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Biochemical Mechanisms of Oxidative Stress and Antioxidant Defense Systems in Disease Progression: A Review

Samer Obaid Hasan Hasan¹, Ghufra Saad Nsaif^{*2}, Alaa Mohammed Etheb³

1,2,3. Department of Chemistry, College of Science, Baghdad University, Baghdad, Iraq

*Correspondence: ghofran.saad@sc.uobaghdad.edu.iq

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Abstract: Oxidative stress is a basic biochemical disturbance resulting from an imbalance and overproduction of reactive oxygen and nitrogen species when the level exceeds the cellular antioxidant capacity. We need controlled reactive species for signaling, immune defense, mitochondrial adaptation and vascular control; yet persistent imbalance in redox equilibrium favors lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction and inflammation which results in progressive tissue damage. Traditionally, the concept of antioxidant defense has been restricted to isolated pathways, but lately it has been emphasized that such mechanisms are coordinated and comprise enzymes (superoxide dismutase, catalase, glutathione peroxidase, peroxiredoxins and thioredoxin systems) in conjunction with nonenzymatic antioxidants (glutathione, vitamins C and E, carotenoids, melatonin, uric acid, selenium-containing molecules, from selenium enriched foods—and dietary polyphenols). Oxidative stress and its contribution to the pathology of cardiovascular disease, diabetes mellitus, carcinogenesis, neurodegenerative disorders, chronic kidney injury with fibrosis in development related liver injury as well as inflammatory bowel disease are highlighted Processes associated with aging-related degeneration Sources of oxidative damage. In this review, we discuss the biochemical origins of reactive species, a multitiered antioxidant protection system, primary redox biomarkers, and disease pathways. Finally, it highlights the need for caution in interpretation of antioxidant therapy as nonstaged or over-supplemented and/or uncontrolled pathways to the disease state may fail where authorities exist.

Keywords: Antioxidants; Biomarkers; Disease progression; Oxidative stress; Reactive oxygen species; Redox balance.

Introduction

Oxidative stress widely accepted biochemically as an enx between cellular reactive metabolism, inflammation and the progression of chronic disease. It occurs when the creation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overloads their antioxidant systems [1], [2] . The imbalance is not just a poisonous event, it is disturbance of redox homeostasis that deranges signaling, gene expression, enzyme activity and organ function [2], [3].

At physiological concentrations, ROS are involved in cell signaling, immune response and defense, vascular tone regulation, apoptosis and adaptation to exercise and metabolic stress [3], [4]. ROS and RNS cause damage to lipids, proteins, carbohydrates and nucleic acids at high or excessive concentrations or after prolonged actions. The resulting change transforms redox signaling into oxidative injury, thereby positioning oxidative stress as a principal mechanism of diabetes, cardiovascular disorders, cancer, neurodegeneration, inflammatory diseases and aging [4], [5].

Antioxidant defense systems are critical for preventing oxidative damage and, in particular, to allow for beneficial redox signaling. Despite this, the human body functions with enzymatic antioxidant systems, low-molecular-weight antioxidants, repair pathways and transcriptional responses including that of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. The biochemical nature of oxidative stress can only reach its full relevance by bridging mechanisms to the clinical course of disease [5], [6].

