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REVIEW ARTICLE

Polyphenol-Mediated Modulation of Non-Coding RNAs: A New Therapeutic Approach for Hypertension - A Review

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Abstract: Hypertension (HTN) is a leading risk factor for cardiovascular diseases (CVDs) and a major contributor to global morbidity and mortality. Conventional pharmacological treatments have been effective but are often accompanied by side effects and do not address all pathological aspects of the disease. Recent advances in molecular biology have identified non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), as key regulators in the pathogenesis of hypertension. These ncRNAs influence various cellular processes, such as gene expression, vascular tone, and inflammation, making them promising targets for therapeutic intervention. This review explores the potential of polyphenols, a diverse group of phytochemicals with potent antioxidant and anti-inflammatory properties, in modulating ncRNA expression and function. We discuss how polyphenols, such as epigallocatechin-3-gallate (EGCG), resveratrol, curcumin, and quercetin impact the regulation of ncRNAs, particularly focusing on their roles in reducing oxidative stress, improving endothelial function, and ameliorating vascular remodeling associated with hypertension. The review synthesizes current evidence from both in vitro and in vivo studies, highlighting significant findings and the mechanisms by which polyphenols exert their effects on ncRNA-mediated pathways.

Moreover, we address the challenges of translating these findings into clinical applications, including issues related to bioavailability, dosing, and the complex interactions of polyphenols with other cellular components. Future directions for research are suggested, with an emphasis on the need for comprehensive clinical trials to establish the efficacy of polyphenol-based therapies targeting ncRNAs in hypertension management. By targeting ncRNAs, polyphenols offer a novel therapeutic strategy that could enhance the treatment landscape for hypertension and potentially other cardiovascular conditions.

Keywords: Cardiovascular diseases, hypertension, polyphenols, microRNAs, long non-coding RNAs, treatment, perspectives.

1. INTRODUCTION

Hypertension (HTN) is a widespread non-communicable cardiovascular disease (CVD), affecting nearly a billion individuals worldwide and standing as a leading cause of significant health complications and death [1]. This complex condition arises from the interplay of genetic predispositions and environmental influences, leading to a chronic increase in blood pressure (BP) [2]. Despite the availability of various treatments, the incidence of HTN is anticipated to rise soon [3]. In this context, the importance of dietary habits in the management of HTN has been increasingly recognized. Dietary intake plays a crucial role in the development and management of chronic diseases, including HTN [4]. The quality, quantity, and balance of nutrients consumed can significantly influence blood pressure and overall cardiovascular health. A diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats has been shown to lower the risk of hypertension and other chronic diseases. Conversely, diets high in sodium, unhealthy fats, and refined sugars are strongly associated with increased blood pressure and a higher risk of HTN [5].

Polyphenols, a group of widely found dietary secondary metabolites, are celebrated for their strong antioxidant and anti-inflammatory actions both in laboratory settings and within the human body [5, 6]. These compounds, found in berries, tea, wine, cocoa, and other sources, help reduce oxidative stress and inflammation, both of which contribute to hypertension. Flavonoids, another type of polyphenol present in citrus fruits, onions, and tea, improve endothelial

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function and reduce inflammation, which are key factors in managing blood pressure. Additionally, dietary nitrates, found in leafy greens like spinach and beetroot, are converted into nitric oxide, a vasodilator that helps lower blood pressure [7]. Potassium, abundant in foods like bananas, oranges, and sweet potatoes, also plays a critical role in counteracting the effects of sodium and reducing BP [8]. Fat consumption further influences the risk of developing hypertension. High intake of saturated fats, commonly found in red meat, butter, and full-fat dairy, is linked to an increased risk of HTN. Saturated fats can lead to the development of atherosclerosis, which narrows blood vessels and raises blood pressure. Trans fats, prevalent in many processed foods, are particularly harmful, contributing to increased cholesterol levels and hypertension.

In contrast, unsaturated fats, such as monounsaturated and polyunsaturated fats found in olive oil, avocados, nuts, and fatty fish, are associated with lower blood pressure. Omega-3 fatty acids, a type of polyunsaturated fat, have potent anti-inflammatory effects that help lower blood pressure. Research has shown that polyphenols can influence various cell signaling pathways, contributing to their ability to lower high BP. The underlying mechanisms of HTN include genetic variations and the abnormal production of transcription factors [9]. Recently, non-coding RNAs (ncRNAs) have garnered attention for their role in numerous cellular functions. These RNA molecules, produced from DNA but not translated into proteins, play a key role in regulating gene expression and affecting the translation and degradation of messenger RNA (mRNA) [10]. The fate of cells is often determined by specific patterns of expression in pathways controlled by long non-coding RNAs (lncRNAs), a subset of ncRNAs. Changes in lncRNAs due to disease processes or genetic alterations can markedly affect disease progression [11]. Although research has extensively explored microRNAs (miRNAs) in relation to various diseases, studies on lncRNAs in HTN are still in their infancy. However, with the identification of ncRNAs, numerous studies have shown how different polyphenols can modulate various ncRNAs, thereby offering antihypertensive and anti-inflammatory benefits in the fight against CVDs [12]. Emerging research on ncRNAs highlights their potential as novel biomarkers and therapeutic targets for hypertension. The association between specific ncRNAs and hypertension risk offers exciting possibilities for the development of personalized medicine approaches in managing this chronic condition. This comprehensive overview underscores the significant role of dietary intake, particularly the consumption of natural compounds like polyphenols and healthy fats, in reducing the risk and managing hypertension. Leveraging polyphenols in the treatment of HTN presents a promising approach to combat this global health issue while also unveiling the complex mechanisms at play in cardiovascular diseases.

1.1. Polyphenols and HTN

Polyphenols, derived from plants, are celebrated for their health benefits and are broadly classified into flavonoids and non-flavonoids. Flavonoids, which include subtypes like flavonols, and anthocyanidins, are known for their hydroxyl-rich aromatic rings. Non-flavonoids, such as phenolic acids and stilbenes, typically possess a single aromatic ring, contributing to unique health benefits (Figs. **1**-**3**) [13, 14].

These compounds have been linked to improved cardiovascular health, showing potential in preventing HTN by modulating signaling pathways for antihypertensive and anti-inflammatory actions (Table **1**) [15, 16].

Vascular health, essential in combating HTN and atherosclerosis, relies on maintaining vascular tone, a redox balance, and preventing platelet aggregation [17]. Endothelial cells, producing crucial substances like nitric oxide (NO), play a significant role in this process [18]. However, oxidative stress can impair NO availability, leading to endothelial dysfunction. Polyphenols boost NO release, enhancing vasodilation and providing antioxidant benefits [19]. Specific flavonoids and compounds like resveratrol increase NO bioavailability, influencing pathways such as PI3K/Akt and AMPK [20]. Moreover, polyphenols directly or indirectly cause vasodilation, with resveratrol also acting through its phytoestrogen properties [21, 22]. These findings underscore polyphenols' potential in cardiovascular therapy.

Long-term hypertension contributes to cardiovascular complications primarily through vascular endothelial dysfunction. This dysfunction is characterized by reduced NO bioavailability, impaired endothelium-dependent hyperpolarization (EDH), and increased production of endothelium-derived contracting factors [23]. Given the need for more effective strategies to manage hypertension and its associated endothelial dysfunction, polyphenols—naturally occurring compounds found in a variety of plant-based foods—have garnered significant attention for their potential therapeutic effects. Endothelial dysfunction in hypertension results from a complex interplay of factors [23]. The endothelium, the inner lining of blood vessels, plays a crucial role in maintaining vascular homeostasis through the release of various factors that regulate vasodilation and vasoconstriction. In hypertension, there is a notable reduction in NO, a key vasodilator, and a decline in EDH, which normally complements NO-mediated vasodilation. Additionally, there is an increase in endothelium-derived contracting factors, which further exacerbates vascular tension and promotes hypertensive pathology. These changes contribute to a vicious cycle of increasing BP and worsening endothelial health, ultimately leading to CVD. The beneficial effects of polyphenols on endothelial function are primarily mediated through their influence on NO and EDH pathways. Polyphenols enhance the bioavailability of NO by promoting its synthesis and inhibiting its degradation [23]. This leads to improved vasodilation and reduces vascular resistance. Additionally, polyphenols may support EDH, further contributing to vasodilation, especially in smaller blood vessels where EDH plays a more prominent role than NO. Preclinical studies using animal models of hypertension have shown that polyphenol supplementation results in decreased BP and improved endothelial function, mirroring the effects observed in clinical settings.

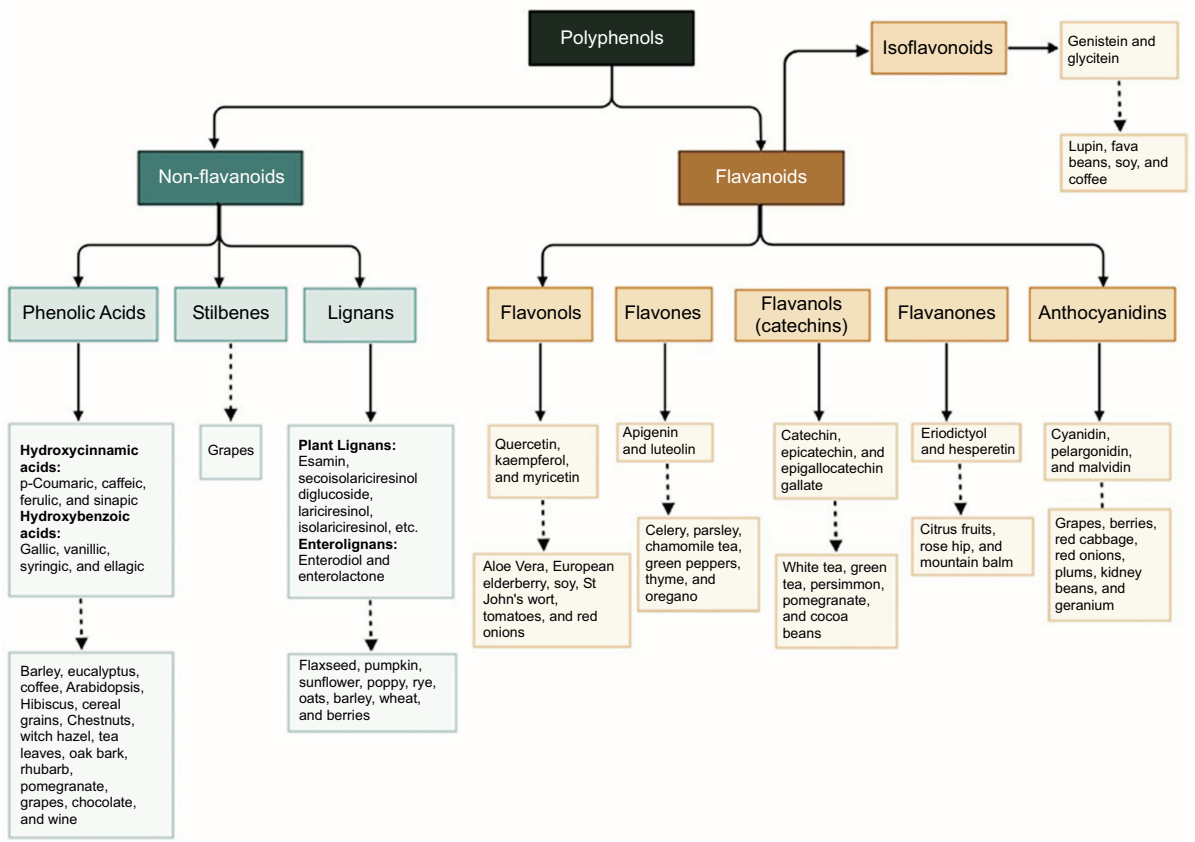

Fig. (1). Classification of polyphenols and the natural origins from which they are derived. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Antihypertensive mechanisms of polyphenols.

