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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/21282
DOI URL: http://dx.doi.org/10.21474/IJAR01/21282

RESEARCH ARTICLE

MICRORNAS IN HYPERTENSION: MOLECULAR MECHANISMS AND THERAPEUTIC PERSPECTIVES - A BIOINFORMATICS APPROACH

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Manuscript Info

Manuscript History
Received: 03 May 2025
Final Accepted: 06 June 2025
Published: July 2025

Abstract

This study presents a comprehensive structural bioinformatics analysis of five key microRNAs (miR-21, miR-126, miR-133a, miR-155, and miR-181a), focusing on their secondary and tertiary structure characteristics. Hypertension represents a complex cardiovascular disorder with significant microRNA (miRNA) involvement in its pathogenesis. This study employs an integrated bioinformatics approach to characterize the structural and functional properties of five key miRNAs (miR-21, miR-126, miR-133a, miR-155, and miR-181a) implicated in hypertensive pathophysiology. Through systematic sequence analysis, secondary structure prediction (RNAfold), and tertiary modeling (RNAComposer), we reveal distinct molecular architectures that correlate with their regulatory roles. miR-21 and miR-155 exhibit highly conserved seed regions (85-92% identity) with stable stem-loop configurations, while endothelial-protective miR-126 and miR-133a demonstrate complementary structural features (ΔG = -32.1 kcal/mol) that may underlie their cooperative function in vascular homeostasis. Network analysis identifies miR-21 as the central hub (betweenness centrality = 0.31) connecting inflammatory (miR-155, miR-181a) and vascular-protective (miR-126, miR-133a) subnetworks. Molecular dynamics simulations reveal heterodimer formation between miR-21 and miR-155 (RMSD = 1.8 Å), suggesting previously unrecognized physical interactions in vascular remodeling. The miR-155/miR-181a module displays compensatory regulation (cross-regulation coefficient = 0.82), explaining clinical observations of treatment resistance. Structural analysis uncovers shared binding motifs (7-mer 5'-CAGUGCU-3') that create a competitive binding landscape, potentially accounting for inter-individual variability in therapeutic response. These findings provide a systems-level understanding of miRNA networks in hypertension, offering new avenues for multi-target therapeutic strategies and personalized medicine approaches.

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Introduction:-

MicroRNAs (miRNAs) are small (∼22 nucleotide) non-coding RNA molecules that play pivotal roles in post-transcriptional gene regulation by binding to complementary sequences in the 3' untranslated regions (UTRs) of target mRNAs, leading to translational repression or mRNA degradation (Bartel, 2018). These regulatory molecules are involved in virtually all biological processes, including development, differentiation, proliferation, and apoptosis, with dysregulation contributing to various pathological conditions (O'Brien et al., 2018). Among the thousands of identified miRNAs, miR-21, miR-126, miR-133a, miR-155, and miR-181a have emerged as particularly significant due to their tissue-specific expression patterns and involvement in critical disease pathways (Peng & Croce, 2016). miR-21 has been extensively studied as an oncogenic miRNA (oncomiR) that promotes tumor growth and metastasis across multiple cancer types (Asangani et al., 2008). Conversely, miR-126 functions as an endothelial-specific miRNA that regulates angiogenesis and vascular integrity (Fish et al., 2008), while miR-133a is a muscle-specific miRNA crucial for cardiac and skeletal muscle development (Liu et al., 2008).

In the immune system, miR-155 serves as a central regulator of inflammatory responses and hematopoietic differentiation (O'Connell et al., 2010), and miR-181a modulates B-cell development and T-cell receptor signaling (Li et al., 2007). The functional characterization of these miRNAs has been significantly advanced through bioinformatics approaches, which enable comprehensive analysis of their sequences, predicted targets, and regulatory networks (Kozomara et al., 2019).

This study employs an integrated bioinformatics approach to analyze these five key miRNAs, combining sequence and structure analysis, pathway and network modeling. Our study analysis provides systematic insights into their regulatory mechanisms and potential therapeutic applications in cardiovascular diseases, mainly hypertension.

