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Context-Dependent Toxicity of Antioxidants: When Protective Molecules Become Harmful

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ABSTRACT

Antioxidants are traditionally viewed as beneficial agents that defend cells against oxidative damage by neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS). However, accumulating evidence demonstrates that their impact is highly context-dependent: under specific biochemical conditions, physiological states, and dosages, antioxidants can shift from protective to harmful roles. This review synthesizes current research showing that antioxidants may act as pro-oxidants, disrupt redox signaling, contribute to disease progression, and interfere with therapeutic outcomes. We explore the molecular mechanisms underlying this duality, including redox potential, concentration-dependent effects, presence of transition metals, and interactions with endogenous antioxidant networks. Clinical and toxicological implications are discussed, with examples from cancer biology, pharmacology, and environmental exposure scenarios. Understanding the nuanced behavior of antioxidants is critical for optimizing their application in diet, supplementation, and therapeutic settings, and for avoiding unintended adverse effects.

Keywords: Antioxidants, Context-dependent toxicity, Pro-oxidant effects, Redox biology, Therapeutic implications.

INTRODUCTION

Antioxidants are a heterogeneous group of molecules, including vitamins C and E, polyphenols, flavonoids, carotenoids, and endogenous antioxidant enzymes, that mitigate oxidative stress by neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS) [1]. Oxidative stress arises when the generation of these reactive species exceeds the capacity of cellular antioxidant defenses, resulting in damage to lipids, proteins, and nucleic acids [2]. Such damage contributes to lipid peroxidation, protein misfolding, enzyme inactivation, and DNA oxidation, processes that are implicated in aging and the pathogenesis of numerous diseases [3]. To counteract these effects, aerobic organisms have evolved complex and tightly regulated antioxidant networks, comprising both enzymatic systems, such as superoxide dismutase, catalase, and glutathione peroxidase, and non-enzymatic molecules that collectively maintain redox homeostasis and support cellular survival and function [4]. Despite their well-recognized protective roles, increasing experimental and clinical evidence indicates that antioxidants do not always confer benefit. Under certain biological contexts, specific concentrations, or chemical environments, antioxidants may exert neutral or even harmful effects [5]. They can disrupt physiological redox signaling, promote pro-oxidant reactions, or interfere with adaptive stress responses [6]. This paradox challenges

the traditional view of antioxidants as universally beneficial agents and highlights the need for a more nuanced understanding of their context-dependent behavior in health and disease [7].

2. Antioxidant Mechanisms and Redox Biology

Antioxidants operate through diverse and interconnected mechanisms that collectively regulate cellular redox homeostasis [8]. These mechanisms include direct scavenging of free radicals, chelation of transition metals that catalyze radical formation, regeneration of oxidized biomolecules, and modulation of redox-sensitive enzymes and transcription factors [9]. Enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase form the core of endogenous defense systems, converting highly reactive species into less harmful molecules [10]. Non-enzymatic antioxidants, including vitamins, polyphenols, and thiols, complement these systems by intercepting radicals and supporting enzymatic recycling processes [11].

These antioxidant actions are embedded within redox biology, a framework that recognizes reactive oxygen species and reactive nitrogen species not only as damaging by-products of metabolism but also as essential signaling molecules [12]. At controlled concentrations, ROS and RNS regulate physiological processes such as immune cell activation, cellular proliferation, differentiation, and adaptive responses to stress [13]. For example, transient increases in ROS are required for effective pathogen killing by immune cells and for redox signaling pathways that mediate cellular adaptation to hypoxia or metabolic stress. Disruption of this finely tuned balance, either by excessive oxidant production or excessive antioxidant activity, can impair normal cellular function.

Consequently, the traditional definition of antioxidants as molecules that merely quench free radicals is overly simplistic [14]. Contemporary perspectives emphasize that antioxidants function within extensive redox networks, where their biological effects depend on intrinsic chemical properties as well as interactions with endogenous antioxidant systems, cellular compartmentalization, metabolic state, and environmental conditions [15]. This systems-level view helps explain why antioxidants may produce divergent outcomes across different tissues and disease states [16].

3. Pro-oxidant Activity and Context-dependent Toxicity

3.1 Pro-oxidant Effects of Antioxidants

Under specific biochemical conditions, compounds commonly classified as antioxidants can act as pro-oxidants, promoting rather than suppressing oxidative stress [17]. A well-documented example is vitamin C, which can reduce ferric or cupric ions to their lower oxidation states. These reduced metals may then participate in Fenton and Haber–Weiss reactions, generating highly reactive hydroxyl radicals capable of damaging DNA, proteins, and lipids [18]. Such effects are particularly relevant in environments rich in free transition metals or under conditions of impaired metal sequestration. Other antioxidants, including carotenoids and flavonoids, may also exhibit pro-oxidant behavior when present at high concentrations or under high oxygen tension [19]. This shift can occur when antioxidant molecules themselves become oxidized and are not efficiently regenerated by complementary antioxidants, leading to propagation of oxidative chain reactions rather than termination [20]. ([Springer][5]) These observations illustrate that chemical behavior is highly sensitive to redox potential, concentration, and surrounding molecular context, and that the designation of a compound as an antioxidant does not guarantee protective action in all settings.

