# The Dual Role of ROS and Antioxidants in Health and Disease

**Dra. (MD) Monica Cristina Carrasco**
Universidad de Carabobo, Venezuela

## Abstract

Reactive oxygen species (ROS) are key players in cellular processes, acting as both damaging agents and vital signaling molecules. The balance between ROS production and antioxidant defenses is essential for maintaining cellular homeostasis and preventing oxidative stress. This review explores the dual role of ROS, emphasizing the paradoxical effects of ROS in both promoting cell survival and causing cellular damage. It also examines the mechanisms of endogenous antioxidant defenses and the impact of excessive antioxidant supplementation, which may lead to antioxidative stress. By analyzing the pathways that regulate ROS production and detoxification, this paper highlights the importance of personalized strategies in managing oxidative stress and optimizing redox homeostasis.

*Keywords*: *Reactive oxygen species, oxidative stress, antioxidants, redox homeostasis, cell signaling, antioxidative stress, personalized therapy.*

## Introduction

The balance between reactive oxygen species (ROS) and antioxidants is a fundamental aspect of cellular function and overall health [1]–[3]. ROS are highly reactive molecules derived from oxygen that can either be free radicals, such as superoxide anion ($O_2^{\bullet -}$) and hydroxyl radical ($OH^{\bullet}$), or non-radical species like hydrogen peroxide ($H_2O_2$). These molecules are produced as natural byproducts of aerobic metabolism, particularly in the mitochondria, and play essential roles in cellular signaling and immune response. However, when their levels exceed the body's antioxidant capacity, ROS can induce oxidative stress, leading to damage of DNA, lipids, and proteins. This oxidative damage is associated with numerous chronic conditions, including cardiovascular diseases, cancer, diabetes, and neurodegenerative disorders.

Antioxidants, both enzymatic (e.g., superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic (e.g., vitamins C and E, glutathione), act as key defenses against oxidative stress. These substances work by neutralizing ROS and preventing cellular damage [4], [5]. The antioxidant system is a crucial part of redox homeostasis, where the balance between ROS production and antioxidant defenses is tightly regulated. Disruptions in this balance—whether through excessive ROS production or insufficient antioxidant defense—can lead to pathological conditions. In recent years, there has been growing interest in understanding not only the harmful effects of ROS but also their beneficial roles as signaling molecules in biological processes like cell proliferation, differentiation, apoptosis, and immune activation [2]. This dual role of ROS presents a complex dynamic, where both excessive ROS and an overabundance of antioxidants can disrupt cellular function.

This paper contributes to the ongoing exploration of the delicate balance between ROS and antioxidants, highlighting how oxidative stress contributes to both cellular damage and essential physiological processes. The review examines historical perspectives on the oxidative stress theory, the mechanisms of endogenous antioxidants, and the paradoxical role of ROS in both promoting cell damage and supporting cell signaling. It also addresses the consequences of oxidative stress and "antioxidative stress" — the state in which excessive antioxidant intake may impair normal cellular processes. By reviewing recent literature, the paper provides a comprehensive understanding of the critical balance between ROS and antioxidants and suggests that managing this balance is key to maintaining health and preventing disease. This paper emphasizes the need for more personalized approaches to managing oxidative stress, considering individual health status, genetic factors, and environmental influences in the design of antioxidant strategies.

## Literature Review

The theory of oxidative stress has evolved significantly since the identification of reactive oxygen species (ROS) and their impact on cellular components. Initially, ROS were considered harmful byproducts of aerobic metabolism, responsible for cellular damage, DNA mutations, lipid peroxidation, and protein oxidation. This damage-centric view dominated early studies on oxidative stress. Over time, however, the understanding of ROS expanded to include their role in essential biological processes such as cellular signaling and homeostasis. Early research focused on the detrimental effects of ROS, but later studies began to explore their paradoxical role in signaling pathways, such as those involved in immune responses and cell proliferation [4]–[6]. The discovery of antioxidants marked another significant milestone in the oxidative stress theory. Antioxidants, including enzymatic antioxidants like superoxide dismutase (SOD) and catalase, and non-enzymatic antioxidants such as vitamins C and E, were found to counterbalance the harmful effects of ROS. These substances scavenge free radicals and maintain cellular redox homeostasis. With further research, it became clear that antioxidants do more than simply neutralize ROS—they are involved in regulating critical cellular functions [7]. Different sources of ROS is shown in Figure 1.

