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Review

Oxidative Stress Fundamentals: Unraveling the Pathophysiological Role of Redox Imbalance in Non-Communicable Diseases

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Abstract

Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and the antioxidant defense system, plays a central role in the pathophysiology of numerous diseases, including cardiovascular, neurodegenerative, and inflammatory disorders. This review explores the biochemical mechanisms of ROS-induced damage to lipids, proteins, cholesterol, and DNA, and analyzes both endogenous (enzymatic and non-enzymatic) and exogenous (nutritional) antioxidant systems that counteract oxidative damage. Key enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, alongside dietary antioxidants like vitamins C and E, polyphenols, and carotenoids, are highlighted for their protective roles. The dual antioxidant/pro-oxidant behavior of these compounds under varying physiological conditions is discussed. Furthermore, this paper reviews the cellular repair systems activated in response to oxidative injury and the biomarkers used to assess oxidative stress in clinical settings. Special attention is given to the implications of oxidative stress in cardiovascular and autoimmune diseases and the potential of antioxidant strategies in disease prevention and therapy. The findings underscore the importance of maintaining redox homeostasis and support further research into antioxidant-based interventions.

Keywords: oxidative stress; antioxidants; reactive oxygen species; lipid peroxidation; chronic diseases; nutritional therapy

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1. Introduction

Oxygen plays a fundamental role in sustaining aerobic life [1] and represents the driving force for the maintenance of metabolism and cellular viability. At the same time, oxygen poses a potential danger to living beings due to the unique paramagnetic characteristics of this gas, which are responsible for the formation of partially reduced intermediates with high reactivity, known as reactive oxygen species (ROS). One of the first known bibliographic references on the toxicity of oxygen comes from Lavoisier, who in 1785 already suggested that an excess of oxygen administration could be as dangerous as its deficiency. Later, in the 18th century, other oxygen-derived products such as H_2O_2 and ozone were discovered, whose effects were identified as clearly harmful from the moment of their synthesis [2].

The study of free radicals and reactive oxygen species (ROS) is a central focus in biomedical research, providing critical insights into the pathophysiology of numerous diseases and guiding therapeutic development. Historically, the existence and role of free

radicals were controversial, as early chemistry viewed "radicals" only as part of molecular structures, and experimental techniques were insufficient to detect them in a free state [3].

The studies on the solution phase of the triphenylmethyl radical carried out by Moses Gomberg in 1900, along with Paneth's 1926 work on the gas phase of the alkyl radical, convinced even the most skeptical scientists of the actual existence of free radicals [4]. Scientific interest in free radicals began in the 1930s with the studies conducted by Kharasch and Mayo, who demonstrated that the anti-Markovnikov addition of hydrogen bromide (HBr) to propene involves radical participation. Similarly, the work of Waters, who clarified the mechanism of homolytic aromatic substitution, demonstrated that radical reactions occurred in a wide variety of organic systems [3]. It was with Michaelis that the hypothesis of the free radical as the cause of oxygen toxicity began to take shape. Indeed, it was Michaelis who, in 1939, published his theory proposing the involvement of free radicals as intermediates in organic oxidations. Both Michaelis in 1946 and Gilbert and Gershman in 1954 provided the first theoretical and scientific foundations that explained oxygen toxicity mediated by highly reactive species [5].

The implications of this toxicity can be considered in biochemical, toxic–metabolic, and pathophysiological processes, whose molecular basis stems from or is the result of a general mechanism known as oxidative stress.

The delicate balance between the production of reactive oxygen species and the antioxidant defenses that neutralize them is crucial for maintaining cellular homeostasis. When this balance is disrupted, a state of redox imbalance or oxidative stress ensues, leading to damage to lipids, proteins, and DNA. This oxidative damage triggers a cascade of pathophysiological events that contribute significantly to the onset and progression of numerous non-communicable diseases (NCDs). These chronic conditions, including cardiovascular, inflammatory, and autoimmune diseases, are increasingly recognized as being driven by oxidative stress-induced cellular and molecular damage [6]. Thus, unraveling the complex interactions between redox processes and disease mechanisms not only deepens our understanding of NCD pathogenesis but also opens new avenues for therapeutic intervention aimed at restoring redox homeostasis and preventing disease progression.

In this regard, understanding the pathophysiological mechanisms by which redox imbalance contributes to non-communicable diseases (NCDs) is essential for identifying novel therapeutic targets and improving disease management strategies. Several excellent reviews, such as the recent article by Halliwell [7], have addressed the mechanisms of antioxidant action and the roles of reactive oxygen species (ROS) in health and disease. However, our review provides added value by adopting a broader, more translational perspective. We expand the analysis to encompass the differential impact of ROS on lipids, proteins, cholesterol, and DNA, and emphasize the dual antioxidant/pro-oxidant behavior of nutritional compounds in distinct redox environments. Furthermore, we present an updated overview of advanced methodologies for detecting oxidative damage, including mass spectrometry and redox proteomics, which have rarely been detailed in prior reviews. Importantly, we connect mechanistic insights with clinical and nutritional interventions, highlighting emerging precision medicine approaches such as NRF2 activators, NOX inhibitors, mitochondria-targeted antioxidants, and ferroptosis modulation. A distinctive feature of our work is the integration of systems biology and artificial intelligence frameworks, which allow multi-omics data and biomarker panels to inform patient stratification and redox-targeted therapies. By combining biochemical fundamentals, nutritional perspectives, disease-specific mechanisms, and digital health innovations, this review provides a comprehensive and forward-looking synthesis of oxidative stress in NCDs.

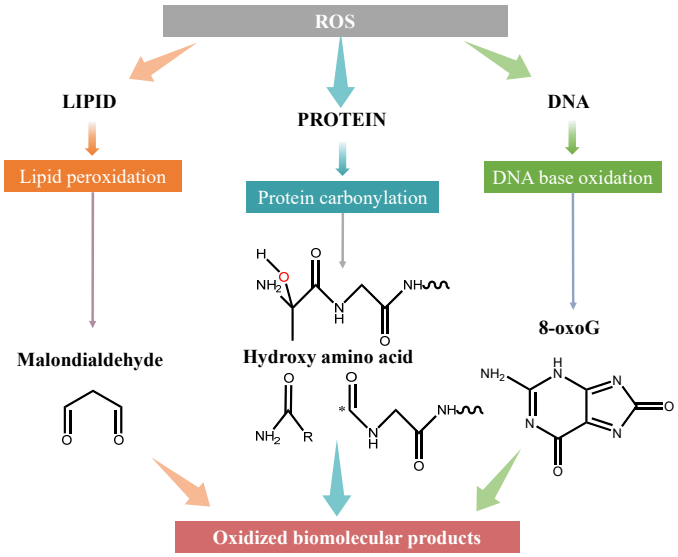
2. Methods

A structured literature search was conducted in the PubMed, Scopus, and Web of Science databases to identify relevant studies published between January 2000 and March 2025. The following keywords and combinations were used: "oxidative stress", "redox imbalance", "reactive oxygen species", "antioxidants", "biomarkers", "non-communicable diseases", "cardiovascular", "neurodegenerative", "autoimmune", "clinical trials", and "nanomaterials". Only articles published in English and indexed in peer-reviewed journals were included. Both clinical and experimental studies, as well as meta-analyses and systematic reviews, were considered. Reference lists of key articles were also screened to identify additional relevant publications. Studies focusing exclusively on acute infections, non-mammalian models, or lacking direct evaluation of oxidative stress mechanisms were excluded. The final selection emphasized recent high-impact research (past 5–10 years) while retaining landmark older studies that provide essential mechanistic insights.

3. Mechanisms of Biomolecular Damage by ROS

3.1. Lipid Peroxidation and Cholesterol Damage

Cell membranes are rich in polyunsaturated lipids, cholesterol, and glycolipids, which make them particularly susceptible to oxidative damage. Reactive oxygen species (ROS) can trigger lipid peroxidation, altering membrane structure, reducing flexibility, and compromising integrity (Scheme 1). These structural changes are not merely passive consequences; they can actively perturb cellular signaling and contribute to disease. For example, the oxidation of low-density lipoprotein (LDL) particles enhances their recognition by macrophage scavenger receptors, promoting foam cell formation and the development of atherosclerotic plaques [8–10].



Scheme 1. Oxidation products upon ROS action. Reactive oxygen species (ROS) induce oxidative modifications in lipids, proteins, and DNA. Lipid peroxidation generates reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE); protein oxidation introduces carbonyl groups that impair protein function; and DNA oxidation produces lesions such as 8-oxoguanine (8-oxoG). Together, these oxidative products serve as key biomarkers of cellular oxidative stress and contribute to aging and disease. * Unpaired electron.

