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REVIEW

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Advances in paper-based biosensors for point-of-care miRNA detection

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Abstract

In healthcare diagnostics, paper-based biosensors are a major breakthrough because they provide a portable, affordable platform for point-of-care applications, especially in precision medicine. These biosensors combine molecular biology and nanotechnology to detect microRNAs (miRNAs), which are important indicators for diseases like cancer and metabolic disorders, with great sensitivity and specificity. By enhancing signal transduction in these devices, the incorporation of nanomaterials like graphene oxide (GO) and gold nanoparticles (AuNPs) improves detection limits and permits quick analysis. The capacity to identify miRNAs at picomolar levels makes it easier to diagnose patients early and start treatment. Additional factors that improve patient compliance and accessibility include their simplicity of use and the possibility of non-invasive sampling utilising biological fluids like blood or saliva. Specific miRNA signatures can be found using sophisticated detection algorithms, opening the door to customised treatment plans. The design concepts, materials, manufacturing processes, and clinical uses of paper-based biosensors for miRNA detection are the main topics of this review, which also emphasises the promise of these devices for affordable and sustainable point-of-care diagnostics. In the end, incorporating paper-based biosensors into standard clinical practice is a step towards proactive and individualised healthcare, highlighting how important early detection and action are to improving patient care.

Keywords Paper-based biosensor, MiRNA, Nanoparticles, Gold nanoparticles, Point-of-care, Precision, Sensitivity, Specificity

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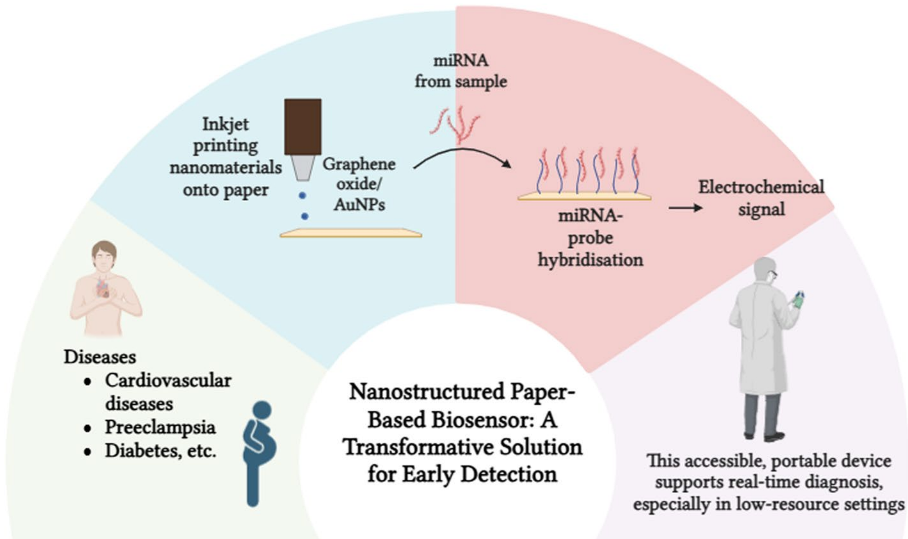
Graphical Abstract



Introduction

The development of nanoscale biosensors represents a revolutionary advancement in the field of healthcare diagnostics, particularly in the realm of precision medicine [1]. Through the integration of molecular biology and nanotechnology, these novel instruments provide so far unheard-of levels of sensitivity and specificity for the detection of biological analytes, including microRNAs (miRNAs) [2]. These small, non-coding RNA molecules are essential for controlling the expression of genes and have become important biomarkers for a number of illnesses, such as cancer and metabolic diseases [3]. Accurate miRNA identification is crucial for early diagnosis and successful therapy, highlighting the significance of miRNAs in contemporary medicine [4].

The capacity of nanoscale biosensors to detect miRNAs at incredibly low concentrations—often picomolar levels—has been greatly improved by recent developments [5]. Compared to conventional methods, techniques that use gold nanoparticles (AuNPs) and quantum dots (QDs) have proved essential for signal amplification and more sensitive detection. In therapeutic settings, where early intervention can significantly improve patient outcomes, this increased sensitivity is very important [6]. Additionally, these biosensors lessen the discomfort that patients experience from traditional diagnostic procedures by enabling routine health monitoring using non-invasive samples like blood or saliva [7].

Paper-based platforms have drawn interest among the different kinds of biosensors because of their low cost, portability, and simplicity of usage. These biosensors are especially useful in a variety of healthcare environments, from highly developed hospitals to underdeveloped regions [8]. According to recent studies, paper-based biosensors can be used successfully for point-of-care (POC) diagnostics in isolated areas, facilitating access to necessary medical treatments [9]. Additionally, by using eco-friendly materials and reducing waste, their design supports sustainable healthcare practices [10].

The capabilities of paper-based biosensors for miRNA detection are further improved by the use of sophisticated detection algorithms and machine learning approaches. These algorithms can detect unique miRNA signatures linked to particular diseases by evaluating intricate biological data, opening the door for personalised medical strategies catered to the unique characteristics of each patient [11, 12]. In addition to increasing diagnostic precision, this collaboration between data analytics and nanotechnology enables real-time tracking of therapy response and illness progression. The prospective uses of these novel biosensors could transform diagnostics and have a big impact on global health outcomes as long as research in this area continues to progress [13].

