

Review

miR-21 in cardiovascular disease: new insights and emerging therapeutic potential

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Abstract

Cardiovascular diseases (CVDs) remain a leading cause of morbidity and mortality worldwide. Among various molecular regulators, microRNAs (miRNAs), small noncoding RNAs averaging 18–24 nucleotides have emerged as key players in CVD pathophysiology. miR-21, particularly, has been widely studied due to its involvement in inflammation, fibrosis, and cardiomyocyte survival. While some studies highlight its cardioprotective functions, others suggest it may contribute to adverse remodeling and disease progression. This review critically examines the dual role of miR-21 in CVDs, exploring both supportive and conflicting evidence. Additionally, miR-21's potential as a diagnostic biomarker and therapeutic target is discussed while outlining key challenges and future research directions for clinical translation.

Article Highlights

- miR-21 plays a critical role in regulating inflammation and tissue damage in cardiovascular diseases.
- Understanding miR-21 could open doors to new diagnostic and treatment options for heart-related conditions.
- Current research reveals both promising and conflicting insights into miR-21's impact on cardiovascular health.

Keywords miR-21 · Cardiovascular diseases · Biomarkers · Gene regulation · Fibrosis · Myocardial infarction · Heart failure

Abbreviations

CVDs	Cardiovascular diseases
miRNAs	MicroRNAs
CAD	Coronary artery diseases
HF	Heart failure
MI	Myocardial infarction
DUSP8	Dual specific phosphatase 8
PTEN	Phosphatidylinositol 3-kinase
AKT	AK strain transforming
NPs	Nanoparticles

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TNRC6a	Trinucleotide repeat-containing gene 6a
CM	Cardiomyopathy
CADs	Coronary artery diseases
ECG	Electrocardiogram
TGF- β	Transforming growth factor- β
TGF β RIII	Transforming growth factor- β receptor 3
Smad	Suppressor of mothers against decapentaplegic
TIMPs	Tissue inhibitor of metalloproteinases
PB-sEVs	Peripheral blood-derived small extracellular vesicles
PCI	Primary percutaneous coronary intervention
ET	Endurance training
ROS	Reactive oxygen species
PDCD4	Programmed cell death protein 4
NF- κ B	Nuclear factor Kappa-light-chain-enhancer of activated B cells
MSNs	Mesoporous silica nanoparticles
IFN- γ	Interferon- γ
VEGF-A	Vascular endothelial growth factor A
EVs	Extracellular vesicles
MSCs	Mesenchymal stromal cells
STAT1	Signal transducer and activator of transcription 1
BTG	B-cell translocation gene
CPCs	Cardiac progenitor cells
IRI	Ischemic/reperfusion injury
LncRNA	Long non-coding RNAs
HIPK3	Homeodomain interacting protein kinase 3
Bax	Bcl-2-associated protein x
Bcl-2	B-cell lymphoma 2
LVR	Left ventricular remodeling
CKD	Chronic kidney disease
T2DM	Type 2 diabetes mellitus
QRT-PCR	Quantitative reverse transcription polymerase chain reaction
DES	Drug-eluting stents
ERK	Extracellular signal-regulated kinase
MAP	Mitogen-activated protein
HCM	Hypertrophic cardiomyopathy
ICM	Ischemic cardiomyopathy
ChCM	Chagas cardiomyopathy
DCM	Dilated cardiomyopathy
VMC	Viral myocarditis
TPM1	Tropomyosin 1
3'UTR	3' Untranslated region
HG	High glucose
HSCs	Hepatic stellate cells
EMT	Epithelial-mesenchymal transition
H ₂ S	Hydrogen sulfide
ARVC	Arrhythmogenic right ventricular cardiomyopathy
VT	Ventricular tachycardia
PPAR	Peroxisome proliferator-activated receptors
NRF2	Nuclear factor erythroid 2-related factor 2
GAS5	Growth arrest-specific 5
CSC	Cardiac stem cell

1 Introduction

The prevalence of cardiovascular diseases (CVD), a group of disorders impacting the heart and blood vessels, gives rise to substantial morbidity and mortality, manifesting as a significant public health burden on a global scale. miRNAs are being investigated for their potential in early CVD diagnosis and treatment due to their ability to modulate gene expression post-transcriptionally by binding to target mRNA sequences in the 3'-untranslated region [1, 2]. Among these miRNAs, miR-21 stands out as it regulates multiple genes and shows high expression levels in human cardiac tissue [3].