Mechanism	Polyphenols	Target Systems/Effects
Endothelial Function Improvement	Flavonoids (*e.g.*, quercetin, epicatechin)	Enhanced nitric oxide (NO) bioavailability; improved endothelial-dependent vasodilation.
Inhibition of Angiotensin-Converting Enzyme (ACE)	Flavonoids (*e.g.*, catechins, procyanidins)	Reduced angiotensin II levels lead to vasodilation and decreased blood pressure.
Antioxidant Activity	Resveratrol, quercetin	Reduction of oxidative stress, prevention of endothelial dysfunction, and vascular inflammation.
Anti-Inflammatory Effects	Curcumin, epigallocatechin gallate (EGCG)	Reduced inflammation in vascular tissues and improved vascular health.
Improvement of Vascular Smooth Muscle Function	Resveratrol, anthocyanins	Modulation of calcium channels and potassium channels, leads to vasodilation.
Reduction of Sympathetic Nervous System Activity	Flavonoids (*e.g.*, hesperidin, naringenin)	Lowered heart rate and reduced vasoconstriction.
Improvement in Lipid Profile	Polyphenols in olive oil, flavonoids	Reduction in LDL oxidation, improved HDL levels, contributing to vascular health.
Modulation of Renin-Angiotensin System	Catechins, procyanidins	Reduction in renin activity, leading to decreased blood pressure.
Enhanced Nitric Oxide Synthase Activity	Resveratrol, epicatechin	Increased production of NO, promoting vasodilation and reduced blood pressure.
Regulation of Endothelin-1 Levels	Resveratrol, flavonoids	Decreased levels of endothelin-1, a potent vasoconstrictor, leading to vasodilation.

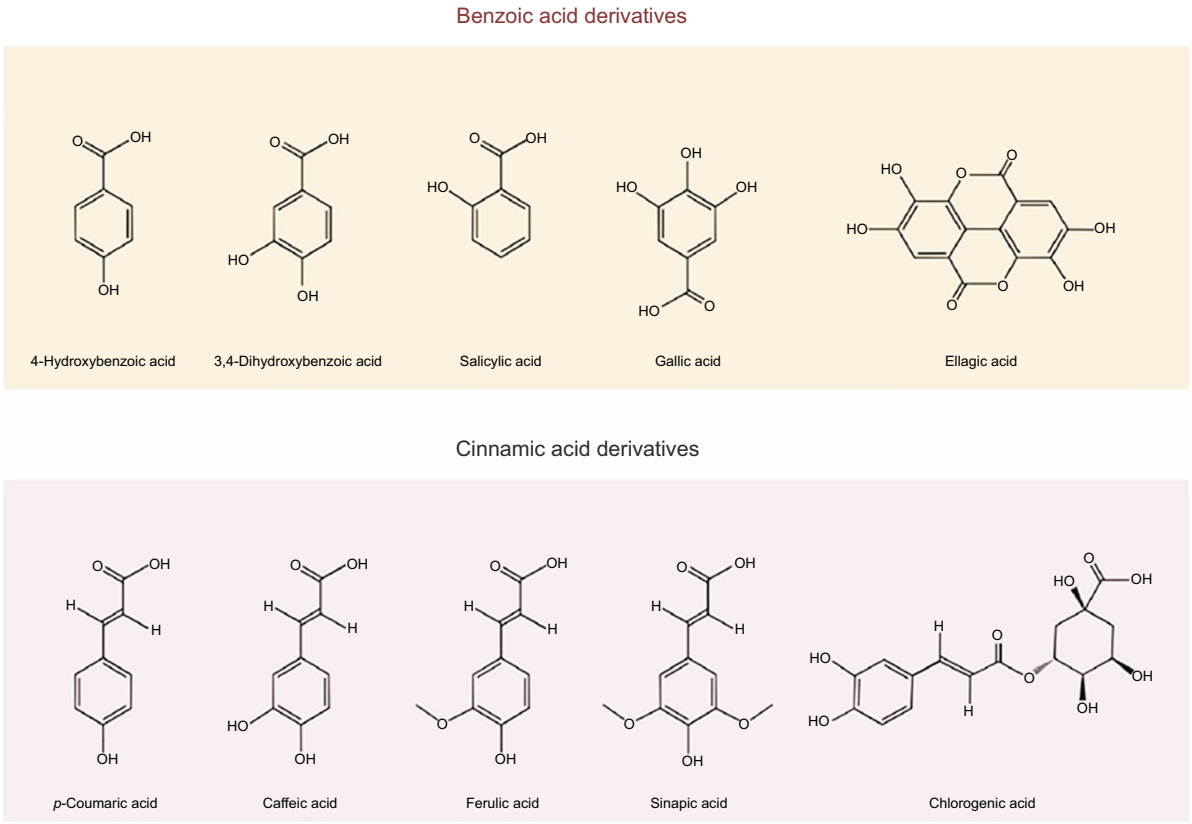

Fig. (2). Simple phenolic acids (chemical structure). This group of phenolic compounds is comprised of benzoic and cinnamic acid derivatives. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

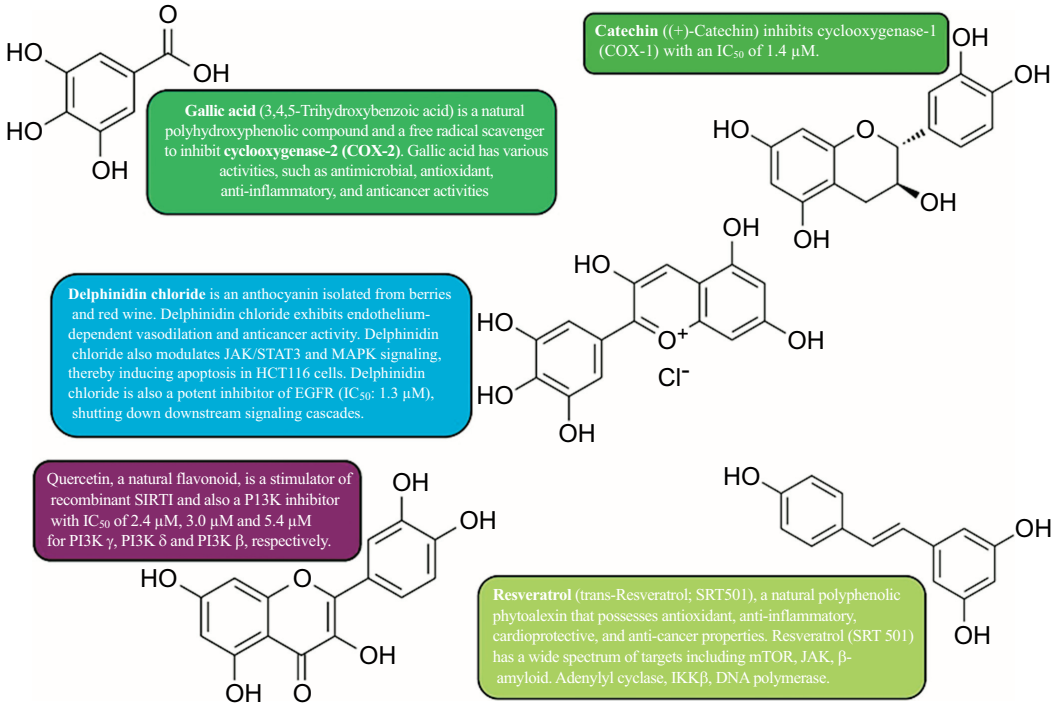

Fig. (3). Main phenolic compound's chemical structure with a description of biological properties. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The mechanisms by which polyphenols exert their effects on BP and endothelial function are multifaceted. These compounds can modulate signaling pathways involved in oxidative stress and inflammation, both of which are closely linked to endothelial dysfunction. By scavenging reactive oxygen species (ROS) and upregulating antioxidant defenses, polyphenols reduce oxidative damage to the endothelium. Furthermore, they inhibit pro-inflammatory signaling, thereby preventing endothelial cell activation and dysfunction. Polyphenols also influence the expression and activity of enzymes involved in NO production, such as endothelial nitric oxide synthase (eNOS), enhancing NO bioavailability.

Persistent inflammation is key in many non-communicable diseases, especially CVD, and HTN, driven by cytokines such as Interleukin (IL) 1, 3, 6, 8, and 18, TNF-α, and macrophage colony-stimulating factor. Phenolic compounds reduce inflammation by inhibiting inflammatory cell recruitment, decreasing pro-inflammatory molecules like TNF-α, IL-6, and CRP, and reducing adhesion molecule production, thus preventing monocyte migration [24]. By modulating gene expression pathways, polyphenols, including flavonoids and resveratrol, target inflammatory markers and influence MAPK, JAK/STAT, and NF-κB pathways, showcasing anti-inflammatory effects [24, 25]. Dyslipidemia, linked with HTN, often starts with oxidized LDL cholesterol accumulation in the vascular intima due to ROS, leading to macrophage-mediated inflammation and subsequent vascular damage [26]. Polyphenols counteract LDL oxidation, protecting CVDs, including HTN [27, 28]. Their role in managing inflammation and lipid levels underscores their potential in CVD and HTN treatment, indicating an area ripe for further exploration.

