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Chapter 9: Antioxidant Nano-Targeted Therapeutics for Oxidative Stress Management in CVS

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Abstract

Oxidative stress functions as a primary disease mechanism which leads to cardiovascular system disorders that affect the entire cardiovascular system through atherosclerosis and myocardial infarction and ischemia-reperfusion injury and heart failure. The body experiences excessive reactive oxygen species (ROS) production which causes cells to lose their redox balance, resulting in lipid peroxidation and protein changes and endothelial cell damage and mitochondrial dysfunction. Conventional antioxidants exhibit limited clinical effectiveness because they suffer from low bioavailability and fast metabolism and their active ingredients spread throughout the body without targeting specific areas. The implementation of nanotechnology-based delivery systems creates a new therapeutic method which enables precise and continuous delivery of antioxidants to specific body regions. Nano formulations consist of polymeric nanoparticles and liposomes and dendrimers and metal-organic frameworks which can protect both natural and synthetic antioxidants by wrapping them in protective shells that prevent degradation while improving their pharmacological effects. The targeted delivery strategies which use ligand-modified nanoparticles to reach both endothelial receptors and ischemic myocardium enable doctors to deliver treatments with greater accuracy while reducing the potential for adverse effects that affect the entire body. The application of stimuli-responsive Nano carriers which respond to pH changes and redox potential fluctuations and enzymatic activity enables researchers to regulate their delivery of contents within oxidative microenvironments. Preclinical studies show that Nano-targeted antioxidant treatments provide better heart protection and lower oxidative damage markers and better heart muscle recovery results when compared to standard treatment methods. The development of commercial products faces three fundamental obstacles which include difficulties in producing large quantities of the product as well as assessing its safety over extended periods and obtaining regulatory approval for its use in medical settings. Antioxidant Nano-targeted therapeutics provide a revolutionary approach to treat oxidative stress problems which exist in cardiovascular systems because these therapies show experimental success but need more testing before they can be used in medical settings.

Keywords*: Antioxidant Nano therapy; Oxidative stress; cardiovascular system; Targeted drug delivery; Reactive oxygen species*

1. INTRODUCTION

CVDs create a worldwide health crisis because they lead to approximately one-third of all global deaths every year. The worldwide CVD problem keeps increasing because aging populations and urban development and the growth of diabetes and obesity-related metabolic disorders create additional health risks despite existing treatment options. The common medical condition of oxidative stress develops into one of several possible pathways that lead to cardiovascular disease through its impact on disease initiation and development and its resulting health effects. The body undergoes oxidative stress when it accumulates excessive reactive oxygen species (ROS) which overpower its natural antioxidant defense system.[1] The protective measures of the body fail to defend against excessive ROS because they generate protein adducts and lead to lipid peroxidation and double strand breaks in DNA. Atherosclerosis and myocardial infarction and heart failure and hypertension emerge when these changes bring about vascular inflammation and endothelial dysfunction and vascular remodelling. Standard antioxidant therapies which include natural products such as vitamins C and E and flavonoids and synthetic antioxidants such as edaravone face difficulty in clinical trials because their standard forms have poor solubility and instability and fast metabolism and lack of site-targeted effects. The scientists have to find a new method to create a solution which uses nanotechnology for better results in both pharmacology and medical treatment. The practice of "Nano medicine" which uses nanotechnology for medical purposes will enable improvements in antioxidants through enhanced bioavailability and extended circulation time and targeted delivery to cardiovascular systems.

2. OXIDATIVE STRESS IN CARDIOVASCULAR DISEASES (CVDS)

2.1 Mechanisms of ROS Generation in the Cardiovascular System

Reactive oxygen species (ROS) are formed as by-products of normal cellular metabolism, mainly within the mitochondria. Under physiological conditions, low levels of ROS have signalling functions. [5] However, excess ROS will result in oxidative damage. The major sources of ROS in the cardiovascular system include:

• **Mitochondrial respiratory chain dysfunction:** During oxidative phosphorylation electrons can leak to produce superoxide anions. [6]

• **NADPH oxidases (NOX enzymes):** These specialized enzymes purposefully produce superoxide, especially in endothelial, vascular smooth muscle, and cardio myocyte cells. [7]

• **Uncoupled endothelial nitric oxide synthase (eNOS):** Uncoupled eNOS produces superoxide, instead of NO, leading to a reduction in NO bioavailability. [8]

• **Xanthine oxidase and cytochrome P450**: There are important contributions to ROS generation from these enzymes, under pathological conditions such as ischemia-reperfusion. [9]