Cholesterol is another critical target of oxidative damage. Oxidation produces hydroperoxides and oxysterols, which are strongly implicated in the pathophysiology of cardiovascular disease. Unlike native LDL, oxidized LDL is preferentially internalized by macrophages, activating toll-like receptor 4, increasing intracellular ROS, and exacerbating

lipid accumulation [11,12]. These mechanistic insights underscore a vicious cycle in which lipid peroxidation both reflects and drives oxidative stress in cardiovascular tissues.

Despite clear process-based links, several debates remain. One central question is the causal versus correlative role of lipid peroxidation in atherosclerosis. While oxidized LDL is strongly associated with plaque formation, it remains debated whether it is the initiating factor or primarily a downstream marker of oxidative stress in vascular tissues [13,14]. Another area of active research concerns the measurement and clinical relevance of lipid peroxidation products. Traditional assays, such as TBARS for malondialdehyde, are inexpensive but limited in specificity, whereas advanced techniques like HPLC and LC-MS/MS provide higher precision but are not yet widely implemented in clinical settings [15,16].

3.2. Protein Carbonylation

Proteins are essential components of cellular structures and functions, but unlike lipids, they are particularly vulnerable to oxidative modifications, most notably carbonylation. This process results from the ROS-mediated oxidation of specific amino acid side chains, producing ketone and aldehyde groups that compromise protein stability, enzymatic activity, and metabolic regulation. Common targets include proline, glutamic acid, lysine, and threonine, which undergo well-characterized transformations into pyrrolidone, glutamic semialdehyde, aminoadipic semialdehyde, and aminoketobutyric acid, respectively [8,9,17].

While there is strong consensus that protein carbonylation serves as a reliable and relatively stable biomarker of oxidative stress, its precise role in disease mechanisms remains debated. Some studies suggest carbonylation is largely a downstream byproduct of ROS exposure, reflecting cellular damage rather than directly driving pathology [18,19]. These reviews emphasized that protein carbonylation is essentially irreversible, tends to accumulate with age, and primarily reflects failed proteolytic clearance rather than initiating pathology. Conversely, other evidence points to a more active contribution, where they discussed how carbonylation of mitochondrial proteins can impair their function, leading to metabolic dysfunction [20]. Additionally, increased protein carbonylation in adipose tissue has been observed in animal models and humans with insulin resistance, suggesting a potential role in disease progression [21]. Together, these findings illustrate the tension between viewing carbonylation as a passive marker versus an active driver of disease processes.

3.3. DNA Damage

DNA is the primary repository of genetic information, and its integrity is essential for proper cellular function. Oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) and cellular antioxidant defenses, can induce a variety of DNA lesions, including base modifications (e.g., 8-oxoguanine) and strand breaks (Scheme 1). These alterations are associated with mutagenesis, apoptosis, necrosis, and cancer development. Chromatin disruption caused by DNA fragmentation further complicates transcriptional regulation, potentially promoting errors that drive disease [8,22–25].

Importantly, ROS are not solely damaging; they also serve as signaling molecules in physiological processes such as immune defense and apoptosis, where they contribute to both the initiation and execution phases [26]. This duality highlights the context-dependent effects of ROS. Some authors propose a more nuanced definition of oxidative stress that incorporates not just the quantity of ROS, but also their site of production, formation kinetics, and duration of exposure [27,28].

Several debates remain in the field. First, the extent to which oxidative DNA lesions directly initiate disease versus acting as markers of broader cellular stress is unresolved [29]. Some evidence suggests that 8-oxoguanine and other oxidized bases actively promote mutagenesis and carcinogenesis, whereas other studies view them primarily as byproducts of

ROS accumulation [29,30]. Second, while DNA repair pathways, such as base excision repair, mitigate oxidative damage, their efficiency varies between cell types and disease states, adding complexity to understanding the link between DNA lesions and health outcomes [31].

In sum, oxidative DNA damage is a central factor in aging, cancer, and genetic disorders, but its precise mechanistic contribution remains debated. Future research should aim to distinguish causal versus correlative roles of DNA lesions and integrate spatial–temporal dynamics of ROS to clarify their true impact on human health.

4. Defense System Against Oxidative Stress

Free radicals have essential physiological roles, acting as mediators in cellular signaling, immune responses, and apoptosis. However, when their levels exceed physiological thresholds, depending on their quantity, localization, and duration, they can cause oxidative damage. Cells maintain a delicate balance between pro-oxidant forces and antioxidant defenses to prevent such damage, and oxidative stress arises when this equilibrium shifts in favor of ROS [1,32]. Antioxidants, defined by Halliwell and Gutteridge as substances that delay or inhibit oxidation even at low concentrations [33], function through efficiency, flexibility, and versatility. Key antioxidant mechanisms include tissue-level control of oxygen availability, enzymatic and non-enzymatic defense systems, and molecular repair pathways, collectively forming a multilayered system to counteract oxidative stress.

4.1. Enzymatic and Non-Enzymatic Antioxidant System

At the enzymatic level, cells employ antioxidant enzymes to neutralize reactive species by converting them into more stable molecules. Key enzymes include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [28,34]. SOD converts superoxide anions (O_2^-) into hydrogen peroxide (H_2O_2), which is subsequently decomposed into water and oxygen by CAT or GPx, forming an integrated defense against oxidative stress (Figure 1).

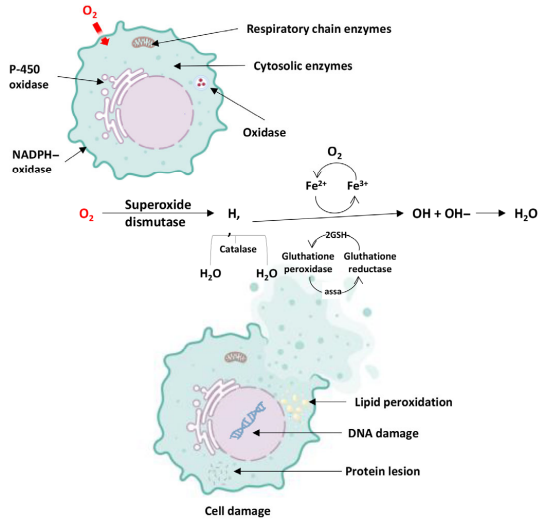


Figure 1. The antioxidant enzymatic and non-enzymatic system in cells. Reactive oxygen species (ROS) are generated during cellular metabolism, particularly in mitochondria. Excess ROS can damage lipids, proteins, and DNA, leading to peroxidation, carbonylation, and oxidative lesions, respectively. Cells counteract this damage through antioxidant defense systems: enzymatic antioxidants such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) convert superoxide and hydrogen peroxide into less reactive molecules, while glutathione reductase regenerates reduced glutathione (GSH), a key redox buffer. Importantly, in the presence of transition metals such as iron or copper, hydrogen peroxide can undergo the Fenton reaction ($Fe^{2+} \rightarrow Fe^{3+}$), producing highly reactive hydroxyl radicals (•OH) that further amplify oxidative stress. Together with non-enzymatic antioxidants, these systems maintain redox balance and protect against oxidative stress.

Cells defend against oxidative stress through both enzymatic and non-enzymatic mechanisms that neutralize reactive oxygen species (ROS). Key antioxidant enzymes include superoxide dismutase (SOD), which converts superoxide into hydrogen peroxide and also protects other enzymes from oxidative damage; catalase (CAT), which decomposes hydrogen peroxide into water and oxygen; and glutathione peroxidase (GPx), which reduces hydrogen peroxide and organic hydroperoxides, with specific isoforms targeting lipid peroxides, protein folding, or tissue-specific functions [28,35–41]. Beyond enzymatic systems, non-enzymatic antioxidants, such as reduced glutathione (GSH), vitamins C and E, beta-carotene, and trace elements like selenium and zinc, scavenge free radicals, regenerate oxidized antioxidants, and maintain redox homeostasis [42,43]. Collectively, these layers of defense ensure cellular resilience against ROS, with variations in enzyme isoforms, localization, and activity influencing susceptibility to oxidative damage and disease.

4.2. Nutritional Antioxidants

Nutritional antioxidants are essential for cellular defense against oxidative stress, as eukaryotic cells cannot synthesize them and must obtain them from the diet. These compounds are generally classified by solubility into lipophilic and hydrophilic antioxidants [44,45]. Lipophilic antioxidants, such as vitamin E and carotenoids, protect cell membranes and DNA from lipid peroxidation. Vitamin E, present in vegetable oils, nuts, and certain vegetables, exists in eight forms (α-, β-, γ-, δ-tocopherols, and tocotrienols), with α-tocopherol being the most studied for its antioxidant and signaling roles. Deficiencies in vitamin E have been linked to neurodegenerative and cardiovascular diseases [44–47].