Endogenous antioxidants are critical for maintaining the balance between ROS production and neutralization. The human body possesses several mechanisms to regulate ROS, with the primary defense system composed of enzymatic antioxidants. These enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), work in a coordinated manner to neutralize ROS and prevent cellular damage. Superoxide dismutase (SOD) plays a key role by converting the superoxide radical ($O_2^{\bullet -}$) into hydrogen peroxide ($H_2O_2$), a less reactive species. Hydrogen peroxide is then detoxified by catalase, which converts it into water and oxygen, or by glutathione peroxidase, which uses glutathione as a substrate for its reduction. This intricate antioxidant network is vital for maintaining cellular homeostasis and protecting cells from oxidative stress [8]–[11]. In addition to enzymatic antioxidants, non-enzymatic antioxidants such as vitamins C and E, glutathione, and flavonoids play a crucial role in neutralizing ROS. Vitamin C, for instance, is a water-soluble

antioxidant that scavenges free radicals and regenerates other antioxidants, including vitamin E, which protects lipid membranes from oxidative damage. Glutathione, a tripeptide composed of glutamine, cysteine, and glycine, is involved in detoxifying hydrogen peroxide and maintaining the redox balance in cells [12]. The body's endogenous antioxidant defenses are tightly regulated to ensure that ROS levels remain within physiological ranges. These defenses are essential for preventing oxidative damage to critical cellular components such as lipids, proteins, and DNA. The failure of antioxidant defenses can result in oxidative stress, which has been implicated in the pathogenesis of numerous diseases, including cardiovascular diseases, cancer, neurodegenerative disorders, and diabetes [13]–[15].

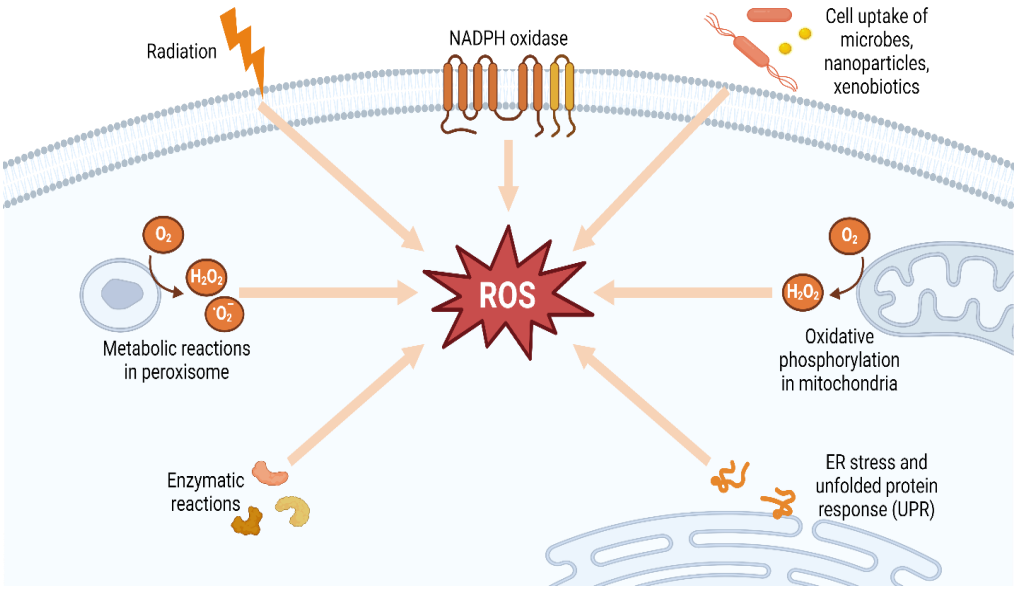


**Figure 1. Sources of Reactive Oxygen Species (ROS). Created with BioRender.com**

Despite their reputation for causing cellular damage, ROS play a dual role in cell biology. At low to moderate levels, ROS serve as important signaling molecules involved in various cellular processes, including cell proliferation, differentiation, and apoptosis. For example, ROS activate several signaling pathways such as mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF-κB), and the phosphoinositide 3-kinase (PI3K)/Akt pathway, all of which are critical for cell survival, immune responses, and programmed cell death [16], [17]. The paradoxical nature of ROS is evident in their involvement in both cell survival and cell death. While high levels of ROS lead to oxidative stress and cellular damage, moderate levels are necessary for proper cell function. ROS-induced oxidative stress can result in mitochondrial dysfunction, DNA mutations, and lipid peroxidation, which are associated with various diseases, including cancer and neurodegenerative disorders. However, low levels of ROS are essential for the activation of signaling pathways that regulate cell proliferation and apoptosis, processes critical for normal cell turnover and

immune response activation [18]. This dual role of ROS highlights the importance of maintaining a balance between ROS production and antioxidant defenses. Excessive antioxidant supplementation, for example, may suppress the beneficial effects of ROS, impairing immune responses and other essential processes. This is particularly concerning in conditions where ROS play a protective role, such as in the immune system's oxidative burst used to kill pathogens [19].