2.2 Mechanisms of Oxidative Stress in Major Cardiovascular Conditions:

- **Atherosclerosis:** ROS oxidize low-density lipoproteins (LDL) to generate oxidized LDL (oxLDL), which is taken up by macrophages to form foam cells. The ROS also promote endothelial dysfunction and inflammation, along with plaque instability. [10]
- **Myocardial Infarction (MI):** Ischemia-reperfusion injury leads to a massive burst of free radicals and ROS, which promote cardio myocyte apoptosis and ultimately necrosis. [11]
- **Heart Failure:** Chronic elevation in ROS promotes maladaptive remodelling, as well as Myofibroblast activation that promotes fibrosis and functionally impairs contractility. [12]
- **Hypertension:** Oxidative stress decreases nitric oxide (NO) bioavailability and initiates vascular smooth muscle proliferation which ultimately increases vascular resistance. [13]

2.3 Biomarkers of Oxidative Stress in CVDs

- Malondialdehyde (MDA): MDA serves as an indicator of oxidative injury to cell membranes because it is a by-product of lipid peroxidation. Patients with atherosclerosis, hypertension, and myocardial infarction frequently have increased plasma MDA. [14]

- 8-hydroxy-2'-deoxyguanosine (8-OHdG): Hydroxyl radical attack on DNA form 8-OHdG, an indicator of oxidative damage to DNA. Increased 8-OHdG in urine and plasma is associated with endothelial dysfunction and plaque instability.
- Protein Carbonyl Levels: Represent irreversible oxidative modification of proteins. Elevated carbonyl levels in blood proteins indicate systemic oxidative stress and are related to the severity of heart failure and ischemic injury. [15]
- Circulating oxidized LDL (oxLDL): Modifications of the LDL particles by reactive oxygen species leads to oxLDL, which directly contributes to both foam cell formation and over time to the growth and progression of atherosclerotic plaque. Because oxLDL is elevated in the circulation and thought of as a strong risk factor for coronary artery disease.
- Antioxidant enzyme contents (SOD, Catalase, and GPx): These enzymes provide the first line of defence for organisms against reactive oxygen species. Reduced activities or contents of superoxide dismutase, catalase, and glutathione peroxidase are frequently reported in subjects with cardiovascular disease, suggesting an impaired antioxidant capacity and disturbed ability to detoxify reactive oxygen species. [16]

Table 9.1: Key biomarkers of oxidative stress in cardiovascular diseases.

Biomarker	Type	Clinical Relevance	Associated Cardiovascular Conditions
Malondialdehyde (MDA)	Lipid peroxidation product	Indicator of membrane lipid damage; elevated in plasma/serum	Atherosclerosis, myocardial infarction, hypertension
F2-Isoprostanes	Lipid peroxidation markers	Gold-standard for oxidative stress assessment	Coronary artery disease, heart failure
Oxidized LDL (oxLDL)	Modified lipoprotein	Promotes foam cell formation and plaque instability	Atherosclerosis, ischemic heart disease
8-Hydroxy-2′-deoxyguanosine (8-OHdG)	DNA oxidation marker	Reflects oxidative DNA damage	Hypertension, cardiomyopathy
Protein Carbonyls	Protein oxidation marker	Irreversible protein modification; associated with dysfunction	Ischemia-reperfusion injury, heart failure
Nitro tyrosine	Marker of peroxynitrite activity	Indicator of nitrosative stress	Endothelial dysfunction, atherosclerosis
Reduced/oxidized glutathione (GSH/GSSG ratio)	Antioxidant balance	Reflects redox homeostasis; lower ratio indicates stress	Heart failure, myocardial infarction
Myeloperoxidase (MPO)	Oxidative enzyme	Generates hypochlorous acid; marker of inflammation and oxidative stress	Coronary artery disease, unstable angina
Superoxide dismutase (SOD) activity	Antioxidant enzyme	Decline indicates impaired ROS neutralization	Hypertension, heart failure
Catalase activity	Antioxidant enzyme	Decomposition of hydrogen peroxide; reduced activity linked with oxidative injury	Ischemia-reperfusion injury, hypertension

3. ANTIOXIDANT THERAPEUTICS: CONVENTIONAL APPROACHES

3.1 Natural Antioxidants

Natural antioxidants have been widely researched for cardio protective properties as it has been found that they could undo the harmful effects of excess ROS, modulate redox signalling, and maintain vascular health and stability. Many of the natural antioxidants are food-based components (i.e., fruits, vegetables, tea, medicinal plants) and most work by being a source of bioactive compounds. [17]

- Flavonoids (quercetin, catechins, EGCG, resveratrol): These are plant based polyphenolic compounds that can improve endothelial function by modulating the bioavailability of nitric oxide (NO), dampening vascular inflammation, and/or suppressing aggregation of platelets. The redox activity of flavonoids can neutralize ROS, reducing lipid per oxidative stress and preventing the formation of atherosclerotic plaque. [18]

