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**To cite this article:** Peyman HalvaeiKhanekahdani, Yuao Wu & Hang Thu Ta (23 Nov 2025): miRNAs in cardiovascular disease and an update on emerging trend in electrochemical biosensors for miRNA detection, Critical Reviews in Biotechnology, DOI: 10.1080/07388551.2025.2584689

**To link to this article:** https://doi.org/10.1080/07388551.2025.2584689

CRITICAL REVIEWS IN BIOTECHNOLOGY
https://doi.org/10.1080/07388551.2025.2584689

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REVIEW ARTICLE

# miRNAs in cardiovascular disease and an update on emerging trend in electrochemical biosensors for miRNA detection

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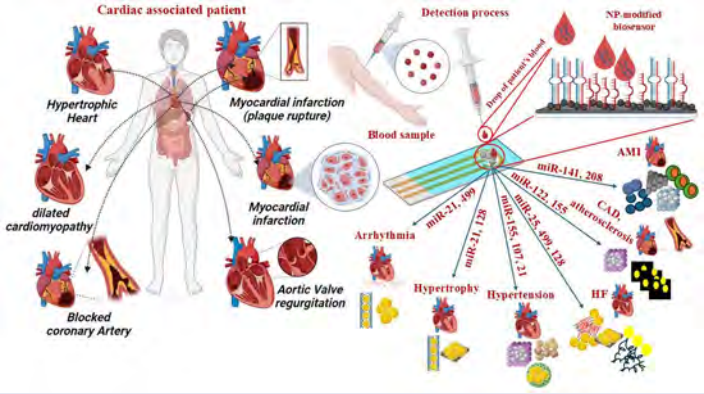
**ABSTRACT**

Cardiovascular disease (CVD) is a leading global cause of death and strains healthcare systems significantly. Early diagnosis is crucial and can be achieved through cardiac biomarker assessment, which enables timely treatment and reduces mortality rates. Traditional diagnostic methods require large hospital equipment for electrocardiography and laboratory analysis, leading to lengthy procedures. To address this, there is increasing interest in advanced biosensing technologies for rapid CVD marker screening. Advances in nanotechnology and bioelectronics have led to new biosensor platforms that offer rapid detection, accurate quantification, and continuous monitoring. This comprehensive review focuses on blood-based RNA cardiac biomarkers, which are widely used in clinical settings, and examines the development of electrochemical nanobiosensors for detecting RNA biomarkers. It provides a thorough evaluation of the benefits and drawbacks of these biosensing devices and offers insights into future research directions for electrochemical nanobiosensors in CVD, particularly those based on RNA markers.

**GRAPHICAL ABSTRACT**




**ARTICLE HISTORY**
Received 10 November 2024
Revised 19 June 2025
Accepted 21 July 2025

**KEYWORDS**
Eectrochemical; biosensor; miRNA; cardiovascular disease; diagnosis; nanotechnology

## Introduction

Cardiovascular disease is one of the leading health complications worldwide, resulting in high mortality [1,2]. The heart's pumping action, compromised mainly by blood vessel blockages, results in inadequate nutrients supplied to the organs, tissue damage, and sudden death [3–11]. According to the 2021 statistics, CVD has taken more than 20.5 million lives around the world [12]. Poor dietary intake, smoking, obesity, and physical inactivity have greatly caused the rising developments of this disease [12–14]. CVD poses a tremendous burden on healthcare systems due to high medical costs and productivity losses from conditions such as myocardial infarctions (MI), heart failure (HF), arrhythmias, etc. [14–16]. Myocardial infarctions, more commonly known as heart attacks, are a result of cessation of blood flow into the heart, often caused by coronary artery disease (CAD) [17]. Heart failure is characterized by the heart's inability to pump blood,

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whereas arrhythmias are due to disturbances in the electrical signals of the heart, leading to irregular heart rhythms with serious consequences [15,16,18] (Figure 1).

Several biomarkers, such as: troponin I/T [19], C-reactive protein [20], myoglobin, and interleukin-6 [21,22], have been important in diagnosing CVD. However, the recent identification of novel biomarkers such as micro-RNAs (miRNAs) and long noncoding RNAs (lncRNAs), including: miR-1 [16,23], miR-122 [23], miR-155 [16], miR-133a,b [16,23], miR-145 [24], miR-208a [25], and LIPCAR [26], which are often measured in the blood samples of patients at risk of CVD, holds immense importance in improving the outcomes of therapies [27]. These new biomarkers have different diagnostic advantages over traditional protein-based biomarkers including troponin I/T or C-reactive protein (CRP) that make them highly attractive for CVDs. Their remarkable stability in circulation owing to their encapsulation within exosomes or association with Argonaute proteins protects them from enzymatic degradation, ensuring reliable detection in various biological fluids including plasma, serum, and even saliva [28]. Moreover, miRNAs exhibit disease- and tissue-specific expression patterns that can reflect early molecular events in cardiovascular pathogenesis, often preceding detectable changes in traditional biomarkers. For instance, circulating levels of miR-499 have been shown to increase within 1 h after MI, ahead of conventional markers including CK-MB and cardiac troponin I in terms of detection window [29]. Moreover, differential expression of some miRNAs, such as the upregulated expressions of miR-133a in MI and downregulated expression in CAD, demonstrate their capability to act as specific molecular fingerprints for disease classification and personalized risk assessment [30]. These features make miRNAs extremely attractive targets for the development of CVD rapid, noninvasive and precise diagnostic assays. Building upon these molecular insights, the development of novel detection technologies has become imperative. Conventional detection methods such as mass spectrometry [31], enzyme-linked immunosorbent assay (ELISA) [32], and immunoassays [33,34] while clinically established, present some limitations, such as complexity, cost, and skilled manpower. Considering these challenges, there appears to be an unmet need for continuing the development of diagnostic tools that are simpler, faster, and more accurate. With this demand, pint of care (POC) biosensors emerged as a possible option. Ideal biosensors are: flexible, affordable, scalable, and highly sensitive to CVD biomarkers [35]. Among POC tools, electrochemical biosensors are prominent owing to their sensitivity, simplicity, and miniaturization capability. The detection of biomolecules on these platforms is through electrochemical signals; hence, these are quite good approaches for the rapid detection of cardiac biomarkers [36]. Recent incorporation of nanotechnology into biosensors has significantly enhanced their

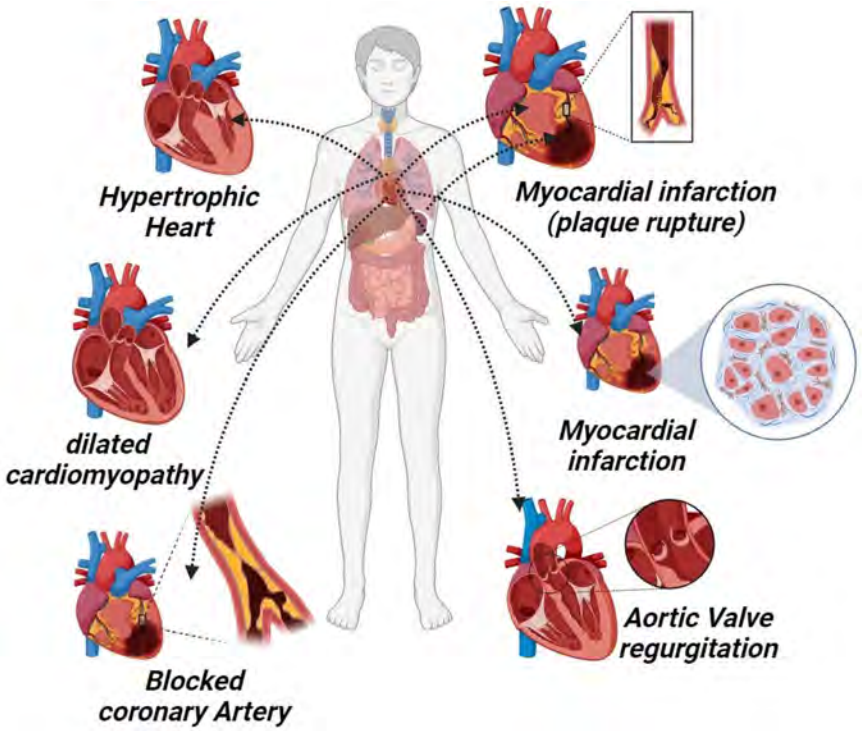


**Figure 1.** Commonly identified CVDs.

functionality by increasing their sensitivity, photostability, and biocompatibility. Therefore, adding nanomaterials improve key biosensor components, leading to more efficient and reliable detection systems [35–37] (Figure 2).

This review discusses recent developments in electrochemical biosensors from 2021 to 2024, with special focus on RNA-based cardiac biomarkers and the use of nanomaterials. Detailed tables and figures encapsulate essential characteristics, thereby serving as important insights for researchers looking to enhance biosensor designs for future cardiovascular diagnostics.

## The biological and diagnostic significance of non-coding RNAs in cardiovascular disease

Non-coding RNAs (ncRNAs) are RNA molecules originating from genomic transcription with functional roles, but lacking translation into proteins. In contrast, protein coding RNAs organize 3% of the human genome, while ncRNAs contain about 97% of the collective pool of mammalian RNAs [5,27,38]. ncRNAs have become essential components and play important roles in the homeostasis and regulation of many cellular systems. These activities include transcriptional regulation, RNA processing, and gene editing. MiRNA and long lncRNA are non-coding RNAs that regulate gene expression and modulate various cellular functions. Considerably, dysregulated expression of these ncRNAs is related to the pathophysiology of several diseases and disorders. The establishment of sequencing methods has revealed both the biomarker potential and therapeutic opportunities intrinsic in non-coding RNAs [12,38]. ncRNAs as biomarkers in CVD diagnosis provide several advantages over traditional protein biomarkers. These include high sensitivity and specificity as ncRNAs, like miRNAs and lncRNAs, serve as precise indicators of disease-related alterations [39]. Additionally, ncRNAs are recognized for their stability in various biological fluids, resisting degradation and providing robust biomarkers in processing and storage. Early detection is accelerated by the dysregulation of ncRNAs at the initial stages of disease development. Furthermore, ncRNAs often play regulatory roles in cellular processes and can be involved in modulating key pathways relevant to cardiovascular health [5]. Their detection in easily accessible body fluids, such as blood, makes ncRNAs noninvasive biomarkers for personalized diagnostic approaches [39,40]. Current research in the non-coding transcriptome continues to recognize new and specific ncRNA biomarkers, developing possibilities for diagnostic innovation in cardiovascular diseases. Figure 3 provides a schematic illustration of the classification of ncRNAs. Among these, regulatory ncRNAs, such as miRNAs, hold dominant significance as they serve as critical modulators of gene expression, employing influence over diverse cellular functions [38]. Given these characteristics of