The significance of miR-21 lies in its diverse effects observed in various cardiovascular disease studies. The findings can be categorized into three principal results: (1) Pathological effects of miR-21. For instance, it was reported that miR-21 increased the amount of collagen in the cardiac cells of myocardial infarction (MI) mice, and its overexpression led to the suppression of TGF β RIII at the post-transcriptional level, promoting the transformation of cardiac fibroblasts into pathological myofibroblasts and enhancing collagen production in cultured fibroblast cells, and ultimately contributes to cardiac fibrosis [4]. Additionally, this microRNA demonstrated a similar effect by promoting fibroblast proliferation and collagen synthesis in diabetic cardiomyopathy through targeting dual specific phosphatase 8 (DUSP8). This interaction increases phosphorylated JNK/SAPK and p38 under high glucose (HG) conditions [5]. As reported, miR-21 expression differs between healthy and injured cardiac cells. Under stress, its upregulation protects cardiomyocytes from apoptosis but also promotes myocardial fibrosis by enhancing transforming growth factor beta-1 (TGF- β 1) signaling. This occurs through Smad7 inhibition, which drives fibroblast differentiation and Spry1 (belongs to the Sprouty family) suppression, leading to sustained ERK-MAPK activation and extracellular matrix accumulation [6]. (2) Protective role of miR-21. For example, by modulating the PTEN/Akt signaling pathway, miR-21 protects myocardium against ischemic-reperfusion injury and inhibits the progression of coronary artery diseases (CAD). It achieves this by suppressing PTEN expression, which leads to increased Akt signaling. This activation enhances anti-apoptotic proteins such as Bcl-2/Bax, inhibits pro-apoptotic factors like caspase-3, and reduces apoptosis [7, 8]. Moreover, the administration of miR-21 mimics by utilizing nanoparticles (NPs) to target cardiac macrophages following myocardial infarction (MI) holds the potential to mitigate the onset of heart failure [9]. (3) The diagnostic and prognostic capacity of miR-21. In this regard, a case-control study including 42 patients with systolic heart failure and 15 healthy individuals as the control group reported that miR-21 exhibited the most notable increase among circulating miRNAs in individuals diagnosed with systolic heart failure [10]. In addition, in the plasma of acute myocardial infarction (AMI) patients ($n = 44$), miR-21 showed increased levels when compared to a matched control cohort ($n = 18$) ($p < 0.01$) [11]. Similarly, a study performed on MI-established rats revealed a change in expression in trinucleotide repeat-containing gene 6a (TNRC6a), leading to an increase in miR-21 expression, which highlights the diagnostic potential of this molecule [12].

By integrating these findings, this review presents a comprehensive analysis of miR-21's role in CVDs and emphasizes the existing gaps and limitations that must be addressed in future studies. While previous studies have explored the role of miR-21, conflicting evidence regarding its beneficial and pathological effects remains unresolved. This review aims to assess both aspects by exploring recent findings and their implications for clinical applications.

2 Myocardial infarction (MI)

Myocardial infarction (MI), also known as heart attack, occurs when there is a decrease in blood flow to the coronary arteries due to coronary artery diseases (CADs), ultimately resulting in the necrosis of myocytes [13]. Up to this point, MI has been detectable through various common methods, including electrocardiographic (ECG) findings, clinical manifestations, imaging results, and the levels of certain biomarkers like cardiac troponin I and T, which an elevation in their blood levels suggest possible injury that could lead to myocyte necrosis [14]. However, recently, miRNAs have been the focus of considerable interest as a novel biomarker that might be associated with the progression and prevalence of MI, given their involvement in regulating a wide range of vital genes [15]. Among these, miR-21 has gained significant attention due to its correlation with MI in multiple studies.

In addition to myocyte necrosis, MI complications like post-myocardial infarction fibrosis contribute to heart failure, driven by cardiac fibroblast proliferation and collagen accumulation. In this regard, a study reported that miR-21 could exert the mentioned effects by regulating the expression levels of TGF β RIII. According to the results of this study, miR-21 was upregulated in the hearts of MI mice and increased the amount of collagen content by targeting TGF β RIII and reducing its expression. In addition, since TGF β RIII is a negative regulator of the TGF- β pathway, it could be hypothesized

