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# The Role of Free Radicals and Oxidative Stress in Chronic Diseases: A Comprehensive Review of Mechanisms and Therapeutic Interventions

Salih muvakit *
Department of Biology, Faculty of Arts and Sciences Gaziantep University, Turkey
* E-mail of the corresponding author: salihmukavit@gantep.edu.tr

**Abstract**
Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, plays a fundamental role in the onset and progression of numerous chronic diseases, including neurodegenerative, cardiovascular, metabolic, and oncological conditions. Although extensive research has elucidated the molecular mechanisms underlying redox homeostasis, therapeutic translation remains elusive. This comprehensive review examines current knowledge on the sources and biochemistry of free radicals, the cellular consequences of oxidative stress, endogenous and dietary antioxidant defense systems, and the clinical and nutritional interventions developed to modulate redox balance. It also examines emerging therapeutic strategies and research gaps within the field. Free radicals inflict significant damage on lipids, proteins, and nucleic acids, contributing to mitochondrial dysfunction and systemic inflammation. Endogenous defense systems such as superoxide dismutase, catalase, and glutathione peroxidase provide partial protection, while exogenous antioxidants, derived from diet or supplements, offer additional but context-dependent benefits. Clinical interventions show inconsistent outcomes due to variable bioavailability, dosing challenges, and inter-individual variability. Advances in omics-based technologies, AI-driven modeling, and redox-sensitive biomarkers present new avenues for targeted therapies. By elucidating the mechanistic underpinnings and therapeutic implications of oxidative stress, the present work aims to inform future research and contribute to the development of targeted antioxidant therapies to combat the chronic disease burden.

**Keywords:** Oxidative Stress; Free Radicals; Chronic Diseases; Antioxidant Defense Systems; Redox Biology; Therapeutic Interventions; Reactive Oxygen Species (ROS); Mechanisms of Damage; Clinical Trials; Disease Prevention.

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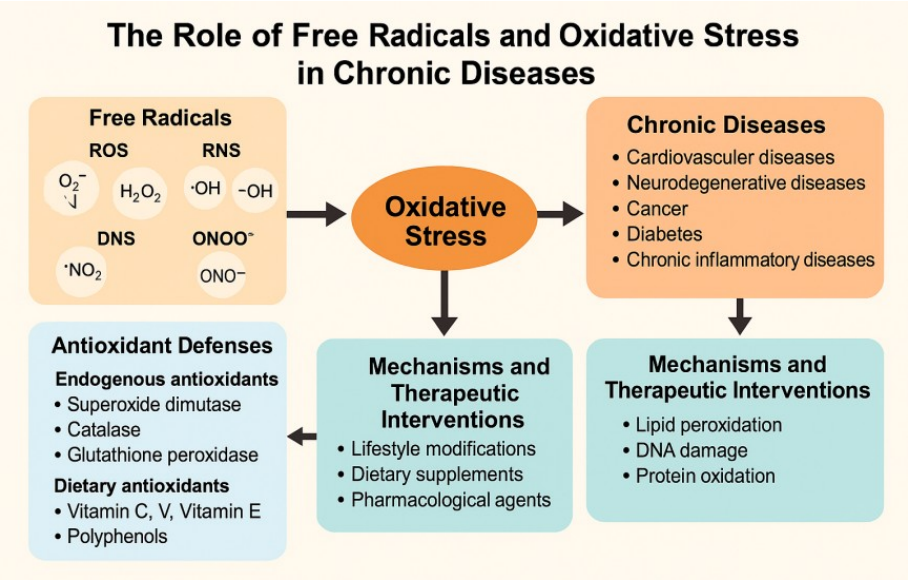


Graphical Abstract

## 1. Introduction

Free radicals, particularly reactive oxygen species (ROS) and reactive nitrogen species (RNS), are highly reactive molecules generated as natural byproducts of cellular metabolism. While they serve essential physiological roles such as in cell signaling, immune defense, and apoptosis, an excess of these species leads to a detrimental condition known as oxidative stress. Oxidative stress occurs when there is an imbalance between free radical production and the body's antioxidant defense mechanisms, resulting in molecular damage to lipids, proteins, and DNA (Di Meo & Venditti, 2020).

Recent decades have seen an explosion of research linking oxidative stress to the pathogenesis of various chronic diseases, including cardiovascular disease, diabetes mellitus, cancer, neurodegenerative disorders, and chronic kidney disease (Vona et al., 2019; Forman & Zhang, 2021; Chaudhary et al., 2023; Al-Madhagi & Masoud, 2024). These chronic conditions contribute significantly to global morbidity and mortality, making the investigation of their underlying mechanisms a critical priority in biomedical research. In fact, oxidative stress is now recognized not just as a byproduct of disease, but as a driver of pathological changes in tissues and organs.

From a biochemical perspective, ROS such as superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide ($H_2O_2$), and hydroxyl radical (•OH) are generated through mitochondrial respiration, enzymatic reactions (e.g., NADPH oxidases), and environmental exposures like pollution and radiation (Di Meo et al., 2020; Yang & Lian, 2020; Tumilaar et al., 2024). Under physiological conditions, antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) efficiently neutralize ROS. However, chronic exposure to oxidative stimuli overwhelms these defense systems, initiating cellular injury and chronic inflammation (Halliwell, 2024).

Importantly, oxidative stress is not an isolated phenomenon. It interacts with inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress to create a self-perpetuating cycle of cellular injury (Chandimali et al., 2025; Ebert et al., 2022). These interactions amplify oxidative damage and contribute to tissue dysfunction, organ failure, and systemic inflammation. For instance, in neurodegenerative diseases such as Alzheimer's and Parkinson's, ROS disrupt neuronal homeostasis and exacerbate protein aggregation and synaptic dysfunction (Tripathi et al., 2022).

Despite the extensive literature, a comprehensive understanding of the mechanisms by which oxidative stress contributes to chronic disease remains fragmented. Moreover, while antioxidant therapies have shown promise in preclinical studies, clinical trials have yielded inconsistent results, raising questions about their efficacy, bioavailability, and mechanistic targeting (Forman & Zhang, 2021; Halliwell, 2024). These inconsistencies highlight the need for a more nuanced understanding of redox biology and its interplay with disease pathogenesis.