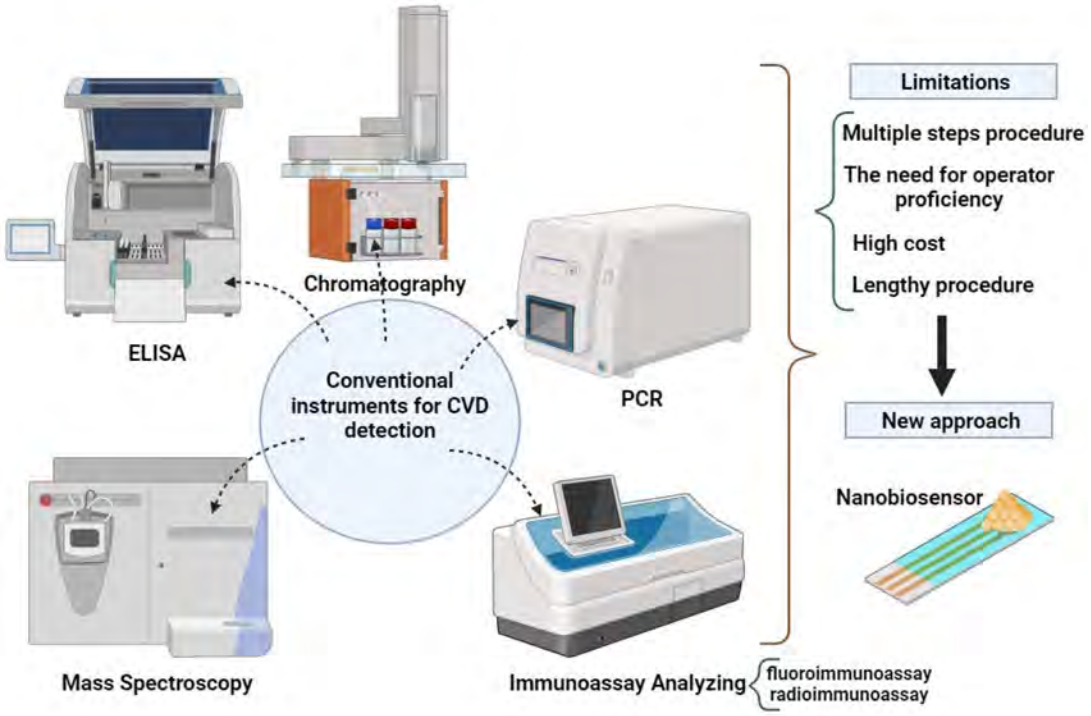


**Figure 2.** Conventional instruments for CVD detection and their limitations.

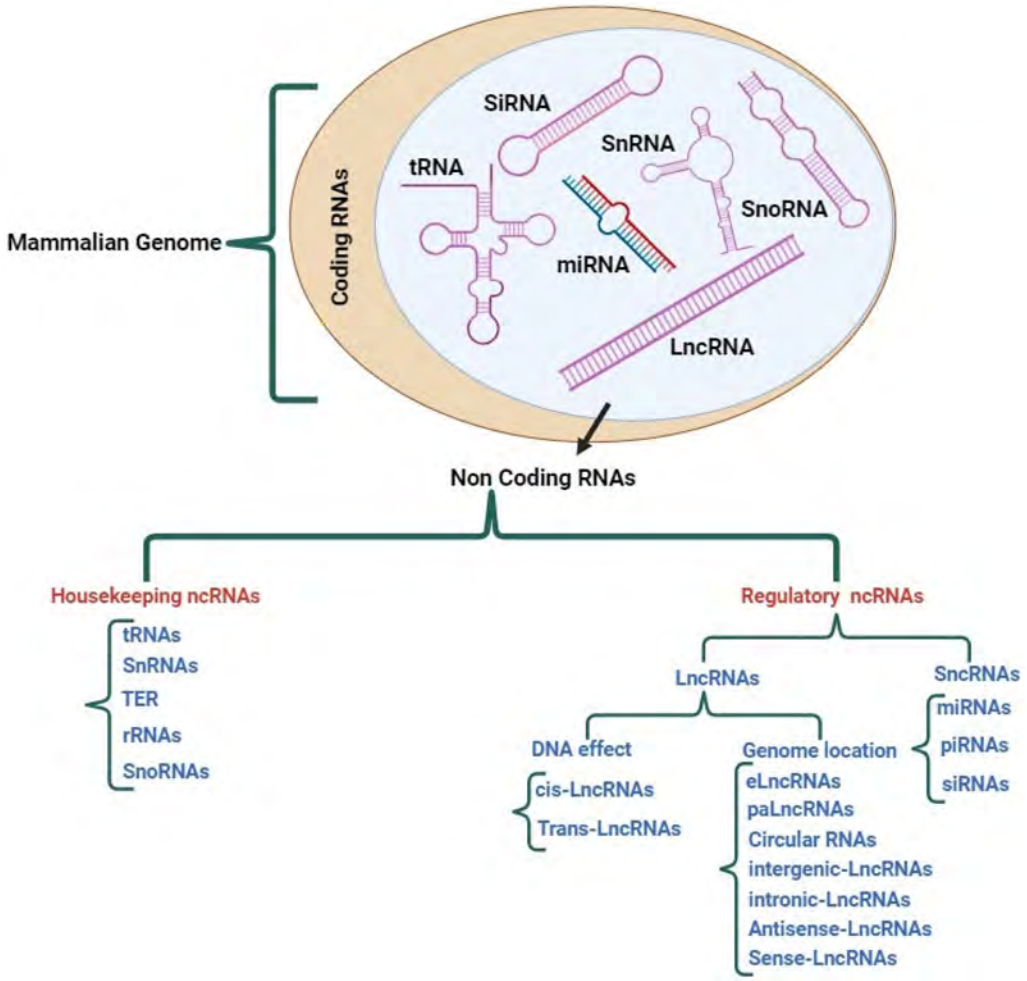


**Figure 3.** The classification of ncRNAs including miRNA, and lncRNAs.

ncRNAs, especially miRNAs, they have emerged as highly efficient and reliable biomarkers for CVDs. In the following sections, we will explore the biogenesis and functional mechanisms of miRNAs, highlighting their relevance in cardiovascular pathophysiology and diagnostic applications.

## Biogenesis and biological function of miRNAs

### *Biogenesis of miRNAs*

The biogenesis of miRNAs and their maturation have been illustrated in Figure 4. Canonical miRNA biogenesis begins from larger hairpin RNA molecules known as primary miRNAs (pri-miRNAs). The transcription of these kinds of miRNAs are performed by RNA Pol II from microRNA genes or clusters. Following transcription, the DiGeorge critical region 8 protein (DGCR8), Drosha, and further associated factors, which are part of a microprocessor complex, splits these primary miRNAs. After transferring the resultant pri-miRNA to the cytoplasm, enzyme Dicer trims it to a length of 21 to 22 nucleotides. In addition, there are non-canonical processes of miRNA biogenesis, some of them prevent the involvement of the microprocessor or Dicer complex. Processed into a duplex structure, each strand, designated the leader strand, is incorporated into the RNA-induced silencing complex (RISC). In this stage, the passenger strand (or *-strand) degrades rapidly. miRNAs coordinate control of gene expression at the level of transcription and translation [41,42].

### *Biological functions of miRNAs*

The miRNAs provided are short, non-coding RNA molecules typically composed of 21 to 23 nucleotide bases. These regulatory RNAs originate from longer precursor transcripts and play a crucial role in post-transcriptional gene regulation. Within eukaryotic cells, miRNAs exert their function primarily by binding to complementary sequences on target messenger RNAs (mRNAs), leading to mRNA degradation or translational inhibition [43]. Through this mechanism,

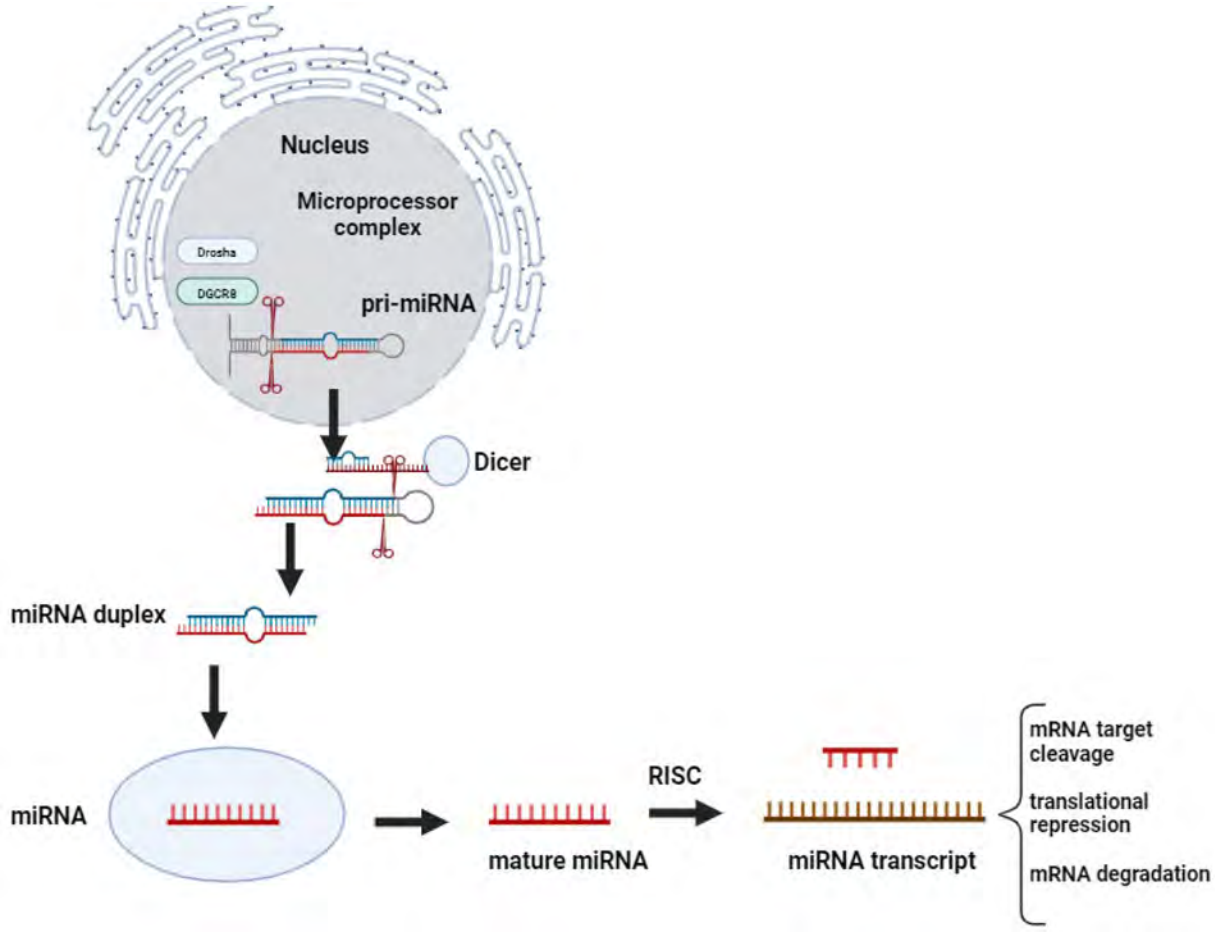


**Figure 4.** The biogenesis of miRNAs and their maturation.

miRNAs critically influence key aspects of different diseases especially cardiovascular pathogenesis, including: cardiac hypertrophy, fibrosis, angiogenesis, myocardial remodeling, and vascular inflammation [30].

Given their critical involvement in cardiovascular pathophysiology, the subsequent section will explore the specific roles of miRNAs in the development and progression of CVD.

## Role of miRNAs in cardiovascular disease

The detection of miRNAs and their effects on disease processes has resulted in significant progress, initiating important studies on their potential as biomarkers for CVD detection [44]. The discovery of miRNAs has experienced tremendous growth in recent decades. It is a well-known phenomenon in serum. This unique point places miRNAs as valuable candidates for biomarkers [45]. Their characteristics, such as easy abstraction from plasma or serum in patients and their compatibility with both present and emerging detection techniques, highlight their potential significance as biomarkers throughout various disease contexts [1,13]. Approximately 150 miRNAs may play critical roles within the cardiovascular system. Among these, a subset of 30 to 35 miRNAs has experienced extensive analysis and confirmed in *in vivo* experimental models [44]. Dysregulated expression of miRNAs has been identified in different vascular conditions, including: stroke, acute myocardial infarction (AMI), coronary artery disease (CAD), heart failure (HF), peripheral vascular disease, and other heart pathologies [46]. These miRNAs have been found to play significant roles in cellular processes closely linked to CVDs, such as: inflammation, cholesterol regulation, oxidative stress, and hypertension [47,48]. Figure 5 shows all discovered miRNAs in different cardiovascular diseases.

### *MiRNAs and different cardiovascular disease*

MiRNAs by changing their expression level could illustrate in different cardiovascular disease. Table 1 illustrate effective miRNAs in hypertension, heart failure, cardiac hypertrophy, acute myocardial infarction, and arrhythmias.

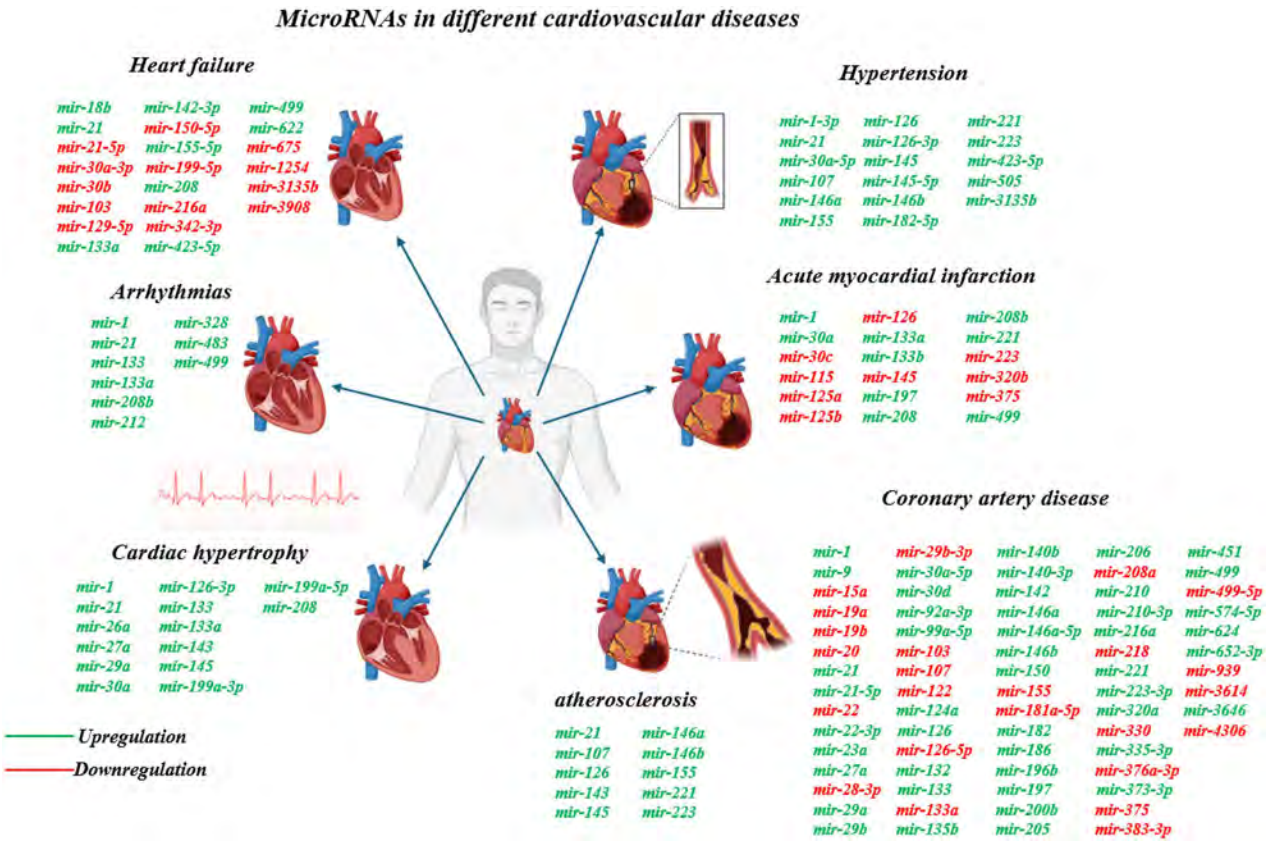


**Figure 5.** microRNAs in different cardiovascular diseases (CVDs).

### *MiRNAs in hypertension*

Hypertensive heart disease involves left atrium and ventricle hypertrophy due to prolonged high blood pressure, leading to heart failure [53]. It is associated with: endothelial dysfunction, reduced nitric oxide, and increased oxidative stress [71]. miRNAs like: miRNA-21, miRNA-126, miRNA-143, miRNA-145, miRNA-146a/b, miRNA-155, miRNA-221, miRNA-505, miRNA-3135b, miRNA-145-5p, miRNA-1-3p, miRNA-423-5p, 30a-5p, 182-5p, and 126-3p and miRNA-223, are upregulated in hypertension while miRNA-107 [38,49–54] downregulated, which emphasizes the diagnostic potential of miRNA profiling in developing detection of hypertensive conditions.

