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SYSTEMATIC REVIEW OPEN ACCESS

Exploring the Role of Oxidative Stress-Related Molecular Biomarkers in Cardiovascular Disease Progression and Therapeutic Modulations: A Systematic Analysis

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ABSTRACT

Background: Oxidative stress plays a significant role in the pathogenesis of cardiovascular diseases (CVD), endothelial dysfunction and hypertension. The purpose of this study was to synthesize the evidence on the role of critical oxidative stress biomarkers in the etiology of associated diseases to determine their therapeutic potential. **Methods:** PRISMA 2020 guidelines were followed to conduct this study. Reported literature was searched using PubMed, Scopus, Web of Science, and Google Scholar from 2014 to 2025. Those studies that investigated certain biomarkers of oxidative stress (ROS, superoxide dismutase (SOD), glutathione peroxidase (GPx), malondialdehyde (MDA)) in the pathophysiology of CVD, endothelial dysfunction and hypertension were included. Non-English articles and studies without mechanistic or therapeutic outcomes were excluded. The risk of bias was evaluated with the help of Newcastle-Ottawa Scale, Cochrane risk of bias 2, and SYRCLE tool, and the certainty of evidence was measured with the help of the GRADE approach. **Results:** Findings of twelve studies were included in this review, which demonstrated that high level of mitochondrial ROS and MDA, and low activity of SOD and GPx were major contributor to endothelial dysfunction, hypertension and CVD. Melatonin, resveratrol, Nicotinamide Adenine Dinucleotide precursors and mitochondrial-targeted antioxidants proved to be effective therapeutic agents. The risks of bias among included studies ranged from low to high, and the confidence of the evidence ranged from low to moderate. **Conclusion:** Oxidative stress biomarkers are critical in cardiovascular disease pathogenesis and hold significant therapeutic potential. Further extensive trials are needed to validate these indicators as diagnostic tools and convert targeted antioxidant therapy into successful precision medicine.

Keywords: Oxidative Stress, Reactive Oxygen Intermediates, Superoxide Dismutase, Malondialdehyde, Endothelial, Hypertension, Cardiovascular Disease, Antioxidant Effects

Oxidative stress is primarily involved in variety of chronic conditions including endothelial dysfunction, cardiovascular diseases (CVD), and hypertension [1-3]. It is characterized by imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense mechanisms [4]. The presence of ROS, antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and lipids peroxidation products such as malondialdehyde (MDA) are the direct measures to determine oxidative stress [5]. The abnormal levels of these biomarkers were associated with cellular injury, inflammation, and development of chronic conditions by disrupting key functions, such as nitric oxide bioavailability and mitochondrial integrity [6].

Precise role of certain oxidative stress biomarkers, including ROS, SOD, and MDA, and their association with stages in cardiovascular diseases remained a critical area of research [7]. It is essential to understand the mechanistic link that how mitochondrial ROS (mtROS) is responsible for endothelial dysfunction or whether the levels of MDA are associated with the onset of acute coronary events [8]. Moreover, identifying reliable biomarkers offer a dual promise; it not only enhanced early diagnostic and prognostic precision, but also the possibility to focus on specific therapeutic targets, paving the way for personalized antioxidant strategies [9]. Innovative hydrogel-drug delivery systems had also been explored to potentially mitigate oxidative stress–related damage in cardiovascular and metabolic contexts [10].

Despite the growing research on oxidative stress in cardiovascular diseases, the fragmented evidence based on different study designs, disease settings, and on different biomarkers resulted in inconsistent findings. A logical synthesis was needed to gather and evaluate the findings on the diagnostic, prognostic, and therapeutic relevance of the critical oxidative stress markers. This systematic review was intended to determine whether oxidative stress biomarkers, including ROS, antioxidant enzymes (SOD, GPx), and lipid peroxidation products (MDA) played a role in the development of diseases, specifically in oxidative stress-based endothelial dysfunction, CVD, and hypertension tress. It also aimed to determine the clinical relevance of regulating these biomarkers in progression of diseases.