This review attempts to investigate the novel architecture and working principles of paper-based miRNA detection biosensors. We will talk about how important miRNAs are for early detection, how nanoscale biosensing has advanced technologically, and how these innovative technologies could be used to improve diagnostic precision and solve urgent public health issues.

Through this analysis, we aim to show how revolutionary nanoscale biosensors may be in enhancing health outcomes around the world.

Transformative Early Diagnosis: The Role of MicroRNAs in Disease Detection

The Importance of Early Disease Detection

The importance of early disease diagnosis in enhancing patient outcomes and cutting healthcare expenses is becoming more widely acknowledged. Because they allow for the identification of biomarkers at extremely low concentrations, nanoscale biosensors are crucial in this regard [14]. Timely interventions, made possible by early detection, can drastically change the course of illnesses like cancer, heart disease, and infectious diseases [15]. Healthcare professionals can optimise treatment plans, put preventive measures into place, and improve the general standard of care by spotting health problems before they become more serious. Early disease identification has been made possible in large part by technological breakthroughs.

Because they can identify biomarkers at incredibly low concentrations, nanoscale biosensors stand out among these advancements [16]. Because these devices function at the molecular level, it is possible to identify particular biological components that may signal the presence of a disease long before clinical symptoms appear. For example, early tumor marker detection in oncology can result in timely treatment decisions that increase survival rates. Early disease detection also has significant economic difficulties. Prompt treatments frequently lead to fewer hospital stays and lower treatment expenses, which eases the strain on healthcare systems. Therefore, it is not only advantageous for individual patients but also crucial for advancing sustainability and public health to include cutting-edge diagnostic tools into standard healthcare procedures [7].

Role of MicroRNAs as Biomarkers

The stability of miRNAs in biological fluids and their regulatory functions in gene expression have made them important players in the field of molecular diagnostics. Apoptosis, differentiation, and proliferation are just a few of the biological functions that these tiny, non-coding RNA molecules are involved in [17]. Because miRNAs control the expression of genes involved in cell development, differentiation, and apoptosis, they are essential for preserving cellular homeostasis in healthy cells [18]. This delicate equilibrium is frequently upset in cancer, though. Targeting tumour suppressor genes, some elevated miRNAs, referred to as oncomiRs, encourage tumour growth and metastasis [19]. Other miRNAs, on the other hand, are downregulated, which causes oncogenes to overexpress. They are desirable indicators for early identification, prognosis, and treatment response prediction due to the changed expression patterns of these miRNAs in cancer [20]. They are useful biomarkers for the early diagnosis of disease because their expression profiles can be used as indicators of underlying state. The discovery of distinct miRNA signatures linked to different illnesses has created new diagnostic opportunities. In order to distinguish between benign and malignant tumors based on their distinct expression patterns, for instance, several miRNAs have been connected to the advancement of cancer. Healthcare professionals can more efficiently customise treatment programs because to these capabilities, which also makes early diagnosis easier and improves prognostic assessments [21].

The integration of technology and molecular biology is best demonstrated by the use of nanoscale biosensors for miRNA detection. Modern materials and innovative detection algorithms are used in these instruments to identify miRNAs at picomolar concentrations, which are frequently hard to achieve with traditional diagnostic techniques. Recent research has demonstrated that the accuracy of diagnosis can be increased with the application of machine learning techniques [22]. These instruments detect miRNAs at picomolar concentrations—levels that conventional diagnostic procedures frequently find difficult to reach—by utilising cutting-edge materials and novel detection algorithms. These biosensors democratise access to vital health monitoring tools by using non-invasive sampling techniques like blood or saliva collection. Additionally, by facilitating the processing of intricate data sets, the combination of machine learning techniques and miRNA identification improves diagnostic accuracy. Compared to traditional single-marker techniques, this technology enables the creation of multi-marker panels that enhance specificity and sensitivity [23].

As more is learnt about the various functions of miRNAs in health and illness, their potential uses in diagnostics will probably grow, opening the door for patient-specific personalised treatment approaches. All things considered, the revolutionary potential of miRNAs as biomarkers highlights their vital significance in promoting early disease identification. Utilising the potential of nanoscale biosensors and incorporating them into clinical procedures can greatly enhance patient outcomes and diagnostic precision while advancing a more sustainable healthcare system that prioritises proactive management and prevention.

Paper-Based Biosensors: Design, Mechanisms, and Materials

For point-of-care applications, paper-based biosensors offer an appealing blend of sophistication and simplicity, marking a substantial development in diagnostic technology. Their affordability, mobility, usability, and appropriateness for environments with limited resources make them appealing, and they also perfectly complement the expanding focus on sustainable healthcare practices. These qualities make them especially appealing for widespread application in a variety of healthcare settings, including contemporary hospitals and distant clinics. A recent review provides a comprehensive overview of paper-based analytical devices for miRNA detection, highlighting recent advances in materials, fabrication techniques, and signal transduction methods [24]. This section will explore the finer points of the design, working principles, and necessary components that support the general performance and usefulness of paper-based biosensors made especially for miRNA detection.

