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Review

Interplay of Reactive Oxygen Species (ROS) and Epigenetic Remodelling in Cardiovascular Diseases Pathogenesis: A Contemporary Perspective

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Abstract

Cardiovascular diseases (CVDs) continue to be the leading cause of mortality worldwide, necessitating the development of novel therapies. Despite therapeutic advancements, the underlying mechanisms remain elusive. Reactive oxygen species (ROS) show detrimental effects at high concentrations but act as essential signalling molecules at physiological levels, playing a critical role in the pathophysiology of CVD. However, the link between pathologically elevated ROS and CVDs pathogenesis remains poorly understood. Recent research has highlighted the remodelling of the epigenetic landscape as a crucial factor in CVD pathologies. Epigenetic changes encompass alterations in DNA methylation, post-translational histone modifications, adenosine triphosphate (ATP)-dependent chromatin modifications, and noncoding RNA transcripts. Unravelling the intricate link between ROS and epigenetic changes in CVD is challenging due to the complexity of epigenetic signals in gene regulation. This review aims to provide insights into the role of ROS in modulating the epigenetic landscape within the cardiovascular system. Understanding these interactions may offer novel therapeutic strategies for managing CVD by targeting ROS-induced epigenetic changes. It has been widely accepted that epigenetic modifications are established during development and remain fixed once the lineage-specific gene expression pattern is achieved. However, emerging evidence has unveiled its remarkable dynamism. Consequently, it is now increasingly recognized that epigenetic modifications may serve as a crucial link between ROS and the underlying mechanisms implicated in CVD.

Keywords: cardiovascular disease; epigenetic; ROS; oxidative stress

1. Introduction

Cardiovascular diseases (CVDs) remain a leading cause of morbidity and mortality worldwide. Despite significant advances in medical treatments and interventions, the complex mechanisms underlying the development and progression of CVDs continue to challenge researchers and healthcare professionals. In recent years, an emerging body of research has shed light on the role of reactive oxygen species (ROS) and epigenetic modifications in cardiovascular health and disease [1]. ROS are highly reactive molecules containing oxygen that are generated during various cellular processes. Under normal physiological conditions, ROS serves as essential signalling molecules involved in cellular communication, immune response, and regulation of vascular tone. However, excessive or uncontrolled ROS production can lead to oxidative stress, causing damage to cellular components such as DNA, proteins, and lipids [2]. This oxidative stress is implicated in the pathogenesis of several cardiovascular disorders, including atherosclerosis, hypertension, heart failure (HF), and ischemic heart disease [3].

At the same time, the field of epigenetics has been making remarkable step in understanding the regulation of gene expression without changes to the underlying DNA sequence. Epigenetic modifications, including DNA methylation, histone modifications, and microRNAs (miRNAs), play a crucial role in modulating gene expression patterns during normal development and cellular function [4]. However, epigenetic alterations can occur in response to various environmental and lifestyle factors, influencing the risk of developing complex diseases, including cardiovascular disorders [5].

Recent research has started to reveal intricate connections between ROS and epigenetic modifications in the context of CVDs. Oxidative stress triggered by ROS can directly impact epigenetic mechanisms, leading to changes in gene expression patterns in cardiovascular cells and tissues [6]. Conversely, epigenetic modifications can regulate the expression of genes involved in ROS production and antioxidant defense, further influencing oxidative stress levels and cardiovascular homeostasis [7].

Understanding the interplay between ROS and epigenetics in the context of CVDs holds immense promise for the development of novel therapeutic strategies and targeted interventions. Identifying key epigenetic regulators affected by oxidative stress may uncover potential drug targets to mitigate the harmful effects of ROS and enhance the body's antioxidant defense systems. Furthermore, investigating how specific environmental factors and lifestyle

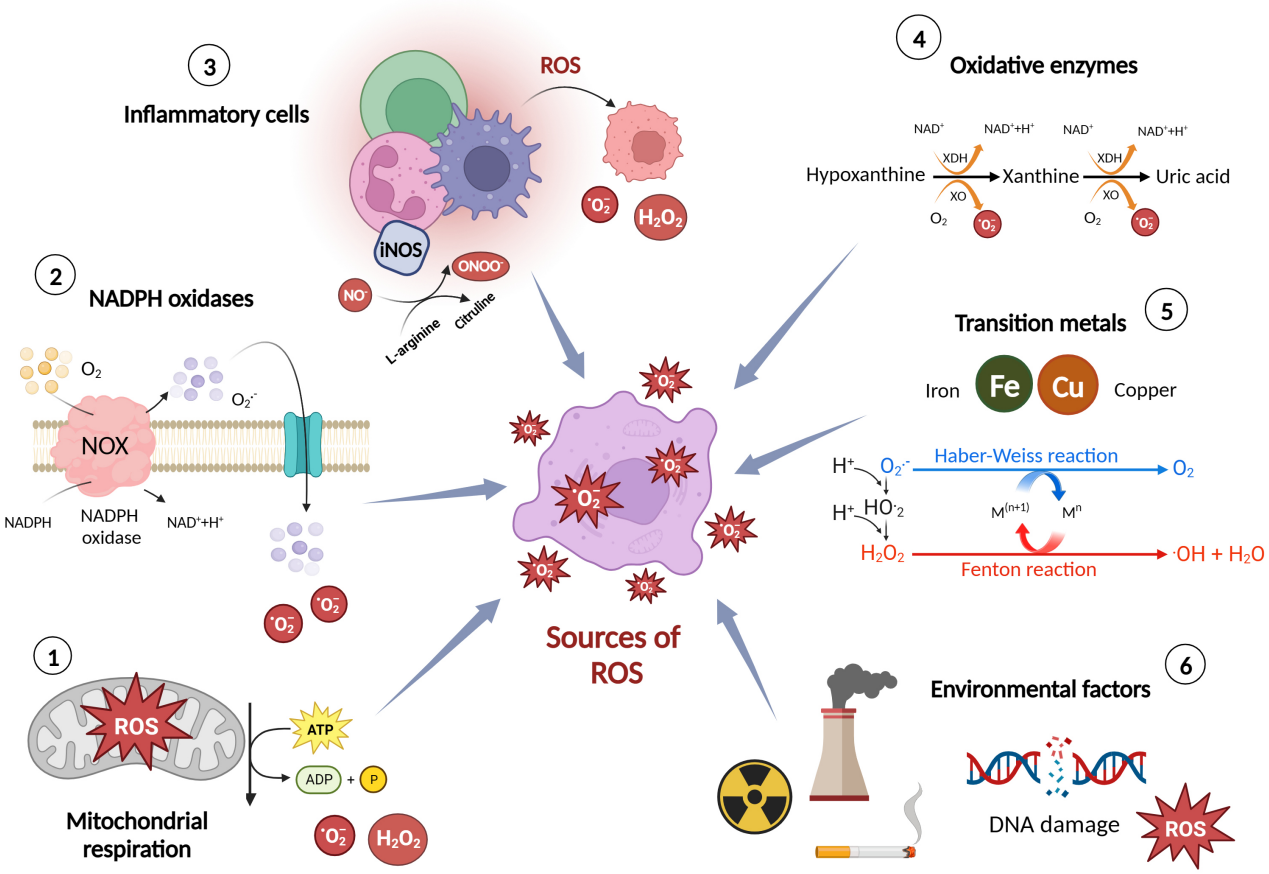

Fig. 1. Major sources and production mechanisms of reactive oxygen species (ROS). Figure was created with Biorender. Abbreviations: ROS, reactive oxygen species; NOX, nitric oxide synthase; NADPH, nicotinamide adenine dinucleotide phosphate; ATP, adenosine triphosphate; ADP, Adenosine diphosphate; O_2^-, superoxide; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; NO^-, nitrogen oxide; $ONOO^-$, peroxynitrite; XO, xanthine oxidase; XDH, xanthine dehydrogenase.

choices influence epigenetic modifications in the presence of ROS can provide invaluable insights into personalized approaches for CVDs prevention and management [8,9].

This review explores the ROS-epigenetics connection in CVDs, examining current research, molecular mechanisms, and potential clinical implications.

2. Production and Sources of ROS

ROS are highly reactive molecules that are formed as natural by-products of cellular metabolism. They play essential roles in normal cellular functions and signalling pathways [10]. However, when their production exceeds the body's antioxidant defense capacity, they can cause oxidative stress and damage to cells, tissues, and biomolecules. Here are some of the major sources and production mechanisms of ROS [11] (Fig. 1).

i. Mitochondrial respiration: Mitochondria, the powerhouse of the cell, generate the majority of ROS during the process of oxidative phosphorylation. In this process, electrons leak from the electron transport chain, leading to the production of superoxide anion ($O_2\bullet^-$) and hydrogen peroxide (H_2O_2) [11].

ii. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX): NOX enzymes are a family of membrane-bound enzymes that are involved in the regulated production of ROS. They transfer electrons across biological membranes to generate $O_2\bullet^-$ and other ROS. NOX enzymes are found in various cell types, including endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and immune cells [12].

iii. Inflammatory cells: Immune cells such as neutrophils, monocytes, and macrophages produce ROS as part of their defense mechanism against pathogens. These cells contain specialized enzymes, such as myeloperoxidase and NOX, which generate ROS to kill invading microorganisms [12].

iv. Oxidative enzymes: Certain enzymes, such as xanthine oxidase and cytochrome P450 enzymes, produce ROS as by-products of their enzymatic reactions. Xanthine oxidase generates $O_2\bullet^-$ during the breakdown of purine nucleotides, while cytochrome P450 enzymes produce ROS during various metabolic processes [11].

v. Transition metals: Transition metals, such as iron and copper, can participate in Fenton and Haber-Weiss reac-

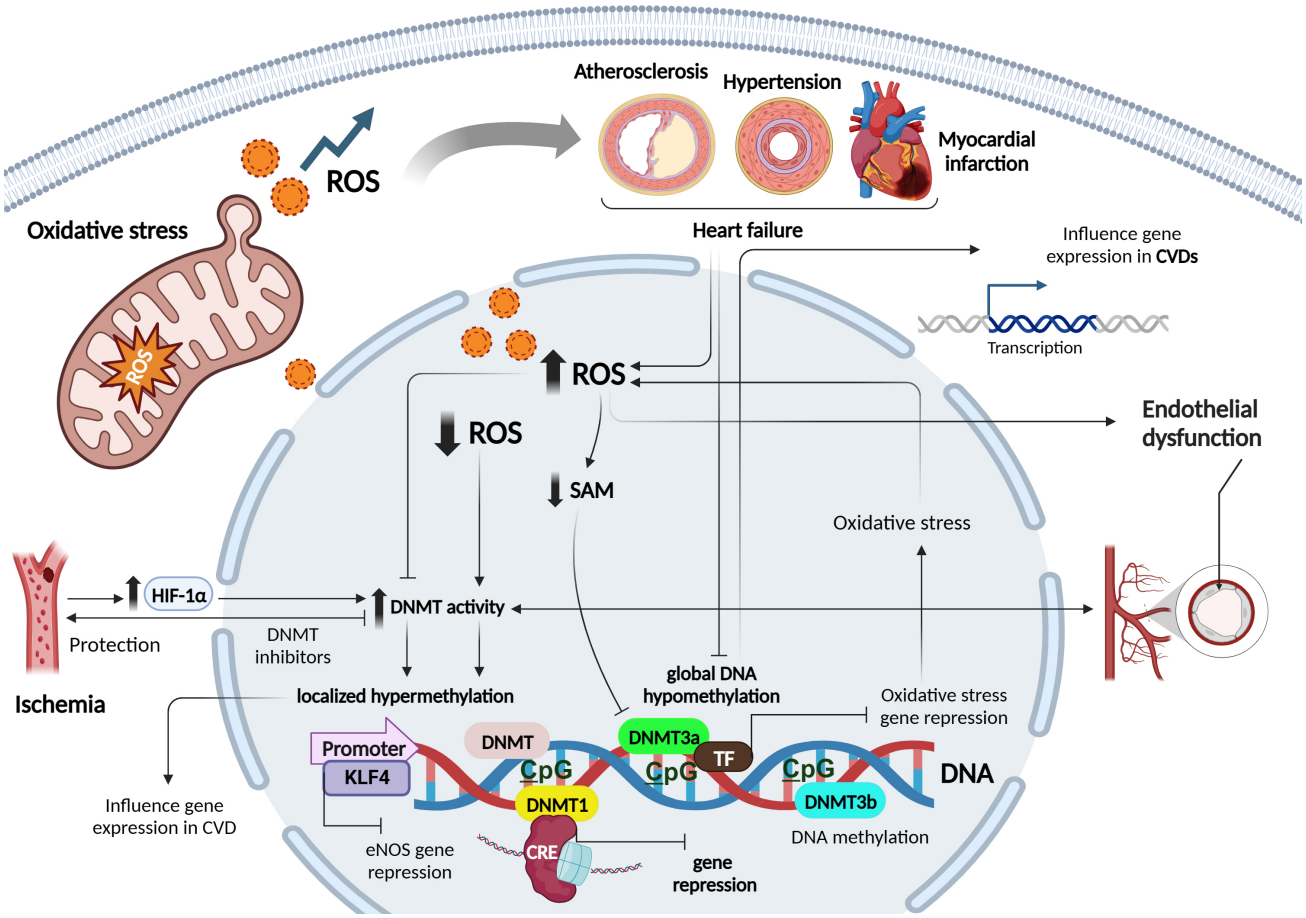

Fig. 2. Role of oxidative stress and redox patterns on DNA methylation mechanisms in cardiovascular diseases. Figure was created with Biorender. Abbreviations: ROS, reactive oxygen species; SAM, S-adenosyl methionine; CVD, cardiovascular diseases; HIF-1α, hypoxia-inducible transcription factor 1-alpha; TF, transcription factor; DNMT, DNA methyltransferase; e-NOS, endothelial nitric oxide synthase; KLF4, kruppel- like factor 4; CpG, cytosine and guanine sites; CRE, Cre recombinase.

tions, where they react with H_2O_2 to produce highly reactive hydroxyl radicals (•OH). These reactions can occur in the presence of excess metal ions and elevated levels of H_2O_2 [11].

vi. Environmental factors: Exposure to environmental pollutants, such as air pollutants, cigarette smoke [13], and radiation [14], can increase ROS production. These external sources of ROS can lead to oxidative stress and contribute to the development of various diseases, including CVDs [15].