Despite decades of research, antioxidant-based therapies have yielded mixed results in clinical trials, demonstrating the complexity of the mechanisms associated with oxidative stress and the need for more targeted, condition-specific interventions (Ali et al., 2020; Al-Madhagi et al., 2024). Therefore, a comprehensive understanding of the biology and molecular basis of oxidative stress in chronic diseases is imperative for the development of new diagnostic markers and therapeutic strategies. This review aims to provide an in-depth analysis of the biochemistry of free radicals, the mechanisms of oxidative damage, their involvement in major chronic diseases, the role of endogenous and exogenous antioxidant systems, clinical and nutritional interventions, and the emerging directions in redox biology and therapeutic innovation.

## 2. Sources and Biochemistry of Free Radicals and Oxidative Stress

Free radicals are atoms or molecules with unpaired electrons, which makes them highly reactive with cellular components such as DNA, proteins, and lipids. In biological systems, the most commonly studied free radicals include reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can be both beneficial and detrimental depending on their concentration and context (Pizzino et al., 2017; Di Meo & Venditti, 2020). As seen in Figure 2, oxidative stress results from an imbalance between reactive species and antioxidant defenses, leading to cellular damage and disease development. Their sources can be broadly classified as endogenous or exogenous.

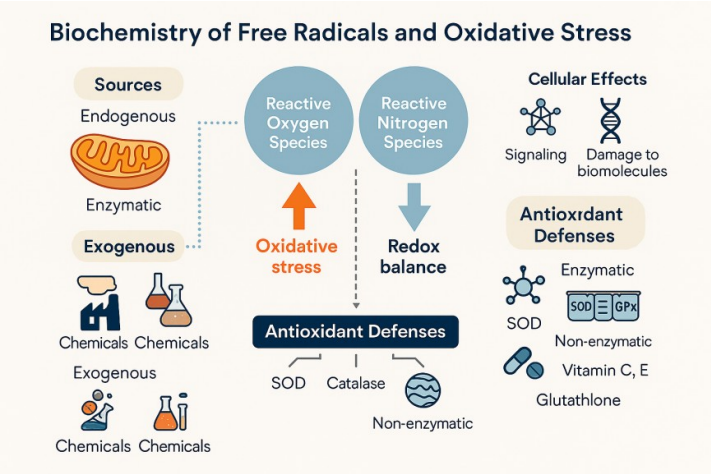


Figure 1. Biochemistry of Free Radicals and Oxidative Stress.

This figure shows the basic biochemical pathways of free radical production and oxidative stress. It depicts both endogenous (e.g., mitochondrial respiration, enzymatic reactions) and exogenous (e.g., pollutants, radiation, toxins) sources that lead to the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These species disrupt redox homeostasis, causing oxidative stress, which can damage DNA, proteins, and lipids. The figure also highlights antioxidant defense systems, including enzymatic antioxidants like superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and non-enzymatic antioxidants such as vitamins C and E, and glutathione. The balance between reactive species and antioxidant defenses is essential for cellular redox homeostasis, and its disruption is implicated in various chronic diseases (Tan et al., 2018; Vona et al., 2019).

### *2.1. Endogenous Sources*

Endogenous free radicals are primarily produced in the mitochondria during cellular respiration. The electron transport chain (ETC) is a major site for the leakage of electrons leading to the partial reduction of oxygen to form superoxide anion ($O_2^{\bullet -}$). Other enzymatic systems including NADPH oxidases (NOX), xanthine oxidase, nitric oxide synthase (NOS), and cytochrome P450 enzymes also contribute to ROS and RNS production (Di Meo et al., 2020; Halliwell, 2024; Yang & Lian, 2020).

During inflammation, activated macrophages and neutrophils release large quantities of ROS and RNS as part of the immune response. These include hypochlorous acid (HOCl), nitric oxide (NO), and peroxynitrite ($ONOO^-$), which contribute to microbial killing and oxidative damage in inflamed tissues (Forman & Zhang, 2021; Pizzino et al., 2017).

### *2.2. Exogenous Sources*

Exogenous sources of free radicals include ionizing radiation, ultraviolet (UV) light, environmental pollutants (e.g., ozone, heavy metals), cigarette smoke, alcohol consumption, and certain medications (García-Sánchez et al., 2020; Tan et al., 2018). These agents either directly generate radicals or upregulate intracellular oxidative pathways.

### *2.3. Key Biochemical Pathways and Intermediates*

Key biochemical ROS include:

- **Superoxide ($O_2^{\bullet -}$)**: Primarily generated in mitochondria; rapidly converted to hydrogen peroxide ($H_2O_2$) by superoxide dismutase.
- **Hydrogen peroxide ($H_2O_2$)**: A non-radical ROS that diffuses across membranes; detoxified by catalase and glutathione peroxidase.
- **Hydroxyl radical (•OH)**: The most reactive ROS; formed via Fenton and Haber-Weiss reactions involving $Fe^{2+}$ or $Cu^+$.
- **Nitric oxide (NO•)**: Produced by nitric oxide synthases; reacts with superoxide to form peroxynitrite (Ali et al., 2020).

These radicals initiate lipid peroxidation, protein carbonylation, and DNA strand breaks. The peroxidation of polyunsaturated fatty acids (PUFAs) leads to the formation of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which are widely used as oxidative stress biomarkers (Sánchez-Rodríguez et al., 2019).

### *2.4. Interplay Between Mitochondria and ROS Generation*

Mitochondria play a dual role: they are both a source and a target of ROS. Mitochondrial ROS production is implicated in the aging process and in the pathophysiology of chronic diseases. Dysfunctional mitochondria generate excessive ROS, leading to a vicious cycle of oxidative damage and further mitochondrial impairment (Sharma et al., 2019; Chandimali et al., 2025).

### *2.5 Regulatory Mechanisms and Redox Signaling*

Although often viewed as harmful, ROS at physiological concentrations function as secondary messengers in redox signaling pathways. For example, $H_2O_2$ modulates protein phosphorylation, gene expression, and transcription factors such as NF-κB, AP-1, and Nrf2 (Halliwell, 2024). It is thought to play a role in pathologies such as some cardiomyopathies, in which the cellular redox environment is excessively reduced (excess reducing equivalents) and normal ROS-dependent signaling is disrupted (Al-Madhagi & Masoud, 2024). However, persistent ROS elevation shifts signaling from adaptation to cytotoxicity.