Methodology

PRISMA 2020 guidelines were followed for the synthesis of this systematic review [11].

Databases and Search Strings Used: The authors selected research from 2014 to September 2025 by using databases PubMed, Scopus, Web of Science, and Cochrane Library.A combination of MeSH and free-text keywords related to oxidative stress biomarkers, diseases, and therapeutic targeting were used such as "oxidative stress", "reactive oxygen species", "lipid peroxidation", "antioxidant enzyme", "cardiovascular disease", "endothelial dysfunction", "hypertension", "superoxide dismutase", "glutathione peroxidase", "malondialdehyde", and "therapeutic target". Literature search was further refined by the use of Boolean operators.

Inclusion and Exclusion Criteria: For a study to be included in this review, it should be original research article, such as experimental, observational, or clinical investigations, examining the mechanistic role or therapeutic potential of specific oxidative stress biomarker(s (ROS, SOD, GPx, MDA) in the pathogenesis of a defined chronic disease (endothelial dysfunction, CVD, and hypertension). Only articles published in English were considered. Studies were excluded if they were reviews and editorials, or if they did not focus on a specific disease, explored oxidative stress biomarkers without a direct link to disease mechanisms or treatment.

Study Selection: The title and abstract of studies were reviewed independently by two researchers on the basis of predefined inclusion criteria. The reviewers settled their selection differences either through group agreement or expert consultation.

Data Extraction: Two independent reviewers performed data extraction, which included information about study design, disease context, key biomarkers analyzed, main findings and therapeutic implications. The reviewers either achieved consensus or consulted a third person to settle any differences. When necessary, corresponding authors were contacted for missing or clarifying data.

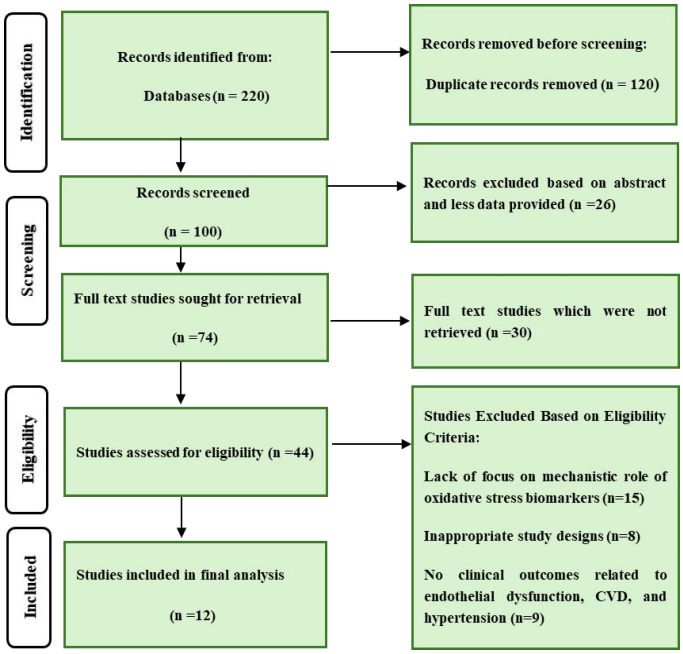

Figure 1: Study Selection Process following PRISMA 2020 guidelines

Primary Outcome and Quality Assessment: The primary outcome of this study was to evaluate the role of critical oxidative stress biomarkers (ROS, SOD, GPx, MDA) in the progression of associated diseases, specifically endothelial dysfunction, CVD, and hypertension, and to assess their potential as therapeutic targets. Risk of bias among the included studies were assessed through the SYRCLE risk of bias (RoB) for preclinical studies, Cochrane RoB 2 for randomized control trial, a combined tool for the hybrid study, and the Newcastle-Ottawa Scale (NOS) for observational studies [12-14]. GRADE criteria were used to evaluate the certainty of evidence.

