

Therapeutic Antioxidants and the Immune Response: Mechanistic Interactions and Clinical Implications

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ABSTRACT

Therapeutic antioxidants have emerged as promising modulators of immune function by mitigating oxidative stress and influencing inflammatory pathways. Reactive oxygen species (ROS), when produced in excess, can damage cellular components including DNA, lipids, and proteins, triggering inflammation and impairing immune cell function. By scavenging ROS and restoring redox balance, antioxidants help preserve cellular integrity, support immune cell viability, and regulate signaling pathways that shape both innate and adaptive immune responses. Clinical studies indicate that supplementation with antioxidants such as vitamins C and E, carotenoids, and polyphenolic compounds can enhance immune parameters - including lymphocyte proliferation, delayed-type hypersensitivity (DTH) responses, and innate immune cell activity. Moreover, in contexts of heightened inflammation or infection, antioxidant therapy may reduce pro-inflammatory cytokine production, attenuate tissue damage, and improve clinical outcomes. However, because ROS also serve essential signaling roles for microbial killing and immune activation, indiscriminate or high-dose antioxidant use may blunt beneficial immune responses or impair immunosurveillance. This review explores mechanistic interactions between antioxidants and immune pathways and examines clinical implications for their use in disease prevention, infection control, and management of inflammatory disorders. Recognizing the dual - and sometimes opposing - roles of ROS, a nuanced application of antioxidants may offer therapeutic benefit, particularly in conditions characterized by oxidative stress and chronic inflammation.

Keywords: Antioxidants, Immune response, Oxidative stress, Inflammation, Immunomodulation

INTRODUCTION

Reactive oxygen species (ROS) and other free radicals are natural byproducts of cellular metabolism, particularly during mitochondrial oxidative phosphorylation and other redox reactions[1]. Under normal conditions, these reactive species play critical roles in cell signaling, regulation of gene expression, and host defense mechanisms[2]. However, when the balance between ROS production and antioxidant defenses is disturbed, oxidative stress ensues - leading to damage of lipids, proteins, and nucleic acids. This disruption can impair cell viability, trigger inflammatory pathways, and undermine proper immune function[3]. Antioxidants - whether endogenous molecules like glutathione and thioredoxin, or exogenous agents including vitamins (C, E), carotenoids, polyphenols, and other bioactives - function to neutralize ROS, repair oxidative damage, and restore redox homeostasis. Through these actions, antioxidant therapy has gained attention not only for preventing oxidative tissue damage but also for modulating immune responses and inflammation[4]. In recent years, growing mechanistic and clinical evidence supports the idea that antioxidants may serve as adjuvant or therapeutic agents in conditions characterized by oxidative stress, chronic inflammation, and immune dysfunction[5]. Yet the relationship between antioxidants and immunity is complex. While scavenging excessive ROS may protect tissues and dampen harmful inflammation, ROS are also required for effective pathogen killing (e.g., oxidative burst by phagocytes), regulation of immune signaling, and cellular activation[6]. Thus, antioxidant therapy must be approached with nuance - balancing the reduction of damaging oxidative stress against preserving physiological

ROS-dependent immune functions. This review synthesizes current knowledge on how therapeutic antioxidants interact with the immune system, delineating key mechanisms, summarizing human clinical evidence, and discussing potential benefits and risks[7]. We focus on how antioxidants influence innate and adaptive immunity, their role in controlling inflammation, the impact on immunometabolism, and the clinical implications for diseases involving oxidative stress, chronic inflammation, or immune imbalance[8].