Design and Operational Principles

Paper substrates, which are usually made of cellulose, are used as a flexible matrix in the basic design of paper-based biosensors [25]. Important biorecognition components, which are in charge of binding to the target miRNA selectively and facilitating effective analyte detection, are incorporated into this matrix. Paper's intrinsic qualities—such as its low cost, large surface area, natural porosity, and exceptional capacity to absorb fluids through capillary action—are essential for efficient sample transportation and for promoting the best possible interaction with the different detection components built into the biosensor [26]. The design frequently includes precisely built microfluidic channels or specified zones to further improve performance. By carefully regulating fluid flow and efficiently enclosing the reaction area, these microfluidic components increase sensitivity and drastically lower the volume of sample needed. This is especially crucial when working with limited or valuable clinical samples [27].

The very specific binding of target miRNAs to carefully selected biorecognition components is the basis for these biosensors'working concept. To guarantee their availability for interaction with the target analyte, these components are purposefully immobilised onto the paper substrate. Depending on the particular transduction technique used in the biosensor design, a detectable signal—which may be optical, electrochemical, or mass-based—is produced upon successful miRNA binding. The presence and concentration of the target miRNA in the sample are then quantified using this signal [22].

Materials and Fabrication Techniques

For paper-based biosensors, choosing the right materials is essential to obtaining optimum performance, long-term stability, and dependable operation. Although cellulose is still the principal substrate, a variety of functional elements are frequently added to enhance the biosensor's detection power and customise its functionality for particular uses.

Paper-based biosensors can now be made more sensitive and selective with the help of nanomaterials [28]. To take advantage of their special qualities, AuNPs, graphene oxide (GO), and carbon nanotubes (CNTs) are commonly added to the paper matrix [29]. For instance, GO greatly improves electrochemical detection by offering a channel for quick electron transit due to its remarkable electrical conductivity and high surface area [30]. AuNPs, on the other hand, have unique optical properties, particularly surface plasmon resonance (SPR), which can be utilised to enhance optical signals and improve the sensitivity of colorimetric assays [31]. For these nanomaterials to be compatible with the paper substrate and the biorecognition components, careful surface modification and functionalisation are frequently needed during integration (Table 1).

Any biosensor's core function is its capacity to identify and attach to the target analyte with selectivity. The most widely used biorecognition components in paper-based miRNA biosensors are peptide nucleic acids (PNAs) and nucleic acid probes, such as complementary DNA (cDNA) or RNA sequences [37]. In order to provide precise and trustworthy detection, these probes are made to specifically hybridise with the target miRNA. These probes are carefully immobilised onto the paper surface using a range of chemical or physical approaches to guarantee effective hybridisation and reduce non-specific binding. Recent developments in surface engineering methods are essential for optimizing the immobilization of biorecognition elements, increasing their stability and accessibility in miniature biosensing devices [38]. In order to provide a robust and usable binding interface, these methods frequently entail the application of cross-linkers or surface modification techniques [39].

To boost detection capabilities, a variety of components, including enzymes, redox mediators, and fluorescent dyes, can be added to paper-based biosensors. The materials chosen are determined by the application and sensing technique, and integrating them is essential to maximising biosensor performance [9]. These biosensors may be produced in large quantities and used in point-of-care settings since their fabrication processes are often straightforward and reasonably priced. Among the methods are screen printing, inkjet printing, and drop casting. While screen printing is scalable and economical

Table 1 Recent studies on paper-based sensors for miRNA detection

Sensor type	Fabrication steps	Linear range	Limit of detection	Target miRNA	Ref
AuNP/RGO Paper Electrochemical Biosensor	Inkjet printing of AuNPs and RGO on paper	Picomolar to nanomolar	25.71 nM	miR- 155	[32]
BRET Paper-Based System	Freeze-dried circular DNA probes and RCA components on paper discs	Femtomolar to picomolar	2.5fM, 0.8fM, 1.3fM	miR- 500, miR- 21, miR- 155	[33]
Gold Inkjet Printing Electrochemical Biosensor	Inkjet printing of gold ink for miR- 21 detection	0.35fM—100 pM	0.35fM	miR- 21	[34]
Cys/AuNPs Colorimetric Biosensor	Immobilization of cysteamine-capped gold nanoparticles (Cys/AuNPs) on paper disks	1 pM – 1 nM	0.5 pM	miR- 21	[35]
GONET and Target-Recycled Signal Amplification	Pre-treatment of Whatman filter paper with GONET	Not specified	Not specified	Not specified	[35]
Impedimetric Detection	Electrode assembly on paper for miRNA detection	Not specified	Not specified	Not specified	[36]

for mass manufacturing, inkjet printing enables precise material deposition and the development of intricate patterns [40]. By managing fluid flow and reagent mixing, integrating microfluidic elements improves sample processing and analysis. This can lower sample volume needs and increase sensitivity [41]. Paper-based biosensors are also environmentally favourable because they use biodegradable materials and reduce waste, which is in line with efforts to develop sustainable diagnostic technologies (Fig. 1).