Results

The study demonstrated the role of oxidative stress biomarkers (ROS, SOD, GPX, MDA) in the progression of endothelial dysfunction, CVD, and hypertension. Among the searched electronic databases and other sources, 220 research articles were initially selected. The number was reduced to 180 records after removing the duplicates. Title and abstract screening further eliminated 26 studies. From the remaining 74 articles, 30 were removed due to unavailability of access to the full-texts. Further 44 articles were screened, and 32 were eliminated due to a lack of stratified data and studies including animals, in vitro findings, reviews, case reports, or languages other than English. Ultimately, twelve studies that passed the inclusion criteria were included in this systematic review. The PRISMA flow diagram presented in Figure 1 illustrates the selection process. The characteristics of the included studies including the disease studied, key biomarkers analyzed, study findings and therapeutic implications were summarized in Table 1.

Table 1: Systematic Review Table Representing Characteristics and Key Findings of Studies

Author & Year	Country of Study	Disease Context	Key Biomarkers Investigated	Study Design & Model(s)	Sample Size / Population Characteristics	Key Findings	Therapeutic Implications
Li et al., 2021 [15]	China	Endothelial dysfunction /Atherosclerosis	Mitochondrial ROS, SOD, GPX, GSH	Experimental Study	Cell Line (HUVECs)	Melatonin reduced mitochondrial ROS, increased SOD, GPX, and GSH activity.	Melatonin enhances antioxidant defense and reduces ROS to protect endothelial cells.

Cao et al., 2022 [16]	China	Endothelial dysfunction /Atherosclerosis	Mitochondrial ROS, SOD2 activity	Experimental Study	Mice models (n not specified)	SIRT3 knockdown elevate ROS. NAD+ supplementation reduced mitochondrial ROS and increased SOD2 activity.	NAD+ precursors reduce mitochondrial ROS and improve endothelial function via SIRT3 and antioxidant upregulation.
Zhou et al., 2014 [17]	China	Endothelial dysfunction / Atherosclerosis	Mitochondrial ROS, SOD2 activity, GSH-Px, IDH2	Experimental Study	Cell Line (HUVECs)	Resveratrol decreased mitochondrial ROS, increased SOD2, GSH-Px, and IDH2 activity.	Resveratrol boosts mitochondrial antioxidant enzyme activity and reduces ROS via SIRT3 activation.
Murray et al., 2023 [18]	United States	Endothelial dysfunction	Mitochondrial ROS	Randomized Control Trial with Ancillary Analysis	Plasma samples from 19 subjects; Cell Line (HAECs)	MitoQ reduced circulating oxLDL and mitochondrial ROS in HAECs. Lower oxLDL correlated with improved NO production and reduced ROS.	Mitochondrial-targeted antioxidants reduce lipid peroxidation and mitochondrial ROS, improving vascular function.
He et al., 2019 [19]	China	Hypertension	SOD2 activity, mtROS	Clinical-Experimental Hybrid Study	20 hypertensive patients, 20 controls; mouse studies (n=6–8/group)	Hypertension reduces SIRT3, increases SOD2 acetylation, elevates mtROS, impairs EPC reendothelialization.	Enhancing SIRT3/SOD2 signaling may improve endothelial repair in hypertension.
Dikalova et al., 2020 [20]	United States	Hypertension	SOD2 acetylation, Vascular ROS	Comparative experimental laboratory study	Mouse models(n=4–8/group); Human tissue from hypertensive & normotensive subjects	Mice models and human hypertensives showed SIRT3 depletion increases SOD2 acetylation, oxidative stress, inflammation, and hypertension.	SIRT3 activation may be a therapeutic target to reduce oxidative stress, inflammation, and hypertension.
García-Sánchez et al., 2023 [21]	Mexico	Hypertension, Obesity	SOD and catalase activity	Cross-sectional study	175 subjects	↓ SOD & catalase activity in hypertension.	Targeting mitochondrial function and antioxidant capacity may help manage obesity-related hypertension.
Huang et al., 2022 [22]	China	Hypertension	SOD activity	Cross-sectional study	1,630 adults	At SOD ≤58 IU/mL, ↓ SOD associated with ↑ diastolic hypertension risk.	Increasing SOD levels within a certain range may reduce diastolic hypertension risk in the elderly.
Moronk	Nigeria	Cardiovascular Diseases	Malondialdehyde	Case-Control Study	121 participants	Significantly elevated levels	Biomarkers may aid in early

