OPEN ACCESS
NIJBAS
Publications 2025
ONLINE ISSN: 2992-5797
PRINT ISSN: 2992-6122

NEWPORT INTERNATIONAL JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES (NIJBAS)

Volume 7 Issue 2 Page 42-47, 2026

https://doi.org/10.59298/NIJBAS/2026/7.2.4247

Regulation of Oxidative Stress by Phytochemicals: Implications for Immunity and Cellular Defense

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ABSTRACT

Oxidative stress, resulting from an imbalance between the production of reactive oxygen and nitrogen species (ROS/RNS) and the capacity of endogenous antioxidant defenses, is a central driver of cellular dysfunction, immune dysregulation, and chronic disease. Phytochemicals, a diverse group of bioactive compounds found in fruits, vegetables, herbs, and spices, have emerged as potent regulators of oxidative stress. These compounds not only directly scavenge reactive species but also modulate key signaling networks involved in antioxidant defense, inflammation, apoptosis, and immune response. Through activation of redox-sensitive transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2) and inhibition of pro-oxidant enzymes, phytochemicals enhance cellular antioxidative capacity and support immune cell function. This review synthesizes current knowledge on the molecular mechanisms by which phytochemicals regulate oxidative stress and explores the implications for immune regulation and cellular defense. We highlight evidence linking dietary phytochemicals to improved immune homeostasis and disease resistance, discuss their effects on chronic inflammation and cellular signaling pathways, and examine challenges in clinical translation, including bioavailability and individualized responses. Understanding how phytochemicals modulate oxidative stress and immunity provides valuable insights into their potential as therapeutic agents and nutritional interventions in health maintenance and disease prevention.

Keywords: phytochemicals; oxidative stress; immunity; redox signaling; cellular defense

INTRODUCTION

Oxidative stress is a pervasive biological phenomenon arising when the generation of reactive oxygen and nitrogen species (ROS/RNS) outpaces the antioxidant systems that detoxify these reactive molecules and repair oxidative damage [1]. While low levels of ROS serve essential roles in cell signaling and host defense, excessive or sustained production can damage lipids, proteins, and DNA, ultimately compromising cellular integrity and function [2]. Oxidative stress has been closely implicated in the pathogenesis of a wide range of diseases, including cardiovascular disorders, cancer, neurodegenerative conditions, diabetes, and immune dysfunction. ROS profoundly influence immune processes, shaping cytokine production, phagocytic activity, T-cell differentiation, and inflammasome activation, underscoring the intricate interplay between redox balance and immune competence [3]. Regulating oxidative stress is therefore essential not only to limit molecular damage but also to preserve effective immunity and cellular resilience [4]. Phytochemicals are plant-derived secondary metabolites that provide physiological benefits beyond basic nutrition. These diverse compounds include polyphenols (flavonoids, phenolic acids, stilbenes), carotenoids, alkaloids, terpenoids, and organosulfur compounds [5]. They are abundant in colorful fruits, vegetables, seeds, nuts, herbs, and spices, and have long been associated with reduced disease risk and health promotion [6]. In recent decades, research has elaborated multiple mechanisms by which phytochemicals influence oxidative stress and immune function, including direct scavenging of reactive species, modulation of antioxidant gene expression, regulation of redox-sensitive signaling pathways, and suppression of pro-inflammatory networks [7]. Importantly, phytochemicals can impact systemic and cellular defense processes, supporting immune cell metabolism and enhancing responses to pathogens or other stressors [8]. This review outlines how phytochemicals regulate oxidative stress at the molecular and cellular levels and examines the implications of these actions for immune regulation and cellular defense [9].