It is important to note that while ROS are produced as natural by-products of cellular metabolism, their levels are tightly regulated by antioxidant defense mechanisms in healthy cells. Antioxidants, including enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), help neutralize ROS and maintain cellular redox balance. However, when there is an imbalance between ROS production and antioxidant defenses, oxidative stress occurs, leading to cellular damage and the development of various diseases, including CVDs [16,17].

3. Epigenetic Mechanisms and the Impact of ROS

3.1 DNA Methylation

DNA methylation is an essential epigenetic modification that plays a crucial role in regulating gene expression and cellular function. It involves the addition of a methyl group to the cytosine base of DNA, primarily occurring in regions known as cytosine-phosphate-guanine (CpG) sites, where a cytosine is followed by a guanine in the DNA sequence [18]. CpG methylation represses gene transcription by directly hampering the binding of transcription factors (TFs) to DNA, or indirectly via the recognition of methylated sites by chromatin-remodelling enzymes [18]. DNA methyltransferases (DNMTs), such as DNA methyltransferase 1 (DNMT1), DNMT3a, and DNMT3b process most DNA methylation. DNMT1 maintains the DNA methylation status during replication by detecting hypermethylated DNA. By contrast, the methyl-writing enzymes DNMT3a and DNMT3b are responsible for establishing a new methylation pattern to unmodified DNA, known as *de novo* methylation [18,19] (Fig. 2).

3.2 Redox Control and DNA Methylation

The relationship between ROS and DNA methylation is complex and can differ between local and global contexts. While elevated ROS levels have been associated with decreased global DNA methylation, primarily observed in cancer and CVDs, caution is necessary when generalizing these findings [7]. In local contexts, ROS can influence DNA methylation patterns in specific genes, contributing to localized changes in gene expression. For example, in cancer, oxidative stress can lead to hypermethylation of tumor suppressor genes, thereby silencing their expression and promoting tumor progression [20,21]. Conversely, hypomethylation of oncogenes can activate their expression, further driving cancer development [20].

3.2.1 Effects of ROS on Influencing DNA Methyltransferases (DNMTs)

ROS can alter DNA methylation by affecting DNMTs, enzymes responsible for adding methyl groups to DNA. ROS may directly oxidize the catalytic site of DNMTs or indirectly modulate their activity via redox signalling pathways. In CVDs, excessive ROS production in cardiovascular cells can directly affect DNMT activity, leading to changes in DNA methylation patterns [7]. Altered DNA methylation profiles have been observed in atherosclerosis, myocardial infarction (MI), hypertension, and HF [22]. Increased ROS can inhibit DNMT activity, resulting in global DNA hypomethylation, while elevated DNMT activity due to ROS can lead to localized DNA hypermethylation. These changes in DNA methylation can influence the expression of genes involved in crucial cardiovascular processes [23,24].

Furthermore, ROS-induced changes in DNMT activity can affect the expression of antioxidant genes, reducing cellular antioxidant defenses and exacerbating oxidative stress [25]. This forms a feedback loop where ROS-induced changes in DNMT activity influence DNA methylation patterns, impacting gene expression networks involved in oxidative stress regulation [26].

ROS-mediated modulation of DNMTs also occurs through changes in cofactor availability and recruitment to DNA. For instance, ROS can reduce the availability of the DNMT cofactor S-adenosyl methionine (SAM), leading to reduced DNMT activity and DNA hypomethylation [27]. On the contrary, ROS can stimulate the expression of DNMTs, leading to increased DNA methylation. In experimental ischemia models, the hypoxia-inducible transcription factor1-alpha (HIF1α) has been implicated in the upregulation of DNMTs, resulting in global or regional DNA hypermethylation [28]. For instance, reductions in HIF1α/VEGF signalling have been linked to hypermethylation of the *Vegfa* gene promoter following renal ischemia [29] (Fig. 2).

DNMT inhibitors have shown protective effects against ischemia or oxidative stress-induced injuries, underlining the therapeutic potential of targeting ROS-DNMT interactions [30]. Moreover, disturbed blood flow, often associated with increased ROS levels and endothelial dysfunction characteristic of atherogenesis, has been linked to elevated expression of DNMT1 and DNMT3A, leading to DNA hypermethylation of CpG islands in various genes involved in mechanotransduction [7]. Notably, hypermethylation of the gene encoding the TF kruppel- like factor 4 (KLF4) has been shown to reduce endothelial nitric oxide synthase (eNOS) expression under these conditions [7]. While these findings suggest that ROS can induce specific hypermethylation by up-regulating DNMTs, other studies have indicated that ROS may also impact DNA methylation by modulating the recruitment of DNMTs to DNA, independent of changes in DNMT expression. For instance, ROS-induced Snail expression has been implicated in the recruitment of DNMT1 to the E-cadherin promoter, leading to hypermethylation [7].

3.2.2 Effects of ROS on Ten-Eleven Translocation (TET) Methylcytosine Dioxygenases

TET proteins, part of the 2-oxoglutarate oxygenase family, rely on cofactors like Fe^{2+} , oxygen, and ascorbate for their function. This enzyme family also includes prolyl hydroxylases (PHDs), whose activity is reduced by hypoxia and ROS, primarily due to decreased availability of Fe^{2+} and ascorbic acid. Similarly, ascorbate enhances TET enzyme activity by interacting with its catalytic domain, resulting in increased levels of 5-hydroxymethylcytosine (5hmC). Thus, ROS-mediated depletion of these cofactors can significantly impact the function of TET enzymes, which are crucial for DNA demethylation and epigenetic regulation [31–34].

In Human Embryonic Kidney (HEK293) cells exposed to hydroquinones, an increase in ROS levels led to enhanced nuclear expression and activity of TET1, resulting in elevated 5hmC levels and reduced 5-methylcytosine (5mC) formation. Consequently, this ROS-induced demethylation affected various genes involved in cell cycle arrest and ROS detoxification [34]. Similar findings were observed in a mouse model of cerebral ischemia, where increased TET2 levels and 5hmC abundance were detected in ischemic regions [35]. Increased 5hmC modifications were particularly found at the promoter of brain-derived neurotrophic factor (BDNF), accompanied by increased *BDNF* mRNA. However, these changes were absent in TET2 knockout mice, showing reduced BDNF mRNA and protein expression [35]. This emphasizes the role of TET proteins may play in response to oxidative stress.

A review by Tan *et al.* [36] on the modulation of DNA methylation by ROS through the regulation of TET family members showed that TET proteins oxidize 5mC to 5hmC, thereby influencing DNA methylation patterns. Notably, double-knockout mice lacking the antioxidant enzymes GPx-1 and GPx-2 showed increased levels of 5hmC,

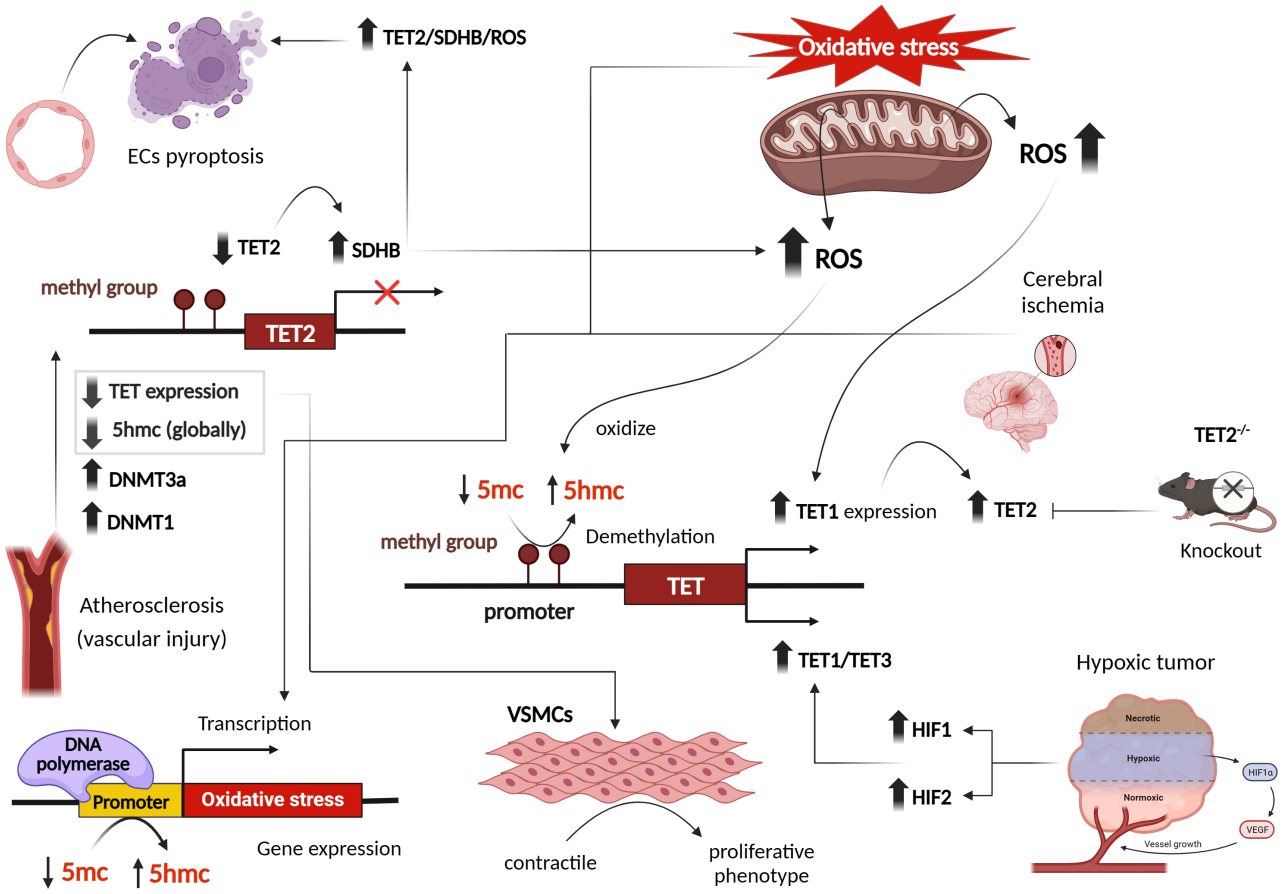

Fig. 3. Effect of oxidative stress and reactive oxygen species on transcriptional patterns of DNA ten-eleven translocation (TET) methylcytosine dioxygenases, in cardiovascular and other disease phenotypes. Figure was created with Biorender. Abbreviations: ROS, reactive oxygen species; DNMT, DNA methyltransferase; TET, ten-eleven translocation; HIF, hypoxia-inducible factor; VSMCs, vascular smooth muscle cells; SDHB, succinate dehydrogenase B; 5hmc, 5-hydroxymethylcytosine; VEGF, vascular endothelial growth factor; ECs, endothelial cells; 5mc, 5-methyl cytosine.

suggesting a complex interplay between oxidative stress, ROS formation and DNA methylation pathways [37].

Moreover, studies have linked hypoxic conditions to alterations in TET protein levels and 5hmC marks through hypoxia-inducible factors (HIFs). Under hypoxia, increased expression of TET1 and TET3, mediated by HIFs, led to global or localized elevation of 5hmC levels in different cancer cell lines [38–40]. Since hypoxic cells respond by inducing a transcriptional program regulated by oxygen-dependent dioxygenases that require Fe^{2+} and alpha-ketoglutarate (αKG)—the same cofactors required by TET enzymes—Mariani *et al.* [38] hypothesized that TETs could regulate the hypoxia-induced transcriptional program in neuroblastoma cells. Their data showed that the upregulation of 5hmC and TET1 was dependent on HIF-1 [38]. Wu *et al.* [40] found that 5hmc levels and TET1/3 expression were significantly associated with hypoxia in breast cancer *in vivo* and *in vitro*. This was mediated by upregulation of HIF-1, tumor necrosis factor alpha (TNFα) and its s downstream p38–MAPK pathway, suggesting a novel signaling axis TET–TNFα–p38–MAPK [40]. As ROS also influence these TFs [41,42], this mechanism suggests a potential connection between ROS, HIFs, and TET protein regulation during oxidative stress (Fig. 3). Interestingly, reduced expression of TET2 resulted in upregulated expression of mitochondrial respiratory complex II subunit succinate dehydrogenase B (SDHB) by decreasing the recruitment of histone deacetylase 2. SDHB overexpression mediated mitochondrial injury, and ROS production in low shear stress-induced endothelial cell pyroptosis through the TET2/SDHB/ROS pathway, offering new insights into atherosclerosis [43].

Studies examining atherosclerosis and vascular injury revealed reduced 5hmC content and TET2 expression. Interestingly, 5hmC and TET2 function as a switch in transforming VSMCs from a contractile to a proliferative phenotype [44]. Gene expression profiles during oxidative stress have demonstrated a global decrease in 5hmC marks [37]. However, specific hydroxymethylated regions associated with oxidative stress were identified on 5hmC-enriched sites [37] (Fig. 3). Endothelial cells (ECs) are also impacted by oxidative stress. Several studies have shown

that ECs exposed to H_2O_2 display decreased TET activity and 5hmC content, while levels of DNMT3A, DNMT1, and 5mC are increased [45–47]. Similar observations were seen in kidneys subjected to ischemia/reperfusion (I/R) injuries, as well as in patients with gestational diabetes and preeclampsia, where reduced 5hmC levels were observed [26,46]. In an ischemic mouse brain, reduced 5hmC levels were observed at intragenic islands and the transcription start site, while increased 5hmC marks were detected in exons, facilitating the expression of neuroprotective genes. This reveals distinct hydroxymethylation patterns [35].

Beyond I/R and vascular injuries, mitochondrial metabolites including fumarate and succinate, associated with ROS and mitochondrial metabolism, can also suppress TET activity. A Study reported that hypoxia-induced reductions in TET activity and 5hmC marks contribute to gene promoter hypermethylation in hypoxic tumors [48]. However, TET activity remains inhibited at oxygen concentrations below or equal to 2%, indicating a broad range of oxygen levels at which TET activity is maintained [48]. Hypoxia-induced TET upregulation and 5hmC marks exhibit cell type-specific responses dependent on TET abundance and oxygen availability [49] (Fig. 3).