An illustrative example of the importance of redox balance is evident in the context of physical exercise. Exercise sharply increases oxygen consumption and ROS production in muscles. Paradoxically, this spike in ROS during exercise serves as a key trigger for beneficial adaptations: it activates pathways that strengthen the body's antioxidant defenses and promote mitochondrial biogenesis, leading to improved endurance and metabolic health (Radak et al., 2009). Studies have shown that when individuals take high-dose antioxidant supplements (like vitamins C and E) during training, it can suppress these molecular signals; in effect, the supplements neutralize the ROS that would have acted as messengers for adaptation, thereby diminishing the exercise benefits (Ristow et al., 2009; Merry & Ristow, 2016; Ali et al., 2020). This phenomenon, called mitohormesis, suggests that a small amount of oxidative stress (as induced by exercise) is necessary to "train" the body's defenses and maintain health. It highlights that context is crucial: ROS can be "friends or foes" depending on the situation, and successful therapeutic intervention requires a nuanced approach rather than one-size-fits-all antioxidant use.

### *2.4. Oxidative Stress and Cellular Damage*

Oxidative stress arises when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates or repair the resulting damage. Persistent oxidative stress has been implicated in the pathophysiology of numerous chronic diseases due to its damaging effects on key cellular components. Below are the primary targets of oxidative stress and the mechanisms through which damage is induced.

Oxidative damage is not limited to a single organelle but affects multiple intracellular compartments. For instance, mitochondrial ROS production leads to a feedback loop of further oxidative stress and bioenergetic failure. Similarly, oxidative DNA damage in the nucleus contributes to aging and carcinogenesis. These cumulative effects across organelles are critical to understanding disease progression (Table 2) (Chandimali et al., 2025; Ebert et al., 2022; Phaniendra et al., 2015).

Table 2. Consequences of Oxidative Damage in Cellular Organelles

| Organelle | Oxidative Target(s) | Consequences of Damage |
|---|---|---|
| **Mitochondria** | mtDNA, ETC complexes, cardiolipin | Impaired ATP production, increased ROS, mitochondrial dysfunction, apoptosis |
| **Nucleus** | DNA bases (e.g., guanine), histones | DNA mutations, impaired transcription, genomic instability |
| **Endoplasmic Reticulum (ER)** | Protein folding enzymes, calcium channels | ER stress, unfolded protein response (UPR), calcium dysregulation |
| **Lysosomes** | Membrane lipids, lysosomal enzymes | Membrane rupture, release of proteolytic enzymes, cellular autolysis |
| **Plasma Membrane** | Phospholipids, membrane proteins | Loss of membrane integrity, altered cell signaling and transport |
| **Peroxisomes** | Oxidase enzymes, catalase | Altered lipid metabolism, accumulation of hydrogen peroxide, increased oxidative burden |

2.4.1. Lipid Peroxidation

Lipid peroxidation is one of the earliest and most studied consequences of oxidative stress, especially in biological membranes rich in polyunsaturated fatty acids (PUFAs). ROS, such as hydroxyl radicals (•OH), initiate the abstraction of hydrogen atoms from methylene groups in PUFAs, forming lipid radicals. These radicals react with molecular oxygen to form lipid peroxyl radicals, perpetuating a chain reaction that damages the structural integrity of membranes (Ayala et al., 2014). Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), secondary products of lipid peroxidation, are often measured as biomarkers of oxidative damage and are known to form adducts with proteins and DNA, amplifying cellular dysfunction (Vona et al., 2019; Schieber & Chandel, 2014; Sadiq, 2023).

Lipid peroxidation compromises membrane fluidity, alters membrane-bound enzyme activity, and promotes membrane leakage, particularly in mitochondrial and lysosomal membranes, thereby triggering apoptosis or necrosis (Sies, 2019). In neurodegenerative diseases such as Alzheimer's, elevated levels of lipid peroxidation products are frequently observed in affected brain regions (Butterfield & Halliwell, 2019). Similarly, Vona et al., (2019) reported a strong association between 4-HNE levels and endothelial dysfunction in cardiovascular diseases.

2.4.2. Protein Oxidation and Carbonylation

Proteins are significant targets of ROS-induced damage due to their abundance and functional diversity. ROS modify amino acid side chains, form protein-protein cross-links, and fragment peptide backbones. The introduction of carbonyl groups into proteins, commonly referred to as protein carbonylation, is a hallmark of oxidative protein damage (Dalle-Donne et al., 2003).

Carbonylated proteins typically exhibit altered structure and function, lose enzymatic activity, and may aggregate or become targeted for degradation via the proteasome system (Chaudhary et al., 2023). These damaged proteins accumulate in cells, particularly under conditions where the proteasomal degradation is impaired, such as during aging or in neurodegenerative diseases (Stadtman & Levine, 2003).

Moreover, oxidative modifications can alter receptor-ligand binding, disrupt signal transduction, and impair cytoskeletal functions, which further accelerate cellular senescence and inflammation (Ebert et al., 2022). Specific markers such as nitrotyrosine and advanced oxidation protein products (AOPPs) are used to assess oxidative protein damage in clinical settings (Pizzino et al., 2017).

2.4.3. DNA and RNA Damage

Nucleic acids are also vulnerable to ROS attack, particularly at guanine bases, leading to the formation of 8-oxo-2'-deoxyguanosine (8-oxo-dG), a widely used biomarker of oxidative DNA damage (Cooke et al., 2003). ROS can induce single- and double-strand breaks, base modifications, and cross-linking with proteins, potentially leading to mutagenesis, carcinogenesis, and cell death (Halliwell, 2024).

RNA, although less studied than DNA in this context, is more susceptible to oxidative damage due to its single-stranded nature and lack of protective histones. Oxidized RNA impairs protein synthesis and has been associated with age-related diseases such as Parkinson's and Alzheimer's (Zhang & Bian, 2021). Additionally, mitochondrial DNA (mtDNA) is highly susceptible due to its proximity to the electron transport chain and lack of protective proteins, and mutations in mtDNA are frequently observed in aging and cancerous tissues (Yang & Lian, 2020).

Failure of DNA repair mechanisms in response to oxidative lesions can lead to genomic instability and apoptosis, linking oxidative DNA damage to the onset and progression of chronic diseases such as cardiovascular disease, diabetes, and cancer (Forman & Zhang, 2021).

#### 2.4.4. Mitochondrial Dysfunction

Mitochondria are both a source and target of oxidative stress. Under pathological conditions, excessive ROS production from the electron transport chain damages mitochondrial components including lipids, proteins, and mtDNA. This results in mitochondrial membrane potential loss, impaired oxidative phosphorylation, and opening of the mitochondrial permeability transition pore (mPTP), which facilitates cytochrome c release and triggers apoptosis (Schieber & Chandel, 2014).