Carotenoids, including β-carotene, lycopene, lutein, and zeaxanthin, not only scavenge reactive oxygen species but also serve as provitamin A sources and have been investigated for potential chemopreventive effects, although clinical results remain variable [48,49]. Hydrophilic antioxidants, such as vitamin C and polyphenols, are readily absorbed but also rapidly excreted. Vitamin C functions as a potent electron donor and cofactor in critical processes like collagen hydroxylation and carnitine synthesis. It also supports neuronal protection, differentiation, and neurotransmitter regulation. Despite its physiological importance, vitamin C deficiency is common in industrialized countries due to poor diet, smoking, and alcohol consumption, and is associated with increased susceptibility to chronic and metabolic diseases [50,51]. Importantly, the activity of antioxidants is dose-dependent and context-dependent. At physiological concentrations, antioxidants scavenge free radicals, support redox balance, and protect against disease. However, when present at very high levels or in particular redox environments, they may paradoxically act as pro-oxidants. For instance, vitamin C can reduce Fe^{3+} or Cu^{2+} ions, thereby driving Fenton chemistry and promoting hydroxyl radical formation; β-carotene can exert pro-oxidant activity at elevated oxygen pressures, as observed in smokers supplemented with high doses; and vitamin E, in the absence of adequate regeneration by vitamin C or coenzyme Q, may propagate lipid peroxidation within LDL particles [52,53]. These observations emphasize that antioxidant effects follow a non-linear, biphasic dose–response curve (hormetic model), where moderate intake supports cellular protection, while excessive supplementation may enhance oxidative stress or disrupt signaling pathways [54] (Figure 2).

Flavonoids and other polyphenols, including phenolic acids, stilbenes (e.g., resveratrol), tannins, and curcuminoids, are abundant in the Mediterranean diet and linked to reduced risk of type 2 diabetes and cardiovascular disease. Even low-phenolic foods like virgin olive oil (1–2% phenolics) provide cardioprotective benefits [51,55–58]. Quercetin is notable for scavenging radicals and lowering malondialdehyde (MDA) levels, potentially reducing oxidative damage during aging and metal accumulation in the brain. Other polyphenols, such as hydroxycinnamates (from coffee), resveratrol (red wine), curcumin, and green tea catechins

(EGCG), may have antioxidant, anti-inflammatory, and metal-chelating properties, though clinical efficacy is limited [59–62]. Mechanistic human studies show that green tea catechins incorporate into LDL particles, protecting them from oxidation [63], and a meta-analysis of randomized trials found catechin supplementation (145–3000 mg/day) significantly reduced total and LDL cholesterol [64]. Similarly, a randomized, placebo-controlled trial reported that resveratrol (1500 mg/day) improved insulin sensitivity, reduced BMI, and lowered waist circumference in patients with metabolic syndrome [65].

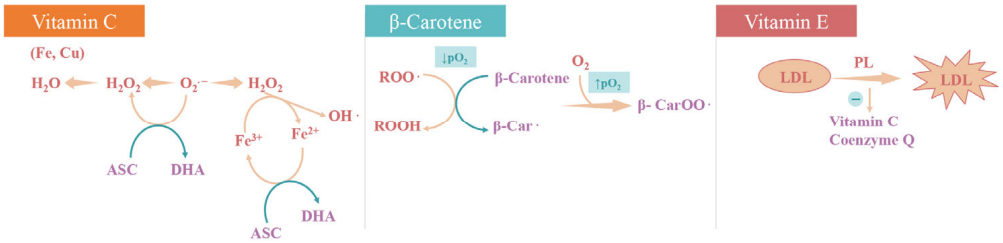


Figure 2. Antioxidant and pro-oxidant activities of vitamin C, vitamin E, and beta-carotene. Vitamin C (ascorbate (ASC)) acts as a water-soluble antioxidant by scavenging free radicals and regenerating oxidized antioxidants, but in the presence of transition metals (Fe or Cu), it can promote hydroxyl radical (·OH) formation through Fenton chemistry, displaying pro-oxidant activity. β-carotene neutralizes peroxyl radicals (ROO·) and quenches singlet oxygen, but at high oxygen tension, may form pro-oxidant species (β-CarOO·). Vitamin E, the major lipid-soluble antioxidant, protects membranes and lipoproteins (LDLs) from lipid peroxidation by donating electrons to lipid radicals, with its oxidized form regenerated by vitamin C and coenzyme Q. Collectively, these vitamins serve as dual modulators of oxidative stress, functioning as antioxidants or pro-oxidants depending on the redox environment.

Under certain conditions, some polyphenols can act as pro-oxidants, generating ROS or affecting drug metabolism via cytochrome P450 interactions [66–71]. Curcumin and green tea catechins may also support antioxidant defenses through metal ion chelation and glutathione elevation, and curcumin derivatives may prevent metal buildup in Alzheimer's disease models [66,67].

In addition to classical antioxidants, B vitamins (B2, B3, B6, B9, and B12) are increasingly recognized as crucial regulators of redox balance, not as direct radical scavengers but as cofactors in enzymatic pathways that sustain the antioxidant network. For example, vitamin B2 (riboflavin) and B3 (niacin) are precursors of FAD and NAD(P)H, which fuel glutathione reductase and thioredoxin reductase, enabling recycling of reduced glutathione and thioredoxin, two central antioxidant systems. Vitamin B6 is required for the transsulfuration pathway, facilitating cysteine and glutathione synthesis. Folate (B9) and vitamin B12 regulate one-carbon metabolism and homocysteine clearance. Elevated homocysteine induces oxidative stress and is a well-established risk factor for cardiovascular and neurodegenerative disorders. Deficiencies in these vitamins compromise mitochondrial energy metabolism and antioxidant defenses, thereby contributing to chronic conditions linked to oxidative stress. Clinical evidence supports these associations: a retrospective case–control study demonstrated that folic acid and B12 supplementation significantly reduce plasma homocysteine levels and lower the risk of stroke and cognitive decline [72]. Moreover, higher B vitamin intake has been correlated with slower brain atrophy rates in elderly patients with mild cognitive impairment [73,74].

5. Oxidative Stress Repair System

Cells rely on coordinated repair and detoxification mechanisms to prevent accumulation of oxidative damage and maintain homeostasis. These systems include enzymatic antioxidants, proteolytic and lipolytic pathways, and DNA repair processes, which collec-

tively preserve protein, lipid, and genomic integrity. Proteasomes and lysosomes remove irreversibly damaged proteins, recycling amino acids and supporting proteostasis, while the thioredoxin and glutathione systems maintain intracellular redox balance [37,39,75–78]. DNA lesions induced by oxidative stress are corrected through pathways such as base excision repair, nucleotide excision repair, and homologous recombination, with cellular sensors like ATM and ATR coordinating repair and cell cycle checkpoints [79,80].

Despite the central role of these systems in maintaining cellular integrity, accurately assessing oxidative stress in vivo remains challenging due to the short half-life of reactive oxygen species and the complexity of redox networks. Biomarkers of oxidative damage and antioxidant capacity are, therefore, often used as indirect indicators, but variability in their measurement and interpretation can limit comparability across studies [81–83]. Overall, direct repair systems (removing or reversing damage) and indirect defenses (preventing damage and activating protective signaling) are crucial for cellular survival, maintenance of genomic stability, and protection against chronic diseases linked to oxidative stress. Conceptually, the main challenge lies in integrating mechanistic understanding with reliable measurement of oxidative balance to inform disease prevention and therapeutic strategies.

6. Detection of Oxidative Stress and Antioxidant Biomarkers

Assessment of oxidative stress in humans typically relies on measuring either the products of oxidative damage or the capacity of antioxidant defenses, as direct quantification of reactive oxygen species (ROS) is impractical due to their extremely short half-lives.