eji et al., 2024 [23]						of MDA in CVD patients.	diagnosis and monitoring. Antioxidant interventions could mitigate oxidative damage.
Amioka et al., 2019 [24]	Japan	Acute Coronary Syndrome	Malondialdehyde - modified LDL	Retrospective cohort study	370 patients	↑ MDA-LDL levels >161 U/L predict major adverse cardiac events, especially revascularization and linked to worse prognosis.	MDA-LDL may serve as a prognostic biomarker for guiding intensive lipid and antioxidant therapy.
Nagusundaram et al., 2025 [25]	India	Acute Myocardial Infarction	Malondialdehyde	Cross-sectional case-control study	86 participants (43 AMI patients, 43 healthy controls)	Serum MDA levels were significantly higher in AMI patients (21.8 ± 4.5 ng/ml) vs. controls (4.4 ± 1.4 ng/ml). MDA correlated with oxidative stress.	MDA may serve as an adjuvant diagnostic/prognostic biomarker. Antioxidant therapy may help reduce oxidative injury in AMI.
Arif et al., 2019 [26]	Iraq	Coronary artery disease (post-surgical)	Malondialdehyde	Longitudinal case-control study	50 patients (open-heart surgery), 30 healthy controls	Elevated MDA levels positively correlated with total cholesterol, indicating surgery-induced oxidative stress and reperfusion injury.	Monitoring MDA may help assess reperfusion injury. Antioxidant strategies during/after surgery could mitigate oxidative stress.

ox-LDL = Oxidized Low-Density Lipoprotein; HUVECs = Human Umbilical Vein Endothelial Cells; ROS = Reactive Oxygen Species; SOD = Superoxide Dismutase; GPX = Glutathione Peroxidase; GSH = Glutathione; MitoSOX = Mitochondrial Superoxide Indicator; mBMECs = Mouse Brain Microvascular Endothelial Cells; SIRT3 = Sirtuin 3; NAD^+ = Nicotinamide Adenine Dinucleotide; IDH2 = Isocitrate Dehydrogenase 2; GSH-Px = Glutathione Peroxidase; t-BHP = tert-butyl hydroperoxide; MitoSOX = Mitochondrial Superoxide; MitoQ = Mitochondria-targeted Antioxidant; HAECs = Human Aortic Endothelial Cells; EPCs = Endothelial Progenitor Cells; mtROS = Mitochondrial Reactive Oxygen Species; AMI = Acute Myocardial Infarction; MDA = Malondialdehyde; CVD = Cardiovascular Diseases; MI = Myocardial Infarction; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; hOGG1 = 8-oxoguanine glycosylase; TNF-α = Tumor Necrosis Factor-alpha; IL-6 = Interleukin-6

The synthesis of twelve studies revealed that dysregulated oxidative stress biomarkers are key contributors to disease progression. In particular, the presence of high levels of mtROS and MDA, as well as the reduction in the activity of antioxidant enzymes (SOD2 and GPx) were directly related to the pathophysiology of endothelial malfunctioning, atherosclerosis, hypertension, and acute cardiovascular events. Moreover, the therapeutic interventions that had been shown to target these pathways, such as melatonin, resveratrol, Nicotinamide Adenine Dinucleotide (NAD+) precursors and the mitochondrial-targeted antioxidant, modulated these biomarkers to reduce oxidative damage in cellular and animal models, and in preclinical human trials.

Study-specific tools for risk of bias evaluation such as, SYRCLE for preclinical studies, Cochrane RoB 2 for randomized control trial, a combined tool for the hybrid study, and the NOS for observational studies were used (Table 2).

