> day)
Chen et al. [54]	Spontaneous abortion	Microarray; Bioinformatics analysis	Humans	miR-498 and miR-4530	Chorionic villi	Increased
Noren Hooten et al. [55]	Donor age	qRT-PCR	Humans	miR-103, miR-107, miR-128, miR-130a, miR-155, miR-24, miR-221, miR-496, and miR-1538	Peripheral blood	Decreased
Tu et al. [56]	Post-mortem assessment	qRT-PCR	<i>In vivo</i>	miR-122, miR-133a, miR-122, and miR-133a	Heart, liver, and skeletal muscle	Increased

## MiRNAs AND MENTAL STATE IN FORENSIC SCIENCE

It was confirmed that miRNAs contribute to the development of the nervous system and its functions [2]. Research showed that they are also involved in neuropsychiatric disorders, including schizophrenia [57]. A forensic psychiatric assessment of schizophrenia includes an evaluation in many aspects, however, there is no effective biological identification of schizophrenia. There is some evidence that the etiology of schizophrenia may include both genetic and environmental factors [58].

Therefore, the environmental contribution to the progression of schizophrenia is implemented through epigenetic mechanisms, and the study of mental illnesses

from the point of view of epigenetics informs and elucidates their pathogenesis [58]. It was shown that some aberrantly expressed miRNAs were isolated from the brain tissue, whole peripheral blood, serum, and plasma and were recognized as potential biomarkers in the diagnosis of schizophrenia [59–65]. These studies confirm that changes in the expression profile of some miRNAs in biological fluids can be used to identify biomarkers of schizophrenia and differentiate it from other mental diseases. It may also help to elucidate the etiology of schizophrenia with ambiguous clinical symptoms and identify potential differences between other psychiatric disorders with similar clinical symptoms [66].

Table 4 presents the studies examining circulating miRNAs as potential biomarkers in schizophrenia, mostly published over the past five years.

Table 4

Circulating miRNAs as potential biomarkers in schizophrenia					
miRNAs	Sample	Expression	Number of participants Schizophrenia / Control	Research methods	Ref.
miR-22-3p, miR-92a-3p, and miR-137	Peripheral blood	Increased	10/10	qRT-PCR	[60]
miR-34a-5p miR-432-5p miR-449a	Serum	Increased Decreased Increased	40/40	qRT-PCR	[61]
miR-30a-5p	Peripheral blood mononuclear cells	Decreased	38/50	qRT-PCR	[62]



Table 4 (continued)

miRNAs	Sample	Expression	Number of participants Schizophrenia / Control	Research methods	Ref.
miR-223	Plasma	Increased	21/21	Microarray; qRT-PCR	[63]
miR9-5p, miR29a-3p, miR106b-5p, miR125a-3p, and miR125b-3p	Peripheral blood	Increased	16/16	qRT-PCR	[64]
miR-132, miR-195, miR30e, miR-212, miR-34a, miR-30e, and miR-7	Peripheral blood mononuclear cells	Increased	25/13	qRT-PCR	[65]

## CONCLUSION

MiRNAs as tissue and / or fluid biomarkers have tremendous potential in forensic science and several applications. In determination of body fluids, detection of specific circulating miRNAs can be very useful in identifying the donor of the sample. Additionally, miRNAs are highly stable and can be detected in damaged samples in the late post-mortem period. Moreover, miRNAs with differentiated expression profiles between healthy individuals and individuals with certain pathologies can be very useful in identifying suspects and / or victims, helping to narrow down the list of suspects.

Although miRNA expression analysis has been widely studied around the world, this research mainly focused on its applications in biomedical / cancer research. To truly unleash the full potential of miRNAs in forensic medicine, it is critical to uncover the molecular complexity of the available samples. Incorporating miRNA analysis into the forensic practice will help address several challenges that forensic experts are currently facing. Ensuring stable performance in adverse conditions, miRNA analysis provides reliable access to information that was previously impossible.

As mentioned earlier, miRNA analysis has just started being implemented. The number of published studies in this area is limited, but it is growing. In forensic medicine, methods that once seemed modern are now obsolete. It is essential that researchers develop methods for use in forensic investigations that produce results in record time, provide a higher degree of discrimination, and are fairly reliable.

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