6.1. Assessment of Lipid Peroxidation, Protein Oxidation, and DNA Damage

In the context of lipid oxidative damage, one of the earliest techniques employed was the measurement of thiobarbituric acid-reactive substances (TBARSs). This assay relies on the reaction of thiobarbituric acid with malondialdehyde (MDA), a byproduct of lipid hydroperoxide formation, though its sensitivity and specificity are limited [84]. More recently, direct determination of MDA by high-performance liquid chromatography (HPLC) has become prevalent due to enhanced sensitivity and precision, allowing detection of trace amounts [85]. Advanced approaches such as LC-MS/MS and GC-MS enable quantification of even smaller quantities of lipid peroxidation products. Measurement of aldehydes like 4-hydroxynonenal (4-HNE), a product of lipoperoxidation, can be performed with high accuracy by HPLC coupled to ultraviolet detection or by gas chromatography–mass spectrometry, which offers improved performance [86]. Additionally, isoprostane quantification, especially F2-IsoPs, is regarded as a highly accurate method for assessing lipid peroxidation (Table 1) [87].

Table 1. Analytical methods for detecting lipid peroxidation products. Comparison of commonly used methods to measure lipid peroxidation, focusing on their analytes, sensitivity, specificity, and sample suitability. While simple assays, such as TBARS, are widely used for screening, mass spectrometry-based methods, particularly LC-MS/MS measurement of F2-isoprostanes, represent the gold standard for sensitivity and specificity in both research and clinical settings [88,89].

Method	Analyte	Sensitivity [1]	Specificity	Sample Type
TBARS [2] assay	MDA [3]	Low–moderate	Low (cross-reactivity with other aldehydes)	Plasma, serum, and tissue homogenates
HPLC [4]	MDA, 4-HNE [5], and other aldehydes	Moderate	Moderate–high (depends on derivatization)	Plasma, urine, and tissue
LC-MS/MS [6]	MDA, 4-HNE, and F2-isoprostanes	High	Very high	Plasma, urine, tissue, and exhaled breath condensate

Table 1. *Cont.*

Method	Analyte	Sensitivity [1]	Specificity	Sample Type
GC-MS [7]	Volatile or derivatized products (e.g., MDA and isoprostanes)	High	High	Plasma, urine, and tissue
Immunoassays (ELISA)	4-HNE adducts and F2-isoprostanes	Moderate	Moderate (depends on antibody)	Plasma, urine, and cell lysates
F2-isoprostanes (LC-MS/MS)	F2-isoprostanes	Very high	Very high	Plasma, urine, CSF [8], and tissue

[1] Sensitivity classification: Low = detection limit in micromolar (μM) range; moderate = high nanomolar to low micromolar (nM–μM); high = low nanomolar (10^{-9} M); very high = picomolar (10^{-12} M) or lower. [2] TBARS, thiobarbituric acid reactive substance. [3] MDA, malondialdehyde. [4] HPLC, high-performance liquid chromatography. [5] 4-HNE, 4-hydroxynonenal. [6] LC-MS/MS, liquid chromatography–tandem mass spectrometry. [7] GC-MS, gas chromatography–mass spectrometry. [8] CSF, cerebrospinal fluid.

Elevated levels of these markers have been associated with cardiovascular disease, diabetes, and neurodegenerative disorders, often correlating with disease severity. For instance, a clinical study in patients with rheumatoid arthritis demonstrated that serum MDA levels were significantly elevated compared with healthy controls, supporting its role as a marker of systemic oxidative stress in chronic inflammatory conditions [90]. Nevertheless, the application of lipid peroxidation markers for disease monitoring is constrained by several methodological and biological limitations. Analytical variability between methods and laboratories, lack of specificity since these products can be elevated in multiple conditions (e.g., aging, obesity, or infection), and biological variability influenced by diet, lifestyle, or circadian rhythms all reduce comparability across studies. Moreover, although F2-IsoPs offer greater reliability, routine clinical application remains limited due to cost and lack of standardized protocols. Consequently, lipid biomarkers are most informative when interpreted in combination with other oxidative stress measures and clinical parameters [91].

Protein oxidation is commonly assessed using biomarkers such as carbonylated proteins, oxidized sulfur-containing amino acids, and advanced glycation end products (AGEs) [92,93]. These markers reflect the cumulative oxidative modification of proteins and have been associated with aging, chronic inflammatory conditions, and metabolic disorders. However, the utility of protein oxidation biomarkers in both clinical and research settings is constrained by ongoing methodological and interpretative controversies. Analytical variability, assay sensitivity, and biological factors, such as impaired protein turnover, can influence measurements, complicating data interpretation. Clinical evidence illustrates both their potential and the need for careful use: for example, plasma protein carbonyls have been shown to reflect oxidative stress status in chronic kidney disease, dialysis, and kidney transplantation, correlating with disease progression and adverse outcomes, including cardiovascular complications and increased mortality risk [94]. This highlights that while protein carbonyls are informative biomarkers of oxidative protein damage, they are most reliable when combined with complementary oxidative stress indicators and considered in the broader clinical context.

Redox proteomics has emerged as a powerful strategy to identify and characterize biomarkers of oxidative stress, moving beyond global measurements to detect site-specific protein changes and to place them in the biological context [95]. Unlike conventional assays, this approach enables precise mapping of specific modifications such as carbonylation, nitrosylation, and sulfenic acid formation (protein sulfenylation), providing a clearer view of redox-dependent molecular alterations linked to disease mechanisms [95]. Building on this foundation, biological proximity-guided platforms now capture localized cysteine oxidation within subcellular compartments in living cells, sharpening the spatial resolution of redox hotspots and revealing where oxidative events actually occur [96]. A complementary line of work synthesizes current understanding of reversible protein sulfenylation

as an early, signal-responsive form of cysteine oxidation and describes practical assays that connect proteomic findings to pathway-level insights [97]. These advances can be leveraged for drug discovery, where cysteine-centered chemoproteomics helps identify covalent ligands and prioritize druggable redox-sensitive proteins [98]. In addition, they can be integrated with human genetic variation to stratify missense variants at cysteine sites, improving functional interpretation and translational relevance [99].

The assessment of oxidative DNA damage commonly involves the measurement of 8-hydroxy-2′-deoxyguanosine (8OHdG or 8-oxodG), typically quantified by HPLC with electrochemical detection (HPLC–ECD) [100]. 8-oxodG is a widely recognized biomarker of oxidative stress-induced DNA modification, reflecting both the extent of damage and the efficiency of DNA repair mechanisms. More advanced approaches, including LC-MS, GC-MS, and HPLC-MS/MS, allow sensitive and specific quantification of 8-oxodG and other oxidized nucleobases. Clinical and experimental studies have highlighted the utility of these markers in various contexts: for instance, 8-oxodG has been proposed as a biomarker of chronic oxidative stress induced by high-LET radiation [101], while elevated 8-oxoG and altered 8-oxoguanine DNA glycosylase 1 (OGG1) activity have been associated with Alzheimer's disease, suggesting potential diagnostic value [102]. Additionally, HPLC–ECD determination of 8-oxodG has been reviewed as a reliable and reproducible method for assessing oxidative DNA damage in diverse disease models and human studies [103]. Despite these advances, interpretation of DNA oxidation markers must consider confounding factors such as diet, lifestyle, and renal clearance, and their clinical utility is maximized when combined with complementary oxidative stress indicators.

6.2. Antioxidant Activity

Total antioxidant capacity (TAC) is widely used to evaluate the overall ability of biological samples to neutralize reactive species. Commonly employed assays include ABTS radical cation decolorization, DPPH radical scavenging, and ferric-reducing antioxidant power (FRAP), which measure the capacity of antioxidants to quench free radicals or reduce oxidants [104–106]. While these methods are convenient and informative, they do not provide a complete or absolute measure of antioxidant status, as they may overlook synergistic interactions and compartmental differences within cells or tissues.

In addition to global antioxidant capacity, the quantification of individual antioxidant compounds is essential. The total polyphenol content can be determined using the Folin–Ciocalteu method, which is based on the oxidation of polyphenols by a reagent composed of phosphomolybdate and phosphotungstate [107]. Vitamins and carotenoids, including α- and β-tocopherol, β-cryptoxanthin, and lycopene, are quantified using high-performance liquid chromatography (HPLC), which also enables accurate determination of vitamin C and its oxidized form, dehydroascorbic acid [108–110]. Indicators of mitochondrial oxidative status, such as coenzyme Q10 content and the activity of respiratory complexes I (NADH ubiquinone oxidoreductase) and IV (cytochrome oxidase), are increasingly measured to provide mechanistic insights into cellular redox balance [111,112].

Clinically, TAC and specific antioxidant measurements have been linked to health outcomes. For example, higher dietary antioxidant capacity has been associated with reduced systemic inflammation in cancer survivors [113], and biological antioxidant potential (BAP) tests have shown predictive value for metabolic syndrome [114]. Comprehensive reviews also highlight the importance of TAC in interpreting redox status in both healthy and diseased populations, underscoring its potential for monitoring nutritional interventions and oxidative stress-related disorders [115].

