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Review Article

# MicroRNAs in Personalized Medicine: Targeted Therapeutic Interventions and Their Emerging Role as Non-Invasive Biomarkers in Cancer Biology

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ABSTRACT

Micro Ribonucleic acids (microRNAs or miRNAs) have gained attention in the research community in the last decade due to their roles in genetics and cancer biology. Initially, when compared to other nucleic acids their roles were considered insignificant.An extensive study conducted recently on miRNAs has provided a wealth of knowledge regarding the background functions of microRNAs, most importantly, their role in the pathophysiology of diseases such as cancer, gene expression or silencing, protein-coding gene modulation, cell differentiation, proliferation, and death.Therehas been significant progress made in the identification of the origin of miRNAs which has given researchers and scientists in Nigeria, Africa and the world at large, the privy to focus on their diagnostic potential usage in both clinical fields for investigating the pathological mechanism of diseases and also in the field of research, thus, creating the opportunity to use miRNAs as a predictive non-invasive biomarker in different disease conditions such as Prostrate cancer, Cervical cancer, Esophageal squamous cell carcinoma, Ovarian Cancer, Breast Cancer, Lung cancer, etc., and thus a potential target in therapeutic inventions for this disease conditions in developing parts of the world, in like countries like Nigeria, where the prevalence of these diseases are increasing.Nonetheless, issues such as the standardisation of miRNA quantity, the normal range of miRNA value within the plasma, and the unification of diagnostic techniques for miRNA quantification continue to be debated among various scientific schools of thought; however, its diagnostic importance continues to outweigh the challenges of this new era diagnostic markers.

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## Introduction

The disintegration of double-stranded RNAs (dsRNAs) yields bi-product fragments, including microRNAs (miRNAs) and other products like siRNAs and shRNAs. miRNAs are naturally occurring, non-coding RNA molecules with between 20 and 24 nucleotide base pairs. They work with target messenger ribonucleic acids (mRNA) to either limit translation or destroy the molecule [1].A brief mention of Francis Crick's 1957 "Central Dogma Biology" [2], Robert Griffith's 1928 experiment, Avery's 1944 experiment, and Meselson & Stahl's 1958 experiment would be incomplete discussing microRNAs without acknowledging these important contributions to the discovery of deoxyribonucleic acid (DNA).

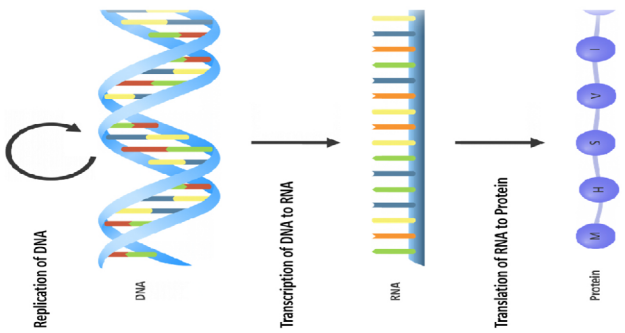
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Deoxyribonucleic acid molecules (dsDNA) that are double-stranded unwind into two single strands. These strands are often transcribed into RNA molecules, which are then translated into protein molecules, which are used to make amino acids. Usually, single-stranded transcripts, ribonucleic acid molecules (RNAs) can couple to generate double-stranded RNA molecules (dsRNAs), which resemble hairpins[4], which serve as the mother strand and starting template for the synthesis of microRNA molecules.

Figure 1: The fundamental principle of life (DNA to RNA to Protein Replication)[5].



**Methodology**

This is a systematic review study that used about 52 journals was used for this review study. They included journals indexed on Google Scholar, EPUB, CrossRef, Scopus, DOAJ, Embase, Global Health, MEDLINE, PubMed Central, and SCImago.