3.3 Histone Modifications

Post-translational modifications of histones, namely methylation, acetylation, ubiquitination, and phosphorylation, are chemical modifications to histone tails. These modifications may affect the organization of chromatin architecture and gene expression patterns [4,50]. Among these modifications, methylation and acetylation are the two modifications most affected by ROS, they will be overviewed in the following sections.

3.3.1 Histone Methylation

Histone methylation is a post-translational modification that is carried out by methyltransferases (MTs), while the removal of methyl groups from histones is mediated by demethyltransferases (DMTs) [51]. Condensation of chromatin structure happens because of methylation of histone proteins. This is associated with either activation or repression of gene transcription, based on which amino acid residues are being methylated [52,53]. For example, MTs are responsible for adding methyl groups (-CH3) to specific amino acids on histone proteins. There are two major families of MTs involved in histone methylation: lysine methyltransferases (KMTs) and arginine methyltransferases (PRMTs) (Fig. 4).

i. Lysine methyltransferases (KMTs): KMTs catalyze the transfer of a methyl group from the methyl donor molecule SAM to specific lysine residues on histones. Different KMTs have preferences for specific lysine residues and can add one, two, or three methyl groups to the target lysine, resulting in mono-, di-, or trimethylation, respectively. The methylation state of lysine residues can have diverse functional consequences for gene expression and cellular processes [52].
ii. Arginine methyltransferases (PRMTs): PRMTs add methyl groups to specific arginine residues on histones. Like KMTs, PRMTs also utilize SAM as the methyl donor. Arginine methylation can occur in different states, including monomethylation, symmetric dimethylation, and asymmetric dimethylation, depending on the specific PRMT involved. Arginine methylation is involved in gene expression regulation and other cellular processes, like lysine methylation [53].

Demethyltransferases (DMTs) are enzymes responsible for removing methyl groups from histones, thus reversing the methylation marks. There are two major families of DMTs involved in histone demethylation: lysine-specific demethylases (KDMs) and Jumonji C (JmjC) domain-containing demethylases.

i. Lysine-specific demethylases (KDMs): KDMs catalyze the removal of methyl groups from lysine residues on histones. They employ a variety of mechanisms, including oxidative reactions, to achieve demethylation. KDMs exhibit specificity for methylation states and lysine residues. For example, some KDMs are specific for removing mono- or di-methyl groups from specific lysine residues, while others can remove trimethyl marks [54].
ii. Jumonji C (JmjC) domain-containing demethylases: JmjC domain-containing demethylases are a family of DMTs that use an iron (Fe^{2+})- and alpha-ketoglutarate (αKG)- dependent mechanism to demethylate histones. These enzymes remove methyl groups from various lysine and arginine residues on histones, depending on their specific substrate preferences [55].

The balance between MT and DMT activities is crucial for maintaining the dynamic and precise regulation of histone methylation patterns, which are essential for gene expression and cellular function. Dysregulation of these enzymes can lead to aberrant gene expression and contribute to CVDs [56,57].

3.3.2 The Relationship between ROS and Histone Methylation

Histone methylation is a heterogeneous process with various sites and distributions, leading to euchromatin or heterochromatin and activating or repressing gene transcription [58]. A large body of evidence supports the notion that histone methylation is essential in maintaining genome integrity, transcriptional gene regulation, and cancer metastasis. It also plays a critical role in heart development, and the pathophysiology of HF [59].

Studies have reported that ROS can alter histone methylation marks such as active marks H3K4me2/3 and repressive marks H3K9me2/3 and H3K27me3 [45]. Human bronchial epithelial cells (BEAS-2B) exposed to short

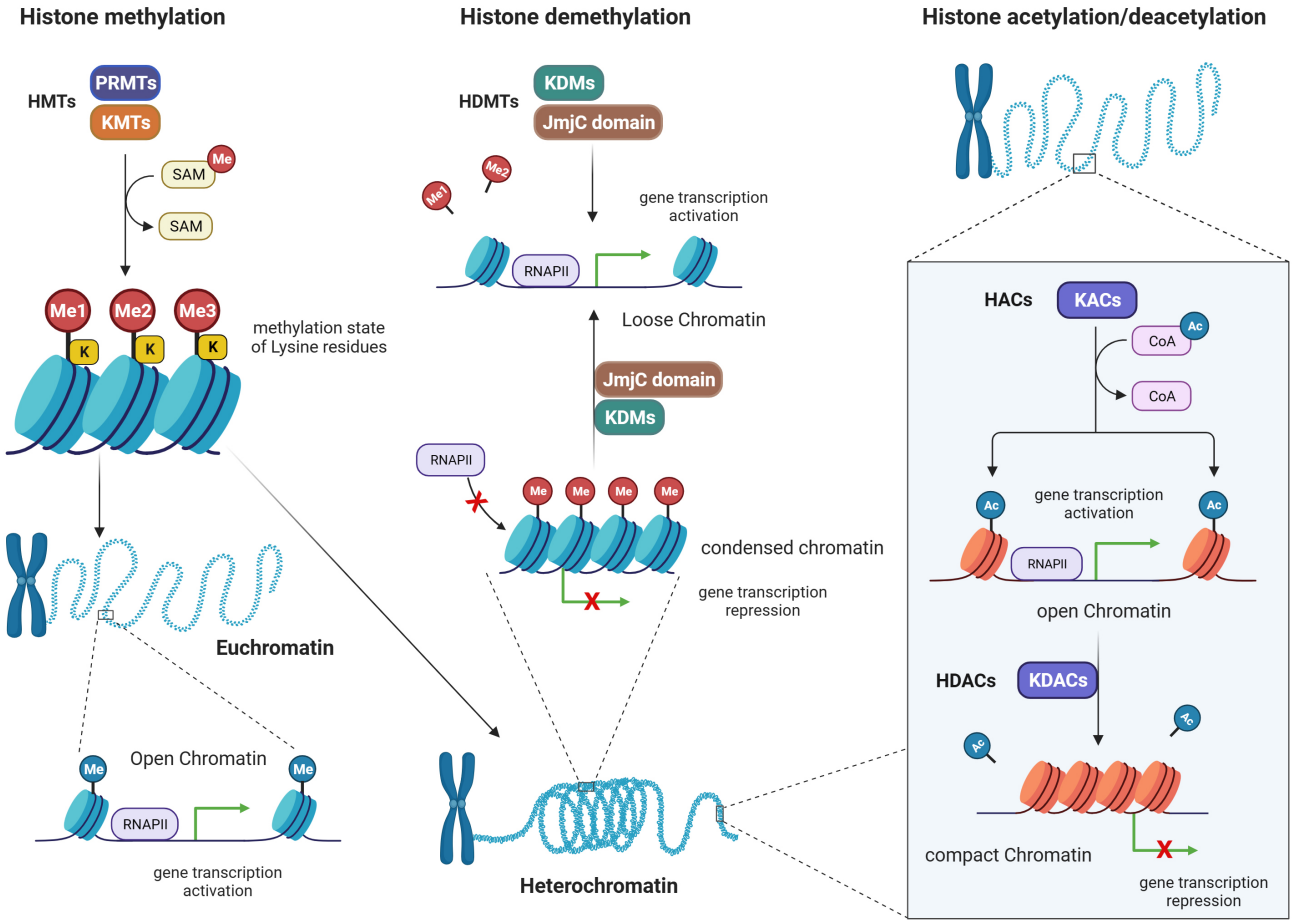

Fig. 4. Histone methylation/demethylation, and histone acetylation/deacetylation patterns. Figure was created with Biorender. Abbreviations: HMTs, histone methyltransferases; PRMTs, arginine methyltransferases; KMTs, lysine methyltransferases; SAM, S-adenosyl methionine; HDMTs, histone demethyltransferases; KDMs, lysine demethyltransferases; JmjC, jumonji C domain- containing demethylases; RNAP, RNA polymerase; HACs, histone acetylases; KACs, lysine acetylases; KDACs, lysine deacetylases; RNAPII, RNA polymerase II; HDACs, histone deacetylases; CoA, coenzyme A.

and long-term of effect of H_2O_2 exhibited an increased level of H3K4me3 and H3K27me3. This effect was mediated by reduction of cofactors Fe^{2+} and αKG dependent dioxygenases activity needed by JmjC-domain-containing histone demethylases (JHDMs) for an oxidative demethylation reaction [45].

However, these mechanisms work bidirectionally, where histone methylation can lead to overproduction of ROS, either by activating or by repressing the transcription of prooxidants or antioxidants, respectively. For example, methylation of H3K9 and its binding at the promoters of prooxidants such as SOD, cause excessive ROS production in vascular walls. While increased H3K4 methylation at the promoter region of nuclear factor kappa B (*NF-κB*) gene, induces the expression of oxidants such as inducible nitric oxide synthase (iNOS), thereby exacerbating oxidative stress in the microvasculature [60]. Paneni *et al.* [60] investigated the role of the chromatin-modifying enzyme Set7 in vascular dysfunction in patients with type 2 diabetes mellitus (T2DM). Their study revealed an increase in Set7 expression and Set7-dependent monomethylation of lysine 4 on histone 3 (H3K4m1) at the *NF-κB p65* promoter in peripheral blood mononuclear cells (PBMCs) isolated from diabetic patients. This modification was associated with the upregulation of NF-κB and subsequent transcription of oxidant and inflammatory genes, including cyclooxygenase 2 (*COX2*), *iNOS*, and increased plasma levels of inflammatory adhesion molecules such as intercellular cell adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1). Additionally, a strong correlation was found between Set7 expression and the oxidative marker 8-isoprostaglandin F2α. Furthermore, human aortic ECs (HAECs) exposed to high glucose levels also exhibited an increase in Set7-driven epigenetic modifications, inflammation, and oxidative stress. Notably, silencing the *Set7* gene abolished NF-κB-dependent oxidant and inflammatory signaling [60]. Previous studies reported that activation COX2 and iNOS lead to ROS generation and reduced nitric oxide (NO) availability [61,62].

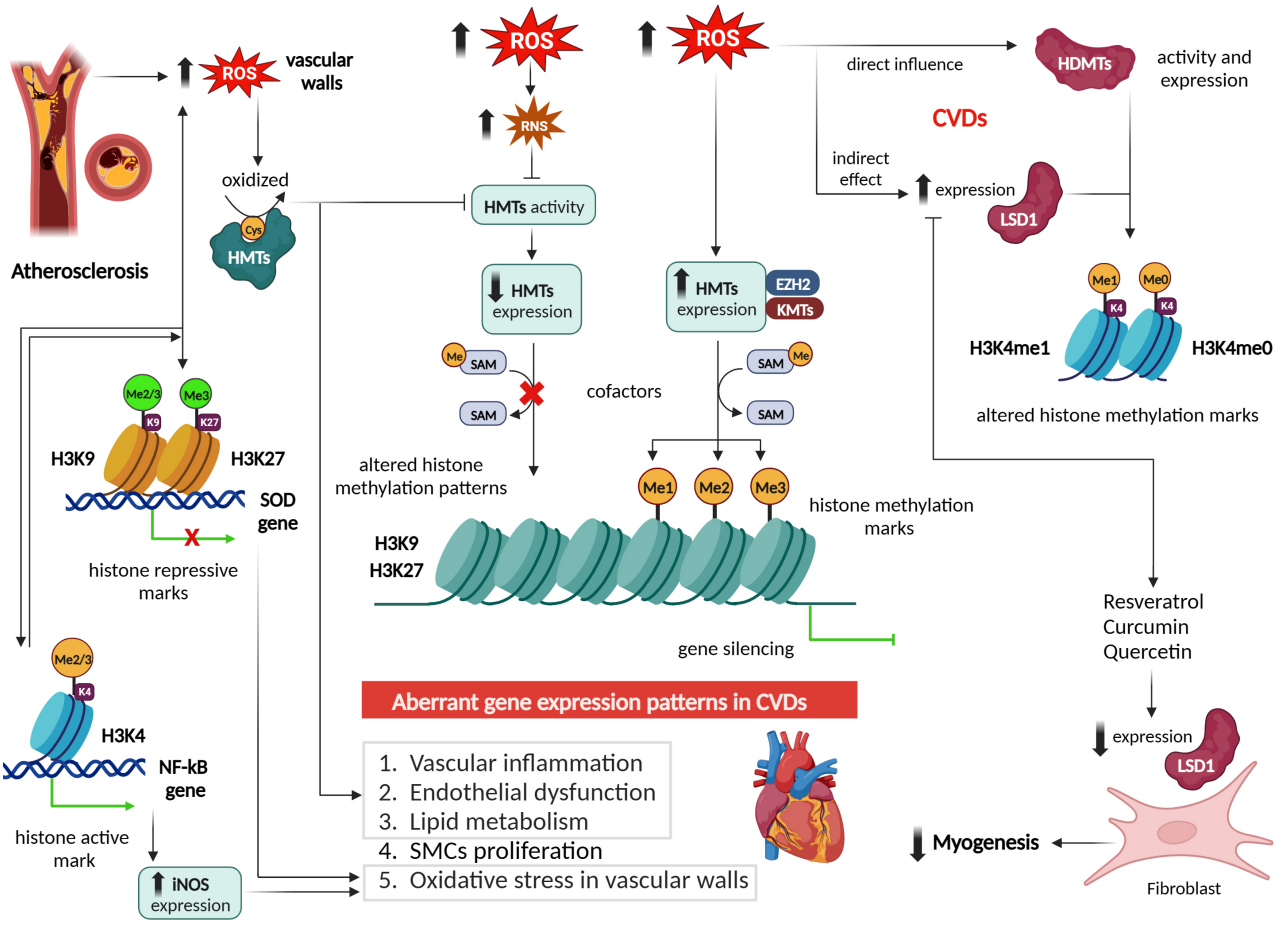

Fig. 5. Effect of reactive oxygen species on histone methylation/demethylation patterns and epigenetic regulation in cardiovascular diseases. Figure was created with Biorender. Abbreviations: ROS, reactive oxygen species; HMTs, histone methyltransferases; H3K9, histone 3 lysine 9; H3K27, histone 3 lysine 27; SOD, superoxide dismutase; H3K4, histone 3 lysine 4; NF-κB, nuclear factor kappa B; iNOS, inducible nitric oxide synthase; RNS, reactive nitrogen species; SAM, S-adenosyl methionine; KMTs, lysine methyltransferases; EZH2, enhancer of zeste homolog 2; CVDs, cardiovascular diseases; HDMTs, histone demethyltransferases; LSD1, lysine-specific demethylase 1; H3K4me1, histone 3 lysine 4 monomethylation; SMCs, smooth muscle cells.