### *Mechanisms of Balance*

The balance between reactive oxygen species (ROS) and antioxidants is a fundamental aspect of cellular function and overall homeostasis, as it governs both physiological signaling and the prevention of oxidative damage. This equilibrium, often referred to as "redox homeostasis," ensures that ROS play their necessary roles in cellular communication without overwhelming the system, leading to oxidative stress and associated pathologies. The mechanisms that regulate this balance are complex and involve multiple pathways that manage both the production of ROS and the activation of antioxidant defenses. Disruptions to this balance can lead to either oxidative stress or, less commonly, antioxidative stress, both of which have profound implications for health and disease.

## Cellular Pathways Involving ROS

ROS are generated through several cellular processes, the most prominent of which is the mitochondrial electron transport chain (ETC) during aerobic respiration. The ETC is responsible for the production of ATP through oxidative phosphorylation, but a small fraction of the oxygen used in this process is converted into superoxide anions ($O_2^{\bullet -}$), a type of ROS. These superoxide anions are typically converted into less reactive species, such as hydrogen peroxide ($H_2O_2$), by the action of superoxide dismutase (SOD). Hydrogen peroxide itself is neutralized by catalase or glutathione peroxidase, converting it into water and oxygen. However, when mitochondrial function is compromised, or when cells are exposed to external stressors like toxins or UV radiation, ROS production can increase, overwhelming the cell's antioxidant capacity. In addition to mitochondria, ROS can be produced by other cellular systems such as NADPH oxidases (NOX). These enzymes are primarily involved in the production of ROS in response to various stimuli, particularly during immune responses. NOX enzymes are present in different cell types, including phagocytic cells like neutrophils and macrophages, where they play a critical role in the destruction of invading pathogens. The generation of ROS in immune cells leads to the formation of highly reactive species such as hypochlorous acid (HOCl), which contributes to microbial killing. While this process is essential for host defense, excessive activation of NOX and overproduction of ROS can lead to tissue damage and inflammation, contributing to conditions such as chronic inflammatory diseases. Figure 2 demonstrates the redox cycling and protonation states accessible to key redox-active molecules, illustrating the sequential electron ($e^-$) and proton ($H^+$) transfers that occur during redox reactions. This model reflects the oxidative and reductive transformations central to redox homeostasis in cells, a concept critical to understanding the dynamic balance between ROS production and antioxidant defenses.

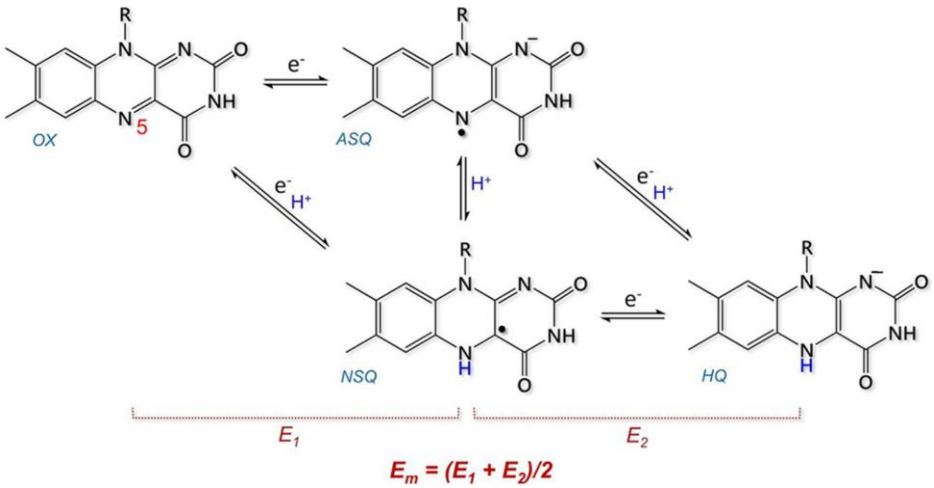


**Figure 2. Redox and protonation states of a key redox-active molecule** [20].

ROS also act as signaling molecules in various pathways, including the activation of mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF-κB), and the phosphoinositide 3-kinase (PI3K)/Akt pathway. For example, moderate levels of ROS activate MAPKs, which regulate cellular processes such as proliferation, differentiation, and apoptosis. Similarly, ROS-induced activation of NF-κB plays a critical role in inflammation and immune responses, whereas PI3K/Akt signaling regulates cell survival and growth. These pathways illustrate the dual role of ROS as both damaging agents and signaling molecules, with their effects largely determined by the level and context of ROS production.