Oxidative stress-induced mitochondrial dysfunction impairs ATP production, increases ROS leakage, and disrupts calcium homeostasis, creating a vicious cycle of cellular injury (Tripathi et al., 2022). Mitochondrial impairment is a central feature in metabolic syndrome, neurodegeneration, and myocardial infarction (Di Meo et al., 2020). Therapeutic approaches targeting mitochondria-specific antioxidants like MitoQ and SkQ1 are being actively explored to restore mitochondrial function and reduce systemic oxidative damage (García-Sánchez et al., 2020).

## 3. Oxidative Stress and Its Role in Chronic Diseases

Oxidative stress is fundamentally defined as an imbalance between the production of reactive species and the capacity of antioxidant defenses, tipping toward an excess of oxidants (Preiser, 2012). Under oxidative stress, the surplus ROS and RNS attack all classes of biomolecules, leading to cumulative cellular damage. Key molecular targets include lipids (especially the polyunsaturated fatty acids in cell membranes), proteins (particularly cysteine and methionine residues, iron-sulfur cluster-containing enzymes, and other redox-sensitive sites), and nucleic acids (DNA and RNA). Oxidation of lipids triggers chain reactions of lipid peroxidation in membranes, yielding reactive aldehydes (like malondialdehyde and 4-hydroxynonenal) that can further damage proteins and DNA. Oxidative modification of proteins can result in enzyme inactivation, altered structural proteins, and tagging of proteins for degradation (Martemucci et al., 2022). This section explores the evidence linking oxidative stress with several major chronic diseases. As shown in Figure 3, it involves diverse mechanisms, such as endothelial dysfunction in cardiovascular disease, mitochondrial impairment in neurodegenerative disorders, and DNA damage leading to oncogenesis.

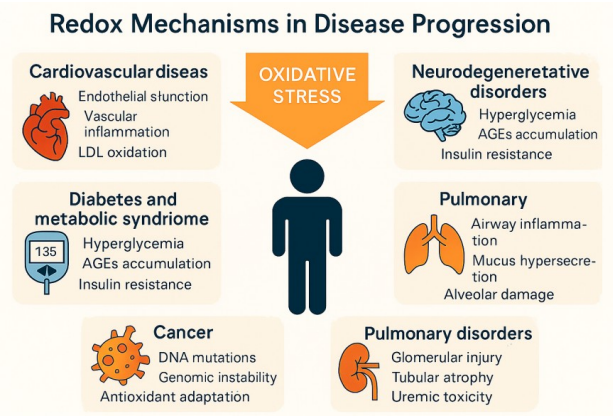


Figure 3. Redox Mechanisms in Disease Progression.

This figure shows how oxidative stress acts as a central trigger in the pathogenesis of major chronic diseases. The figure places "Oxidative Stress" at the center, showing directional pathways leading to cardiovascular disease (via LDL oxidation and endothelial dysfunction), neurodegenerative disorders (via β-amyloid accumulation and insulin resistance), diabetes (via insulin resistance and AGE accumulation), cancer (via DNA mutations and genomic instability), chronic kidney disease (via glomerular and tubular damage), and pulmonary disorders (via airway inflammation and alveolar injury).

### *3.1. Cardiovascular Diseases*

In cardiovascular pathology, oxidative stress plays a key role in endothelial dysfunction, atherogenesis, and ischemia-reperfusion injury. Oxidized low-density lipoprotein (oxLDL) induces endothelial cell apoptosis and promotes foam cell formation, accelerating atherosclerosis (Forman & Zhang, 2021). ROS also decrease nitric oxide bioavailability, impairing vasodilation and promoting hypertension (Pizzino et al., 2017). Moreover, NADPH oxidase and mitochondrial dysfunction are critical sources of ROS in hypertensive and ischemic heart diseases (Vona et al., 2019; Di Meo & Venditti, 2020). Furthermore, myocardial infarction and heart failure are associated with elevated oxidative stress and mitochondrial damage.

### *3.2. Diabetes Mellitus*

Hyperglycemia-induced ROS production causes β-cell dysfunction, insulin resistance, and microvascular damage in diabetes. ROS activate pathways like polyol, hexosamine, and protein kinase C, leading to oxidative damage and chronic inflammation. Mitochondrial dysfunction is also evident in diabetic tissues, with a shift in redox balance contributing to disease complications such as nephropathy, retinopathy, and neuropathy (Yang & Lian, 2020; Di Meo et al., 2020).

### *3.3. Neurodegenerative Disorders*

Oxidative stress is heavily implicated in the pathophysiology of Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). In AD, β-amyloid peptides increase ROS production and impair mitochondrial function. Similarly, in PD, dopaminergic neurons are particularly vulnerable to oxidative injury due to dopamine auto-oxidation and impaired antioxidant defense (Tripathi et al., 2022; Sharma et al., 2019). Chronic oxidative stress exacerbates neuroinflammation and protein misfolding in these conditions.

### *3.4. Cancer*

ROS play a dual role in cancer. At low levels, they promote cell proliferation and survival via redox-sensitive signaling pathways. However, chronic oxidative stress induces DNA mutations, genomic instability, and epigenetic alterations, thereby initiating the carcinogenesis process. Elevated ROS also promotes angiogenesis and metastasis in established tumors (Halliwell, 2024; Tumilaar et al., 2024; Chandimali et al., 2025). Oxidative DNA lesions such as 8-OHdG are considered early biomarkers of carcinogenic transformation.

### *3.5. Chronic Kidney Disease*

In chronic kidney disease (CKD), oxidative stress contributes to glomerular injury, tubular apoptosis, and fibrosis. Renal ischemia and uremic toxins increase ROS levels, while antioxidant enzymes are downregulated. This redox imbalance worsens with disease progression and correlates with cardiovascular comorbidities (Chaudhary et al., 2023; García-Sánchez et al., 2020).

### *3.6. Pulmonary Disorders*

Chronic obstructive pulmonary disease (COPD), asthma, and idiopathic pulmonary fibrosis (IPF) involve oxidative stress-mediated epithelial injury and inflammation. Environmental oxidants such as cigarette smoke and air pollution are primary inducers of ROS in the lungs (Tan et al., 2018). Oxidative damage to surfactant proteins and DNA contributes to alveolar collapse and fibrosis.