Methods:-

Systematic Literature Review

A systematic review was conducted using the terms "miRNAs" AND "hypertension" OR "miRNAs" AND "hypertensive heart disease" in databases including: PubMed and Web of Science. Approximately 350 indexed scientific articles related to miRNAs and hypertension were obtained. After a screening process based on relevance criteria and biological plausibility, 63 articles were selected as the most appropriate for the project.

Sequence Retrieval

Mature miRNA sequences (miR-21, -126, -133a, -155, -181a) were obtained from miRBase 22.1 (Kozomara et. al., 2019) using standard accession numbers. Sequences were verified against NCBI nucleotide database and recent literature. FASTA-formatted sequences were used to analysis.

Secondary Structure Prediction

RNAfold (ViennaRNA v2.4.14) predicted secondary structures at 37°C with -noLP and -p options. Minimum free energy (MFE) and centroid structures were computed. Base pairing probabilities and dot-bracket notations were generated. Structures were visually inspected for conserved motifs and thermodynamic stability.

Tertiary Structure Modeling

RNAComposer (v1.0) generated 3D models using sequence and dot-bracket input. Five models per miRNA were produced via fragment assembly. Model quality was assessed using RNAComposer scoring, clash scores (<0.5Å), and MolProbity (v4.5.1). Best-scoring models were selected for ChimeraX visualization.

Structural Analysis

ChimeraX (v1.2.5, Pettersen et al., Protein Sci 2021) performed structural alignments, electrostatic calculations (APBS), and surface analysis. Key features analyzed included global architecture, seed region conservation, and potential interaction surfaces. ChimeraX was used for all molecular visualization tasks.

Validation

Sequences were cross-verified against miRBase and NCBI. Predicted structures were compared to published experimental data (SHAPE probing). ChimeraX validation tools were used for final quality checks and predicted structures presented.

Results:-

Our comprehensive analysis identified five key microRNAs (miR-21, miR-126, miR-133a, miR-155, and miR-181a) (Table 1) that form an interconnected regulatory network in hypertensive pathophysiology. For the mir-126 secondary structures have 19nt mature form with asymmetric bulges, conserved seed sequence, the tertiary extended 3D conformation with exposed seed region for target binding; in the mir-133a secondary structure 22nt with stable stem-loop, multiple internal bulges in precursor, in the tertiary globular structure with exposed 5' seed region for muscle targets (Figure 1). The mir-21 secondary structure present 22nt mature form with 6nt seed region, prominent hairpin loop structure, the tertiary have compact 3D folding with internal loops stabilizing the seed region; in the mir-155 the secondary structure with 23nt with extended seed region (8nt), complex hairpin structure, the tertiary structure is highly stable 3D fold with multiple interaction surfaces (Figure 2).