- Vitamins (C, E, carotenoids, tocopherols): These vitamins are classical antioxidants in that they donate an electron to neutralize free radicals. Vitamin C is an aqueous compartment protector and able to reduce oxidized vitamin E; while vitamin E and carotenoids can prevent lipid peroxidation of membranes or lipoproteins circulating in the blood reducing the amount of oxidative damaged vascular tissue. [19]
- Polyphenols (curcumin, tannins): In addition to the antioxidant action, polyphenols are actively anti-inflammatory and anti-apoptotic. For example, curcumin modulates the inflammatory or oxidative stress pathways, NF-κB or Nrf2, to enhance the endogenous antioxidant defences. Tannins may contribute to vascular tissue protection through their affinity for LDL to reduce oxidative modification and provide a cushion to oxidative stress in vascular endothelium. [20]
- **3.2 Synthetic Antioxidants**

  Scientists designed multiple synthetic antioxidants to create compounds which function as natural defense systems of the body while boosting their ability to eliminate free radicals. The agents show potential to treat cardiovascular damage which occurs through oxidative stress but their effectiveness in medical practice has produced inconsistent outcomes. [21]

3.3 Clinical Limitations

The research demonstrates that antioxidants have a function in treating cardiovascular diseases yet current medical practices do not show effective results from antioxidant treatment. The process of turning research into practical application faces multiple obstacles which create the current situation. [24]

• Bioavailability clearance Many antioxidants especially but not limited to polyphenols and vitamins exhibit two main problems because they both have low absorption rates and they get metabolized quickly while their active components stay in the body for only a short time. The limitations of this method make it impossible to achieve the needed antioxidant concentration required for effective treatment at target locations. [25]

• Non-targeted delivery Patients receive standard antioxidant treatments which travel through their bodies without stopping to treat specific damaged parts of their heart. The lack of targeting should emerge as a critical element which determines the achieved therapeutic results because it happens in areas where endothelial cells experience severe oxidative damage and myocardial tissue suffers from ischemia. [26]

• Non-targeted systemic general effects most antioxidants show multiple effects which lead some of them to disrupt essential redox signaling pathways that maintain basic cellular operations thereby decreasing their ability to treat medical conditions.

• Pro-oxidant activity Certain antioxidants possess dual functions since they work as antioxidants while also becoming pro-oxidants at specific high doses and at particular situations which produce oxidative reactive species that increase oxidative stress. [27]

4. NANOTECHNOLOGY IN CARDIOVASCULAR MEDICINE

4.1 Principles of Nano medicine

Nano medicine is an emerging discipline that harnesses the unique properties of **nanoscale materials (1–100 nm)** for the diagnosis, prevention, and treatment of diseases. At this scale, materials exhibit distinct physicochemical behaviours such as high surface-to-volume ratio, tuneable surface charge, and enhanced reactivity that can be exploited to improve therapeutic outcomes in cardiovascular medicine. [28]

The central principles of Nano medicine in drug delivery include:

- **Enhanced solubility:** Many antioxidants and cardiovascular drugs suffer from poor water solubility. Encapsulation in Nano carriers such as liposomes, polymeric nanoparticles, or micelles improves dissolution and bioavailability.
- **Controlled pharmacokinetics:** Nano carriers protect therapeutic molecules from rapid degradation and clearance, prolonging circulation time and ensuring sustained drug release.

- **Targeted delivery:** Functionalized nanoparticles can selectively accumulate in diseased tissues (e.g., inflamed endothelium, ischemic myocardium, atherosclerotic plaques) via passive mechanisms like the enhanced permeability and retention (EPR) effect or active targeting through ligand-receptor interactions.
- **Therapeutic efficiency:** By concentrating antioxidants or drugs at the site of oxidative damage, Nano medicine enhances therapeutic efficacy while minimizing systemic side effects. In cardiovascular applications, these principles enable **precise delivery of antioxidants,** improved vascular protection, and potential integration with diagnostic imaging (theranostics). Nano medicine therefore represents a promising paradigm shift from conventional systemic therapy toward **site-specific, efficient, and safer treatment strategies** for oxidative stress–related cardiovascular disorders. [29]

4.2 Nano carriers in Cardiovascular Initiatives:

Nano carriers are specially engineered nanoscale delivery systems that are used to deliver therapeutic agents more efficiently than would otherwise be possible with conventional formulations. In cardiovascular medicine, Nano carriers can protect antioxidants from degradation, boost solubility, prolong circulation, and deliver the compound targeted to within tissues affected by oxidative stress. Multiple classes of Nano carriers have been created to have various advantages. [30]