## *Redox Homeostasis and Its Regulation*

The concept of redox homeostasis refers to the dynamic equilibrium between the production of ROS and the activity of antioxidants, ensuring that cells maintain appropriate levels of ROS for signaling without tipping into oxidative stress. This balance is tightly regulated by the cell's antioxidant defense systems, which are composed of both enzymatic and non-enzymatic components. The primary enzymatic antioxidants include superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), each of which neutralizes different types of ROS. SOD catalyzes the conversion of superoxide radicals into hydrogen peroxide, which is less reactive but still potentially harmful. Hydrogen peroxide is then further detoxified by catalase, which breaks it down into water and oxygen, or by GPx, which uses glutathione as a substrate to reduce hydrogen peroxide to water. This sequential detoxification ensures that ROS levels are kept under control. Other antioxidant enzymes include peroxiredoxins and thioredoxins, which also play critical roles in maintaining redox balance by reducing peroxides and controlling the oxidation state of proteins involved in redox signaling.

Non-enzymatic antioxidants, such as vitamins C and E, glutathione, and flavonoids, provide an additional layer of defense against oxidative stress. These molecules scavenge free radicals and prevent the propagation of lipid peroxidation and other forms

of oxidative damage. Vitamin E, for example, is a lipid-soluble antioxidant that protects cell membranes from oxidative damage by neutralizing lipid radicals. Vitamin C, a water-soluble antioxidant, works synergistically with vitamin E by regenerating its active form, thus amplifying the cell's antioxidant capacity.

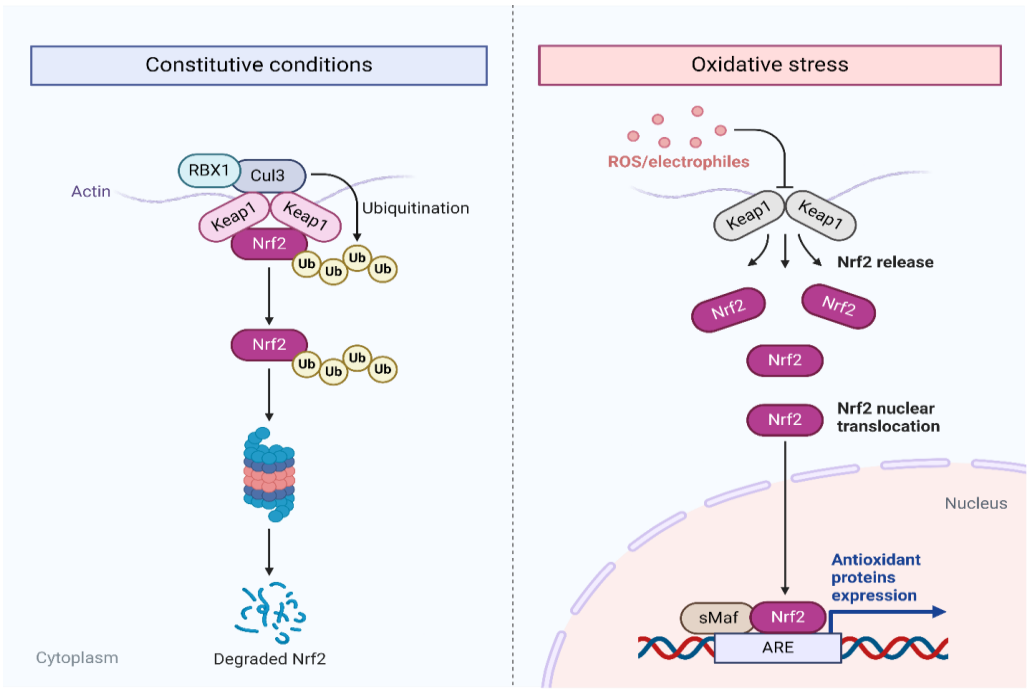


**Figure 3. The Nrf2-Keap1 pathway under constitutive conditions and oxidative stress. Created with BioRender.com**

The regulation of antioxidant defenses is controlled by several transcription factors, the most important of which is nuclear factor erythroid 2–related factor 2 (Nrf2). Under normal conditions, Nrf2 is sequestered in the cytoplasm by its inhibitor, Keap1. However, in response to oxidative stress, Nrf2 is released from Keap1, translocates to the nucleus, and activates the expression of genes encoding antioxidant enzymes, such as SOD, catalase, and GPx. This adaptive response ensures that cells can ramp up their antioxidant defenses in response to increased ROS production, thus restoring redox balance. Another regulatory mechanism involves feedback loops in ROS signaling. For instance, low to moderate levels of ROS can activate antioxidant gene expression via Nrf2, providing a negative feedback loop that reduces ROS levels. This self-regulatory system helps maintain ROS at physiological levels, supporting their role in cell signaling while preventing excessive accumulation that could lead to oxidative damage. Figure 3 illustrates the molecular regulation of Nrf2 under constitutive conditions and during oxidative stress. Under normal conditions, Nrf2 is bound to Keap1 and targeted for degradation. However, during oxidative stress, ROS and electrophiles disrupt this interaction, allowing Nrf2 to translocate to the nucleus, where it promotes the expression of antioxidant proteins.