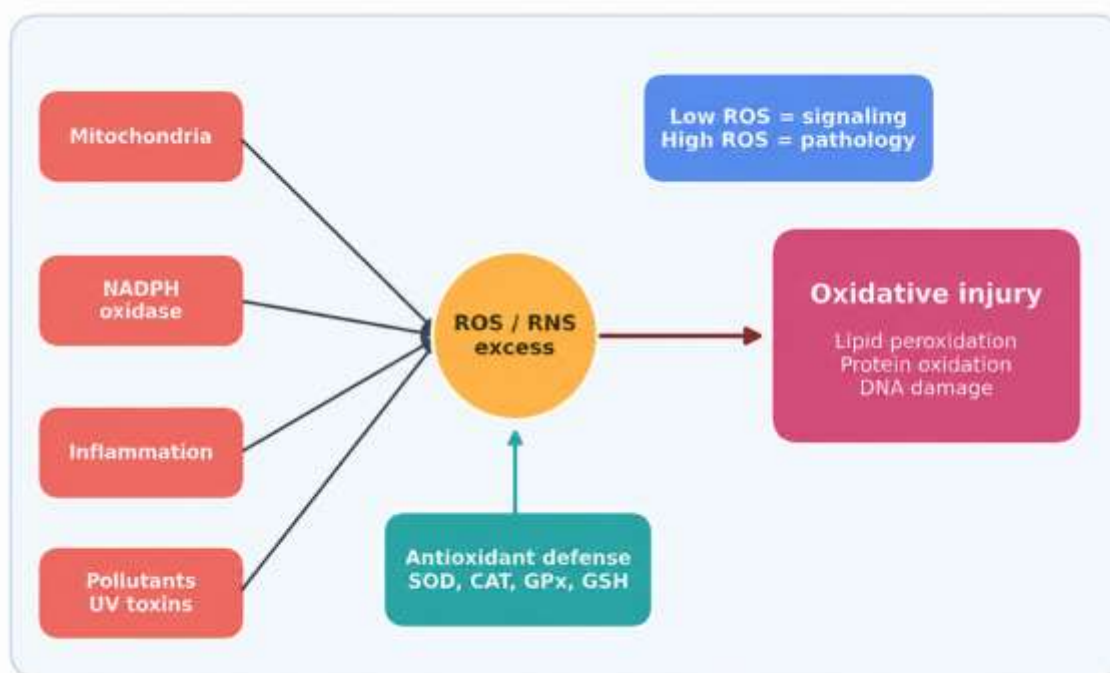


Figure 1. Biochemical transition from physiological redox signaling to oxidative damage.

Sources and Biochemical Chemistry of Reactive Species

The ROS include superoxide anion, hydrogen peroxide (H₂O₂), hydroxyl radical (HO·), singlet oxygen ¹O₂ and other related intermediates derived from oxygen [7]. Nitric oxide, nitrogen dioxide and peroxynitrite are all RNS. Molecules The half-life, diffusibility and chemical reactivity of these molecules is variable. Superoxide, the simplest free radical species, is usually originating from one-electron reduction of oxygen; hydrogen peroxide then could be produced by superoxide dismutase or oxidase enzymes, diffusing across membranes and controlling signaling [7], [8].

The most harmful species are hydroxyl radical for reacting fast with the biomolecules present nearby. Perhaps via Fenton-type reactions of hydrogen peroxide in the presence of transition metals. Peroxynitrite, the product of reaction between superoxide and nitric oxide, decreases bioavailability of

nitric oxide, induces protein nitration, causes mitochondrial damage and leads to endothelial dysfunction [8], [9].

Significant sources of ROS include the mitochondrial electron transport chain, NADPH oxidases, xanthine oxidase, uncoupled nitric oxide synthase species (NOS), cytochrome P450 enzymes and peroxisomes and activated immune cells. Ultraviolet radiation, cigarette smoke and alcohol, heavy metals (mercury), toxins in the air we breathe or pesticides from plants as well as particulate matter chewed (inhaling) or swallowed drugs are other exogenous contributors [9], [10]. For example, the relationship between ROS generation (intensity, duration, cellular compartment) and disease impact is largely context-dependent.

Antioxidant Defense Systems

The antioxidant defence system is more like multilayered network than a single reaction. Enzymatic antioxidants form the first line of defence by preventing or rapidly detoxifying reactive species. Superoxide dismutase reduces the superoxide to hydrogen peroxide, catalase breaks down hydrogen peroxide into water and oxygen while glutathione peroxidase reduce hydrogen peroxide and lipid hydroperoxides by utilizing reduced glutathione [11].

The glutathione trafficking system is essential for cellular homeostasis of redox. Reduced glutathione serves as an electron donor to glutathione peroxidase; and plays roles in detoxification, thiol protection, and redox signaling. First, the ratio of reduced to oxidized glutathione (GSH:GSSG) is widely considered an indicator of intracellular redox state but care must be taken in its interpretation due to variations in tissue type, sampling conditions and analytical method [12].