Increased methylation of H3K4 on the nuclear factor erythroid 2-related factor 2 (*Nrf2*) and kelch like ECH associated protein 1 (*Keap1*) promoters was also addressed in the context of diabetic microvascular pathology (Fig. 5), showing a modulating effect on intracellular antioxidant glutathione (GSH) biosynthesis [63,64]. Nrf2 is a TF involved in regulating the expression of glutamate-cysteine ligase catalytic subunit (Gclc), an enzyme crucial for GSH synthesis. In diabetes, however, Nrf2 binding at the antioxidant response element 4 (ARE4) is reduced [63,64]. Mishra *et al.* [63,64] investigated the role of epigenetic modifications of H3K4 in the diminished Nrf2 binding at Gclc-ARE4 in diabetic retinopathy. Their results from chromatin immunoprecipitation from diabetic rat retinas showed an increase in the H3K4me2 signature at Gclc-ARE4, while H3K4me3 and H3K4me1 levels were decreased. Transfecting retinal ECs with lysine-specific demethylase (*LSD1*) small interfering RNA (siRNA) reversed the glucose-induced decrease in H3K4me1 at Gclc-ARE4, restoring Nrf2 binding at Gclc-ARE4 and increasing Gclc transcripts. These findings suggest that the histone methylation signature at Gclc-ARE4 regulates the Nrf2–Gclc–GSH cascade and targeting this epigenetic modification could help inhibit or slow the progression of diabetic retinopathy [63]. Epigenetic modifications at the *Keap1* promoter, a cytoplasmic repressor of *Nrf2*, were investigated in the context of diabetic retinopathy using streptozotocin-induced diabetic rats and retinal ECs. The study revealed that in hyperglycemic conditions, there was an increase in the binding of the TF Sp1 at the *Keap1* promoter, accompanied by an enrichment of the H3K4me1 signature at this site. Additionally, the methyltransferase enzyme Set7/9 (SetD7) was activated in retinal ECs. Transfecting these cells with *SetD7* siRNA prevented the hyperglycemia-induced increase in Sp1 binding at the Keap1 promoter, thereby suppressing Keap1 expression. This intervention also ameliorated the decrease in Nrf2-regulated antioxidant genes [64].

Consistent results were observed in the retinas of streptozotocin-induced diabetic rats, even after cessation of hyperglycemia. Notably, the increase in Sp1 binding at the *Keap1* promoter, ongoing methylation of the *Keap1* promoter, increased *Keap1* expression, and decreased expression of *Nrf2*-mediated antioxidant genes persisted despite normalization of blood glucose levels. These findings highlight the pivotal role of epigenetic regulation at the *Keap1* promoter in influencing the Nrf2 antioxidant pathway in diabetic retinopathy [64].

3.3.3 Effects of ROS on Histone Methyltransferases (HMTs)

Numerous studies have demonstrated that ROS can influence HMT activity and histone methylation patterns in CVDs [65–67]. ROS can directly oxidize critical residues within HMTs, leading to alterations in their enzymatic activity. For example, in atherosclerosis, increased ROS levels can oxidize cysteine residues within HMTs, resulting in the inhibition of their MT activity [68]. This inhibition can disrupt the normal regulation of genes involved in vascular inflammation, endothelial dysfunction, and lipid metabolism, contributing to disease progression [56] (Fig. 5).

Moreover, ROS can indirectly modulate HMT activity by affecting the availability of cofactors required for their function. In CVDs, ROS can promote the production of reactive nitrogen species (RNS) such as peroxynitrite ($ONOO^-$), which can oxidize and inactivate enzymes involved in SAM biosynthesis, the methyl donor for HMTs [69]. Consequently, reduced levels of SAM impair HMT activity, leading to altered histone methylation patterns and subsequent changes in gene expression associated with CVDs [7] (Fig. 5).

In line with this, a study by Li *et al*. [70] demonstrated that arsenic induces serine 21 phosphorylation of the EZH2 protein in BEAS-2B cells via JNK, STAT3, and Akt pathway activation, with ROS playing a crucial role. Pretreatment with the antioxidant N-acetyl cysteine (NAC) inhibited both EZH2 phosphorylation and kinase activation, supporting ROS involvement. H_2O_2, a key ROS, also induced EZH2 phosphorylation and activation of JNK, STAT3, and Akt. Moreover, arsenic and H_2O_2 triggered EZH2 translocation from the nucleus to the cytoplasm. These findings indicate that ROS-driven oxidative stress is central to arsenic-induced EZH2 phosphorylation [70]. Furthermore, it is well established that exposure to ROS can lead to DNA damage and activation of DNA damage response [71]. In this context, a study by Takahashi *et al*. [72] demonstrated that, in senescent cells, the DNA damage response triggers the proteasomal degradation of H3K9 methyltransferases G9a and GLP through Cdc14B- and p21-mediated activation of the APC/CCdh1 ubiquitin ligase. This degradation results in decreased H3K9 dimethylation and increased expression of Interleukin (IL)-6 and IL-8, which are key components of senescence-associated secretory phenotype. Collectively, these findings underscore the critical role of the APC/CCdh1-G9a/GLP axis in integrating the DNA damage response with epigenetic regulation to drive senescence-associated gene expression [72]. This integration may have a significant impact on CVDs, given the critical role that cellular senescence plays in shaping cardiovascular phenotypes [71]. It is crucial to recognize that the relationship between ROS and HMTs is bidirectional. On one hand, ROS can impact HMT activity and expression; on the other hand, alterations in HMT activity through various mechanisms can also lead to increased ROS production. A recent study revealed that EZH2-mediated H3K27me3 is a key epigenetic driver of hyperglycemia- induced ROS generation and endothelial dysfunction in HAECs and aortas from db/db mice, while its inhibition may attenuate oxidative stress and prevent vascular disease in diabetes setting [57].

Furthermore, ROS-mediated alterations in histone methylation can have specific effects on key genes and pathways associated with CVDs [2]. For instance, ROS-induced dysregulation of HMTs has been linked to the aberrant expression of genes involved in inflammation, oxidative stress, endothelial dysfunction, and smooth muscle cell proliferation, all of which contribute to the development and progression of CVDs [3] (Fig. 5). A study by El-Osta *el al*. [73] it was demonstrated that brief exposure of aortic ECs to hyperglycemia induces persistent epigenetic changes in the promoter of the *NF-κB p65* subunit. This effect was observed in both cultured HAECs and non-diabetic mice. Specifically, they observed increased monomethylation of histone 3 lysine 4 mediated by the histone methyltransferase Set7 in the proximal promoter region of *p65*. This modification led to sustained upregulation of *p65* gene expression, subsequently increasing the expression of proatherogenic genes *MCP-1* and *VCAM-1*, which are responsive to NF-κB. These epigenetic changes were linked to increased methylglyoxal production due to hyperglycemia-induced ROS generated by the mitochondrial electron transport chain [73].

In summary, ROS play a significant role in modulating HMTs and histone methylation patterns in CVDs. ROS can directly oxidize HMTs, modulate the availability of cofactors, and influence HMT expression and stability, leading to dysregulated gene expression associated with cardiovascular pathophysiology. On the other hand, histone methylation can also lead to ROS production in CVDs, such as by repressing or activating antioxidant or prooxidant genes. For example, H3K9 methylation and binding at the promoter region of SOD causes excessive ROS formation in vascular walls. Increase methylation of H3K4 at the promoter of *NF-κB*, stimulates the expression of prooxidant iNOS and exacerbates oxidative stress in the microvasculature [74].

3.3.4 Effects of ROS on Histone Demethylases (HDMs)

Emerging evidence suggests that ROS may play a role in histone methylation regulation by influencing the expression and activity of HDMs, while HDMs can also lead to overproduction of ROS [75]. For instance, in the setting of obesity, the demethylase JMJD2C decreases H3K9me2/me3 signatures at $p66^{Shc}$ promoter, leading to overproduction of mitochondrial ROS in visceral fat arteries [56]. Vascular ECs (VECs) exposed to hypoxia-reoxygenation, lysine demethylase 3A (KDM3A) interacts with Brahma-related gene 1 (*BRG1*) to decrease H3K9me2 binding to the promoters of *NOX2* and *NOX4*, thereby activating the expression of these genes and inducing overproduction of ROS, contributing to myocardial ischemia-reperfusion injury (MIRI) [76]. In one study on ECs exposed to hyperglycemia, it was revealed that LSD1 knockdown lead to an increase in H3K4me1 at the promoters of *NOX4* and endothelial nitric oxide synthase (*eNOS*) genes and ROS production, suggesting that LSD1 is a key factor in endothelial dysfunction and an important target in reducing diabetes-associated endothelial dysfunction [77]. Increased levels of LSD1 have been observed in CVDs such as cardiomyopathy and hypertension, resulting in changes to H3K4me1 and H3K4me0 methylation marks. This suggests that ROS may influence LSD1 expression and contribute to these conditions [17,78] (Fig. 5).

Interestingly, natural polyphenols like resveratrol, curcumin, and quercetin, which are known for their ability to lower ROS levels, have also been shown to inhibit LSD1 activity in C2C12 fibroblasts [79], subsequently reducing myogenic expression and differentiation [80]. Despite these insights, a direct connection between ROS and the regulation of LSD1 in cardiovascular events has not yet been established. Additionally, LSD1 activity is linked to H_2O_2 bursts, which can lead to the formation of 8-oxo-2′-deoxyguanosine (8-oxodG) and trigger the activation of base excision repair enzymes for DNA repair [81]. These findings suggest a complex interplay, where ROS may influence HDMTs like LSD1, while HDMTs themselves could contribute to ROS generation [81]. Further research is needed to thoroughly investigate and clarify these interactions.

3.4 Histone Acetylation

Histone acetylation is a reversible post-translational protein modification process by lysine acetyltransferases (KATs), where an acetyl group is added to histone proteins, which engage in packaging DNA [82]. This modification neutralizes the positive charge of lysine residues on histones, loosening their interaction with DNA and other proteins [82]. As a result, the chromatin structure becomes more open, allowing easier access for regulatory proteins and TFs to bind to DNA. This modification plays a crucial role in regulating gene expression, as acetylated histones are associated with active transcription [82,83]. Conversely, removing the acetyl group, carried out by histone deacetylases (HDACs), leads to a more compact chromatin structure and gene silencing [84]. Histone acetylation is an important mechanism in epigenetics that influences cellular processes and is implicated in CVDs including atherosclerosis, MI, and cardiomyopathy [85]. Modulating histone acetylation has potential therapeutic applications in CVDs, where increased acetylation is associated with active gene transcription and deacetylation associated with gene repression [85] (Fig. 6).

3.4.1 Relationship between ROS and Histone Acetylation

Histone acetylation is crucial for the epigenetic regulation of gene expression. This process is regulated by histone acetyltransferases (HATs), which enhance transcription by adding acetyl groups that reduce the interaction between histones and DNA, and by HDACs, which repress transcription by removing these acetyl groups [85]. The relationship between ROS and histone acetylation is complex, as ROS can influence not only the acetylation status of histones, but also the activity of key regulatory proteins involved in cell survival and death [86]. In this context, de la Vega *et al*. [86] demonstrated that moderate concentrations of ROS act as essential signaling molecules, while excessively high levels can lead to cell death. Their research identified ROS-induced acetylation of the pro-apoptotic kinase HIPK2 as a critical mechanism that determines a cell's sensitivity or resistance to ROS-mediated cell death [86]. At normal ROS levels, HIPK2 undergoes sumoylation, allowing it to maintain its association with HDAC3 and remain in a non-acetylated state. However, elevated ROS levels disrupt this sumoylation, decreasing HIPK2's interaction with HDAC3 and resulting in its acetylation [86]. Reconstitution experiments revealed that HIPK2-regulated genes contribute to reduced ROS levels. Notably, a HIPK2 mutant that cannot be acetylated increased ROS-induced cell death, while an acetylation-mimicking variant promoted cell survival even under high oxidative stress [86].