Mechanistic Interactions Between Antioxidants and Immune Function

Redox Regulation and Maintenance of Immune Cell Integrity

Immune cells, like all cellular populations, are highly susceptible to oxidative damage due to the reactive nature of oxygen species (ROS)[9]. Excessive ROS can oxidize membrane lipids, denature proteins, and fragment DNA, thereby compromising cell viability, disrupting membrane integrity, and impairing intracellular signaling pathways. This oxidative damage is particularly detrimental to immune cells, which often operate under conditions of high metabolic demand, rapid proliferation, and exposure to pathogens[10]. Antioxidants play a pivotal role in neutralizing ROS, mitigating oxidative modifications, and safeguarding cellular structures. Endogenous antioxidants such as glutathione (GSH) are especially crucial; GSH not only directly scavenges free radicals but also maintains redox-sensitive thiol groups in proteins, preserving enzyme function and regulating redox-dependent signaling networks[11]. By maintaining redox homeostasis, antioxidants ensure immune cells remain functional, support their proliferation, and prevent premature apoptosis. This protective effect is vital for lymphocytes during clonal expansion in adaptive immune responses and for phagocytes executing oxidative bursts during pathogen elimination[12]. Moreover, antioxidants enhance the resilience of immune cells under stress, helping them withstand inflammatory microenvironments without succumbing to oxidative damage[13]. For example, adequate levels of GSH and other redox buffers help preserve T-cell receptor signaling, phagocytic activity, and the generation of cytotoxic molecules, ensuring effective immune surveillance and defense.

Modulation of Inflammatory Signaling and Cytokine Production

Antioxidants influence immune function not only by direct ROS scavenging but also by modulating redox-sensitive signaling pathways that govern inflammation and immune activation[14]. ROS often activate transcription factors such as nuclear factor kappa B (NF- κ B) and activator protein-1 (AP-1), which drive the expression of pro-inflammatory cytokines and chemokines. Excessive or prolonged activation of these pathways contributes to chronic inflammation and tissue damage[15]. By lowering ROS levels, antioxidants can attenuate aberrant transcription factor activation, thereby reducing overproduction of inflammatory cytokines and mitigating prolonged inflammatory responses[16]. Natural phenolic compounds and other bioactive antioxidants have demonstrated the capacity to regulate the release of IL-1 β , IL-6, TNF- α , and other mediators, while also modulating redox-sensitive enzymes involved in immune activation[17]. This immunomodulatory effect is particularly valuable in chronic inflammatory conditions, autoimmune disorders, and settings of persistent oxidative stress, where controlling cytokine overproduction can prevent tissue damage and improve immune homeostasis.

Influence on Immunometabolism

The emerging field of immunometabolism underscores the importance of metabolic pathways in dictating immune cell behavior[18]. ROS are byproducts of cellular metabolism, including mitochondrial oxidative phosphorylation and NADPH oxidase activity, and excessive ROS can disrupt metabolic fluxes essential for immune function[19]. Antioxidants help modulate oxidative load, maintain mitochondrial health, and preserve energy homeostasis, allowing immune cells to sustain energy-intensive processes such as proliferation, differentiation, effector molecule production, and migration[20]. Preservation of mitochondrial integrity is particularly critical, as mitochondrial dysfunction can lead to energetic collapse, impaired signaling, and immune cell death. By supporting both redox balance and metabolic efficiency, antioxidants provide a dual mechanism that ensures immune competence under stress, enhances resilience against infection, and mitigates the deleterious effects of chronic inflammation[21]. Collectively, these mechanistic interactions illustrate how antioxidants maintain immune cell integrity, regulate inflammatory signaling, and support immunometabolic health, forming a foundation for their therapeutic potential in immune-mediated and oxidative stress-related disorders.

Clinical Evidence: Antioxidant Supplementation and Immune Outcomes

Human trials and observational studies have explored how dietary or supplemental antioxidants affect immune function[22]. For example, supplementation with vitamins C and E, carotenoids, or combinations thereof has been associated with enhanced innate immune cell activity, improved lymphocyte proliferation, and stronger delayed-type hypersensitivity (DTH) responses in both younger and older adults[23]. In elderly populations - especially susceptible to immunosenescence and oxidative stress - antioxidants have shown capacity to support T-cell mediated immunity, possibly mitigating age-associated immune decline. In the context of infectious disease, antioxidant supplementation has been evaluated as an adjunctive therapy. A recent pilot study in hospitalized patients with viral pneumonia found that an immune-boosting antioxidant and anti-inflammatory supplement

correlated with improved clinical outcomes and reduced inflammatory markers[24]. Similarly, in diseases characterized by oxidative stress and inflammation - such as chronic kidney disease (CKD) - therapies targeting redox imbalance (e.g., using dietary antioxidants, pharmacologic activators of endogenous antioxidant systems) have been proposed to mitigate tissue damage and inflammation[25]. Moreover, natural phenolic antioxidants (like polyphenols) have drawn increasing interest because of their dual antioxidant and anti-inflammatory properties, with the capacity to modulate cytokine production, suppress overactivation of immune responses, and support immune homeostasis[26].