Oxidative stress, marked by excessive free radicals and reactive oxygen species (ROS), plays a crucial role in various health issues, especially CVDs [29]. Polyphenols, recognized for their potent antioxidant action, neutralize these harmful radicals, significantly reducing oxidative stress [30]. Scientific research underscores flavonoids' vast antioxidant effects, revealing they act beyond simple radical scavengers. They regulate cellular activities by targeting specific kinase signaling pathways [5]. Flavonoids lower BP primarily through their ability to scavenge free radicals and ROS, forming stable, less reactive products and thus serving as effective reducing agents [31]. Key antioxidants like flavonols (*e.g.*, quercetin), flavanones (*e.g.*, naringenin), and stilbenes (*e.g.*, resveratrol) are notable for directly neutralizing radicals and improving vascular health [32]. Dietary pro-anthocyanidins, acting as antioxidants and signaling molecules, contribute to this process by scavenging ROS [33]. Polyphenols also mitigate cellular aging and enhance mitochondrial function in vascular cells via modulation of signal transduction pathways [4].

Certain flavonoid subgroups, such as flavanones and anthocyanins, along with phenolic acids like caffeic acid, have been shown to possess antioxidant capabilities by bolstering cellular defense systems. This bolstering occurs through the activation of transcription factors that regulate antioxidant and cell-protective enzymes, notably through the ERK/Nrf2 signaling pathway [34]. Polyphenols also play a role in modulating various cellular pathways, leading to the enhanced expression of crucial antioxidant genes like HO-1, NQO1, GCLC, and the stimulation of endogenous antioxidant enzymes including GPX, SOD, catalase, and GR, essential for reducing oxidative stress [35]. In CVDs and HTN, the renin-angiotensin-aldosterone system (RAAS) is often overactive, raising angiotensin II (Ang II) levels, a key factor in HTN development. Increased oxidative stress markers correlate with Ang II levels in heart failure (HF) patients. Delphinidin, an anthocyanidin, has been shown to counteract Ang II-mediated hypertrophy by reducing ERK1/2, MAPK, and JNK activation, as well as diminishing H2O2 and O2•− levels through lowered NADPH oxidase activity, especially Nox2 [36]. The strategy of utilizing antioxidants and free radical scavengers to target ROS linked with excessive Ang II production is becoming more central in CVD management. Antioxidant therapy could offer benefits beyond conventional treatments like ACEIs and ARBs by neutralizing ROS from Ang II and pro-inflammatory cytokines involved in CVDs, including HTN [36]. This research path highlights the significant potential of antioxidants in cardiovascular health, promising further insights into their use in treating CVD and HTN.

1.2. NcRNAs AND HTN

The formation of new drugs focuses on targeting specific genes and proteins within key signaling pathways. Despite various drug classes improving cardiovascular outcomes—reducing mortality by 33%, major adverse events by 29%, and heart failure by 37% HTN continues to be a significant global health issue [37]. This highlights the need for a deeper understanding of HTN's molecular basis and the development of targeted therapies. HTN's complexity arises from the interplay between systems that are either overactivated (like the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system) or underactivated (such as the parasympathetic nervous system), leading to increased vascular reactivity, sodium retention, and endothelial dysfunction [38-41]. The role of genetics in HTN emphasizes the importance of identifying genetic predispositions to high BP, although gene polymorphisms explain only a small part of HTN susceptibility [42]. NcRNAs are pivotal in regulating transcription and are increasingly recognized for their roles in HTN, affecting nearly all cardiovascular-relevant cell types [43]. Advances in genomic technologies like microarrays and next-generation sequencing have spotlighted ncRNAs, especially miRNAs and lncRNAs, in the study of HTN in both human and animal models [44]. The regulatory scope of miRNAs across multiple genes and the significant roles of lncRNAs in HTN suggest their potential as biomarkers and therapeutic targets [45, 46]. Epigenetic mechanisms, including histone modification, DNA methylation, and ncRNA-regulated gene expression, also play roles in HTN. For instance, the phosphorylation of histone deacetylase 1 (HDAC1) by G-protein-coupled receptor kinase type 4 (GRK4) affects the expression of the Angiotensin II receptor

type 1 (AT1R), influencing the body's response to Angiotensin II [47]. This streamlined understanding underscores the potential of targeted therapeutic strategies in managing HTN, leveraging insights into genetics, ncRNA regulation, and epigenetic mechanisms.

1.3. LncRNAs and HTN

LncRNAs are a class of RNA molecules over 200 nucleotides long, not coding for proteins but playing key roles in epigenetic regulation and genetic processes [48]. They influence splicing, imprinting, epigenetic modifications, and gene transcription, adding a new layer to biological understanding [49]. LncRNAs are categorized based on their proximity to protein-coding genes into intergenic (lincRNAs), intronic (within introns), sense (on the same strand), and antisense (on the opposite strand) lncRNAs. Their presence in the blood of HTN patients suggests potential as diagnostic biomarkers [50]. Despite their emerging significance in health and disease, studies on lncRNAs in HTN remain limited. These molecules play a role in the development of HTN by directly affecting vascular cells and indirectly influencing various bodily systems [51]. Research shows that the lncRNA XR007793 is notably upregulated in vascular smooth muscle cells (VSMCs), with its downregulation leading to reduced VSMC proliferation and migration, impacting factors like IRF7, STAT2, and LIMO2 [52]. Inhibiting miR-23b was found to decrease the expression of VSMC markers, increasing VSMC proliferation and migration. This reveals how XR007793 impairs VSMC function by negatively influencing miR-23b [53]. Genome-wide association studies (GWAS) have identified various genetic loci related to BP regulation, adding complexity to understanding HTN. For instance, the lncRNA H19 locus is linked to systolic BP variations, and SNPs like rs10757274 and rs1333049 on lncRNA CDKN2B-AS1 increase HTN risk [54]. The discovery of lncRNAs, such as AK098656 and AK125261, which show altered expression in hypertensive patients' plasma, highlights the potential of lncRNA-based biomarkers for HTN [55]. Furthermore, lower levels of plasma lncRNA GAS5 in coronary artery disease (CAD) patients suggest lncRNAs' broader significance in cardiovascular health (Table **2**) [56].

1.4. miRNAs and HTN

miRNAs are crucial for gene regulation, impacting gene expression by mRNA cleavage or translation inhibition. They influence a broad range of genes and are regulated by multiple miRNAs themselves. Operating post-transcriptionally in eukaryotes, miRNAs are vital in various biological functions and significantly affect conditions like HTN [62, 63]. Certain miRNAs, showing high expression in healthy cardiac tissue, play roles in maintaining cardiac health. Research has identified miRNAs, such as miR-126 and miR-155, as potential CVD biomarkers, with variable expression levels noted in HTN development [64]. Microarray studies pinpointed miRNAs like miR-425 and miR-505 as upregulated in hypertensive patients, with miR-505 particularly consistent across HTN cases [65]. Furthermore, variations in miRNA levels in fluids like serum highlight their connection to specific conditions, *e.g.*, serum miR-29/a levels link to hypertensive cardiac hypertrophy [66]. miRNAs' diagnostic value lies in their circulation stability and detection in bodily fluids, resisting degradation by RNases. Their expression changes are closely associated with HTN, making them potential biomarkers for the condition (Table **3**) [67].

Table 2. LncRNAs in HTN.

LncRNA	Regulation	Tissue/Cell Type	Function	References
XR007793	Up	Sprague-Dawley rats/ VSMCs	Inhibition of XR007793 leads to the suppression of vascular smooth muscle cell (VSMC) proliferation and migration. Decreased transcript levels of stat2, lmo2, and irf7 accompany this downregulation.	[53]
AK098656	Up	Human plasma/HASMCs	Stimulates the proliferation and migration of vascular smooth muscle cells (VSMCs).	[54]
GAS5	Down	VSMC/ EC	The expression of GAS5 is reduced in HTN. When GAS5 is knocked down, there is an increase in systolic BP, diastolic BP, and mean arterial BP (in spontaneously hypertensive rats, SHR). This knockdown also leads to enhanced retinal neovascularization, capillary leakage, endothelial activation, and proliferation.	[56]
sONE	Down	BHRs	*Lycium Barbarum L.* improved hypertension, decreased the expression of sONE, and enhanced eNOS expression when compared to rats on a high-salt diet.	[57]
749 lncRNAs	Differential expression between SHR and normotensive rats	SHRs/ normotensive Wistar-Kyoto (WKY) rats	Asb3, Chac2, Pex11b, Sp5	[58]
MALAT1	Up	HUVECs	Vessel growth, and endothelial cell function.	[59]

(Table 2) Contd…

LncRNA	Regulation	Tissue/Cell Type	Function	References
CDKN2B-AS1	Up	HT patients/ VSMC	There is a notable variance in the genotype frequencies of the four SNPs between individuals with HTN and normotensive individuals (NT). An association has been identified between the genotypes AA of the SNPs rs10757274 and rs2383207 and systolic blood pressure (SBP).	[60]
H19	Up	PASMCs/ SD rats, C57/BL6 mice/ PAH model	The H19-let-7b-AT1R axis plays a role in the development of pulmonary arterial hypertension (PAH) by promoting the proliferation of pulmonary arterial smooth muscle cells (PASMCs).	[61]

Table 3. miRNAs in HTN.

miRNA	Regulation	Tissue/Cell Type	Function	Reference
miR-1	Up	HASMCs/ VSMC/SHRs	MiR-1 controls vascular smooth muscle cell (VSMC) proliferation by directing its actions toward IGF-1.	[68]
let-7 g	Down	Human PASMCs and mouse lungs induced by hypoxia	Let-7g and LOX-1 have a reciprocal inhibitory effect on each other's expression.	[69]
miR-21	Down	LEAOD, MCT, hypoxia, hypoxia/Sugen5416, lung and serum of PH patients	MiR-21 reduces BP in spontaneously hypertensive rats.	[70]
miR-153	Up	SHR/ Mas/ MCAs/ NT MAs	MiR-153, by targeting KCNQ4, plays a role in vascular dysfunction associated with hypertension.	[71]
miR-199a-5p	Up	HPASMCs/ HPAECs	MiR-199a-5p affects pulmonary artery HTN by reducing the expression of Smad3.	[72]
miR34b	Down	VSMCs	The reduction in miR-34b levels is accountable for the increase in BP.	[73]
miR-125a	Up	PAH/ CTEPH	MiR-125a encourages the proliferative characteristics of endothelial cells in the context of pulmonary hypertension.	[74]
miR-98	Down	PAECs from PH patients, PAECs under hypoxia and in lungs from mice induced by Sugen5416/hypoxia	PPARγ controls miR-98 to adjust the expression of ET-1 and the proliferation of pulmonary artery endothelial cells (PAEC).	[75]
miR-210	Up	Ovine Uterine Arteries, PAECs induced by hypoxia	MiR-210 influences the response of human pulmonary artery smooth muscle cells (PASMCs) to hypoxia through its interaction with MKP-1.	[76]
miR-30c	Down	PAECs from PH patients/ Rat induced by hypoxia and pulmonary arteries (PA) from PH patients.	MiR-30c plays a role in the progression of pulmonary HTN caused by hypoxia.	[77]