- **Liposomes:** Liposomes are spherical vesicles which consist of phospholipid bilayers. They can encapsulate hydrophilic and hydrophobic compounds, making them useful in encapsulating antioxidants such as vitamin E and polyphenols. They maintain a favourable biocompatibility profile, are structurally similar to biological membranes which are beneficial for cardiovascular applications, and liposomal formulations for the delivery of vitamin E and polyphenols to endothelial cells have shown improvements in stability and amounts taken up by the endothelial cells. [31]
- **Polymeric Nanoparticles (PLGA, Chitosan, PEG-based):** Biodegradable polymers (for example, poly (lactic-co-glycolic acid) (PLGA), chitosan and polyethylene glycol) are popular to engineer nanoparticles for sustained and controlled release. Polymeric nanoparticles can protect antioxidants (ex: resveratrol, quercetin) from metabolic processes, thereby granting a greater therapeutic window in cardiac and vascular tissues, and are useful in such applications.
- **Dendrimers:** Highly branched, tree-like macromolecules with multiple terminal functional groups. Their surface chemistry can be modified to conjugate antioxidants or targeting ligands. Dendrimers can achieve more precise drug loading and controlled release, making them valuable vehicles to deliver flavonoids or vitamin derivatives to inflamed vascular areas. [32]
- **Metal Nanoparticles (Gold, Cerium Oxide, and Platinum):** While some metallic nanoparticles possess intrinsic antioxidant or "Nano enzyme" activity, they do not act as traditional carriers. Specifically, cerium oxide nanoparticles mimic superoxide dismutase and catalase and scavenge reactive oxygen species (ROS) directly. Gold and platinum nanoparticles also exhibited free radical neutralization and anti-inflammatory effects. These are being researched to provide cardio protection in ischemia-reperfusion injury and atherosclerosis. [33]
- **Nano micelles:** Self-assembled amphiphilic structures with a hydrophobic core and hydrophilic shell. Nano micelles have also been employed to enhance the solubility of otherwise poorly water-soluble antioxidants such as curcumin and resveratrol, providing increased absorption and bioavailability. Furthermore, their small size allows for passive accumulation to vascular lesions. [34]

4.3 Targeting Strategies

The targeted delivery of antioxidant therapeutics is important to maximize their efficacy in cardiovascular disease (CVD), given that oxidative stress occurs locally in vascular lesions, ischemic myocardium, or inflamed endothelium. There are many ways that nanotechnology can be employed to target antioxidants to diseased tissues, while minimizing any residual side effects on the rest of the body. [35]

- **Passive Targeting:**

Passive targeting relies on the pathophysiologic characteristics of a disease state in the cardiovascular system, including increased vascular permeability and retention (EPR effect) in traditional inflamed/ischemic regions. In these regions, there is enhanced accumulation of the passive targeted nanoparticles due to their leaky endothelium, impaired bulk lymphatic clearance, and changes in the local microenvironment. For

example, a liposomal antioxidant could passively accumulate within an atherosclerotic plaque, or within the ischemic myocardium. [36]

- **Active Targeting:** Active targeting provides even more specificity by modifying a Nano carrier based on bio recognition elements for the intended target. These may include peptides, antibodies, or small molecules, which lead to binding to receptors overexpressed on the target cells including endothelial (e.g., CD-31), macrophage (e.g., Receptor for Advanced Glycation End products) or vascular smooth muscle (e.g., Transferrin, RGD). [37]
  - **GD peptides:** Recognize and bind integrin's (e.g., αvβ3, α5β1) that are elevated on activated endothelial cells during vascular injury and inflammation.
  - **Antibodies:** Monoclonal antibodies or antibody fragments can be conjugated to Nano carriers allowing for selective recognition of adhesion molecules (intercellular adhesion molecules-1 or ICAM-1; vascular cell adhesion molecules-1 or VCAM-1) that are upregulated in atherosclerotic endothelium.
  - **Mannose or folate groups:** These ligands enable the uptake of the nanoparticles by macrophages located in atherosclerotic plaques for the targeted delivery of antioxidants to chronic inflammatory sites.
- **Conditions-Responsive Systems:** Conditions-responsive Nano carriers can release antioxidants only in pathological conditions and offers a means to enhance therapeutic specificity. For example:
  - **ROS-responsive nanoparticles** that degrade or release drugs when exposed to high concentrations of superoxide or hydrogen peroxide.
  - **PH-responsive Nano carriers** that release their payload in acidic tissue compartments such as (inflamed/ischemic) tissues.
  - **Enzyme-responsive systems** that respond to matrix metalloproteinase (MMPs) or lipases at enhanced levels (primarily) in atherosclerotic lesions. [38]

5. POLYPHENOL-ENCAPSULATED NANO CARRIERS

Polyphenols - a naturally occurring group of phytochemical constituents found in plants - have received a great deal of attention due to their antioxidant and anti-inflammatory antioxidant as well as their cardio protective agents. Despite their beneficial properties, polyphenols hinder their therapeutic applications either due to poor water solubility, unstable release characteristics in physiological conditions, and rapid metabolism in biological systems. As previously described, Nano carrier delivery systems have demonstrated a wide array of methods used to improve the solubility, absorption, specificity, bioavailability, and prolong delivery of polyphenols used in cardiovascular diseases (CVDs), as supported in the latter section. [39]