## *Effects of Imbalance: Oxidative Stress vs. Antioxidative Stress*

When the balance between ROS production and antioxidant defenses is disrupted, cells can enter a state of oxidative stress, where excessive ROS levels cause damage to cellular macromolecules such as DNA, proteins, and lipids. This damage can lead to mutations, protein dysfunction, and membrane instability, ultimately contributing to the development of various diseases, including cardiovascular diseases, cancer, and neurodegenerative disorders. Oxidative stress is also implicated in aging, as the cumulative damage caused by ROS over time accelerates the decline in cellular function and tissue integrity.

Oxidative stress can result from both increased ROS production and impaired antioxidant defenses. For example, environmental factors such as pollution, radiation, and smoking can elevate ROS levels, while genetic mutations or nutritional deficiencies can compromise antioxidant systems. In certain pathological conditions, such as ischemia-reperfusion injury, ROS production spikes due to mitochondrial dysfunction and inflammatory responses, leading to severe oxidative damage in affected tissues. While oxidative stress is well-recognized for its role in disease, recent research has introduced the concept of "antioxidative stress," where excessive antioxidant intake disrupts normal redox signaling and impairs physiological functions. High doses of exogenous antioxidants, such as vitamin C or E supplements, can lower ROS levels to the point that they interfere with essential cellular processes. For example, ROS are necessary for the proper functioning of immune cells, particularly in the oxidative burst used by phagocytes to kill pathogens. Over-suppression of ROS through excessive antioxidant intake can weaken the immune response, increasing susceptibility to infections.

Moreover, studies have shown that excessive antioxidant supplementation may have unintended consequences in cancer therapy. ROS play a critical role in triggering apoptosis in cancer cells, and reducing ROS levels through high antioxidant intake can inhibit this process, potentially promoting the survival of malignant cells. This paradox highlights the need for careful regulation of antioxidant use, particularly in individuals undergoing cancer treatment or those with conditions where ROS-mediated cell death is beneficial.

### *Impact of Imbalance*

The imbalance between reactive oxygen species (ROS) production and antioxidant defenses, whether through an excess of ROS (oxidative stress) or through excessive antioxidant intake (antioxidative stress), has far-reaching implications for human health. The disruption of redox homeostasis can lead to the development of various diseases and pathologies, particularly those associated with chronic oxidative stress. This section explores the health impacts of oxidative and antioxidative stress, detailing their roles in the pathophysiology of several major diseases and immune dysfunction. Figure 4 provides an overview of how varying levels of oxidative stress can lead to different physiological outcomes. While moderate oxidative stress (eustress) supports

cellular signaling and adaptation, excessive oxidative stress (distress) leads to chronic cellular damage and disease progression