Biorecognition Elements and Signal Transduction

A biosensor's ability to identify the target analyte with high selectivity is crucial to its functioning, and this is where the biorecognition factor comes in. RNA strands, single-stranded DNA (ssDNA) probes complementary to the target miRNA, and PNAs are the most often used biorecognition components in paper-based miRNA biosensors [42]. Various physical or chemical methods are used to immobilise these probes on the paper substrate to ensure effective hybridisation. The use of surface modification techniques, including as polymer coatings and self-assembled monolayers (SAMs), is common to guarantee that the probes are accessible and orientated correctly for miRNA binding [43].

The process by which the target miRNA binds to the probe and transforms the biorecognition event into a detectable signal is known as signal transduction. Numerous signal transduction methods, including electrochemical, optical, and colorimetric methods, can be employed by paper-based biosensors [44]. High sensitivity and real-time monitoring are provided by electrochemical methods, which monitor changes in electrical current or impedance caused by miRNA hybridisation

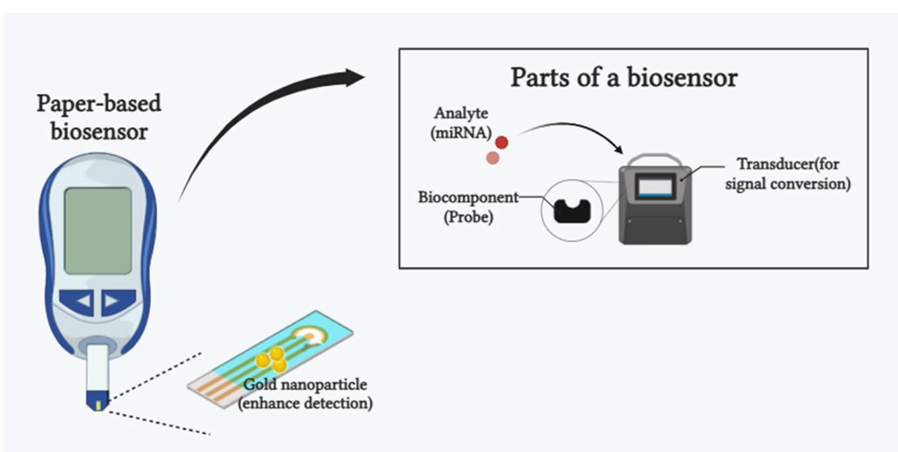


Fig. 1 Illustration of a paper-based biosensor for miRNA detection, highlighting key components such as the probe, target analyte (miRNA), and transducer. AuNPs are used to enhance detection sensitivity

[45]. Colorimetric assays use enzymes connected to the detection probe to create a colour shift that may be seen with the naked eye or measured with a spectrophotometer [46]. On the other hand, optical techniques improve signal identification and offer multiplexing possibilities by using fluorescence or SPR (Fig. 2) [47].

Nanoscale Enhancements in Paper-Based miRNA Biosensors

Although paper-based biosensors have many inherent benefits, especially in terms of affordability, portability, usability, and environmental sustainability, their overall performance can be greatly improved by carefully combining nanoscale materials and cutting-edge, nanotechnology-based techniques [27]. According to a study by Purohit et al. (2019), in addition to miRNA detection, nanomaterials and biosensors are being investigated for cancer cell detection in miniature settings, highlighting the wide range of applications of these technologies for cancer diagnostics [48]. The effective use of nanotechnology to enhance key features of paper-based miRNA biosensors, such as sensitivity, specificity, limit of detection, and general functionality, will be thoroughly examined in this section. This will open the door to more dependable and precise point-of-care diagnostics.

The capacity of nanotechnology to enhance the signal produced by miRNA binding is among its most important contributions to paper-based biosensors. For the detection of low-abundance miRNAs, which could exist in trace amounts in clinical samples, this amplification is essential. In this technique, nanomaterials like quantum dots (QDs) and AuNPs are essential [49]. A visual readout of the miRNA concentration can be obtained, for example, by functionalising AuNPs with enzymes that catalyse processes that result in observable colour changes. Because of their remarkable brightness and photostability, QDs are used as highly fluorescent markers, greatly increasing the sensitivity of optical detection [44]. Researchers can detect even traces of the target analyte by conjugating QDs to miRNA-specific probes, which results in impressive signal amplification. The interaction between the miRNA and the capture probe can be optimised by engineering nanomaterials to produce more potent biorecognition interfaces [50]. Kumar et al. (2019), for instance, showed the potential of such nanocomposites for sensitive biosensing applications by creating a nanosensor for label-free electrochemical detection of a biomarker associated with non-alcoholic fatty liver disease using gold-iron bimetallic nanoparticles impregnated on reduced GO [51]. Alkanethiol SAMs on AuNPs, for instance, offer a highly ordered and well-defined surface for immobilising nucleic acid probes. By presenting the probes in the best possible orientation, this method maximises their accessibility and binding affinity for target miRNAs. Additionally, these interfaces'nanoscale size diminishes non-specific binding and steric hindrance, improving specificity and lowering background noise [52].

