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Review Article

MicroRNAs; their therapeutic and biomarker properties

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ABSTRACT

MicroRNAs (miRNAs) are, small (roughly 19–25 nucleotides in length), conserved, non-coding, single-stranded, and functional RNA molecules with the properties of gene expression regulation through mRNA degradation, translation repression, mRNA deadenylation as well as gene silencing via histone methylation. They even have the ability to increase gene expression levels. The biogenesis of miRNAs is divided into two canonical and non-canonical pathways. The second pathway has a divergent mechanism for the biogenesis of miRNAs. miRNAs can be transcribed from specific genes or introns of protein-coding genes. A single miRNA species can control the expression of hundreds of genes, and also one gene can be the target of different miRNAs. These molecules have been identified in eukaryotic organisms such as mammals and plants and even in viruses. miRNAs play an inevitable role in the life cycle of eukaryotic cells. They are involved in any biological processes such as the regulation of cell proliferation and differentiation, apoptosis, signaling, and defense responses through their spatio-temporal expression manner. Aberrant expression of miRNAs is involved in a large number of biological disorders, which illustrates their great potential to be applied in the diagnosis and treatment of various diseases. miRNA inhibitors (anti-miRs) and artificial miRNAs (miRNA mimics) are two general approaches to balance the dysregulated miRNA levels that make it possible to treat various biological disorders. In this study, in general, the biogenesis and the role of miRNAs, the origin of miRNAs, viral miRNAs, miRNA detection procedures, *in silico* miRNA analysis tools, miRNA-based therapies and their obstacles, and miRNAs as potential non-invasive biomarkers are discussed. Finally, it is stated the importance of dietary miRNAs.

1. Introduction

MiRNAs are endogenous, evolutionary conserved [1], small (19-25), single-stranded, non-coding, and functional RNA molecules [2, 3]. The first miRNAs were discovered in *Caenorhabditis elegans* in the early 1990s [4] and in the early 2000s year, miRNAs were determined as biological gene expression regulators units. These molecules are produced from specific genes or even from introns of protein-coding genes. miRNAs regulate a large number of critical biological processes, including cell proliferation and differentiation, signaling, apoptosis, and response to pathogen by fine-tuning the transcriptome [5-8]. For example, mouse mir-

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1 family members have distinct roles in muscle development [9]. For miRNA-21, several hundred target genes in humans have been predicted with various percentages of validity in different miRNA target prediction databases, which indicate the importance, multitasking, and behavioral complexity of these types of non-coding RNA species. The transcription of miRNAs genes is genetically determined in a spatiotemporal-dependent manner [10-12] which means that the transcription of miRNAs genes occurs in the specific tissues of a living organism at a particular time during development. Deviation from this spatiotemporal expression pattern of miRNAs was identified in numerous biological disorders such as cancer and other diseases in humans [13, 14]. In this review, the various biogenesis pathways of miRNAs, the mechanism of action of miRNAs, the presence and importance of miRNAs in viruses, miRNA detection procedures, *in silico* analysis of miRNAs, miRNA-based therapies and their obstacles, the application of miRNA as biomarkers, and the importance of dietary miRNAs was discussed.

2. MicroRNAs biogenesis

The biogenesis of miRNAs is carried out in two different pathways called canonical and non-canonical biogenesis. The first pathway is dominant in the cell life cycle [15].

2.1. Canonical miRNAs biogenesis

In the canonical pathway, primary miRNA (pri-miRNA) is transcribed from genes of miRNAs by RNA polymerase II (RNA pol II) or Pol III [16]. Pri-miRNAs are usually more than one kilobase long and have a stem-loop-like secondary structure in their structure [17]. Base pair mismatches are common in the stem part of this secondary structure. Then, these pri-miRNA are processed by the nuclear RNase III Drosha enzyme. They have a cleavage effect on pri-miRNAs, which enables the maturation process of miRNAs. After this step, the newly processed RNA is called precursor miRNA (pre-miRNA). In the next step, pre-miRNAs (approximately 70 nucleotides) are exported from the nucleus to the cytoplasm, which is mediated by exportin-5 (EXP-5). In the cytoplasm, they undergo another process with another endonuclease, the enzyme Dicer, which results in the production of a mature duplex miRNA (21-25 nucleotides) [18]. One of the strands of duplex miRNA is loaded onto a multiprotein complex called RISC (RNA-induced silencing complex) complex containing Argonaute 2 (Ago2) and the other strand (miRNA*) is degraded. The loaded strand is called mature miRNA [19, 20]. Finally, the miRNA-RISC complex interacts with its target or targets (mRNAs) to suppress their expression through mRNA cleavage or translation repression. In table 1, the major components of the canonical pathway are listed.