- **Curcumin Nano carriers and Resveratrol Nano carriers :** The polyphenol curcumin which scientists extracted from the turmeric plant (Curcuma longa) exhibits antioxidant properties together with anti-inflammatory effects and cardio protective benefits; its low solubility and slow body elimination hinder its medical use. The combination of liposomes with polymeric nanoparticles and solid lipid nanoparticles enables better curcumin solubility and stability and cellular absorption of the compound. Different studies about cardiovascular systems have shown that curcumin nanoparticles protect the heart by reducing myocardial ischemia-reperfusion injury together with lipid peroxidation and mitochondrial dysfunction. Resveratrol (also known as tri-phenol) belongs to the stilbene plant defense substances which various plant species such as grapes and berries synthesize and release into their environment. Multiple research studies have shown that resveratrol produces physiological effects which include anti-atherogenic and protective and anti-inflammatory effects. The use of nano carrier encapsulation systems allows polyphenols to maintain stability because the system protects them from light and enzymatic degradation when they are combined with polymeric nanoparticles and micelles and lipid-based Nano carrier systems. Through transcriptional and cell signaling pathways resveratrol-loaded Nano carriers increase endothelial nitric oxide synthase (eNOS) signaling while they induce vascular oxidative stress and reduce smooth muscle cell proliferation according to pre-clinical studies on rats.
- **Nanoparticles with Quercetin:** Quercetin, a flavonoid found in many fruits and vegetables, is a powerful antioxidant and has anti-apoptotic properties. Despite this, its efficacy in therapy is limited because it has low oral bioavailability and undergoes significant first-pass metabolism. When quercetin is included with chitosan nanoparticles, polymeric micelles, or dendrimers much of its absorption and circulation time is increased. Studies have shown that quercetin-loaded nanoparticles prevent oxidative stress-induced

apoptosis in cardio myocytes, reduced inflammation, and improved cardiac function in preclinical animal ischemic heart disease models. [41]

5.1 Nanozymes

Nanozymes are nanomaterials that exhibit enzyme-mimicking catalytic properties, representing a new therapeutic strategy for cardiovascular diseases (CVD) associated with oxidative stress. In contrast to traditional antioxidants, nanozymes may afford persistent, catalytic and site-specific scavenging of ROS thereby prolonging the protective effect. Given their stability, tuneable properties, and multifunctional ties, nanozymes hold great promise as new-generation antioxidant therapeutics. [42]

- **Cerium Oxide Nanoparticles (CeO_2) and Gold Nanoparticles (AuNPs):**

Cerium oxide nanoparticles are considered to be the most researched nanozymes due to their ability to cycle between Ce^{3+} and Ce^{4+} and mimic SOD-like and catalase-like activity, in addition to detoxifying superoxide radicals and hydrogen peroxide (both important contributors to cardiovascular oxidative stress). Preclinical research demonstrates cardio protection from CeO_2 nanoparticles in ischemia-reperfusion injury, as well as reduction in infarct size and improvement in mitochondrial function. [43]. AuNPs have intrinsic ROS scavenging properties and anti-inflammatory capabilities, and are also good delivery vehicles for antioxidant molecules. Due to their high surface area, gold nanoparticles can be functionalized with peptides, drugs, or targeting ligands. AuNPs have been shown to reduce oxidative stress in vascular endothelial cells, release of pro-inflammatory cytokines, and provide protection from myocardial injury. Their biocompatibility and tenability in size are well positioned for cardiovascular applications. [44]

- **Manganese Oxide Nanoparticles:**

Manganese oxide nanoparticles have been shown to mimic the activity of catalase by facilitating the decomposing of hydrogen peroxide into water and oxygen. Since no other reactive species are formed, by reducing the excessive hydrogen peroxide they contribute to restoring redox balance in cardiovascular tissues. Based on experimental studies manganese oxide nanoparticles can reduce oxidative related tissue damage in vascular smooth muscle cells, improve endothelial function, and reduce vascular remodelling related to hypertension. [45]

5.2 Applications for Targeted Delivery

The ability to deliver antioxidant drugs, antioxidants bound to Nano carriers (e.g., nanoparticles), or nanozymes to particular types of cardio myocytes that have been affected by oxidative stress is one of the greatest advantages of nanotechnology-based ultrasensitive antioxidant therapeutics. Targeting delivery of the antioxidant-loaded Nano carriers or nanozymes to the pathological site substantially improves the therapeutic effects and lowers side effects on the systemic level. [46]

- **Endothelial Cells and Macrophages :** Endothelial dysfunction serves as an initial warning signal for cardiovascular disease because it leads to two effects which involve reduced availability of nitric oxide and increased production of reactive oxygen species and the onset of inflammation. The process of delivering antioxidants directly to endothelial cells enables them to restore their redox equilibrium and achieve better blood vessel expansion while showing reduced levels of adhesion molecule expression that includes VCAM-1 and ICAM-1. When resveratrol nanoparticles or quercetin nanoparticles reach the endothelium they boost eNOS activity while reducing oxidative harm and enhancing blood vessel function. [47]. Macrophages function as main actors in atherothrombosis because they contribute to atheroma development through foam cell creation and atheroma destabilization through their production of reactive oxygen species and pro-inflammatory cytokines and their ability to scavenge oxidized low-density lipoprotein. Antioxidants become effective at preventing oxidative stress in macrophages and foam cells when scientists use Nano carriers which specifically target these two cell types because this method decreases foam cell formation while making vulnerable plaques more stable. Macrophages preferentially take up mannose or folate-decorated Nano carriers which enables the delivery of antioxidants to inflamed atheromatous plaques through the natural antioxidant curcumin and nanozyme compounds. The targeted treatment of plaques through this method shows actual potential to decrease both the risk of plaque rupture and the risk of myocardial infarction. [48]