In relation to cardiovascular conditions such as cardiac hypertrophy, coronary artery disease (CAD), and cardiac dysfunction, histone acetylation changes have been observed [87,88]. It is worth noting that increased levels of ROS have generally been linked to increased histone acetylation, although some studies have reported conflicting results [89,90]. Increased cellular and mitochondrial ROS under ischemic condition in rat ventricular cardiomyocytes (CMCs) significantly reduced the histone active mark H3K27ac, however, treatment with antioxidants, restored H3K27 acetylation accompanied with improved cellular viability and reduced oxidative stress through regulation of *HMGN1* gene and protein expression [52,53] (Fig. 6). In regard to atherosclerosis, EC activation induced by hyperlipidemia is a critical initial step in monocyte recruitment and the progression of atherosclerotic disease [91]. Li *et al*. [91] discovered that Interleukin-35

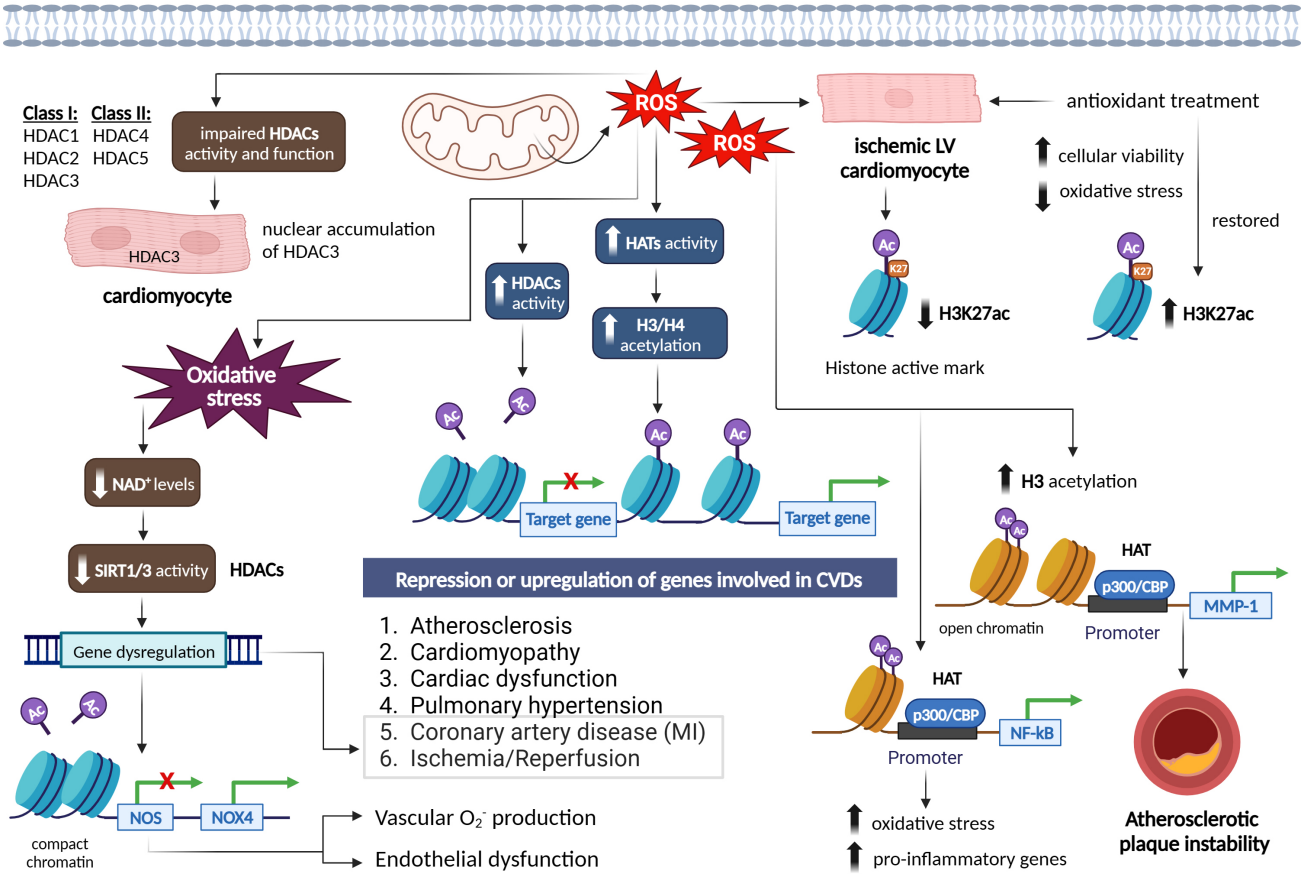

Fig. 6. Epigenetic signatures via the effect of reactive oxygen species on histone acetylation/deacetylation patterns in different cardiovascular diseases and vascular function. Figure was created with Biorender. Abbreviations: ROS, reactive oxygen species; HATs, histone acetyltransferases; HDACs, histone deacetylases; NAD^+, nicotinamide adenine dinucleotide; SIRT, sirtuin; NOS, nitric oxide synthase; NOX4, NADPH oxidase 4; H3K27ac, histone 3 lysine 27 acetylation; NF-κB, nuclear factor kappa B; MMP-1, matrix metalloproteinase-1; LV, left ventricular.

(IL-35) was markedly elevated in the aortas and plasma of an apolipoprotein E (*ApoE*) knockout mouse model of atherosclerosis, as well as in plasma samples from hypercholesterolemic patients. They observed that IL-35 exerted an inhibitory effect on mitochondrial ROS-induced acetylation of histone H3 lysine 14 (H3K14), leading to the suppression of EC activation and effectively halting the progression of atherosclerosis [91].

3.4.2 Effects of ROS on Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs)

ROS have been found to enhance HAT activity in various cell types, leading to increased acetylation of histones H3 and H4 [92]. This increase in acetylation has been associated with the upregulation of genes involved in CVDs. For instance, increased ROS levels resulting from the overexpression of SOD2 facilitate H3 acetylation and the recruitment of the HAT p300/CBP to the *MMP-1* promoter, leading to increased instability of atherosclerotic plaques [92]. ROS generation has also been linked to increased HAT activity of p300/CBP, which is associated with NF-κB DNA binding and elevated levels of oxidative stress and pro-inflammatory genes [93]. Furthermore, studies have implicated ROS in the repression of SOD1 and GPx-1, leading to altered H3 acetylation and gene regulation in conditions such as diabetes, inflammation, and cardiac hypertrophy (CH) [94,95] (Fig. 6).

ROS can also modify histones through post-translational modifications, including S-nitrosylation, S-glutathionylation, phosphorylation, and acetylation. These modifications can impair the enzymatic activity or binding of class I HDACs (e.g., HDAC1, HDAC2, and HDAC3) and class II HDACs (e.g., HDAC4 and HDAC5), resulting in a state of euchromatin [84]. ROS-induced modifications of HDACs include alkylation, carbonylation, tyrosine nitration, and phosphorylation, which can lead to impaired HDAC function and increased histone acetylation. Loss of HDAC function and subsequent histone acetylation have been associated with the release of pro-inflammatory cytokines and have been observed in diseases such as chronic obstructive pulmonary disease (OPD) [96] (Fig. 6).

Interestingly, ROS can have both activating and inhibitory effects on HDACs. Mitochondrial ROS, for example, can induce nuclear accumulation and activity of HDAC3 in CMCs [97], while ROS can increase HDAC2 activity in various cellular contexts [95]. ROS-induced oxidative stress can also influence the activity of class III HDACs, known as sirtuin (SIRT) proteins, which require NAD^+ for their activation. Oxidative stress conditions reduce cellular NAD^+ levels and decrease SIRT1 activity, leading to the dysregulation of genes involved in aging, metabolic syndrome, and CVDs, such as MI and I/R [88,98,99]. The activity of SIRT proteins is dependent on its highly conserved zinc tetra-thiolate motif in the deacetylase domain. ROS can oxidize or S-nitrosylate critical motifs in SIRT1 and SIRT3 proteins, impairing their deacetylase activity of target genes, such as *NOS*, and contributing to endothelial dysfunction and vascular oxidative stress [100,101]. Inhibition of SIRT1 by ROS also mediated the increased expression of NOX4, vascular $O_2^{\bullet -}$ production, and endothelial dysfunction [102]. Decreased levels and activity of SIRT1 were also addressed in the setting of oxidative stress- induced MI and ischemic stroke [103] (Fig. 6).

Taken together, the evidence suggests that ROS play a role in modulating histone acetylation through various mechanisms, including altering HAT expression and activity, modifying HDACs, and affecting the activity of SIRT proteins. These ROS-mediated effects on chromatin remodelling have significant implications for cardiovascular health and diseases.

3.5 Non-Coding RNAs (ncRNAs)

Noncoding RNAs (ncRNAs) are a diverse class of RNA molecules that do not encode proteins but exert regulatory functions by modulating gene expression at various levels. MicroRNAs (miRNAs) and long noncoding RNAs (lncRNAs), are two well-characterized classes of ncRNAs that have been implicated in the development and progression of several disease within the cardiovascular system [104,105]. MicroRNAs (miRNAs) are small RNA molecules (18–22 nucleotides) that bind to the 3′ untranslated region (3′UTR) of target mRNAs, resulting in their cleavage and degradation or translational inhibition [106]. When miRNAs are aberrantly expressed, they are implicated in pathophysiological processes that underlie the development of atherosclerosis and other CVDs, including endothelial dysfunction, vascular smooth muscle cell (VSMC) proliferation and migration, macrophage function, and foam cell formation [107]. On the other hand, lncRNAs are longer than 200 nucleotides and can regulate gene expression through cis and trans-regulation and by various mechanisms, including chromatin modification and remodelling, transcriptional regulation, post-transcriptional modulation, and nucleosome localization changes [108].

The Interplay between ROS and Non-Coding RNAs (ncRNAs)

The interplay between ROS and ncRNAs in CVDs is complex and bidirectional. Interactions between cardiac miRNAs and ROS are established in different cardiovascular events including atherosclerosis, diabetic cardiomyopathy (DCM), MI in animal models [109]. Increased ROS production initiates fibrosis, necrosis, apoptosis, proliferation and hypertrophy of smooth and cardiac muscles, ECs, and cardiac fibroblasts [110,111].

On one hand, ROS can modulate the expression and activity of ncRNAs. For example, H_2O_2-induced oxidative stress has been shown to upregulate the expression of specific miRNAs, such as miR-21 and miR-155, in cardiovascular cells [109]. These miRNAs, in turn, target genes involved in antioxidant defense and inflammation pathways, further exacerbating oxidative stress, and promoting the development of dilated cardiomyopathy (DCM), CH and heart failure (HF). Additionally, ROS can also modify the biogenesis and stability of ncRNAs [112]. For instance, ROS-mediated oxidation of RNA-binding proteins can affect their interaction with miRNA precursors, leading to altered miRNA processing and expression [112].

On the other hand, ncRNAs can regulate ROS production and detoxification pathways, thereby influencing oxidative stress levels in cardiovascular cells. Several studies have identified ncRNAs that directly target key components of ROS signalling pathways. For example, miR-92a has been shown to target the antioxidant enzyme sirtuin 1 (SIRT1), resulting in increased ROS production and endothelial dysfunction [113]. Similarly, lncRNA MALAT1 has been implicated in the regulation of ROS levels through its interaction with ROS-responsive TFs, such as Nrf2 [114]. Dysregulation of these ncRNAs can disrupt redox homeostasis and contribute to CVD development [114].

Importantly, the dysregulation of ROS and ncRNAs is observed in various cardiovascular pathologies. For instance, miR-21 has been found to be upregulated in atherosclerotic plaques and promotes smooth muscle cell proliferation and migration by targeting phosphatase and tensin homolog (*PTEN*) [115]. Similarly, the lncRNA H19 has been implicated in CH and HF by modulating ROS production and the expression of genes involved in cardiac remodelling [116]. Increased expression of miR-154-5p was associated with angiotensin II (AngII)- induced CH by targeting arylsulfatase-b (ARSB), which plays a critical role in sulphate reduction in CMCs. Downregulation of ARSB by miR-154-5p led to increased ROS generation and activation of NF-κB, contributing to CH [117]. Suppressed expression of the TF FoxO3 by miR-122 was also observed in AngII-induced hypertrophic CMCs, contributing to oxidative stress [118]. Furthermore, enhanced expression of miR-132, miR-212, and miR-152 in sympathomimetic ISO and endothelin receptor (ET-1) antagonist- induced hypertrophy in rats was reverted using antioxidants, indicating its

regulation by ROS production [119]. In a congestive heart failure (CHF) rat model following MI, decreased protein levels of Nrf2 were observed in left ventricles, accompanied with high expression of three miRNAs (miR-27a, miR-28a, and miR-34a), and consequent decrease in Nrf2-dependent antioxidant enzymes (haem oxygenase-1 (HO-1), SOD2, and CAT). This suggests an inhibition of Nrf2 translation by the latter miRNAs [120]. In the setting of MI, miR-22 was found to be associated with the damage caused by mitochondrial oxidative stress in I/R injured-CMCs [121]. Another study by Du *et al*. [122] showed that miR-22 was upregulated in rats subjected to I/R injury, and its inhibition reduced the injury. Increased levels of miR-22 were also studied in *in vitro* I/R-induced mitochondrial damage, showing a direct targeting effect on Sirt1 and coactivator 1 alpha (PCG-1α), inducing oxidative stress [109,122]. Endothelial progenitor cells (EPCs) exposed to H_2O_2-induced oxidative stress exhibited low expression of miR-126. But overexpression of miR-126 could revert the injury in these cells, by reducing ROS production and increasing SOD, angiopoietin (Ang) 1 and 2 expression. This antioxidant effect was demonstrated by the activation of PI3K/Akt/SK-3b and ERK1/2 signalling pathway [123]. Similarly, overexpression of miR-340-5p, suppressed the enhanced levels of ROS and restored SOD activity in I/R-induced cardiomyocytes. This anti-oxidative role of miR-340-5p was mediated by negative regulation of NF-κB pathway activator protein 1 (Act1) which plays an important role in intracellular signalling processes, leading to cell death [124,125]. In H_2O_2-treated CMCs, PTEN inhibitor exhibited an increased expression of miR-23a expression accompanied by increased antioxidant activity of SOD, glutathione (GSH), and CAT, suggesting a beneficiary role of PTEN/miR-23a axis in acute myocardial infarction (AMI) [126].

The cardioprotective and antioxidative role of miRNA took a vast attention in DCM. For instance, miR-203 is downregulated in high-glucose treated myocardial cells (MCs). *In vivo* investigations on diabetic mice supported the notion that miR-203 exerts protective role on myocardial hypertrophy, by targeting the PtdIns-3-kinase subunit alpha (PIK3CA), which induced malondialdehyde (MDA) and ROS levels in the fibrotic tissue. By mediating the PI3K/Akt pathway, miR-203 can attenuate oxidative stress and apoptosis in MCs [127]. MiR-92a-5p expression in the heart of diabetic mice decreased mitochondrial ROS production, by modulating mitochondria cytochrome-b (mt-Cytb), a subunit of the complex III where ROS is abundantly produced [128] (Table 1, Ref. [109,114–127,129,130]).

Understanding the intricate crosstalk between ROS and ncRNAs provides new insights into the molecular mechanisms underlying CVDs, and targeting these interactions could offer potential therapeutic strategies for disease management. For instance, modulating the expression or activity of specific ncRNAs involved in ROS regulation could potentially restore redox balance and ameliorate oxidative stress in cardiovascular cells. However, further research is needed to unravel the complex regulatory networks and identify specific ncRNAs and ROS-related pathways that could serve as potential therapeutic targets.

3.6 ATP-Dependent Chromatin Remodelling

ATP-dependent chromatin-remodelling complexes play a crucial role in regulating gene expression by modifying the structure, organization, and accessibility of chromatin [131]. These complexes possess a shared Snf2-like ATPase catalytic domain, and by utilizing the energy derived from ATP hydrolysis, they can reposition nucleosomes on the chromatin, thereby altering chromatin accessibility [132,133]. The specific binding to the genome and catalytic activity of these complexes are dictated by different associated members of the ATPase complex.