Table 1. Major components of the canonical miRNA biogenesis pathway in the animal kingdom

Components	Function
miRNAs genes	Coding miRNAs ORFs
RNApoly II/III	Transcription of miRNAs genes
Drosha enzyme	Cleavage of pri-miRNA and produce pre-miRNA
Exportin-5	Exportation of pre-miRNA from the nucleus to the cytoplasm
Dicer enzyme	Cleavage of pre-miRNA and generate an imperfect miRNA:miRNA* duplex
RISC complex	Post-transcriptional gene silencing

2.2. Non-canonical miRNA biogenesis

Recent bioinformatics and experimental data have led to the discovery of non-canonical miRNAs that escape the primary biogenesis pathway of canonical miRNAs. For example, mitrons biogenesis occurs in a Drosha-independent and splicing-dependent manner. Mitrons, along with simtrons [21], agotrons [22], sno-derived miRNAs [23], tRNA-derived miRNAs [24], and shRNA-derived miRNAs [25] are non-canonical miRNAs whose biogenesis pathway is in a Drosha-independent or Dicer-independent manner [26]. Here, we describe the biogenesis of mitrons as a well-studied non-canonical miRNA.

Mirtrons are located in the introns of mRNAs of protein-coding genes. These types of miRNAs were first discovered in *Drosophila melanogaster* and *C. elegans*, and now their existence has been confirmed in mammals [27, 28]. The main difference in the biogenesis of this type of miRNAs with canonical miRNAs

is that their biogenesis is independent of the Drosha enzyme but dependent on the splicing process, which is mediated by the lariat debranching enzyme. This information about mitrons biogenesis was confirmed by experimental tests. Mutation of nucleotides that are required for splicing of introns caused disruption of mitrons production, as well as knocking down of the lariat debranching enzyme gene, reduced the extent of mitrons, but had no effect on the extent of canonical miRNAs. Furthermore, the knocking down of the Drosha enzyme gene affected canonical miRNAs but not mirtrons [29]. Despite all these differences, mitrons and canonical miRNAs utilize similar pathways for gene regulation. It should be noted that in addition to eukaryotes, non-canonical biogenesis of miRNAs has also been reported in viruses [30].

3. Mechanisms of action of miRNAs

miRNAs are a critical component of gene expression regulation in eukaryotic cells. Dysregulation of miRNAs is associated with many human diseases [31]. A particular miRNA may have hundreds of different mRNA targets, and a given mRNA may be regulated by several miRNAs [32, 33]. Although there are many similarities between plant and animal miRNAs, there are also differences. The enzymes involved in the maturation of miRNAs are different in plants and animals. For example, instead of the Drosha enzyme in animals, the RNase-III-like protein, Dicer-like 1 (DCL1) is found in plants. miRNAs appear to work through two main mechanisms: mRNA cleavage and translation repression mechanism. These mechanisms of action are induced by the degree of complementarity of miRNAs with mRNAs of target genes. When the miRNA/mRNA base pair matching is perfect or nearly perfect, post-transcriptional regulation of gene expression occurs by the excision mechanism, and in the other scenario (in the lower or partial complementarity state), the translation repression mechanism is activated. The first scenario prevails in plants and the second scenario in animals [34]. Overall, miRNA's Fine-tuned gene expression regulation is associated with mRNA cleavage, translation repression, mRNA deadenylation, and gene methylation. Some miRNAs that localize in the nucleus of the cells are involved in inducing gene expression or gene silencing [35]. In most cases, miRNAs interact with the 3' untranslated region (3' UTR) of target mRNAs to cause mRNA cleavage and translation suppression. However, miRNAs have also been reported to interact with other regions, including the 5' UTR, coding sequence, and gene promoters [15].

4. miRNAs in virals

miRNAs that originate from viruses are known as vir-miRNAs. The first vir-miRNA was identified in Epstein-Barr virus (EBV) in 2004 [36]. vir-miRNAs were identified in both viruses with DNA or RNA genomes [37, 38]. Nowadays, A number of vir-miRNAs were identified based on bioinformatic prediction and even experimentally in a large number of viruses such as HIV-1 [39] and SARS-COV-2 [40]. In the miRBase database that is publicly and freely available at http://mirbase.org/, miRNAs from 34 different viruses were recorded and deposited. Among these viruses, 34 precursors and 70 mature miRNAs have been recorded from Rhesus lymphocryptovirus, which is the largest number of miRNAs recorded among these obligate parasites. Understanding various aspects of viral miRNA biology and recognizing its accurate function can be applied in the fight against viral infections.