7. Oxidative Stress in Disease Pathogenesis

Many pathophysiological processes are currently linked to the production of free radicals, including mutagenesis, cellular transformation, cancer, diabetes, atherosclerosis, ischemia–reperfusion injuries, neonatal diseases (e.g., retinopathy of prematurity), autoinflammatory disorders, neurodegenerative diseases, and aging itself [77,116]. Oxidative stress plays a crucial role in these conditions, either as a primary cause or as an associated factor, participating in multiple mechanisms that induce cellular oxidation [117,118]. This integrative perspective aligns with the free radical theory of aging and its subsequent modifications, which link mitochondrial oxidative damage to impaired oxidative phosphorylation, increased transcriptional and translational errors, and gradual loss of cellular homeostasis [119]. As repair mechanisms deteriorate with age, a vicious cycle ensues; mitochondrial DNA damage leads to defective oxidative phosphorylation, generating more reactive species, which, in turn, further amplify mitochondrial DNA injury. Supporting this, experimental data from our group in aged rats showed elevated oxidative indices, diminished antioxidant defenses, and an increased incidence of tumors [120]. Within this framework, the role of nutritional antioxidants is increasingly recognized. Lutein and zeaxanthin have been studied for preventing age-related macular degeneration [121], and a recent meta-analysis suggests that dietary carotenoids may delay the onset and progression of diabetic retinopathy [122], highlighting the clinical relevance of dietary interventions to counteract age-related oxidative stress [119–121].

This mechanistic foundation is also evident in neurodegenerative diseases such as Parkinson's, Alzheimer's, Huntington's disease, and amyotrophic lateral sclerosis, where mitochondrial dysfunction, excessive production of reactive species, impaired antioxidant defenses, protein oligomerization, cytokine release, inflammatory responses, blood–brain barrier disruption, and proteasome malfunction collectively contribute to progressive neuronal injury [77,123]. Although curative treatments are lacking, ongoing research is focused on interventions that attenuate oxidative stress-mediated damage and potentially slow disease progression [124]. In oncology, cancer represents an intrinsically pro-oxidant state, in which free radicals induce DNA damage and mutagenesis, while neoplastic metabolic rewiring, infiltration by inflammatory cells, malnutrition, and anticancer therapies further exacerbate oxidative burden [125,126]. Epidemiological studies indicate that a high dietary intake of fruits and vegetables is associated with a reduced risk, by up to 50%, of cancers of the digestive and respiratory tracts [127]. In addition, higher plasma lycopene concentrations have been inversely correlated with prostate cancer risk, supporting its proposed anticancer, anti-proliferative, and pro-apoptotic properties [128–130].

Oxidative stress is also critical in neonates, where immature antioxidant systems face rapid postnatal ROS increases. Maternal cranberry supplementation and alcohol-free beer intake enhance milk antioxidant capacity and reduce oxidative damage [131,132].

Oxidative stress is also central to other clinical contexts. During ischemia–reperfusion events, as seen in solid organ transplantation, a burst of oxygen-derived free radicals is generated because ischemia depletes intracellular ATP and leads to hypoxanthine accumulation, while xanthine dehydrogenase is converted to xanthine oxidase. Upon reperfusion, xanthine oxidase uses hypoxanthine and molecular oxygen to produce superoxide anions at rates that overwhelm endogenous antioxidant defenses and precipitate oxidative stress [133]. Notably, in animal models, supplementation with alpha-tocopherol and beta-carotene has been shown to enhance hepatic antioxidant and energy status after ischemia–reperfusion injury [134].

Collectively, these observations establish oxidative stress and redox dysregulation as unifying mechanisms across a wide spectrum of highly prevalent diseases and physiological transitions, ranging from aging to reperfusion injury. The following sections provide a

detailed analysis of their involvement in cardiovascular diseases and inflammatory and autoimmune disorders, and discuss emerging therapeutic strategies targeting redox biology.

7.1. Cardiovascular Diseases

Oxidative stress contributes significantly to arterial damage and the formation of atherosclerotic plaques, which underlie major cardiovascular conditions such as hypertension, myocardial infarction, and stroke [135,136]. Among the key mediators are advanced protein oxidation products (APOPs), whose elevated plasma levels correlate with atherosclerosis progression and carotid intima–media thickness [137,138]. A major driver of this process is the oxidative modification of low-density lipoproteins (LDLs). Once oxidized, LDL particles are preferentially internalized by macrophages, leading to foam cell formation, endothelial dysfunction, and necrosis of lipid-laden cells [139–142] (Figure 3).

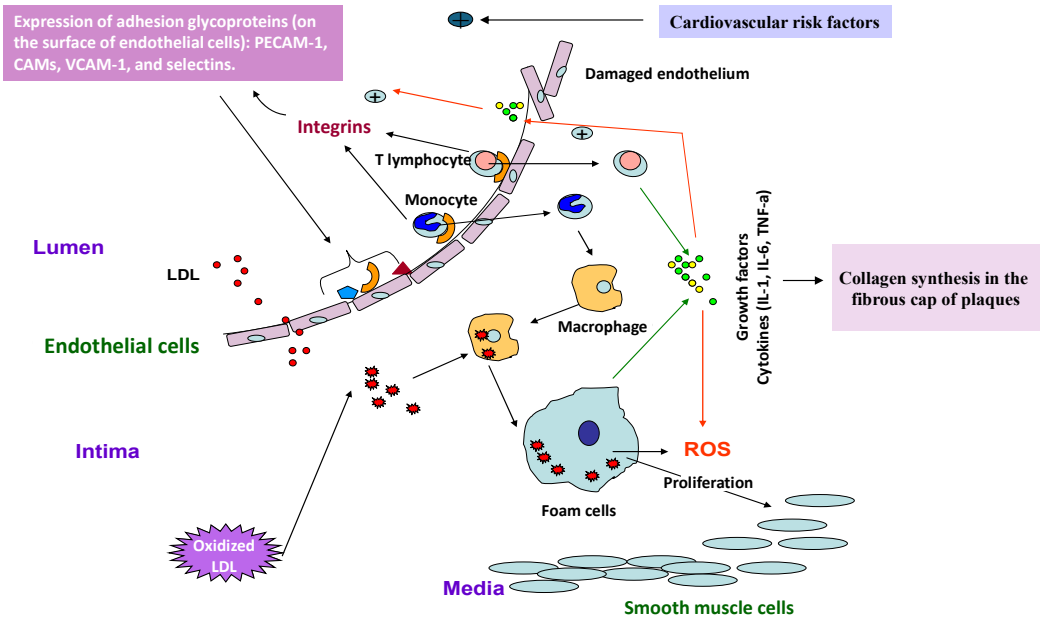


Figure 3. Hypothesis of atherosclerosis. Endothelial injury caused by cardiovascular risk factors promotes the expression of adhesion molecules (PECAM-1, CAMs, VCAM-1, and selectins), enabling leukocyte adhesion and transmigration. Oxidized LDL is taken up by macrophages, leading to foam cell formation and ROS production. These processes trigger cytokine release (e.g., IL-1, IL-6, and TNF-α), smooth muscle cell proliferation, and collagen synthesis, contributing to fibrous plaque development.

Diet and lifestyle play an important role in modulating this redox imbalance. Excess energy and cholesterol intake impair antioxidant enzyme activity [143], whereas moderate consumption of antioxidant-rich foods and beverages, such as non-alcoholic beer or mandarin juice, improves antioxidant status and reduces oxidative biomarkers in both healthy individuals and patients with dyslipidemia [140,144]. Similar protective effects are observed with adherence to the Mediterranean diet, which improves endothelial function and reduces insulin resistance in type 2 diabetic patients [145]. These findings highlight the shared oxidative mechanisms linking cardiovascular disease and metabolic disorders.

Population-level studies further support the protective role of antioxidants. Higher consumption of fruits and vegetables in Mediterranean countries, compared with northern Europe and the USA, parallels a lower incidence of cardiovascular diseases and certain cancers [146]. Antioxidant vitamins and flavonoid intake have also been associated with reduced depressive symptoms and improved prognosis after ischemic stroke [147]. A systematic review confirmed that intake of six major carotenoids (lycopene, α/β-carotene,

lutein, zeaxanthin, and astaxanthin) reduces the risk of stroke and cardiovascular events through mechanisms that extend beyond direct radical scavenging [148].