There are four main families of chromatin remodelling complexes. The first is the switch/sucrose nonfermentable (SWI/SNF) family, which was initially discovered in prokaryotes and yeast [131]. The second is the imitation switch family, initially identified in Drosophila. The third is the chromodomain helicase DNA-binding family, found in mice. Finally, the fourth family is the INO80 family, which was initially identified in yeast [134]. These various families of chromatin remodelling complexes play a vital role in development, as many developmental processes rely on proper chromatin regulation. By modulating chromatin structure and accessibility, these complexes contribute to the precise control of gene expression during development and other biological processes [134].

The Relationship between ROS and ATP-Dependent Chromatin Remodelling

ATP-dependent chromatin remodeling complexes play a crucial role in cardiac development and are implicated in various cardiovascular conditions, including cardiomyopathy, congenital heart disease, atherosclerosis, pulmonary hypertension, and HF [7].

There is compelling evidence that ROS can significantly influence the activity of these complexes. One critical component, the ATPase Brahma-related gene 1 (*BRG1*), a part of the Brg1-associated factors (BAF) complex, and the vertebrate equivalent to the SWI/SNF complex [133]. BRG1, plays a crucial role in regulating Nrf2-mediated antioxidant responses, specifically enhancing the induced expression of HO-1. This specificity arises from BRG1's ability to facilitate Z-DNA formation at the *HO-1* promoter, which is essential for recruiting RNA polymerase II and driving *HO-1* transcription. Unlike other Nrf2 target genes such as *NQO1*, the regulation of HO-1 by BRG1 underscores its unique function in selective gene activation during oxidative stress, presenting a potential therapeutic target for improving antioxidant defenses [135].

Table 1. Summary of important non-coding RNAs involved in ROS interactions within different cardiovascular events.

Non-coding RNA	Target	ROS generation	Phenotype	*In vivo* or *in vitro*	Reference
miR-155	FoxO3a	increased	hypertrophy	CMCs	[109]
miR-92a	SIRT1, oxLDL	increased	endothelial dysfunction & atherosclerotic lesions	ECs & mouse arteries	[129,130]
lncRNA MALAT1	Nrf2	increased	disrupt redox homeostasis	HUVECs	[114]
miR-21	PTEN, ERK-MAP kinase	increased	SMCs proliferation & migration, CH	atherosclerotic plaques, cardiac fibroblasts	[115]
lncRNA H19	NFAT	increased	CH & HF	CMCs	[116]
miR-154-5p	ARSB, NF-κB	increased	AngII- induced CH	CMCs	[117]
miR-122	transcription factor FoxO3	increased	AngII- induced hypertrophic cardiomyocytes	CMCs	[118]
miR-132	BNP, GATA4	increased	CH	rats	[119]
miR-212					
miR-152					
miR-27a	Nrf2	increased	congestive heart failure following MI	rats	[120]
miR-28a					
miR-34a					
miR-22	P38a, SIRT1, PGC-1α	increased	MI, I/R injury	I/R-injured CMCs	[121]
miR-22	SIRT1, PCG-1α	increased	MIRI	rats & CMCs	[109,122]
miR-126	PI3K/AKt/SK-3b axis, ERK1/2	decreased	I/R injury	EPCs	[123]
miR-340-5p	NF-κB, Act1	decreased	I/R injury	CMCs	[124,125]
miR-23a	PTEN/miR-23a axis	decreased	AMI	CMCs	[126]
miR-203	PIK3CA, PI3K/Akt axis	decreased	DCM, myocardial fibrosis attenuates oxidative stress & apoptosis	CMCs, diabetic mice	[127]

Abbreviations: SIRT1, sirtuin 1; Nrf2, nuclear factor erythroid 2-related factor 2; PTEN, phosphatase & tensin homolog; NFAT, hypertrophic nuclear factor of activated T cells; ARSB, arylsulfatase-b; NF-κB, nuclear factor kappa B; BNP, beta natriuretic peptide; PCG-1α, coactivator 1 alpha; Act1, activator protein 1; PIK3CA, PtdIns-3-kinase subunit alpha; SMCs, smooth muscle cells; CH, cardiac hypertrophy; HF, heart failure; AngII, angiotensin II; MI, myocardial infarction; I/R, ischemia-reperfusion; MIRI, myocardial ischemia-reperfusion injury; AMI, acute myocardial infarction; DCM, diabetic cardiomyopathy; CMCs, cardiomyocytes; ECs, endothelial cells; HUVECs, human umbilical vein endothelial cells; EPCs, endothelial progenitor cells; ERK1/2, extracellular signal-regulated kinase 1/2; FoxO3, Forkhead box O3; OxLDL, oxidized low-density lipoprotein; lncRNA, long non-coding RNA.

In experimental models of I/R injury in diabetic mice, larger post-ischemic infarct size (IS), severe CMC apoptosis, and increased oxidative stress were observed alongside reduced expression of HO-1, nuclear Nrf2, and BRG1 protein. This indicates a potential link between BRG1 and oxidative stress in I/R injury [136]. Notably, a deficiency of BRG1 inhibited Nrf2 binding to the *HO-1* promoter, further depressing *HO-1* expression and exacerbating oxidative stress in diabetes [136]. Research by Liu *et al.* [137] further explored BRG1's role in experimental models of AMI. The study found that BRG1 expression significantly increased in the peri-infarct zone compared to the sham group, which was accompanied by upregulation of NRF2 and HO-1, and downregulation of KEAP1. Overexpression of BRG1 through adenoviral intramyocardial injection in AMI mice resulted in reduced IS and improved cardiac function, along with increased NRF2 and HO-1 levels, further leading to decreased oxidative damage and cell apoptosis. Conversely, shRNA-mediated knockdown of *BRG1* produced opposite effects, further confirmed in cultured primary neonatal rat CMCs subjected to oxygen-glucose deprivation [137]. These findings demonstrate that upregulation of BRG1 during AMI enhances NRF2 levels and promotes its nuclear accumulation, facilitating HO-1 expression and alleviating oxidative stress in CMCs, thereby improving their viability [137].

Additionally, a recent study by Li *et al.* [76] showed that BRG1 interacts with KDM3A to activate the transcription of NOX isoforms (1, 2, and 4) in ECs. The ROS generated from increased *NOX* expression may exacerbate cardiac I/R injury [76]. Findings by Fish *et al.* [138] indicated that BRG1 restores eNOS expression during the anoxia/reoxygenation cycle by preventing the loss of acetylated histones H3 and H4 on eNOS promoters, suggesting that BRG1 protects endothelial function under oxidative stress by enhancing *eNOS* expression [138]. Conversely, Shao *et al.* [139] reported that endothelial BRG1 limits eNOS activity and nitric oxide (NO) bioavailability by activating caveolin-1 (CAV1) transcription, potentially contributing to thioacetamide-induced liver fibrosis in mice [139]. This necessitates further investigation of the precise effects of BRG1 on eNOS expression and activity.

Moreover, ROS have been shown to upregulate Cockayne syndrome group B protein (CSB), a member of the SWI/SNF family, enhancing its interaction with the long-range chromatin regulator CCCTC-binding factor [140]. This interaction increases promoter occupancy of genes involved in RNA and protein homeostasis, energy control, oxidative phosphorylation (OXPHOS), and mitochondrial ROS production [140]. Mutations in the CSB gene are linked to Cockayne syndrome, characterized by developmental and neurological defects, sun sensitivity, premature aging, and increased susceptibility to oxidative stress [140].

Components of the SWI/SNF complex were also found to upregulate the transcription of DAF-16/FOXO, a redox-sensitive transcription factor in *Caenorhabditis elegans*, enhancing stress resistance and longevity [141]. Since mammalian FOXO TFs play crucial roles in regulating redox homeostasis and are sensitive to ROS in the vasculature [142], it would be interesting to investigate whether a similar pathway operates in mammalian adaptation to ROS.

Furthermore, SWI/SNF components like BAF57 have been associated with the promoters of *HIF-*α genes, enhancing their trans-activation under hypoxic conditions [143].

Further studies are required to determine if the SWI/SNF complex also regulates HIF-α expression in response to ROS. Conversely, active components of ISWI, such as hSNF2h and hSNF2l, have been shown to suppress HIF activity under hypoxia by increasing the levels of HIF-associated dioxygenase FIH, thus functioning as hypoxia survival factors [144]. While depletion of SNF2h leads to early embryonic lethality, its specific role in cardiac development remains unclear [133]. Recent evidence indicates that in response to H_2O_2, SNF2h interacts with XRCC1 protein, phosphorylated by CK2, to initiate DNA repair processes [145].

In summary, there are growing evidences that ROS can significantly influence ATP-dependent chromatin remodeling complexes. Further research is needed to elucidate the underlying mechanisms and their implications in cardiovascular health.

3.7 Direct Actions of ROS on Epigenetic Processes

ROS can have a direct impact on DNA by modifying its bases. One example is the conversion of 5mC to 5hmC through the removal of a hydrogen atom from the methyl group [20,146]. This modification can interfere with the activity of DNMT1, preventing the inheritance of methylation patterns and indirectly leading to demethylation of CpG sites [20,147]. While this mechanism has been proposed, direct proof is still lacking.

In addition to 5hmC formation, ROS can influence DNA methylation by oxidizing guanosine to 8-oxo-7,8-dihydroguanine (8-oxodG). The mutagenic effect of ROS is countered by the enzyme 8-oxoguanine DNA glycosylase (OGG1), which removes the 8-oxodG residue, followed by base excision repair mechanisms to fill the gap [148]. However, when 8-oxodG persists, adjacent cytosines cannot be methylated, resulting in hypomethylation and transcriptional activation [149]. OGG1 recruitment to 8-oxodG sites can also facilitate DNA demethylation in coordination with TET enzymes [150].

The formation of 8-oxodG preferentially occurs at G-rich promoter regions of well-known proto-oncogenes such as *KRAS*, *Bcl-2*, *VEGF*, *c-MYC*, and *HIF1*α [151,152]. This suggests that 8-oxodG formation may contribute to the transcriptional activation of these potent oncogenes, shedding light on the role of ROS in cancer progression [151]. Simi-

larly, 8-oxodG formation has been implicated in cardiovascular inflammation [153]. For instance, it promotes NF-κB-dependent expression of pro-inflammatory molecules in response to TNFα and alters HIF1 binding to the *VEGF* promoter and other proangiogenic genes in ECs [152,154].

In vitro models of oxidative stress have demonstrated that 8-oxodG formation can activate the TF Tbx5 and enhance the differentiation of murine embryonic stem cells into CMCs [155]. Increased levels of 8-oxodG were observed in atherosclerotic vessels and correlated with disease progression [156]. Recent meta-analyses have also shown higher levels of 8-oxodG in urine and blood samples of patients with atherosclerosis, hypertension, CAD and HF [157,158], although more extensive prospective studies are needed to establish 8-oxodG as a potential predictor of these diseases.

Apart from DNA modifications, ROS can also modify histones, which are proteins involved in chromatin structure and gene regulation. For example, histone H2B is sensitive to $ONOO^-$, and under nitrosative and oxidative stress, it can adopt different structures to protect DNA from the damaging effects of $ONOO^-$ [159]. This suggests that H2B may have additional roles in chromatin remodelling and maintaining DNA stability. ROS can oxidize arginine and lysine residues in histone H3, leading to the formation of protein-bound carbonyl groups that affect chromatin structure and its accessibility to TFs. Additionally, H3, the only histone containing cysteine, can sense redox signalling through S-glutathionylation of Cys110, which influences euchromatin formation [160]. Furthermore, lipid peroxidation products, such as 4-oxo-2-nonenal, can form adducts with lysine residues at acetylation and methylation sites on histones H2, H3, and H4. These modifications have been detected in macrophages stimulated with lipopolysaccharide (LPS) and can impact the epigenetic landscape associated with various diseases, including CDVs [161].

3.8 Mitochondrial ROS and Epigenetic Changes

In recent years, there has been growing evidence suggesting that epigenetic mechanisms can also affect mitochondria, in addition to their well-established role in nuclear DNA [162]. Mitochondria, which have their own separate genome called mitochondrial DNA (mtDNA), play a crucial role in cellular function and energy production. It has been estimated that over 1100 proteins are required for mitochondrial function, the majority of which are encoded by nuclear DNA and imported into mitochondria [162].

When the members of the oxidative phosphorylation (OXPHOS) system within mitochondria are impaired, it can lead to mitochondrial dysfunction [163]. Mitochondrial dysfunction has been extensively studied both in human and animal models of heart failure (HF) revealing compromised mitochondrial OXPHOS activity, elevated ROS levels, and aberrant dynamics of mitochondria [164]. This dysfunction not only affects the generation of ROS and mitochondrial metabolites, but also has consequences on nuclear epigenetic alterations [165]. Various epigenetic mechanisms have been identified in mitochondria, including DNA methylation, histone modifications, chromatin remodelling, and the expression of ncRNAs. These mechanisms can modulate mitochondrial function and are potentially sensitive to ROS [165].

For instance, methylation of nuclear DNA promoter of the mitochondrial transcription factor A (TFAM), a key protein involved in mtDNA organization, can influence TFAM gene expression, thereby influencing mtDNA copy numbers [166]. Lv *et al* [166] showed that acetylation of mitochondrial TFAM at lysine 76 (K76) mediated by GCN5L1 (General Control of Amino-Acid Synthesis, yeast homolog-like 1), inhibits the binding of TFAM to the mitochondrial transporter TOM70, leading to reduced TFAM import into mitochondria and mitochondrial biogenesis [166]. However, deacetylation of TFAM by Sirt3 and its phosphorylation at serine 177 by ERK2, both increased its binding to mtDNA, accompanied by gene transcription repression and suppression, respectively [167,168].

ROS can also influence mtDNA copy numbers, but the effects may vary depending on the dose, time, and type of ROS modulation [169]. Redox agents such as hydrogen sulfide (H_2S) have been implicated in reduced TFAM promoter methylation in VSMCs and aortas isolated from cystathionine gamma-lyase knockout (CSE-KO) mice [170]. Taking into account CSE, a major H_2S-producing enzyme, H_2S deficiency has led to reduced mtDNA copy numbers. Targeting CSE/H_2S system may provide a therapeutic avenue for CVDs [170].

