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Role of Antioxidants in Biological Systems: Mechanisms, Sources and Clinical Implications

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Abstract:
Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are continuously generated in biological systems as inevitable by-products of aerobic metabolism. Although these reactive molecules play important physiological roles in cell signaling and immune defense, their excessive production leads to oxidative stress, a condition characterized by imbalance between pro-oxidants and antioxidant defense systems. Oxidative stress damages essential biomolecules including lipids, proteins, carbohydrates, and nucleic acids, thereby contributing to the pathogenesis of various disorders such as cardiovascular diseases, cancer, diabetes mellitus, neurodegenerative diseases, and reproductive dysfunction. The human body possesses an integrated antioxidant defense system comprising enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase, along with non-enzymatic antioxidants including vitamins C and E, carotenoids, flavonoids, glutathione, and uric acid. Dietary antioxidants further support endogenous defense mechanisms. This article reviews the formation of free radicals, classification and mechanisms of antioxidant action, levels of antioxidant defense, sources of antioxidants, clinical significance, and limitations associated with antioxidant therapy. Understanding antioxidant biology is essential for developing preventive and therapeutic strategies against oxidative stress-mediated diseases.

Keywords: Free radicals; Reactive oxygen species; Antioxidants; Oxidative stress; Lipid peroxidation; Enzymatic antioxidants.

1. Introduction

Oxygen is indispensable for aerobic life, as it plays a central role in mitochondrial energy production through oxidative phosphorylation. However, during this process, a small fraction of oxygen undergoes incomplete reduction, leading to the formation of reactive oxygen species (ROS). In addition to ROS, reactive nitrogen species (RNS) are also generated during physiological and pathological processes. Free radicals are molecules containing one or more unpaired electrons, making them highly reactive and unstable. They are produced endogenously during cellular metabolism and exogenously through environmental exposure such as pollution, radiation, cigarette smoke, heavy metals, and psychological stress. While moderate levels of reactive species participate in host defense mechanisms and cellular signaling, excessive accumulation results in oxidative stress. Oxidative stress damages lipids (lipid peroxidation), proteins (protein oxidation), and DNA (mutagenesis), thereby contributing to the development of chronic diseases including atherosclerosis, hypertension, diabetes mellitus, cancer, neurodegenerative disorders, infertility, and aging-related conditions. Growing evidence highlights the crucial role of antioxidants in maintaining redox homeostasis and protecting biological systems from oxidative injury.

2. Materials and Methods

This study is a structured narrative review based on peer-reviewed journal articles, textbooks, and authoritative publications related to oxidative stress and antioxidant biology. Literature was collected from indexed scientific databases, and studies focusing on mechanisms of oxidative damage, antioxidant classification, enzymatic and non-enzymatic defense systems, and clinical implications were analyzed. Information was systematically organized under IMRAD structure to ensure scientific clarity and coherence.

3. Results

3.1 Formation of Free Radicals

Free radicals are generated primarily in mitochondria during electron transport chain activity. Leakage of electrons leads to the formation of superoxide anion ($O_2^{\bullet -}$), which can subsequently form hydrogen peroxide (H2O2) and hydroxyl radicals (•OH). Reactive nitrogen species such as nitric oxide (NO•) and peroxynitrite ($ONOO^-$) are formed during inflammatory processes.

Physiological roles of ROS include:

- Microbial killing by immune cells
- Regulation of cell signaling pathways
- Apoptosis and gene expression modulation

Pathological overproduction results in:

- DNA strand breaks
- Lipid peroxidation
- Protein carbonylation
- Mitochondrial dysfunction

3.2 Classification of Antioxidants

Antioxidants are classified into:

3.2.1 Enzymatic Antioxidants

- Superoxide dismutase (SOD)
- Catalase
- Glutathione peroxidase (GPx)
- Glutathione-S-transferase (GST)

3.2.2 Non-Enzymatic Antioxidants

- Vitamin C (ascorbic acid)
- Vitamin E (tocopherols)
- Carotenoids (lycopene, beta-carotene)
- Flavonoids
- Glutathione
- Uric acid
- Bilirubin

3.2.3 Dietary Antioxidants

- Fruits and vegetables
- Fish oils (Omega-3 fatty acids)
- Nuts and seeds
- Whole grains

3.3 Mechanisms of Antioxidant Action

Antioxidants function through two principal mechanisms:

3.3.1 Chain-Breaking Mechanism

Primary antioxidants donate electrons or hydrogen atoms to neutralize free radicals, thereby terminating chain reactions of lipid peroxidation.

3.3.2 Preventive Mechanism

Secondary antioxidants prevent radical formation by:

- Chelating transition metals (iron, copper)
- Decomposing hydroperoxides
- Regulating antioxidant enzyme gene expression

3.4 Levels of Antioxidant Defense

First Line: Preventive Antioxidants

- Glutathione peroxidase reduces hydrogen peroxide to water.
- Catalase decomposes hydrogen peroxide into water and oxygen.
- PHGPx reduces phospholipid hydroperoxides in membranes.

Second Line: Radical Scavengers

- Vitamin C (water-soluble)
- Vitamin E (lipid-soluble)
- Uric acid
- Bilirubin
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- Ubiquinol

Third Line: Repair and De Novo Systems

- Proteases remove oxidized proteins.
- DNA repair enzymes correct oxidative DNA damage.

Fourth Line: Adaptation

Upregulation of antioxidant enzymes via gene expression in response to oxidative stress.

3.5 Clinical Implications

Oxidative stress is implicated in:

- Cardiovascular diseases (atherosclerosis, hypertension)
- Cancer (DNA mutation, genomic instability)
- Neurodegenerative diseases (Alzheimer's, Parkinson's)
- Diabetes mellitus
- Reproductive dysfunction
- Liver and kidney disorders
- Age-related macular degeneration

Smokers exhibit reduced plasma levels of vitamins C and E due to increased oxidative burden. Chronic psychological stress also elevates oxidative markers, contributing to aging and immune dysfunction.

4. Discussion

The balance between oxidants and antioxidants determines cellular homeostasis. While reactive species are essential for physiological functions, uncontrolled production results in pathological consequences. The integrated antioxidant system—comprising enzymatic and non-enzymatic components—provides multi-level protection against oxidative damage. Dietary antioxidants significantly contribute to systemic redox balance. However, limitations such as poor bioavailability, rapid metabolism, limited tissue penetration, and lack of specificity restrict therapeutic outcomes. Some antioxidants may interfere with beneficial ROS involved in cellular signaling. Current research emphasizes targeted antioxidant delivery systems, nanotechnology-based formulations, gene-regulatory approaches to enhance antioxidant efficacy.

5. Limitations

- Limited bioavailability of certain antioxidants
- Inadequate site-specific delivery
- Potential interaction with beneficial ROS
- Variable clinical outcomes in supplementation studies

6. Conclusion

Free radicals play a central role in the pathogenesis of multiple chronic diseases through oxidative damage to biomolecules. Antioxidants, both endogenous and exogenous, serve as critical protective agents by neutralizing reactive species and maintaining redox homeostasis. Although antioxidant supplementation may provide therapeutic benefits, optimal dosage, bioavailability, and targeted delivery remain challenges. Future research should focus on precision antioxidant therapy and molecular-level interventions to effectively combat oxidative stress-related disorders.

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Conflict of Interests

The authors declare no conflict of interest

Ethics Approval: Not applicable

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AI Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Data Availability

Data will be available on request

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