

ORIGINAL RESEARCH ARTICLE

Profiling the 8-nucleotide microRNA targets in genes involved in type 2 diabetes mellitus in association with oxidative and endoplasmic reticulum stress

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Abstract

Type 2 diabetes mellitus (T2DM) is one of the top 10 global killers. The association between oxidative stress and T2DM has been reported, in which oxidative stress triggers the life-threatening consequences, including stroke, nephropathy, and myocardial infarction. MicroRNA (miRNA)-based therapies are thought to revolutionize early medical interventions, potentially enabling the treatment of T2DM. miRNAs are 20–22 nucleotide non-coding sequences used to silence genes at the post-transcriptional level. Gene testing registry, TargetScan, and other bioinformatic databases were used to identify the oxidative- and endoplasmic reticulum (ER) stress-linked genes and their targeted miRNAs (8-mers and species conserved) associated with T2DM. ShinyGO was used to establish links between T2DM and its associated genes. We identified putative common miRNAs, such as miR-26-5p/miR-124-3p.1/miR-124-3p.2/miR-98-5p/miR-17-5p/miR-519-3p/miR-20-5p/miR-93-5p/miR-106-5p, which may involve in the regulation of T2DM-associated genes. In addition, several common miRNAs were also considered in the regulation of pathological conditions. The miRNAs for T2DM associated with oxidative stress are as follows: miR-33-5p/miR-506-3p/miR-7-5p/miR-107/miR-93-5p, and for T2DM associated with ER stress are as follows: miR-195-5p/miR-181-5p/miR-101-3p.1/miR-424-5p/miR-145-5p/miR-519-3p/miR-16-5p. Overall, this study provides a framework for the rational selection of miRNAs for nucleic acid-based therapies and guides future studies in maximizing the potential of miRNAs against oxidative- and ER-stress associated with T2DM.

Keywords: miRNAs; Type 2 diabetes mellitus; Oxidative stress; Endoplasmic reticulum stress

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1. Introduction

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene activity after transcription and mediate RNA interference, leading to gene silencing or inhibition of translation to control gene expression.¹ In the human genome, around 2,600 miRNAs have been identified, which regulate thousands of protein-coding genes.² These miRNAs are associated with apoptosis, immunity, stress response, and angiogenesis, and they

act as biomarkers in the diagnosis of several disorders.³ Numerous studies have shown a link between miRNAs and various diseases.⁴ Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance and progressive β -cell dysfunction, resulting in chronic hyperglycemia and dyslipidemia, triggering downstream oxidative and endoplasmic reticulum (ER) stress.⁵ Oxidative stress is an imbalance between the production and clearance of reactive oxygen species (ROS), resulting in the accumulation of oxidants.⁶ ER stress also contributes to oxidative stress by generating ROS.⁷ Insulin resistance refers to a reduced responsiveness of insulin-target tissues—primarily the liver, skeletal muscle, and adipose tissues—to circulating insulin, whether at normal or elevated levels.⁸ In the initial phase, this dysfunction is often compensated for by increased insulin production from pancreatic β -cells, leading to hyperinsulinemia. However, as the condition progresses, β -cell compensation frequently becomes insufficient, leading to elevated fasting and postprandial blood glucose levels and the transition from insulin resistance to overt T2DM.⁹ Persistent hyperglycemia and lipid accumulation subsequently promote excessive mitochondrial ROS generation and disrupt ER protein folding homeostasis. Consequently, oxidative and ER stress develop as secondary insults that intensify insulin resistance, impair β -cell function, and contribute to diabetic complications.¹⁰ Recent clinical and experimental findings therefore conceptualize T2DM as a disease arising from the interplay between systemic insulin resistance and inadequate β -cell adaptive capacity, rather than solely from oxidative stress.¹¹ Both classical metabolic studies and modern molecular signaling analyses reveal that individuals with T2DM display reduced insulin-driven glucose uptake in skeletal muscle, impaired hepatic glucose suppression, and defects in the insulin receptor (INSR), INSR substrate (IRS)1/2–phosphoinositide 3-kinase (PI3K)–protein kinase B (Akt) signaling cascade; these defects include diminished expression or activity of *IRS* and *AKT2*, altered association of PI3K subunits, and occasionally decreased INSR density or surface availability.¹² While receptor binding affinity is usually normal in typical T2DM, it can be altered in rare receptoropathies or specific receptor isoform variants. Within this mechanistic context, several genes highlighted in the current *in silico* analysis, such as *IRS1*, *IRS2*, *AKT2*, and *PIK3R1*, serve as key modulators of insulin signaling and sensitivity.¹³ This suggests that the miRNAs identified here may influence not only oxidative and ER stress responses but also the core mechanisms driving primary insulin resistance and the subsequent diabetic cascade.

In T2DM, persistent high glucose and lipid levels create a self-reinforcing interaction between secondary

parameters, such as oxidative stress and ER stress, based on the vicious cycle of insulin resistance and impaired INSR signaling in classic target tissues (liver, skeletal muscle, and adipose tissue), which collectively worsen β -cell dysfunction and increase insulin resistance.¹⁴ Continuous metabolic overload increases the production of ROS from mitochondria and nicotinamide adenine dinucleotide phosphate oxidases, disrupting the ER's redox environment and impairing the formation of disulfide bonds necessary for proper proinsulin folding. This disturbance activates unfolded protein response (UPR) pathways through sensors such as protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 α (IRE1 α), and activating transcription factor 6 (ATF6).¹⁵ Prolonged engagement of these UPR mechanisms elevates pro-apoptotic factors, including CCAAT/enhancer-binding protein homologous protein and ER oxidoreductases like ER oxidoreductin 1, promoting additional ROS production and inducing calcium leakage from the ER to mitochondria. These events enhance mitochondrial damage, oxidative injury, and β -cell apoptosis.¹⁶ Evidence from diabetic models and human studies indicates that, due to their limited antioxidant capacity, β -cells accumulate misfolded proinsulin and ER stress indicators together with increased lipid peroxidation and oxidative load. This supports the notion that oxidative stress not only arises from but also intensifies ER stress, ultimately driving β -cell dedifferentiation, muscle wasting, and diabetic complications.¹⁷ Consequently, therapeutically targeting the ER-oxidative stress interplay using chemical chaperones, ER stress inhibitors, or antioxidant strategies has shown potential to re-establish redox equilibrium, reduce UPR-mediated apoptosis, and enhance metabolic regulation, making this interaction a major focus of current diabetes research.¹⁸