Decades of scientific research have focused on the non-enzymatic antioxidants: glutathione, vitamin C (ascorbic acid), vitamin E (α -tocopherol), carotenoids, melatonin, uric acid, bilirubin, lipoic acid and selenium-dependant species such as selenocysteine and methionine. Vitamin C works mainly in aqueous environments (blood plasma, cytosol), and vitamin E is responsible for preventing oxidative damage to unsaturated fatty acids in lipid membranes, whilst polyphenols decrease directly this oxidative damage through anti-inflammatory and signaling effects. Yet, their clinical impact is governed by bioavailability and metabolism [13].

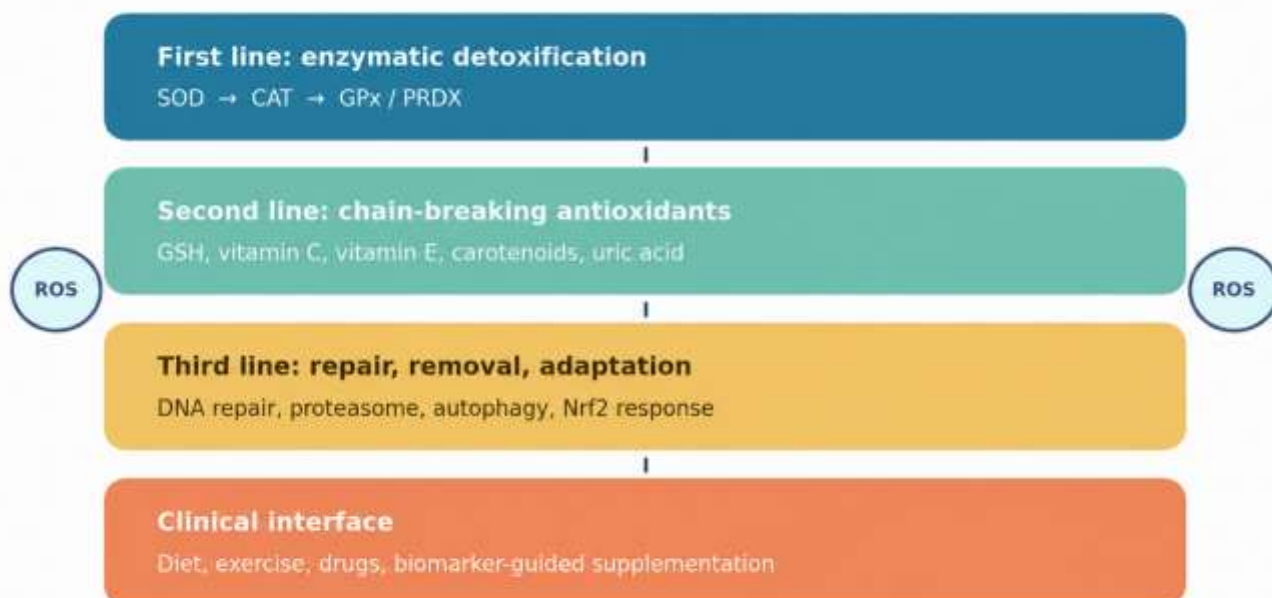


Figure 2. Layered antioxidant defense system: enzymatic detoxification, chain-breaking antioxidants, repair, and clinical interface.

Oxidative Stress and Disease Progression

Several overlapping mechanisms exist, allowing oxidative stress to accelerate disease progression. It stimulates redox-sensitive inflammatory pathways, disrupts mitochondrial function, damages endothelial cells, induces lipid peroxidation, restructures proteins and creates genomic instability. This results in a vicious cycle where inflammation leads to ROS which then promote the inflammatory signal causing continued tissue injury .

Oxidative stress reduces nitric oxide bioavailability in cardiovascular disease, encourages endothelial dysfunction, oxidizes low-density lipoprotein (LDL), activates vascular inflammation and promotes atherosclerosis and hypertension. Abstract: In cardiovascular disorders, it has been further examined but standardization still lacking for this biomarkers in clinical settings.