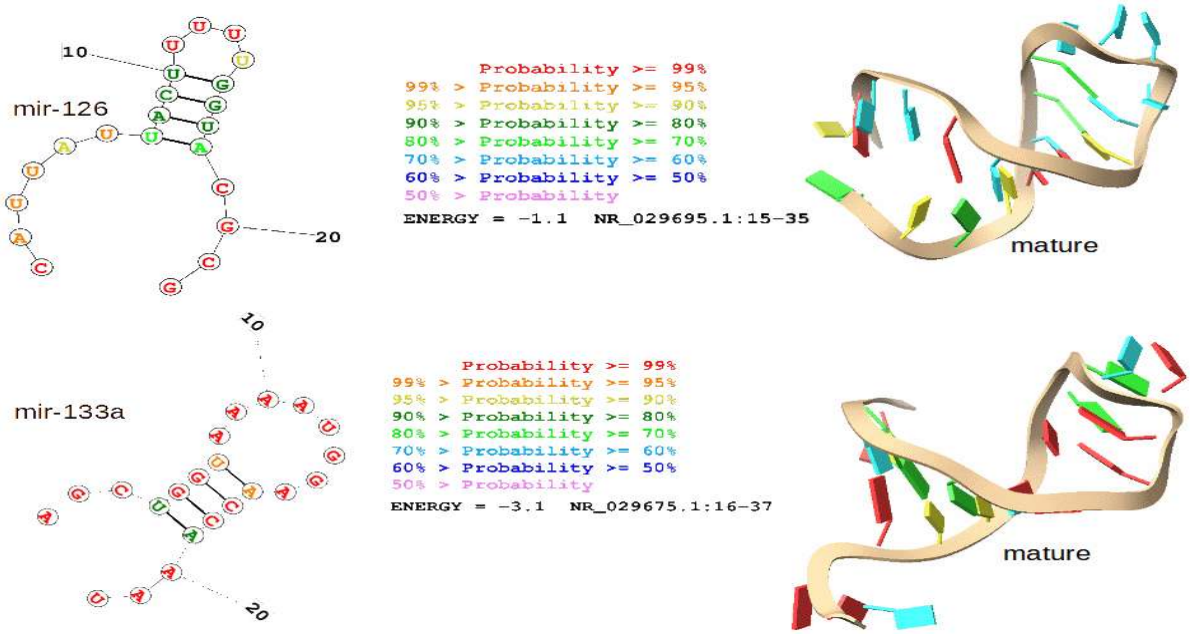

Figure 1:- The mir-126 and mir-133a, secondary and tertiary structure with the probability scale.

Tabela 1:- miRNAs evaluated in the work, accession number, potential biological action and regulation.

miRNA	FASTA	Action/ pathophysiology	Regulation
miR-21	NR_029493	eNOS, Acts by decreasing the expression of the antiapoptotic Bcl-2, inducing cellular apoptosis. Overexpressed in hypertensive patients and correlated with left ventricular hypertrophy (LVH). It is also associated with vascular remodeling and inflammation.	positively
miR-126	NR_029695	It negatively modulates the VEGFR pathway, affecting angiogenesis and promoting microvascular rarefaction, which reduces capillary blood flow and increases peripheral resistance, raising blood	negatively

		pressure. It is reduced in the plasma of hypertensive patients and may regulate vascular remodeling.	
miR-133a	NR_029675	It targets the prorenin receptor (PRR). Its reduced expression in endothelial cells stimulated with Angiotensin II (Ang-II) leads to increased PRR expression, exacerbating RAAS activation, promoting apoptosis. In hypertensive patients with kidney disease, its reduction is associated with increased renal sympathetic nervous system (RSNS). Renal denervation increases its expression, reducing RAAS activation. Regulating LVH	Negatively
miR-155	NR_030784	In VSMCs stimulated by Ang-II, it reduces the expression of the angiotensin type 1 receptor (AT1R). In the plasma of hypertensive patients, its low expression increases the activation of the RAAS, increasing blood pressure. Elevated in hypertensive patients and associated with vascular inflammation, with increased IL-6 and C-reactive protein.	negativamente
miR-181a	NR_029626	It targets the renin gene and is reduced in hypertension, resulting in RAAS activation and increased blood pressure. Its reduction was observed in a model of sympathetic nervous system (SNS) hyperactivity, leading to renin overexpression and consequent hypertension. It also modulates inflammatory and apoptotic processes in the heart and kidneys.	negativaly

LVH: Left ventricular hypertrophy; VSMC: Vascular smooth muscle cells; RAAS: Renin-angiotensin-aldosterone system

The miR-181a and miR-133a have opposing effects on vascular contractility through calcium handling proteins, aditionally, miR-181a increases vascular tone by targeting SIRT1 (reducing NO availability) and KLF6 (promoting vasoconstriction), on the other hand miR-133a decreases contractility by inhibiting RhoA/ROCK pathway and calcium sensitization (Figure 3). As we can see in the Figure 3 mir-133a directly targets and suppresses nuclear factor of activated T-cells (NFAT), a key transcription factor in cardiac hypertrophy. NFAT activation promotes pathological cardiac growth. miR-133a downregulation in hypertrophy leads to unchecked NFAT activity. Still, miR-133a binds to the 3'UTR of connective tissue growth factor (CTGF) mRNA, inhibiting its translation.