that miR-21 is indirectly applying its effects on this signaling pathway [4, 16]. In this pathway, TGF- β decreases Smad7, which negatively regulates the phosphorylation levels of Smad2 and Smad3, the two molecules that possess a pivotal role in fibroblast activation. To further investigate whether miR-21 contributes to cardiac fibrosis through the TGF- β /Smad7 signaling pathway, miR-21 mimics were used and confirmed the mentioned hypothesis (Table 1) [17–19]. Additionally, ventricular remodeling is a further complication that can occur following a myocardial infarction (MI) and has the potential to not only predict but also lead to the development of heart failure. This process is closely linked to fibrosis, which is significantly influenced by miR-21. By modulating TGF- β 1 signaling, miR-21 promotes fibroblast proliferation and extracellular matrix accumulation, which are key components in fibrosis that drive ventricular remodeling [6, 20, 21]. Furthermore, in a study aiming to define the effects of MitoQ (an antioxidant that suppresses the production of reactive oxygen species) and endurance training (ET) on cardiovascular function, it was determined that these two variables prevent MI in people with hypertension by reducing miR-21 and enhancing antioxidant defense [22].

However, the results of many of the studies in this topic area betoken the positive impacts of miR-21 on MI across various aspects. For instance, contrary to the results of the previously mentioned study, it was reported that miR-21 could play a protective role against myocardial injuries caused by reactive oxygen species (ROS) by regulating its target gene, PDCD4 (Table 1) [23, 24]. Also, in a myocardial ischemia–reperfusion (MI/R) injury model, pre-treatment with argon increased miR-21 expression ($P < 0.01$). The upregulation of miR-21 subsequently reduced the levels of PDCD4 and PTEN ($P < 0.001$), resulting in a decrease in apoptosis, inflammation, and oxidative stress [25]. Thus, it was suggested that the localized injection of engineered extracellular vesicles (EVs) containing miR-21 could potentially benefit patients following a myocardial infarction (MI) by suppressing the expression of PDCD4 [26]. Similarly, it was reported that ursolic acid protects the heart by reducing ROS levels, partly through miR-21 activation. This regulation enhances antioxidant defenses, suppresses inflammation via NF- κ B inhibition, and modulates apoptotic pathways like Bcl-2/Bax and PI3K/Akt [27]. Additionally, the general observations indicate that miR-21 is up-regulated under hypoxic conditions and has the ability to mitigate hypoxic injury and cardiac dysfunction by inhibiting the NF- κ B signaling pathway (Table 1) [28, 29].

Above the mentioned findings, further therapeutic applications of this miRNA can be classified into four chief categories. First, it was reported that the delivery of miR-21-5p by mesoporous silica nanoparticles (MSNs) to endothelial cells of a porcine model of myocardial infarction increased the expression of Vascular endothelial growth factor A (VEGF-A) and promoted angiogenesis. Therefore, an MSN/miR-21-5p complex was engineered to be injected as an angiogenic therapy, which is a strategy for treating myocardial infarction (Table 1). This approach holds promise for clinical translation, as MSN/miR-21-5p complexes could be developed as an injectable pro-angiogenic therapy for patients with MI, potentially enhancing post-infarction myocardial repair and reducing adverse remodeling [30].

Second, the beneficial effect of this microRNA on the myocyte's apoptosis and the size of the infarcted area observed in a couple of studies shed light on the therapeutic potential of miR-21 [31, 32]. For instance, it was reported that the activation of mesenchymal stromal cells (MSCs) with IFN- γ led to the upregulation of miR-21 in the exosomes derived from these cells through the induction of STAT1. Then, increased miR-21 suppressed the expression of BTG anti-proliferation factor 2 (BTG2), a molecule known for its anti-proliferative effects, resulting in the reduction of apoptosis in H9c2 cells (Table 1) [33]. In addition, in another study, MSC-derived exosomes effectively mitigated hypoxia-induced inflammation and apoptosis in H9c2 cells, primarily by upregulating miR-21-5p. Notably, miR-21-5p directly targeted the 3'UTR of YAP1, leading to its inhibition and enhancing the protective effects of the exosomes [34]. Furthermore, the disruption of miR-21-5p function significantly weakened these beneficial outcomes. Also, miR-21 diminishes apoptosis induced by hydrogen peroxide in C-Kit⁺ cardiac stem cells (Cardiac stem cells that

Table 1 Possible molecular pathways regulated by miR-21, their effects, and associated cardiovascular diseases