Beyond their established role in glucose regulation, miRNAs are now recognized as key modulators of adipose tissue function, coordinating processes such as adipocyte differentiation, lipid metabolism, inflammation, and insulin responsiveness.¹⁹ Experimental evidence from 3T3-L1 cell models and animal studies indicates that miR-103, miR-107, and miR-143 are upregulated during adipogenesis, facilitating the maturation of preadipocytes into adipocytes by promoting adipogenic transcription factor expression and triglyceride deposition.²⁰ However, in the context of obesity, the expression of these lipid- and differentiation-related miRNAs becomes dysregulated within white adipose tissue; this alteration contributes to chronic low-grade inflammation, adipocyte enlargement, and disturbances in insulin signaling.²¹ Mechanistic research has further shown that miR-103/107 target caveolin1 and other components of the INSR complex,

meaning that their aberrant expression in obesity can exacerbate insulin resistance and disrupt downstream cascades, such as Akt/mechanistic target of rapamycin and ER stress-related pathways, processes that also play pivotal roles in T2DM pathogenesis.²² Clinical and translational investigations increasingly suggest that obesity imprints a specific circulating miRNA profile that evolves further in the presence of diabetes. High-throughput sequencing studies in human cohorts reveal distinct circulating and exosomal miRNA signatures discriminating obese individuals with T2DM from those without, with progressive shifts observed from healthy controls to obese non-diabetic and diabetic subjects.²³ Growing evidence identifies adipose-derived and extracellular vesicle-associated miRNAs as critical mediators of inter-organ metabolic communication and as promising biomarkers for obesity-related disorders, including T2DM and cardiovascular disease.²⁴ Within the framework of the current *in silico* analysis, these observations suggest that obesity-induced remodeling of adipose and circulating miRNA patterns may intensify or modify the regulatory influence of stress-associated miRNAs on their T2DM, oxidative stress, and ER stress-related gene targets, thereby shaping both disease progression and the translational applicability of the predicted miRNA gene interaction networks.

For disease prevention and therapy, various bioinformatics tools have been used to identify novel molecular therapeutic interventions.²⁵ We intended to evaluate the importance of different miRNAs in controlling the expression of various biomarkers implicated in the development and progression of disease. The gene testing registry of the National Center for Biotechnology Information (NCBI) was used to obtain T2DM gene names associated with oxidative and ER stress. Potential miRNA targets for all genes were identified using Human TargetScan (7.2.2018, Whitehead Institute, United States of America). Several novel miRNA-gene pairs emerged from this prediction, guiding the discovery of new miRNA-based biomarkers for T2DM in association with oxidative and ER stress diagnosis. We aim to identify the most suitable miRNAs to design an effective therapeutic strategy against T2DM-linked oxidative and ER stress.

2. Materials and methods

2.1. Gene selection from the NCBI (gene testing registry) and Online Mendelian Inheritance in Man

The NCBI offers a comprehensive set of online biological information and data resources, including biomedical and biotechnology information. It collects data from a variety of databases, including NCBI epigenomics, GenBank

nucleic acid sequence database, and PubMed. NCBI is the repository for information on related diseases and the underlying genes. Online Mendelian Inheritance in Man (OMIM) is a comprehensive, reliable, and up-to-date repository of human genes and genetic disorders, assembled to support clinical genetic investigations and human biological research. We used the NCBI (Figure 1A) and the OMIM website (Figure 1B) to obtain sequencing panels for T2DM- and stress-related genes.

2.2. TargetScan as an *in silico* tool for the prediction of miRNA-targeted genes

Various software uses different approaches to predict miRNA targets. Site accessibility, free energy, seed compatibility, and conservation are the four most commonly used characteristics for miRNA target prediction methods. miRTarBase, miRDB, miRWalk, and miRSystem²⁶ are the most extensively used software for predicting miRNA targets and facilitate statistically based comparison of results from various established tools. The most extensively used popular miRNA prediction tools are SVMicrO,²⁷ miRanda,²⁸ and TargetScan.²⁹

TargetScan is a bioinformatics web server that identifies biological targets of miRNAs by checking for conserved 8mer, 7mer, and 6mer regions that are related to each miRNA's seed region (Figure 1C). We filtered candidates based on miRNA conservation across human, rat, and mouse, together with 8-nucleotide (8-nt) seed-site analysis (Figure 1D). This approach also provided percentile scores and context++ values, which helped to assess the reliability of the predicted interactions.

The TargetScan interface allows users to query the database by entering either gene or miRNA identifiers to retrieve predicted targets. We applied TargetScan to analyze all NCBI-documented genes associated with disease pathogenesis and stress-related pathways. We selected the species (human, rat, and mouse), entered the names of targeted genes, and obtained information on miRNA targets for different sites. We also adopted a complementary strategy by entering our miRNA candidates into the second search field, which returned a comprehensive list of genes sharing those miRNA targets. From this output, we identified our genes of interest and retrieved detailed information on conserved binding sites and miRNA positional context.

3. Results

3.1. Genes associated with T2DM and their interacting miRNAs

Our analysis included 13 genes involved in T2DM pathogenesis progression regulated by miRNAs with an 8-nt