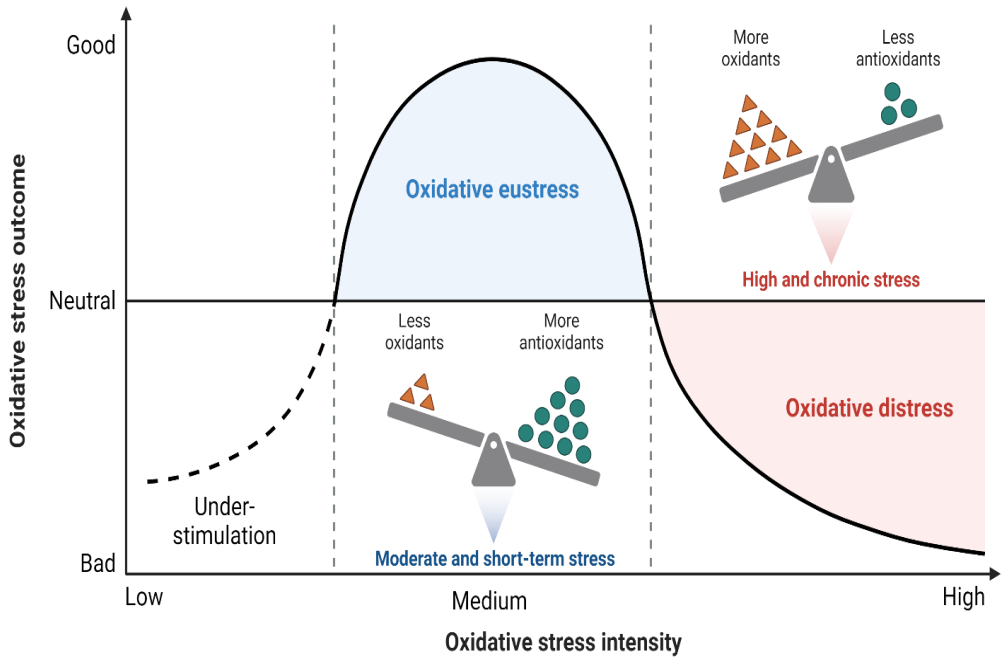


**Figure 4. The outcomes of varying oxidative stress intensity**

## *Diseases Associated with Chronic Oxidative Stress*

Chronic oxidative stress is a well-established contributing factor in the pathogenesis of numerous diseases. When ROS levels persistently exceed the body's antioxidant defenses, oxidative damage to DNA, proteins, and lipids accumulates, leading to cellular dysfunction and tissue injury. Below are key examples of diseases where chronic oxidative stress plays a central role:

**Cardiovascular Diseases:** Cardiovascular diseases (CVD), including atherosclerosis, hypertension, and heart failure, are closely linked to oxidative stress. ROS can induce endothelial dysfunction by impairing nitric oxide (NO) signaling, which is critical for vasodilation and maintaining vascular health. Furthermore, the oxidation of low-density lipoprotein (LDL) by ROS is a key event in the formation of atherosclerotic plaques. These oxidized LDL particles are taken up by macrophages, forming foam cells that contribute to the progression of atherosclerosis. Chronic inflammation, which is often sustained by ROS, exacerbates these processes, leading to plaque instability and increased risk of cardiovascular events such as myocardial infarction and stroke.

**Cancer:** Oxidative stress plays a dual role in cancer, contributing to both the initiation and progression of tumors. On one hand, ROS-induced DNA damage can lead to mutations, genomic instability, and the activation of oncogenes, thereby driving carcinogenesis. On the other hand, cancer cells can exploit oxidative stress to promote

their own survival, as ROS can activate signaling pathways that enhance proliferation, angiogenesis, and metastasis. Moreover, cancer cells often exhibit elevated levels of endogenous antioxidants, enabling them to tolerate the high ROS levels associated with rapid growth and metabolic reprogramming. The complexity of ROS in cancer underscores the importance of maintaining redox balance, as both excessive ROS and excessive antioxidant defenses can support tumorigenesis.

**Neurodegenerative Diseases:** Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), are characterized by progressive neuronal loss and dysfunction, much of which is driven by oxidative stress. Neurons are particularly vulnerable to ROS due to their high metabolic activity and the abundance of polyunsaturated fatty acids in neuronal membranes, which are susceptible to lipid peroxidation. In Alzheimer's disease, for example, the accumulation of β-amyloid plaques and tau tangles is associated with increased ROS production and mitochondrial dysfunction, contributing to synaptic loss and cognitive decline. Similarly, in Parkinson's disease, the death of dopaminergic neurons in the substantia nigra is linked to oxidative damage caused by dopamine metabolism and mitochondrial dysfunction.

## Consequences of Excessive Antioxidant Intake: Antioxidative Stress

While oxidative stress is widely recognized for its harmful effects, emerging research suggests that an excessive intake of antioxidants can also disrupt normal physiological functions, a condition referred to as antioxidative stress. The notion that "more is better" in terms of antioxidant consumption has been challenged by studies showing that high doses of exogenous antioxidants, particularly in supplement form, can have adverse effects.

**Impairment of Cellular Signaling:** ROS play an essential role in intracellular signaling, particularly in pathways that regulate cell proliferation, differentiation, and apoptosis. Excessive antioxidant intake can reduce ROS levels to the point where these signaling processes are impaired. For instance, ROS are critical for the activation of transcription factors such as NF-κB and Nrf2, which regulate the expression of genes involved in inflammation and antioxidant defense. By overly reducing ROS, high doses of antioxidants can disrupt these regulatory networks, potentially leading to impaired cellular responses to stress.

**Adaptation to Oxidative Stress:** Cells possess adaptive mechanisms that allow them to respond to mild oxidative stress by upregulating endogenous antioxidant defenses. This adaptive response, often termed hormesis, is a protective mechanism that enhances the cell's ability to cope with future stressors. However, excessive intake of antioxidants can blunt this adaptive response, reducing the cell's ability to naturally defend itself against oxidative challenges. This diminished capacity to adapt may leave individuals more vulnerable to oxidative damage in the long term, despite the temporary reduction in ROS levels achieved by antioxidants.