### *MiRNAs in acute myocardial infarction*

Myocardial infarction is expected to be one of the major causes of death worldwide due to a sudden lack of oxygen and nutrients to the myocardium, leading to cardiac tissue damage [26,31]. Currently, recent released data points out the crucial role of miRNAs in diagnosing acute myocardial infarction. Upregulated expression of circulating: miRNA-1, miRNA-133, miRNA-30a, miRNA-141, miRNA-197, miRNA-133a,b, miRNA-208b, miRNA-499, and miRNA-208, has been associated with AMI patients. In contrast, downregulated miRNAs, such as: miRNA-126, miRNA-125a,b, miRNA-221, miRNA-145, miRNA-320b, miRNA-30c,miRNA-115, miRNA-223, miRNA-1246, and miRNA-375, also hold the promise of being used as AMI diagnostic markers [38,51,52,55–57,59–61]. Indeed, plasma expression levels of miR-499 can be detected as early as an hour after AMI onset, earlier than traditional markers like CK-MB and cardiac troponin I. Besides, miRNA-133a is likely to be a better biomarker for prompt detection and monitoring of myocardial injury [56].

### *MiRNAs in heart failure*

Heart failure is one of the leading burdens to global healthcare, resulting in high morbidity and mortality. Heart failure is generally defined by structural or functional abnormalities of the heart, leading to an insufficient blood-pumping capacity. Current studies have illustrated the critical role of miRNAs in the pathophysiology of heart failure [62]. Investigation showed that: miR-499, miRNA-210, miRNA-208, miR-423-5p, miR-128, miR-21, miR-2-5p, miR-30a-3p, miR-155-5p, miR-216a, miR-3135b, miR-3908, miR-150-5p and miR-199a-5p, are overexpressed and: miRNA-103, miRNA-142-3p, miRNA-30b and miR-342-3p, are down-expressed in plasma [62–64]. Additionally, another study demonstrated that: miRNA-18b, miRNA-129-5p,

**Table 1.** miRNAs in hypertension and atherosclerosis, heart failure, cardiac hypertrophy, acute myocardial infarction, and arrhythmias.

| miRNAs | Heart disease | Expression | Ref |
|---|---|---|---|
| miR-1-3p | Hypertension | Upregulated | [49] |
| miR-21 | Hypertension | Upregulated | [38,50] |
| miR-30a-5p | Hypertension | Upregulated | [51] |
| miR-107 | Hypertension | Downregulated | [52] |
| miR-126 | Hypertension | Upregulated | [38] |
| miR-126-3p | Hypertension | Upregulated | [51] |
| miR-143 | Hypertension | Upregulated | [38] |
| miR-145 | Hypertension | Upregulated | [38] |
| miR-145-5p | Hypertension | Upregulated | [49,53] |
| miR-146a | Hypertension | Upregulated | [38] |
| miR-146b | Hypertension | Upregulated | [38] |
| miR-155 | Hypertension | Upregulated | [38] |
| miR-182-5p | Hypertension | Upregulated | [51] |
| miR-221 | Hypertension | Upregulated | [38] |
| miR-223 | Hypertension | Upregulated | [38] |
| miR-423-5p | Hypertension | Upregulated | [49] |
| miR-505 | Hypertension | Upregulated | [54] |
| miR-3135b | Hypertension | Upregulated | [52] |
| miR-1 | AMI | Upregulated | [51,55] |
| miR-30a | AMI | Upregulated | [56] |
| miR-30c | AMI | Downregulated | [56] |
| miR-115 | AMI | Downregulated | [57] |
| miR-125a | AMI | Downregulated | [38,56] |
| miR-125b | AMI | Downregulated | [38,56] |
| miR-126 | AMI | Downregulated | [38] |
| miR-133a | AMI | Upregulated | [38] |
| miR-133b | AMI | Upregulated | [38,55,56] |
| miR-141 | AMI | Upregulated | [58] |
| miR-145 | AMI | Downregulated | [38] |
| miR-197 | AMI | Upregulated | [59] |
| miR-208 | AMI | Upregulated | [38,60] |
| miR-208b | AMI | Upregulated | [52] |
| miR-221 | AMI | Upregulated | [59] |
| miR-223 | AMI | Downregulated | [38] |
| miR-320b | AMI | Downregulated | [38] |
| miR-375 | AMI | Downregulated | [38] |
| miR-499 | AMI | Upregulated | [38,60] |
| miR-1246 | AMI | Downregulated | [61] |
| miR-18b | Heart failure | Upregulated | [62] |
| miR-21 | Heart failure | Upregulated | [62,63] |
| miR-21-5p | Heart failure | Upregulated | [62,63] |
| miR-30a-3p | Heart failure | Upregulated | [62,63] |
| miR-30b | Heart failure | Downregulated | [62,63] |
| miR-103 | Heart failure | Downregulated | [62,63] |
| miR-128 | Heart failure | Upregulated | [64] |
| miR-129-5p | Heart failure | Upregulated | [64] |
| miR-133a | Heart failure or left ventricular (LV) remodeling after MI | Upregulated | [3] |
| miR-142-3p | Heart failure | Upregulated | [62,63] |
| miR-150-5p | Heart failure | Upregulated | [62,63] |
| miR-155-5p | Heart failure | Upregulated | [62,63] |
| miR-199-5p | Heart failure | Upregulated | [62,63] |
| miR-208 | Heart failure | Upregulated | [62] |
| miR-216a | Heart failure | Upregulated | [62,63] |
| miR-342-3p | Heart failure | Upregulated | [62,63] |
| miR-423-5p | Heart failure or left ventricular (LV) remodeling after MI | Upregulated | [3,62,63] |
| miR-499 | Heart failure | Upregulated | [62,63] |
| miR-622 | Heart failure | Upregulated | [64] |
| miR-675 | Heart failure | Upregulated | [64] |
| miR-1254 | Heart failure | Upregulated | [64] |
| miR-3135b | Heart failure | Upregulated | [62,63] |
| miR-3908 | Heart failure | Upregulated | [62,63] |
| miR-1 | Arrhythmias | Upregulated | [62,65,66] |
| miR-21 | Arrhythmias | Upregulated | [65] |
| miR-133 | Arrhythmias | Upregulated | [66] |
| miR-133a | Arrhythmias | Upregulated | [62,65,66] |
| miR-208b | Arrhythmia | Upregulated | [62,65,66] |
| miR-212 | Arrhythmia | Upregulated | [62,65,66] |
| miR-328 | Arrhythmia | Upregulated | [62,65,66] |

(*Continued*)

**Table 1.** Continued.

| miRNAs | Heart disease | Expression | Ref |
|---|---|---|---|
| miR-483 | Arrhythmias | Upregulated | [66] |
| miR-499 | Arrhythmias | Upregulated | [66] |
| miR-1 | Cardiac hypertrophy | Upregulated | [67] |
| miR-21 | Cardiac hypertrophy | Upregulated | [45,67–69] |
| miR-26a | Cardiac hypertrophy | Upregulated | [45,67–69] |
| miR-27a | Cardiac hypertrophy | Upregulated | [45,67–69] |
| miR-29a | Cardiac hypertrophy | Upregulated | [45,67–69] |
| miR-30a | Cardiac hypertrophy | Upregulated | [45,67–69] |
| miR-126-3p | Cardiac hypertrophy | Upregulated | [69] |
| miR-128 | Cardiac hypertrophy | Upregulated | [69] |
| miR-133 | Cardiac hypertrophy | Upregulated | [45] |
| miR-133a | Cardiac hypertrophy | Upregulated | [69] |
| miR-143 | Cardiac hypertrophy | Upregulated | [69] |
| miR-145 | Cardiac hypertrophy | Upregulated | [69] |
| miR-199a-3p | Cardiac hypertrophy | Upregulated | [69] |
| miR-199a-5p | Cardiac hypertrophy | Upregulated | [68,69] |
| miR-208 | Cardiac hypertrophy | Upregulated | [69] |
| miR-541 | Cardiac hypertrophy | Downregulated | [70] |

miRNA-1254, miRNA-675, and miRNA-622 expressions were increased in the patients with heart failure. This result sustains that miR-423-5p would be a good biomarker in diagnosing heart failure cases [3,64].

### *MiRNAs in arrhythmias*

Cardiac arrhythmias are changes of normal heart rate or rhythm, which provide substantial morbidity and mortality. Ventricular arrhythmias form a main source for cardiac death, remarkably unexpected cardiac death in the setting of heart failure and myocardial infarction [72]. To explore the impact of miRNAs in arrhythmias, studies revealed that expression of: miRNA-1, miRNA-21, miRNA-133, miRNA-133a, miRNA-208b, miRNA-212, miRNA-328, miRNA-483, and miRNA-499, miR-133b upregulates in arrhythmias patient while expression of: miRNA-23a, miRNA −26a, miRNA −30d, miRNA −150, and miRNA −590 down regulates [62,65,66].

### *MiRNAs in cardiac hypertrophy*

Cardiac hypertrophy is a critical adaptive response to numerous pathophysiological stimuli. Originally conceived to sustain contractile function and normalize wall stress, chronic hypertrophy can culminate in heart failure and result in altered gene expression. Emerging evidence suggests that miRNAs are vital for controlling cardiac hypertrophy, development, and function [73]. Most studies have indicated that: miRNA-21, miRNA-27a, miRNA-30a, miRNA-29a, miRNA-128, miRNA-133, miRNA-145, miRNA-133a, miRNA-143, miRNA-199a-3p, miRNA-199a-5p, miRNA-221, miRNA-26a, miRNA-155, and miRNA-126-3p, are often upregulated in hypertrophic cardiomyopathy. Especially, miRNA-29a and miRNA-1 present stable strong results, which reveals their great potential as promising biomarkers for the diagnosis of this disease [45,67–69]. Also new research revealed that miRNA-541 reduces in this disease which could be an important biomarker in diagnosis of this abnormality [70].

### *MiRNAs in atherosclerosis and coronary artery disease (CAD)*

Atherosclerosis results from lipid buildup and inflammation, leading to plaques that narrow arteries anywhere in the body [40]. CAD is a condition wherein narrowing or blockage (atherosclerosis) occurs in the coronary arteries that could eventually reduce blood flow to the heart. This may give rise to symptoms, such as: chest pains, angina, shortness of breath, and may further increase the risk of heart attacks, MI, and other serious cardiovascular events. Recent studies have underscored the important role miRNAs play in diagnosis of CAD, and atherosclerosis. Upregulated and downregulated miRNAs in atherosclerosis and CAD are summarized in Table 2. Results revealed that, miRNA profiles offer valuable insights for early diagnosis, disease progression monitoring, and therapeutic intervention assessment in CAD.

## *Identification of disease-specific miRNAs across cardiovascular diseaseses*

Tables 1 and 2 revealed that numerous miRNAs exhibit overlapping expression patterns, either upregulation or downregulation, across multiple cardiovascular conditions. This commonality reduces their specificity and limits their effectiveness as differential diagnostic biomarkers. Therefore, in this section, we systematically analyze the expression profiles of shared and unique miRNAs across various CVDs with the aim of identifying miRNAs that display disease-specific regulation