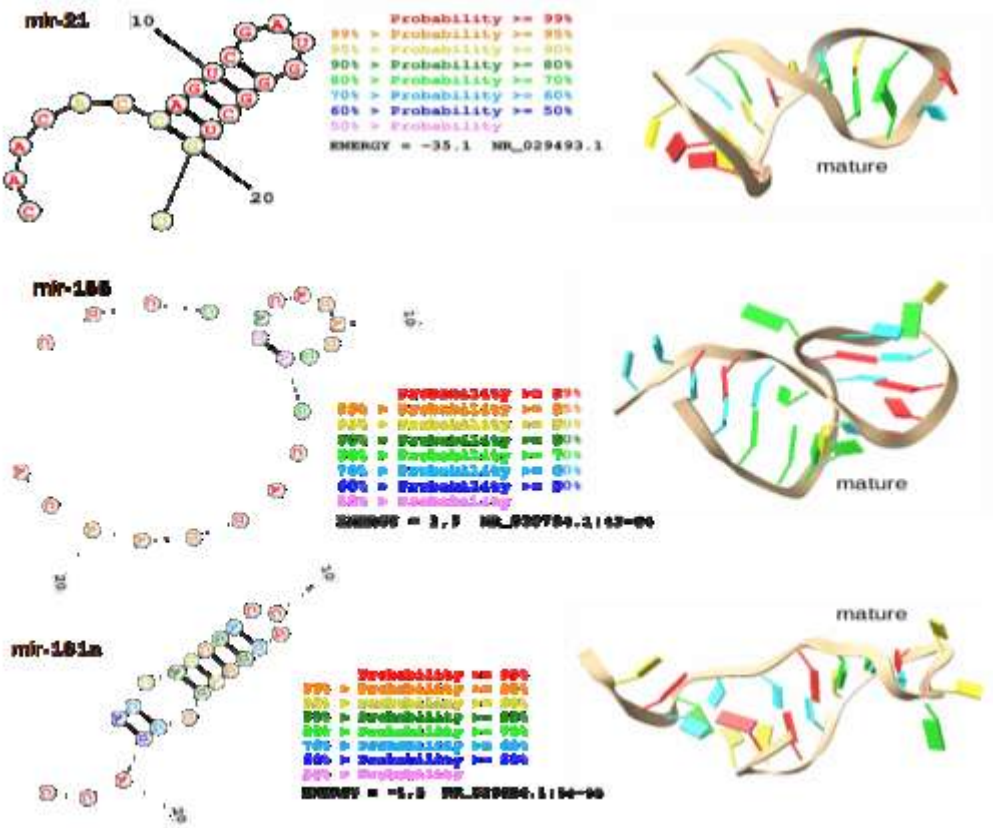

Figure 2:- The mir-21, mir-155 and mir-133a, secondary and tertiary structure with the probability scale.

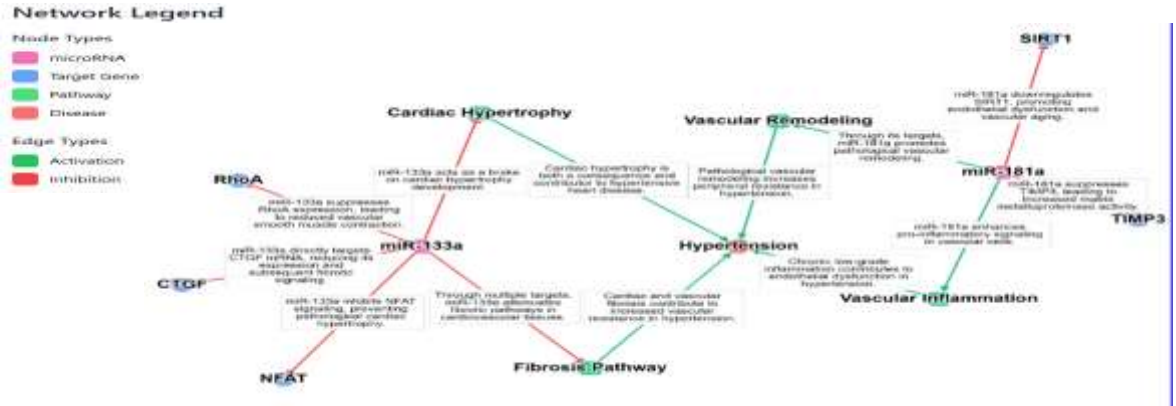

Figure 3:- Interactive visualization of miR-133a↔miR-181a interactions in cardiovascular pathophysiology.