### *3.7. Aging and Frailty*

Aging is characterized by a progressive decline in physiological function and increased susceptibility to diseases, many of which are influenced by oxidative stress. Mitochondrial ROS production increases with age, leading to cellular senescence, telomere shortening, and impaired proteostasis (Ebert et al., 2022; Halliwell, 2024). The "oxidative stress theory of aging" suggests that cumulative oxidative damage drives the aging process and the onset of age-related diseases. Together, these insights underscore oxidative stress as a unifying pathological mechanism across chronic diseases, offering opportunities for targeted antioxidant therapies and redox-based diagnostics.

## 4. Antioxidant Defense Mechanisms

Oxidative stress arises when the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) surpasses the capacity of the biological antioxidant defense systems, leading to cellular and molecular damage. To combat this imbalance, organisms have evolved complex antioxidant defense mechanisms that function at multiple levels: prevention, interception, and repair of oxidative damage.

### *4.1. Enzymatic Antioxidants*

Endogenous antioxidant enzymes represent the first line of defense against oxidative stress. Superoxide dismutase (SOD), for instance, catalyzes the dismutation of superoxide radicals into less reactive hydrogen peroxide, which is then decomposed by catalase or glutathione peroxidase (Table 3). This coordinated enzymatic cascade is vital in preventing cellular dysfunction and disease progression (Yang & Lian, 2020; Forman & Zhang, 2021; Halliwell, 2024).

Table 3. Key Endogenous Antioxidant Enzymes and Their Mechanisms

| Enzyme | Mechanism of Action | Targeted Reactive Species | Cellular Location |
|---|---|---|---|
| **Superoxide Dismutase (SOD)** | Converts superoxide radicals ($O_2^{\bullet-}$) into hydrogen peroxide ($H_2O_2$) | Superoxide ($O_2^{\bullet-}$) | Cytosol (SOD1), mitochondria (SOD2), extracellular space (SOD3) |
| **Catalase (CAT)** | Breaks down hydrogen peroxide into water and oxygen | Hydrogen peroxide ($H_2O_2$) | Peroxisomes |
| **Glutathione Peroxidase (GPx)** | Reduces hydrogen peroxide and lipid hydroperoxides using glutathione | $H_2O_2$, lipid peroxides | Cytosol, mitochondria |
| **Glutathione Reductase (GR)** | Regenerates reduced glutathione (GSH) from oxidized glutathione (GSSG) | Indirect ROS scavenging | Cytosol, mitochondria |
| **Thioredoxin Reductase (TrxR)** | Maintains thioredoxin in its reduced form, enabling detoxification of peroxides | Peroxides, indirectly ROS | Nucleus, cytosol, mitochondria |
| **Peroxiredoxins (Prx)** | Catalyze reduction of hydrogen peroxide, organic peroxides, and peroxynitrite | $H_2O_2$, $ONOO^-$ | Cytosol, mitochondria, nuc |

The first line of defense consists of antioxidant enzymes that neutralize ROS before they inflict cellular damage. These include:

**Superoxide Dismutases (SODs):** SOD catalyzes the dismutation of superoxide anion ($O_2^{-\bullet}$) into hydrogen peroxide ($H_2O_2$) and molecular oxygen. Three isoforms exist in humans: cytosolic Cu/Zn-SOD (SOD1), mitochondrial Mn-SOD (SOD2), and extracellular SOD (SOD3). Mutations or downregulation in SOD enzymes have been linked to neurodegeneration and aging-related disorders. (Phaniendra et al., 2015; Di Meo et al., 2016; Ali et al., 2020).

**Catalase (CAT):** This enzyme, concentrated in peroxisomes, converts hydrogen peroxide into water and oxygen. Since $H_2O_2$ can diffuse through membranes and generate hydroxyl radicals (via Fenton reactions with $Fe^{2+}$), eliminating $H_2O_2$ is crucial. Catalase works at high concentrations of $H_2O_2$, complementing the activity of peroxidases (Sharma, 2014).

**Glutathione Peroxidase (GPx):** A selenium-dependent enzyme that reduces lipid hydroperoxides and $H_2O_2$ using glutathione (GSH) as a substrate. GPx1 is ubiquitous, whereas GPx4 plays a specific role in regulating lipid peroxidation and ferroptosis (Halliwell, 2024; Tumilaar et al., 2024).

**Peroxiredoxins (Prx) and Thioredoxins (Trx):** These work as redox regulators, detoxifying peroxides and maintaining the redox state of proteins. The Trx system also modulates transcription factors and apoptosis pathways (Chandimali et al., 2025).

**Supporting proteins:** There are also metal-binding proteins like ferritin and transferrin that sequester iron, and ceruloplasmin that binds copper, preventing these transition metals from catalyzing free radical reactions (such as Fenton chemistry). Similarly, haptoglobin binds free hemoglobin (which contains redox-active iron) and metallothioneins bind heavy metals, all acting indirectly as antioxidant safeguards (Martemucci et al., 2022).

Enzyme expression is tightly regulated by redox-sensitive transcription factors, primarily Nrf2 (Nuclear factor erythroid 2–related factor 2), which upregulates a battery of antioxidant genes upon oxidative challenge (Forman & Zhang, 2021).

### *4.2. Non-Enzymatic Antioxidants*

Non-enzymatic antioxidants function by scavenging free radicals, chelating transition metals, and regenerating oxidized molecules. These include:

**Glutathione (GSH):** A tripeptide composed of glutamate, cysteine, and glycine. GSH is central to intracellular antioxidant defense, detoxification, and maintenance of protein thiol groups. Glutathione can likewise regenerate oxidized forms of other antioxidants, and enzymes like glutathione reductase ensure a steady supply of reduced glutathione using NADPH (Tan et al., 2018).

**Vitamin E** (tocopherols and tocotrienols): These are fat-soluble vitamins primarily located in cell membranes and lipoproteins. α-Tocopherol, the most active form in humans, can donate a hydrogen atom to lipid radicals, terminating lipid peroxidation chain reactions (Martemucci et al., 2022). In doing so, vitamin E becomes a stable radical that can be regenerated by other antioxidants like vitamin C.

**Vitamin C** (ascorbic acid): A water-soluble vitamin that directly scavenges a variety of reactive oxygen and nitrogen species (e.g. hydroxyl radical, superoxide, peroxynitrite) and can also regenerate vitamin E from its oxidized form (Martemucci et al., 2022). Vitamin C operates in aqueous environments like the cytosol and blood plasma.

**Carotenoids** (β-carotene, lycopene, lutein, etc.): These pigments found in fruits and vegetables can quench singlet oxygen and scavenge peroxyl radicals. β-carotene is a precursor of vitamin A (retinol); in the context of lung tissue, however, high-dose supplementation in smokers was unexpectedly found to increase lung cancer risk, as will be discussed later (Bates et al., 2024).