Therapeutic Implications and Challenges

Potential Benefits

Prevention or mitigation of chronic inflammation: In conditions where persistent oxidative stress drives low-grade inflammation, such as metabolic syndrome, chronic infections, chronic kidney disease, or autoimmune disorders, antioxidant therapy may help restore redox balance, reduce cytokine overproduction, and limit tissue damage.

Support of immune function in vulnerable populations: Elderly individuals, people with nutritional deficiencies, or those exposed to environmental oxidative stress may benefit from antioxidant supplementation to maintain immune competence and improve resilience against infections[27]. **Adjunct therapy in infections or acute inflammatory conditions:** During infections or diseases accompanied by oxidative injury, such as pneumonia or sepsis, antioxidants may reduce oxidative damage, modulate harmful inflammation, and improve clinical outcomes when used alongside standard therapies[28].

Support for immunometabolic health: By preserving mitochondrial and metabolic integrity in immune cells, antioxidants can enhance energy supply necessary for immune responses, cellular proliferation, and tissue repair, which is crucial for maintaining long-term immune resilience[29].

Important Caveats and Risks

Reactive oxygen species also play essential roles as signaling molecules, including microbial killing, immune cell activation, and regulation of gene expression[31]. Indiscriminate suppression of ROS may therefore impair these beneficial immune functions. High-dose or chronic antioxidant supplementation can blunt oxidative bursts in phagocytes, weaken pathogen clearance, or dampen adaptive immune activation[32]. In some contexts, prolonged high-dose supplementation has been associated with reduced adaptive responses to stressors, such as exercise-induced adaptation or suppression of beneficial stress-mediated signals[32]. Timing, dosage, and baseline redox status are critical considerations, as antioxidants may benefit individuals experiencing oxidative stress but provide limited or even detrimental effects in those with balanced redox systems[33]. The heterogeneity of antioxidants adds another layer of complexity. Differences in chemical structure, bioavailability, tissue distribution, and mechanism of action mean that not all antioxidants exert equivalent effects[34]. Natural phenolics, dietary vitamins, enzyme-supportive micronutrients, and synthetic derivatives exhibit diverse immunomodulatory profiles, necessitating tailored use depending on clinical context and therapeutic goals[35]. Overall, while antioxidants hold promise for mitigating oxidative stress and supporting immune function, their use must be carefully calibrated to avoid unintended interference with physiological redox signaling and immune defenses.

CONCLUSION

Therapeutic antioxidants occupy a complex but promising niche at the interface of redox biology, immune regulation, and clinical medicine. By neutralizing excessive ROS, preserving cellular integrity, modulating inflammatory signaling, and supporting immune cell metabolism, antioxidants can contribute to improved immune function, reduction of chronic inflammation, and better outcomes in various diseases - from infections to chronic inflammatory and metabolic conditions. However, given the dual role of ROS in both harmful oxidative stress and essential immune signaling, antioxidant interventions must be applied judiciously, taking into account patient age, baseline oxidative stress, disease context, and dosage. Future research should focus on well-designed human clinical trials that assess not only redox markers but also immune function, clinical outcomes, and long-term safety. Additionally, exploring combination therapies - for example, antioxidants plus agents that modulate immunometabolism, mitochondrial function, or inflammation - may unlock more targeted and effective therapeutic strategies. Ultimately, a nuanced understanding of redox-immune interactions will be essential to harness antioxidants as reliable tools for immunomodulation and disease management.

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