Table 2: Risk of bias among Included Studies

Risk of Bias for In Vitro & Preclinical Experimental Studies using SYRCLE's RoB Tool							
Author & Year	**Selection Bias**	**Performance Bias**	**Detection Bias**	**Attrition Bias**	**Reporting Bias**	**Other Bias**	**Overall Risk**
Li et al., 2021 [15]	Low (Cell line source stated)	Unclear (Blinding of investigators not stated)	Unclear (Blinding of outcome assessment not stated)	Low (Full data reported)	Low (All methods reported)	Low	Moderate

Cao et al., 2022 [16]	Low (Animal/genotype details clear)	Low (Randomization to groups mentioned)	Unclear (Blinding of assessors not stated for all outcomes)	Low (No attrition mentioned)	Low (Methods comprehensive)	Low	Low
Zhou et al., 2014 [17]	Low (Cell isolation & culture detailed)	Unclear (No blinding mentioned)	Unclear (No blinding of analysis mentioned)	Low (Full data shown)	Low (Protocols detailed)	Low	Moderate
Dikalova et al., 2020 [20]	Low (Animal models well-described, randomization used)	Low (Randomized group allocation)	Unclear (Blinding not explicitly stated for all measures)	Low	Low (All outcomes reported)	Low	Moderate

Risk of Bias for Randomized Controlled Trial using Cochrane RoB-2 Tool

Author & Year	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk
Murray et al., 2023 [18]	Low (Randomized, double-blind, crossover, counter-balanced)	Low (Double-blind, placebo-controlled)	Low (19/20 subjects analyzed, reasons provided)	Low (Objective lab measures, standardized protocols)	Low (Pre-specified outcomes, trial registered)	Low

Risk of Bias for Clinical-Experimental Hybrid Study using Hybrid Tool

Author & Year	Human Subject Selection	Exposure Bias	Animal Study Bias	Measurement Bias	Reporting Bias	Overall Risk
He et al., 2019 [19]	Unclear (Convenience sampling of patients/controls)	High (No blinding in human observational part)	Unclear (Animal procedures described, blinding not stated)	Unclear (Some assays blinded, others not specified)	Low (Complete Data provided)	Moderate-High

Table 5: Risk of Bias for Observational Studies using Newcastle-Ottawa Scale (NOS) Tool

Author & Year	Selection Bias	Comparability Bias	Outcome/Exposure (Risk of Bias)	Overall Risk of Bias
Cross-Sectional Studies				
García-Sánchez et al., 2023 [21]	Medium (Defined cases, community-based, but recruitment details limited)	High (Matched for some factors, but many confounders present)	Medium (Validated assays, but single measurement)	Moderate-High
Huang et al., 2022 [22]	Low (Large national cohort, clear inclusion/exclusion)	Low (Adjusted for multiple key confounders in models)	Low (Standardized BP measurement, assay used)	Low
Nagusundaram et al., 2025 [25]	High (Convenience sampling, matched controls)	High (No adjustment for confounders like age/sex beyond matching)	Medium (Standard lab assay)	High
Case-Control Study				
Moronkeji et al., 2024 [23]	High (Cases from hospital, controls from community; source not identical)	High (Limited adjustment for confounders reported)	Medium (Blinded lab analysis likely, but methods brief)	High
Retrospective Cohort Study				
Amioka et al., 2019 [24]	Medium (Consecutive ACS patients, clear criteria)	Low (Multivariable adjustment for key prognostic factors)	Medium (Blinded outcome assessment, objective endpoint)	Moderate
Longitudinal Case-Control Study				
Arif et al., 2019 [26]	Medium (Clear patient group, healthy controls)	High (No adjustment for confounders; design is within-subject comparison)	Medium (Repeated measures, assay described)	Moderate-High

Orange color represents "Moderate-High" risk of bias; Yellow color represents "Moderate" risk of bias; Green color represents "Low" risk of bias; Red color represents "High" risk of bias