**The Process of MicroRNA Biosynthesis.**

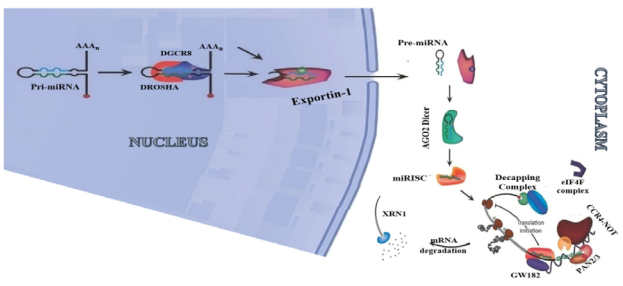
Double-stranded RNA is used in the complex, multi-step manufacturing of miRNA molecules, which takes place in both the cytoplasm and the nucleus [6]. The double stranding of RNA molecules is peculiar. A terminal looped Hairpin-like double-stranded RNA molecule, known as the Pri-microRNA, is created when RNA polymerase II transcribes DNA molecules into RNA molecules. These RNA molecules are typically single-stranded and have a long nucleotide base sequence. Because the bases have complements between them, the nucleotide bases have a high affinity to bind together by hydrogen bond. Pri-microRNAs are about 100–120 nucleotides long.

The Pri-miRNA is broken down into shorter Pre-miRNA by the action of the enzymes Drosha and DGCR8 (Di George syndrome critical region 8).A transmembrane protein molecule known as Exportin-5 then moves the pre-miRNA molecule from the nucleus into the cytoplasm. It attaches to the pre-miRNA molecule and positions it for cleavage by a double-stranded RNA-specific endonuclease Dicer enzyme, known as RNase III enzyme. Typically, this process prepares the Pre-miRNA for activation by cleaving off the hairpin region of the Pre-miRNA, producing a 5' monophosphate region and a two-nucleotide overhang at 3' dsRNA known as miRNA:miRNA*duplex, which is attached to the RNA interference complex known as RISC (RNA interference silencing complex) [7]. A slicer enzyme and an Argonaut protein makeup RISC.

The Argonaut protein, an RNase H type possessing a Paz domain and a PIWI region, is the exclusive target of the miRNAs.The dsmiRNA:miRNA* duplex is unravelled by the argonaut into two single miRNA strands: a guide strand and a passenger strand. Only the guide strand, which makes up the active mature miRNA molecule, remains when the passenger strand is released [8]. To form a nuclear hybrid structure (Nucleation), these mature miRNA strands and the RISC complex bind to the target messenger RNA strand (mRNA). This is done by first identifying a complementary 2-4 nucleotide on the target mRNA and then forming a double-stranded messenger RNA (ds mRNA), which would be cleaved and broken/degraded by the RNase H.

This process plays a crucial role in gene silencing and has been applied to the diagnosis and prognosis of conditions such as cancer [1], diabetic nephropathy [9], and neurological illnesses. [10], key biomarkers for the detection of specific cancers, such as ovarian cancer [10]. According to Condrat et al. [6], miRNAs are also helpful in the diagnosis and prognosis of neurodegenerative illnesses, spinal cord injuries, epilepsy, and Alzheimer's disease. They also have a significant impact on endemic tropical parasitic infections, including those caused by Plasmodium falciparum, Toxoplasma gondii, and Cryptosporidium parvum [7,12].

**Figure 2: Modified microRNAs' biological production[8]**




**MicroRNAs in Disease pathophysiological and Role in diagnosis and Prognosis**

Through their roles in mRNA degradation, transcription and translation regulation, and intercellular signalling, miRNAs are essential for the regulation of genes in the human body. The majority of microRNAs are located inside cells, but a sizable fraction also leaves the cell and is present in physiological fluids such as breast milk, urine, saliva, blood, and seminal fluid [8]. This movement, known as plasma miRNAs, has been the subject of much study over the past 20 years [6]. It can also arise from tissue injury, apoptosis, and necrosis, as well as from an active passage in microvesicles, exosomes, or binding to a protein.