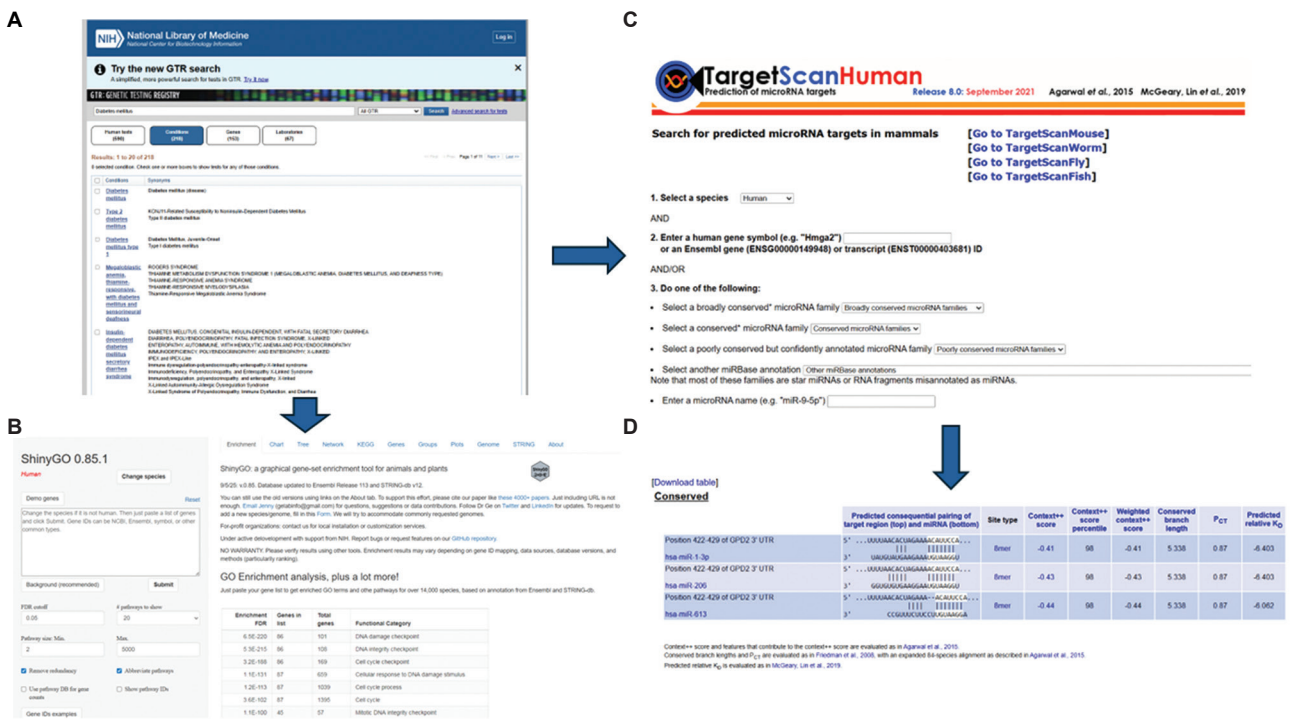


Figure 1. Bioinformatics analysis. (A) Disease-linked genes selection from the National Center for Biotechnology Information (gene testing registry). (B) Gene enrichment analysis using ShinyGO. (C) microRNA predicted by TargetScan. (D) Species conserved 8mer miRNA selection.

binding seed region, as shown in Table 1. *GPD2* expression was regulated by more than seven miRNAs, *HMGAI* was regulated by nine miRNAs, and *IRS2* was regulated by six miRNAs. All the main genes are represented graphically together with their corresponding 8-nt miRNAs, as shown in Figure 2. This distribution highlights the complex post-transcriptional regulation of key metabolic and signaling pathways implicated in T2DM. The higher number of 8-nt miRNA interactions for *HMGAI*, *GPD2*, and *IRS2* suggests that these genes may act as critical regulatory hubs in disease progression.

3.2. Genes associated with oxidative stress and their corresponding miRNA regulators

Our analysis focused on 18 genes involved in oxidative stress progression regulated by miRNAs with an 8-nt binding seed region, as shown in Table 2. *ERCC6*, *STK3*, *DHCR24*, and *ANK2* were regulated by three miRNAs, *AIFM1* was regulated by five distinct miRNAs, and *STC1* by 10 miRNAs. Figure 3 shows all the important genes together with their corresponding 8-nt miRNAs. This pattern suggests a layered regulatory network in which a subset of oxidative stress-related genes receives particularly dense miRNA input. The higher number of 8-nt miRNA interactions observed for *STC1* and *AIFM1* indicates

Table 1. List of microRNA targeting type 2 diabetes-associated genes

No.	Target genes	Species conserved microRNAs
1	<i>KCNJ11</i>	miR-98-5p, let-7-5p
2	<i>IRS1</i>	miR-145-5p, miR-183-3p. 1
3	<i>NEUROD1</i>	miR-30-5p, miR-101-3p. 2, miR-137, miR-153-5p, miR-101-3p. 1, miR-190-5p
4	<i>HMGAI</i>	miR-142-3p. 1, miR-15-5p, miR-16-5p, miR-195-5p, miR-424-5p, miR-497-5p, miR-26-5p, miR-103-5p, miR-107
5	<i>IGF2BP2</i>	miR-98-5p, miR-181-5p, let-7-5p, miR-9-5p
6	<i>WFS1</i>	miR-519-3p, miR-17-5p, miR-93-5p, miR-20-5p, miR-106-5p
7	<i>PTPN1</i>	miR-1-3p, miR-206, miR-124-3p. 2, miR-506-3p
8	<i>TCF7L2</i>	miR-155-5p, miR-1271-5p, miR-96-5p
9	<i>HNF1B</i>	miR-217, miR-375, miR-802, miR-24-3p, miR-101-3p. 2
10	<i>IRS2</i>	let-7-5p, miR-33-5p, miR-98-5p, miR-203a-3p. 1, miR-7-5p miR-181-5p
11	<i>GPD2</i>	miR-128-3p, miR-1-3p, miR-132-3p, miR-27-3p, miR-206, miR-181-5p, miR-212-3p
12	<i>AKT2</i>	miR-126-3p. 2, miR-137, miR-124-3p. 1, miR-194-5p
13	<i>PPARG</i>	miR-27-3p, miR-130-3p, miR-454-3p, miR-301-3p

Table 2. List of microRNA targeting oxidative stress-associated genes

No.	Putative target genes	Species conserved microRNAs
1	<i>MRPS25</i>	miR-33-5p
2	<i>FOXO4</i>	miR-142-3p. 1, miR-23-3p
3	<i>CTNNB1</i>	miR-142-3p. 2
4	<i>LRRK2</i>	miR-205-5p
5	<i>PARP1</i>	miR-7-5p, miR-129-3p
6	<i>CACNA1C</i>	miR-19-3p, miR-33-5p, miR-26-5p
7	<i>STC1</i>	miR-101-3p. 1, miR-101-3p. 2, miR-146-5p, miR-30-5p, miR-190-5p, miR-17-5p, miR-20-5p, miR-93-5p, miR-106-5p, miR-519-3p
8	<i>TP73</i>	miR-455-3p. 2, miR-200bc-3p, miR-429
9	<i>NFE2L2</i>	miR-142-5p, miR-153-3p, miR-140-5p, miR-144-3p
10	<i>G3BP2</i>	miR-19-3p, miR-7-5p, miR-130-3p, miR-301-3p, miR-454-3p, miR-199-3p, miR-26-5p
11	<i>OSR1</i>	miR-17-5p, miR-20-5p, miR-93-5p, miR-106-5p, miR-519-3p, miR-451
12	<i>STK4</i>	miR-124-3p. 2, miR-506-3p, miR-23-3p
13	<i>ANK2</i>	miR-9-5p, miR-139-5p, miR-142-3p. 2
14	<i>ITPR3</i>	miR-302c-3p. 2, miR-520-3p, miR-124-3p. 2, miR-506-3p
15	<i>DHCR24</i>	miR-96-5p, miR-1271-5p, miR-124-3p. 1
16	<i>KLHDC10</i>	miR-9-5p, miR-383-5p. 1
17	<i>AIFM1</i>	miR-103-3p, miR-107, let-7-5p, miR-98-5p, miR-125-5p
18	<i>ERCC6</i>	let-7-5p, miR-98-5p, miR-29-3p

that these genes may serve as key regulatory nodes in the cellular response to oxidative stress.