For biosensor applications, nanoparticles'intrinsic high surface area-to-volume ratio provides a major benefit. By integrating nanomaterials into the paper substrate, it becomes able to immobilize a greater density of

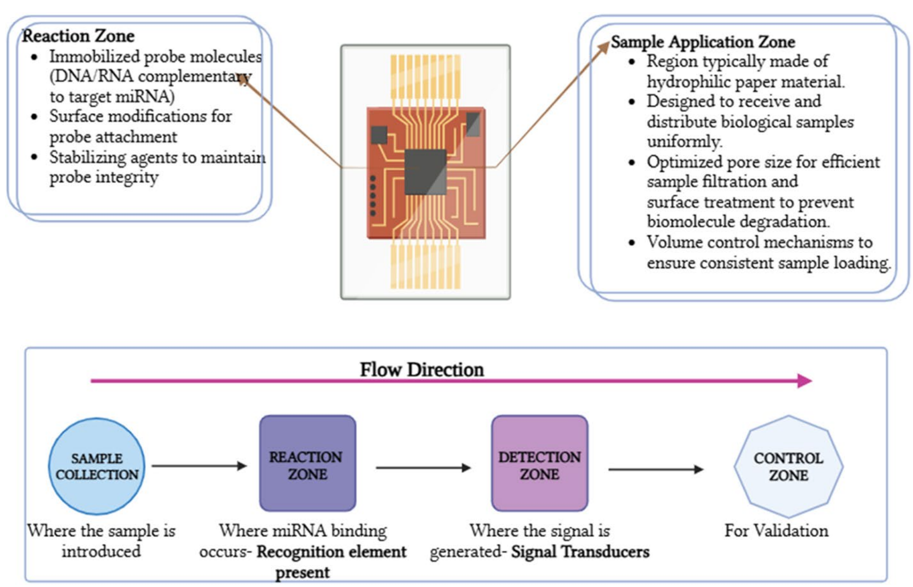


Fig. 2 Mechanism of a paper-based miRNA biosensor, showcasing how it utilizes a paper substrate with integrated biorecognition elements to selectively capture target miRNAs, resulting in a detectable signal for sensitive quantification

biorecognition elements, effectively enhancing the capture efficiency of target miRNAs [28]. This is especially crucial for enhancing the biosensor's sensitivity so that it can identify even minute changes in miRNA quantities. Because of their remarkable surface area and ease of functionalisation with biorecognition components, CNTs and graphene-based materials are especially well-suited for this use [53].

To improve the electrochemical detection of miRNA, nanomaterials with remarkable electrical conductivity, including graphene and carbon nanotubes, can be strategically used. These substances make it easier for electrons to move between the electrode surface and the biorecognition element, which increases the biosensor's sensitivity and dynamic range [5]. These nanoparticles can enhance the electrochemical signal produced upon miRNA binding by forming a conductive network within the paper substrate, allowing for more precise and trustworthy measurement. There is great potential for the creation of extremely sensitive, specific, and approachable diagnostic instruments for point-of-care miRNA detection through the cooperative integration of nanotechnology and paper-based biosensors [2]. In order to improve performance and broaden the spectrum of applications for these game-changing biosensors, ongoing research efforts are concentrated on investigating novel nanomaterials, refining fabrication processes, and creating creative signal transduction algorithms [54]. The ultimate objective is to convert these developments into useful, inexpensive, and easily available diagnostic tools that will enhance patient outcomes and revolutionise healthcare delivery globally (Fig. 3).

Enhancing Sensitivity and Specificity

Integration of Nanomaterials in Paper-Based Sensors

In the field of diagnostics, the incorporation of nanomaterials into paper-based biosensors represents a major breakthrough, improving the sensitivity and specificity of biological analyte detection [55]. Nanomaterials with special physical and chemical characteristics, like carbon nanotubes, GO, and AuNPs, are excellent options for enhancing biosensor performance. The exceptional optical characteristics of AuNPs, for example, enable signal amplification via SPR [56]. AuNPs'surface electrons interact with light to produce enhanced light scattering, which makes the phenomena easy to detect [57]. With colorimetric assays, where a discernible colour shift signifies the presence of a specific biomarker, this feature is especially helpful. Because of its large surface area and superior electrical conductivity, GO is essential for electrochemical detection [58]. Sensitive measurements of current variations in response to biomolecular interactions are made possible by its capacity to promote rapid electron transfer. Incorporating graphene oxide into paper-based sensors not only increases sensitivity but also improves the biosensor's overall stability and repeatability [59]. Another type of nanomaterial that enhances the performance of paper-based biosensors is