Viral miRNAs have many functions and play an important role in the life cycle of viruses. They have a vital role in regulating the gene expression of viruses and their hosts, which demonstrates their fundamental function in virus-host interactions [41]. The expression of vir-miRNAs can extend the lifespan of infected cells, enhance their immune response evasion, and regulate the transition to lytic infection [42].

Several viral infections have found ways to disrupt the miRNAs expression of their hosts. Many researchers have reported the downregulation of miRNA Lt-7 of hosts in many viral diseases compared to control individuals. The recently have been published paper elucidated the mechanisms of action of this miRNA which provides insight into the development of novel therapeutic strategies

to manage and control viral infections [43]. To date, the development of miRNA-based vaccines against viral diseases has been reported [44]. Moreover, the implementation of miRNA mimics and inhibitors for the treatment of Covid-19 disease is underway, which could be an alternative way to fight this pandemic [45].

5. miRNA detection procedures

miRNAs as a non-invasive blood biomarker are relatively stable and easily detectable. Various analytical methods have been developed to detect miRNAs. These methods are categorized into two groups. The first group is traditional methods that include northern blotting [46], microarrays, [47] and RT-qPCR [48]. In general, traditional miRNA detection methods have challenges and obstacles. The northern blotting technique is poorly sensitive, time-consuming, and requires a large number of RNA samples. The microarray method has poor sensitivity and a long hybridization time. RT-qPCR is a complex method that requires special laboratory skills and a false positive may occur during the amplification process. The second group is the newly developed methods that include nanomaterial-based miRNA detection, nucleic acid amplification techniques, and a combination of amplification strategies. Details of these new detection methods have been described in a review article entitled research advances in the detection of miRNA [49].

6. Bioinformatic analysis of miRNAs

Bioinformatics tools are used to analyze different aspects of miRNA molecules. These tools are applied to predict miRNA presence and discovery of miRNA, structure analysis of miRNA, and predict target genes of miRNA molecules. In general, there is no comprehensive tool for the analysis of any aspects of miRNA. For robust analysis, researchers can use several *in silico* tools that have been reported to date [50]. miRNA identification tools include MiRscan [51], RNAz [52], triplet–SVM [53], MiPred [54], miRDeep [55], etc.

Generally, one of the most important topics related to microRNA is the identification of their target molecules. Several computational approaches have been developed to facilitate the experimental design and predict miRNA targets. Creating a number of complementary base pairs is essential for the interaction between the MicroRNA molecule and the target molecule sequence. In most cases, the creation of complementary base pairs occurs in 6-7 units of nucleotide, which are usually situated at the positions of 2-8 from the 5′ end of microRNA toward the 3′ end, and this region is called the seed region [56]. Different computational methods are used to predict microRNA target regions. It is still difficult to accurately predict the target location of the microRNA, and one of the algorithms for predicting the target molecule is designed based on the base pairing and conserved sequence of the microRNA at the 3′ ends of different organisms [57]. miRNA target prediction tools are very broad which include iRanda [58], RNAhybrid [59], TargetScan [60], PicTar [61], TargetFinder [62], TarBase [63], etc. Other tools to study miRNA function include, miRBase a searchable database of published miRNA sequences and annotation [64], ViennaRNA to predict RNA secondary structure [65], mirPath for pathway analysis of miRNA [66], and other bioinformatics tools. In conclusion, every tool has its own merit and application, and these tools can be used based on the purpose of the work.

7. miRNA-based therapies

As previously mentioned, miRNAs play an essential role in most cellular processes. The balance of miRNAs in cells is very vital, and disturbing this balance due to various internal and external stimuli can cause mild and severe disorders and aberrant expression of miRNAs is involved in the onset and progression of many diseases. With strong evidence that miRNAs are involved in the initiation and progression of diverse biological abnormalities, there has been intense interest in miRNA-based therapies in the last few decades [67]. miRNA-based therapies are categorized into two distinct approaches that attempt to restore miRNA levels to normal conditions. In one of these approaches, scientists use miRNA mimics to restore down-regulated miRNAs, and in the second strategy, they use anti-miRNAs (antagomirs) to suppress up-regulated miRNAs [68].