The phenomenon of a "message in a bottle" type of intercellular communication has been discovered in some research studies, where the assimilation of exosomes by neighbouring cells is demonstrated in vitro. This has now been researched as a means of getting information through miRNAs on several pathological mechanisms and the state of diseases within the human body, and this is the most promising role of miRNAs, as a "biomarker" [1,6]. Because microRNAs facilitate intercellular communication through exosomes, they play a significant role as biomarkers in the diagnosis and prognosis of cancer.

**Some significant Micro RNAs as Biomarkers in Cancer Biology**

Cancer is a leading cause of mortality worldwide, making it an important public health problem and research priority.A breakthrough in the scientific study of microRNAs, particularly as a biomarker, is that they are stable, have a wide pH range, can resist the activity of endonuclease enzymes, can be stored for long periods, and are readily found in plasma, resulting in a non-invasive method for the early detection of various types of cancer and the significant role they play in cancerogenesis.

**1. miRNAs in Breast Cancer (BC).**

Studies have suggested that microRNAs miR-10b, miR-196a, and miR-4417 play an important role in the pathology of breast cancer. miR-10b is up-regulated in BC and overexpressed in metastatic BC. A high level of miR-10b correlates with breast cancer progression, inducing cell invasion and metastasis, suspected to increase oncogene RhoC.Similarly, miR-196a is up-regulated in BC and plays an oncogenic function by altering apoptosis and angiogenesis; high levels of miR-196a are seen in advanced BC. miR-4417, on the other hand, is found to be down-regulated in BC, indicating the progression of the disease. Furthermore, it has been revealed that ncRNA-regulated reprogramming of glucose metabolism in breast cancer through glycolysis, lactate production, glycogen synthesis and catabolism, and the tricarboxylic acid cycle [6,13].

**2. miRNAs in Ovarian Cancer (OVC)**

miR-200 cluster, miR-506, let-7 cluster, miR-183, and miR-22 all play important roles in the diagnosis and prognosis of OVC. In addition, the miR-200 cluster is up-regulated in OVC, and a low level of it is associated with cell invasion and metastasis and is used to predict a poor treatment outcome and possible recurrence. It also acts as an angiogenesis inhibitor by targeting IL-8 and CXCL-1 produced by tumour cells. They inhibit transcriptional inhibitors of E-cadherin, ZEB1, and ZEB2, promoting E-cadherin expression and the transformation into epithelial cells of mesenchymal cells (EMT). Additionally, they are linked to TGF-β, affecting cell invasion and migration, both of which are crucial in cancer progression [6,14].

This cluster can influence tumour development and metastasis, making them potential biomarkers for OVC prognosis. miR-506 is a modulator of E-cadherin and inhibits cell invasion, migration, and EMT through another one of its transcriptional suppressors, known as SNAI2 [15]. When expressed in ovarian cancer, miR-506 was reported to be associated with a good prognosis. Its contribution to OVC is seen in its pathway's modulation, such that it is involved in proliferation, metastasis, and apoptosis. It affects cellular processes essential for cancer progression by targeting genes in the PI3K/Akt/mTOR pathway [16].

The let-7 cluster was found to have a suppressing effect on tumour growth and cell invasion [16], and it influences cell proliferation, differentiation, and apoptosis by Ras and HMGA2 pathways regulation [18]. Similarly, miR-183 and miR-22 were found in low metastatic OVC having a metastasis-inhibiting role. The former impacts cell proliferation and migration by its action on the PI3K/Akt/mTOR and TGF- β signalling pathways [19] while the latter affects tumour growth and prognosis in OVC with its involvement in the regulation of genes that are responsible for cell cycle control and apoptosis [20].