**Table 2.** miRNAs in coronary artery disease and atherosclerosis.

| miRNAs | Heart disease | Expression | Ref |
|---|---|---|---|
| miR-1 | CAD | Upregulated | [38] |
| miR-9 | CAD | Upregulated | [38] |
| miR-15a | CAD | Downregulated | [38] |
| miR-17-5p | CAD | Downregulated | [38] |
| miR-19a | CAD | Downregulated | [16] |
| miR-19b | CAD | Downregulated | [74] |
| miR-20 | CAD | Downregulated | [75] |
| miR-21 | CAD, and atherosclerosis | Upregulated | [76,77] |
| miR-21-5p | CAD | Upregulated | [78] |
| miR-22 | CAD | Downregulated | [74] |
| miR-22-3p | CAD | Upregulated | [79] |
| miR-23a | CAD | Upregulated | [76] |
| miR-27a | CAD | Upregulated | [38] |
| miR-28-3p | CAD | Downregulated | [38] |
| miR-29a | CAD | Upregulated | [78] |
| miR-29b | CAD | Upregulated | [74] |
| miR-29b-3p | CAD | Downregulated | [80] |
| miR-30a-5p | CAD | Upregulated | [38] |
| miR-30d | CAD | Upregulated | [38] |
| miR-92a-3p | CAD | Upregulated | [76] |
| miR-99a-5p | CAD | Upregulated | [22] |
| miR-103 | CAD | Downregulated | [38] |
| miR-107 | CAD | Downregulated | [76] |
| miR-107 | atherosclerosis | Upregulated | [76] |
| miR-122 | CAD | Downregulated | [80] |
| miR-124a | CAD | Upregulated | [38] |
| miR-126 | CAD, and atherosclerosis | Upregulated | [38,76,77] |
| miR-126-5p | CAD | Downregulated | [77] |
| miR-132 | CAD | Upregulated | [81] |
| miR-133 | CAD | Upregulated | [38] |
| miR-133a | CAD | Downregulated | [77] |
| miR-135b | CAD | Upregulated | [77] |
| miR-140b | CAD | Upregulated | [77] |
| miR-140-3p | CAD | Upregulated | [38,81] |
| miR-142 | CAD | Upregulated | [22] |
| miR-143 | atherosclerosis | Upregulated | [38] |
| miR-145 | atherosclerosis | Upregulated | [38] |
| miR-146a | CAD, and atherosclerosis | Upregulated | [38,74,76,77] |
| miR-146a-5p | CAD | Upregulated | [78] |
| miR-146b | CAD, and atherosclerosis | Upregulated | [22,38] |
| miR-150 | CAD | Upregulated | [38] |
| miR-155 | CAD | Downregulated | [77] |
| miR-155 | atherosclerosis | Upregulated | [38] |
| miR-181a-5p | CAD | Downregulated | [76] |
| miR-182 | CAD | Upregulated | [77] |
| miR-186 | CAD | Upregulated | [76] |
| miR-196b | CAD | Upregulated | [82] |
| miR-197 | CAD | Upregulated | [22] |
| miR-200b | CAD | Upregulated | [77] |
| miR-203 | CAD | Upregulated | [83] |
| miR-205 | CAD | Upregulated | [77] |
| miR-206 | CAD | Upregulated | [77] |
| miR-208a | CAD | Downregulated | [77] |
| miR-210 | CAD | Upregulated | [38,81] |
| miR-210-3p | CAD | Upregulated | [38,80] |
| miR-216a | CAD | Upregulated | [76] |
| miR-218 | CAD | Downregulated | [76] |
| miR-221 | CAD, and atherosclerosis | Upregulated | [77] |
| miR-223 | atherosclerosis | Upregulated | [38] |
| miR-223-3p | CAD | Upregulated | [13] |
| miR-320a | CAD | Upregulated | [38] |
| miR-330 | CAD | Downregulated | [77] |
| miR-335-3p | CAD | Upregulated | [81] |
| miR-376a-3p | CAD | Downregulated | [76] |
| miR-373-3p | CAD | Upregulated | [78] |
| miR-375 | CAD | Downregulated | [38] |
| miR-383-3p | CAD | Downregulated | [76] |
| miR-451 | CAD | Upregulated | [76,80] |
| miR-499 | CAD | Upregulated | [76,80] |
| miR-499-5p | CAD | Downregulated | [84] |
| miR-574-5p | CAD | Upregulated | [77] |
| miR-624 | CAD | Upregulated | [80] |
| miR-652-3p | CAD | Upregulated | [81] |

(*Continued*)

**Table 2.** Continued.

| miRNAs | Heart disease | Expression | Ref |
|---|---|---|---|
| miR-939 | CAD | Downregulated | [76] |
| miR-3614 | CAD | Downregulated | [74,76] |
| miR-3646 | CAD | Upregulated | [80] |
| miR-4306 | CAD | Downregulated | [76] |

patterns. By eliminating those miRNAs that are commonly dysregulated in multiple conditions, we will highlight the subset of miRNAs that have the potential to serve as specific and reliable biomarkers for the distinct identification of each CVD which will enhance the diagnostic utility of miRNAs in CVDs.

### *Specific miRNAs in hypertension*

Comparative exploration of common miRNAs in hypertension and CAD exposes that: miRNA-21, miR-126, miR-146a/b, and miR-221 exhibit similar expression patterns, with upregulation observed in both conditions. This consistent upregulation suggests that these miRNAs may require specificity and hence may not be appropriate as differential biomarkers for recognizing between hypertension and CAD. In comparison, miR-107 and miR-155 show diverse expression profiles, being upregulated in hypertension and downregulated in CAD. These differential expression patterns evoke that miR-107 and miR-155 have potential functionality as biomarkers for the detection and differentiation of these cardiovascular diseases.

In comparing hypertension and AMI, results point that miR-221, which is upregulated in both conditions, requires specificity and is therefore not a suitable biomarker for differential diagnosis. On the opposite, miR-145, miR-223, and miR-126 are upregulated in hypertension and downregulated in AMI, making them appropriate biomarkers for recognizing between these diseases due to their differential expression profiles.

miR-21 is the sole common biomarker in hypertension and arrhythmias that is upregulated in both conditions. Due to its steady expression pattern across these illnesses, miR-21 lacks the required specificity for differential diagnosis and, therefore, may not serve as an appropriate biomarker for marking between hypertension and arrhythmias. This biomarker, in conjunction with miR-126a-3p, miR-143, and miR-145, is upregulated in both hypertension and cardiac hypertrophy. Hypertension and heart failure demonstrate limited connection, with miR-21 being the only miRNA regularly upregulated in both conditions. Due to its uniform expression profile across: hypertension, CAD, AMI, cardiac hypertrophy, and heart failure, miR-21 lacks the required specificity needed to serve as a reliable biomarker for these discrete cardiovascular diseases.

Therefore, it can be concluded that the majority of miRNAs identified in hypertension, such as: miR-21, miR-145, miR-126, miR-146a/b, miR-221, miR-143, miR-107, miR-145, miR-223, miR-126, and miR-155, also exhibit similar expression profiles in other cardiovascular diseases, thereby limiting their diagnostic specificity for the detection of hypertension. Accordingly, they may not be appropriate for use as specific biomarkers in these patients. The remaining biomarkers listed in Table 1 show potential for application as specific biomarkers for this cardiovascular disease.

### *Specific miRNAs in coronary artery disease*

In a similar analysis for CAD biomarkers, results revealed that in the comparison of CAD and AMI, these disorders share the most common miRNAs amid heart-related conditions. miR-1, miR-133b, miR-197, miR-221, and miR-499 are normally upregulated in both CAD and AMI while miR-375 is downregulated. Due to the similar expression profiles of these miRNAs in both conditions, they may not be suitable as distinction biomarkers for the detection of these pathology conditions. In contrast, miR-133a being downregulated in CAD and upregulated in AMI, proposes its potential as a particular biomarker for distinguishing between these two conditions.

To spot common miRNAs in CAD and arrhythmias, we found that miR-1, miR-21, miR-499 and miR-133 are upregulated in both conditions, inferring they need specificity as biomarkers. Also, miR-133a as a common biomarker in AMI, CAD, and arrhythmias, demonstrate different expression patterns, downregulated in CAD while upregulated in arrhythmias, and AMI, proposes its potential as a specific biomarker for differentiating in these diseases.

miR-1, miR-21, miR-27a, miR-29a, and miR-133 are commonly upregulated in both CAD and cardiac hypertrophy patients. In contrast, miR-133a presents differential expression profiles, being downregulated in CAD but upregulated in cardiac hypertrophy patients. Increasing of: miR-21, miR-21-5p, miR-103, miR-216a, and miR-499 is common in CAD and heart failure patients while miR-133a shows a different pattern which decreases in CAD patients and increases in heart failure patients. These biomarkers, except miR-133a, due to their presence in both diseases with the same

expressions are not specific for detection of heart related diseases.

Therefore, it can be concluded that most of miRNAs, such as: miR-1, miR-21, miR-133b, miR-197, miR-221, miR-375, miR-27a, miR-29a, miR-21-5p, miR-103, miR-216a, miR-30a-5p, miR-107, miR-146a, miR-146b, miR-145, miR-155, and miR-499, are common biomarkers in CAD and other heart-related diseases, suggesting they may not be suitable for separating between different heart conditions. In contrast, the remaining biomarkers listed in Table 2, which are not common within various heart-related diseases, could serve as proper biomarkers for detecting CAD specifically.

### *Specific miRNAs in acute myocardial infarction*

To further identify disease-specific biomarkers, we extended our analysis to AMI, comparing its miRNA profile with those of related cardiovascular conditions. Analyzing results of common miRNAs in AMI and arrhythmia patients demonstrate that: miR-1, miR-133a, miR-208b, and miR-499 are upregulated in both diseases, implying they may not be suitable for differentiating between these conditions. Similarly, miR-1, miR-30a, miR-133a, and miR-208 are raised in both AMI and cardiac hypertrophy patients, advance proposing a need of specificity for these heart abnormalities. To differentiate, miR-145 exhibits a differential expression profile, being downregulated in AMI patients but upregulated in cardiac hypertrophy patients. Additionally, miR-133a, miR-208, and miR-499 are upregulated in both AMI and heart failure patients. These discoveries propose that whereas a few miRNAs need specificity, others like miR-145 may have potential as differential biomarkers. Subsequently: miR-1, miR-133a, miR-208, miR-208b, miR-499, miR-30a, miR-145, miR-208, miR-126, miR-223, miR-197, miR-375, and miR-221 are common biomarkers which display in both AMI and other heart-related illnesses, thus they may not be appropriate for the particular detection of AMI. In opposition, the remaining biomarkers listed in Table 1 display potential for the specific detection of AMI patients.

### *Specific miRNAs in arrhythmias*

To identify common miRNA biomarkers in arrhythmias and cardiac hypertrophy, results showed that: miR-1, miR-21, miR-133, and miR-133a are upregulated in both conditions, indicating they may not be suitable for detecting these abnormalities. Moreover, the upregulation of miR-21, miR-133a, and miR-499 was observed as common biomarkers in both arrhythmia and heart failure. Consequently, miR-212, miR-328, and miR-483 are only expressed in these patients and could be potential biomarkers the specific detection of arrhythmias patients.

### *Specific miRNAs in hypertrophy*

Cardiac hypertrophy reveals common miRNA biomarkers with heart failure, including miR-21, miR-133a, and miR-208, which are upregulated in both conditions. this means that they are not precise markers to identify cardiac hypertrophy. Results demonstrate that: miR-1, miR-21, miR-27a, miR-29a, miR-30a, miR-133, miR-133a, miR-145, miR-208 are common in cardiac hyperthrophy and other heart related abnormalities. However, the remaining biomarkers shown in Table 1 show a relevant specified detection of cardiac hypertrophy patients.

Overall, this comparative analysis demonstrated the critical importance of identifying disease-specific miRNA biomarkers for the accurate diagnosis of CVD. While several miRNAs, such as miR-21, miR-155, and miR-499 are commonly dysregulated across multiple CVDs, their overlapping expression patterns limit their utility in distinguishing between these conditions. Conversely, miRNAs, such as miR-133a, miR-155, and miR-145 exhibit differential regulation in some CVDs and may serve as promising candidates for disease-specific diagnostics. These insights affirm that miRNAs, although highly valuable for early detection and monitoring, must be carefully selected based on unique expression profiles and, ideally, incorporated into well-defined biomarker panels to enhance diagnostic specificity.

Importantly, the outcomes of this analysis strongly highlight the role of miRNA profiling in selecting the most appropriate and specific biomarkers for each CVD, which is essential for the rational design of precise and high-performance biosensors. Such biosensors, tailored to detect uniquely expressed miRNAs, have the potential to significantly improve diagnostic accuracy by enabling both sensitive detection and clear differentiation between CVD subtypes. This strategic approach to biomarker selection serves as a foundational step for the next section, which will focus on the development of electrochemical biosensors utilizing these refined biomarker profiles.

## NP-based electrochemical biosensors for CVD-associated miRNA detection

Building on the established relevance of biomarker selection in disease diagnostics, this section begins

with an overview of biosensors and their various types, laying the groundwork for understanding their role in disease detection. It then delves into electrochemical biosensors, highlighting their widespread application in medical diagnostics. The discussion will progress toward electrochemical nanobiosensors, which offer enhanced sensitivity and specificity due to their nanoscale features. Finally, the section will explore the working mechanisms of nanobiosensors in detecting various diseases, with particular emphasis on their integration for miRNA-based diagnostics.

## Biosensors in disease detection

Biosensors, sophisticated analytical devices, combine biological sensors with physicochemical transducers. Its main purpose is to produce a digital power signal that is directly proportional to the magnitude of a single filter or set of separate filters. In the biosensing process, researchers identify changes in physical parameters and translate them into changes in electrical properties, such as: changes in time, voltage, or temperature. Biosensors, also known as biospecific electrodes, are specialized devices designed for the: continuous detection, measurement and monitoring of gases, ions and biological compounds in complex procedures. Biosensor systems are structured around three fundamental components: the biomolecule with its selective recognition system, a converter, and the electronic section. These elements work together to convert the physicochemical signals generated by the interaction of the biomolecule with the target agent into electrical signals. Biological agents used in sensors are usually: microorganisms, tissue fragments enzymes, antibodies, organelles, nucleic acids, and chemical receptors, often inserted in biological membranes (Figure 6) [85].

Biosensors have a wide range of applications, characterized by different types, which are classified based on the biological elements used and the applied transduction mechanisms. Different types of biosensors are visually shown in Figure 7. Among these, the most suitable for disease detection are amperometric and potentiometric electrochemical biosensors due to their high sensitivity, rapid response, and compatibility with miniaturization for point-of-care applications [86]. The next part will explore deeper into the principles, advantages, and applications of electrochemical biosensors in disease diagnostics.