Recent advances in cardiovascular redox biology are shifting the focus from general ROS overproduction to specific, druggable molecular pathways. High-resolution structural studies of NADPH oxidase 5 (NOX5) have enabled the development of structure-guided inhibitors [149]. Standardization of cysteine sulfenylation (SOH) as an early redox biomarker is progressing, with circulating SOH-modified proteins showing correlations with plaque burden and myocardial infarction outcomes [97]. Ferroptosis, an iron-dependent cell death process, has also emerged as a critical driver of atherosclerosis and ischemia–reperfusion injury. Preclinical studies demonstrate that targeting ferroptosis or enhancing the GPX4 and NRF2 signaling pathways provides vascular protection [128]. In addition, ROS-mediated activation of the NLRP3 inflammasome links oxidative stress to vascular inflammation, and the development of direct NLRP3 inhibitors is ongoing [150].

Therapeutically, there is a clear shift from non-specific antioxidant supplementation toward precision redox medicine. Approaches under investigation include NOX inhibitors, NRF2 activators, and mitochondria-targeted antioxidants such as MitoQ. Treatment strategies are increasingly guided by redox phenotyping and patient-specific molecular profiles. Nevertheless, large-scale, long-term clinical trials with robust cardiovascular outcomes remain essential [151,152]. At the epidemiological level, higher oxidative balance scores in NHANES cohorts correlate with lower rates of hypertension and arterial stiffness, linking molecular mechanisms to modifiable lifestyle factors [153].

7.2. Inflammatory and Autoimmune Diseases

Inflammatory response processes are complex and often involve reactive oxygen species (ROS) [144]. An imbalance between oxidative agents promoting damage and antioxidant defenses is implicated in many diseases, including rheumatoid arthritis, asthma, psoriasis, contact dermatitis, and obesity [154,155] (Table 2). Various mediators such as histamine, serotonin, cytokines, and tumor necrosis factor (TNF) have been described as initiators and amplifiers of inflammation [140,156]. Indeed, inflammation plays a key role in the development of many diseases, including cancer, where deregulated inflammatory pathways contribute to symptom expression [156].

Some authors suggest antioxidants may reduce airway inflammation and hyperreactivity in asthmatic patients [157]. Studies have shown that antioxidants can reduce expression of cytokines such as interleukin-18 (IL-18) by inhibiting NF-kappa B activity, indicating that reactive oxygen species may regulate interleukin expression [156,157].

There is growing interest in the role of antioxidants in controlling inflammation-based diseases. Increasing evidence shows that natural antioxidants are more effective than synthetic ones in reducing oxidative stress, inflammation, and disease activity [158]. For example, recent studies demonstrate that lycopene lowers serum lipid levels, endothelial dysfunction, inflammation, and blood pressure while enhancing antioxidant potential [159]. These effects are significantly amplified when tomatoes (rich in lycopene) are combined with extra virgin olive oil [159]. These natural antioxidants, which can also improve the nutritional value of foods, may lead to novel applications in food products.

Table 2. Immune molecule–ROS interactions and their roles in inflammatory and autoimmune diseases [160]. Reactive oxygen species (ROS) modulate key immune pathways by activating pro-inflammatory transcription factors (e.g., NF-κB1), suppressing antioxidant defenses (Nrf2), and influencing cytokine production (e.g., TNF-α). ROS also affect immune cell differentiation and function, including T cells (Th17/Treg balance), macrophages, B cells, and dendritic cells, leading to impaired tolerance and sustained inflammation. These redox-driven alterations contribute to the pathogenesis of autoimmune diseases such as rheumatoid arthritis, lupus, multiple sclerosis, type 1 diabetes, psoriasis, and inflammatory bowel disease.

Immune Molecule	Oxidative Stress Interaction	Associated Diseases
NF-κB [1]	Activated by ROS. Promotes pro-inflammatory cytokine production (e.g., TNF-α and IL-6).	Rheumatoid arthritis, IBD [5], and lupus
Nrf2 [2]	Suppressed by chronic ROS. Impaired Nrf2 function increases oxidative stress and inflammation.	Multiple sclerosis, lupus, and type 1 diabetes
TNF-α [3]	Induces ROS generation via NADPH oxidase. Sustains inflammation and tissue damage.	Rheumatoid arthritis and psoriasis
T cells (Th17)	ROS modulate differentiation. Skewed Th17/Treg balance promotes autoimmunity and chronic inflammation.	Multiple sclerosis, psoriasis, and type 1 diabetes
Macrophages (M1/M2)	Excess ROS generated by M1 macrophages sustain inflammatory environment.	Atherosclerosis and IBD
B cells	ROS affect B-cell receptor signaling and survival. ROS-mediated dysregulation promotes autoantibody production.	Lupus erythematous and autoimmune thyroiditis
Dendritic cells (DCs)	ROS influence antigen processing and presentation. Enhanced ROS in DCs can break tolerance and activate autoreactive T cells.	Type 1 diabetes and lupus
Tregs [4]	High ROS impairs Treg suppressive function. Reduced immunosuppression allows unchecked autoimmune responses.	Type 1 diabetes and multiple sclerosis

[1] Nuclear factor kappa B. [2] Nuclear factor erythroid 2-related factor 2. [3] Tumor necrosis factor alpha. [4] Regulatory T cells. [5] Inflammatory bowel disease.

Recent research has redefined inflammatory and autoimmune diseases through the emerging field of redox-immunometabolism, in which ROS are recognized not only as metabolic byproducts but as active second messengers that modulate transcriptional networks and cell death pathways. ROS initiate the activation of redox-sensitive signaling hubs, including NF-κB and the NLRP3 inflammasome, thus promoting cytokine production and exacerbating tissue injury [161]. In parallel, ROS promote metabolic reprogramming via HIF-1α and NF-κB signaling pathways, shifting cellular energy metabolism toward glycolysis and resulting in increased lactate production. The elevated lactate subsequently acts as a substrate for protein and histone lactylation, an epigenetic modification that maintains the activation of pro-inflammatory gene expression programs in the context of autoimmune disease [162].

In systemic lupus erythematosus (SLE), oxidative stress is closely linked to inflammation, disease activity, and organ involvement. Patients consistently present higher levels of oxidized lipids, proteins, and DNA compared with healthy controls, and these changes are associated with more severe symptoms and complications, such as lupus nephritis [163]. Persistent mitochondrial dysfunction, impaired mitophagy, and the release of mitochon-

drial DNA are observed in SLE, contributing to sustained type I interferon signaling and redox imbalance, underscoring the mitochondrion as a therapeutic target [164]. Recent reviews also highlight that oxidative imbalance can alter immune cell activation. In particular, it triggers innate immune pathways such as the inflammasome, which amplify systemic inflammation [165]. At the same time, redox-sensitive signaling in T and B cells affects proliferation and autoantibody production, linking oxidative stress not only to tissue damage but also to the autoimmune response itself [165]. This reinforces the role of oxidative stress as both a marker of disease activity and a potential therapeutic target. From a translational perspective, interventions such as N-acetylcysteine have been tested to restore glutathione levels and modulate redox-sensitive signaling pathways, with clinical reports showing improvement in disease activity and T-cell dysfunction, suggesting a promising avenue for adjunct therapy in SLE [166].

In multiple sclerosis, oxidative stress contributes to both neuroinflammation and progressive neuronal damage. Clinical studies show that patients often have increased markers of oxidative damage and reduced antioxidant defenses, which are related to the number of lesions detected by MRI and to the frequency of relapses [167]. More recently, oxidative imbalance has also been associated with non-motor symptoms such as fatigue and cognitive decline, highlighting its contribution to impairment of quality of life in MS and suggesting that oxidative stress markers could help monitor these less visible but highly disabling aspects of the disease [168]. A clinically relevant therapeutic strategy focused on oxidative stress is dimethyl fumarate, which is approved for relapsing multiple sclerosis; while it activates the Nrf2 antioxidant pathway, recent work also shows Nrf2-independent anti-inflammatory effects, underscoring its multimodal mechanism relevant to oxidative stress biology [169].

In rheumatoid arthritis, persistent oxidative stress fuels synovial inflammation and joint damage, with elevated oxidative biomarkers consistently observed in patients and reflecting disease severity [170]. Importantly, oxidative stress also appears to contribute to the high cardiovascular burden in rheumatoid arthritis, as patient serum can induce oxidative damage and proangiogenic and profibrotic responses in endothelial cells, thereby linking redox imbalance to systemic complications [171]. From a prevention standpoint, large population studies report that a higher oxidative balance score, which reflects a diet and lifestyle rich in antioxidants, is associated with a lower prevalence of rheumatoid arthritis, suggesting that strategies to improve redox balance may aid both risk reduction and patient counseling [172].