1.5. The Regulatory Impact of Polyphenols on Key ncRNAs Associated with HTN

Polyphenols, derived from natural sources such as fruits, vegetables, tea, and traditional herbs, have shown significant protective effects against diseases associated with oxidative stress, including HTN [78-80]. This protective capability stems primarily from their potent antioxidant properties and their influence on cellular mechanisms through modulation of critical signaling pathways. Polyphenols exert antihypertensive effects by interacting with key signaling pathways such as AKT/PI3K and NF-KB [81]. These pathways play crucial roles in regulating various cellular functions that are pivotal in the pathophysiology of hypertension. By modulating these pathways, polyphenols help to regulate vascular tone, reduce inflammatory responses, and prevent vascular remodeling, all of which are essential for managing elevated blood pressure levels. The ability of polyphenols to combat ROS is another vital aspect of their therapeutic potential [82, 83]. They provide both direct and indirect antioxidant effects, neutralizing ROS and thus mitigating oxidative stress, a major contributing factor to the development and progression of hypertension. This antioxidant action helps to preserve the integrity of vascular cells and improves endothelial function, reducing the risk of hypertension-related complications. In addition to their antioxidant and signaling modulation properties, polyphenols also induce significant epigenetic changes within myocytes. These changes include chromatin restructuring, DNA methylation, and alterations in the expression of miRNAs [84]. Such epigenetic modifications can influence gene expression and are crucial for the long-

term regulation of blood pressure and vascular health. Overall, the comprehensive role of polyphenols in managing HTN underscores their potential as a valuable component of hypertension treatment strategies. Their natural origin, coupled with their broad spectrum of beneficial effects on cellular and molecular levels, highlights their potential as an adjunct therapy for managing not only hypertension but also other oxidative stress-related conditions.

1.6. Polyphenols and lncRNAs

LncRNAs, with specific expression patterns across cell types and tissues, play critical roles in development and disease mechanisms [85]. Research has shown that *Lycium barbarum* can lower BP by inhibiting lncRNA sONE in a rat model, suggesting anti-hypertensive properties [57]. Furthermore, overexpression of H19 in human microvascular endothelial cells enhances their proliferation, migration, and angiogenesis while also downregulating miR-181a to activate JNK and AMPK pathways, suggesting H19's potential in treating atherosclerosis and peripheral artery disease (PAD) [86]. Fisetin, a flavonoid with antioxidant and anti-inflammatory effects, suppresses hypertrophy in cardiac cells and improves heart function in hypertensive rats, indicating its therapeutic value against cardiac hypertrophy [87]. It also protects against Ang II-induced apoptosis via the IGF-IR-PI3K-Akt pathway, underscoring the potential of targeting lncRNAs with polyphenols in HTN management [81].

1.7. Polyphenols and miRNAs

Recent findings highlight polyphenols' ability to interact with cellular pathways, affect transcription factors, and thus modify gene expression, notably influencing miRNA expression, which can be affected by diet and phytochemicals [88]. This interaction illustrates miRNAs' role in the effects of polyphenols [89]. Specifically, flavanones like Hesperidin and Naringenin, found in citrus fruits, have been studied in ApoE mice and shown to alter 97 and 69 miRNAs, respectively, with 31 miRNAs commonly affected, indicating their potential in cardiovascular protection [89]. The miR-29 family, important in cardiovascular health, can improve cardiac function when upregulated, while its downregulation has been associated with reduced BP and better cardiac outcomes in hypertensive rats [90]. Polyphenols such as EGCG and resveratrol modulate miRNAs across all HTN stages [91]. EGCG treatment in pulmonary hypertension fibroblasts (PH-Fibs) alters gene and miRNA expression, affecting oxidative and inflammatory pathways, indicating potential effects on MAPK, NF-κB, and AMPK pathways and epigenetic mechanisms like DNA methylation and histone acetylation [92]. Studies highlight EGCG's ability to reduce fibroblast proliferation, enhance antioxidant defenses, and decrease inflammation, including upregulation of miR-29/b-2-5 linked to hypertension. Green tea extract, rich in polyphenols, has been shown to improve cardiomyocyte metabolism by lowering miR-29 levels [93]. Research indicates that miRNAs like miR-21, miR-181b, and miR-155, involved in the inflammatory response, were significantly altered in those consuming resveratrol-enriched grape extract, suggesting an anti-inflammatory effect in hypertensive T2DM patients [94]. Resveratrol influences miRNAs in ischemic hearts (*e.g.*, miR-21), affecting cardiac health by modulating pathways like ERK-MAP kinase, and is proposed to counteract pulmonary vascular remodeling via miR-638 [95, 96]. EGCG's antihypertensive properties may involve miRNA-150-5p through the SP1/AT1R pathway in hypertensive rats [97]. Quercetin's potential in treating pulmonary HTN could be via regulating PARP1 and miR-204, impacting HIF1a and NFATc2 [98]. MiR-155's regulation by polyphenols, particularly in macrophages, suggests its role as a biomarker and target in HTN management [99, 100]. Resveratrol's diverse effects include modulating miRNAs like miR-663 and miR-155 in monocyte cells, with implications for inflammation and muscle function [101]. Quercetin and isorhamnetin's anti-inflammatory action are linked to increasing haem oxygenase 1 levels and down-regulating miR-155, underlining the therapeutic potential of polyphenols in HTN and inflammation (Figs. **4** and **5**) [102].

2. DISCUSSION

Polyphenols have garnered significant attention as therapeutic agents in managing HTN due to their robust antioxidant properties and potential to modulate ncRNAs, such as miRNAs lncRNAs. These naturally occurring compounds combat oxidative stress, a major factor contributing to HTN and broader CVDs. Notable polyphenols like EGCG, resveratrol, and curcumin can influence biological pathways related to vascular function and BP regulation. By targeting ncRNAs, polyphenols have the potential to significantly affect gene expression associated with endothelial function, vascular smooth muscle cell proliferation, and inflammation, offering a multifaceted approach to cardiovascular health management. Despite these promising attributes, polyphenols face notable challenges, particularly concerning their bioavailability. These compounds typically exhibit poor absorption, rapid metabolism, and quick elimination from the human body, severely limiting their therapeutic effectiveness. Furthermore, the complexity of polyphenols' actions at the molecular level is not fully understood, with the exact mechanisms through which they exert their effects remaining partially elusive. Clinical trials exploring the effects of polyphenols on cardiovascular health have been numerous, yet studies specifically targeting ncRNAs in the context of HTN are relatively scarce. The mixed results from these studies, largely due to variations in polyphenol sources, dosages, and study designs, underscore the urgent need for more standardized and rigorous research to delineate their potential better and define their limitations in clinical settings. Achieving and maintaining effective plasma concentrations of polyphenols is a significant hurdle in their therapeutic use, primarily due to their low bioavailability. This challenge is compounded by individual variations in gut microbiota, which can alter the metabolism and efficacy of these compounds. Consequently, innovative formulation strategies, such as nanoparticle-based carriers, liposomal encapsulation, and complexation with cyclodextrins, have been developed to enhance the absorption and stability of polyphenols

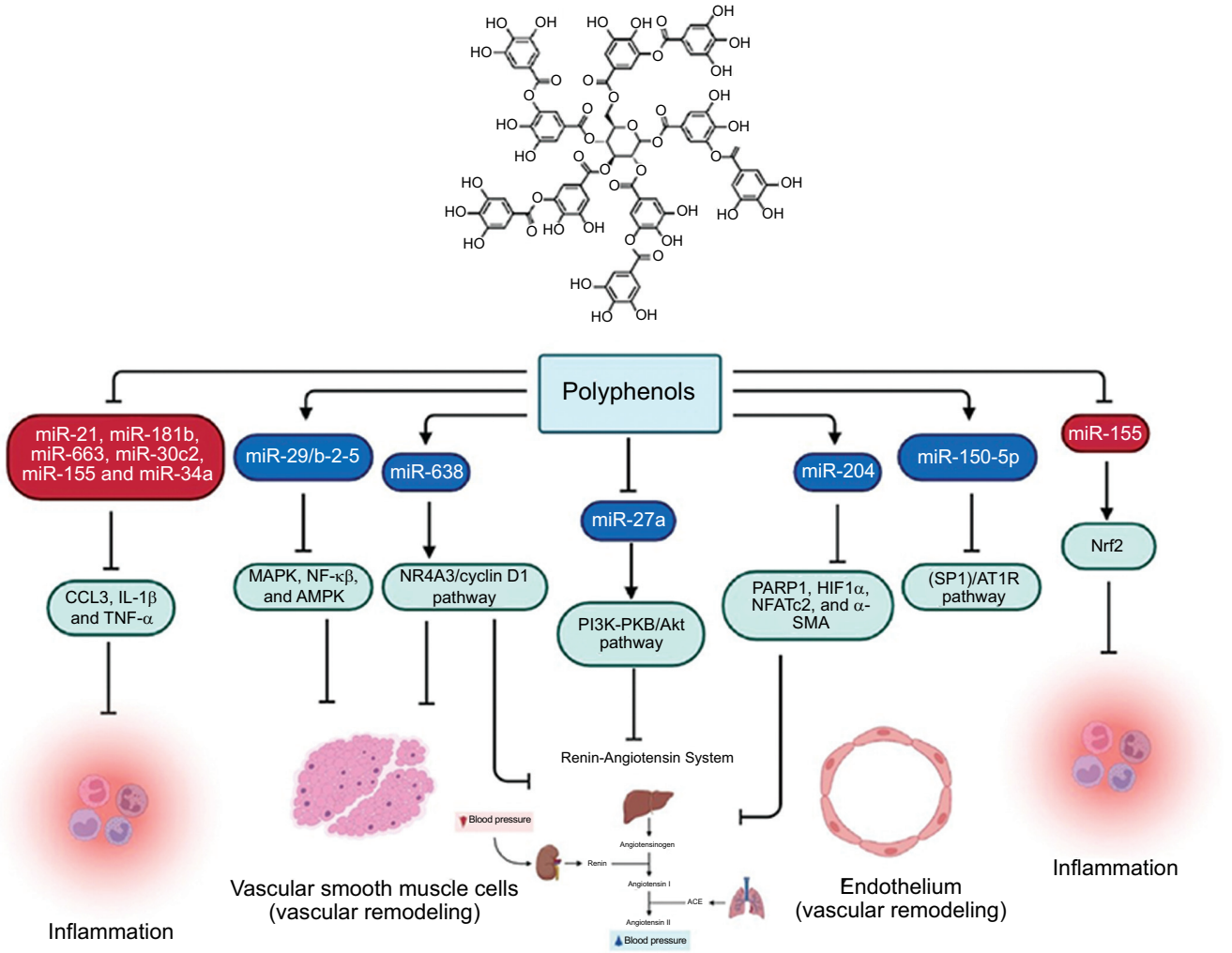

Fig. (4). Schematic representation illustrating the pathological pathways by which polyphenols regulate the expression levels of microRNA (miRNA) and its target genes in hypertension. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