## Electrochemical biosensors in disease detection

Electrochemical biosensors, which play a key role in detecting and analyzing biological targets, provide exceptional sensitivity and specificity due to their direct transduction mechanisms that convert biochemical events into measurable electrical signals [87]. Such biosensors like other biosensors' types composed of three major parts, including: a working electrode to convert a signal, a biorecognition element, and a signal transducer or detector [88]. The electrodes are normally made of conductive materials, such as: gold, platinum, carbon, or indium tin oxide (ITO), which can provide a desirable conductivity and facile modification surface for biosensor application [89–91]. Electrochemical detection methodologies broadly include: amperometric, potentiometric, conductometric, and impedimetric approaches, each characterized by specific modes of detecting biochemical interactions. In amperometric biosensors, the interaction of

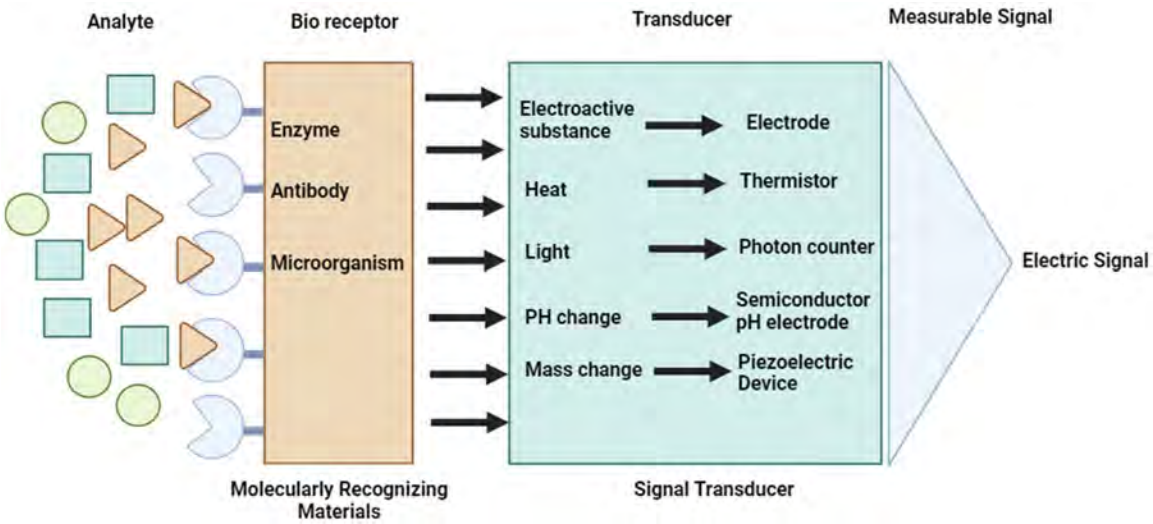


**Figure 6.** The biosensor and its components.

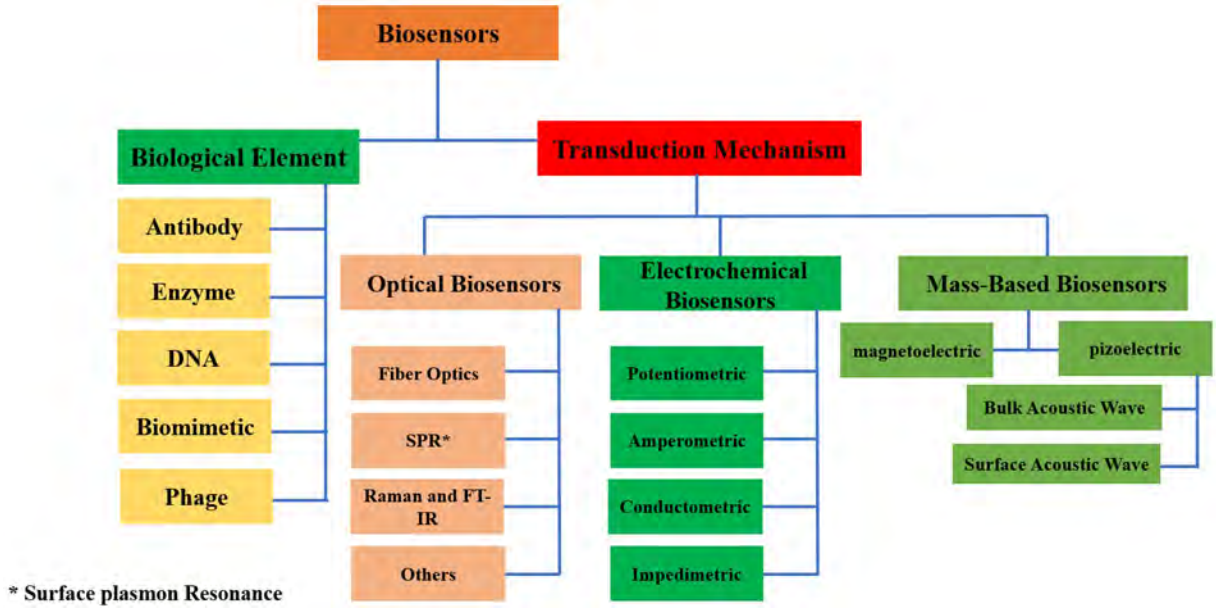


**Figure 7.** Different types of biosensors based on biological element, and transduction mechanism.

an analyte produces a current that is proportional to its concentration. Potentiometric biosensors are sensitive to changes of electric potential, due to biochemical reactions. Conductometric biosensors measure variations in electrical conductivity arising from biochemical interactions, while impedimetric biosensors sense changes in electrical impedance following analyte interaction with the immobilized bioreceptor, which provides label-free and highly sensitive detection [92]. The suitability of electrochemical biosensors for disease biomarker detection is particularly noteworthy due to their capacity for: miniaturization, robustness, cost-effectiveness, rapid analysis, and real-time monitoring potential [93]. There has been a wide range of diseases to which such biosensors have shown application. In oncology, they have been applied for the sensitive and early detection of tumor markers, such as: carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), prostate-specific antigen (PSA), cancer antigen 125 (CA-125), and several cancer-related microRNAs, aiding in early diagnosis, treatment monitoring, and prognosis assessments [94–96]. In infectious diseases, they are used to detect specific viral or bacterial nucleic acids and antigens, including: markers for HIV, hepatitis B and C, Zika virus, and COVID-19 [97–101]. In metabolic disorders, such as: diabetes, electrochemical glucose biosensors have shown outstanding results that provided an opportunity for them to be the gold standard for blood glucose monitoring [102]. Additionally, these biosensors are gaining attention in neurodegenerative diseases like Alzheimer's and Parkinson's, where biosensors help detect biomarkers like beta-amyloid and tau proteins [103]. Also, in cardiovascular diseases, electrochemical biosensors by detection of important biomarkers, such as: troponins, myoglobin, creatine kinase-MB (CK-MB), CRP, and miRNAs in biological fluids, providing early diagnosis, risk assessment, and monitoring of therapeutic efficacy [104,105]. These biosensor's high sensitivity, specificity, and their potential for multiplexed analysis make them useful tools for disease diagnostics in different medical fields. Recent advancements in electrochemical biosensing include: integration with microfluidic platforms which significantly enhance the portability, sample processing speed, and overall user-friendliness of these devices [106,107]. Moreover, advanced features, such as: multiplexed detection, wireless signal transmission and smartphone-based readers integration enable those biosensors to be suitable for POC diagnostics [107,108]. Besides, advanced materials and novel fabrication technologies, such as screen-printing, ink-jet printing, and 3D printing, are widely integrated into electrochemical biosensors for accurate electrode patterning with mass production and reproducibility, thus facilitating wider clinic application [109]. Notably, the introduction of new materials, specifically NPs, has substantially enhanced the performance of these biosensors. NPs enhance signal transduction, increase surface area for biomolecule immobilization, and provide greater sensitivity, lower detection limits, and faster response times [110]. The application of such nanomaterials helps to overcome several limitations for biosensing development and also meets the need for the development of more accurate and sensitive tools for

the diagnosis of diseases. The next section will explore deeper into the critical role of NPs in improving electrochemical biosensor performance; in addition, the working mechanisms of these electrochemical biosensors will also be discussed.

## Role of nanomaterials in electrochemical biosensors

Nanomaterials are preferred as transducer materials in several biosensing strategies because of their prominent characteristics, such as: elevated surface area, quantum confinement, specific functionality, biocompatibility, stability, outstanding electrical and optical features, efficient charge transfer, and sensitivity [111]. A range of nanomaterials, including: carbon nanomaterials (such as graphene-based materials, carbon dots, graphitic carbon, and carbon nanotubes) [112], noble metal nanoparticles (like AuNPs and AgNPs) [113], metal oxide nanoparticles [114], and metal organic frameworks (MOFs) [115], have been utilized in the construction of electrochemical biosensors. Recently, the attractiveness of biosensors containing nanomaterials has increased significantly. This is largely due to the biological properties and distinct recognition properties of nanomaterials, which facilitate the detection of various analytes, including nucleic acids (DNA or RNA), aptamers, and proteins, in clinical samples. In addition, advances in nanotechnology have included the ability to create efficient detection systems for POC electrochemical biosensors. This innovation could make it easier to detect different diseases, such as cancer, and cardiovascular disease [37]. In the field of biosensors for monitoring CVD biomarkers, nanomaterials have found a wide application, especially in the creation of electrochemical and optical aptasensors [16]. In particular, materials, such as: AuNPs [116], graphene oxide (GO), reduced GO (rGO) [117], metal-organic frameworks (MOFs) [118], $MoS_2$ nanosheets [117], and silica nanoparticles [119] were used to build electrochemical sensing platforms for the detection of cardiovascular diseases. Several electrochemical measuring techniques, including: square wave voltammetry (SWV), differential pulse voltammetry (DPV), electrochemical impedance spectroscopy (EIS), and cyclic voltammetry (CV), can be used by these sensor systems alone or in combination [36]. Researchers have looked into electrochemical biosensors a lot as a dependable way to find cardiac biomarkers in clinical settings. A number of novel electrochemical biosensors have been created recently to quickly identify cardiac biomarkers [49]. In the next part, the working mechanisms of these electrochemical nanobiosensors will be discussed in detail, highlighting how their design and operation are tailored for sensitive and specific disease detection.

## Working mechanism of NP-based electrochemical biosensors in miRNA detection

An electrochemical biosensor for miRNA detection, using a DNA probe, functions by preparing the functionalized electrode to allow DNA probe attachment. Nanoparticles due to their high surface area and conductivity are immobilized on the electrode surface to improve the sensor's signal. Additional single-stranded DNA probes for the target RNA are then immobilized on the electrode. The target RNA from the sample hybridizes to the DNA probe upon triggering, forming an RNA-DNA duplex that changes the electrical properties of the electrode. Methods that measure changes in impedance, current or potential are used to detect this change, such as CV, DPV, and EIS. A calibration curve determined by interpretation of these signals is often used to accurately quantify RNA concentration. By using multiple probe sequences, this method improves sensitivity and increases specificity. It also optimizes sensor density and surface chemistry [36] (Figure 8). Electrochemical biosensors can be significantly enhanced by incorporating various types of NPs, each offering unique advantages in terms of sensitivity, selectivity, and signal amplification. The following section explores in detail the integration of these NPs into electrochemical biosensors specifically designed for the detection of CVD-associated miRNAs.

## NP-based electrochemical biosensors for CVD diagnosis via miRNA biomarkers

Nanomaterials have been extensively used in electrochemical biosensors, leading to impressive improvement in sensitivity, selectivity, and convenience for detecting low-abundance biomarkers including circulating miRNAs. These include metal NPs (such as gold, silver, and copper) which are commonly employed due to their remarkable electrical conductivity, high surface-to-volume ratio, and outstanding chemical stability, features that greatly improve signal transduction and enable effective probe immobilization [36,85,120]. These properties make metal NPs especially valuable for achieving ultra-low limits of detection and broad linear ranges [21,121]. Following this, metal oxide NPs (such as $CeO_2$, CuO) have also gained attention for their intrinsic redox activity and the ability to introduce additional functional groups, which can improve both signal output and surface compatibility with

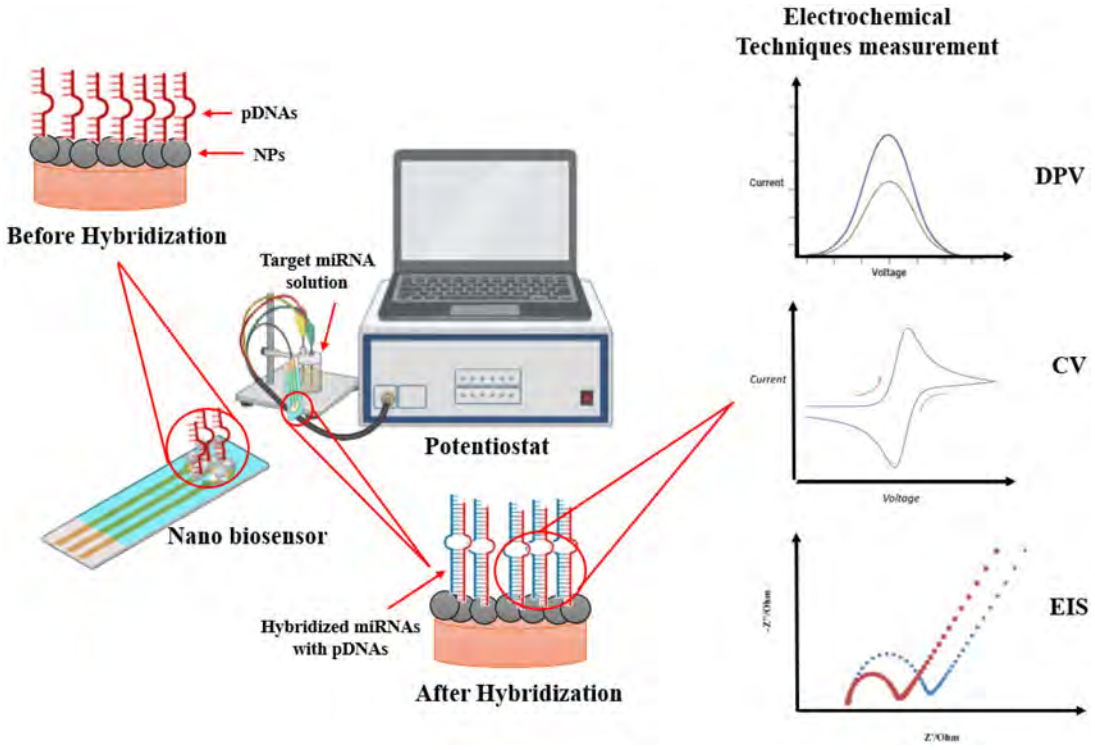


**Figure 8.** Working mechanism of the electrochemical nanobiosensor in miRNA detection.

biomolecular recognition elements [120,122]. In addition to mentioned nanomaterials, magnetic NPs serve a dual purpose in biosensor systems, they facilitate target separation and concentration while also supporting portable, miniaturized, and reusable sensing devices. Their integration with metals like gold or silver can further amplify signals and improve the specificity and dynamic range of detection [120,122–124]. Besides, carbon-based nanostructures, such as: graphene derivatives, carbon nanotubes (CNTs), and carbon nanodots (CNDs), are valued for their: excellent electron transfer characteristics, chemical and mechanical stability, and flexible surfaces, that allow for their covalent or non-covalent functionalization. They have great compatibility with various biomolecular probes, so they can be used for enhancing the resolution and reproducibility of signal [125–127]. Moreover, quantum dots (QDs) have emerged as highly effective signal amplifiers in biosensing platforms. Due to their unique optoelectronic properties such as high photostability, tunable fluorescence, and large specific surface area, they provide a platform for enhancing the sensitive detection of biomarkers, particularly in label-based electrochemical and photoelectrochemical biosensors [128]. Altogether, NP-based materials constitute a highly adaptable and integrated toolkit for the development of next-generation electrochemical biosensors capable of detecting CVD-associated miRNAs with exceptional accuracy and clinical relevance. Table 3 illustrates the application and impact of various nanoparticles on electrochemical biosensors performance for detecting a broad range of CVD-related miRNAs in complex biological samples, including serum, and plasma. Building on this data, we critically and systematically analyze the role of different NP types in enhancing biosensor sensitivity, specificity, and detection range. This evaluation allows the identification of the most effective and promising NP-based biosensor designs tailored to each CVD-associated miRNAs, supporting early and precise diagnosis of cardiovascular diseases.