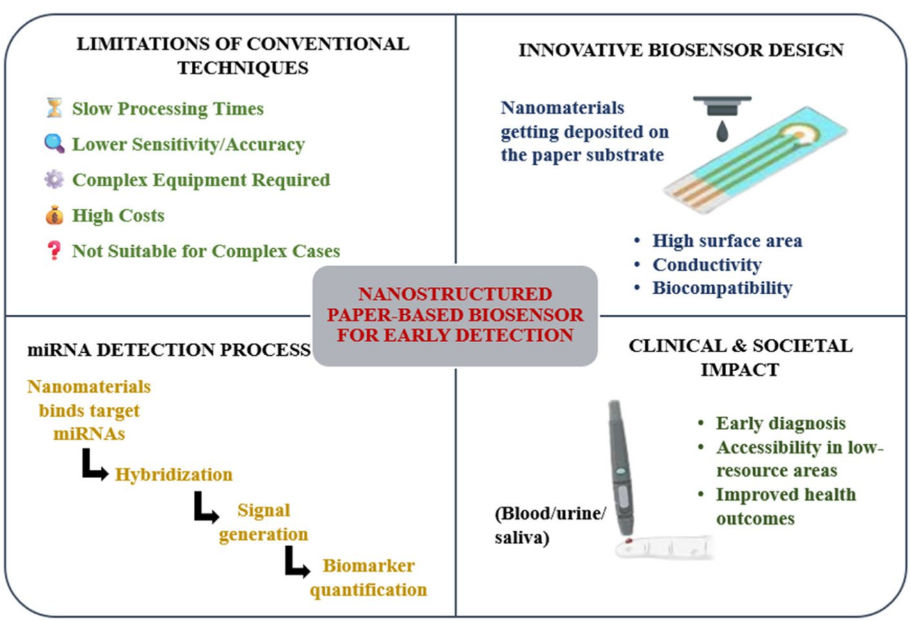


Fig. 3 The innovative design and functionality of a nanostructured biosensor, highlighting its role in revolutionizing diagnostics through enhanced sensitivity and specificity for detecting miRNAs. By integrating advanced nanomaterials and biorecognition elements, the biosensor enables early disease detection, facilitating timely interventions and personalized treatment strategies

carbon nanotubes. Because of their remarkable mechanical strength and large surface area, CNTs allow for higher loading of biorecognition components, which can greatly improve sensor sensitivity [60]. Their adaptability makes it possible to include them into a variety of sensor designs, which makes them appropriate for uses ranging from environmental monitoring to medical diagnostics.

Researchers can develop paper-based biosensors that can identify biomarkers at concentrations as low as picomolar levels (10^{-12} M) by employing these nanomaterials. In medical diagnostics, where early detection can result in prompt therapies that enhance patient outcomes, this increased sensitivity is particularly important. These sensors are highly helpful instruments for preventative healthcare management because they may detect tiny changes in biomarker levels long before clinical symptoms manifest [61–63].

Multiplexed Detection of miRNAs

Multiplexed detection is a revolutionary feature of contemporary biosensors that enables the simultaneous analysis of multiple biomarkers in a single assay. This is especially important in the context of miRNA detection, where certain miRNA profiles can offer crucial insights into a range of health conditions, such as cancers and metabolic disorders [64]. By using multiplexed detection strategies, medical professionals can get a comprehensive picture of a patient's health status with a single test. The strategic design of biorecognition elements that are suited to bind particular miRNAs allows multiplexing in paper-based biosensors. Several target miRNAs can be detected in parallel from a single sample since each biorecognition element is immobilised on different zones of the paper substrate. Colorimetric readouts or advanced imaging techniques make it easier to comprehend results by visually differentiating between various biomarkers according to their distinct responses [65].

These sensors'multiplexing capabilities are further improved by the incorporation of nanomaterials. AuNPs of various sizes or shapes, for instance, can produce unique optical signatures for every target miRNA, allowing for simultaneous detection without cross-reactivity [66]. Additionally, complex data sets produced by multiplexed assays can be analysed using machine learning algorithms, increasing diagnostic precision and facilitating patient-specific personalised therapy strategies [67].

In addition to simplifying the diagnostic procedure, the use of paper-based biosensors for multiplexed tests lowers the costs of reagents and sample volumes [68]. In environments with limited resources, where access to cutting-edge laboratory facilities may be restricted, this efficiency is especially advantageous. Multiplexed miRNA detection supports larger public health efforts focused on early disease identification and intervention by democratising access to thorough diagnostic testing. All things considered, the use of nanoparticles into paper-based sensors allows for multiplexed detection capabilities while also greatly increasing their sensitivity and specificity [69]. Because of these developments, paper-based biosensors are now considered to be highly effective instruments in contemporary diagnostics, especially when it comes to detecting disease-associated miRNAs that are essential for maintaining health and managing illness. We may expect more advancements that will increase the usefulness and uses of these amazing technologies in healthcare settings across the globe as research in this area develops.

Applications in Clinical Diagnostics

Early Detection of Cancer Biomarkers

One of the most important developments in oncology is the early identification of cancer biomarkers, which has a big impact on treatment plans and patient outcomes. Nanoscale biosensors have become extremely effective tools for detecting particular biomarkers linked to different forms of cancer, especially those that use paper-based platforms. The molecular recognition principle underlies the operation of these biosensors, whereby biorecognition components like antibodies or nucleic acids bind specifically to target cancer biomarkers found in biological samples [70]. The remarkable sensitivity of nanoscale biosensors, which enables them to detect biomarkers at concentrations as low as picomolar levels, is one of the main benefits of employing them for cancer diagnosis [71]. Since many cancer-associated biomarkers are very weakly detectable in the early stages of disease progression, this increased sensitivity is essential for early diagnosis. For example, some miRNAs and circulating tumor DNA (ctDNA) have been found to be promising biomarkers for a number of malignancies. The capacity to identify these biomarkers via non-invasive techniques, like blood or saliva testing, makes routine screenings and monitoring easier and allows medical professionals to take prompt action [72].