3.3. Genes associated with ER stress and their interacting miRNAs

We evaluated 21 genes involved in ER stress regulated by miRNAs with an 8-nt binding seed region, as shown in Table 3. *KLF11* expression was regulated by more than seven miRNAs, *GATA6* was regulated by four miRNAs, *PIK3R1* was regulated by seven miRNAs, and *SEC16B* and *SERP1* were regulated by three miRNAs. Figure 4 shows all the important genes together with their corresponding 8-nt miRNAs. This distribution of miRNA-gene interactions underscores the complex regulatory architecture governing ER stress signaling. The higher density of 8-nt miRNA binding sites observed for *KLF11* and *PIK3R1* suggests that these genes may function as major regulatory hubs within the UPR.

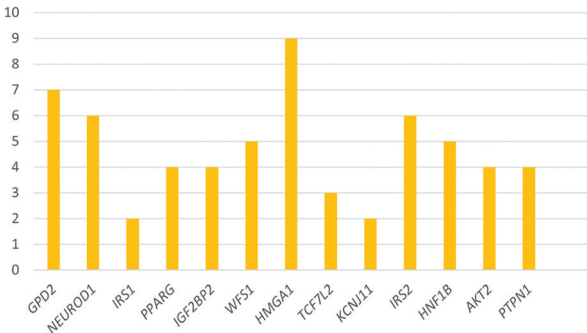


Figure 2. Number of 8-mer microRNAs predicted to target type 2 diabetes mellitus-associated genes

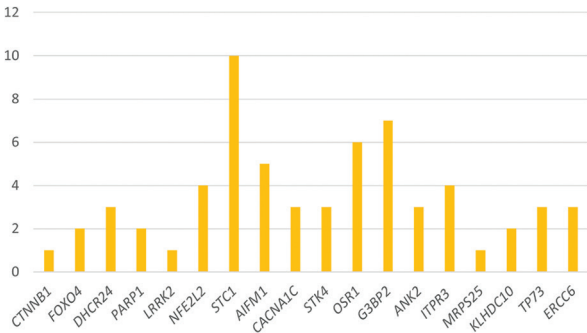


Figure 3. Number of 8-mer microRNAs predicted to target oxidative stress-associated genes

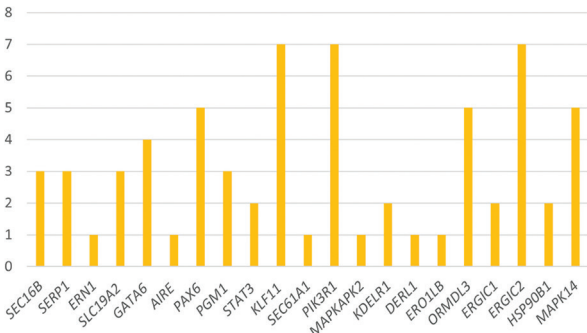


Figure 4. Number of 8-mer microRNAs predicted to target endoplasmic reticulum stress-associated genes

3.4. Commonly expressed miRNAs and their corresponding target genes in T2DM under oxidative stress

We evaluated 25 miRNAs involved in T2DM with oxidative stress. miR-98-5p is considered a key regulator of genes implicated in T2DM and oxidative stress. The *KCNJ11* gene is positioned at 11p15.1 with no introns.³⁰ The pancreatic beta-cell's Kir6.2 component of the ATP-sensitive potassium ion channels is encoded by the *KCNJ11*

Table 3. List of microRNAs targeting endoplasmic reticulum stress-associated genes

No.	Putative target genes	Species conserved microRNAs
1	<i>SEC16B</i>	miR-98-5p, miR-199-3p, let-7-5p
2	<i>HSP90B1</i>	miR-23-3p, miR-181-5p
3	<i>ERGIC2</i>	miR-25-3p, miR-32-5p, miR-92-3p, miR-363-3p, miR-367-3p, miR-194-5p, miR-135-5p
4	<i>SLC19A2</i>	miR-205-5p, miR-26-5p, miR-101-3p. 1
5	<i>KDELRL1</i>	miR-182-5p, miR-142-3p. 2
6	<i>PIK3R1</i>	miR-153-3p, miR-218-5p, miR-15-5p, miR-16-5p, miR-195-5p, miR-424-5p, miR-497-5p
7	<i>AIRE</i>	miR-212-5p
8	<i>ERO1LB</i>	miR-153-3p
9	<i>STAT3</i>	miR-124-3p. 1, miR-125-5p
10	<i>KLF11</i>	miR-17-5p, miR-138-5p, miR-10-5p, miR-93-5p, miR-106-5p, miR-519-3p, miR-20-5p
11	<i>SEC61A1</i>	miR-218-5p.
12	<i>ORMDL3</i>	miR-17-5p, miR-20-5p, miR-93-5p, miR-106-5p, miR-519-3p
13	<i>MAPKAPK2</i>	miR-137
14	<i>GATA6</i>	miR-10-5p, miR-141-3p, miR-181-5p, miR-200a-3p
15	<i>DERL1</i>	miR-181-5p
16	<i>PGM1</i>	miR-34-5p, miR-449-5p, miR-30-5p
17	<i>PAX6</i>	miR-455-3p. 1, miR-129-5p, miR-190-5p, miR-383-5p. 1, miR-223-3p
18	<i>ERGIC1</i>	let-7-5p, miR-98-5p
19	<i>ERN1</i>	miR-145-5p
20	<i>SERP1</i>	miR-137, miR-183-5p. 1, miR-124-3p. 1
21	<i>MAPK14</i>	miR-128-3p, miR-124-3p. 2, miR-506-3p, miR-124-3p. 1, miR-19-3p

gene; defects in this gene may contribute to T2DM.³¹ Its expression is regulated by miR-98-5p. The *IGF2BP2* and *IRS2* genes modulate the actions of insulin and insulin-like growth factor 1, and their cytoplasmic products function as T2DM-related biomarkers under the regulatory control of miR-98-5p.³² miR-9-5p targets *KLHDC10*, a regulator of ASK1, thereby modulating oxidative stress-induced cell death by inhibiting protein phosphatase 5.³³ miR-137 targets *GPX7*, which helps prevent hydrogen peroxide-induced oxidative stress in esophageal epithelia.³⁴ Various other miRNAs and their targets are listed in Figure 5.