in the human body. These advanced formulations aim to protect polyphenols from premature degradation and facilitate their more efficient delivery to targeted sites, potentially enhancing their therapeutic effects. The therapeutic implications of harnessing polyphenols to modulate ncRNAs are particularly promising, given the low toxicity and natural abundance of these compounds. Unlike many synthetic drugs, polyphenols are widely available in the diet, making them accessible to a broad population. This accessibility, combined with their potential to target ncRNAs, positions polyphenols as attractive candidates for developing new therapeutic strategies against HTN. Polyphenol-based interventions could serve as a novel, non-pharmacological approach to HTN management, either as a primary treatment or in conjunction with conventional antihypertensive therapies. Preliminary studies suggest that such combinations might produce synergistic effects, potentially allowing for lower dosages of pharmaceuticals and reducing side effects. However, detailed studies and clinical trials are necessary to establish safe and effective combination therapies fully. Further research is needed to identify specific ncRNA targets most responsive to polyphenol intervention and to understand the dose-response relationships that optimize their therapeutic efficacy. Understanding these nuances is crucial for translating preclinical findings into clinical applications, where tailored dietary recommendations or supplements could be used to prevent or treat HTN effectively. As research in this area continues to evolve, there is hope that polyphenol-based interventions could become a cornerstone of HTN management, providing a natural and effective means of reducing the global burden of this condition. The intricate interplay between polyphenols and ncRNAs offers valuable mechanistic insights into how dietary components can influence HTN at the molecular level, potentially leading to improved cardiovascular outcomes and enhanced public health.

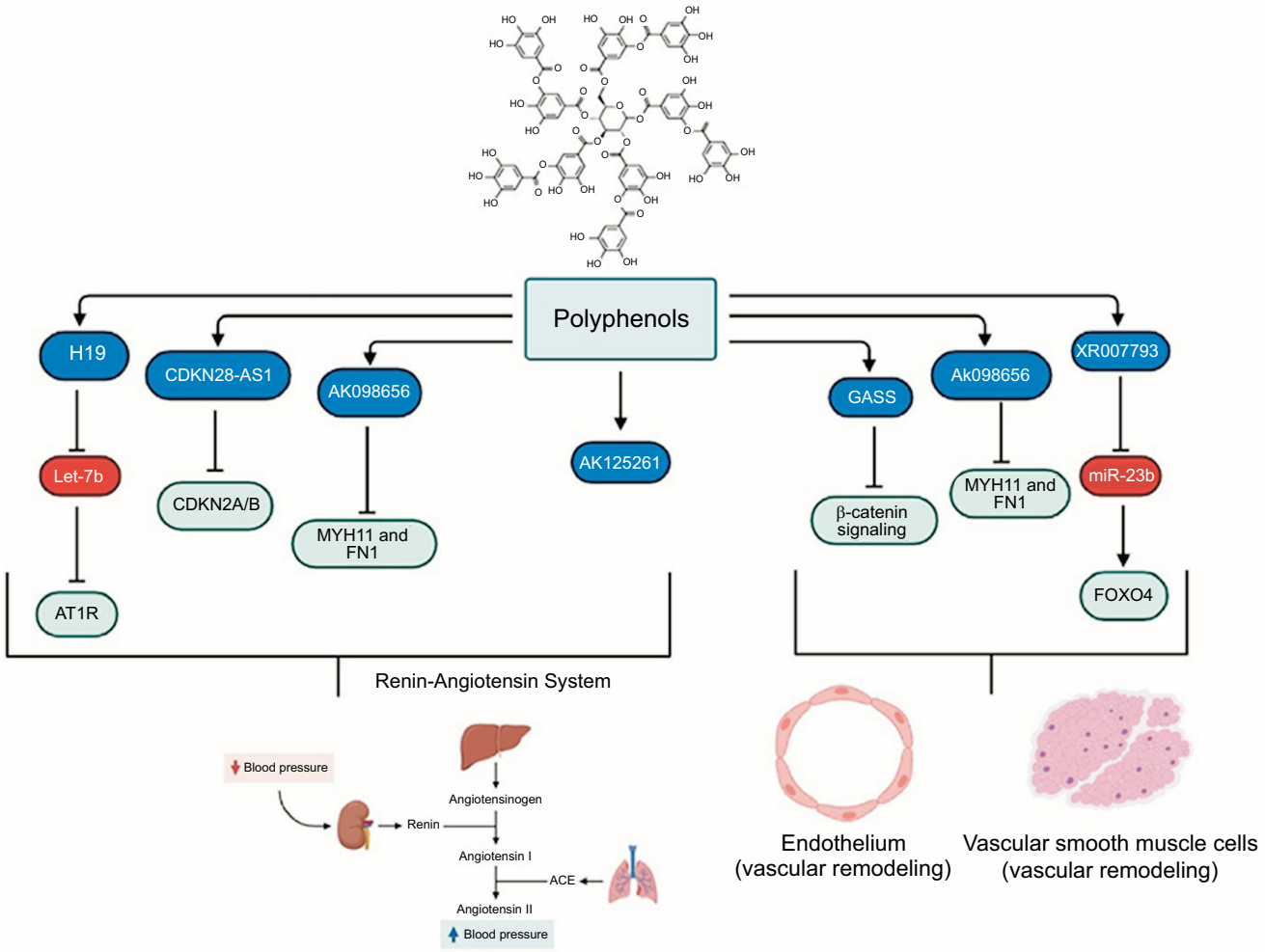

Fig. (5). Schematic representation illustrating the pathological pathways by which polyphenols regulate the expression levels of long non-coding RNAs (lncRNAs) and their targets in hypertension. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CONCLUSION

While the scientific community has persistently striven to unravel the molecular intricacies of HTN, a significant portion of its molecular underpinnings continues to elude understanding. Nonetheless, the deployment of advanced RNA sequencing technologies, particularly small RNA sequencing, has emerged as a powerful tool, offering a glimpse into the complex molecular processes that underlie HTN. This, coupled with the discovery of ncRNAs targets implicated in the pathogenesis of HTN, presents an exciting and promising avenue that could potentially lead to the development of groundbreaking therapies aimed at preventing and even reversing the adverse consequences of this pervasive condition. It is noteworthy, however, that despite the growing body of evidence supporting the involvement of ncRNAs in the regulation of BP and their role in HTN, this field of investigation remains relatively fledgling within the domain of HTN research. Yet, the potential implications are profound, hinting at a sea change in our approach to understanding and managing this complex condition. These ncRNAs, spanning miRNAs and long non-coding RNAs (lncRNAs), have unlocked doors to fresh opportunities and breakthroughs, especially when considered within the context of clinical trials exploring RNA interference (RNAi) as the next frontier in medical therapy. Novel strategies in drug development can home in on the suppression or inhibition of overexpressed ncRNAs, offering a potent means of intervening in the molecular processes at the heart of HTN. Conversely, in cases of deficient ncRNAs, they can be bolstered or enhanced through overexpression or by leveraging synthetic ncRNAs. The distinguishing hallmark of ncRNAs compared to traditional drug molecules lies in their ability to pinpoint any gene of interest and their potential to repress gene expression. This feat may elude certain conventional drug compounds. The application of ncRNAs in the domain of CVDs, with a spotlight on HTN, holds the key to unlocking a new frontier in intelligent

and precise medical interventions. By harnessing the formidable capabilities of these enigmatic molecules, the realm of HTN research is poised for a transformative leap forward, bringing with it the promise of more effective and personalized treatments for this widespread medical condition. As our understanding deepens and the research advances, the potential benefits for patients dealing with HTN become increasingly tangible.

AUTHORS' CONTRIBUTIONS

I.G. and O.B. contributed to the study conception and design; T.I. contributed to data collection. C.W. analysed the data and interpreted the results, and I.G. drafted the manuscript. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

HTN	=	Hypertension
CVDs	=	Cardiovascular Diseases
miRNAs	=	microRNAs
ncRNAs	=	Non-Coding RNAs
lncRNAs	=	Long Non-Coding RNAs
mRNA	=	Messenger RNA
EGCG	=	Epigallocatechin-3-Gallate
BP	=	Blood Pressure
NO	=	Nitric Oxide
EDH	=	Endothelium-Dependent Hyperpolarization
ROS	=	Reactive Oxygen Species
eNOS	=	Endothelial Nitric Oxide Synthase
GWAS	=	Genome-wide Association Studies
CAD	=	Coronary Artery Disease
PAD	=	Peripheral Artery Disease

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Raja B, Saranya D, Prabhu R. Role of flavonoid troxerutin on blood pressure oxidative stress and regulation of lipid metabolism. Front Biosci (Elite Ed) 2019; 11(1): 121-9. http://dx.doi.org/10.2741/e851 PMID: 30468643

[2] Rossi GP, Rossitto G, Maifredini C, *et al.* Modern management of hypertensive emergencies. High Blood Press Cardiovasc Prev 2022; 29(1): 33-40. http://dx.doi.org/10.1007/s40292-021-00487-1 PMID: 34813055

[3] Stampouloglou PK, Siasos G, Bletsa E, *et al.* The role of cell-derived microparticles in cardiovascular diseases: Current concepts. Curr Pharm Des 2022; 28(21): 1745-57. http://dx.doi.org/10.2174/1381612828666220429081555 PMID: 35986552