Target pathway or molecule	Effect of miR-21	Related cardiovascular disease	References
TGF- β /Smad7 pathway	Promotes fibrosis by activating fibroblasts	Myocardial infarction (MI)	[4, 17, 19]
PTEN/Akt pathway	Protects against ischemia-induced apoptosis	Coronary artery disease (CAD)	[7, 8]
PDCD4	Protects against reactive oxygen species	Myocardial infarction (MI)	[24–26]
HIPK3/FAS	Reduces apoptosis	Myocardial infarction (MI)	[40]
VEGF-A	Enhances angiogenesis	Myocardial infarction (MI)	[29]
NF- κ B pathway	Mitigates hypoxic injury	Myocardial infarction (MI)	[27, 28]
GAS5/miR-21-5p interaction	Reduces inflammation	Cardiomyopathy (CM)	[68]
STAT1/BTG2	Reduces apoptosis	Myocardial infarction (MI)	[32]

express the c-Kit receptor, which is a marker for identifying these cells) in male rats via the PTEN/PI3K/Akt signaling pathway (Fig. 1) [35].

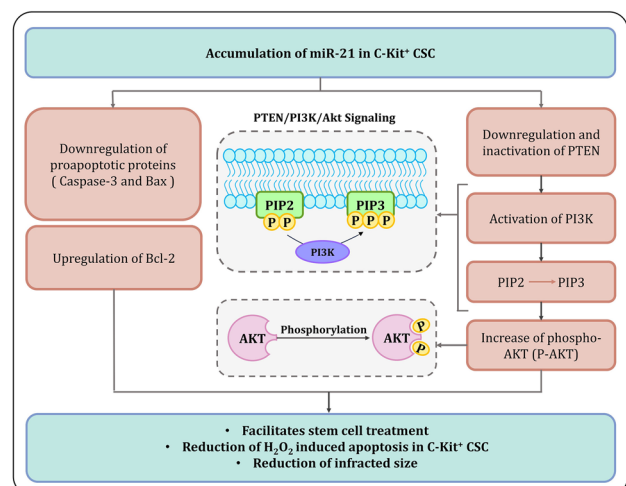
Third, it was noted that miR-21 might have a crucial role in stem cell therapy, a treatment for myocardial infarction. In this regard, a study has indicated that the overexpression of miR-21 can enhance the migration and localization of mesenchymal stem cells (MSCs) to the infarcted region [36]. Nevertheless, resident progenitor cells within the myocardium, known as cardiac progenitor cells (CPCs), have provided a new perspective on a potentially more effective approach to treating MI. However, there exists a minor issue when utilizing CPCs as a treatment approach, which is the limited survival rate of these cells. Fortunately, research has revealed that miR-21 and other miRNAs can enhance the viability of CPCs, offering a promising long-term therapeutic strategy [37].

Fourth, due to the protective effect of miR-21 against apoptosis, this miRNA could be applicable for preventing the damage caused by reperfusion after an ischemic condition called ischemic/reperfusion injury (IRI) [8, 38, 39]. Extensive research has revealed that miR-21 is upregulated after the knockdown of lncRNA GAS5, leading to reduced PTEN mRNA levels. This, in turn, leads to the activation of AKT through phosphorylation, which induces miR-21 expression and decreases apoptosis in hypoxic conditions [40]. Additionally, elevated levels of miR-21, suppress the expression of homeodomain interacting protein kinase 3 (HIPK3), decrease FAS-mediated apoptosis, inhibit BAX expression, and increase the expression of BCL2 (Table 1) [41]. While these observations elucidate how miR-21 decreases the size of the infarct and exhibits its potent cardioprotective function, the findings of another study show that the levels of miR-21 were not associated with the occurrence of IRI, highlighting an urgent need for further research to clarify whether this miRNA could be used for preventing IRI [42].

Moreover, miR-21's beneficial effects extend beyond its potential therapeutic uses to include its diagnostic and predictive capabilities as well. It was reported that the expression of miR-21 was higher in patients diagnosed with acute myocardial infarction (AMI) and could be used as a diagnostic marker for this disease [43]. In a study of 198 patients with AMI measured five days after primary percutaneous coronary intervention (PCI), miR-21 levels were found to be higher in those with LVR compared to patients without LVR. This suggested that miR-21 (OR = 1.119, $p < 0.0001$) could serve as a predictor of LVR in these patients [20].

Discrepancies in results may be due to differences in experimental models, delivery methods, or cellular environments, highlighting the need for standardized research protocols. Also, one of the major obstacles in miR-21-based interventions is their lack of organ and cell specificity. miR-21 functions differently depending on the tissue type and disease progression, making it challenging to precisely target cardiovascular cells without affecting other physiological processes [44]. However, due to the mentioned promising characteristics and potential that is attributed to miR-21, further investigations could result in favorable advancements in the fields of therapy and diagnosis.