3.5. Commonly expressed miRNAs and their target genes in T2DM under ER stress

We evaluated 24 miRNAs involved in T2DM with ER stress. High mobility group AT-hook 1 (HMGA1) protein is a key activator of *INSR* gene expression. Aberrant

miR-454-3p	<i>PPARG : G3BP2D</i>
miR-301-3p	<i>PPARG : G3BP2D</i>
miR-130-3p	<i>PPARG : G3BP2D</i>
miR-101-3p.2	<i>NEUROD1, HNF1B : STC1</i>
miR-101-3p.1	<i>NEUROD1 : STC1</i>
miR-190-5p	<i>NEUROD1 : STC1</i>
miR-30-5p	<i>NEUROD1 : STC1</i>
miR-506-3p	<i>PTPN1: STK4, ITPR3</i>
miR-124-3p.2	<i>PTPN1: STK4, ITPR3</i>
miR-124-3p.1	<i>AKT2: DHCR24</i>
miR-1271-5p	<i>TCF7L2: DHCR24</i>
miR-96-5p	<i>TCF7L2: DHCR24</i>
miR-107	<i>HMGA1: AIFM1</i>
miR-142-3p.1	<i>HMGA1: FOXO4</i>
miR-7-5p	<i>IRS2: G3BP2, PARP1</i>
miR-519-3p	<i>WFS1: STC1, OSR1</i>
miR-106-5p	<i>WFS1: STC1, OSR1</i>
miR-93-5p	<i>WFS1: STC1, OSR1</i>
miR-20-5p	<i>WFS1: STC1, OSR1</i>
miR-17-5p	<i>WFS1: STC1, OSR1</i>
miR-33-5p	<i>IRS2: CACNA1C, MRPS25</i>
miR-26-5p	<i>HMGA1: CACNA1C, G3BP2</i>
miR-98-5p	<i>IGF2BP2, KCNJ11, IRS2: AIFM1, ERCC6</i>
let-7-5p	<i>IGF2BP2, KCNJ11, IRS2: AIFM1, ERCC6</i>
miR-9-5p	<i>IGF2BP2: ANK2, KLHDC10</i>

Figure 5. The most common microRNAs involved in type 2 diabetes mellitus (T2DM) and oxidative stress. Black color highlights the target genes involved in T2DM. The yellow color highlights the target genes involved in oxidative stress.

expression of the *HMGA1* gene and its protein product has been linked to increased risk of T2DM and insulin resistance.³⁵ During sepsis-related myocardial damage, miR-195-5p acts on *ATF6* to suppress inflammatory responses, apoptotic cell death, oxidative stress, and ER stress.³⁶ *PIK3R1* is a potential candidate gene involved in insulin signaling pathways in T2DM development.³⁷ These genes are modulated by miR-195-5p. miR-145-5p targets *ERN1*, a UPR sensor in the ER.³⁸ Numerous other miRNAs and their targets are listed in Figure 6.

3.6. Co-expressed miRNAs and their targets in oxidative and ER stress associated with T2DM

We identified 14 miRNAs targeting common genes associated with T2DM, oxidative stress, and ER stress, as shown in Figure 7. It has been reported that individuals with T2DM are particularly susceptible to various forms of cellular stress, and the shared miRNAs identified here could inform the development of improved RNA-based therapies to reduce T2DM-associated oxidative and ER stress. In particular, miR-98-5p and let-7-5p may regulate seven putative genes closely linked to T2DM under oxidative and ER stress. All these miRNAs target more than one gene, as shown in Figure 7.

miR-506-3p	PTPN1 : MAPK14
miR-124-3p.2	PTPN1 : MAPK14
miR-194-5p	AKT2 : ERGIC2
miR-124-3p.1	AKT2 : SERP1,STAT3,MAPK14
miR-26-5p	HMGA1 : SLC19A2
miR-497-5p	HMGA1 : PIK3R1
miR-424-5p	HMGA1 : PIK3R1
miR-195-5p	HMGA1 : PIK3R1
miR-16-5p	HMGA1 : PIK3R1
miR-15-5p	HMGA1 : PIK3R1
miR-519-3p	WFS1 : KLF11,ORMDL3
miR-106-5p	WFS1 : KLF11,ORMDL3
miR-93-5p	WFS1 : KLF11,ORMDL3
miR-20-5p	WFS1 : KLF11,ORMDL3
miR-17-5p	WFS1 : KLF11,ORMDL3
miR-98-5p	KCNJ11,IRS2,IGF2BP2 : ERGIC1,SEC16B
let-7-5p	KCNJ11,IRS2,IGF2BP2 : ERGIC1,SEC16B
miR-145-5p	IRS1 : ERN1
miR-101-3p.1	NEUROD1 : SLC19A2
miR-190-5p	NEUROD1 : PAK6
miR-137	NEUROD1, AKT2 : MAPKAPK2,SERP1
miR-30-5p	NEUROD1 : PGM1
miR-181-5p	GPD2,IRS2,IGF2BP2 : DERL3,GATA6,HSP90B1
miR-128-3p	NEUROD1 : MAPK14

Figure 6. The most common microRNAs involved in type 2 diabetes mellitus (T2DM) and endoplasmic reticulum (ER) stress. Black color highlights the target genes involved in T2DM. Red color highlights the target genes involved in ER stress.

miR-506-3p	PTPN1 : STK4, ITPR3 : MAPK14
miR-124-3p.2	PTPN1 : STK4, ITPR3 : MAPK14
miR-124-3p.1	AKT2 : DHCR24 : SERP1, MAPK14, STAT3
miR-26-5p	HMGA1 : CACNA1C, G3BP2 : SLC19A2
miR-519-3p	WFS1 : STC1, OSR1 : KLF11, ORM DL3
miR-106-5p	WFS1 : STC1, OSR1 : KLF11, ORM DL3
miR-93-5p	WFS1 : STC1, OSR1 : KLF11, ORM DL3
miR-20-5p	WFS1 : STC1, OSR1 : KLF11, ORM DL3
miR-17-5p	WFS1 : STC1, OSR1 : KLF11, ORM DL3
miR-98-5p	IGF2BP2, KCNJ11, IRS2 : AIFM1, ERCC6 : SEC16B, ERGIC1
let-7-5p	IGF2BP2, KCNJ11, IRS2 : AIFM1, ERCC6 : SEC16B, ERGIC1
miR-101-3p.1	NEUROD1 : STC1 : PGM1
miR-190-5p	NEUROD1 : STC1 : PGM1
miR-30-5p	NEUROD1 : STC1 : PGM1

Figure 7. The most common microRNAs involved in type 2 diabetes mellitus (T2DM) associated with oxidative and endoplasmic reticulum (ER) stress. Black color highlights the target genes involved in T2DM. The yellow color highlights the target genes involved in oxidative stress. Red color highlights the target genes in ER stress.

3.7. Gene enrichment analysis for T2DM in relation to oxidative and ER stress

Figures 8-10 show the enriched biological function, pathways, domains, and networks associated with the upregulated genes in T2DM, oxidative stress, and ER stress, respectively, validated using the ShinyGO database. The

associated pathways converge on protein folding, UPR, and ER-associated degradation, indicating that dysregulated proteostasis is a key component of the diabetic cellular environment.