Exposure to cigarette smoke was also shown to decrease TFAM expression, increase mtDNA damage, reduce mtDNA copy numbers, and impair endothelial function [171]. Similarly, lower mtDNA copy numbers have been observed in patients with chronic obstructive pulmonary disease, a disorder associated with oxidative stress. Decreased mtDNA copy numbers have also been linked to an increased risk of HF in humans. It was found that hypermethylation of D-loop regions in peripheral blood leukocytes from patients with stable coronary artery diseases (SCAD) and acute coronary syndrome (ACS), were associated with reduced synthesis of mtDNA [172]. A study on VSMCs showed the effect of the platelet-derived growth factor-BB (PDGF-BB) in triggering the translocation of the nuclear DNMT1 to mitochondria, increasing mtDNA methylation and suppressing gene expression in VSMCs. This was associated with mitochondrial dysfunction and altered contractility of VSMCs [173]. CVDs are closely associated with mitochondrial dysfunction and ROS imbalance. Experimental models have shown that increasing mtDNA copy numbers through the increased transcription and overexpression of *TFAM* or other factors can protect against oxidative stress and provide cardioprotection. For instance, CMCs subjected to hypoxia, exhibited an increased ex-

pression of TFAM as a compensatory mechanism. However, a progressive decrease in its level was clear following the increase in ROS production and calcium dysregulation [174]. It is well established that I/R injury- induced oxidative stress triggers the nuclear translocation of nuclear respiratory factor 1 (NRF1) and upregulation of PPARG coactivator 1 alpha (PGC-1α), contributing to increased TFAM transcription, mitochondrial biogenesis and repair [175]. This strongly supports the phenomenon that restoring TFAM levels by increasing mitochondrial biogenesis and reducing ROS generation could protect CMCs from the oxidative damage of mtDNA induced by I/R injury. Furthermore, activation of AMP-activated protein kinase (AMPK)-PGC-1α-Sirt3 signalling pathway was observed in a rat model of I/R injury [162]. PGC-1α increased Sirt3 expression, which in turn deacetylated NRF1, the TF responsible for *TFAM* transcription. Sirt3 can also directly act on TFAM, facilitating its translocation to mitochondria and the transcription of mitochondrial genes [176,177].

Recent research has indicated increased mtDNA methylation in certain mitochondrial proteins in thrombocytes of patients with hypertension, atherosclerosis, atrial fibrillation (AF), and ischemic heart disease [178,179]. However, this field of study is still relatively unexplored, and more research is needed to further understand the relationship between ROS and epigenetic changes.

4. Clinical Implications and Therapeutic Interventions

The detailed findings in this review underscore the significant impact of ROS on epigenetic modifications, which profoundly influence the pathophysiology of CVDs. Translating these insights into therapeutic interventions presents several promising avenues.

4.1 Antioxidant Therapies

Antioxidant therapies hold significant promise in mitigating oxidative stress and its associated epigenetic modifications in CVDs [180]. Oxidative stress, primarily driven by an excess of ROS, plays a critical role in the pathogenesis of CVDs [181]. Antioxidants can neutralize ROS, thereby reducing oxidative damage and modulating epigenetic changes [181]. Various mechanisms of antioxidants include scavenging free radicals, upregulating endogenous antioxidant defenses, and preventing aberrant modifications such as DNA methylation and histone modifications [180,182]. Several antioxidants have been studied in clinical trials, highlighting their therapeutic benefits [183]. N-Acetylcysteine (NAC), a precursor to GSH, has shown promising results; a recent randomized, double-blind, placebo-controlled, multicentre study assessed the effects of high-dose intravenous NAC with nitroglycerin on early cardiac MRI outcomes in ST-segment–elevation MI patients. NAC significantly reduced cardiac infarct size (IS) by 5.5% compared to placebo ($p = 0.02$) and doubled myocardial salvage ($p < 0.01$). These results suggest potential benefits of NAC in reducing IS and improving outcomes in AMI [184]. According to a recent review by Cui *et al*. (2023) [185], NAC has demonstrated efficacy in mitigating diabetes-related cardiovascular complications, cardiopulmonary bypass issues, and cardiac surgery complications. These include reducing early R/I, attenuating the inflammatory response induced by the pump, and alleviating myocardial stress associated with surgery [185]. However, a systematic review has found that NAC lacks significant efficacy in improving major adverse outcomes following cardiac surgery. These outcomes include mortality, acute renal failure (ARF), HF, length of stay in the intensive care unit, arrhythmias, and AMI [186]. Several clinical studies have shown that NAC treatment effectively lowers the incidence of AF post cardiac surgery [185]. However, one study indicates that high-dose oral NAC treatment did not provide benefits for postoperative AF [187]. Additionally, NAC has been reported to improve HF [188], but no positive effects were noted in patients with doxorubicin-induced cardiomyopathy [189]. Vitamin C and E have also been extensively studied. The Heart Protection Study investigated the effects of antioxidant vitamin supplementation in high-risk individuals and found no significant reduction in cardiovascular events [190]. Similarly, meta-analysis by Vivekananthan *et al*. (2003) [191] found no benefit of vitamin E in reducing mortality, cardiovascular death, or stroke, while β-carotene slightly increased all-cause and cardiovascular mortality. These results do not support the routine use of vitamin E or β-carotene for cardiovascular protection [191]. Coenzyme Q10 (CoQ10), an essential component of the mitochondrial electron transport chain, acts as an antioxidant by preventing lipid peroxidation [192]. The Q-SYMBIO trial evaluated the effects of CoQ10 on HF patients and found significant improvements in survival rates and hospitalization frequencies [192]. Shargorodsky *et al*. (2010) [193] reported that antioxidant supplementation with vitamin C, vitamin E, CoQ10, and selenium significantly improved large and small artery elasticity in patients with multiple cardiovascular risk factors. These improvements were associated with better glucose control, indicated by lower HbA1C levels, and improved lipid profiles, including increased HDL-cholesterol. No significant changes were observed in the placebo group, underscoring the potential benefits of antioxidant therapy in enhancing vascular health and metabolic measures [193]. Polyphenols, such as resveratrol found in red wine, exert antioxidant effects through direct ROS scavenging and activation of endogenous antioxidant pathways, including the upregulation of SIRT1 [194]. Tomé-Carneiro *et al*. (2013) [195] demonstrated that long-term supplementation with a resveratrol-enriched grape extract reduces key pro-inflammatory cytokines and alters inflammation-related miRNAs in hypertensive male patients with T2D. This suggests a beneficial

Table 2. Summary of epigenetic drugs targeting DNA methylation and histone modifications with potential cardioprotective effect.

Epigenetic drug family	Drug/natural product name	Cardioprotective effect	Reference
DNMTis	5-Aza-dC (decitabine)	alleviates atherosclerotic lesions	[196]
	Cocoa extract	improves atherosclerosis and CAD	[197]
	RG108	reduces MH and MF	[22]
	5-azacytidine (azacytidine)	improves MH, reduces MF	[22]
	5-aza-2-deoxycytidine	reduces MH improves cardiac contractility reduces ischemic injury	[198]
HDACis	Nullscript, scriptaid, TSA	prevents myocardial I/R injury reduces MI	[199]
	SAHA	reduces IS in myocardial I/R injury attenuates takotsubu-like myocardial injury	[200,201]
	SK-7041	reverses MH	[202]
	Vorinostat	attenuates MH, RHF, and MF reduces left ventricular dysfunction	[203–205]
	Romidepsin	attenuates atherosclerosis protects against hypertension	[203,204,206,207]
	Givinostat	improves cardiac performance	[208]
	Valproate	protects against MI	[208]
HMTis	Tanshinone IIA	reduces MH prevents against cardiac remodeling	[209]

Abbreviations: DNMTis, DNA methyltransferase inhibitors AD; HDACis, histone deacetylase inhibitors; HMTis, histone methyltransferase inhibitors; MH, myocardial hypertrophy; MF, myocardial fibrosis; MI, myocardial infarction; CAD, coronary artery disease; I/R injury, ischemia-reperfusion injury; RHF, right heart failure; LV, left ventricular; TSA, Trichostatin-A; SAHA, suberoylanilide hydroxamic acid.

immunomodulatory effect despite no significant changes in body weight, blood pressure, glucose, HbA1c, or most serum inflammatory markers [195].

While the therapeutic potential of antioxidants is promising, challenges and limitations remain. The efficacy of antioxidant therapies in clinical trials has been variable, which may be due to differences in study design, patient populations, and antioxidant dosages. Many antioxidants have poor bioavailability, limiting their therapeutic effectiveness. Future research should focus on improving the delivery and bioavailability of these compounds, exploring combination therapies, and developing targeted antioxidant therapies that can specifically modulate redox-sensitive signalling pathways and epigenetic modifications. By addressing these challenges and focusing on targeted interventions, antioxidant therapies could play a crucial role in the prevention and treatment of CVDs.

4.2 Epigenetic Drugs

The flexibility of the epigenome has prompted the exploration and development of a range of epigenetic compounds, many of which have already gained FDA approval for treating different diseases. Epigenetic drugs target DNA methylation (Table 2, Ref. [22,196–209]), histone modifications (Table 2), and ncRNAs offer novel therapeutic strategies [210]. DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis) have shown promise in preclinical models of CVDs [22]. These drugs can reverse aberrant epigenetic changes linked to ROS levels, restoring normal gene expression and cardiovascular function [57].

4.2.1 DNA Methyltransferase Inhibitors (DNMTis)

DNMTis, such as azacytidine and decitabine, are well-studied for their ability to inhibit DNA methylation, a key epigenetic modification implicated in CVDs pathogenesis [210,211] (Table 2). These compounds function by incorporating into DNA during replication, thereby blocking the action of DNMTs and leading to global hypomethylation of DNA [210]. This hypomethylation can reverse the silencing of genes critical for cardiovascular health, such as those involved in endothelial function and cardiac remodeling processes [210].

Studies have demonstrated the efficacy of DNMTis in preclinical models of HF and CAD [22]. For instance, treating $Ldlr^{-/-}$ mice with 5-Aza-dC (decitabine) can inhibit macrophage migration and adhesion to epithelial cells, decrease macrophage infiltration into atherosclerotic plaques, and reduce the expression of inflammatory genes in macrophages [196]. These effects help alle-

viate atherosclerotic lesions and slow the progression of atherosclerosis [212]. Another study reported that cocoa extract improved atherosclerosis and coronary heart disease by inhibiting DNMTs and reducing methylenetetrahydrofolate reductase (*MTHFR*) gene expression levels *in vitro* [197]. Additionally, in adults with cardiovascular risk factors, cocoa combined with statins lowered cholesterol levels, providing a protective effect on the cardiovascular system (ClinicalTrials.gov identifier: NCT00502047) [197]. DNA methylation is closely linked to HF treatment [22]. RG108 has been reported to inhibit DNMTs, reducing myocardial hypertrophy and fibrosis progression [22]. The DNA methylation inhibitor 5-azacytidine decreases the negative impact of tumor necrosis factor-α on SECRA2a expression and may improve CH and reduce myocardial fibrosis (MF) by inhibiting DNMTs [22]. Xiao *et al*. [198] demonstrated that 5-aza-2-deoxycytidine reversed myocardial proteome changes in rats, reducing hypertrophy, improving contractility, and eliminating susceptibility to ischemic injury (Table 2).

Clinical trials investigating DNMTis in cardiovascular settings are ongoing, aiming to translate these preclinical findings into therapeutic strategies for human patients. These trials are evaluating the safety, efficacy, and long-term effects of DNMTis in various CVDs conditions, including HF, CAD, and AF [213].

4.2.2 Histone Deacetylase Inhibitors (HDACis)

HDACis represent another class of epigenetic drugs that modify histone proteins, thereby influencing gene expression patterns in cardiovascular cells [22,210]. By inhibiting HDAC enzymes, these drugs promote histone acetylation, which typically correlates with enhanced gene transcription. In the context of CVD, HDACis have shown promise in reducing CH, fibrosis, and inflammation—key processes implicated in HF and ischemic heart disease progression [22,210] (Table 2). Early experimental studies in mice indicate the potential of HDACis in cardiovascular treatments. HDACis nullscript, scriptaid and TSA, prevented from MIRI and reduced IS in mice [199]. Suberoylanilide hydroxamic acid (SAHA) reduced IS by 50% in MIRI models, restored autophagic flux, and attenuated takotsubu-like myocardial injury [200,201], while class I HDAC-selective inhibitor, SK-7041, partially reversed CH in mice [202]. These inhibitors modulate genes involved in cardiac fibrosis, hypertrophy, mitochondrial biogenesis, and inflammation, which are key features of HF [210]. Notable HDACi, such as vorinostat and romidepsin, initially used in cancer therapy, have shown cardiovascular benefits [203,205–207]. Vorinostat is a pan-HDACi, while romidepsin specifically targets class I HDACs [204]. Givinostat improved cardiac performance in experimental diastolic dysfunction models, and valproic acid (valproate), initially used for epilepsy, protected against MI-induced LV remodeling [208] (Table 2).

4.2.3 Histone Methyltransferase Inhibitors (HMTis)

HMTs add methyl groups to lysine residues in proteins. Few HMTis have entered clinical trials, including DOT1L inhibitors for leukemia, tazemetostat for B cell lymphoma, and EPZ015938 for cancer [214,215]. Among these, tanshinone IIA, a compound from Danshen, has shown direct cardiovascular benefits. It reduces H3K9 trimethylation by inhibiting JMJD2A, silences prohypertrophic genes, and prevents maladaptive cardiac remodeling. Tanshinone IIA also increases *Nrf2* expression through promoter hypomethylation and HDAC inhibition [209] (Table 2).