Fig. 1 The implications of miR-21 accumulation in C-Kit⁺ CSC. miR-21 exerts a negative regulatory effect on PTEN, resulting in the conversion of PIP2 to PIP3 via the activation of PI3K. Consequently, this process leads to an increase in phosphorylated AKT levels. Additionally, this specific microRNA downregulates the expression of caspase 3 and Bax while simultaneously upregulating Bcl-2, thereby influencing cellular survival pathways



3 Coronary artery disease (CAD)

The accumulation of lipoprotein droplets is the main reason behind atherosclerosis, which is also known as coronary artery disease (CAD). These droplets go through the process of oxidation and attract scavenger macrophage cells, which then form foamy cells. This sequence of events ultimately leads to the formation of atherosclerotic lesions, which can also be associated with the development of other diseases such as chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM) [45–47]. Therefore, it is crucial to identify this disease at an early stage as it can prevent the development of further complications. In this respect, miR-21 is associated with this medical condition, suggesting that monitoring its expression levels could be beneficial.

It was suggested that miR-21-5p and miR-21-3p could potentially be utilized as a non-invasive diagnostic tool for CAD, serving as a new biomarker [48]. In a study, the plasma levels of miR-21 were measured by Quantitative reverse transcription polymerase chain reaction (QRT-PCR) in 80 of 105 screened patients with stable coronary artery disease. These individuals participated in dobutamine stress echocardiography before undergoing coronary angiography, which revealed a notable up-regulation of miR-21 in this patient population. Also, among the studied patients, 41 of them that exhibited coronary stenosis exceeding 80%, showed an increase in the levels of circulating miR-21 [49]. On the contrary, in another study including 67 patients with CAD among other patients, it was observed that the serum levels of miR-21-5p were decreased [50]. The differences in the results of these studies may be attributed to variations in methodology, sample processing, and study design. In the first study, plasma samples were used, and miR-21 levels were assessed dynamically at multiple time points, including before, immediately after, and 24 h following dobutamine-induced stress, capturing its acute response to ischemia [49]. In contrast, the other study utilized serum samples, and unlike the earlier study, it measured baseline miR-21-5p levels at a single time point without evaluating the effects of acute stress [50].

Shear stress is a key regulator of endothelial function and contributes to several pathological processes in CAD [51]. miR-21 has been identified as a key factor in modulating endothelial cell biology in response to shear stress. The expression of this molecule is significantly upregulated in human endothelial cells subjected to unidirectional shear stress (USS), with a 5.2-fold increase observed in treated cells compared to controls ($p = 0.002$). This upregulation of miR-21 contributes to reduced apoptosis and enhanced nitric oxide (NO) production via activation of the PI3K/Akt/eNOS pathway, highlighting miR-21's potential role in protecting endothelial function under shear stress conditions, which could be beneficial in managing CAD [52].

Moreover, based on a few findings, the possible therapeutic application of this molecule seems quite appealing. In some research, it was noticed that miR-21 may act as a supplementary aid in the management of CAD. For example, drug-eluting stents (DES) have been one of the treatments for CAD. However, similar to numerous other treatment approaches that come with unexpected complications, this method is no exception and the utilization of rapamycin-coated stents has raised concerns about the possibility of thrombosis and apoptosis. Hence, it was suggested that a supplementary factor might help to prevent the mentioned complications, which was later identified as miR-21 found in MSC-derived exosomes due to being a pro-angiogenic miRNA [53]. In addition, as mentioned previously, miR-21 could protect the myocardium against ischemia injury by regulating the PTEN/Akt signaling pathway. Consequently, it can also protect the coronary wall tissue from hypoxia-induced damage and inhibit the progression of CAD (Table 1) [7, 8]. Research on Apoe/miR-21 knockout mice revealed more severe atherosclerotic lesions and increased foam cell formation. It also showed greater macrophage infiltration, highlighting miR-21's role in atherosclerosis. Moreover, targeted delivery of a miR-21 mimic using ultrasound-targeted microbubbles has demonstrated the potential to stabilize vulnerable plaques, presenting miR-21 as a promising therapeutic agent for managing CAD [54].