Furthermore, these biosensors work better when nanomaterials are incorporated into them. GO and AuNPs are frequently utilised to boost signals and increase detection precision. These substances allow for electrochemical or colorimetric readouts that yield precise and measurable outcomes. The potential for multiplexed detection—the simultaneous identification of many cancer biomarkers within a single assay—further expands the usefulness of nanoscale biosensors in clinical diagnostics as this field of study develops.

Beyond increased survival rates, early cancer detection has implications for more individualised treatment plans [73]. By determining particular biomarkers linked to a patient's cancer kind, medical professionals can customise treatments to focus on the fundamental processes causing tumor growth. Patients'quality of life is eventually improved by this individualised strategy, which also reduces needless side effects and increases therapeutic efficacy.

Monitoring Chronic Diseases through miRNA Profiling

Using miRNA profiling to monitor chronic diseases is a revolutionary way to manage ailments like diabetes, autoimmune disorders, and cardiovascular diseases [74–76]. miRNAs are useful indicators for disease monitoring because pathological situations can cause considerable changes in their expression profiles [77]. In order to give medical professionals up-to-date information on a patient's health, nanoscale biosensors have been designed to identify particular miRNAs linked to chronic illnesses. This feature is especially helpful for diseases like diabetes or heart disease that need to be continuously monitored. For instance, in patients with heart failure, particular miRNA signatures have been connected to cardiac remodelling and inflammation. Clinicians can learn more about the course of a disease and modify treatment regimens by routinely evaluating these miRNAs using non-invasive samples like blood or urine [78].

Among the many benefits of using paper-based biosensors for miRNA profiling are their affordability and user-friendliness. These gadgets can be used in a range of healthcare environments, from cutting-edge hospitals to isolated clinics with little funding. Because of their portability, they can be used for POC testing, which enables prompt therapies that can avert chronic illness consequences [79]. Moreover, the combination of miRNA profiling and machine learning techniques improves diagnostic precision by making it possible to analyse intricate data sets produced by multiplexed tests. By identifying distinct miRNA patterns that could signal a disease aggravation or remission, this method enables pre-emptive therapy plans catered to the requirements of each patient.

Applications of nanoscale biosensors in clinical diagnostics, especially in the early identification of cancer biomarkers and the use of miRNA profiling to track chronic diseases, show how revolutionary they might be in contemporary healthcare [80]. While tackling important public health issues, these cutting-edge technologies greatly enhance patient outcomes by facilitating prompt interventions and individualised treatment plans. We may expect more developments that will expand the capabilities and uses of these amazing devices in a variety of health domains as long as research in this area continues to progress.

Sustainability and Accessibility in Healthcare

Eco-Friendly Design of Paper-Based Biosensors

In healthcare diagnostics, the design of paper-based biosensors reflects a dedication to sustainability. Utilising paper as a substrate, these cutting-edge devices take advantage of its intrinsic qualities—such as biodegradability, affordability, and accessibility—to produce environmentally friendly diagnostic instruments [81]. Paper-based biosensors help to lessen medical waste and the environmental effect of standard diagnostics by decreasing the usage of plastic and other non-biodegradable materials. The use of sustainable materials in the production of these biosensors further improves their environmentally friendly design [82]. For example, adding nanomaterials such as AuNPs and GO enhances the sensors'sensitivity and specificity while also adhering to green chemistry principles [83]. Environmentally friendly techniques can be used to synthesise these nanomaterials, guaranteeing the sustainability of the entire production process.

Furthermore, the straightforward fabrication methods used to create paper-based biosensors, like screen printing or inkjet printing, lower resource and energy requirements. In addition to reducing production costs, this efficiency aids in the creation of diagnostic technologies that can be used in environments with limited resources [84]. Paper-based biosensors contribute to the democratisation of healthcare by offering accessible and reasonably priced diagnostic tools, enabling underprivileged communities to obtain necessary medical services [85].

Additionally, because these biosensors are non-invasive, readily available biological samples, such as urine or saliva, can be used. In addition to improving patient comfort, this strategy promotes regular health monitoring and a proactive approach to health care. The incorporation of environmentally friendly designs into diagnostic technologies, such as paper-based biosensors, is a major step towards a more accountable and fair healthcare landscape, as healthcare institutions place a greater emphasis on sustainability.

Point-of-Care Testing: Bridging Healthcare Gaps

Rapid diagnostic results at or close to the patient treatment site are made possible by POC testing, which is transforming the way healthcare is delivered [86]. This strategy is extremely helpful in filling in healthcare gaps, particularly in underserved or remote places where access to cutting-edge lab facilities may be restricted [87]. POC testing's speed and ease enable medical professionals to make prompt decisions based on up-to-date information, which eventually improves patient outcomes. Because of their low manufacturing costs, mobility, and ease of use, paper-based biosensors are perfect for POC testing. These gadgets can be made for a number of uses, such as identifying infectious agents or tracking chronic illnesses [88]. For instance, by looking for particular biomarkers in urine samples, paper-based biosensors can help with the early detection of disorders like preeclampsia in maternal healthcare [25]. This ability enables prompt interventions that can greatly improve the health results for both the mother and the foetus.