### *Acute myocardial infarction*

MiRNAs implicated in AMI detection biosensors include: miR-141 [37,127,138,139], miR-133a [143], miR-208 [143], miR-328 [143], miR-499 [120,143,145], and miR-1246 [146]. Doped metal oxide nanospheres, specifically $CeO_2$ doped with Cu and Co, showed perfect performance for miR-141 with detection limits around 33 aM [139], supported by boron nitride quantum dots (BN-QDs), achieving an even superior limit of detection at 0.1 aM due to their excellent photostability and electron transfer properties [127]. For miR-133a, AuNPs integrated with tetrahedral DNA provided high sensitivity (0.33 fM) due to DNA's structural precision for enhanced specificity [143]. MiR-208, miR-328, and

**Table 3.** Application and performance of NP based-electrochemical biosensors in CVD diagnosis *via* miRNA biomarkers.

| miRNA | Nanoparticles | Electrochemical method | Linear range | Detection Limit | Potential target CVD | Applied biological sample | Ref |
|---|---|---|---|---|---|---|---|
| | miRNA-21 | | | | | | |
| | Metal and metal oxide-modified biosensors in detection of miRNA-21 | | | | | | |
| miRNA-21 | RGO/AuNPs | DPV | 10 pM–1 mM | 1 aM | Hypertension, HF, Arrhythmias, | Spiked artificial saliva | [36] |
| miRNA-21 | AuNPs | DPV-CV-EIS | – | 1 aM | Cardiac hypertrophy, CAD, | Spiked serum sample | [36] |
| miRNA-21 | $MoS_2$ nanosheet decorated by Au NPs | DPV | 10 fM–1 nM | 0.78 fM | and Atherosclerosis | Spiked serum sample | [129] |
| miRNA-21 | AuNPs with $MoS_2$ nanosheets | DPV | 1 pM to 10 nM | 0.26 pM | | Spiked serum sample | [120] |
| miRNA-21 | AuNPs | CV-DPV | 1 aM–500 pM | 1 aM | | PBS (pH 7.4) | [120] |
| miRNA-21 | Graphene Oxide; Pd NPs | CV-DPV | 1 fM–50 pM | 63.1 aM | | Spiked serum sample | [120] |
| miRNA-21 | CuNPs | DPV | 10 fM–10 pM | 45 aM | | Spiked serum sample | [85] |
| miRNA-21 | $CuCo_2O_4$ | EIS-CV-DPV | 100 fM–1 aM | 1 aM | | Spiked serum sample | [120] |
| miRNA-21 | Sn-$In_2O_3$ nanoflower decorated by Pt | DPV | 5 pM–0.5 fM | 1.92 fM | | miRNA extraction sample | [130] |
| miRNA-21 | AuNPs | DPV-CV-EIS | 0.1 fM–100 pM | 43.3 aM | | miRNA extraction sample | [131] |
| miRNA-21 | MWCNTs@GONRs/ AuNPs | CV-DPV | 1 aM–500 pM | 0.034 fM | | Spiked Serum sample | [120] |
| miRNA-21 | $CeO_2$-Au@$Fe_3O_4$ | CV-DPV | 1–1000 fM | 0.33 fM | | Spiked Serum sample | [122] |
| miRNA-21 | $CeO_2$-Au@GOx | CV-DPV | 1–1000 fM | 0.434 fM | | Spiked Serum sample | [122] |
| | QD-modified biosensors in detection of miRNA-21 | | | | | | |
| miRNA-21 | Graphene QDs | DPV | 1 fM to 1 nM | 0.04 fM | | Spiked Serum sample | [124] |
| miRNA-21 | Boron nitride (BN) QDs | EIS-DPV | 1 aM to 0.1 nM | 0.33 aM | | miRNA extraction sample | [124] |
| | Magnetic NP-modified biosensors in detection of miRNA-21 | | | | | | |
| miRNA-21 | β-FeOOH (NRs) on pd-$MoS_2$ NSs | CV-DPV | 1 fM–5 nM | 0.11 fM | Hypertension, HF, Arrhythmias, | Spiked serum sample | [124] |
| miRNA-21 | pt@AuNPs | DPV | 1 fM–10 nM | 0.63 fM | Cardiac hypertrophy, CAD, | Spiked serum sample | [124] |
| miRNA-21 | Au-coated $CoFe_2O_4$ | EIS-CV-DPV | 1 fM–2 nM | – | and Atherosclerosis | Spiked serum sample | [120] |
| miRNA-21 | Mixture of Magentic and PtNPs | DPV | 50 aM–5 nM | 47 aM | | Spiked serum sample | [124] |
| miRNA-21 | Magnetic beads in combination of AuNRs, and AuNF | EIS-DPV | 1 aM–1 nM | 0.32 aM | | Spiked serum sample | [124] |
| miRNA-21 | Nickel phosphate flower-shaped NS | CV-EIS-DPV | 0.1–2500 pM | 0.034 pM | | Spiked serum sample | [122] |
| | Carbon NP-modified biosensors in detection of miRNA-21 | | | | | | |
| miRNA-21 | SWCNTs | DPV | 10 fM–1.0 nM | 1.95 fM | Hypertension, HF, Arrhythmias, | Spiked serum sample | [126] |
| miRNA-21 | Carbon nanofibers | DPV | 1 aM–10 pM | 0.5 aM | Cardiac hypertrophy, CAD, | Spiked Serum sample | [82] |
| miRNA-21 | MWCNTs | SWV-EIS | 0.1 pM–12 nM | 0.032 pM | and Atherosclerosis) | Spiked serum sample | [132] |
| miRNA-21 | SWCNT | CV-DPV | – | 0.01 fM | | Spiked serum sample | [120] |
| miRNA-21 | SWCNT | DPV | 0.01–100 pM | 3.5 fM | | Spiked serum sample | [126] |
| miRNA-21 | CNTs | DPV | 1 fM–1 μM | – | | Spiked serum sample | [37] |
| miRNA-21 | SWCNTs/dendritic Au | EIS-DPV | 0.01 fM–1 μM | 0.01 fM | | Spiked Serum sample | [133] |
| miRNA-21 | CNDs | CV-EIS-DPV | – | 0.03 fM | | PBS containing $H_2O_2$ | [132] |
| miRNA-21 | MWCNTs@GONRs/ AuNPs | EIS-DPV | 0.1 nM–0.1 fM | 0.034 fM | | Spiked Serum sample | [125] |
| miRNA-21 | CNDs | DPV | – | 1 pM | | Spiked Serum sample | [134] |
| | miRNA-155 | | | | | | |
| | Metal and metal oxide NP-modified biosensors in detection of miRNA-155 | | | | | | |

(*Continued*)

**Table 3.** Continued.

| miRNA | Nanoparticles | Electrochemical method | Linear range | Detection Limit | Potential target CVD | Applied biological sample | Ref |
|---|---|---|---|---|---|---|---|
| miRNA-155 | Ag-PEI NPs | DPV-CV-EIS | 20 zM–2 pM | 20 zM | Hypertension, Atherosclerosis, HF, | Spiked Serum sample | [82] |
| miRNA-155 | Mixture of AuNWs and RGO | DPV | 2 fM–8 pM | 0.6 fM | CAD | Spiked plasma sample | [135] |
| miRNA-155 | RGO modified with AgQD, and gold nanostars (GNS) | DPV-CV-EIS | 0.05 fM–50.0 pM | 20.2 aM | | Spiked serum sample | [135] |
| | QD-modified biosensors in detection of miRNA-155 | | | | | | |
| miRNA-155 | Graphene QDs | EIS-ECL | 1 fM–0 pM | 0.14 fM | Hypertension, Atherosclerosis, HF, | Spiked serum sample | [136] |
| miRNA-155 | Ag-doped graphene (GQD)-Ag, and CdSQDs | EIS-ECL | 0.3 fM-500 pM | 0.1 fM | CAD | Spiked serum sample | [137] |
| | Magnetic NP-modified biosensors in detection of miRNA-155 | | | | | | |
| miRNA-155 | $Fe_3O_4$NPs@Ag | DPV | 0.5 fM–1 nM | 0.15 fM | Hypertension, Atherosclerosis, HF, CAD | Spiked serum sample | [122] |
| | Carbon NP-modified biosensors in detection of miRNA-155 | | | | | | |
| miRNA-155 | CNDs | | – | 0.1 aM | Hypertension, Atherosclerosis, HF, | Spiked serum sample | [125] |
| miRNA-155 | graphene films | SWV-EIS | – | 5.2 pM | CAD | Spiked serum sample | [135] |
| | miRNA-141 | | | | | | |
| | Metal and metal oxide NP-modified biosensors in detection of miRNA-141 | | | | | | |
| miRNA-141 | CuNPs | CV-DPV | 0.1 pM to 0.1 fM | 0.45 aM | AMI | miRNA extraction sample | [138] |
| miRNA-141 | Doped Cu and Co in $CeO_2$ nanospheres | DPV | 0.1 fM-10 nM | 33 aM | | miRNA extraction sample | [139] |
| | Magnetic NP-modified biosensors in detection of miRNA-141 | | | | | | |
| miRNA-141 | Porous $Fe_3O_4$ NPs | DPV | 10 fM–10 pM | 1.4 aM | AMI | Spiked serum sample | [37] |
| | QD-modified biosensors in detection of miRNA-141 | | | | | | |
| miRNA-141 | Boron nitride (BN) QDs | DPV | 10 aM to 0.1 µM | 0.1 aM | AMI | PBS (pH 7.4) | [127] |
| | miRNA-25 | | | | | | |
| | Metal NP-modified biosensors in detection of miRNA-25 | | | | | | |
| miRNA-25 | Cysteamine-Gold NPs | DPV-EIS | 1 pM–0.1 nM | 0.25 pM | HF | Spiked serum sample | [120] |
| miRNA-25 | AgNPs/SWCNTs | DPV-EIS | 1 pM–0.1 nM | 31.3 pM | | Spiked plasma sample | [120] |
| | QD-modified biosensors in detection of miRNA-25 | | | | | | |
| miRNA-25 | Graphene QDs | DPV-EIS | 0.3 nM–1.0 µM | 0.95 pM | HF | Spiked plasma sample | [128] |
| | Other miRNAs | | | | | | |
| | Metal and metal oxide NP-modified biosensors in detection of miRNAs | | | | | | |
| miRNA-103 | AuNPs | CV-DPV | 100 fM–5 nM | 100 fM | HF, CAD | PBS (pH 7.4) | [37] |
| miRNA-107 | Nanoporous Ferric oxide nanocubes loaded by gold NPs | CV | – | 100 aM | Atherosclerosis, Hypertension, CAD | Spiked miRNA extraction sample | [140] |
| miRNA-122 | pBA-Au-MXene QD | DPV-CV-EIS | 0.001 aM to 1000 nM | 0.8 zM | CAD | Spiked serum sample | [141] |
| miRNA-128 | RGO and AuNPs | DPV-CV-EIS | – | 0.087 fM | HF, Cardiac hypertrophy | Spiked serum sample | [142] |
| miRNA-133a | TDN/AuNPs | EIS-ECL | 1 fM to 1 nM | 0.33 fM | AMI | Spiked serum sample | [143] |
| miRNA-182 | Nanohybrids of $MoS_2/Ti_3C_2$ | DPV-CV-EIS | 1fM–0.1 nM | 0.43 fM | CAD, Hypertension | Exosome extracted serum sample | [144] |
| miRNA-199a-5p | GO /GNR | DPV-EIS | 15 fM–148 pM | 4.5 fM | Cardiac hypertrophy, HF | Spiked serum sample | [75] |
| miRNA-203 | PtNP decorated by ssDNA | ECA | 0.10–10.0 nM | 100 pM | CAD | Spiked serum sample | [82] |
| miRNA-205 | Copper ferrite nanoparticles decorated $MoS_2$ nanosheets | SWV | 1 pM–1.5 nM | 0.48 fM | CAD | Spiked erum sample | [140] |
| miRNA-208 | AuNPs/ Ag NC | CV-EIS-ECL | 0.1 fM to 1 nM | 29.6 aM | AMI | Spiked serum | [143] |
| miRNA-328 | AuNPs/ Ag NC | CV-EIS-ECL | 0.1 fM to 1 nM | 47.9 aM | AMI | Spiked serum | [143] |
| miRNA-499 | AuNPs/ Ag NC | CV-EIS-ECL | 0.1 fM to 1 nM | 52.5 aM | AMI | Spiked serum sample | [143] |