- **Cardio myocytes:** Cardio myocytes demonstrate high vulnerability to ischemia-reperfusion injury which occurs through abrupt oxygen restoration and subsequent mitochondrial failure that results in cell death through apoptosis. The use of Nano carriers to deliver antioxidants specifically to cardio myocytes enables mitochondria to perform vital functions as they eliminate reactive oxygen species while maintaining mitochondrial functions which protects cells from death. The study found that cerium oxide nanoparticles and polymeric nanoparticles containing quercetin successfully reduced oxidative damage which resulted in better contractile function and faster heart recovery after ischemic damage.[49]

6. MECHANISTIC INSIGHTS

- Antioxidant Nano-targeted systems provide therapeutic benefits for cardiovascular diseases (CVDs) because their delivery system shows improved treatment capability; the system functions through its cellular uptake mechanisms together with its continuous antioxidant distribution to cells which affects key cellular processes that control oxidative stress and inflammatory response and cell survival. [50]
- Cellular Uptake: Nanoparticles enter cardiovascular cells through several well-characterized endocytic mechanisms, including:
- Catherin-mediated endocytosis: This occurs with the most commonly tested small nanoparticles and many ligand-functionalized carriers, where the nanoparticles are taken into endosomes and released intracellularly.
- Caveolin-mediated endocytosis: This uptake process permits nanoparticles to escape destruction inside lysosomes, which results in better antioxidant distribution to cytosolic regions.
- Receptor-mediated endocytosis: This process achieves functionalized uptake through ligands which include RGD peptides, antibodies, and mannose, to achieve selective endothelial cell uptake through endothelial cells, macrophages, and cardio myocytes. These endpoints ensure efficient enrichment of antioxidants at intracellular locations (e.g., mitochondria and lysosomes) where reactive oxygen species (ROS) are produced. [51]
- **ROS Scavenging:** Nano carrier-based formulations enable sustained and high intracellular quantities of antioxidants. This is beneficial because free radical compounds have low solubility and they undergo fast metabolic processes. NPs which contain polyphenols and cerium oxide nanozymes together with metal based Nano carriers demonstrate the ability to eliminate superoxide anions and hydroxyl radicals and hydrogen peroxide in order to shield lipids and proteins and DNA from damage.
- Signalling Pathway Modulation: Nano-antioxidants demonstrate two functions because they directly eliminate ROS while simultaneously affecting redox-sensitive molecular signalling pathways. Nrf2/ARE activation: Nano carriers can increase nuclear translocation of Nrf2 which leads to the transcriptional upregulation of antioxidant enzymes including superoxide dismutase (SOD) and catalase and heme oxygenase-1 (HO-1). This process will create a self-sustaining antioxidant protection system that lasts for an extended period.

  NF-κB inhibition: Nano-antioxidants have the ability to prevent ROS-driven NF-κB activation which leads to a decrease in pro-inflammatory cytokine production and the expression of adhesion molecules and chemokines. This process will lead to a decrease in vascular inflammation together with reduced plaque formation. NPs have demonstrated their ability to control MAPK pathways through their effects on ERK and JNK and p38 while they also create PI3K/Akt pathways which protect the heart by stopping cell death during ischemia-reperfusion injury according to [52].

7. IN VITRO STUDIES

In vitro studies are the first line of evidence for the therapeutic potential of antioxidant Nano formulations in cardiovascular therapeutics. The in vitro studies allow researchers to better evaluate cellular uptake, ROS scavenging activity, cytoprotection, and signalling pathway modulation as they may conduct the studies with cultured endothelial cells, vascular smooth muscle cells, and cardio myocytes. [53]

- **Enhanced ROS Scavenging**: Antioxidants with nanoparticle loading have consistently demonstrated increased ROS scavenging activity compared to free antioxidants. For example, curcumin-positive nanoparticles have demonstrated prolonged intracellular half-life which facilitates reductions in hydrogen peroxide-induced oxidative stress in endothelial cells when compared with free curcumin. In a similar manner, quercetin-loaded polymeric nanoparticles produced a reduction in mitochondrial ROS production in cardio myocytes under conditions of hypoxic stress.