These mechanistic advances build upon the longstanding concept that disruptions in oxidant–antioxidant balance underpin the previously described autoimmune diseases, as well as other chronic inflammatory conditions such as psoriasis, asthma, and obesity, and further clarify the roles of ROS in the regulation of pro-inflammatory cytokines, including interleukin-1 and interleukin-18 [173].

7.3. Neurodegenerative Diseases

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) are marked by progressive neuronal loss leading to cognitive and motor decline. One of the main pathogenic mechanisms is oxidative stress, which acts as both a driver and consequence of mitochondrial dysfunction, protein misfolding, and neuroinflammation, and it has been proposed as a common contributor across multiple conditions [174]. Recent research emphasizes that oxidative stress not only contributes to neuronal damage but also exacerbates systemic metabolic dysfunction and muscle degeneration, particularly in ALS, suggesting broader implications for disease progression and therapeutic targeting [175].

Oxidative stress is tightly linked to Alzheimer's disease pathophysiology, with ROS accumulating early and associated with protein aggregation, synaptic failure, and neuroinflammation [176]. Mechanistically, oxidative stress and DNA damage can be detected early in neurons affected by beta-amyloid peptide accumulation, preceding the formation of amyloid plaques and highlighting these redox alterations as early markers of neuronal vulnerability [177]. In parallel, mitochondrial dysfunction (impaired bioenergetics, altered dynamics, and defective mitophagy) sustains ROS overproduction and creates a self-amplifying loop of neuronal injury [164]. Therapeutically, antioxidant strategies for Alzheimer's disease, including ROS scavengers, Nrf2 pathway activators, mitochondria-targeted antioxidants, and polyphenols, have shown limited evidence, and inconsistent clinical results have raised skepticism about their effectiveness [178].

In Parkinson's disease, oxidative stress contributes to neuroinflammation and progressive dopaminergic neurodegeneration; patients show increased oxidative damage and reduced antioxidant defenses that correlate with disease severity [179]. One key mechanism is the interaction between ROS and mitophagy, where defective mitochondrial quality control amplifies oxidative injury and accelerates neuronal loss [180]. Another relevant pathway is dopamine oxidation, where reactive quinones and their adducts activate microglia and promote α-synuclein aggregation, linking oxidative imbalance to inflammation and protein misfolding [175]. On the therapeutic front, melatonin, an antioxidant with mitochondrial and anti-inflammatory properties, has shown signals of benefit for sleep disturbances and motor symptoms in Parkinson's disease [181].

Amyotrophic lateral sclerosis exhibits strong oxidative stress signatures shaped by both genetic factors (such as SOD1, TARDBP, FUS, and C9orf72) and environmental exposures, with redox imbalance intersecting with excitotoxicity, proteostasis failure, and neuroinflammation [182]. Mitochondrial dysfunction represents a convergent hub, as altered bioenergetics, calcium handling, and mitochondrial dynamics amplify ROS production and increase motor neuron vulnerability [183]. Redox-sensitive pathways, particularly Nrf2, are also dysregulated in ALS and are being investigated as therapeutic targets to restore antioxidant defenses [184]. Clinically, edaravone, an approved free radical scavenger, exemplifies strategies aimed at oxidative stress; however, together with riluzole, it only modestly prolongs survival by a few months, and numerous other agents are still under investigation in clinical trials for ALS [185].

8. Targeting Redox Imbalance in Precision Therapy

8.1. Challenges in Translating Antioxidant Research into Clinical Practice

Despite the extensive preclinical evidence supporting the role of antioxidants in mitigating oxidative stress and associated pathologies, the translation of these findings into effective clinical interventions remains challenging. A major limitation lies in the complex duality of antioxidant compounds, which can exhibit pro-oxidant behavior under certain physiological conditions, influenced by factors such as dose, redox environment, and the presence of transition metals [186]. Furthermore, interindividual variability in antioxidant bioavailability, absorption, metabolism, and tissue distribution complicates the establishment of standardized therapeutic protocols. Previous studies have highlighted the challenges, which include improper dosing, oversimplification of redox biology, and the lack of validated biomarkers [187]. Similar studies point out that the failure of antioxidants in clinical trials is largely due to trial designs that neglect the complexity of oxidative stress dynamics, including the timing of intervention, the heterogeneous patient populations, and the failure to select appropriate endpoints [188]. Clinical trials often suffer from inconsistent methodologies, small sample sizes, and a lack of patient stratification, leading to inconclusive or conflicting outcomes. Moreover, non-specific scavenging of ROS may interfere with

essential physiological signaling pathways. These challenges underscore the necessity for a more targeted, biomarker-driven, and personalized approach to antioxidant therapy.

Additionally, systems biology approaches that integrate redox network modeling, multi-omics data, and signaling dynamics enable the stratification of redox phenotypes and the prioritization of context-specific therapeutic targets, moving the field toward precision redox medicine [189]. These approaches connect heterogeneous molecular measurements to emergent properties of biological systems, including multi-stability that modulates redox homeostasis in human cells, and they provide a quantitative framework for investigating redox regulation [190]. At the cellular scale, structural networks such as intermediate filaments can act as redox sentinel systems that detect and orchestrate responses to oxidative and electrophilic stress, illustrating how system-level organization links redox signals to phenotype [191].

Artificial intelligence and machine learning are promising tools to increase the clinical value of oxidative stress biomarker panels. By learning from combinations of multiple biomarkers and routine clinical variables, these methods can improve risk classification and diagnostic stratification in human cohorts [192]. They also capture patterns that go beyond standard clinical assessments and single biomarker measurements, and, with rigorous external validation and transparent reporting, they could mature into clinical decision support tools [192,193].

8.2. Therapeutic Applications of Vitamins and Supplements: Evidence from Recent Clinical Studies

Vitamins C and E are among the most extensively studied antioxidants for their potential therapeutic benefits in oxidative stress-related diseases. Recent clinical trials have explored their use as adjuncts in various conditions. For instance, vitamin C supplementation has shown promise in reducing fatigue and improving endothelial function in post-COVID-19 patients, especially when combined with L-arginine. High-dose intravenous vitamin C has been investigated as an adjuvant in cancer therapy due to its pro-oxidant cytotoxic effects in tumor microenvironments. In cardiovascular diseases, vitamin C exerts protective effects by improving endothelial nitric oxide bioavailability, reducing vascular oxidative damage, and modulating inflammatory responses. A recent study provides compelling evidence that vitamin C supplementation enhances endothelial function, attenuates atherosclerosis progression, and decreases arterial stiffness, with potential therapeutic applications in hypertension and coronary artery disease [194]. These effects are attributed to both its direct antioxidant activity and its role as a cofactor in enzymatic processes essential for vascular health.

Vitamin E, particularly in its α-tocopherol form, has demonstrated potential in attenuating lipid peroxidation and improving cardiovascular outcomes in patients with dyslipidemia and non-alcoholic fatty liver disease. Mechanistically, vitamins C and E act synergistically: Vitamin C regenerates oxidized vitamin E back to its active reduced form, thus maintaining lipid-soluble antioxidant protection in cellular membranes [195]. Beyond their antioxidant actions, both vitamins modulate immune responses. Moreover, vitamin E enhances T-cell-mediated immunity and interleukin-2 production, while vitamin C supports neutrophil activity, lymphocyte proliferation, and protects immune cells against oxidative stress-induced dysfunction [196]. This immunomodulatory capacity is especially relevant in populations with heightened oxidative and inflammatory burdens, such as elderly individuals or patients with chronic diseases.

Nevertheless, large-scale meta-analyses have revealed that the benefits of vitamin supplementation are context-dependent, with factors such as baseline nutritional status, disease severity, and co-treatment regimens playing critical roles in determining clinical efficacy. Future clinical trials incorporating precise redox biomarkers, immune function

endpoints, and stratified patient populations are essential to delineate the therapeutic roles of vitamins C and E in clinical practice.