### 3. miRNAs in Cervical Cancer (CC)

In cervical cancer, miRNA-20a, miRNA-21, miRNA-203, miRNA-205, miRNA-485-5, miR-7, miR-10a, miR135b, and miR-149 were found to be over expressed. miR-21a plays a crucial role in CC as reported by Farzami [21] who noted a significant increase in miR-21 expression in cancerous samples. It was found to stimulate inflammation and proliferation and inhibit apoptosis through angiogenesis, cell invasion, and transduction of the NF-kB pathway [22]. Also, miR-944 was reported to be significantly up-regulated in CC. miR-138, miR-148b, miR-195, and miR-214 were reported to be down-regulated and are suspected to be tumour suppressors [23,24,25]. miR-138 is being found to stimulate apoptosis and prevent cell migrations; similarly, miR-664 in HeLa cells is found to allow a higher sensitivity of cervical cancer cells to cisplatin and lowered cell migration in the course of the disease [26].

### 4. miRNAs in Prostrate cancer

According to Moya et al. [27], there is dysregulation of several microRNAs in prostate cancer patients as compared to healthy individuals. These microRNAs include miR-4289, miR-326, miR-152-3p, and miR-98-5p. However, the mechanism by which these miRNAs impact cell proliferation and metastasis in prostate cancer remains unclear.

### 5. miRNAs in oesophagal squamous cell carcinoma

This cancer is regarded to be one of the most aggressive malignancies; it is diagnosed using an invasive biopsy method and the CK-19 and Cyfra21-1 markers. Certain microRNAs from the miR-17-92 cluster were significantly expressed in ESCC [28], particularly MiR-19a, which was found to be more sensitive than the previously used tumour markers, CK-19 and Cyfra21-1, as well as more specific, as MiR-19a was found to be significantly reduced after cancer removal [29].

### 6. miRNAs in Lung Cancer

Lung cancer is a frequent disease that kills millions of people worldwide each year. Szelenberger et al. [1] found that plasma miR-145, miR-20a, miR-21, miR-223, miR-324-3p, and miR-19b were up-regulated in the plasma of lung cancer patients, whereas miR-1285, miR-25, and miR-183 were down-regulated; however, miR-19b was dysregulated [1]. They also found that miR-145 targeted PDK1 on the mTOR signalling pathway, preventing lung cancer cell invasion and migration. MiR-210 has also been connected to regulating tumour cells' hypoxia response in lung cancer.

### Micro RNAs in targeted gene therapy

MicroRNAs have emerged as promising targets for gene therapy due to their ability to fine-tune gene expression and control various cellular processes [30].By targeting specific miRNAs, researchers aim to manipulate gene expression patterns and restore normal cellular function, making miRNAs a potential therapeutic strategy for various diseases, including cancer [31]. MiRNAs have shown promise in cancer treatment by targeting oncogenes or tumour suppressor genes. For instance, miR-34a mimics have been developed to mimic the tumour-suppressing function of this miRNA, which is often down-regulated in various cancers [32].

These mimics have been tested in preclinical models to inhibit tumour growth.MiRNAs have also been investigated as potential therapeutic targets for cardiovascular diseases, neurological disorders, and viral infections [33]. MiR-208, for example, plays a role in cardiac hypertrophy. In preclinical studies, inhibiting miR-208 has shown potential in reducing heart failure progression. In Alzheimer's disease, miR-29 has been implicated in the regulation of amyloid precursor protein (APP) processing.Modulating this miRNA might offer a therapeutic strategy for altering APP metabolism. In viral infections such as hepatitis C, MiR-122, abundantly expressed in the liver, is necessary for hepatitis C virus (HCV) replication [32].

Antisense oligonucleotides against miR-122 have been investigated as a potential therapy to inhibit HCV replication.One of the key advantages of miRNA-based gene therapy is its ability to target multiple genes simultaneously [34]. Unlike traditional gene therapy approaches that target a single gene, miRNAs can regulate the expression of numerous genes that are involved in the same biological pathway or disease process [30]. This multifaceted approach allows for a more comprehensive and effective treatment strategy, particularly for complex diseases with multiple gene abnormalities.

The development of synthetic miRNAs and anti-miRs has further accelerated the progress of miRNA-based therapies. Synthetic miRNAs are designed to mimic the function of endogenous miRNAs, while anti-miRs are designed to inhibit the activity of specific miRNAs. Both approaches can be used to restore or modulate gene expression patterns in disease cells [34]. Synthetic miRNAs can be delivered to target cells using various delivery systems, such as nanoparticles, liposomes, or viral vectors. These delivery systems protect the miRNAs from degradation and facilitate their uptake by target cells, ensuring efficient and specific delivery to the desired tissues or organs[34].