Altogether, these enrichment analyses indicate that oxidative and ER stress pathways in T2DM largely represent downstream amplification loops of cellular injury arising from systemic insulin resistance and impaired insulin action, rather than initiating pathogenic events. Chronic hyperglycemia and lipotoxicity arising from impaired insulin signaling activate these stress networks, which, in turn, feed-back to further damage β -cells and insulin-responsive tissues, thereby exacerbating insulin resistance and accelerating disease progression.

4. Discussion

miRNAs have been extensively investigated to determine their functions and roles in disease. For numerous diseases, miRNAs have shown potential as early-detection biomarkers.³⁹ In the present study, we proposed a computational approach using bioinformatics to identify key miRNA regulators of gene sets implicated in T2DM related to oxidative and ER stress. Using stringent conservation criteria across human, rat, and mouse, we performed target prediction and selected conserved 8nt miRNAs that regulate multiple target genes involved in key cellular processes. The primary obstacle in clinical translation of miRNAs is Food and Drug Administration approval; a single miRNA may affect a large number of genes without discrimination.⁴⁰ However, it could be relevant for biomedical research.

T2DM is intricately linked to chronic cellular stress responses, particularly oxidative stress and ER stress that develop in response to persistent nutrient overload and metabolic imbalance. These stress pathways function as crucial molecular mediators connecting excess nutrient flux with cellular dysfunction and insulin resistance.⁴¹ Sustained activation of oxidative and ER stress not only disrupts insulin signaling and β -cell integrity but also amplifies systemic inflammation and metabolic dysregulation, thereby accelerating disease progression and the onset of complications.⁴² Insulin resistance, an early hallmark of T2DM, occurs when muscle, liver, and adipose tissues respond poorly to insulin, leading to compensatory hyperinsulinemia that eventually fails due to genetic, nutritional, and lipid-induced impairments in INSR and PI3K-Akt signaling, thereby reducing glucose uptake and glycogen synthesis while increasing hepatic glucose production.⁴³ Under these conditions, pancreatic β -cells experience sustained exposure to elevated glucose levels, which intensifies glucose metabolism and increases

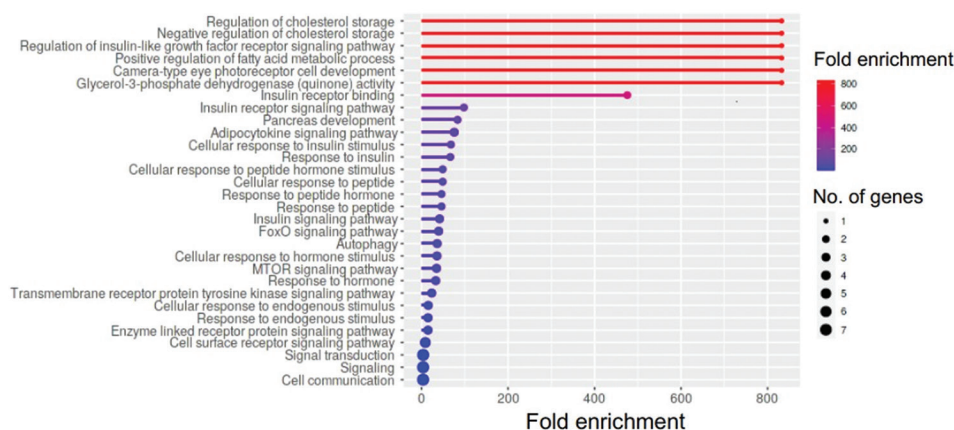


Figure 8. Functional enrichment analysis of genes associated with type 2 diabetes mellitus

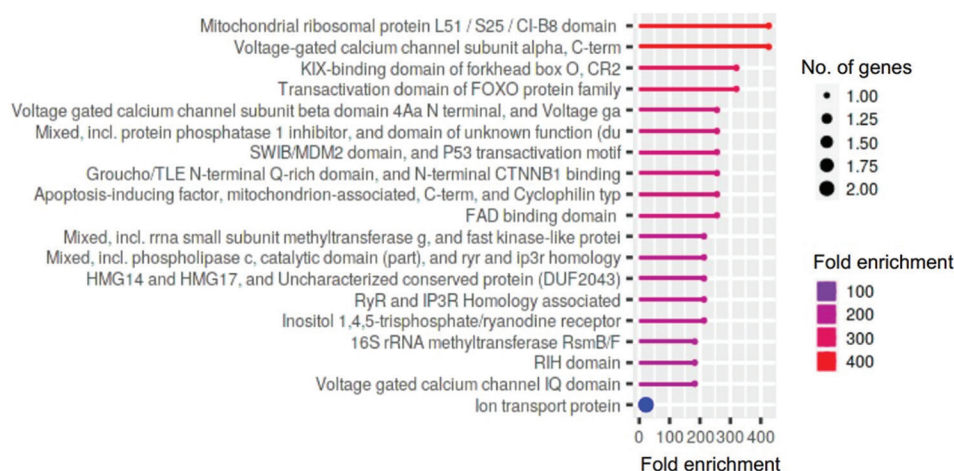


Figure 9. Functional enrichment analysis of genes associated with oxidative stress

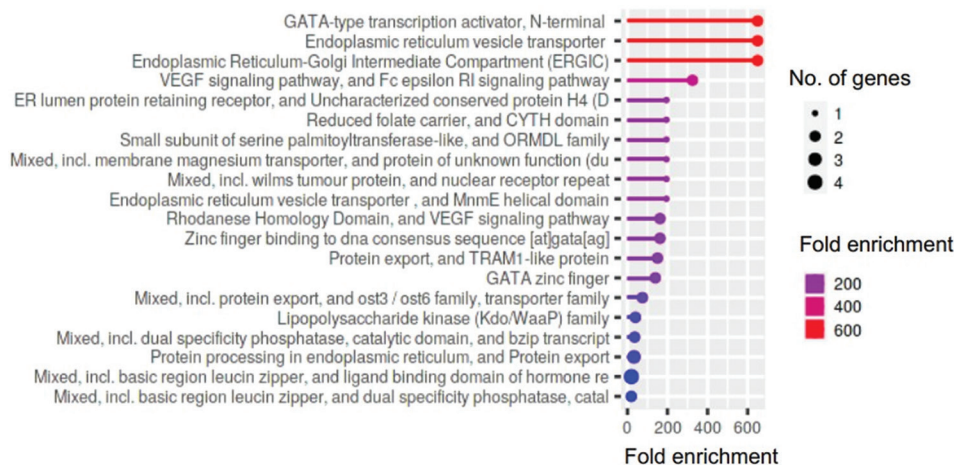


Figure 10. Functional enrichment analysis of genes associated with endoplasmic reticulum stress