Despite the very minimal results and some minor inconsistencies in the findings above, the reported changes in the level of this miRNA in patients with CAD suggest a very likely association between miR-21 and CAD. However, as noted, the exact alternation pattern in the level of this molecule in patients with CAD is antithetical and not fully understood yet. The dynamic nature of miR-21 in response to ischemic stress suggests that its diagnostic utility may depend on the timing of measurement, which could explain the observed inconsistencies across studies. Furthermore, differences in plasma and serum miRNA profiles highlight the need for standardized protocols in miRNA isolation and quantification to improve reproducibility and clinical applicability. Without such standardization, variations in methodology may continue to hinder the establishment of miR-21 as a reliable biomarker for CAD. Also, the possible therapeutic application of miR-21 as a pro-angiogenic factor merits further research in this field, particularly concerning the long-term clinical outcomes of miR-21-based interventions.

4 Heart failure (HF)

Heart failure (HF) is a condition in which the heart's pumping function is impaired. This medical condition typically manifests through breathlessness, lower limb swelling, and orthopnea and is diagnosed by following the symptoms [55, 56]. However, based on the results of a few studies, promising applications of miR-21 hold potential as a diagnostic and therapeutic tool for HF, marking a notable advancement in the field of cardiac healthcare.

A study aimed to define the biomarker potential of miRNAs in HF patients revealed that miR-21 was significantly up-regulated in the sera of patients with systolic heart failure [10]. It was reported that in the failing heart, miR-21 expression is notably increased in fibroblasts, leading to enhanced ERK-MAP kinase activation through the suppression of sprouty homologue 1 [57].

While miR-21 shows promise in diagnostics, its therapeutic potential could be equally beneficial. As reported, the up-regulation of this molecule reduces inflammation by shifting macrophages from a pro-inflammatory to an anti-inflammatory state. This transition helps resolve inflammation more effectively and supports cardiac healing after myocardial infarction. Therefore, it raises the hypothesis that it could be utilized as a therapeutic tool. In this regard, nanoparticles (NPs) were used to deliver a miR-21 mimic to cardiac macrophages following myocardial infarction (MI). The results of this procedure demonstrated that as expected, miR-21 could prevent ventricular remodeling and HF after MI [9]. However, this method has some limitations such as limited cellular uptake and insufficient stability in vivo [58]. Also, in mice undergoing pressure-overload modeling, the silencing of miR-21 resulted in decreased cardiac ERK-MAP kinase activity, which led to cardiac dysfunction [55]. Similarly, in an in vivo study, blocking miR-21 with a specific antagomir reduced ERK-MAP kinase activity, inhibited interstitial fibrosis, and suppressed cardiac dysfunction, further supporting the potential of miR-21 as a therapeutic target for heart disease [57].

The mentioned findings provide important insights into the potential use of miR-21 as a tool for treating cardiac failure, given its impact on inflammation. However, challenges such as optimal dosing, targeted delivery, and long-term safety remain to be addressed before clinical application. Moreover, the results indicate that miR-21 may be useful in diagnosing and prognosing this medical condition. But, due to the limitations of the available studies, advancing in this field will necessitate a more comprehensive understanding of the mechanisms underlying HF development.

5 Cardiomyopathy

Cardiomyopathy is a critical myocardial disorder that disrupts the heart's operation. It is categorized into two main groups: dilated and hypertrophic cardiomyopathies. The main characteristics of hypertrophic cardiomyopathy (HCM) include myocardial hypertrophy and fibrosis, primarily attributed to mutations in different structural genes [59–61]. The impact of these conditions highlights the need for accurate diagnosis and effective treatment to improve health and prevent complications. In this context, miR-21 has gained significant attention, offering new insights and potential advancements in the field.

The relevance between the levels of miR-21 and the progression of cardiomyopathy has been investigated in several studies with particular emphasis on the diagnostic capacity of this molecule [62]. For instance, in a case–control study including 10 control individuals, 27 individuals with HCM, and 13 individuals with hypertensive cardiomyopathy, it was observed that the expression of miR-21 was increased in patients with HCM and hypertensive cardiomyopathy ($p < 0.001$) [60]. Similarly, in another case–control analysis comparing control subjects and subjects with dilated cardiomyopathy, it was evident that the expression of this microRNA was significantly upregulated in patients with dilated cardiomyopathy [63]. In addition, the results of other studies conducted on patients with ischemic cardiomyopathy (ICM) and Chagas cardiomyopathy (ChCM) were in line with the mentioned findings, indicating an increased level of miR-21 in ICM and ChCM patients [64, 65]. In this regard, these increases in the levels of miR-21 in ICM patients could merit its diagnostic capacity [66]. Also, in patients diagnosed with diabetes mellitus who are prone to diabetic cardiomyopathy, miR-21 was increased when compared to healthy individuals [67, 68]. More importantly, this molecule, which is also overexpressed in viral myocarditis (VMC), could potentially contribute to the advancement of VMC to dilated cardiomyopathy (DCM) [69]. However, a study on T2DM patients examined miR-21 expression in those with and without diabetic cardiomyopathy. The results showed a decreased level of this