**Increased Cancer Risk:** Antioxidants are often promoted for their potential anti-cancer properties, but paradoxically, high doses of antioxidants may increase the risk of certain cancers. In particular, studies on high-dose vitamin E and β-carotene supplementation have shown that these antioxidants can increase the risk of lung cancer in smokers and those with a high cancer risk. One proposed mechanism is that antioxidants may prevent ROS-induced apoptosis in precancerous or cancerous cells, thereby allowing abnormal cells to survive and proliferate. This highlights the importance of carefully considering antioxidant supplementation, particularly in populations at risk for cancer.

### *Interaction Between ROS and Immune System Functioning*

ROS play a crucial role in the immune system, particularly in the functioning of phagocytic cells like neutrophils and macrophages, which rely on ROS to destroy invading pathogens. This process, known as the oxidative burst, involves the rapid production of ROS by NADPH oxidase in response to microbial invasion. The ROS generated during the oxidative burst are highly reactive and contribute to the killing of bacteria, viruses, and other pathogens.

However, both oxidative stress and antioxidative stress can dysregulate immune function. Chronic oxidative stress, for instance, can lead to sustained inflammation, which is a hallmark of many autoimmune and chronic inflammatory diseases. Excessive ROS production can damage healthy tissues, exacerbate inflammation, and impair the resolution of immune responses. This persistent inflammatory state contributes to the pathogenesis of diseases such as rheumatoid arthritis, inflammatory bowel disease, and lupus. Conversely, excessive antioxidant intake can suppress the immune response by reducing the ROS needed for effective pathogen destruction. Studies have shown that high doses of antioxidants can impair the ability of neutrophils to carry out the oxidative burst, thereby weakening the body's defense against infections. In individuals with compromised immune systems or those at risk of infection, this suppression of ROS-dependent immune responses can increase susceptibility to infections and delay recovery.

## Conclusion

In recent years, the complex interplay between reactive oxygen species (ROS) and antioxidants has emerged as a critical area of study, as it has significant implications for understanding both normal cellular processes and the pathogenesis of various diseases. ROS, once viewed solely as harmful byproducts of cellular metabolism, are now recognized for their dual roles—acting as both damaging agents and essential signaling molecules. At low to moderate levels, ROS contribute to vital cellular functions, including cell proliferation, apoptosis, and immune responses, while excessive levels of ROS can lead to oxidative stress, causing damage to cellular components such as DNA, lipids, and proteins.

This paper underscores the importance of maintaining a balance between ROS production and antioxidant defenses, a state often referred to as "redox homeostasis." This balance is not only crucial for preventing oxidative damage but also for ensuring

that ROS can fulfill their signaling roles in normal biological processes. The body's endogenous antioxidant systems, which include both enzymatic defenses (such as superoxide dismutase, catalase, and glutathione peroxidase) and non-enzymatic antioxidants (such as vitamins C and E, and glutathione), are designed to neutralize excess ROS and preserve cellular integrity. However, disruptions in this delicate balance can lead to two contrasting conditions—oxidative stress and antioxidative stress. Oxidative stress occurs when ROS levels exceed the capacity of the body's antioxidant defenses, leading to cumulative damage that contributes to the development of chronic diseases, including cancer, cardiovascular disorders, neurodegenerative diseases, and conditions associated with aging. Environmental factors such as pollution, radiation, and lifestyle choices like smoking and poor diet can exacerbate oxidative stress, further overwhelming the body's antioxidant capacity.

On the other hand, this review also highlights the less-discussed but equally important concept of antioxidative stress, which arises when antioxidant levels are too high. Excessive intake of exogenous antioxidants, particularly through supplements, can interfere with the physiological roles of ROS in signaling and immune responses. For instance, ROS play a critical role in the immune system's oxidative burst, which is essential for destroying pathogens. Over-suppression of ROS can impair immune function and leave the body vulnerable to infections. Furthermore, in cancer therapy, excessive antioxidants may hinder the beneficial effects of ROS-induced apoptosis in cancer cells, potentially promoting the survival of malignant cells. The dual nature of ROS underscores the importance of a personalized approach to managing oxidative stress. Genetic predispositions, health status, environmental exposures, and dietary habits all influence an individual’s oxidative and antioxidative balance. Therefore, antioxidant therapy and supplementation should be tailored to the specific needs of individuals, rather than following a one-size-fits-all approach. While antioxidants have been promoted for their potential health benefits, indiscriminate use, especially in high doses, can have unintended consequences.

## References

[1] L. Argaev-Frenkel and T. Rosenzweig, “Redox balance in type 2 diabetes: Therapeutic potential and the challenge of antioxidant-based therapy,” *Antioxidants (Basel)*, vol. 12, no. 5, Apr. 2023.