Recent meta-analyses of randomized controlled trials provide a nuanced view of the effects of antioxidant interventions on oxidative stress biomarkers. Propolis supplementation significantly reduced inflammatory mediators, decreased lipid peroxidation, and enhanced antioxidant defenses (GSH, GPx, and SOD), with effects depending on dose and treatment duration [197]. Coenzyme Q10 supplementation also improved antioxidant capacity and reduced inflammatory and oxidative markers, with additional reductions in TNF-α and IL-6 observed depending on the analytic method, although heterogeneity and risk of bias warrant cautious interpretation [198]. In contrast, magnesium supplementation reduced C-reactive protein but showed no consistent effects on canonical oxidative stress markers, underscoring variability across antioxidant strategies [199]. Pharmacological interventions have likewise been evaluated, where GLP-1 receptor agonists and SGLT2 inhibitors have also demonstrated clinically relevant antioxidant effects [200]. Collectively, these findings highlight that although several antioxidant therapies can modulate oxidative stress biomarkers, their translation into robust clinical outcomes remains uncertain and context dependent. Indeed, many randomized controlled trials of antioxidant supplementation have failed to demonstrate clear clinical benefits. This may reflect fundamental limitations of testing isolated antioxidants in complex diseases, where redox balance is regulated by integrated networks that are not easily modified by single compounds [189]. These inconclusive results suggest that conventional trials using nutritional supplements may not be sufficient to capture the true therapeutic potential of redox-targeted strategies, and that more approaches guided by validated biomarkers and precision medicine are needed.

8.3. Targeting Redox Imbalance in Precision Therapy

The redox state of cells plays a crucial role in maintaining a stable microenvironment that supports the proper functioning of biological macromolecules. Disruptions in redox homeostasis are strongly associated with the onset and progression of numerous diseases, including cancer, neurodegeneration, metabolic disorders, and inflammation. Therapeutic strategies targeting this imbalance are emerging as promising interventions capable of restoring cellular homeostasis and selectively eliminating diseased cells. Nevertheless, clinical outcomes of redox-targeted strategies have so far been limited and remain below expectations [201].

In cancer, especially in cancer stem cells (CSCs), redox imbalance is often exploited to maintain proliferative and survival advantages. CSCs exhibit a finely tuned redox environment: while maintaining lower ROS levels than differentiated tumor cells, they upregulate antioxidant defenses (e.g., glutathione, superoxide dismutase, and the NRF2 pathway) to avoid oxidative damage and apoptosis. Targeting these antioxidant shields, such as inhibiting glutathione synthesis or disrupting thioredoxin reductase, can sensitize CSCs to chemotherapy and radiation, offering a novel route to overcome therapeutic resistance [202]. Recent studies have further demonstrated that CSCs are particularly susceptible to ferroptosis, a non-apoptotic form of cell death driven by iron-dependent lipid peroxidation. Agents like salinomycin and ironomycin can selectively induce ROS and ferroptosis in mesenchymal CSCs by disrupting iron metabolism and lysosomal function. Moreover, metal-based complexes, such as copper (II) and ruthenium nanocatalysts, have been shown to deplete intracellular antioxidants and trigger oxidative collapse in CSC populations. These approaches bypass the conventional resistance mechanisms and exploit the delicate redox balance in CSCs as a therapeutic vulnerability. As a result, redox-targeted therapies represent a promising strategy for eradicating therapy-resistant tumor cell subsets and improving long-term cancer treatment outcomes.

Similarly, in neurodegenerative diseases such as Alzheimer's and Parkinson's, redox dysregulation leads to mitochondrial dysfunction, protein aggregation, and neuronal death. Therapeutics aimed at enhancing endogenous antioxidant systems (e.g., NRF2 activators and mitochondria-targeted antioxidants like MitoQ) or reducing ROS formation have shown neuroprotective effects in preclinical models, although translation into clinical efficacy remains challenging [203].

An emerging area of interest is the development of metal-based redox modulators, particularly coordination complexes that interfere with redox signaling. Some of these metal complexes (e.g., Cu, Ru, or Fe-based compounds) induce oxidative stress selectively in cancer cells by disrupting thiol-based antioxidant defenses or generating ROS in situ. These agents can act synergistically with conventional therapies or serve as standalone cytotoxic drugs by exploiting the redox vulnerability of tumor microenvironments [204]. Redox-targeted therapies also include small molecules such as pro-oxidants (e.g., β-lapachone, a NAD(P)H:quinone oxidoreductase 1 bioactivator), NRF2 inhibitors in cancer (to prevent resistance), or NRF2 activators in neuroinflammation and aging. This duality underscores the need for precise, context-dependent therapeutic strategies.

Nanotechnology has recently provided innovative strategies to modulate oxidative stress through the development of redox-responsive nanomaterials. These platforms are designed to directly neutralize excessive ROS or to release therapeutic antioxidants in response to local redox conditions, thereby achieving improved stability, bioavailability, and site-specific targeting compared with conventional small molecules [205]. A key advance is that several nanomaterials act as nanozymes, mimicking enzymatic antioxidant activities such as SOD and CAT, providing sustained redox regulation rather than transient scavenging [206]. In autoimmune contexts, steroid-loaded reconstituted high-density lipoprotein nanoparticles have reduced inflammatory cytokines and kidney damage in preclinical models, highlighting their potential as adjunct therapies [207]. In neuroinflammatory conditions, cerium oxide nanoparticles have demonstrated neuroprotective and anti-inflammatory actions through continuous ROS scavenging, suggesting utility in slowing progression of neurodegeneration [208]. Taken together, redox-based nanomaterials act either by mimicking antioxidant enzymes to provide continuous ROS scavenging or by releasing antioxidants in a controlled manner, offering more effective and targeted strategies against oxidative stress than conventional therapies.

While targeting redox imbalance holds significant therapeutic promise, it also presents challenges: redox networks are highly context-specific, with outcomes dependent on cell type, disease stage, and intracellular ROS thresholds. Future work must prioritize selective delivery systems (e.g., nanoparticles), precise biomarkers of redox status, and combinatorial approaches to maximize therapeutic efficacy while minimizing systemic toxicity.

9. Conclusions

Redox homeostasis is essential for preserving the structural and functional integrity of biological systems. When this balance is disturbed, excess reactive oxygen species (ROS) contribute to the initiation and progression of various non-communicable diseases (NCDs), including cardiovascular, neurodegenerative, inflammatory, and autoimmune disorders. The dual role of ROS, as both signaling molecules and agents of cellular damage, underlines the complexity of redox biology.

This review highlights the critical impact of oxidative stress on biomolecular damage, immune modulation, and disease pathogenesis. Specific immune responses, such as NF-κB activation, Th17 polarization, and Treg impairment, are directly influenced by redox imbalance, further linking ROS to chronic inflammation and autoimmunity (e.g., in IBD and SLE). Enzymatic and non-enzymatic antioxidant systems serve as primary defenses against

ROS, while nutritional antioxidants and emerging therapeutic strategies offer potential avenues for intervention.

Despite promising preclinical data, redox-targeted therapies have yet to deliver consistent clinical benefits, partly due to the complexity and context-dependence of oxidative signaling. Future therapeutic approaches must consider the specificity, timing, and cellular context of redox interventions to achieve effective and personalized treatments. Continued research into redox-sensitive pathways, biomarkers, and targeted delivery systems will be key to advancing precision medicine in oxidative stress-related diseases.

Advancing our understanding of redox biology requires a shift from generalized antioxidant supplementation toward a more nuanced, precision-based approach. Emerging strategies, including modulation of specific redox-sensitive pathways (e.g., NRF2 activation, NOX inhibition, and NLRP3 inflammasome suppression) and the development of redox-responsive drug delivery systems, are paving the way for more targeted interventions. Integrating advanced omics technologies with clinical biomarker profiling will enable patient stratification based on redox phenotype, facilitating personalized antioxidant therapies. Large-scale, well-designed clinical trials that consider interindividual variability and utilize robust biomarkers will be essential for translating these strategies into effective treatments. Embracing the complexity of redox networks and prioritizing context-specific therapeutic approaches is critical to unlocking the full potential of redox-based interventions in combating NCDs.

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Abbreviations

The following abbreviations were used in this manuscript:

8-oxoG	8-Oxoguanine
ABTS	2,2′-Azino-Bis(3-Ethylbenzothiazoline-6-Sulfonic Acid)
AGEs	Advanced Glycation End Products
ALS	Amyotrophic Lateral Sclerosis
APOP	Advanced Protein Oxidation Products
ATM	Ataxia-Telangiectasia Mutated
ATO	Arsenic Trioxide
ATR	ATM and Rad3-Related
CAT	Catalase
CSCs	Cancer Stem Cells
DPPH	2,2-Diphenyl-1-Picrylhydrazyl
EGCG	Epigallocatechin Gallate
FRAP	Ferric-Reducing Antioxidant Power
GC-MS	Gas Chromatography–Mass Spectrometry
GPx	Glutathione Peroxidase
GSH	Glutathione (Reduced Form)
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry
NCDs	Non-Communicable Diseases
SLE	Systemic Lupus Erythematosus
SOD	Superoxide Dismutase

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