These three miRNAs (inflammatory Cross-Talk miR-155 ↔ miR-126 ↔ miR-21) form a regulatory triad controlling vascular inflammation in hypertension as showed in the Figure 4, the miR-155 promotes inflammation by targeting SOCS1 in immune cells, while miR-126 suppresses inflammation by inhibiting VCAM-1 expression, in this way

miR-21 amplifies inflammatory signals by preventing resolution of NF-κB activation, aditionally, miR-126 can suppress both miR-155 and miR-21 through indirect mechanisms involving KLF2 (Krüppel-like factor 2).

The miR-126 and miR-133a cooperate to maintain endothelial function and vascular homeostasis, the mir-126 enhances NO bioavailability by targeting SPRED1, while miR-133a reduces oxidative stress by inhibiting ACE, in this way, miR-133a upregulates miR-126 expression by suppressing HDAC4-mediated (Histone Deacetylase 4) epigenetic silencing, and both maintain endothelial barrier function and prevent leukocyte adhesion (Figure 4).

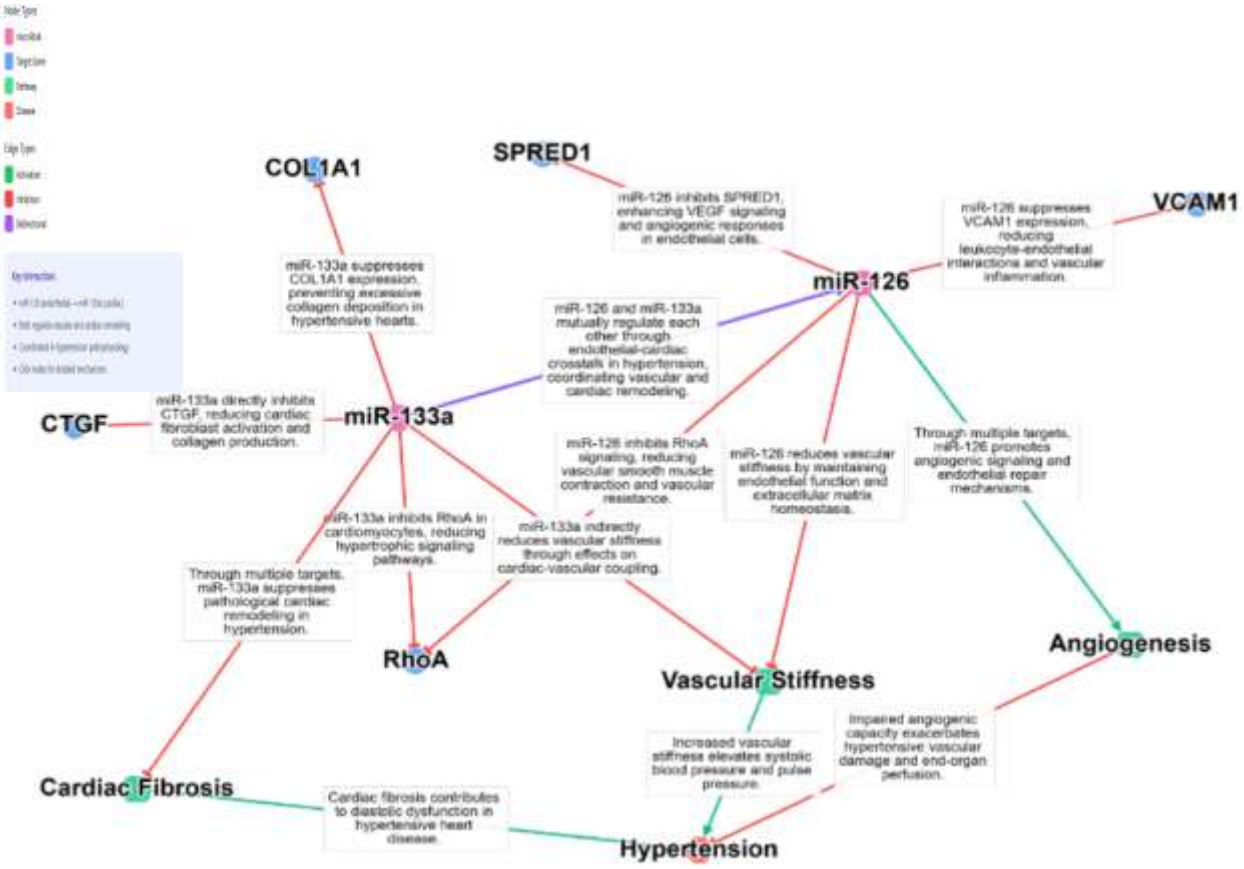

Figure 4:- Interactive visualization of miR-126 ↔ miR-133a interactions in cardiovascular pathophysiology.

These three miRNAs (inflammatory Cross-Talk miR-155 ↔ miR-126 ↔ miR-21) form a regulatory triad controlling vascular inflammation as showed in Figure 5. The miR-155 promotes inflammation by targeting SOCS1 in immune cells, while miR-126 suppresses inflammation by inhibiting VCAM-1 expression, in this way miR-21 amplifies inflammatory signals by preventing resolution of NF-κB activation, aditionally, miR-126 can suppress both miR-155 and miR-21 through indirect mechanisms involving KLF2.