- **Cytoprotective Effects:** The use of Nano formulations has produced a significantly greater impact on cell viability and function in cells subjected to oxidative stress through induction of cytoprotective mechanisms. Resveratrol nanoparticles produced an increase in eNOS activity, and provided cytoprotection against oxidative apoptosis in human endothelial cells. Gold and cerium oxide nanozymes were able to mimic antioxidant enzyme activity and produced a significant reduction in protein carboxylation and lipid peroxidation in cardio myocyte cultures.
- **Mechanistic Validation:** In vitro studies have also provided insight into molecular mechanisms of Nano-antioxidant actions. Delivery of cerium oxide nanoparticles to endothelial cells initiated the Nrf2/ARE pathway, increased expression of antioxidant enzymes, and inhibited NF-κB signalling, which decreased inflammatory responses. Quercetin nanoparticles also modulated MAPK/ERK signalling to inhibit stress-induced apoptosis.
- **Comparative Advantage over Free Antioxidants:** In numerous studies, Nano formulated antioxidants provide advantages over free compounds through improved solubility, stability, and enhanced intracellular delivery. For example, free resveratrol cannot maintain stability due to rapid degradation by light and by enzymatic processes, which can be inhibited while the resveratrol is encapsulated, solidifying the liability of free resveratrol. Furthermore, resveratrol is taken up with much higher levels into endothelial cells when encapsulated. [54]

7.1 Animal Models

Animal studies are important for understanding in vivo efficacy, bio distribution and safety of antioxidant Nano formulations applied to cardiovascular diseases (CVDs). When pathological conditions (e.g. atherosclerosis, myocardial ischemia-reperfusion injury, and hypertension) are reproduced using a preclinical model, it is possible to ascertain any advantage that the action of a Nano formulation may impart to overcome the limitations of conventional antioxidants. [55]

- **Curcumin-loaded Nanoparticles in myocardial ischemia-reperfusion (I/R) injury:** The use of free curcumin has limited cardio protective effects in the I/R context as it has poor solubility and rapid clearance from the body. Conversely, curcumin-loaded nanoparticles have been demonstrated to substantially decrease infarct size, maintain left ventricular function and mitigate lipid peroxidation in rodent models of me /R injury. Mechanistically, these nanoparticles reduce mitochondrial dysfunction (the triggers for cell death), lower apoptosis markers (the consequence of cell death), and upregulate endogenous antioxidant enzymes (e.g. SOD, catalase).
- **Cerium oxide nanoparticles in hypertension and cardiac dysfunction:** Nanoceria are established to be active in hypertensive rat models in which oxidative stress acted as one of the pathways causing vascular remodelling and cardiac hypertrophy. Nanoceria act as a mimic of superoxide dismutase and catalase, decreasing the burden of ROS, decreasing blood pressure and improving both cardiac contractility and diastolic relaxation. Further, it has been shown that long-term administration of nanoceria prevented the onset of heart failure in the hypertensive rat model without significant systemic toxicity.
- **Nano carriers of Resveratrol and Quercetin in Atherosclerosis:** Polyphenol loaded Nano carriers such as resveratrol and quercetin formulations are shown to have better anti-atherogenic effects in Apo-E mice and cholesterol-fed rabbits. These nanoparticles reduce plaque volume, inhibit foam cell formation, improve endothelial nitric oxide bioavailability, and limit the inflammatory response.
- **Gold and Manganese Oxide Nanoparticles for Cardiac Protection:** Gold nanoparticles show intrinsic antioxidant activity and inhibit myocardial apoptosis in rodent models of ischemia. Manganese oxide nanoparticles also have catalase-like activity, and effectively eliminate hydrogen peroxide in the myocardium. Manganese oxide nanoparticles limit oxidative damage from reperfusion by reducing oxidative damage in the heart and improving cardiac function. [56]

7.2 Emerging Clinical Trials:

- The research shows that antioxidant-based Nano carriers can be used as therapeutic agents but scientists have started to study these materials in clinical settings. The first phase of research studies investigates how safe Nano-antioxidant products are and how they absorb into the body and how effective they are in treating heart disease.
- Human tests of resveratrol embedded in biodegradable polymeric nanoparticles have shown that this treatment can reverse endothelial dysfunction which serves as a known precursor to atherosclerosis and

hypertension. The new formulations demonstrated better results than free resveratrol because their bioavailability through oral consumption reached higher levels while they maintained longer plasma existence and caused major changes in endothelial nitric oxide synthase (eNOS) activity studies. The initial findings show that both vascular reactivity and flow-mediated dilation have improved yet scientists need to conduct more extensive randomized controlled experiments to reach definitive conclusions. [57]

- Scientists are currently studying liposomal antioxidant formulations which include vitamin E and quercetin and curcumin to determine their effectiveness in treating atherosclerotic plaque burden and plaque accumulation and vascular inflammation and related pathologies. The first clinical research studies show that liposomal delivery system enhances plasma stability while directing medication to specific vascular areas which leads to better results for patients who have carotid artery disease and coronary atherosclerosis.
- **Nano formulated Vitamins and Polyphenols:** Vitamin E and polyphenol supplements that are packaged as Nano carriers have also emerged from numerous small studies on metabolic syndrome and dyslipidaemia, which involves CVD risk-related factors. Studies reported improved lipid profiles, reduced circulating oxidized LDL, and decreased oxidative stress disease markers as compared to standard oral supplements. [58]