(*Continued*)

**Table 3.** Continued.

| miRNA | Nanoparticles | Electrochemical method | Linear range | Detection Limit | Potential target CVD | Applied biological sample | Ref |
|---|---|---|---|---|---|---|---|
| miRNA-499 | TTP/AuNPs | EIS-ECL | 10 aM to 1 nM | 10 aM | AMI | Spiked serum sample | [145] |
| miRNA-499 | Au NPs | DPV-EIS | 10 aM to 1 nM | 3.3 aM | HF, AMI, CAD, Arrhythmias | Spiked serum sample | [120] |
| | QD-modified biosensors in detection of miRNAs | | | | | | |
| miRNA-92a-3p | CNDs | DPV-EIS | – | 0.14 nM | CAD | Spiked serum sample | [125] |
| miRNA-200a | ZnS QDs | CV-DPV | 10 fM–1.0 µM | 8.4fM | CAD | Spiked plasma sample | [137] |
| miRNA-210 | Graphene QDs | DPV | 1 fM to 1 nM | 0.28 fM | CAD | Spiked serum sample | [124] |
| miRNA-541 | Graphene QDs | DPV-EIS | 1 fM to 1 nM | 0.7 fM | Cardiac hypertrophy | Spiked plasma sample | [124] |
| miRNA-1246 | PbS QDs encapsulated MOF | DPV | – | 0.19 fM | AMI | Spiked serum sample | [146] |
| miRNA-4521 | CdSQDs encapsulated MOF | DPV-EIS | – | 0.28 fM | Diabetic associated CVD | Spiked serum sample | [146] |
| | Magnetic NP-modified biosensors in detection of miRNAs | | | | | | |
| miRNA-9-2 | Magnetic beads on applied mesoporous gold electrode | DPV | 100 aM–1 nM | 100 aM | CAD | Spiked serum sample | [123] |

CVD: Cardiovascular Disease CNTs: carbon nanotubes; CNDs: carbon nanodots MWCNTs: multi-walled carbon nanotubes; QD: quantum dots SWCNT: single-walled carbon nanotubes; NR: nano rod GONRs: graphene oxide nanorods; QD: quantum dots NR: nano rod; NS: nanosheet BN QDs: boron nitride quantum dots ; AMI: Acute myocardial infarction CAD: Coronary Artery Disease; HF: Heart failure NWs: nano wires ; RGO: reduced graphene oxide GO: graphene oxide ; GNS: gold nanostars PAMAM: Poly(amidoamine); MOF: metal oxide framework NC: nano cube; Sn-$In_2O_3$: Tin-Indium oxide TDN: Tetrahedral DNA Nanostructure; ECL: Electrochemiluminescence TTP: Truncated Triangular Pyramid DNA

miR-499 detection achieved excellent sensitivity (LOD ~30–50 aM) using AuNP and Ag nanocluster composites, showing better performance of metallic nanoclusters due to improved catalytic properties and efficient electron transfer capabilities [120,143,145]. PbS QDs encapsulated within metal-organic frameworks (MOFs) displayed suitable sensitivity to miR-1246 (detection limit of 0.19 fM), combining the porous structure of MOFs with high photoluminescence efficiency of QDs [146]. Overall, for AMI detection, metal oxide hybrids, boron nitride QDs, and metallic nanoclusters provide the most sensitive and reliable biosensor structures.

***Coronary artery diseases (CAD), and atherosclerosis:*** For CAD-related miRNAs, such as: miR-21 [36,85,120,122, 124,126,129,131,132], miR-155 [82,122,125,135–137], miR-122 [141], miR-499 [120], miR-9-2 [123] and miR-210 [124], NP-based electrochemical biosensors exhibited superior sensitivity and diverse performance. For miR-21, carbon nanofibers demonstrated superior performance, achieving an impressive detection limit of 0.5 aM [82]. In comparison, AuNPs combined with graphene oxide or $MoS_2$ nanosheets also showed strong performance, with detection limits ranging from 1 aM to 0.26 pM, owing to gold's excellent conductivity and enhanced charge transport resulting from hybridization with 2D materials [36,120,129]. However, for miR-155, Ag-based NPs, especially Ag-PEI and Ag-doped graphene quantum dots, showed outstanding sensitivity, reaching ultra-low detection limits down to 20 zM [82,135]. MiR-122, uniquely detected with extreme sensitivity (LOD = 0.8 zM), using a hybrid Au-MXene-QD platform, emphasizing the synergy of MXene's conductivity and AuNP's stable surface area. Notably, as shown in Figure 9(A) this platform enabled direct detection of miR-122 in serum without the need for RNA extraction, greatly simplifying clinical workflows and outperforming traditional RT-qPCR [141]. Meanwhile, AuNPs also provided strong detection of miR-499 (LOD as low as 3.3 aM), especially when combined with truncated triangular pyramid DNA structures or silver nanoclusters, enhancing specificity and sensitivity [120]. Additionally, a magnetic beads equipped electrochemical biosensor could detect miR-9-2 with an outstanding LOD of 100 aM [123]. MiR-210 also optimally detected using graphene quantum dots, providing excellent sensitivity at 0.28 fM due to a strong electron transfer efficiency [124]. Besides, miR-107, an important atherosclerosis-related biomarker was detected using nanoporous ferric oxide loaded with AuNPs, providing an LOD of 100 aM, demonstrating the utility of metal-oxide hybrids [140]. Thus, for CAD and atherosclerosis, gold and silver-based nanocomposites demonstrate the best overall performance and versatility, while carbon-based nanomaterials, such as carbon nanofibers provide excellent sensitivity, particularly for targets like miR-21. MXene-based platforms provide extraordinary sensitivity

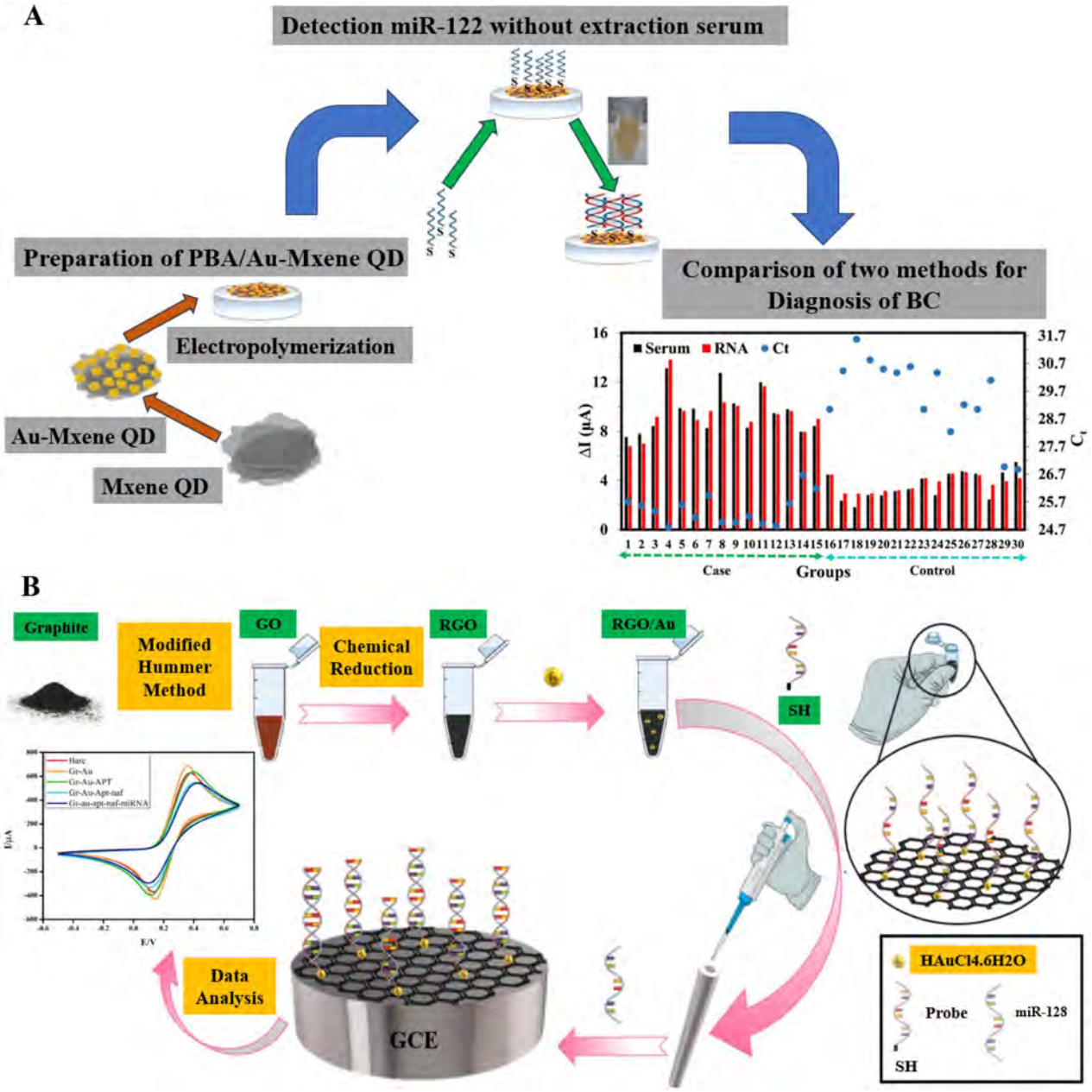


**Figure 9.** Typical biosensors for detecting miR-122 and miR-128. (A) A schematic of preparing PBA-Au-MXene QD based biosensor to detect miR-122 [141]. (B) A schematic of preparing RGO/Au NPs based biosensor for detection of miR-128 [142] [Reprinted with permission from Elsevier and springer nature].

for miR-122 specifically, and metal oxide NPs add unique value in inflammation-associated vascular diseases like atherosclerosis.

### *Heart failure (HF):*

Key miRNAs that incorporate in HF electrochemical biosensors include: miR-21 [36,85,120,122,124,126,129,131,132], miR-155 [82,122,125,135–137], miR-25 [120,128], miR-128 [142], miR-199a-5p [75], and miR-499 [120]. AuNP-based biosensors dominated miR-21 detection, especially when combined with carbon nanostructures, achieving detection limits as low as 1 aM [36,120]. For miR-155, silver-based NPs, notably Ag-PEI, showed exceptional sensitivity (20 zM), outperforming alternative materials such as carbon nanodots (LOD: 0.1 aM) [82,125]. In contrast, miR-25 was suitably detected using cysteamine-capped AuNPs (LOD = 0.25 pM) [128], surpassing AgNP/SWCNT composites [120] due to gold's better electron transfer and ease of surface functionalization. The advantage of preparing an RGO/Au mixture using the modified Hummers method and a chemical reduction procedure yielded an electrochemical miR-128 biosensor to detect HF with impressive LOD of 0.087 fM. The hybrid structure

enabled excellent signal amplification through gold's conductivity and RGO's large surface area for efficient probe immobilization [142] (Figure 9(B)). For miR-199a-5p, GO decorated with gold nanorods provided sensitivity at 4.5 fM, highlighting effective signal amplification through plasmonic interactions [75]. MiR-499 showed reliable detection *via* AuNP-based systems (LOD = 3.3 aM) [120]. Consequently, gold-based hybrid nanomaterials emerge as the most reliable and consistent choice for HF detection, due to their versatility and consistently high sensitivity.

### *Hypertension*

MiRNAs including: miR-21 [36,85,120,122,124,126,129,131,132], miR-155 [82,122,125,135–137], and miR-107 [140] are biomarkers that have been applied in electrochemical biosensors for hypertension. MiR-21 biosensors using AuNPs and magnetic NP composites (LOD around 0.32 aM) provide outstanding practical advantages, facilitating preconcentration and purification of target miRNA from complex biological samples, thereby enhancing sensitivity, selectivity, and overall assay efficiency [124]. MiR-155 detection attained excellent sensitivity through silver-based NPs (Ag-PEI, LOD 20 zM), again demonstrating silver's strong electron-transfer efficiency and conductivity [82]. Additionally, gold nanostar (GNS)-modified RGO biosensors incorporating GQD-Ag and Fe-Ni@rGO nanohybrids have been used for miR-155 detection, demonstrating sensitive electrochemical results *via* improved electron transfer and signal amplification, as illustrated in Figure 10 by clear visual DPV shifts upon target hybridization [135]. Nanoporous ferric oxide cubes with AuNPs optimally detected miR-107 (LOD = 100 aM), benefitting from the nanoporous structures' improved surface area and redox activity [140]. Collectively, silver-based NPs, specifically Ag-PEI, stay superior for ultralow sensitivity requirements, while magnetic-AuNP hybrids, GNS-RGO nanohybrids, and