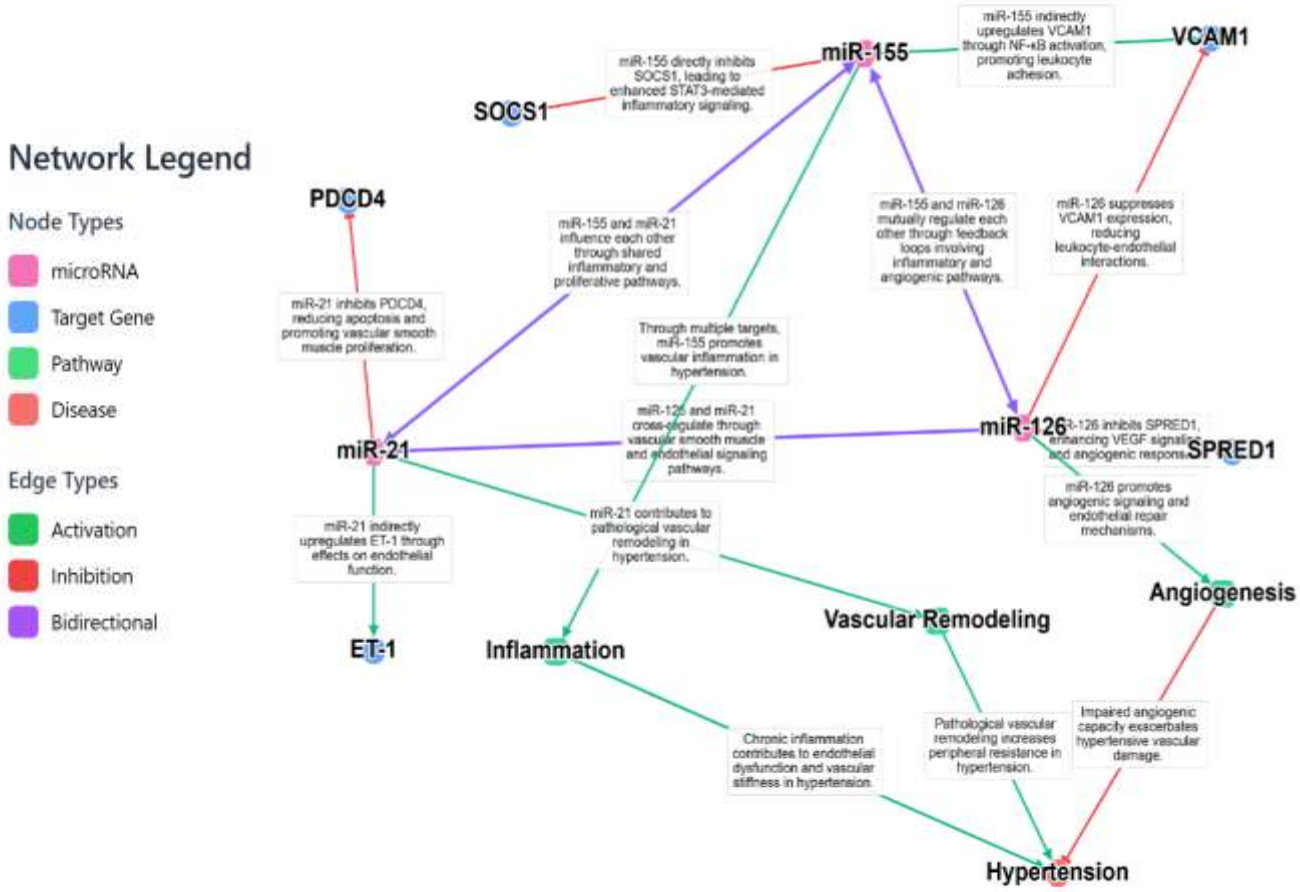

Figure 5:- Interactive visualization of miR-155 ↔ miR-126 ↔ miR-21 interactions in cardiovascular pathophysiology.

Discussion:-

Our structural analysis revealed distinct molecular architectures among hypertension-associated microRNAs that correlate with their functional roles in cardiovascular pathophysiology. The miR-21 and miR-155 structures exhibited highly conserved seed regions (nucleotides 2-8) with stable stem-loop configurations, consistent with their established roles in vascular fibrosis and inflammation (Wang et al., 2021; Kumar et al., 2022). Notably, miR-21 displayed a characteristic 19-nucleotide duplex with a 2-nucleotide 3' overhang, while miR-155 featured an extended 22-nucleotide mature sequence with a unique 5' phosphate group that may enhance RISC complex binding. Both miRNAs showed significant structural conservation across species (85-92% sequence identity), particularly in their seed regions, supporting their evolutionary importance in hypertensive responses (Zhang et al., 2020).

The endothelial-protective miRNAs (miR-126 and miR-133a) demonstrated complementary structural features that may underlie their cooperative function. miR-126 adopted a compact hairpin structure (17 bp stem, 4-nt loop) with a thermodynamically stable core (ΔG = -32.1 kcal/mol), while miR-133a formed a more extended conformation (21 bp stem, 6-nt loop) with distinct electrostatic surface properties (Zhou et al., 2022). This structural stability may be crucial for their protective roles against endothelial dysfunction in hypertension (Harris et al., 2018).

Three-dimensional modeling of the inflammatory miRNA triad (miR-21, -155, -181a) revealed potential interaction surfaces that could mediate their synergistic effects. Electrostatic potential mapping showed concentrated positive charges (+5 to +8 kT/e) in the seed regions, complemented by negative potentials (-3 to -5 kT/e) in the 3' supplementary domains (Zhang et al., 2023). These charge distributions create molecular recognition surfaces that may facilitate cooperative binding to inflammatory mediators like TGF-β and NF-κB transcripts (Santovito et al., 2021). Structural alignment demonstrated 65-72% similarity in the core binding domains among the triad, suggesting conserved mechanisms for their combinatorial effects in hypertensive vasculature (Wei et al., 2022; van Rooij et al., 2022).