Nanoparticles, in particular, have revolutionized the field of miRNA delivery. These tiny particles can be engineered to encapsulate and protect miRNAs, enhancing their stability and bioavailability. Additionally, nanoparticles can be surface-modified with ligands that specifically recognize and bind to receptors on target cells, enabling precise targeting and delivery [36]. This targeted approach minimizes off-target effects and improves the therapeutic efficiency of miRNA-based therapies.

### Possible Perspective Role of miRNAs in Medicine

It has been reported that developing nations haveutilised miRNAs in medical diagnostics to improve disease diagnosis and prognosis. In the case of prostate cancer, a study conducted in South Africa identified and quantified EV miRNAs in the blood plasma of patients with low and high Gleason score prostate cancer. The researchers found that the ratio between two miRNAs (miR-194-5p/miR-16-5p) was significantly higher in prostate cancer patients compared to those with benign prostatic hyperplasia (BPH). This ratio can serve as a non-invasive marker for evaluating the aggressiveness of prostate cancer in the South African population [37].In the context of breast cancer, microRNAs have also shown promise as non-invasive biomarkers for diagnosis [38]. However, it is important to consider genetic and environmental factors that may influence the accuracy of these biomarkers.

A study by Uyisenga et al. [39] conducted in Rwanda evaluated the effectiveness of a diagnostic circulating microRNA signature for breast cancer in different populations with findings showing that the circulating microRNA signatures identified were not accurate enough for use as a diagnostic test in both populations. However, accurate signatures were found for each specific population separately further highlighting the importance of considering population-specific factors when utilizing microRNAs for diagnostic purposes [39].These studies demonstrate how Africa, including Nigeria, is actively involved in harnessing the potential of microRNAs for medical diagnostics. By identifying and quantifying specific miRNAs, researchers can develop non-invasive markers to aid in the diagnosis and prognosis of diseases such as prostate cancer and breast cancer.

However, further research is needed to validate and refine these miRNA biomarkers to ensure their accuracy and applicability in different populations [37,39].Nigeria, as one of the leading countries in Africa, has been making strides in exploring the potential of miRNAs in medical diagnostics. Nigeria, like many African nations, faces significant challenges with infectious diseases such as malaria, HIV/AIDS, and tuberculosis [40]. Researchers in Nigeria have been investigating miRNA profiles associated with these diseases. For instance, studies have examined miRNA expression patterns in malaria-infected individuals, aiming to identify potential biomarkers for early detection and monitoring of treatment response [41]. Efforts have also been directed towards understanding miRNA involvement in cancers prevalent in the region, like breast and cervical cancers.

Research endeavours have aimed to identify specific miRNA signatures that could aid in the early diagnosis and prognosis of these cancers [42]. Such studies are vital considering the high incidence and mortality rates associated with these cancers in Nigeria. Furthermore, given the increasing burden ofnon-communicable diseases in Nigeria,

including cardiovascular diseases and diabetes, investigations into miRNA biomarkers for early detection and monitoring of these conditions have gained attention [43]. Research efforts have explored the association between certain miRNAs and disease progression, paving the way for potential diagnostic applications.

Nigerian researchers and institutions have collaborated domestically and internationally to further explore miRNA-based diagnostics. Efforts have included collaborative studies, workshops, and capacity-building programs aimed at enhancing expertise in miRNA research and its application in diagnostics within the country and while progress has been made in exploring miRNA diagnostics in Nigeria, challenges such as limited infrastructure, funding constraints, and the need for extensive clinical validation persist. Collaborations between Nigerian researchers, healthcare professionals, and global partners are essential to overcome these challenges and translate miRNA research into practical and accessible diagnostic tools for the Nigerian population.