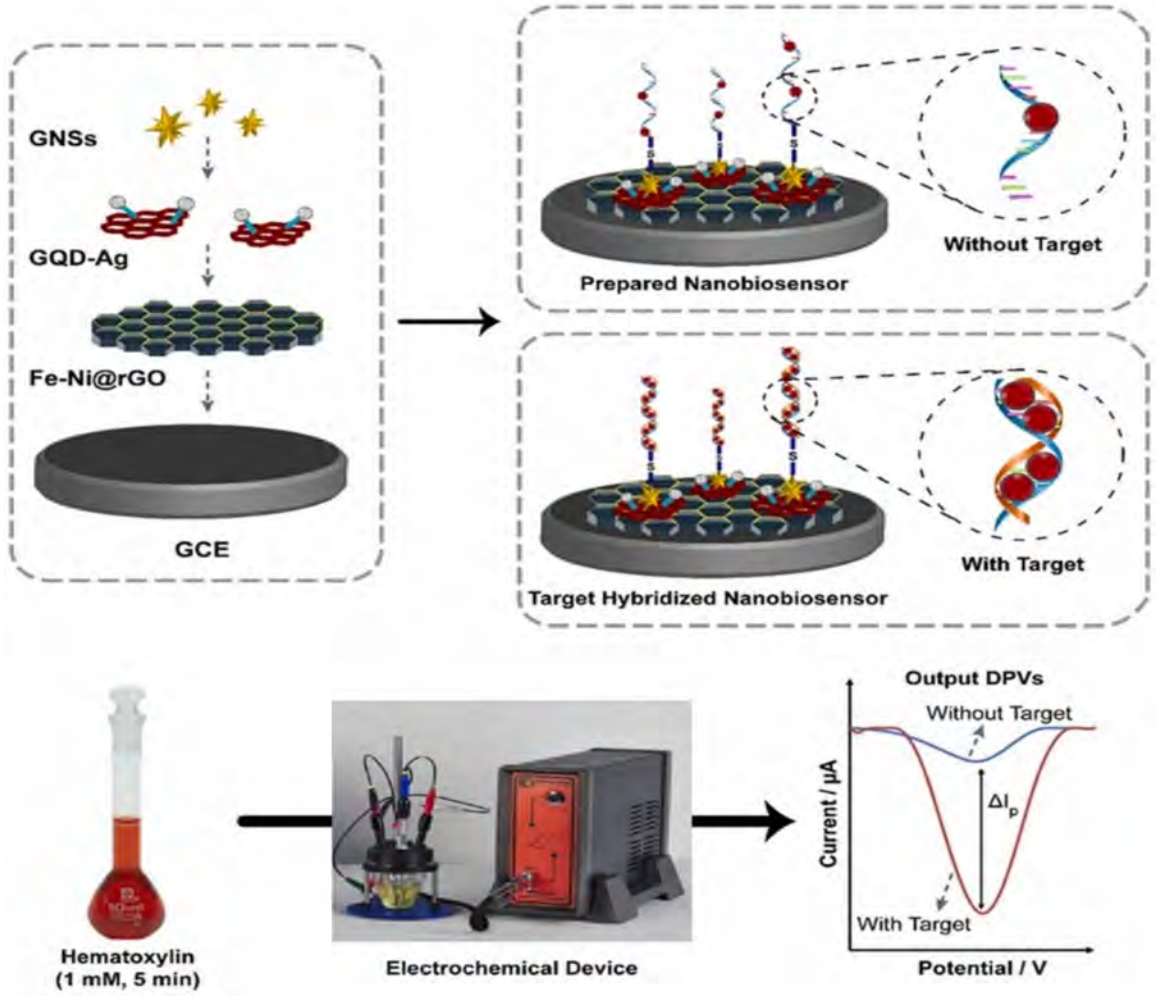


**Figure 10.** A process of preparing GNS modified RGO biosensor to detect miR-155 in hypertension [135] [Reprinted with permission from Elsevier].

nanoporous ferric oxide demonstrate valuable practical applications.

### *Cardiac hypertrophy*

MiRNAs, like miR-21 [36,85,120,122,124,126,129,131,132], miR-128 [142], miR-199a-5p [75], and miR-541 [124], are important biomarkers in cardiac hypertrophy that applied in electrochemical biosensors. AuNP composites for miR-21 showed excellent sensitivity (down to 1 aM), especially when combined with carbon nanotubes [36]. MiR-128 also best detected by using Au-RGO hybrids (LOD: 0.087 fM), since graphene oxide's structural stability and gold's electron mobility aided in this perform. MiR-199a-5p, effectively detected using GO-gold nanorod hybrids (LOD = 4.5 fM), benefited from the nanorods' plasmonic enhancement [75]. MiR-541 achieved optimal detection sensitivity using graphene quantum dots (LOD = 0.7 fM), capitalizing on excellent electron-transfer properties and fluorescent signaling capacity [124]. Overall, gold-based hybrids combined with carbon or graphene nanostructures consistently provide high sensitivity and practicality for cardiac hypertrophy-associated miRNA detection.

### *Arrhythmias*

miR-21 [36,85,120,122,124,126,129,131,132], and miRNA-499 [120] are two relevant applied biomarkers in arrhythmias electrochemical biosensors. These biosensors showed outstanding detection ability using AuNP-based biosensors, especially when combined with carbon-based and DNA-structured materials [36,82,120], consistently providing sensitivity below 1 aM [36,82,120]. Gold's excellent conductivity and ability to amplify signals through hybrid nanostructures make it the most suitable choice for miRNA detection in arrhythmias.

### *Comparative analysis and optimal NPs for electrochemical biosensors targeting CVD-related miRNAs*

Building upon the comparative analysis of NP-enhanced biosensors for CVD-associated miRNA detection presented in Table 3, this study provides key insights into optimal nanomaterial formations for CVD diagnostics, showing that NP-based biosensors provide unparalleled performance in detecting a wide spectrum of CVD-associated miRNAs. For AMI, the most effective biosensors included BN QDs targeting miR-141 achieved the lowest LOD [127], while porous $Fe_3O_4$, CuNPs, $CeO_2$–Cu/Co nanospheres, and Au–Ag nanoclusters provided strong performance for miR-141, and miR-208 respectively [37,138,139,143]. For atherosclerosis and CAD, Au–MXene QD hybrids targeting miR-122 achieved a zeptomolar LOD [141], while Ag-PEI NPs for miR-155 reached an ultra-sensitive detection limit [82]. In heart failure, cysteamine-capped AuNPs for miR-25 [120] and TTP/AuNP hybrids for miR-499 [120] showed the best detection performance, supplemented by RGO–AuNP platforms for miR-128 [142]. In hypertension, while Ag-PEI-based biosensors for miR-155 achieved the best performance [82], nanoporous ferric oxide loaded with AuNPs showed high sensitivity for miR-107 [140], and magnetic–AuNP hybrids effectively detected miR-21 in attomole LOD [124]. In cardiac hypertrophy and arrhythmias, carbon-based electrochemical biosensors either alone or in combination with AuNPs, exhibited superior performance for the detection of miR-21 [36,82]. Following this, Au-RGO hybrids demonstrated high efficacy in detecting miR-128 associated with hypertrophy [75], while AuNP-based platforms showed strong performance in the detection of miR-499 relevant to arrhythmias [120] (Figure 11).

This analysis highlights that no single nanoparticle is universally superior for all CVD associated miRNAs. Instead, the optimal choice depends on the specific physicochemical interactions between the miRNA target, detection platform, and disease context. However, AuNPs, and AgNPs are identified as the most high-performance nanomaterial, exhibiting with a high performance no matter alone or in combination with other conductive, magnetic, or catalytic materials. Metal oxide NPs, Quantum dots-based nanomaterials also play an important role due to their versatility and signal amplification properties. Magnetic nanoparticles are not always the most sensitive materials, but they provide considerable advantages in the practicality of biosensors, particularly within clinical environments where sample purification and miniaturization are important.

Consequently, the inclusion of nanoparticles, such as: metallic, magnetic, carbonaceous, oxide-based, QDs or semiconductor, is critical for the enhancement of sensitivity, selectivity, and clinical utility of electrochemical biosensing platforms. These properties make them essential in improving the next generation of miRNA detection in cardiovascular diagnostics by enhancing electron transfer, increasing surface functionalization and target enrichment.

## Challenges and future directions

Electrochemical biosensors as a new tool on diagnosis hold an inspiration for the detection of RNA based CVD biomarkers. Yet, several challenges must be adopted. Firstly, as a priority, the stability and

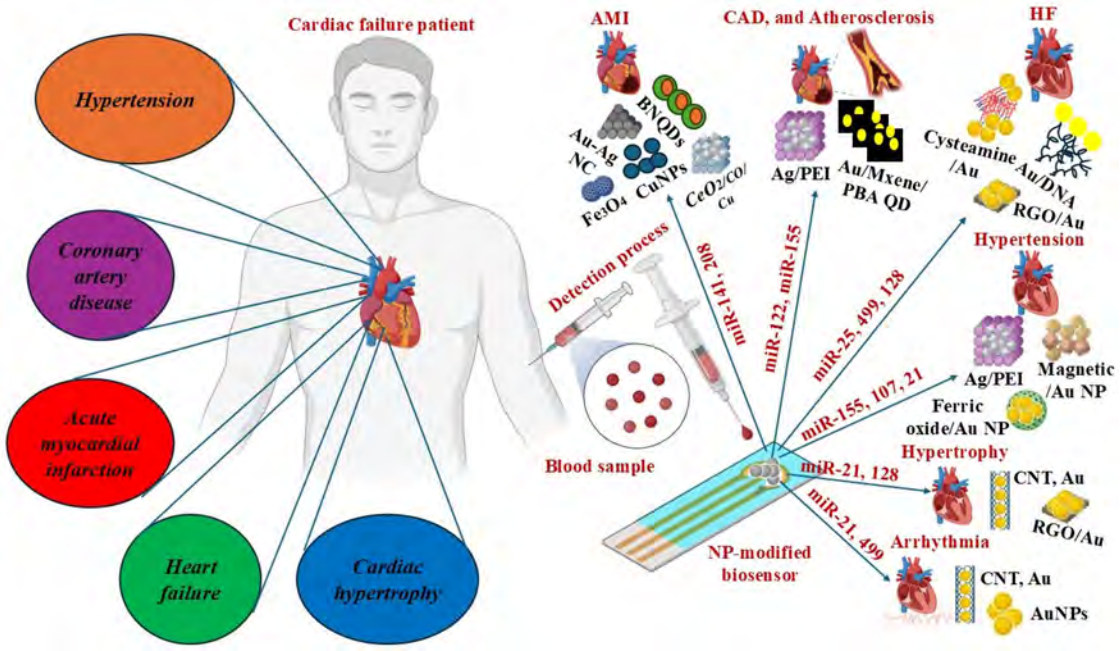


**Figure 11.** Optimal NPs in electrochemical biosensors for targeting CVD-related miRNAs in CVD detection.

specificity of RNA-based biomarkers need to be taken into consideration. These molecules are vulnerable to degradation, and several similar biomarkers are present in various CVD subtypes, limiting their specificity. To maintain RNA integrity, strong probes and protective measures are essential. Secondly, clinical confirmation is important. Moving from research to a clinical field needs serious studies to create diagnostic reliability and precision. Well prepared clinical trials are necessary to assess the clinical potential of electrochemical biosensors. Thirdly, the ability of multiplexed detection is essential. CVD often involves multiple biomarkers, therefore providing electrochemical biosensors to identify several RNA-based biomarkers simultaneously is a substantial challenge. Overcoming this issue will significantly improve diagnostic power.

To improve the application of miRNA-based biosensors, several promising future directions have appeared. Firstly, providing a bridge between electrochemical biosensors and simulation is significantly important. Simulation can help in identifying subtle biomarker patterns and improve predictive accuracy. Secondly, sustainable sensor design is important, with a focus on eco-friendly materials and cost-effective, environmentally friendly biosensors. Thirdly, translation of research discoveries into clinical applications can be accelerated by interdisciplinary collaborations between engineers, clinicians, biologists, and data scientists. Fourthly, the development of miniaturized, user-friendly, and reasonable point-of-care electrochemical biosensors will improve early CVD diagnosis and monitoring. Finally, linking the gap between laboratory improvement and clinical impact is crucial, engaging regulatory approvals, scalability, and arrangement with healthcare systems. Electrochemical biosensors focused on RNA-based CVD biomarkers provide considerable promise, and defeating these challenges promises more accurate, accessible, and personalized CVD diagnostics.

## Conclusion

Electrochemical biosensors have become the focus of numerous efforts for the rapid and precise detection of CVD biomarkers. This review summarized the current evidence on miRNA-based biomarkers for CVD, including: CAD, AMI, HF, arrhythmias, CHD, cardiac hypertrophy, hypertension and, atherosclerosis, highlighting specific biomarkers for each. Moreover, this review provided a complete outline of the latest electrochemical biosensors with a specific emphasis on their application in detecting miRNA biomarkers associated with CVDs in serum or plasma. Notably, AMI detection benefits most from metal oxide nanospheres, boron nitride QDs, and metallic nanoclusters, which offer excellent sensitivity for miR-141, miR-499, and miR-1246. For CAD and atherosclerosis, carbon nanofibers excel for miR-21, Ag-based NPs perform best for miR-155, MXene-Au hybrids enable ultra-sensitive detection of miR-122, and metal oxides enhance the detection of miR-107. When addressing heart failure, gold-carbon hybrids allow

sensitive detection of miR-21, miR-128, and miR-499. Regarding hypertension, magnetic-AuNPs facilitate miR-21 preconcentration, while Ag-PEI and ferric oxide effectively detect miR-155 and miR-107. In the context of cardiac hypertrophy and arrhythmias, AuNP-carbon and Au-RGO platforms perform well for miR-21, miR-128, and miR-499, achieving sub-aM sensitivity. Incorporating these nanostructures leads to enhanced biosensor performance by targeting capture, electron transfer, and signal amplification, paving the way to ultra-sensitive sensing. In synthesis electrochemical nanobiosensors reflect on high-sensitivity, fast response and high point-of-care potential, making them as an important tool for early CVD diagnosis and management. The specific miRNA biomarkers and their corresponding optimal NP-based biosensors identified and critically discussed in this review provide not only a roadmap for advancing CVD diagnostics but also a valuable foundation for future research. These insights can guide the development of next-generation biosensors and inspire further studies focused on real-time, point-of-care, and multiplexed detection platforms in cardiovascular medicine.

## Acknowledgments

H.T.T. was supported by a Future Leader Fellowship from National Heart Foundation of Australia (102761). P.H.K. was supported by a Griffith University scholarship.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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