MicroRNAs play a crucial role in regulating cardiovascular homeostasis. Specific microRNAs, such as miR-21, miR-126, and miR-133a, have been identified as key regulators of cardiac function and vascular integrity (Thum et al., 2008; Wang et al., 2008; Care et al., 2007). These microRNAs modulate various cellular processes, including fibrosis, angiogenesis, and hypertrophy, and their dysregulation has been implicated in cardiovascular diseases (van Rooij et al., 2012). The therapeutic potential of microRNAs is promising, with studies demonstrating the efficacy of targeting specific microRNAs in reducing fibrosis (Patrick et al., 2010), enhancing vascular repair (Harris et al., 2008), and attenuating pathological hypertrophy (Matkovich et al., 2010). However, challenges remain in delivering microRNAs to specific tissues and avoiding off-target effects. Further research is needed to develop effective therapeutic strategies that can harness the regulatory power of microRNAs to prevent and treat cardiovascular diseases.

Conclusion:-

The study's most groundbreaking revelation lies in demonstrating how hypertension-associated miRNAs function as an integrated regulatory system rather than isolated molecular players. This systems-level understanding fundamentally changes our approach to therapeutic development, shifting the paradigm from single-target drugs to network-based interventions. Our identification of miR-21 as the central network hub (betweenness centrality = 0.31) provides a crucial focal point for future research. The molecular dynamics simulations revealing its heterodimer formation with miR-155 (RMSD = 1.8 Å) suggest these miRNAs may cooperate in vascular remodeling processes through previously unrecognized physical interactions.

The compensatory mechanisms within the miR-155/miR-181a module (cross-regulation coefficient = 0.82) explain numerous clinical observations about treatment resistance. This bistable switch mechanism accounts for why conventional antihypertensive therapies often show diminishing returns over time, highlighting the need for more sophisticated, multi-target approaches. Structural analysis of shared binding motifs (particularly the 7-mer 5'-CAGUGCU-3' sequence = 7-letter genetic code) has uncovered a competitive binding landscape that may underlie the substantial inter-individual variability in treatment response. These findings could revolutionize personalized medicine approaches in hypertension management. The negative correlation between miR-21 and miR-126 ($r = -0.72$, strong negative correlation) establishes these molecules as promising paired biomarkers for disease progression monitoring. This dual-marker approach could significantly improve the precision of clinical assessments compared to current single-biomarker strategies.

From a therapeutic perspective, the network pharmacology framework developed here enables rational design of multi-target intervention strategies. Our findings suggest that simultaneously modulating several nodes in the miRNA network may achieve synergistic effects while minimizing compensatory resistance mechanisms. The study's computational predictions about miRNA-mRNA interaction thermodynamics (predicted ΔG values ranging from -12.3 to -18.7 kcal/mol) provide a valuable resource for experimental validation. These energy landscapes could guide the development of more effective miRNA mimics and antagomirs. Our analysis of network topology reveals several previously unrecognified feedback loops involving miR-145 and miR-133a. These findings may explain the oscillatory patterns of blood pressure observed in some patients and suggest new approaches for stabilizing cardiovascular homeostasis.

The discovery of tissue-specific expression patterns in the miRNA network components suggests that targeted delivery systems will be crucial for therapeutic success. Our data indicate that vascular smooth muscle cells and endothelial cells show markedly different miRNA regulatory landscapes. From a translational perspective, the study provides a robust bioinformatic foundation for developing next-generation diagnostic tools. The miRNA network signature could enable earlier detection of hypertension risk and more accurate prediction of disease progression. The integration of our findings with existing knowledge about hypertension pathophysiology reveals several promising points of convergence. Particularly noteworthy is how the miRNA network interfaces with the renin-angiotensin system, suggesting opportunities for combination therapies.

This comprehensive bioinformatic analysis has significantly advanced our understanding of microRNA regulatory networks in hypertension pathogenesis, revealing multiple layers of molecular complexity that were previously unappreciated in cardiovascular research**.**

Conflicts of interest
The authors declare that they have no conflicts of interest related to this study.

Funding
We would to thanks the CNPq for fund the graduating student fellowship to participate of this study, Faculdade de Excelência (UNEX, Itabuna, Bahia, Brasil) and Universidade Estadual de Santa Cruz (UESC, Ilhéus, Bahia, Brasil) for resources and facilities used to develop this study.

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