In the case of diabetes mellitus, chronic hyperglycaemia enhances ROS production by mitochondrial overload, advanced glycation end products giving rise to protein kinase C activation and inflammatory signalling. Oxidative stress impairs beta-cell function and exacerbates insulin resistance, leading to diabetic nephropathy, neuropathy and retinopathy as well as cardiovascular complications.

ROS have a dual role in cancer [14]. The moderate ROS can promote mutation accumulation, proliferation, angiogenesis, invasion and resistance signalling, while the severe kinds could induce apoptosis or ferroptosis or any other cell-death mechanisms. The dual role of ROS also accounts for the complexity of antioxidant therapy in cancer, which is often inappropriate without incorporating tumor type, disease stage, and treatment context.

In neurodegenerative disorders, the brain is vulnerable because it has high oxygen consumption, abundant polyunsaturated lipids, and relatively limited antioxidant reserves. Oxidative stress contributes to mitochondrial dysfunction, protein aggregation, neuroinflammation, and neuronal loss, which are relevant to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other progressive neurological conditions [15].

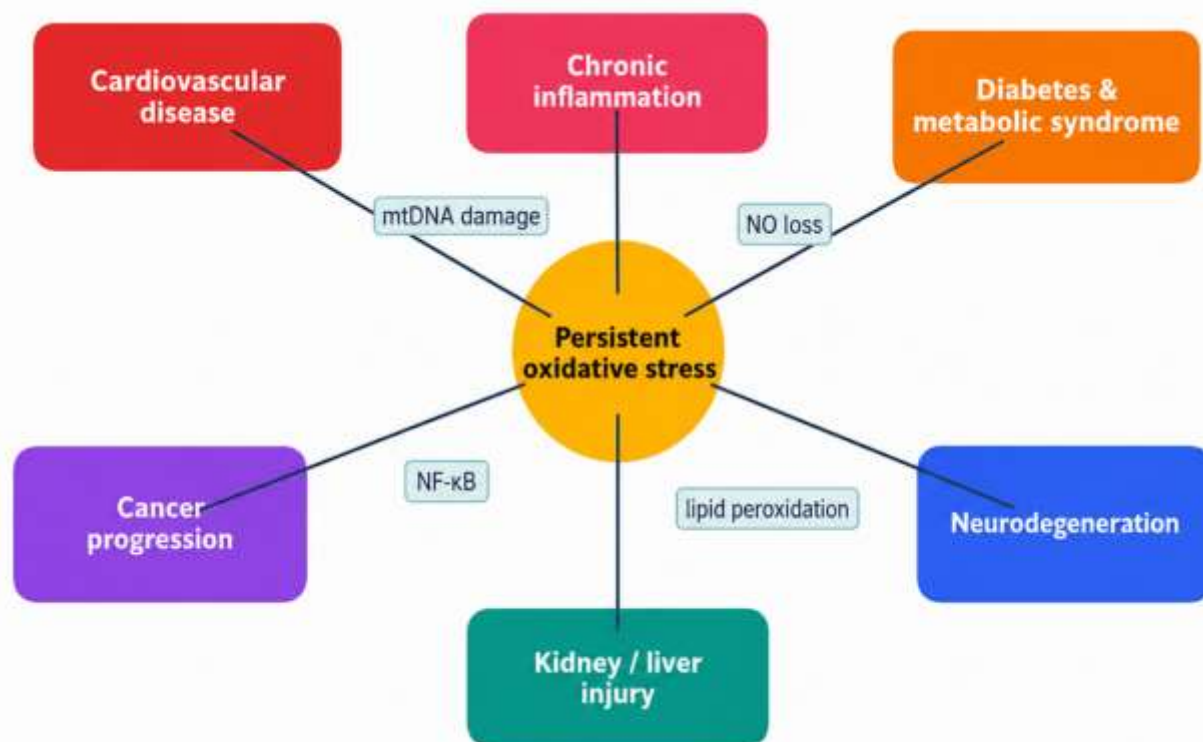


Figure 3. Major disease pathways influenced by persistent oxidative stress.