electron flow through the mitochondrial electron transport chain (ETC). This heightened activity elevates mitochondrial ROS production.⁴⁴ Continuous nutrient oversupply and defective insulin signaling further burden the tricarboxylic acid cycle and ETC complexes, promoting electron leakage and the generation of superoxide and related reactive species. These reactive species progressively damage mitochondrial DNA, membrane lipids, and respiratory proteins.⁴⁵ Excess mitochondrial ROS amplifies ER stress, especially in β -cells, which face a persistent demand for proinsulin synthesis, folding, and secretion under hyperglycemic conditions.⁴¹ ROS-mediated injury disrupts calcium homeostasis and impairs ER protein-folding capacity, activating the UPR. When this response becomes maladaptive, it engages pro-apoptotic signaling pathways, leading to β -cell loss and diminished insulin production.⁴⁶ Consequently, under these insulin-resistant conditions, persistent nutrient oversupply markedly enhances mitochondrial ROS production, and ER stress sustains a self-reinforcing cycle of oxidative stress that drives β -cell dysfunction, systemic insulin resistance, and the progression of diabetic complications.⁴⁷ Therefore, the vicious cycle between oxidative and ER stress should be viewed as a secondary amplifier of tissue damage, triggered by primary insulin resistance, which, in turn, feeds back to impair insulin signaling and β -cell failure.⁴⁸ Collectively, these mechanisms position oxidative and ER stress as both downstream consequences and reinforcing drivers of insulin dysfunction, promoting the transition from compensated dysglycemia to overt T2DM and its associated complications.

Recent evidence highlights that miRNAs act as crucial post-transcriptional regulators of the INSR signaling pathway, thereby influencing insulin sensitivity across skeletal muscle, liver, and adipose tissue.⁴⁹ Numerous studies have demonstrated that miRNAs can directly target key components, such as *INSR*, *IRS1/2*, *PIK3R1*, *AKT2*, and *GLUT4*, leading to impaired glucose uptake, reduced glycogen synthesis, and defective suppression of hepatic glucose output.⁵⁰ Consequently, insulin resistance in T2DM is driven not only by genetic and environmental factors but also by disrupted miRNA networks that dampen proximal insulin signaling. Recent *in silico* analysis identified several miRNAs previously linked to insulin resistance, including members of the miR-103/107, miR-143, miR-27, miR-29, and miR-144 families that modulate key nodes of the INSR-IRS-PI3K-Akt cascade and *GLUT4* expression. These alterations can initiate or exacerbate insulin resistance before overt oxidative and ER stress develops.⁵¹ Notably, predicted miRNA-gene interactions involving canonical targets, such as *IRS1*, *IRS2*, *AKT2*, and *PIK3R1*, suggest that these miRNAs function not merely as stress markers

but as early mechanistic drivers of insulin signaling defects. Collectively, the proposed miRNA-gene networks may contribute to a two-phase pathogenic process in T2DM, first by impairing insulin signaling and second by enhancing oxidative and ER stress during chronic metabolic overload.⁵²

We identified various master regulators prevalent in T2DM with oxidative and ER stress. In addition, we searched for 8-nt-binding targeted genes related to T2DM, oxidative, and ER stress. Key genes identified in this study, including *KCNJ11*, *IRS2*, *IGF2BP2*, *AIFM1*, *ERCC6*, and *SEC16B*, are increasingly recognized as pivotal regulators connecting chronic hyperglycemia with oxidative and ER stress-driven β -cell dysfunction.⁵³ Among these, *KCNJ11* and *IRS2* play essential roles in insulin secretion and signaling, and their dysregulation heightens glucotoxicity-induced ROS production and stress kinase activation.⁵⁴ Meanwhile, *IGF2BP2* and *ERCC6* act as integrators of metabolic signals with RNA stability and DNA damage repair mechanisms under oxidative challenge.⁵⁵ The above genes were identified as the targets of miR-98 using TargetScan. As shown in the study by Yu *et al.*,⁵⁶ miR-98-5p exerts anti-apoptotic and antioxidative effects in mice, protecting against brain ischemia/reperfusion damage. Targeting *PPP1R15B* in keratinocytes dysregulates miR-98-5p levels in the blood of diabetic patients, thereby limiting proliferation and leading to apoptosis.⁵⁷ These results demonstrate that miR-98, which targets specific genes, is a promising miRNA for the treatment of T2DM and oxidative stress. In parallel, genes such as *NEUROD1*, *GPX7*, *AKT2*, *STK4*, *MAPK14*, *SERP1*, and *STAT3* are increasingly viewed as components of a dynamic stress-adaptation network in T2DM, coordinating transcriptional regulation of the insulin gene, antioxidant responses, the UPR, and inflammatory pathways.⁵⁸

Through literature review, we discovered numerous genes associated with T2DM (Table 1), oxidative stress (Table 2), and ER stress (Table 3). Extensive research on miR-93-5p demonstrated its role in T2DM. By targeting *HGF*, this miRNA appears to reduce insulin resistance in HepG2 cells, thereby slowing progression toward T2DM.⁵⁹ *OSR1* involves a signaling cascade controlled by the PI3K-Akt signaling pathway, which increases sodium-chloride cotransporter phosphorylation in hyperinsulinemic mice.⁶⁰ These studies have demonstrated that miR-93-5p can be an effective target for various stress-mediated signaling related to T2DM. The decreased ER stress induced by miR-9 overexpression reduces ischemic damage and provides a target for ischemic stroke therapy.⁶¹ miR-9 can regulate insulin secretion by suppressing the expression of *ONECUT2* and *SIRT1*. Reduced insulin production, which

contributes to T2DM, has been shown to correlate with *IGF2BP2*.⁶² miR-9 contributes to the regulation of these genes. miR-137 also regulates various genes, including *NEUROD1* and *GPX7*. The insulin gene's expression is regulated by the *NEUROD1* gene. T2DM is associated with mutations in the *NEUROD1* gene.⁶³ Maintaining redox homeostasis, glutathione peroxidase 7 (*GPX7*) has been shown to indirectly regulate signal transduction in the insulin and nuclear factor κ B (NF- κ B) signaling pathways.⁶⁴ One miRNA may bind to several targets, and miR-124 is anticipated to control the expression and silencing of genes, including *AKT2*, *DHCR24*, *STK4*, *MAPK14*, *SERP1*, and *STAT3*.⁶⁵