A specific miRNA can target more than one gene, and a specific gene can be targeted by several miRNAs. The multi-targeted functions of miRNAs are an attractive property for use in the development of anti-cancer therapies [15]. It is becoming increasingly apparent that miRNAs are dysregulated in most, if not all, cancers. miRNAs can help or suppress the proliferation of tumor cells. miRNAs that are upregulated in cancer cells are called oncomiRs. In most cases, oncomiRs target tumor suppressors and promote tumorigenesis but some miRNAs have tumor suppressor features and have the properties to downregulate oncogenes and they often downregulate or are lost in cancer cells [69]. Here we discuss some incurable diseases and the role of miRNAs in their development and treatment.

7.1. Breast cancer

This cancer is the second most common cancer around the world. In a systematic review with the goal of exploring miRNAs related to the treatment of breast cancer, 19 miRNAs were detected that 12 (miR-497, miR-544, miR-34a, let-7b, miR-603, miR-203, miR-26a, miR-142-3p, miR-21, miR-221, and miR-205), 7 (miR-214, miR-222, miR-223, miR-205-5p, miR-100, miR-4306, miR-708, and miR-3613-3p) and 2 (miR-10b and miR-34a) of the miRNAs, recognized as a potential anti-tumor, potential antimetastatic and potentially with both antitumor and antimetastatic properties, respectively[70]. In the mentioned research, it was concluded that the application of miRNA-based therapeutics against breast cancer is a double-edged sword due to the pleiotropic role of miRNAs. These multifunctional properties of miRNAs make it very difficult to predict their side effects, but we hope that this bottleneck will be overcome with a complete understanding of any targets of miRNAs.

7.2. Uveal melanoma (UM)

It is the most common intraocular malignant tumor in adults and when it becomes metastatic remains fatal and irremediable [71]. To date, UM has no effective standard therapy and the median survival time for the metastatic form of this disease is roughly 6–12 months after diagnosis [72, 73]. miRNAs have emerged as vital epigenetic regulators in UM pathogenesis [74] and some of these short functional non-coding miRNAs affect the transcription and/or translation of many essential genes and pathways involved in UM [75, 76]. Scientists identified some oncomiRs (miR-21, miR-367, miR-454, and so on) and tumor suppressor miRNAs (miR-34a, miR-137, miR-144, miR-182, and so on) related to this disease that can help to find new treatment strategies to cure this cancer [77].

7.3. Lung cancer

It is the most common cause of cancer-related death in both women and men. It has a restricted resource of therapy throughout the world. miRNAs have an essential role in lung cancer development [78]. In one experiment, the proliferation and migration of lung cancer cells were suppressed using miRNA-126 [79].

7.4. Covid-19 disease

In one research, 20 types of serum microRNA expression levels were investigated in patients with covid-19 and healthy individuals. The results showed that the expression levels of seven miRNAs (hsa-let-7d, hsa-miR-17, hsa-miR-34b, hsa-miR-93, hsa-miR-200b, hsa-miR-200c, and hsa-miR-223) and the expression levels of 2 miRNAs (hsa-miR-190a and hsa-miR-203) significantly decreased and increased in compared to healthy people, respectively. They proposed that miRNA profiling can be a useful strategy for the diagnosis of Covid-19 disease. They also concluded that increased levels of hsa-miR-190a may be a prognostic factor associated with the covid-19 disease [80].

Also, intense research is being done to use miRNAs in the treatment of diseases such as Inflammatory bowel disease [81], Glioblastoma multiforme [82], Alzheimer's disease [83], Spinal muscular atrophy [84], SARS-CoV-2 [85], Cardiovascular disease [86], etc.

8. Barriers to the application of miRNA-based therapies

Of the ten miRNAs that entered the clinical phase, none of them could pass clinical trials, and no drug from this group has been

approved to date. In addition, there is rare news about the progress of miRNA-based drugs [87]. A single microRNA can regulate large subsets of mRNA targets. Although this property of miRNAs is a potentially powerful therapeutic tool, it presents a major challenge in terms of controlling side effects observed in clinical trials [88]. As a therapeutic option, anti-miRs (miRNA inhibitors) and miRNA mimics (artificial miRNAs) are very interesting for pharmaceuticals. However, due to the ubiquitous occurrence of miRNAs and the many different functions of individual miRNAs, choosing an appropriate miRNA target for disease therapy may be difficult.