**Coenzyme Q10 (ubiquinone):** Functions in the mitochondrial respiratory chain and acts as an antioxidant by reducing lipid peroxidation (Di Meo & Venditti, 2020).

**Polyphenols and Flavonoids:** A broad class of plant-derived compounds (e.g., quercetin, resveratrol, catechins, curcumin) known for their antioxidant activities in vitro. They can donate electrons/hydrogens to neutralize radicals and chelate metal ions. Polyphenols are abundant in fruits, vegetables, tea, coffee, wine, and cocoa, and collectively they contribute significantly to the antioxidant capacity of the diet (Martemucci et al., 2022).

**Polyphenols, flavonoids, and carotenoids:** Plant-derived compounds with direct radical-scavenging activity, metal chelation ability, and signaling functions (García-Caparrós et al., 2021; Yang & Lian, 2020).

**Minerals and Trace Elements:** Certain minerals support antioxidant enzyme function, notably selenium (required for glutathione peroxidase and thioredoxin reductase), zinc and copper (both needed for SOD1, the cytosolic SOD enzyme), and manganese (required for mitochondrial SOD2) (Martemucci et al., 2022). A diet deficient in these trace elements can weaken enzymatic antioxidant defenses. For example, selenium deficiency can compromise GPx activity, and low zinc can reduce SOD function.

The synergy between enzymatic and non-enzymatic systems ensures dynamic and adaptive control over redox balance under physiological and pathological conditions.

### *4.3. Mitochondrial Antioxidant Systems*

Mitochondria are both a major source and target of ROS. To protect mitochondrial integrity, cells deploy specific antioxidant defenses:

- **Mn-SOD (SOD2):** Protects mitochondrial DNA and enzymes from superoxide damage.
- **Mitochondrial GPx and Prx isoforms:** Detoxify $H_2O_2$ generated by electron transport chain (ETC) leakage.
- **Uncoupling Proteins (UCPs):** These proteins reduce membrane potential, limiting superoxide generation by ETC complexes (Ebert et al., 2022).

Mitochondrial antioxidant systems are regulated via retrograde signaling pathways that communicate redox imbalance to the nucleus and modulate gene expression accordingly.

### *4.4. Regulation via Nrf2 and Other Transcription Factors*

The Keap1-Nrf2-ARE pathway serves as the master regulatory system for antioxidant gene expression. Under basal conditions, Nrf2 is bound to Keap1 and targeted for degradation. Upon oxidative stress, Keap1 is oxidized, freeing Nrf2 to translocate to the nucleus, where it binds ARE and activates genes such as HO-1, NQO1, GPx, and GCLC (Forman & Zhang, 2021).

Other transcription factors involved include:

- **NF-κB:** Often activated in parallel to oxidative stress, NF-κB modulates immune and inflammatory responses.
- **AP-1 and HIF-1α:** Regulate genes involved in cellular survival, metabolism, and adaptation to hypoxia (Halliwell, 2024).
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### *4.5. Redundancy, Crosstalk, and Adaptive Remodeling*

Antioxidant systems exhibit functional redundancy and cross-regulation. For instance:

- GSH can regenerate oxidized Vitamin C, which in turn recycles oxidized Vitamin E.
- Trx and GSH systems can compensate for each other under certain conditions.
- Epigenetic mechanisms and circadian rhythms also modulate antioxidant capacity (Chaudhary et al., 2023).

These interlinked pathways provide resilience against oxidative insults and are often dysregulated in disease states such as cancer, diabetes, neurodegeneration, and cardiovascular disorders.

## 5. Clinical and Nutritional Interventions Targeting Oxidative Stress

Oxidative stress is a central factor in the onset and progression of chronic diseases such as cardiovascular disease, diabetes, neurodegenerative disorders, and cancer. Therefore, targeting oxidative stress through clinical and nutritional interventions has gained considerable interest. Both pharmacological therapies and dietary strategies aim to restore redox balance by enhancing endogenous antioxidant defenses or by direct scavenging of reactive oxygen species (ROS). The Figure 5 infographic summarizes the current therapeutic and nutritional strategies to counter oxidative stress, a major contributor to chronic disease pathogenesis.

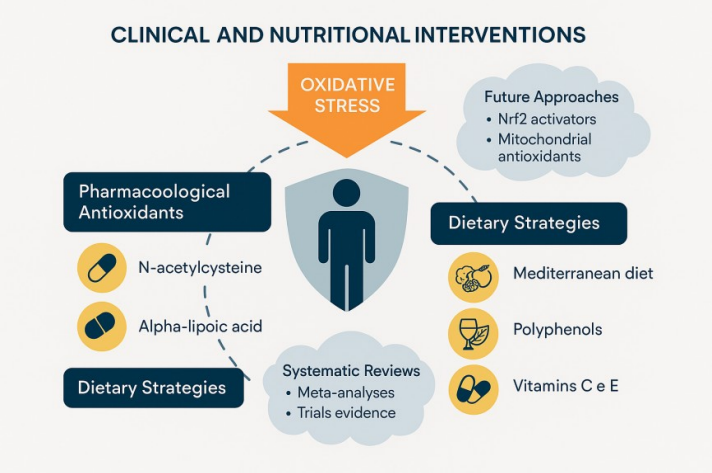


Figure 5. Overview of clinical and nutritional interventions targeting oxidative stress.

This infographic provides a comprehensive visual summary of current and emerging strategies aimed at mitigating oxidative stress through clinical and nutritional interventions. At the core, oxidative stress is represented as a central pathological trigger impacting human health. The strategies to counteract its effects are categorized into four domains: This figure encapsulates the multifaceted nature

### *5.1. Pharmacological Antioxidant Therapies*

Pharmacological interventions often include supplementation with exogenous antioxidants or agents that induce endogenous antioxidant enzyme expression. Some commonly studied compounds include:

**Vitamin C and E** supplementation, particularly in high-risk cardiovascular patients, has produced inconsistent results in randomized controlled trials. While their role as ROS scavengers is established, long-term supplementation did not yield significant improvements in large trials such as HOPE (Sadiq, 2023; Halliwell, 2024). As Firuzi et al. (2011) aptly commented, after many well-known antioxidants (particularly vitamins) failed to show benefit in clinical trials, it prompted the realization that we might have been focusing on the "wrong" antioxidants or approaches.