[4] Di Pietro N, Baldassarre MPA, Cichelli A, Pandolfi A, Formoso G, Pipino C. Role of polyphenols and carotenoids in endothelial dysfunction: An overview from classic to innovative biomarkers. Oxid Med Cell Longev 2020; 2020: 1-19. http://dx.doi.org/10.1155/2020/6381380 PMID: 33133348

[5] Shirazi-Tehrani E, Chamasemani A, Firouzabadi N, Mousaei M. ncRNAs and polyphenols: new therapeutic strategies for hypertension. RNA Biol 2022; 19(1): 575-87. http://dx.doi.org/10.1080/15476286.2022.2066335 PMID: 35438046

[6] Rana A, Samtiya M, Dhewa T, Mishra V, Aluko RE. Health benefits of polyphenols: A concise review. J Food Biochem 2022; 46(10): e14264. http://dx.doi.org/10.1111/jfbc.14264 PMID: 35694805

[7] Nattagh-Eshtivani E, Gheflati A, Barghchi H, *et al.* The role of Pycnogenol in the control of inflammation and oxidative stress in chronic diseases: Molecular aspects. Phytother Res 2022; 36(6): 2352-74. http://dx.doi.org/10.1002/ptr.7454 PMID: 35583807

[8] Sufianova G, Gareev I, Beylerli O, *et al.* Modern aspects of the use of natural polyphenols in tumor prevention and therapy. Front Cell Dev Biol 2022; 10: 1011435. http://dx.doi.org/10.3389/fcell.2022.1011435 PMID: 36172282

[9] Putera HD, Doewes RI, Shalaby MN, *et al.* The effect of conjugated linoleic acids on inflammation, oxidative stress, body composition and physical performance: a comprehensive review of putative molecular mechanisms. Nutr Metab (Lond) 2023; 20(1): 35. http://dx.doi.org/10.1186/s12986-023-00758-9 PMID: 37644566

[10] Xu L, Jiao S, Zhang D, Wu S, Zhang H, Gao B. Identification of long noncoding RNAs with machine learning methods: a review. Brief Funct Genomics 2021; 20(3): 174-80. http://dx.doi.org/10.1093/bfgp/elab017 PMID: 33758917

[11] Pandima Devi K, Rajavel T, Daglia M, Nabavi SF, Bishayee A, Nabavi SM. Targeting miRNAs by polyphenols: Novel therapeutic strategy for cancer. Semin Cancer Biol 2017; 46: 146-57. http://dx.doi.org/10.1016/j.semcancer.2017.02.001 PMID: 28185862

[12] Nascimento-Souza MA, de Paiva PG, Pérez-Jiménez J, do Carmo Castro Franceschini S, Ribeiro AQ. Estimated dietary intake and major food sources of polyphenols in elderly of Viçosa, Brazil: a population-based study. Eur J Nutr 2018; 57(2): 617-27. http://dx.doi.org/10.1007/s00394-016-1348-0 PMID: 27873069

[13] Durazzo A, Lucarini M, Souto EB, *et al.* Polyphenols: A concise overview on the chemistry, occurrence, and human health. Phytother Res 2019; 33(9): 2221-43. http://dx.doi.org/10.1002/ptr.6419 PMID: 31359516

[14] Bellavia D, Caradonna F, Dimarco E, *et al.* Terpenoid treatment in osteoporosis: this is where we have come in research. Trends Endocrinol Metab 2021; 32(11): 846-61. http://dx.doi.org/10.1016/j.tem.2021.07.011 PMID: 34481733

[15] Williamson G. The role of polyphenols in modern nutrition. Nutr Bull 2017; 42(3): 226-35. http://dx.doi.org/10.1111/nbu.12278 PMID: 28983192

[16] Vetrani C, Vitale M, Bozzetto L, *et al.* Association between different dietary polyphenol subclasses and the improvement in cardiometabolic risk factors: evidence from a randomized controlled clinical trial. Acta Diabetol 2018; 55(2): 149-53. http://dx.doi.org/10.1007/s00592-017-1075-x PMID: 29151225

[17] Fuentes E, Palomo I. Mechanisms of endothelial cell protection by hydroxycinnamic acids. Vascul Pharmacol 2014; 63(3): 155-61. http://dx.doi.org/10.1016/j.vph.2014.10.006 PMID: 25459650

[18] Daiber A, Steven S, Euler G, Schulz R. Vascular and cardiac oxidative stress and inflammation as targets for cardioprotection. Curr Pharm Des 2021; 27(18): 2112-30. http://dx.doi.org/10.2174/1381612827666210125155821 PMID: 33550963

[19] Yamagata K, Yamori Y. Inhibition of endothelial dysfunction by dietary flavonoids and preventive effects against cardiovascular disease. J Cardiovasc Pharmacol 2020; 75(1): 1-9. http://dx.doi.org/10.1097/FJC.0000000000000757 PMID: 31613843

[20] Garcia C, Blesso CN. Antioxidant properties of anthocyanins and their mechanism of action in atherosclerosis. Free Radic Biol Med 2021; 172: 152-66. http://dx.doi.org/10.1016/j.freeradbiomed.2021.05.040 PMID: 34087429

[21] Tolba MF, Omar HA, Azab SS, Khalifa AE, Abdel-Naim AB, Abdel-Rahman SZ. Caffeic acid phenethyl ester: a review of its antioxidant activity, protective effects against ischemia-reperfusion injury and drug adverse reactions. Crit Rev Food Sci Nutr 2016; 56(13): 2183-90. http://dx.doi.org/10.1080/10408398.2013.821967 PMID: 25365228

[22] Bartáková A, Nováková M. Secondary metabolites of plants as modulators of endothelium functions. Int J Mol Sci 2021; 22(5): 2533. http://dx.doi.org/10.3390/ijms22052533 PMID: 33802468

[23] Davinelli S, Scapagnini G. Polyphenols: a promising nutritional approach to prevent or reduce the progression of prehypertension. High Blood Press Cardiovasc Prev 2016; 23(3): 197-202. http://dx.doi.org/10.1007/s40292-016-0149-0 PMID: 27115149

[24] Ditano-Vázquez P, Torres-Peña JD, Galeano-Valle F, *et al.* The fluid aspect of the mediterranean diet in the prevention and management of cardiovascular disease and diabetes: the role of polyphenol content in moderate consumption of wine and olive oil. Nutrients 2019; 11(11): 2833. http://dx.doi.org/10.3390/nu11112833 PMID: 31752333

[25] Song S, Xiao X, Guo D, *et al.* Protective effects of Paeoniflorin against AOPP-induced oxidative injury in HUVECs by blocking the ROS-HIF-1α/VEGF pathway. Phytomedicine 2017; 34: 115-26. http://dx.doi.org/10.1016/j.phymed.2017.08.010 PMID: 28899493

[26] Zhong L, Simard MJ, Huot J. Endothelial microRNAs regulating the NF-κB pathway and cell adhesion molecules during inflammation. FASEB J 2018; 32(8): 4070-84. http://dx.doi.org/10.1096/fj.201701536R PMID: 29565737

[27] Tung WC, Rizzo B, Dabbagh Y, *et al.* Polyphenols bind to low density lipoprotein at biologically relevant concentrations that are protective for heart disease. Arch Biochem Biophys 2020; 694: 108589. http://dx.doi.org/10.1016/j.abb.2020.108589 PMID: 33010229

[28] Ahmadi A, Jamialahmadi T, Sahebkar A. Polyphenols and atherosclerosis: A critical review of clinical effects on LDL oxidation. Pharmacol Res 2022; 184: 106414. http://dx.doi.org/10.1016/j.phrs.2022.106414 PMID: 36028188

[29] Kohil A, Al-Asmakh M, Al-Shafai M, Terranegra A. The interplay between diet and the epigenome in the pathogenesis of type-1 diabetes. Front Nutr 2021; 7: 612115. http://dx.doi.org/10.3389/fnut.2020.612115 PMID: 33585535

[30] Amiot MJ, Latgé C, Plumey L, Raynal S. Intake Estimation of Phytochemicals in a French Well-Balanced Diet. Nutrients 2021; 13(10): 3628. http://dx.doi.org/10.3390/nu13103628 PMID: 34684628

[31] Ren J, An J, Chen M, Yang H, Ma Y. Effect of proanthocyanidins on blood pressure: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2021; 165: 105329. http://dx.doi.org/10.1016/j.phrs.2020.105329 PMID: 33465473

[32] Ding F, Ma B, Nazary-Vannani A, *et al.* The effects of green coffee bean extract supplementation on lipid profile in humans: A systematic review and meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2020; 30(1): 1-10. http://dx.doi.org/10.1016/j.numecd.2019.10.002 PMID: 31748178

[33] Rodríguez-Pérez C, García-Villanova B, Guerra-Hernández E, Verardo V. Grape seeds proanthocyanidins: an overview of in vivo bioactivity in animal models. Nutrients 2019; 11(10): 2435. http://dx.doi.org/10.3390/nu11102435 PMID: 31614852

[34] Blesso CN. Dietary anthocyanins and human health. Nutrients 2019; 11(9): 2107. http://dx.doi.org/10.3390/nu11092107 PMID: 31491856

[35] dos Santos Baião D, Vieira Teixeira da Silva D, Margaret Flosi Paschoalin V. A narrative review on dietary strategies to provide nitric oxide as a non-drug cardiovascular disease therapy: beetroot formulations—a smart nutritional intervention. Foods 2021; 10(4): 859. http://dx.doi.org/10.3390/foods10040859 PMID: 33920855

[36] Samodien E, Johnson R, Pheiffer C, *et al.* Diet-induced hypothalamic dysfunction and metabolic disease, and the therapeutic potential of polyphenols. Mol Metab 2019; 27: 1-10. http://dx.doi.org/10.1016/j.molmet.2019.06.022 PMID: 31300352

[37] Zhang W, Zhang S, Deng Y, *et al.* Trial of intensive blood-pressure control in older patients with hypertension. N Engl J Med 2021; 385(14): 1268-79. http://dx.doi.org/10.1056/NEJMoa2111437 PMID: 34491661

[38] Dangwal S, Schimmel K, Foinquinos A, Xiao K, Thum T. Noncoding RNAs in heart failure. Handb Exp Pharmacol 2016; 243: 423-45. http://dx.doi.org/10.1007/164_2016_99 PMID: 27995387