[2] H. Kawagishi and T. Finkel, “Unraveling the truth about antioxidants: ROS and disease: finding the right balance,” *Nat. Med.*, vol. 20, no. 7, pp. 711–713, Jul. 2014.

[3] B. Poljsak, D. Šuput, and I. Milisav, “Achieving the balance between ROS and antioxidants: when to use the synthetic antioxidants,” *Oxid. Med. Cell. Longev.*, vol. 2013, p. 956792, Apr. 2013.

[4] J. K. Willcox, S. L. Ash, and G. L. Catignani, “Antioxidants and prevention of chronic disease,” *Crit. Rev. Food Sci. Nutr.*, vol. 44, no. 4, pp. 275–295, 2004.

[5] M. Meydani, “Antioxidants in the prevention of chronic diseases,” *Nutrition in clinical care: an official publication of Tufts University*, vol. 5, no. 2. Wiley, pp. 47–49, Mar-2002.

[6] "Tea as a source of dietary antioxidants with a potential role in prevention of chronic diseases," in *Herbs, Botanicals and Teas*, CRC Press, 2000, pp. 283–306.
[7] A. M. Pisoschi and A. Pop, "The role of antioxidants in the chemistry of oxidative stress: A review," *Eur. J. Med. Chem.*, vol. 97, pp. 55–74, Jun. 2015.
[8] M.-J. Zhao, S. Yuan, H. Zi, J.-M. Gu, C. Fang, and X.-T. Zeng, "Oxidative stress links aging-associated cardiovascular diseases and prostatic diseases," *Oxid. Med. Cell. Longev.*, vol. 2021, no. 1, p. 5896136, Jul. 2021.
[9] I. Liguori *et al.*, "Oxidative stress, aging, and diseases," *Clin. Interv. Aging*, vol. 13, pp. 757–772, Apr. 2018.
[10] P. X. Shaw, G. Werstuck, and Y. Chen, "Oxidative stress and aging diseases," *Oxid. Med. Cell. Longev.*, vol. 2014, p. 569146, May 2014.
[11] H. Van Remmen, "Oxidative stress and age-related diseases," *Innov. Aging*, vol. 2, no. suppl_1, pp. 347–347, Nov. 2018.
[12] L. He, T. He, S. Farrar, L. Ji, T. Liu, and X. Ma, "Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species," *Cell. Physiol. Biochem.*, vol. 44, no. 2, pp. 532–553, Nov. 2017.
[13] T. Iwabuchi, C. Yoshimoto, H. Shigetomi, and H. Kobayashi, "Oxidative stress and antioxidant defense in endometriosis and its malignant transformation," *Oxid. Med. Cell. Longev.*, vol. 2015, p. 848595, Jun. 2015.
[14] A. M. Vincent, K. Kato, L. L. McLean, M. E. Soules, and E. L. Feldman, "Sensory neurons and schwann cells respond to oxidative stress by increasing antioxidant defense mechanisms," *Antioxid. Redox Signal.*, vol. 11, no. 3, pp. 425–438, Mar. 2009.
[15] S. Srisaipraj and B. Zutshi, "Oxidative stress and antioxidant defense to acute changes of water pH in liver and muscle of three ornamental fish," *Research Square*, 17-Apr-2024.
[16] P. Revathi and K. Nirubama, "Role of antioxidants in cancer therapy and chemoprevention," in *Bioactive Compounds from Medicinal Plants for Cancer Therapy and Chemoprevention*, BENTHAM SCIENCE PUBLISHERS, 2024, pp. 1–9.
[17] V. Fuchs-Tarlovsky, "Role of antioxidants in cancer therapy," *Nutrition*, vol. 29, no. 1, pp. 15–21, Jan. 2013.
[18] Y. Gilgun-Sherki, E. Melamed, and D. Offen, "Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier," *Neuropharmacology*, vol. 40, no. 8, pp. 959–975, Jun. 2001.
[19] T. R. Dias, D. Martin-Hidalgo, B. M. Silva, P. F. Oliveira, and M. G. Alves, "Endogenous and exogenous antioxidants as a tool to ameliorate male infertility induced by reactive oxygen species," *Antioxid. Redox Signal.*, vol. 33, no. 11, pp. 767–785, Jun. 2020.
[20] B. G. Galuzzi, A. Mirarchi, E. L. Viganò, L. De Gioia, C. Damiani, and F. Arrigoni, "Machine learning for efficient prediction of protein redox potential: The flavoproteins case," *J. Chem. Inf. Model.*, vol. 62, no. 19, pp. 4748–4759, Oct. 2022.