2. Oxidative Stress and Immune Regulation

Oxidative stress plays a fundamental role in shaping immune responses, as reactive oxygen species act both as antimicrobial agents and as intracellular signaling molecules [10]. Immune cells such as macrophages, neutrophils, and dendritic cells deliberately generate reactive oxygen species during respiratory bursts to destroy invading pathogens and facilitate antigen processing [11]. At physiological levels, these reactive species participate in signaling pathways that regulate immune cell activation, migration, and communication. However, excessive or prolonged production of reactive oxygen species can overwhelm antioxidant defenses, resulting in immune dysregulation and tissue injury [12]. Redox balance is a critical determinant of both innate and adaptive immune function. In macrophages, oxidative status influences phagocytic efficiency, cytokine secretion, and polarization toward pro-inflammatory or anti-inflammatory phenotypes. In T lymphocytes, reactive oxygen species regulate T-cell receptor signaling, differentiation of T-helper cell subsets, and maintenance of immune tolerance [13]. Disruption of redox homeostasis can skew immune responses toward chronic inflammation, impair pathogen recognition, and contribute to autoimmune and inflammatory diseases. Sustained oxidative stress further amplifies inflammatory signaling loops, leading to progressive tissue damage and disease progression [14]. Efficient antioxidant systems are therefore essential for maintaining immune competence while limiting collateral damage. Phytochemicals contribute to immune regulation by modulating intracellular redox balance, suppressing excessive reactive oxygen species generation, and enhancing endogenous antioxidant defenses [15]. Through these actions, phytochemicals support immunometabolic stability, promote immune cell resilience, and help preserve effective immune responses under conditions of oxidative and inflammatory stress.

3. Phytochemicals: Natural Regulators of Oxidative Stress

3.1 Direct Antioxidant Actions

Many phytochemicals possess intrinsic chemical structures that allow them to neutralize ROS directly [16]. Phenolic compounds such as flavonoids and phenolic acids donate electrons or hydrogen atoms to reactive species, interrupting radical chain reactions and minimizing oxidative damage to cellular components. Carotenoids quench singlet oxygen and attenuate lipid peroxidation [17]. Organosulfur compounds and certain alkaloids also exhibit free radical scavenging activities in cellular systems. Such direct interactions with ROS help to reduce oxidative burden in tissues exposed to environmental stressors or metabolic dysregulation.

3.2 Modulation of Antioxidant Pathways

Beyond direct scavenging, phytochemicals strongly influence endogenous antioxidant defenses by modulating redox-responsive signaling pathways [18]. One of the most studied pathways is the Nrf2-ARE (antioxidant response element) axis. Nrf2 is a transcription factor that governs the expression of a suite of antioxidant and detoxification enzymes, including glutathione peroxidase, superoxide dismutase, catalase, and heme oxygenase-1[19]. Under oxidative challenge, Nrf2 dissociates from its inhibitor KEAP1, translocates to the nucleus, and activates antioxidant gene expression [20]. Multiple phytochemicals, such as curcumin, resveratrol, epigallocatechin gallate (EGCG), and sulforaphane, have been shown to activate Nrf2 signaling, enhancing cellular capacity to counteract oxidative stress and support metabolic homeostasis [21].

3.3 Suppression of Pro-Inflammatory Signaling

Oxidative stress and inflammation are tightly linked. ROS can activate pro-inflammatory transcription factors such as nuclear factor-κB (NF-κB), which drives expression of cytokines, chemokines, and adhesion molecules [22]. Phytochemicals such as quercetin, curcumin, and resveratrol can inhibit NF-κB activation and related pathways, reducing production of pro-inflammatory mediators and limiting ROS amplification loops[23]. By modulating both oxidative and inflammatory pathways, phytochemicals provide integrated support to cellular defense mechanisms [24].

3.4 Regulation of Immune Cell Metabolism and Function

Phytochemicals not only affect redox balance but also influence immune cell metabolism [25]. Redox status modulates metabolic processes such as glycolysis, oxidative phosphorylation, and fatty acid metabolism, which are essential determinants of immune cell differentiation and effector functions [26]. Compounds like flavonoids and

ONLINE ISSN: 2992-5797
PRINT ISSN: 2992-6122
polyphenols have been reported to support mitochondrial function, enhance antioxidant enzyme activities, and regulate signaling pathways that underlie immune cell adaptation to stress.

4. Implications for Immunity and Cellular Defense

4.1 Enhancement of Innate Immune Responses

Phytochemical regulation of oxidative stress supports innate immune mechanisms [27]. By optimizing redox balance, these compounds help preserve phagocytic capacity, pathogen killing, and antigen presentation [28]. Controlled ROS levels facilitate efficient elimination of microbes while minimizing collateral tissue damage, thereby supporting a balanced innate response.