4.2.4 Non-Coding RNA (ncRNA) as Therapeutic Agents

Beyond DNA methylation and histone modifications, ncRNAs particularly miRNAs and lncRNAs have emerged as critical regulators of gene expression in cardiovascular cells [22,210] (Table 3, Ref. [22,216–230]). These molecules play pivotal roles in modulating oxidative stress responses, vascular inflammation, and endothelial dysfunction, all of which contribute to CVDs pathophysiology [231]. Rapid advancements in nucleotide gene therapy, including antisense oligonucleotides (ASOs) and siRNA, highlight their potential as treatments due to their ease of synthesis and low cytotoxicity [22]. In atherosclerosis, ncRNAs are pivotal therapeutic targets; for instance, inclisiran (ALN-PCSSC), an RNAi therapeutic, lowers LDL cholesterol by inhibiting PCSK9 synthesis and has shown efficacy in clinical trials [216,217]. Additionally, AKCEA-APOCIII-LRx and IONIS-ANGPTL3-LRx target apolipoprotein *C-III* and *ANGPTL3* mRNA, respectively, reducing atherosclerotic lipoproteins and delaying disease progression [218,219]. LncRNA small nucleolar host gene-12 (*SNHG12*), and volanesorsen have shown promise in treating atherosclerosis by protecting against DNA damage and reducing hypertriglyceridemia [22,220,221]. For MI, ncRNA-based drugs like alirocumab, which targets proprotein convertase subtilisin- kexin type 9 (PCSK9), reduces ischemic cardiovascular events and prevents from ACS [222,223]. Moreover, lncRNA MIAT and cirRNA MFACR have been identified as potential targets for protection against MI and reducing cardiomyocyte apoptosis [224,225]. In the treatment of HF, MRG-110 and CDR132L, targeting miRNA-92a and miRNA-132 respectively, are in clinical trials, while other ncRNAs like cirRNA HRCR and circ-FOXO3 showed potential effect in blocking CH and delaying cardiac aging [22,226,227]. Additionally, ncRNAs such as lncRNA-ANCR and lncRNA H19 regulate osteoblast differentiation and vascular calcification, presenting new therapeutic strategies [22,228,229]. The Wnt- β-catenin signaling pathway inhibitor XAV939, inhibits the lncH19-induced hRIFs osteogenic differentiation and serves as a potential drug for treatment of vascular calcification [229].

Table 3. Summary of non-coding RNA-based drugs and targets with potential cardioprotective effects.

ncRNA based drugs	Target	Cardioprotective effect	Reference
Inclisiran (ALN-PCSSC)	PCSK9	reduces LDL-C	[216,217]
AKCEA-APOCIII-LRx	apo C-III	reduces atherosclerosis	[218,219]
IONIS-ANGPTL3-LRx	ANGPTL3 mRNA	reduces atherosclerosis	[218,219]
SNHG12	DNA-PK	reduces atherosclerosis	[22,220]
Volanesorsen	C3 (APOC3)	reduces hypertriglyceridemia	[22,221,230]
Alirocumab	PCSK9	reduces ischemic cardiovascular events	[222,223]
		protects from ACD	
lncRNA MIAT	miRNA-150-5p, VEGF	protects from MI	[224]
		reduces cardiomyocyte apoptosis	
cirRNA MFACR	miRNA-125b	protects from MI	[225]
		reduces cardiomyocyte apoptosis	
MRG-110	miRNA-92a	protects from HF	[22]
CDR132L	miRNA-132	protects from HF	[22]
cirRNA HRCR	miR-223	protects from CH	[22,227]
		protects from HF	
circ-FOXO3	CDK1 (P21), CDK2	protects from cardiac aging	[22,226]
lncRNA-ANCR	Runx2, BMP2	prevents vascular calcification	[22,228]
XAV939	lncRNA H19, Wnt- β-catenin	regulates and prevents vascular calcification	[22,229]

Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; LDL-C, low density lipoprotein C; DNA-PK, DNA-dependent protein kinase; apo C-III, apolipoprotein C-III; CV, cardiovascular; ACD, acute coronary disease; VEGF, vascular endothelial growth factor; MI, myocardial infarction; CMC, cardiomyocyte; HF, heart failure; CH, cardiac hypertrophy; CDK1, cyclin-dependent kinase inhibitor 1; CDK2, cyclin-dependent kinase inhibitor 2; miRNA, micro RNA; lncRNA, long non-coding RNA; cirRNA, circular RNA; ANGPTL3, angiopoietin like 3.

Exosomal hsa_circRNA_0006859 has been identified as a potential therapeutic gene for preventing vascular calcification through miRNA-431-5p [232]. Overall, targeting ncRNAs offers a novel approach to treating CVDs [22]. Future clinical applications may include detecting ncRNA plasma levels to diagnose and determine the severity of CVDs and reversing pathological changes through gene-targeted therapies. Most studies on the ncRNA are in preclinical or early clinical stages, but ongoing research is expected to yield new treatments that improve patient outcomes.

4.3 Lifestyle Interventions

Lifestyle interventions, such as diet and exercise, are pivotal in modulating epigenetic marks and reducing ROS levels, thereby offering a comprehensive strategy to mitigate CVDs risk [233,234]. For instance, caloric restriction has been found to reduce oxidative damage to DNA, proteins, and lipids, which in turn can decrease the incidence of age-related diseases, including CVDs [235]. Additionally, caloric restriction can influence DNA methylation and histone modifications, leading to the activation of protective genes and the suppression of deleterious ones [236].

Regular physical activity also plays a crucial role in maintaining cardiovascular health by modulating epigenetic mechanisms. Exercise has been shown to induce beneficial epigenetic changes in genes involved in antioxidant defense, inflammation, and metabolism [237]. For example, aerobic exercise can increase the expression of antioxidant enzymes, such as SOD and GPx, through epigenetic modifications [238]. Moreover, hypertension is a major preventable cause of death. A study investigated the impact of a three-month aerobic exercise program on DNA methylation and blood pressure (BP) in 68 volunteers. The findings revealed increased VO2peak and decreased diastolic BP post-intervention. Exercise elevated methylation levels of *ALU*, long interspersed nuclear element-1 (*LINE-1*), *EDN1*, *NOS2*, and *TNF* genes. Positive associations were found between VO2peak and methylation of *ALU*, *EDN1*, *NOS2*, and *TNF*, while systolic and diastolic BP were inversely associated with *LINE-1*, *EDN1*, and *NOS2* methylation. These results suggest that DNA methylation may play a role in exercise-induced BP reduction [239]. Furthermore, our study investigated the impact of 12 weeks of high-intensity interval training (HIIT) on retinal microvascular function, $p66^{Shc}$ gene expression, and oxidative stress in ageing subjects with multiple CV risk factors. HIIT significantly improved microvascular phenotype by widening arterioles and narrowing venules. It also restored $p66^{Shc}$ promoter methylation, reduced $p66^{Shc}$ gene expression, and lowered plasma 3-nitrotyrosine levels, suggesting HIIT's potential to mitigate age-related oxidative stress through DNA methylation changes [240]. In conclusion, non-pharmacological interventions such as caloric restriction and regular physical activity can significantly influence epigenetic marks and ROS levels, offering a holistic and

effective approach to mitigating the risk of CVDs. These lifestyle changes not only improve overall health but also complement pharmacological therapies, providing a comprehensive strategy for the prevention and management of CVDs.

5. Future Directions

Future research should prioritize several key areas to enhance the efficacy and applicability of antioxidant and epigenetic therapies for CVDs. Improving bioavailability and delivery systems is crucial, with a focus on advanced delivery methods such as nanoparticles, liposomes, and prodrug strategies to enhance stability and targeted delivery of antioxidants. Additionally, exploring combination therapies that include antioxidants with traditional cardiovascular drugs or other therapeutic agents may provide synergistic effects, improving outcomes for CVDs patients. Personalized medicine approaches can further optimize treatment efficacy by tailoring therapies to individual genetic and epigenetic profiles.

Developing targeted antioxidant therapies that specifically modulate redox-sensitive signaling pathways and epigenetic modifications is another important direction. Understanding the impact of antioxidants on DNA methylation, histone modifications, and ncRNA expressions will be crucial. Moreover, extensive clinical trials across diverse populations and long-term studies are necessary to evaluate the long-term safety and efficacy of these therapies, ensuring their broad applicability.

Non-coding RNA (ncRNA) therapies, including gene therapy approaches using miRNAs and lncRNAs, should be a focus of future research. Investigating how ncRNAs regulate oxidative stress responses and contribute to the pathogenesis of CVDs will be essential for developing targeted ncRNA-based therapies. Additionally, lifestyle interventions such as diet and exercise should be explored for their impact on epigenetic modifications and oxidative stress. Nutrigenomics and studies on the epigenetic effects of physical activity can lead to personalized lifestyle recommendations that complement pharmacological therapies.

6. Limitations

The current research on antioxidant and epigenetic therapies for CVDs is subject to several limitations. The efficacy of antioxidant therapies in clinical trials has been inconsistent, possibly due to differences in study design, patient populations, and antioxidant dosages. Standardizing these variables could help produce more reliable results. Many antioxidants also suffer from poor bioavailability, limiting their effectiveness. Improving delivery mechanisms is essential to overcome this challenge.

The complex nature of epigenetic modifications and their interactions with other cellular processes can make it difficult to develop targeted therapies. More research is needed to fully understand these interactions and their implications for treatment. Additionally, while targeted therapies hold promise, there is a risk of side and off-target effects. Thorough preclinical testing is necessary to identify and mitigate these risks. Long-term studies are required to evaluate the safety and efficacy of new therapies over extended periods, focusing on understanding the potential long-term impacts of altering epigenetic and oxidative stress pathways.

7. Conclusion

In conclusion, the emerging role of ROS as a novel therapeutic target influencing the epigenetic landscape of the entire genome offers profound insights into the pathophysiology of CVDs. Research into epigenetic modifications and their connections to cardiovascular redox signaling pathways has uncovered compelling phenomena. Enzymes and mitochondrial metabolic factors activated in response to metabolic and environmental changes associated with heightened cardiovascular risk contribute significantly to ROS production. ROS exerts substantial influence on DNA and histone modifications, ncRNA transcripts, and chromatin remodeling, thereby altering gene expression in both the nucleus and mitochondria, impacting cardiovascular pathophysiology. However, advancing state-of-the-art technologies and conducting more extensive analyses are crucial to reconcile conflicting data from older studies, particularly in distinguishing methylation from hydroxymethylation.

The integration of antioxidant and epigenetic therapies presents a promising frontier in preventing and treating CVDs. Current research highlights potential benefits, yet significant challenges persist, including variable efficacy, poor bioavailability, and the intricate nature of epigenetic modifications. Future research should prioritize improving delivery systems, exploring combination therapies, and conducting robust clinical trials to establish long-term safety and efficacy. Moreover, advancing ncRNA-based therapies and understanding the role of lifestyle interventions can offer a comprehensive approach to managing CVDs. By addressing these challenges and exploring targeted interventions, antioxidant and epigenetic therapies hold the potential to significantly enhance outcomes for CVDs patients. This integrated strategy not only addresses the complex interplay of oxidative stress and epigenetic mechanisms but also paves the way for more effective therapeutic strategies in the future, aiming to improve cardiovascular health on multiple fronts.

Abbreviations

5hmC, 5-hydroxymethylcytosine; 5mC, 5-methylcytosine; 8-oxodG, 8-oxo-2′-deoxyguanosine; BAF, Brg1-associated factors; BRG1, ATPase Brahma-related gene 1; CpG, cytosine-phosphate-guanine; CVD, Cardiovascular disease; DNMT, DNA methyltransferase; GPx, glutathione peroxidase; HAT, histone acetyltrans-

ferase; HDAC, histone deacetylase; HDM, histone demethylase; HIF1α, hypoxia-inducible transcription factor 1-alpha; HMT, histone methyltransferase; HO-1, haem oxygenase-1; JmjC KDM, jumonji-C domain-containing HDM; LINE-1, long interspersed nuclear element-1; lncRNA, long non-coding RNA; LSD1, lysine-specific demethylase 1A; miRNA, microRNA; mtDNA, Mitochondrial DNA; NAD, adenine dinucleotide; ncRNA, noncoding RNA; NOS, nitric oxide synthases; NOX, NADPH oxidase; OGG1, 8-oxoguanine DNA glycosylase; OXPHOS, oxidative phosphorylation; PHD, prolyl hydroxylase; ROS, Reactive oxygen species; SAM, S-adenosyl methionine; SIRT, sirtuin; SOD, superoxide dismutase; SWI/SNF, switch/sucrose nonfermentable; TET, ten-eleven translocation; TFAM, mitochondrial transcription factor A; H_2O_2, hydrogen peroxide; ECs, endothelial cells; VSMCs, vascular smooth muscle cells; BDNF, brain-derived neurotrophic factor; TF, transcription factor; αKG, alpha-ketoglutarate; SDHB, succinate dehydrogenase B; I/R-injury, ischemia-reperfusion injury; KMT, lysine methyltransferase; PRMT, arginine methyltransferase; MTs, methyltransferases; DMTs, demethyltransferases; KDMs, lysine-specific demethylases; NF-κB, nuclear factor kappa B; PBMCs, peripheral blood mononuclear cells; COX2, cyclooxygenase 2; iNOS, inducible nitric oxide synthase; ICAM-1, cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; Nrf2, erythroid 2-related factor 2; RNS, reactive nitrogen species; EZH2, zeste homolog 2; HAECs, human aortic endothelial cells; VECs, vascular endothelial cells; MIRI, myocardial ischemia-reperfusion injury; eNOS, endothelial nitric oxide synthase; KATs, lysine acetyltransferases; MI, myocardial infarction; PH, pulmonary hypertension; CAD, coronary artery disease; ApoE, apolipoprotein E; HDACs, histone deacetylases; CH, cardiac hypertrophy; DCM, dilated cardiomyopathy; AngII, angiotensin II; CHF, congestive heart failure; Act1, NF-κB pathway activator protein 1; GSH, glutathione; AMI, acute myocardial infarction; DCM, diabetic cardiomyopathy; MCs, myocardial cells; MDA, malondialdehyde; mt-Cytb, mitochondria cytochrome-b; DNMT, DNA methyltransferase; CMCs, cardiomyocytes; TFAM, transcription factor A; ACS, acute coronary syndrome; NRF1, nuclear respiratory factor 1; IS, infarct size; ARF, acute renal failure; AF, atrial fibrillation; DNMTis, DNA methyltransferase inhibitors; HDACis, histone deacetylase inhibitors; MF, myocardial fibrosis; HMTis, Histone Methyltransferase Inhibitors. CAV1, activating caveolin-1; CSE, cystathionine gamma-lyase.

Author Contributions

AA and SH conceptualized the study, wrote, reviewed and edited the manuscript. AA: wrote the original draft, prepared the tables, and the illustrations using BioRender software. SH: supervised the study. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. Both authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

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