Recent experimental research highlights that ongoing oxidative and ER stress in T2DM induces maladaptive activation of key signaling pathways, including c-Jun N-terminal kinase, NF- κ B, and the PERK-IRE1 α -ATF6 axis. These pathways place various implicated genes at critical junctions for β -cell failure and diabetes complications, such as cardiomyopathy and neuropathy.⁶⁶ Within this context, miRNA-mediated regulation is increasingly recognized as a mechanism that affects insulin signaling, antioxidant enzymes, such as *GPX7*, and ER stress-modulating genes, such as *SERP1* and *STAT3*, suggesting that subtle changes in miRNA expression can broadly impact stress responses in metabolic tissues.⁶⁷ In addition, contemporary investigation into diabetic complications, including retinopathy, cardiomyopathy, and slow-healing wounds, demonstrates that miRNAs linking persistent hyperglycemia to oxidative and ER stress are being explored as biomarkers of drug response and secondary therapeutic targets.⁶⁸ Clinical and translational studies have shown that glucagon-like peptide-1 receptor agonists, such as liraglutide, can regulate miRNAs, including miR-93-5p and miR-9-5p, in T2DM patients, with changes in these miRNA levels associated with better insulin signaling, reduced oxidative injury, and improved metabolic profiles, supporting the relevance of stress-related mechanisms.⁶⁹ Network analyses further reinforce the centrality of redox-sensitive miRNAs, such as miR-126, miR-146a, miR-98, miR-935p, miR-9, miR-124, and miR-137, in advanced glycation end-products (AGE)-receptor for AGE and inflammatory pathways, highlighting them as rational candidates for future T2DM therapeutics targeting oxidative and ER stress.⁷⁰

Several miRNAs identified in our *in silico* analysis have been previously linked to adipose tissue biology and obesity-associated metabolic disturbances. Both experimental and clinical evidence indicate that miRNAs regulating adipogenesis exhibit opposing expression patterns in differentiated adipocytes compared with those

in obese adipose tissue, implicating their dysregulation in local inflammation and insulin resistance.⁷¹ Circulating miRNAs, such as miR-34a and miR-122, have also been correlated with obesity and obesity-related T2DM, underscoring the notion that excessive adiposity can reprogram systemic miRNA expression profiles. These observations imply that in obese individuals with T2DM, chronic nutrient surplus, adipose inflammation, and altered adipokine signaling may further influence the expression of stress-responsive miRNAs identified in our analysis as shared regulators of T2DM, oxidative stress, and ER stress.⁷² While the current bioinformatic findings cannot quantify these effects, it is reasonable to propose that obesity may potentiate or modify the functional impact of specific miRNAs on their target genes, thereby shaping disease progression and therapeutic responsiveness. Future studies incorporating body mass index and adiposity stratification will be essential to clarify whether the miRNA networks described in our study are differentially regulated in lean and obese subjects with T2DM.

Oxidative stress plays a central role not only in cellular dysfunction and insulin resistance in T2DM but also in the development of atherosclerosis, where excess ROS drives endothelial injury, lipid peroxidation, and vascular inflammation.⁷³ Within the vascular system, miRNAs constitute complex regulatory networks that modulate redox homeostasis, endothelial activation, and smooth muscle cell proliferation, with several redox-responsive miRNAs already implicated in plaque initiation and progression.⁷⁴ Emerging evidence further suggests that circulating miRNAs, such as miR-122 and other oxidative stress-related variants, may serve as predictive biomarkers for coronary atherosclerosis and correlate closely with systemic indicators of oxidative injury.⁷⁵ Given that numerous miRNAs highlighted in our study target genes governing oxidative and ER stress responses, it is plausible that these same regulatory axes contribute to both T2DM pathogenesis and its macrovascular complications under chronic metabolic and oxidative stress.⁷⁶ Nonetheless, our *in silico* analysis did not include clinical vascular parameters; these proposed associations remain speculative and warrant validation in patient cohorts characterized for cardiovascular outcomes.

Additional *in vivo* analyses employing real-time quantitative polymerase chain reaction, next-generation sequencing, luciferase reporter assays, and western blotting are required to experimentally confirm the therapeutic miRNA targets proposed in this study. miRNA mimics and antagomirs are the two main categories for miRNA-based therapies. The miRNA mimics restore a specific miRNA's concentration that has decreased due to disease.

Antagomirs, on the other hand, silence disease-related miRNAs that are overexpressed.⁷⁷ Depending on the target gene's function, miRNA mimics or antagonists may be used to alter gene expression. Numerous biotechnology associations are developing miRNA-based therapeutics. In parallel, challenges related to delivery, off-target effects, and tissue specificity mean that rigorous preclinical testing in relevant T2DM models will be essential before clinical translation. However, exploration of miRNAs as therapeutic agents for T2DM involving oxidative and ER stress remains at an early stage. Early concept studies in diabetic animals suggest that modulating specific miRNAs can improve insulin sensitivity, glucose tolerance, and lipid metabolism, but large-scale clinical trials in humans are still lacking.

5. Conclusion

Various abnormalities, such as T2DM and related oxidative and ER stress, can be treated using miRNAs. We focused on TargetScan and *in silico* bioinformatic analysis using NCBI databases. Our study identifies potential therapeutic targets for treating diseases. A subset of these targets appears to be novel, and these newly identified candidates could support the design of new diagnostic biomarkers and treatment approaches for disease. Both *in vivo* and *in vitro* experiments are crucial to validate our findings.

Taken together, this study is limited by its purely *in silico* design, which relies exclusively on bioinformatic predictions and publicly available miRNA and gene databases without functional or experimental validation. The absence of individual patient information, such as body mass index, obesity status, or atherosclerotic disease, precludes assessing how these comorbidities, which are common in T2DM, might modulate the identified miRNA-gene interactions. Given that both obesity and atherosclerosis are characterized by distinct miRNA expression profiles and sustained oxidative stress, they could substantially influence the circulating and tissue miRNA signatures observed *in vivo*. Therefore, the predicted regulatory axes should be interpreted cautiously until validated in wellphenotyped T2DM cohorts with comprehensive clinical and metabolic data.

Moreover, our study simplified the complex network linking oxidative stress, ER stress, and inflammation by focusing on selected miRNAs and genes while excluding other critical regulators, such as long non-coding RNAs, transcription factors, and posttranslational modifications. The lack of tissue-specific or experimental validation further limits generalizability, as miRNA and gene expression patterns are highly context-dependent across pancreatic β -cells, liver, adipose tissue, and the endothelium. Finally,

translational aspects, such as targeted delivery, off-target effects, immune activation, and pharmacokinetics, remain unexplored, leaving a significant gap between computational predictions and clinical application. As such, the present findings should be viewed as hypothesis-generating and warrant rigorous *in vitro*, *in vivo*, and clinical validation.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Ayesha Jabeen

Investigation: Ayesha Jabeen

Methodology: Ayesha Jabeen

Writing–original draft: Ayesha Jabeen

Writing–review & editing: All authors

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

No datasets were generated or analyzed during the present study.

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