**Coenzyme Q10 (CoQ10)**, a mitochondrial cofactor, has antioxidative properties by directly reducing lipid peroxidation and supporting electron transport. CoQ10 supplementation has improved endothelial function in cardiovascular diseases and reduced fatigue in fibromyalgia (Saini, 2011; Littarru & Tiano, 2007).

**N-acetylcysteine (NAC),** replenishes intracellular glutathione (GSH) levels and has shown efficacy in treating chronic obstructive pulmonary disease (COPD), liver toxicity, and psychiatric disorders (Rushworth & Megson, 2014; Dekhuijzen, 2004).

**Alpha-lipoic acid (ALA),** regenerates other antioxidants and acts as a metal chelator. It is used in diabetic neuropathy and neurodegenerative conditions (Ghibu et al., 2009).

**Melatonin** and its analogs have shown neuroprotective and cardioprotective antioxidant effects, acting both directly and through receptor-mediated signaling pathways (Forman & Zhang, 2021; Halliwell, 2024).

**Edaravone,** a radical scavenger approved for amyotrophic lateral sclerosis (ALS), which reduces oxidative neuronal injury (Yoshino & Kimura, 2006).

However, long-term use of pharmacological antioxidants has shown mixed clinical outcomes. Some trials report limited efficacy or paradoxical pro-oxidant effects at high doses, indicating that antioxidant therapy must be personalized and disease-specific (Forman & Zhang, 2021; Halliwell, 2024).

### *5.2. Dietary Antioxidants and Functional Foods*

Nutritional interventions have gained significant attention as adjunct strategies for managing oxidative stress in chronic diseases. A wide range of dietary antioxidants, including vitamins, minerals, and polyphenols, contribute

to neutralizing ROS and enhancing endogenous antioxidant defense systems. Table 4 summarizes some of the most well-characterized dietary antioxidants, their natural sources, primary biological effects, and molecular mechanisms of action.

Table 4. Dietary Antioxidants and Their Primary Effects.

| **Dietary Antioxidant** | **Main Natural Sources** | **Primary Biological Effects** | **Mechanism of Action** |
|---|---|---|---|
| Vitamin C (Ascorbic Acid) | Citrus fruits, berries, peppers | Regeneration of other antioxidants, immune support | Direct ROS scavenging, regenerates vitamin E |
| Vitamin E (Tocopherols & Tocotrienols) | Nuts, seeds, vegetable oils | Protects membrane lipids from peroxidation | Inhibits lipid peroxidation by stabilizing membrane phospholipids |
| Carotenoids (e.g., β-Carotene, Lycopene) | Carrots, tomatoes, leafy greens | Protects against oxidative damage and photooxidation | Quenches singlet oxygen and peroxyl radicals |
| Polyphenols (e.g., Flavonoids, Resveratrol) | Tea, red wine, cocoa, berries | Anti-inflammatory, cardioprotective, neuroprotective | Modulates signaling pathways, chelates metal ions |
| Selenium | Brazil nuts, seafood, whole grains | Supports antioxidant enzyme activities | Cofactor for glutathione peroxidase (GPx) |
| Zinc | Meat, legumes, dairy | Immune function, supports antioxidant enzymes | Cofactor for SOD, stabilizes membranes |
| Coenzyme Q10 (Ubiquinone) | Fatty fish, organ meats, whole grains | Mitochondrial support, cardiovascular protection | Electron transport, regenerates vitamin E |
| Curcumin | Turmeric | Anti-inflammatory, anticancer, antioxidant | Inhibits ROS-generating enzymes, induces antioxidant genes |

The inclusion of antioxidant-rich foods such as citrus fruits, leafy greens, nuts, and seeds has been linked to reduced biomarkers of oxidative damage and inflammation (Halliwell, 2024; García-Caparrós et al., 2021). These compounds not only scavenge free radicals but also modulate gene expression and signaling pathways related to redox balance.

The Mediterranean diet, characterized by high intake of fruits, vegetables, whole grains, and olive oil, has been associated with lower incidence of cardiovascular and neurodegenerative disorders (Delgado-Lista et al., 2016). Its polyphenol-rich content modulates oxidative signaling, reduces inflammation, and improves endothelial function (Ebert et al., 2022).

Foods high in polyphenols (including berries, green tea, turmeric, and dark chocolate) have shown antioxidant, anti-inflammatory, and neuroprotective effects. Compounds such as resveratrol (grape), curcumin (turmeric), quercetin (onion), and epigallocatechin gallate (green tea) regulate NF-κB and Nrf2 pathways and have therapeutic importance in metabolic syndrome and Alzheimer's disease and even act as gene regulators (Hewlings & Kalman, 2017; Salehi et al., 2019; Tripathi et al., 2022; Chaudhary et al., 2023).

Omega-3 fatty acids, such as EPA and DHA, reduce lipid peroxidation, stabilize mitochondrial membranes, and modulate redox-sensitive transcription factors (Broome et al., 2024). Their anti-inflammatory properties contribute to cardiovascular and neurological benefits.

Functional foods such as olive oil, berries, dark chocolate, red wine, and nuts are rich in polyphenols and have demonstrated ROS-lowering effects and vascular protection. Moreover, functional foods enriched with probiotics and prebiotics can also restore gut redox balance, influencing systemic oxidative markers via gut–brain and gut–liver axes (García-Caparrós et al., 2021).

### *5.3. Personalized and Combined Therapies*

Recent research emphasizes the importance of personalized antioxidant therapy tailored to genetic background, redox status, and disease phenotype:

- Polymorphisms in SOD2, GPx1, and NQO1 genes influence antioxidant enzyme efficiency and patient response to antioxidant interventions (Ebert et al., 2022).
- Combining pharmacologic agents with dietary antioxidants offers synergistic effects, e.g., vitamin E + statins, or curcumin + CoQ10 in cardiometabolic disorders (Forman & Zhang, 2021). Some studies suggest that a mix of dietary-derived antioxidants can have synergistic effects, which is already somewhat validated by the success of diets versus single supplements (Al-Madhagi & Masoud, 2024).
- There are a variety of biomarkers (e.g., lipid peroxidation products like MDA, protein carbonyl levels, 8-oxo-2′-deoxyguanosine in DNA) that can indicate oxidative damage burden, and assays (like total antioxidant capacity, glutathione levels, etc.) to gauge antioxidant status (Martemucci et al., 2022). Integration of oxidative stress biomarkers in clinical practice aids in treatment monitoring and stratification.
- Use of antioxidant-loaded nanoparticles and targeted drug delivery systems are under investigation to overcome bioavailability issues (Stevanović & Filipović 2024).
-

*5.4. Future Perspectives and Limitations*

Despite promising preclinical and early clinical results, several challenges remain:

- Low bioavailability, short half-lives, and poor tissue distribution limit the efficacy of many antioxidants.
- Over-supplementation risks exist, including interference with redox-sensitive signaling and potential pro-oxidant effects.
- Heterogeneous trial designs, varying dosages, and inconsistent endpoints hinder meta-analytical conclusions (Siti et al., 2015).