3.2 Concentration and Dose Effects

A key feature of antioxidant toxicity is dose dependence. Many antioxidants display biphasic or hormetic responses, where low or physiological concentrations exert beneficial effects, while higher doses induce pro-oxidant activity and cellular damage [21]. Beta-carotene, for instance, protects against oxidative DNA damage at low micromolar concentrations but becomes pro-oxidative at higher levels, enhancing lipid peroxidation and DNA oxidation [22]. Similarly, alpha-tocopherol neutralizes lipid radicals but forms a tocopheroxyl radical in the process. If this radical is not promptly reduced by vitamin C or glutathione, it may propagate lipid oxidation, undermining membrane integrity [23]. Such dose-dependent behavior complicates antioxidant supplementation, as the threshold between benefit and harm varies across tissues, physiological states, and individuals [24].

3.3 Interactions with Transition Metals

Transition metals such as iron and copper play a pivotal role in determining antioxidant behavior [25]. While tightly bound metals support normal cellular function, loosely bound or excess metals can catalyze redox cycling

reactions that convert antioxidants into sources of oxidative stress. Ascorbate-driven iron reduction and subsequent hydroxyl radical formation exemplify how metal–antioxidant interactions can amplify oxidative damage [26]. These interactions underscore the importance of both intrinsic and extrinsic biochemical context in shaping antioxidant effects and toxicity [27].

4. Antioxidants in Disease Contexts

4.1 Cancer Biology

The role of antioxidants in cancer represents one of the clearest examples of context-dependent biological effects [28]. Although antioxidants have long been promoted for cancer prevention due to their ability to reduce oxidative DNA damage and mutagenesis, growing evidence indicates that their effects vary markedly depending on tumor type, genetic background, and disease stage. In several experimental and clinical settings, antioxidants have been shown to support tumor progression, metastasis, and angiogenesis by lowering intracellular ROS to levels that favor cancer cell survival and proliferation [29]. In this context, ROS are not merely damaging agents but also barriers that limit tumor growth. Studies using genetically defined cancer models illustrate this duality. Antioxidant supplementation has been reported to accelerate tumor growth in KRAS-driven lung cancer and BRAF-mutant melanoma, while in other malignancies, such as MYC-driven lymphoma, antioxidants may delay disease progression [30]. These contrasting outcomes reflect differences in oncogenic signaling, metabolic demands, and redox dependencies across cancer types. Importantly, many cancer cells exhibit elevated antioxidant capacity to counteract high intrinsic ROS production associated with rapid proliferation and metabolic reprogramming [31]. This enhanced redox buffering can contribute to resistance against chemotherapy and radiotherapy, both of which rely partly on oxidative stress for efficacy [32]. Paradoxically, this dependency also presents therapeutic opportunities, as selective disruption of antioxidant pathways may sensitize tumors to treatment [33].

4.2 Inflammation and Chronic Disease

Beyond cancer, excessive antioxidant intake may adversely affect inflammatory and chronic disease processes. High antioxidant levels can suppress physiological redox signaling required for effective immune responses, a phenomenon described as antioxidative stress [34]. This state may impair pathogen clearance and immune regulation, increasing vulnerability to infections [35]. Long-term high-dose supplementation has also been linked to unfavorable outcomes in neurodegenerative, cardiovascular, and metabolic diseases, likely due to disturbed redox homeostasis and interference with endogenous defense mechanisms.

5. Pharmacological and Toxicological Implications

5.1 Supplementation and Health Claims

Antioxidant supplements are widely consumed based on the perception that they universally promote health and prevent disease. However, systematic reviews and meta-analyses have consistently reported insufficient or inconsistent evidence to support many of these claims. In several cases, large-scale clinical trials have failed to demonstrate clear benefits, and some have even reported neutral or adverse outcomes [36]. These inconsistencies often reflect the underlying complexity of antioxidant behavior, including differences in dose, chemical form, baseline nutritional status, and disease context, rather than a simple lack of biological activity. The context-dependent nature of antioxidant effects makes the development of standardized dosing guidelines particularly challenging. What may be beneficial in one physiological or pathological setting can be ineffective or harmful in another [37]. Safety concerns are especially relevant for synthetic antioxidants and high-dose supplementation, which may induce pro-oxidant effects, interfere with endogenous stress-response pathways, or interact adversely with prescription medications. Such interactions may alter drug pharmacokinetics or pharmacodynamics, leading to reduced efficacy or increased toxicity.

5.2 Drug Interactions and Redox Signaling

In clinical practice, antioxidant supplementation can significantly influence the outcomes of conventional therapies [38]. During chemotherapy or radiotherapy, antioxidants may reduce treatment efficacy by scavenging the ROS required to induce cancer cell death. Conversely, in some contexts, antioxidants may reduce treatment-related toxicity, highlighting the importance of timing and therapeutic mechanism [39]. At the molecular level, antioxidants can modulate redox-sensitive signaling pathways governing cell proliferation, apoptosis, and

detoxification, reinforcing the need to view redox biology as an integrated and dynamic network rather than a collection of isolated reactions.

CONCLUSION

Antioxidants are not universally protective molecules; rather, their biological effects are strongly influenced by context, dosage, timing, and the surrounding chemical environment. Accumulating evidence shows that antioxidants can become harmful by acting as pro-oxidants, disturbing physiological redox balance, promoting disease progression, or reducing the effectiveness of therapeutic interventions. These observations challenge the long-standing assumption that increasing antioxidant intake is inherently beneficial and emphasize the limitations of generalized supplementation strategies. A deeper understanding of redox biology and the dynamic interplay between reactive oxygen species, antioxidant systems, and cellular signaling networks is essential for informed application. Appreciating context-dependent effects will allow researchers and clinicians to distinguish situations in which antioxidants are protective from those in which they may be detrimental. Future research should focus on mechanistic insights and carefully designed, context-aware clinical trials to establish evidence-based guidelines that maximize benefits while minimizing risks associated with antioxidant use.

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