8. TOXICITY, SAFETY, AND REGULATORY ISSUES

- The potential of nanotechnology to transform cardiovascular treatment approaches faces major obstacles because of existing safety requirements and regulatory frameworks which need to be addressed before medical practitioners can use this technology. The physicochemical characteristics of nanomaterials create safety issues despite the fact that Nano carriers improve antioxidant delivery and effectiveness. Medical practitioners need to understand toxicological risks regarding Nano-antioxidant applications which require testing in standard cardiovascular treatment methods.
- Nano toxicology: Although the aim is therapeutic, some nanomaterials may actually induce adverse biological effects. Metal nanoparticles generate reactive oxygen species (ROS) when certain conditions exist, which leads to oxidative stress. Some substances will stimulate immune system response, which will activate the complement system , or produce inflammatory reactions that result in undesired outcomes. Studies on bio distribution demonstrate that nanoparticles affect multiple organs, including the liver and spleen and kidneys, which creates worries about bioaccumulation and toxicity, especially regarding chronic toxic effects. Any situation needs to control off-target effects through establishing dose limits and managing shape and size and surface chemistry parameters.
- Biocompatibility: Nano carriers are often developed to include surface modifications such as polyethylene glycol (PEGylating) to increase safety, increase circulation time, decrease opsonisation by immune cells, and improve biocompatibility. Natural polymers (e.g. chitosan, alginate, PLGA) are generally safer than synthetic or inorganic nanoparticles and are more biodegradable, while the latter requires monitoring for degradation products, as well as monitoring for clearance pathway. Current Nano toxicology research focuses on achieving therapeutic efficacy while maintaining safety throughout an extended period.

- Regulatory Hurdles: The intricate design and multiple functions of Nano medicines require them to overcome substantial regulatory barriers which depend on their essential regulatory classification for their approval. The existing regulatory system does not provide common methods to evaluate and determine the safety and pharmacokinetics and effectiveness of cardiovascular Nano medicines. The process of reproducibility faces difficulties because of different methods used to create nanoparticles and manufacturing processes and their effects on product stability at industrial production levels. Regulatory agencies such as the FDA and EMA require developers to conduct validated preclinical testing and controlled clinical trials about their product before they receive market approval. The post-market monitoring of Nano medicine safety will probably require additional monitoring procedures which regulatory agencies will supervise after the products receive approval for medical use. [59]

9. FUTURE PERSPECTIVES

The advancement of antioxidant Nano-targeted therapeutics within the cardiovascular medicine domain is fast-paced, with several attractive pathways expected to define its future. The integration of information from materials science, molecular biology and translational research enables progressively better defined, effective and multifunctional Nano medicine platforms. [60]

- **Nano medicine is becoming personalized:**

Future approaches will provide more personalized and tailored antioxidant Nano therapies related to a patient's genetic make-up, circulating biomarkers, and stage of disease. For example, a patient with a high oxidative stress profile (e.g., high levels of MDA or oxidized LDL) require more potent or multi-combination Nano-antioxidant regimens. Furthermore, the potential to integrate genomic and proteomic profiling will permit clinical staff to successful couple patient-specific (and translatable) Nano-carrier systems for the patient, providing maximal therapeutic benefits with minimal adverse reactions.

- **Combination therapies:**

An expectation of future antioxidant Nano carriers will be their capacity to co-deliver antioxidant therapies with concomitant and complementary therapeutics, as oxidative stress is unlikely (nearly impossible) to occur in isolation. Examples of future Nano carriers targeting antioxidants with concomitant therapeutic and/or regenerative components may include:

  - **Nitric oxide (NO):** Donors to restore endothelial function.
  - **Anti-inflammatory agents:** That block the vascular inflammatory cascade.
  - **Additional vectors for gene therapy:** Targeting redox-sensitive transcription factors (such as Nrf2). Any therapeutics which utilize a multiplexed or combination approach profiting from synergism toward a combination or multimodal therapeutic approach to treat the multifactorial pathology of cardiovascular disease provide greater advantages than a monotherapy approach. [61]

CONCLUSION

Oxidative stress serves as the leading cause which triggers and advances cardiovascular disease. The standard "antioxidant" treatments in clinical settings have proven to be ineffective yet the application of nanotechnology for delivering antioxidants will enhance their body distribution and tissue absorption and product stability. The toxic effects of nanotechnology-based antioxidant delivery systems need assessment in relation to current translational obstacles although their preclinical evidence shows strong potential. The smart Nano carrier platform will enable future medical applications through its use of combination therapies and personalized medicine and this development will transform cardiovascular drug delivery methods which will decrease worldwide cardiovascular disease impacts.

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Authors' Contributions

All authors contributed equally to the conception, design, writing, and finalization of this work. Each author was actively involved in literature review, data interpretation, manuscript preparation, and critical revision. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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