[39] Tadic M, Cuspidi C, Frydas A, Grassi G. The role of arterial hypertension in development heart failure with preserved ejection fraction: just a risk factor or something more? Heart Fail Rev 2018; 23(5): 631-9. http://dx.doi.org/10.1007/s10741-018-9698-8 PMID: 29619635

[40] Firouzabadi N, Tajik N, Bahramali E, *et al.* Association of angiotensin-converting enzyme polymorphism with coronary artery disease in Iranian patients with unipolar depression. Clin Biochem 2012; 45(16-17): 1347-52. http://dx.doi.org/10.1016/j.clinbiochem.2012.05.033 PMID: 22683751

[41] Bahramali E, Firouzabadi N, Rajabi M, *et al.* Association of renin–angiotensin–aldosterone system gene polymorphisms with left ventricular hypertrophy in patients with heart failure with preserved ejection fraction: A case–control study. Clin Exp Hypertens 2017; 39(4): 371-6. http://dx.doi.org/10.1080/10641963.2016.1267196 PMID: 28513230

[42] Sufianov A, Begliarzade S, Beilerli A, Liang Y, Ilyasova T, Beylerli O. Circular RNAs as biomarkers for lung cancer. Noncoding RNA Res 2023; 8(1): 83-8. http://dx.doi.org/10.1016/j.ncrna.2022.11.002 PMID: 36407660

[43] Marques FZ, Charchar FJ. microRNAs in Essential Hypertension and Blood Pressure Regulation. Adv Exp Med Biol 2015; 888: 215-35. http://dx.doi.org/10.1007/978-3-319-22671-2_11 PMID: 26663185

[44] Kohagura K, Kochi M, Zamami R, Ohya Y. Understanding the Complex Interaction Between Uric Acid and Hypertension. Am J Hypertens 2020; 33(9): 822-4. http://dx.doi.org/10.1093/ajh/hpaa050 PMID: 32267516

[45] Poller W, Dimmeler S, Heymans S, *et al.* Non-coding RNAs in cardiovascular diseases: diagnostic and therapeutic perspectives. Eur Heart J 2018; 39(29): 2704-16. http://dx.doi.org/10.1093/eurheartj/ehx165 PMID: 28430919

[46] Beilerli A, Begliarzade S, Sufianov A, Ilyasova T, Liang Y, Beylerli O. Circulating ciRS-7 as a potential non-invasive biomarker for epithelial ovarian cancer: An investigative study. Noncoding RNA Res 2022; 7(3): 197-204. http://dx.doi.org/10.1016/j.ncrna.2022.07.004 PMID: 35991513

[47] Martini AG, Danser AHJ. Juxtaglomerular Cell Phenotypic Plasticity. High Blood Press Cardiovasc Prev 2017; 24(3): 231-42. http://dx.doi.org/10.1007/s40292-017-0212-5 PMID: 28527017

[48] Mou X, Wang J, Wang L, Wang S. Correlation Between Single Nucleotide Polymorphisms of the rs664589 Locus in the Long-Chain Noncoding RNA Lung Adenocarcinoma Metastasis-Associated Gene 1, Hypertension, and Its Mechanism. Genet Test Mol

Biomarkers 2020; 24(3): 120-30.
http://dx.doi.org/10.1089/gtmb.2019.0193 PMID: 32109146
[49] Fang G, Qi J, Huang L, Zhao X. LncRNA MRAK048635_P1 is critical for vascular smooth muscle cell function and phenotypic switching in essential hypertension. Biosci Rep 2019; 39(3): BSR20182229.
http://dx.doi.org/10.1042/BSR20182229 PMID: 30833363
[50] Gareev I, Kudriashov V, Sufianov A, *et al.* The role of long non--coding RNA ANRIL in the development of atherosclerosis. Non-coding RNA Res 2022; 7(4): 212-6.
http://dx.doi.org/10.1016/j.ncrna.2022.09.002 PMID: 36157350
[51] Jiang X, Ning Q. Long noncoding RNAs as novel players in the pathogenesis of hypertension. Hypertens Res 2020; 43(7): 597-608.
http://dx.doi.org/10.1038/s41440-020-0408-2 PMID: 32020084
[52] Zahid KR, Raza U, Chen J, Raj UJ, Gou D. Pathobiology of pulmonary artery hypertension: role of long non-coding RNAs. Cardiovasc Res 2020; 116(12): 1937-47.
http://dx.doi.org/10.1093/cvr/cvaa050 PMID: 32109276
[53] Yao QP, Xie ZW, Wang KX, *et al.* Profiles of long noncoding RNAs in hypertensive rats. J Hypertens 2017; 35(6): 1195-203.
http://dx.doi.org/10.1097/HJH.0000000000001304 PMID: 28319593
[54] Yu CK, Xu T, Assoian RK, Rader DJ. Mining the Stiffness-Sensitive Transcriptome in Human Vascular Smooth Muscle Cells Identifies Long Noncoding RNA Stiffness Regulators. Arterioscler Thromb Vasc Biol 2018; 38(1): 164-73.
http://dx.doi.org/10.1161/ATVBAHA.117.310237 PMID: 29051139
[55] Li Y, Yang N. Microarray expression profile analysis of long non--coding RNAs in thoracic aortic aneurysm. Kaohsiung J Med Sci 2018; 34(1): 34-42.
http://dx.doi.org/10.1016/j.kjms.2017.09.005 PMID: 29310814
[56] Tang R, Mei X, Wang YC, *et al.* LncRNA GAS5 regulates vascular smooth muscle cell cycle arrest and apoptosis via p53 pathway. Biochim Biophys Acta Mol Basis Dis 2019; 1865(9): 2516-25.
http://dx.doi.org/10.1016/j.bbadis.2019.05.022 PMID: 31167125
[57] Zhang X, Yang X, Lin Y, *et al.* Anti-hypertensive effect of *Lycium barbarum L.* with down-regulated expression of renal endothelial lncRNA sONE in a rat model of salt-sensitive hypertension. Int J Clin Exp Pathol 2015; 8(6): 6981-7.
PMID: 26261587
[58] Yeh CF, Chang YCE, Lu CY, Hsuan CF, Chang WT, Yang KC. Expedition to the missing link: Long noncoding RNAs in cardiovascular diseases. J Biomed Sci 2020; 27(1): 48.
http://dx.doi.org/10.1186/s12929-020-00647-w PMID: 32241300
[59] Zhang X, Tang X, Hamblin MH, Yin KJ. Long Non-Coding RNA *Malat1* Regulates Angiogenesis in Hindlimb Ischemia. Int J Mol Sci 2018; 19(6): 1723.
http://dx.doi.org/10.3390/ijms19061723 PMID: 29891768
[60] Kunnas T, Piesanen J, Nikkari ST. Association of a Chromosome Locus 9p21.3 *CDKN2B-AS1* Variant rs4977574 with Hypertension: The TAMRISK Study. Genet Test Mol Biomarkers 2018; 22(5): 327-30.
http://dx.doi.org/10.1089/gtmb.2017.0249 PMID: 29791233
[61] Su H, Xu X, Yan C, *et al.* LncRNA H19 promotes the proliferation of pulmonary artery smooth muscle cells through AT_1R via sponging let-7b in monocrotaline-induced pulmonary arterial hypertension. Respir Res 2018; 19(1): 254.
http://dx.doi.org/10.1186/s12931-018-0956-z PMID: 30547791
[62] Fabian MR, Sonenberg N, Filipowicz W. Regulation of mRNA Translation and Stability by microRNAs. Annu Rev Biochem 2010; 79(1): 351-79.
http://dx.doi.org/10.1146/annurev-biochem-060308-103103 PMID: 20533884
[63] Liu L, Wang X, Zhao W, *et al.* Systematic characterization of small RNAs associated with C. elegans Argonautes. Sci China Life Sci 2023; 66(6): 1303-22.
http://dx.doi.org/10.1007/s11427-022-2304-8 PMID: 37154856
[64] Badawy HK, Abo-Elmatty DM, Mesbah NM. Differential expression of MicroRNA let-7e and 296-5p in plasma of Egyptian patients with essential hypertension. Heliyon 2018; 4(11): e00969.
http://dx.doi.org/10.1016/j.heliyon.2018.e00969 PMID: 30519661
[65] Shen K, Xu L, Chen D, Tang W, Huang Y. Human cytomegalovirus-encoded miR-UL112 contributes to HCMV-mediated vascular diseases by inducing vascular endothelial cell dysfunction. Virus Genes 2018; 54(2): 172-81.
http://dx.doi.org/10.1007/s11262-018-1532-9 PMID: 29330663
[66] Liu GX, Li YQ, Huang XR, *et al.* Smad7 inhibits AngII-mediated hypertensive nephropathy in a mouse model of hypertension. Clin Sci (Lond) 2014; 127(3): 195-208.
http://dx.doi.org/10.1042/CS20130706 PMID: 24511990
[67] Klimczak D, Jazdzewski K, Kuch M. Regulatory mechanisms in arterial hypertension: role of microRNA in pathophysiology and therapy. Blood Press 2017; 26(1): 2-8.
http://dx.doi.org/10.3109/08037051.2016.1167355 PMID: 27177042
[68] Liu K, Ying Z, Qi X, Shi Y, Tang Q. MicroRNA-1 regulates the proliferation of vascular smooth muscle cells by targeting insulin--like growth factor 1. Int J Mol Med 2015; 36(3): 817-24.
http://dx.doi.org/10.3892/ijmm.2015.2277 PMID: 26166810
[69] Zhang WF, Xiong YW, Zhu TT, Xiong AZ, Bao H, Cheng XS. MicroRNA let-7g inhibited hypoxia-induced proliferation of PASMCs via G/G_1 cell cycle arrest by targeting c-myc. Life Sci 2017; 170: 9-15.
http://dx.doi.org/10.1016/j.lfs.2016.11.020 PMID: 27889560
[70] Zhang B, Yao Y, Sun QF, *et al.* Circulating mircoRNA-21 as a predictor for vascular restenosis after interventional therapy in patients with lower extremity arterial occlusive disease. Biosci Rep 2017; 37(2): BSR20160502.
http://dx.doi.org/10.1042/BSR20160502 PMID: 28250135
[71] Chadha PS, Zunke F, Zhu HL, *et al.* Reduced KCNQ4-encoded voltage-dependent potassium channel activity underlies impaired β-adrenoceptor-mediated relaxation of renal arteries in hypertension. Hypertension 2012; 59(4): 877-84.
http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.187427 PMID: 22353613
[72] Liu Y, Liu G, Zhang H, Wang J. MiRNA-199a-5p influences pulmonary artery hypertension via downregulating Smad3. Biochem Biophys Res Commun 2016; 473(4): 859-66.
http://dx.doi.org/10.1016/j.bbrc.2016.03.140 PMID: 27038547
[73] Yang F, Li H, Du Y, Shi Q, Zhao L. Downregulation of microRNA-34b is responsible for the elevation of blood pressure in spontaneously hypertensive rats. Mol Med Rep 2017; 15(3): 1031-6.
http://dx.doi.org/10.3892/mmr.2017.6122 PMID: 28098882
[74] Huber LC, Ulrich S, Leuenberger C, *et al.* Featured Article: microRNA-125a in pulmonary hypertension: Regulator of a proliferative phenotype of endothelial cells. Exp Biol Med (Maywood) 2015; 240(12): 1580-9.
http://dx.doi.org/10.1177/1535370215579018 PMID: 25854878
[75] Kang BY, Park KK, Green DE, *et al.* Hypoxia mediates mutual repression between microRNA-27a and PPARγ in the pulmonary vasculature. PLoS One 2013; 8(11): e79503.
http://dx.doi.org/10.1371/journal.pone.0079503 PMID: 24244514
[76] Jin Y, Jin Y, Chen B, Tipple TE, Nelin LD. Arginase II is a target of miR-17-5p and regulates miR-17-5p expression in human pulmonary artery smooth muscle cells. Am J Physiol Lung Cell Mol Physiol 2014; 307(2): L197-204.
http://dx.doi.org/10.1152/ajplung.00266.2013 PMID: 24879052
[77] Zhang W, Tao Z, Xu F, *et al.* An Overview of miRNAs Involved in PASMC Phenotypic Switching in Pulmonary Hypertension. BioMed Res Int 2021; 2021: 1-18.
http://dx.doi.org/10.1155/2021/5765029 PMID: 34660794
[78] Bouyahya A, Omari NE, EL Hachlafi N, *et al.* Chemical Compounds of Berry-Derived Polyphenols and Their Effects on Gut Microbiota, Inflammation, and Cancer. Molecules 2022; 27(10): 3286.
http://dx.doi.org/10.3390/molecules27103286 PMID: 35630763
[79] Yang R, Dong Y, Gao F, *et al.* Comprehensive Analysis of Secondary Metabolites of Four Medicinal Thyme Species Used in Folk Medicine and Their Antioxidant Activities In Vitro. Molecules 2023; 28(6): 2582.
http://dx.doi.org/10.3390/molecules28062582 PMID: 36985554
[80] Turner AJ, Nalivaeva NN. Angiotensin-converting enzyme 2 (ACE2): Two decades of revelations and re-evaluation. Peptides 2022; 151: 170766.