**Challengesand issues related to MicroRNA as a therapeutic**

Although multiple subtypes of miR-19 have been identified in many cancer types, the use of miRNAs for cancer diagnosis and prognosis has shown to be rather particular for the cancer type in question. The standardization of the amount of miRNA to be utilized for the assay and the lack of knowledge and clinical acceptance of the typical range of miRNA values that should be observed in the plasma are two key problems with the usage of miRNAs.

To test patient plasma samples, several researchers [44, 45, 46] had to develop their panel of miRNAs using PCR techniques; a thorough investigation is still required in this field of miRNA science to ensure proper standardization. As a result, researchers continue to employ a variety of methodologies to investigate plasma miRNA levels, with microarrays being one of the most popular methods due to their reputation as the most suitable for handling huge amounts of data.

Additionally, quantitative real-time PCR, or QRT-PCR, is employed. It is said to be the most accurate, sensitive, and specific diagnostic test for identifying a small number of miRNAs due to its high repeatability, sensitivity, and precision. Another technique for monitoring miRNA gene expression in clinical practice is next-generation sequencing (NGS), although it is very costly and time-consuming. According to Mestdagh's research [47], there were variations in the sensitivity, repeatability, specificity, and accuracy of all the methodologies employed for miRNA investigation.

The traditional techniques include northern blotting, quantitative polymerase chain reaction (qPCR), and microarray analysis; these are all noted for their limitations, emphasizing the exploration of newer techniques for the highly sensitive detection of miRNAs [48]. Of all these techniques, Quantitative Real-Time PCR (QRT-PCR) showed the best levels of sensitivity, specificity, and detection rate of the miRNAs [49].

Despite the enormous potential of miRNA therapeutics, there are still several challenges that need to be overcome. One major hurdle is the efficient delivery of miRNAs to target cells [50]. The delivery systems must be able to navigate biological barriers, such as the extracellular matrix and cell membranes, to reach the desired intracellular compartments. Additionally, the stability and release kinetics of miRNAs within the delivery systems need to be optimized to ensure sustained and controlled release at the target site.

Another challenge is the identification and validation of disease-specific miRNA targets [51]. It is crucial to identify the miRNAs that are dysregulated in specific diseases and determine their functional roles in disease progression. This information is essential for the rational design of miRNA-based therapies and the selection of appropriate therapeutic targets.Furthermore, the safety and potential off-target effects of miRNA-based therapies need to be thoroughly evaluated [52]. Since miRNAs can regulate multiple genes, there is a risk of unintended consequences and off-target effects. It is important to carefully assess the specificity and selectivity of miRNA-based therapies to minimize potential adverse effects.

**Conclusion**

Although the need to bring this technique to a unified, globally accepted standard and determine a normal range is urgent, miRNAs are the newest diagnostic tools for optimizing investigations, diagnosis, and treatment. MicroRNA profiling for the diagnosis and prognosis of diseases is quickly becoming a major cornerstone, especially in Western medicine, and has great "unmined" potential that should be researched and explored for non-invasive methods of early detection and management of diseases such as cancer.Medical researchers and practitioners, particularly in African nations such as Nigeria, should endeavour to incorporate it as a diagnosis approach for cancer, therapy, and management, as this would help to reduce the growing occurrence of these disorders.

**List of abbreviations**

miRNAs : Micro Ribonucleic acids
RNAs : Ribonucleic acids
dsDNA : Deoxyribonucleic acid
DGCR8 : Di George syndrome critical region 8
RISC : RNA interference silencing complex
OVC : Ovarian Cancer
HCV : hepatitis C virus

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**Authors' contributions**

KA and OOconceptualized the study. All authors collected and analysed data and drafted the manuscript. KA and OO reviewed and edited the manuscript. All authors approved the final manuscript.

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**Availability of data and materials**

They included journals indexed on Google Scholar, EPUB, CrossRef, Scopus, DOAJ, Embase, Global Health, MEDLINE, PubMed Central, and SCImago.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

Authors declare no competing interest

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