4.2 Modulation of Adaptive Immunity

Adaptive immunity relies on redox-sensitive signaling for lymphocyte activation, cytokine production, and differentiation of T-helper subsets [29]. Phytochemicals can modulate these processes by influencing ROS levels and downstream signaling networks. For example, flavonoids have been shown to support regulatory T-cell function and limit excessive pro-inflammatory T-helper cell responses, which may contribute to immune tolerance and reduced chronic inflammation [30].

4.3 Protection Against Chronic Inflammation

Chronic inflammation is a hallmark of many age-related diseases and is closely linked to oxidative stress [31]. By suppressing pro-oxidant and pro-inflammatory pathways, phytochemicals help break the cycle of inflammation and oxidative damage. This integrated modulation of redox and immune networks may reduce the risk and progression of conditions such as cardiovascular disease, metabolic syndrome, neurodegeneration, and autoimmune disorders [32].

4.4 Support for Cellular Stress Responses

Cells exposed to stressors such as infection, toxins, or metabolic disturbances rely on coordinated signaling to repair damage and restore homeostasis [33]. Phytochemicals enhance stress response pathways, including heat shock proteins, autophagy, and DNA repair systems, which are sensitive to redox balance [34]. Through their regulatory effects, phytochemicals help maintain cellular integrity under diverse stress conditions.

5. Challenges and Considerations in Translational Applications

Despite strong mechanistic and preclinical evidence supporting the antioxidant and immunomodulatory roles of phytochemicals, several challenges hinder their effective translation into clinical practice [35]. A major limitation is bioavailability and metabolism. Many phytochemicals exhibit poor gastrointestinal absorption, rapid biotransformation, and limited tissue distribution, resulting in low systemic concentrations that may be insufficient to reproduce effects observed in vitro or in animal models [36]. Extensive first-pass metabolism in the liver and modification by the gut microbiota further influence their biological activity, sometimes generating metabolites with altered or reduced efficacy. To address these issues, advanced formulation strategies such as nanoencapsulation, liposomal delivery systems, and structural analog development are being explored to improve stability, absorption, and target specificity [37]. Dose optimization and safety present additional complexities. Phytochemicals often exert hormetic effects, where low to moderate doses are beneficial while excessive intake may disrupt physiological redox signaling or exert pro-oxidant effects [38]. High-dose supplementation can also interfere with drug metabolism pathways or attenuate the effectiveness of therapies that rely on oxidative mechanisms, such as certain chemotherapeutic agents. Consequently, defining safe and effective dosing regimens requires well-designed clinical trials that consider duration, formulation, and disease context [39].

Individual variability further complicates clinical translation. Genetic polymorphisms affecting antioxidant enzymes, differences in baseline nutritional status, and variations in gut microbiome composition can significantly influence individual responses to phytochemical intake. Age, sex, lifestyle factors, and comorbid conditions also contribute to heterogeneity in outcomes. These factors underscore the need for personalized or precision-based nutritional and therapeutic approaches. Finally, the biological complexity of phytochemicals poses interpretative challenges. These compounds interact with multiple molecular targets and signaling pathways simultaneously, producing pleiotropic and context-dependent effects. Disentangling direct antioxidant actions from secondary regulatory effects requires integrated systems-level approaches that combine genomics, metabolomics, and network biology.

CONCLUSION

Phytochemicals represent a rich and diverse group of natural compounds capable of regulating oxidative stress and modulating immune and cellular defense processes. Through direct antioxidant actions, activation of redox-sensitive signaling pathways, suppression of inflammation, and support of immune cell function, these plant-derived molecules contribute to health maintenance and disease resilience. While clinical translation presents challenges, emerging evidence highlights the therapeutic promise of phytochemicals as modulators of redox balance and immunity in human health.

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CITE AS: Mpora Kakwanzi Evelyn (2026). Regulation of Oxidative Stress by Phytochemicals: Implications for Immunity and Cellular Defense. NEWPORT INTERNATIONAL JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES 7(2):42-47. https://doi.org/10.59298/NIJBAS/2026/7.2.4247