Discussion

The synthesized evidence from the twelve studies was investigated for oxidative stress biomarkers in various disease pathologies including endothelial dysfunction, CVD, and hypertension. The findings consistently demonstrated the presence of high levels of mtROS and MDA, as well as suppressed activity of antioxidant enzymes such as SOD2 were strongly associated with disease progression [27-30]. The mtROS acted as a mediator in endothelial dysfunction and atherosclerosis, whereas in acute coronary syndrome and myocardial infarction, MDA had become one of the main prognostic factors [31]. Studies on cardiovascular disease have also highlighted the importance of biochemical and functional markers in assessing disease severity and recovery outcomes [32]. Melatonin, resveratrol, NAD+ precursors, and mitochondrial-targeted antioxidants like mitochondria-targeted coenzyme Q were effective therapeutic interventions to restore the balance of these biomarkers and improving functional outcomes [33-35].

Overall, the results suggested that oxidative stress biomarkers including mtROS, SOD2 activity, and MDA should be included in stratified risk assessment of CVD and hypertension during clinical practice. The analyzed articles established a clear mechanistic link between oxidative biomolecular imbalances to tissue injury [36]. Experimental studies have demonstrated that oxidative stress and antioxidant imbalance play a central role in cellular injury and disease progression across multiple organ systems [30,33,37]. In endothelial dysfunction, excess mtROS inactivated nitric oxide promoted a pro-inflammatory state, directly contributing to atherosclerotic plaque development [38]. Mitochondrial SOD2 acetylation and inactivation led to sustained oxidative stress in hypertension which hindered vascular repair [39].

In acute cardiovascular events, lipid peroxidation product MDA not only served as the damage marker but also as a mediator of further oxidative damage and inflammation, increasing the reperfusion injury and poor prognosis after myocardial infarction [40-42]. These findings were consistent with the existing literature emphasizing oxidative stress as a broad-spectrum pathology. The recurrent involvement of SIRT3 in the regulation of mitochondrial antioxidant defenses (SOD2) in various studies supported its new emerging status as a key regulatory node [43]. Similarly, the association of adverse cardiac events and MDA also proved its application with clinical biomarkers [44]. However, the difference in the magnitude of effect and optimal cut-off values of biomarkers like SOD reflected the impact of the population peculiarities and disease progression [45].

This study had several limitations. The heterogeneity in the study designs of included studies, model systems and patient populations limited the direct comparability of the findings. The assessment of risk of bias indicated some concerns especially related to cases with observational and experimental studies which included lack of clarity regarding blinding, selection bias, and confounding factors. The preclinical models were based on many cell lines and animal models, and could not be directly translated to human pathophysiology. Moreover, unpublished or non-English studies were excluded, introducing a publication bias. Further studies are required to conduct large-scale, longitudinal cohort studies that will determine the causal timelines and reference ranges. Rigorous, randomized controlled trials in combination with mitochondrion-specific antioxidant therapies, should be undertaken in order to convert these mechanistic effects into definitive clinical benefits. The policy-makers should promote the standardization of these oxidative stress biomarker assays to facilitate comparison across studies.

Conclusion

This review concluded that certain oxidative stress biomarkers (ROS, SOD, GPx, and MDA) played a crucial role in the pathogenesis of endothelial dysfunction, CVD, and hypertension, and could be exploited as therapeutic targets. However, the evidences were considered weak due to the methodological heterogeneity among included studies. Thus, large-scale clinical trials should be conducted to confirm the potential of these biomarkers and to translate targeted therapies into precision medicine.

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Authors' Contribution: SF conceived the idea and participated in study design, data collection and assembly, critical revision of manuscript and statistical analysis. JI participated in data collection and assembly, data analysis and interpretation. SA participated in writing manuscript and statistical analysis; PD participated in critical revision of the manuscript. All authors approved the final manuscript and agree to be accountable for its content.

Ethical Statement: Not Applicable

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