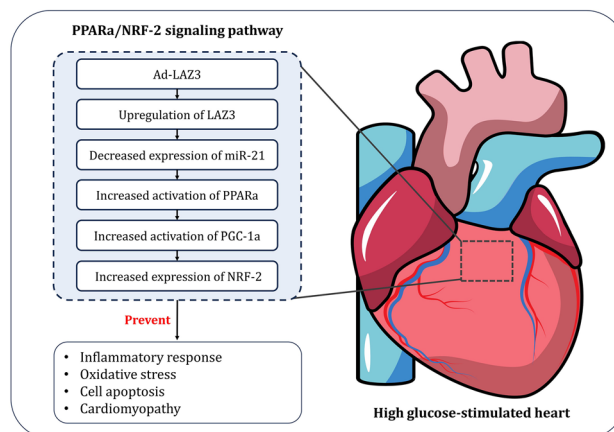
microRNA in the diabetic cardiomyopathy group, which contradicts other results and highlights the need for further studies in this area [70]. Also, in the diastolic dysfunctional heart of leptin receptor-deficient (db/db) mice, a decrease in miR-21 levels was observed [71, 72].

Tropomyosin 1 (TPM1) protein is a crucial component of the sarcomere and facilitates the interaction between actin and myosin during muscle contraction. Therefore, researchers have investigated the connection between the TPM1 gene and DCM. In this regard, a case–control study involving 245 patients with DCM and 245 healthy controls investigated the association between TPM1 3'UTR polymorphisms and DCM susceptibility, along with their potential interaction with miR-21 levels. The study found that individuals carrying the G allele at the rs6738 locus had a 1.69-fold increased risk of developing DCM compared to A allele carriers (95% CI: 1.22–2.33, $P=0.001$). Furthermore, plasma levels of miR-21 were significantly higher in individuals with the AA genotype at rs6738 compared to AG and GG genotypes ($P<0.001$). This suggests that genetic variations in TPM1 could influence miR-21 expression levels, potentially affecting TPM1 regulation and contributing to DCM progression [72]. Furthermore, one of the factors that contribute to cardiac dysfunction is cardiac fibrosis due to excessive collagen production. Through investigations, it was reported that high glucose could increase the rate of fibroblast proliferation and collagen synthesis [5]. miR-21 has been widely recognized as a pro-fibrotic factor, not only in the heart but also in other organs such as the liver and lungs. For instance, in liver fibrosis, miR-21 promotes collagen synthesis by activating hepatic stellate cells (HSCs) through Spry1/ERK/NF- κ B, PTEN/Akt, PDCD4/AP-1, and Smad7/Smad2/3/NOX4 pathways, leading to oxidative stress and inflammation. Similarly, in pulmonary fibrosis, miR-21 is upregulated by TGF- β 1, which suppresses Smad7 and enhances p-Smad2, driving epithelial-mesenchymal transition (EMT) and fibroblast activation [73, 74]. Consistently, its expression has been increased in cardiac fibroblasts exposed to high glucose (HG), leading to enhanced fibroblast proliferation and collagen accumulation. This highlights miR-21's crucial role in high glucose-induced cardiac fibrosis and its contribution to the progression of diabetic cardiomyopathy [5]. Therefore, targeting this microRNA could potentially help prevent diabetic cardiomyopathy [75]. Following this result, in another study, it was reported that overexpression of LAZ3 (by gene delivery of LAZ3 with Ad-LAZ3) protects the heart against high glucose and prevents the progression of diabetic cardiomyopathy through the miR-21/PPAR α /NRF-2 signaling pathway. The sequence of events in this pathway includes the overexpression of LAZ3, which decreases the expression of miR-21, ultimately leading to an increase in the activation of NRF-2 and consequently to protection against the advancement of diabetic cardiomyopathy (Fig. 2) [76].

Moreover, the presence of hyperglycemia enhances the expression of a specific long noncoding RNA known as GAS5. This molecule interacts with miR-21-5p, hence the inhibition of miR-21-5p causes a decrease in GAS5 levels, which protects human cardiomyocytes against inflammation. This underscores the potential therapeutic significance of regulating GAS5/miR-21-5p in diabetic cardiomyopathy (Table 1) [77].