http://dx.doi.org/10.1016/j.peptides.2022.170766 PMID: 35151768

[81] Chen BC, Hung MY, Wang HF, *et al.* GABA tea attenuates cardiac apoptosis in spontaneously hypertensive rats (SHR) by enhancing PI3K/Akt-mediated survival pathway and suppressing Bax/Bak dependent apoptotic pathway. Environ Toxicol 2018; 33(7): 789-97.
http://dx.doi.org/10.1002/tox.22565 PMID: 29708300

[82] Patel SS, Acharya A, Ray RS, Agrawal R, Raghuwanshi R, Jain P. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. Crit Rev Food Sci Nutr 2020; 60(6): 887-939.
http://dx.doi.org/10.1080/10408398.2018.1552244 PMID: 30632782

[83] Diao P, He H, Tang J, Xiong L, Li L. Natural compounds protect the skin from airborne particulate matter by attenuating oxidative stress. Biomed Pharmacother 2021; 138: 111534.
http://dx.doi.org/10.1016/j.biopha.2021.111534 PMID: 34311532

[84] Beylerli O, Beilerli A, Shumadalova A, *et al.* Therapeutic effect of natural polyphenols against glioblastoma. Front Cell Dev Biol 2022; 10: 1036809.
http://dx.doi.org/10.3389/fcell.2022.1036809 PMID: 36268515

[85] Gawronski AR, Uhl M, Zhang Y, *et al.* MechRNA: prediction of lncRNA mechanisms from RNA–RNA and RNA–protein interactions. Bioinformatics 2018; 34(18): 3101-10.
http://dx.doi.org/10.1093/bioinformatics/bty208 PMID: 29617966

[86] Jia P, Cai H, Liu X, *et al.* Long non-coding RNA H19 regulates glioma angiogenesis and the biological behavior of glioma-associated endothelial cells by inhibiting microRNA-29a. Cancer Lett 2016; 381(2): 359-69.
http://dx.doi.org/10.1016/j.canlet.2016.08.009 PMID: 27543358

[87] Chiang JT, Badrealam KF, Shibu MA, *et al. Eriobotrya japonica* ameliorates cardiac hypertrophy in H9c2 cardiomyoblast and in spontaneously hypertensive rats. Environ Toxicol 2018; 33(11): 1113-22.
http://dx.doi.org/10.1002/tox.22589 PMID: 29974613

[88] Chiang JT, Badrealam KF, Shibu MA, *et al.* Anti-Apoptosis and Anti-Fibrosis Effects of *Eriobotrya Japonica* in Spontaneously Hypertensive Rat Hearts. Int J Mol Sci 2018; 19(6): 1638.
http://dx.doi.org/10.3390/ijms19061638 PMID: 29857545

[89] Cione E, La Torre C, Cannataro R, Caroleo MC, Plastina P, Gallelli L. Quercetin, Epigallocatechin Gallate, Curcumin, and Resveratrol: From Dietary Sources to Human MicroRNA Modulation. Molecules 2019; 25(1): 63.
http://dx.doi.org/10.3390/molecules25010063 PMID: 31878082

[90] Fu Q, Shi H, Ni W, *et al.* Lentivirus-mediated Bos taurus bta-miR-29b overexpression interferes with bovine viral diarrhoea virus replication and viral infection-related autophagy by directly targeting ATG14 and ATG9A in Madin–Darby bovine kidney cells. J Gen Virol 2015; 96(1): 85-94.
http://dx.doi.org/10.1099/vir.0.067140-0 PMID: 25234643

[91] Lee HY, Chen YJ, Chang WA, *et al.* Effects of Epigallocatechin Gallate (EGCG) on Urinary Bladder Urothelial Carcinoma—Next-Generation Sequencing and Bioinformatics Approaches. Medicina (Kaunas) 2019; 55(12): 768.
http://dx.doi.org/10.3390/medicina55120768 PMID: 31805718

[92] Liu J, Wu P, Xu Z, Zhang J, Liu J, Yang Z. Ginkgolide B inhibits hydrogen peroxide-induced apoptosis and attenuates cytotoxicity via activating the PI3K/Akt/mTOR signaling pathway in H9c2 cells. Mol Med Rep 2020; 22(1): 310-6.
http://dx.doi.org/10.3892/mmr.2020.11099 PMID: 32377729

[93] Tomé-Carneiro J, Gonzálvez M, Larrosa M, *et al.* Grape resveratrol increases serum adiponectin and downregulates inflammatory genes in peripheral blood mononuclear cells: a triple-blind, placebo-controlled, one-year clinical trial in patients with stable coronary artery disease. Cardiovasc Drugs Ther 2013; 27(1): 37-48.
http://dx.doi.org/10.1007/s10557-012-6427-8 PMID: 23224687

[94] Tarbit E, Singh I, Peart JN, Rose'Meyer RB. Biomarkers for the identification of cardiac fibroblast and myofibroblast cells. Heart Fail Rev 2019; 24(1): 1-15.
http://dx.doi.org/10.1007/s10741-018-9720-1 PMID: 29987445

[95] Gareev I, Beylerli O, Yang G, *et al.* Diagnostic and prognostic potential of circulating miRNAs for intracranial aneurysms. Neurosurg Rev 2021; 44(4): 2025-39.
http://dx.doi.org/10.1007/s10143-020-01427-8 PMID: 33094424

[96] Li Y, Li L, Qian Z, *et al.* Phosphatidylinositol 3-Kinase–DNA Methyltransferase 1–miR-1281–Histone Deacetylase 4 Regulatory Axis Mediates Platelet-Derived Growth Factor–Induced Proliferation and Migration of Pulmonary Artery Smooth Muscle Cells. J Am Heart Assoc 2018; 7(6): e007572.
http://dx.doi.org/10.1161/JAHA.117.007572 PMID: 29514810

[97] Chang YC, Liu HW, Chan YC, Hu SH, Liu MY, Chang SJ. The green tea polyphenol epigallocatechin-3-gallate attenuates age-associated muscle loss via regulation of miR-486-5p and myostatin. Arch Biochem Biophys 2020; 692: 108511.
http://dx.doi.org/10.1016/j.abb.2020.108511 PMID: 32710883

[98] Rajabi S, Najafipour H, Jafarinejad-Farsangi S, *et al.* Quercetin, Perillyl Alcohol, and Berberine Ameliorate Right Ventricular Disorders in Experimental Pulmonary Arterial Hypertension: Effects on miR-204, miR-27a, Fibrotic, Apoptotic, and Inflammatory Factors. J Cardiovasc Pharmacol 2021; 77(6): 777-86.
http://dx.doi.org/10.1097/FJC.0000000000001015 PMID: 34016844

[99] Ishisaka A, Kawabata K, Miki S, *et al.* Mitochondrial dysfunction leads to deconjugation of quercetin glucuronides in inflammatory macrophages. PLoS One 2013; 8(11): e80843.
http://dx.doi.org/10.1371/journal.pone.0080843 PMID: 24260490

[100] Solich J, Kuśmider M, Faron-Górecka A, Pabian P, Dziedzicka-Wasylewska M. Restraint Stress in Mice Alters Set of 25 miRNAs Which Regulate Stress- and Depression-Related mRNAs. Int J Mol Sci 2020; 21(24): 9469.
http://dx.doi.org/10.3390/ijms21249469 PMID: 33322800

[101] Zaiou M, El Amri H, Bakillah A. The clinical potential of adipogenesis and obesity-related microRNAs. Nutr Metab Cardiovasc Dis 2018; 28(2): 91-111.
http://dx.doi.org/10.1016/j.numecd.2017.10.015 PMID: 29170059

[102] Dostal Z, Modriansky M. The effect of quercetin on microRNA expression: A critical review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2019; 163(2): 95-106.
http://dx.doi.org/10.5507/bp.2019.030 PMID: 31263290