Going forward, strategies such as Nrf2 activators, multi-omics-based personalization, and clinical integration of oxidative stress markers will be pivotal in advancing antioxidant-based therapies.

## 6. Discussion and Perspective

*6.1. Synthesis of Key Findings and Conceptual Integration*

Reactive oxygen species (ROS) and oxidative stress have emerged as central mechanisms in the pathogenesis of numerous chronic diseases, including neurodegenerative disorders, cardiovascular pathologies, metabolic syndrome, and cancer. This review has highlighted the intricate biochemical pathways involved in ROS generation and detoxification, the role of endogenous and dietary antioxidants, and the therapeutic strategies aimed at modulating redox balance. Collectively, the data underscore that while antioxidants hold significant promise in mitigating oxidative stress, their clinical translation remains inconsistent and context-dependent (Forman & Zhang, 2021; Halliwell, 2024).

However, in many other chronic diseases, antioxidant strategies have struggled to show clear benefits. Part of the challenge is that reactive species also play essential roles in normal signaling and defense responses. The body maintains a redox balance where ROS are kept at moderate levels; enough to fulfill useful functions but not so high as to cause damage (Poljsak et al., 2013). Think of a seesaw, with one side representing oxidant production and the other representing antioxidant defenses. Under healthy conditions, this seesaw stays balanced (or fluctuates within a range), allowing ROS to act as signaling molecules (for example, low levels of ROS stabilize and activate certain transcription factors like Nrf2 that trigger adaptive antioxidant responses) without causing oxidative harm (Auten, & Davis, 2009).

*6.2. Persistent Research Gaps*

Despite decades of investigation, several research gaps persist:

- **Lack of Clinical Translation:** Many antioxidant compounds that show efficacy in vitro fail in clinical trials, likely due to poor bioavailability, metabolism, and off-target effects (Chaudhary et al., 2023; Ebert et al., 2022).
- **Dosing and Kinetics:** Optimal dosing regimens for various antioxidants remain unclear. Some compounds display biphasic effects, acting as antioxidants at low concentrations and as pro-oxidants at high doses (Halliwell, 2024).

- **Individual Variability:** Genetic polymorphisms in antioxidant enzymes (e.g., SOD2, GPx) significantly alter therapeutic efficacy, but few clinical trials account for such differences (Phaniendra et al., 2015).
- **Synergistic or Antagonistic Interactions:** The interactive effects of multiple antioxidants or their combination with conventional therapies are insufficiently studied.

### *6.3. Methodological and Theoretical Challenges*

One of the major obstacles in oxidative stress research is the lack of standardized biomarkers. Currently used indicators such as malondialdehyde (MDA) or 8-OHdG suffer from variability and lack disease specificity (Tripathi et al., 2022). Additionally:

- **Pro-Oxidant Effects of Antioxidants:** Several compounds, including vitamin C and E, have demonstrated pro-oxidant activity under certain conditions, complicating therapeutic outcomes (Pizzino et al., 2017).
- **Inadequate Modeling Systems:** Animal models often fail to recapitulate the complexity of human redox biology, and many findings do not translate to human pathophysiology (Yang & Lian, 2020).

### *6.4. Future Directions in Redox Research*

- **Multi-Omics and Systems Biology Integration:** Combining genomics, transcriptomics, proteomics, and metabolomics offers a promising way to capture the complexity of redox regulation. These approaches can identify novel redox-regulated pathways and potential drug targets (García-Caparrós et al., 2021).
- **Artificial Intelligence in Redox Therapeutics:** Machine learning models can help stratify patients based on oxidative stress profiles and predict responses to antioxidant therapy. Early trials have shown promise in oncology and neurodegeneration.
- **Personalized Redox Medicine:** Integration of personal genetic profiles, dietary patterns, and lifestyle factors can pave the way for personalized antioxidant therapies, reducing the one-size-fits-all limitations of current approaches (Chandimali et al., 2025).

### *6.5. Proposed Conceptual Framework: Redox-Informed Personalized Therapeutics*

We propose a model integrating individual redox status, genetic predisposition, microbiome composition, and dietary habits to guide tailored interventions. This model aligns with precision medicine initiatives and provides a framework for developing next-generation antioxidants.

### *6.6. Public Health and Policy Implications*

Given the global burden of chronic diseases, public health strategies should promote dietary patterns rich in natural antioxidants (e.g., Mediterranean diet), regulate the use of antioxidant supplements, and educate healthcare providers about the nuanced role of oxidative stress.

## 7. Conclusion

Oxidative stress, driven by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, plays a pivotal role in the etiology and progression of numerous chronic diseases, including neurodegenerative, cardiovascular, metabolic, and neoplastic disorders. This review has synthesized the complex interplay between free radicals, oxidative damage to biomolecules, and the protective role of both endogenous and exogenous antioxidants. Despite substantial advances in our molecular understanding of redox biology, translating these insights into effective clinical interventions remains a significant challenge.

Therapeutic approaches targeting oxidative stress are complicated by diverse factors such as poor bioavailability, dose-dependent pro-oxidant activity, individual genetic variability, and the lack of standardized redox biomarkers. Current evidence suggests that antioxidant therapies are most effective when integrated into personalized medicine frameworks, considering individual redox profiles, lifestyle, and dietary patterns.

The use of systems biology, multi-omics technologies, and artificial intelligence is paving the way for redox-informed precision medicine, where antioxidant interventions are tailored to specific disease mechanisms and patient characteristics. Furthermore, dietary strategies emphasizing natural antioxidant intake, such as

polyphenol-rich foods and phytochemicals, represent a promising, low-risk complement to pharmacological therapies.

In conclusion, while the promise of antioxidant-based therapeutics remains substantial, its realization depends on overcoming methodological limitations, refining clinical trial design, and embracing interdisciplinary strategies. Advancing this field requires not only mechanistic research but also integrative frameworks that align basic science, clinical application, and public health policy. Only through such a comprehensive approach can the full therapeutic potential of antioxidants in combating oxidative stress and chronic disease be realized.

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