9. miRNAs as a biomarkers

miRNAs were identified in the serum and plasma of different human and animal models. The tracing and detection of specific expression patterns of miRNAs in various cancers, as well as other diseases, leads to the conclusion that miRNAs can provide robust fingerprints for various diseases and thus could serve as a potential biomarker for early disease diagnosis [89]. In some diseases, miRNA expression modification can be distinguished by a non-invasive taking specimen method such as extraction of miRNAs from blood, urine, and saliva specimens.

Circulating miRNAs have been identified in biological fluids such as breast milk, tears, saliva, bronchial lavage, peritoneal fluid, semen, urine, serum, plasma, cerebrospinal fluid, colostrum, as well as ovarian follicular fluid and they have a high potential to be available biomarkers for the diagnosis and prognosis of various disorders in the human body [15]. Unlike cellular RNA species, extracellular/circulating miRNAs are strongly stable and resistant to degradation at room temperature for up to 4 days. They are resistant to adverse conditions such as boiling, multiple freeze-thaw cycles, and high or low pH [89, 90]. Circulating miRNAs can be protected from endogenous RNase activity. It was assumed that this protection is caused by several factors. Released miRNAs from cells into the plasma are packaged in microparticles (exosomes, microvesicles, apoptotic bodies), also they bind to RNA binding proteins (Argonaut 2) or are associated with lipoprotein complexes (high-density lipoprotein (HDL) which prevent their destruction. These aforementioned characteristics of circulating miRNAs make them potential molecules for the diagnosis of a large number of diseases. Detection of miRNA profiles in different stages of diseases can be used in diagnosis, prognosis, and treatment [91]. In Table 2, we have shown different types of miRNA that have differential expression patterns in abnormal conditions of the human body. These up- and down-regulated miRNAs are recognized as potential biomarkers for the diagnosis of various types of disorders in the human body.

Table 2. List of miRNAs as potential non-invasive biomarkers for the diagnosis of various diseases

Disorder	Up-regulated miRNAs	Down-regulated miRNAs	Source of miRNA	Year	Validated with qPCR	Reference
Colorectal cancer	miR-129-1-3p and miR-566		Urinary miRNA	2022	+	[92]
Bipolar II disorder		miR-7-5p, miR-23b-3p, miR-142-3p, miR-221-5p, and miR-370-3p	Serum miRNA	2020	+	[93]
Metastasis of gastric cancer	miR-10b-5p, miR-101-3p, and miR-143-5p		Plasma	2020	+	[94]
prostate cancer	Combination of miR-17-3p and miR-1185-2-3p		Serum	2019	-	[95]
Metastatic colorectal cancer	miR-320d		Serum	2019	+	[96]
Heart failure	miRNA‑21		Serum	2017	+	[97]
Lung Cancer	miRNA-21		Plasma	2018	+	[98]
Lupus nephritis	miR-146a-5p		Blood	2018	+	[99]
Colorectal cancer	miR-30e-3p and miR-146a-5p	miR-148a-3p	Serum	2020	+	[100]

10. Importance of dietary miRNAs

miRNAs that are present in the diet are called dietary miRNAs. These miRNAs are considered exogenous miRNAs for the human body. Endogenous miRNAs in humans are found in plasma, urine, saliva, and other body fluids and have been shown to be associated with many diseases such as obesity, diabetes, and cancer [101]. In this regard, miRNAs can act as biomarkers in the diagnosis and monitoring of these diseases [101]. In contrast, exogenous miRNAs, especially those in the human diet, received little attention and consequently are hidden food ingredients. Until recently, a rice miRNA named MIR168a was identified in human and mouse serum and various tissues [102]. This works motivated research on exogenous dietary miRNAs, including their sources, stability, uptake, and biological activities. The stability of dietary miRNAs in different harsh conditions such as high temperature, acidic conditions, and *in-vitro* digestion has been reported [103]. The presence of dietary miRNAs in the circulatory system of mammals has been proven [104, 105]. Moreover, the positive effect of these sorts of miRNAs on various diseases has been reported, [106-109] which highlights their vital role in human health. 243 of cow (Bos Taurus) miRNAs were evidenced in its milk [110] but the effects of these exogenous dietary miRNAs on human health have not been well studied. The other important thing about human diets is their effect on human endogenous miRNA profiles. The effects of plant secondary metabolites and their extracts on miRNA profile changes in mammalian cells have been reported [111]. The anti-tumor effects of green tea are related to its anti-angiogenic, pro-apoptotic, and immunomodulatory properties [112]. Green tea can affect miRNA profiles and activation/repression of different cellular/molecular pathways that are involved in angiogenesis in different types of cancer [112]. All these mentioned research emphasize that the human diet is important both as a source of dietary miRNAs and as a stimulus for making modifications in the expression profile of endogenous miRNAs. However, further investigation of dietary miRNAs and their effect on the human body and other mammals and poultry should be further investigated to pave the way for the implementation of these types of miRNAs as food supplements or pharmaceuticals.