Oxidative Stress Biomarkers

Memorization of the biomarkers of lipid peroxidation such as malondialdehyde, 4-hydroxynonenal, F2-isoprostanes and oxidized LDL. Protein carbonyls, nitrotyrosine, and advanced oxidation protein products may be assessed as indicators of protein oxidation. DNA oxidative modification is often evaluated by means of 8-hydroxy-2'-deoxyguanosine, whereas antioxidant status can be indirectly assessed using total antioxidant capacity, glutathione ratio and the activity of antioxidant enzymes.

Biomarker interpretation is difficult because ROS are short-lived and many measurements are indirect. The results may be influenced by many factors, including sample handling and storage temperature, hemolysis, diet, medications, inflammation, age, or the presence of any comorbidities. Consequently, a biomarker panel is more powerful than one single marker in assessing oxidative stress in the disease evolution.

More recently, a growing number of studies have advocated that both oxidative damage markers and antioxidant defence markers should be intermixed into an index. This allows differentiation between increased oxidant production and decreased antioxidant capacity. This too would likely enhance disease monitoring, risk stratification, and the evaluation of antioxidant or lifestyle interventions.

Table 1. Practical oxidative stress biomarkers used in biochemical studies

Biochemical target	Representative biomarkers	Interpretation	Limitations
Lipids	MDA, 4-HNE, F2-isoprostanes, oxLDL	Membrane lipid oxidation and atherosclerotic risk	Affected by diet, handling, and assay specificity
Proteins	Protein carbonyls, nitrotyrosine, AOPP	Oxidative/nitrative modification of enzymes and structural proteins	May not identify the exact protein target
DNA/RNA	8-OHdG, oxidized nucleosides	Genomic and mitochondrial oxidative injury	Requires validated collection and storage
Antioxidant status	SOD, CAT, GPx, GSH/GSSG, TAC	Capacity of antioxidant defense systems	A single marker rarely reflects total redox state

Antioxidant Strategies and Clinical Limitations

These redox-directed strategies involve a variety of interventions, including dietary modification, physical exercise, body weight control, cessation of smoking, hyperglycemia control/management (exercise and drugs), micronutrient supplementation/natural products/radical scavengers-rich food and/or pharmacological manipulation of the redox pathways. Although high fruit and vegetable-, polyphenols-, carotenoids-, selenium- and vitamin-rich diets contribute to the maintenance of antioxidant capacity, dietary antioxidants act within a circumscribed metabolic network instead of free-radical scavengers.

But the results from clinical trials of antioxidant supplementation have been inconsistent. The first facet of this is that oxidative stress is compartment specific: mitochondrial ROS, membrane lipid peroxidation and inflammatory ROS may benefit from different interventions. Furthermore, in healthy adults reduced levels of ROS are required for normal signaling; therefore, excess antioxidant supplementation might dampen the adaptive response or never leave the relevant tissue compartment.

The future direction would be even stronger: Personal Redox Medicine. This covers selective identification of oxidative biomarkers, selective targeting of antioxidants for diseases, bioavailability enhancement strategies, Nrf2 and mitochondrial pathway modulation methods, and combinations of various antioxidants with standard therapies. Mechanism, timing, dose and patient phenotype may be better characteristic for such more than generalized supplementation approaches.

Conclusion

Oxidative stress represents one of the most critical biochemical links between cellular metabolism and disease evolution. It initiates when ROS and RNS generation exceeds the ability of antioxidant capacity or when misregulation in antioxidant responses occurs. This imbalance causes damage to lipids, proteins, DNA, mitochondria and membranes using ROS (reactive oxygen species) while also activating inflammatory pathways and triggering cell-death programs. Mechanisms of antioxidant defense are layered involving enzymatic detoxification, glutathione-based redox buffering, low-molecular-weight antioxidants as well as repair mechanisms and transcriptional adaptations. Science has recently tur[ned] strongly on to the links between oxidative stress and cardiovascular disease, diabetes mellitus, cancer, neurodegeneration, renal and liver injury, inflammatory diseases and aging. However, due to the context dependency of redox biology, mechanistic and biomarker-guided antioxidant therapy should be implemented. Future biochemical studies should ultimately focus on standardization of biomarker panels, delivery of therapeutic antioxidants to targeted tissues and modulation of endogenous defense pathways, as well as personalized redox-based interventions.

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