The findings presented suggest that miR-21 holds considerable promise as both a diagnostic and therapeutic target in cardiomyopathy. Its consistent up-regulation across various cardiomyopathy subtypes, such as hypertrophic, dilated, ischemic, and diabetic forms, underscores miR-21's potential as a valuable biomarker for early diagnosis and monitoring. However, inconsistencies in study results, especially in the context of diabetic cardiomyopathy, highlight the need for further investigations to better define miR-21's precise impact. Advancing research in this area could pave the way for innovative diagnostic tools and treatments.

Fig. 2 PPAR α /NRF-2 signaling pathway. The heightened expression of Laz 3 results in a reduction of miR-21 levels, ultimately contributing to an enhanced activation of NF2. This process plays a significant role in providing a protective effect against the progression of dilated cardiomyopathy (DCM)



6 Discussion

miR-21 has emerged as a key regulatory molecule in cardiovascular diseases, demonstrating both protective and pathological roles depending on the disease context. This review highlights its dual function in various cardiovascular conditions, particularly its involvement in endothelial function, vascular inflammation, and myocardial remodeling. Consistent with previous studies, miR-21 has been shown to modulate inflammatory responses, influence fibrosis, and regulate cellular survival mechanisms, reinforcing its potential role in cardiovascular pathology [6, 17, 57].

Therapeutic strategies targeting miR-21, although promising, present several challenges. Off-target effects are a major concern, as miR-21 is involved in multiple physiological pathways beyond cardiovascular regulation [44]. Furthermore, previous studies have also indicated that miR-21 modulation may contribute to fibrosis and immune dysregulation, underscoring the necessity for targeted delivery systems and precise dosing strategies [4, 5, 19]. Another crucial consideration is balancing its protective and pathological roles, as excessive expression in certain conditions may lead to unintended adverse effects. Moreover, interactions between miR-21 and other molecular pathways involved in cardiovascular disease progression require further exploration.

While existing research supports the involvement of miR-21 in endothelial function and cardiovascular pathology, the precise mechanisms underlying its influence on vascular homeostasis remain partially elucidated. Emerging evidence suggests that miR-21 exerts its effects through regulation of key signaling pathways such as PTEN/Akt and PI3K/Akt/eNOS, which govern inflammation and apoptosis [7, 8, 52]. However, the extent to which these pathways interact with broader regulatory networks remains an open question.

From a translational perspective, miR-21 shows significant potential as a biomarker for early detection and prognosis of cardiovascular disease. Several studies have shown that miR-21 can predict myocardial remodeling after injury, making it useful for assessing risk [20]. Furthermore, miR-21 mimics or inhibitors could offer new therapeutic options for reducing inflammation and preserving endothelial function, which would complement current treatment strategies [54, 77]. Future studies should prioritize large-scale clinical trials to validate these findings and optimize miR-21-based interventions for broader clinical application.

The role of extracellular vesicles, especially exosomes, in delivering miR-21 is another key area of research. Exosomal miR-21 plays a role in communication between cells in the cardiovascular system. It offers advantages over viral vectors, such as delivering LAZ3 with Ad-LAZ3, as it has low immunogenicity and high biocompatibility [33, 76, 78]. Investigating the mechanisms of exosomal miR-21 transport and its uptake by target cells may facilitate the development of miRNA-based therapies with improved stability and therapeutic efficacy.

Despite these promising insights, several critical knowledge gaps remain. One significant limitation is the inconsistency in reported miR-21 levels across different cardiovascular conditions, which may be attributed to variations in patient populations, sample collection methods, and analytical techniques. Additionally, while experimental models suggest a strong cardioprotective effect of miR-21, the long-term consequences of its overexpression in human subjects are not yet fully understood. To enhance reproducibility and facilitate clinical translation, standardization of miRNA quantification methods is essential.

7 Conclusion

This study underscores the multifaceted role of miR-21 in cardiovascular diseases, emphasizing its influence on endothelial function, inflammation, and myocardial remodeling. While miR-21 holds significant promise as a biomarker and therapeutic target, several challenges persist, including inconsistencies in reported findings and potential risks associated with miRNA-based therapies. Standardization of detection methods and further validation through clinical trials are critical to ensuring its successful translation into clinical practice. Ultimately, miR-21 presents an exciting target for future cardiovascular research, offering a potential link between molecular mechanisms and therapeutic advancements.

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Author contributions E.M. performed data collection, conceptualized the review article, prepared the figures (by Microsoft PowerPoint, Microsoft Excel, and Adobe Illustrator), and was the major contributor to writing the manuscript. S.H.M. critically revised the manuscript, made

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Declarations

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