11. Concluding remarks and future views

Since the discovery of endogenous miRNAs, extensive studies have been conducted on them and different pathways of their biogenesis have been identified. Canonical and non-canonical are two main pathways to the biogenesis of miRNAs. In terms of function, non-canonical miRNAs are similar to canonical miRNAs, but their biogenesis pathway is different and different enzymes are involved in their maturation. To date, various origins have been reported for the production of non-canonical miRNAs which include introns, snoRNAs, endogenous shRNAs, and tRNAs [113].

It has been identified that the presence of miRNAs has a vital role in the life cycle of organisms and dysregulation in their expression has caused the occurrence of various disorders. Today, the relationship between different diseases such as different cancers [114, 115], diabetes [116, 117], obesity [118, 119], liver fibrosis [120], osteosarcoma [121], disorders related to the nervous system [83], etc., have been reported with aberrant expression of miRNAs [122], and this field is of great interest to many researchers. In this day and age, the number of researchers working in this field is increasing day by day. The effects of miRNA expression disorder on different diseases have led to an idea for the treatment of different diseases by restoring the miRNA levels to normal conditions. In this regard, researchers generally use two methods, including the use of synthetic anti-miRNAs and analogs of miRNAs (mimic miRNAs) to treat these diseases. But despite much work, this is still in its early stages, and further studies are needed to use these miRNAs as a drug in the treatment of various diseases, including unbearable diseases. One of the major problems with the miRNA-based treatment is the presence of multi-targets for each miRNA that lead to undesirable and unpredictable side effects at the time of miRNA-based medicine implementation.

Extracellular miRNAs (Such as circulating miRNAs) in comparison to cellular miRNAs species are highly stable in harsh conditions [89] which improves their great potential to be an applicable non-invasive biomarker in near future in clinics. One of the applications of miRNA-based biomarkers is to use them in the diagnosis of various diseases and even as biosensors for early knowledge of the occurrence of various diseases, including heart attacks. A lot of work is being done in this field, but not much progress has been made in the field of using these biomarkers in practice, and more extensive studies are needed to identify the presence of specific miRNAs in the onset and progression of various diseases. Moreover, accurate measurement of miRNAs is more difficult than previously thought [123] and this is a major obstacle to recognizing dysregulated miRNAs that can be used as a biomarker.

One of the important issues related to miRNAs is the effect of exogenous miRNAs that enter the human body through the nutrition or consumption of medicinal herbs and the other important subject is the assessment of the effect of prescribed medicines on the expression of endogenous miRNAs. Not much work has been done on the aforementioned topics and these fields need more studies. In general, exogenous miRNAs can be used as dietary supplements or as medicines to treat various diseases one day.

Overall, despite extensive research into the applications of miRNAs, there is still a long way to go before routinely using miRNAs in the treatment and diagnosis of diseases. But with various advances in molecular biology and other related fields, it is possible to use miRNAs to diagnose and treat diseases in the near future. Furthermore, miRNA-based therapy will pave the way for personalized medicine. It is also important to investigate these cases further in the future. These cases include the use of various bioinformatic analyzes to find any target of specific miRNAs to prevent their side effects as a therapeutic option, the introduction of a simple, automated, and cost-effective method to accurately detect the level of miRNAs, the investigation of dysregulated miRNAs in various disorders to introduce them as biomarkers and draw therapeutic strategies, working on the production of synthetic miRNAs to investigate their therapeutic properties, finding different strategies to simply deliver synthetic miRNAs into the human body, further investigation of the effect of exogenous miRNAs on human health and finally exploring the effect of medicinal herbs on the expression level of endogenous miRNAs.

Conflict of Interest

All authors state that they are free of any conflicts of interest related to this paper.

Author's contributions

All authors confirm that they have read and approved this manuscript.

Consent for publications

All authors have read and approved the final manuscript for publication.

Availability of data and material

The authors have embedded all data in the manuscript.

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