In addition to promoting health equity, the availability of POC testing using paper-based biosensors guarantees that people from a variety of backgrounds can obtain necessary diagnostic services. Portable biosensors allow local healthcare providers to conduct tests without the requirement for specialised laboratory equipment in remote or low-resource environments [89]. In order to enable communities to take control of their health and well-being, this accessibility is essential. Also, by motivating people to take an active role in their own health care, POC testing promotes patient involvement. What if a pregnant woman could test her urine at home for preeclampsia biomarkers using a basic handheld device? These developments encourage well-informed healthcare decision-making while also lowering the anxiety related to pregnancy monitoring.

Considerable progress has been made in sustainable healthcare practices with the incorporation of environmentally friendly designs into paper-based biosensors and their use in POC testing. These technologies support a more equitable healthcare system that prioritises early identification and proactive management of health issues by improving accessibility and bridging healthcare disparities. We may expect more advancements as this field of study develops, which will expand the potential and uses of these amazing gadgets in a variety of medical domains.

Future Perspectives and Challenges

Innovations on the Horizon

The potential for revolutionary advancements in biosensing technology could expand the capabilities and uses of nanoscale biosensors. The incorporation of cutting-edge nanomaterials, such as two-dimensional materials like transition metal dichalcogenides and novel carbon allotropes, is one of the most interesting advances planned for the future [90]. This could further increase the sensitivity and specificity of sensors. Because of their special electrical and optical characteristics, these materials can be used to create biosensors that can identify biomarkers at even lower concentrations than are possible with existing technology. Furthermore, data processing and interpretation are about to undergo a revolution due to the confluence of biosensing technologies with artificial intelligence (AI) and machine learning. Through the use of advanced algorithms, scientists can examine intricate datasets produced by multiplexed tests, allowing for the discovery of distinct biomarker signatures linked to certain illnesses [91]. This ability will support personalised medicine tactics, enabling medical professionals to modify treatment plans according to the unique characteristics of each patient.

Another field that is ready for innovation is microfluidics technology. Microfluidic systems can improve the efficiency of biosensors and expedite sample processing by allowing the on-chip manipulation of tiny fluid volumes [27]. Especially at POC settings, the speed and accuracy of diagnostics will be greatly increased by the development of integrated microfluidic platforms that integrate sample preparation, detection, and data analysis into a single device [92]. The development of environmentally friendly biosensing systems is also receiving more attention. Biodegradable materials are being investigated by researchers for the production of sensors, which is in line with international sustainability objectives. In addition to lessening the impact on the environment, these developments will encourage healthcare professionals to use resources responsibly [93].

Regulatory Considerations and Clinical Implementation

Regulatory factors will be essential to the therapeutic application of biosensing technologies as they develop further. To receive regulatory approval from health authorities, nanoscale biosensors must be guaranteed to be safe, effective, and reliable [94]. In order to prove that these devices fulfil predetermined performance standards, a thorough testing and validation procedure is required. Standardising testing procedures for biosensors, especially those that use cutting-edge nanomaterials or intricate detecting systems, is a major problem [13]. Clear regulations that take into account the special qualities of nanoscale biosensors and guarantee that they produce precise and repeatable findings in a variety of applications must be established by regulatory bodies.

Furthermore, resolving usability and accessibility concerns is necessary to achieve broad clinical use of these technologies. Effective use of these cutting-edge diagnostic techniques requires training for healthcare professionals, and efforts should be taken to guarantee that they are accessible and inexpensive for all populations, especially in settings with low resources [95]. Addressing such challenges will require cooperation between researchers, industry stakeholders, and regulatory agencies. Stakeholders can collaborate to establish an atmosphere that is supportive of innovation while maintaining patient safety by encouraging candid communication and exchanging best practices.

Nanoscale biosensors have a bright future ahead of them thanks to a number of upcoming improvements that should improve their clinical diagnostic capabilities. However, achieving their full potential will depend on resolving regulatory issues and guaranteeing a successful clinical deployment. As we proceed, overcoming obstacles and developing these game-changing innovations in healthcare will require teamwork.

Conclusion

A revolutionary development in diagnostic technology, nanoscale biosensors provide previously unheard-of sensitivity and specificity for identifying important biomarkers like miRNAs. These biosensors allow for early disease identification and individualised treatment plans thanks to nanomaterials like GO and gold nanoparticles. Diagnostics has been further transformed by the incorporation of miRNAs as biomarkers, which enable accurate, quick, and non-invasive health monitoring.

By enhancing data processing, diagnostic precision, and sample handling, emerging technologies like AI and microfluidics hold the potential to improve the performance of these biosensors. Additionally, by offering portable and reasonably priced solutions for environments with limited resources, paper-based biosensors have democratised access to healthcare. Nanoscale biosensors have enormous potential to improve global health outcomes and create a proactive approach to medical diagnostics by facilitating early identification, individualised treatment, and fair access to healthcare.

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