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Toxicological Risks of Long-Term Antioxidant Supplementation: Evidence From Preclinical and Clinical Studies

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ABSTRACT

Widespread use of antioxidant supplements-vitamins (A, C, E), provitamin A carotenoids, selenium, coenzyme Q10, and numerous polyphenolic preparations-has been driven by epidemiological associations between dietary antioxidants and reduced chronic disease risk, and by the intuitive appeal of "neutralizing" oxidative stress. However, a growing body of preclinical and clinical evidence indicates that long-term or high-dose supplementation may carry toxicological risks, particularly when it perturbs physiological redox signaling, acts as a pro-oxidant in certain contexts, interacts adversely with environmental exposures or medications, or is given to susceptible populations. This review synthesizes mechanistic and experimental findings from animal models, cellular systems, and randomized clinical trials, and examines observational data and meta-analyses that document adverse outcomes including increased cancer incidence in specific subgroups, higher all-cause mortality at supraphysiologic doses, interference with chemotherapy and radiotherapy, impaired exercise adaptations, and developmental toxicity. We analyze underlying mechanisms-hormetic disruption of redox signaling, pro-oxidant chemistry, altered phase I/II metabolism, and genomic instability-and discuss how dose, form (synthetic versus food matrix), duration, timing, and host factors (smoking, existing disease, age, pregnancy, and genetic polymorphisms) determine safety. Finally, the review outlines pragmatic clinical guidance, regulatory and quality-control concerns, and research priorities needed to define safe use and to develop precision approaches that balance potential benefits against demonstrable risks.

Keywords: antioxidant supplements, pro-oxidant, hormesis, clinical trials, safety

INTRODUCTION

Antioxidant supplements are widely consumed across the globe, often marketed as simple and effective tools for preventing or treating oxidative-stress–related diseases [1]. Their popularity is reinforced by epidemiological studies linking high intake of fruits, vegetables, and other antioxidant-rich foods with reduced risk of cardiovascular disease, cancer, metabolic disorders, and accelerated ageing [2]. The commercial marketplace now contains a vast array of products, ranging from single-nutrient supplements at pharmacological doses-such as vitamins C and E, β-carotene, selenium, and coenzyme Q10-to complex botanical extracts enriched in polyphenols, flavonoids, and carotenoids [3]. Despite the intuitive appeal of "boosting antioxidant defenses," scientific evidence shows a more complex and sometimes contradictory picture. Observational nutrition studies generally reflect dietary patterns rather than the isolated effects of specific antioxidant molecules, whereas randomized controlled

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trials (RCTs) and preclinical experiments reveal that outcomes with supplements can differ markedly from those associated with whole foods [4]. In many RCTs, high-dose antioxidant supplementation has yielded neutral or even harmful results, including increased cancer risk in at-risk populations, elevated all-cause mortality at supraphysiologic doses, and reduced therapeutic efficacy of some cancer treatments [5]. One key distinction lies in the context of delivery: foods provide antioxidants within a matrix of fiber, micronutrients, and synergistic compounds that shape absorption, metabolism, and physiological effects [6]. Isolated antioxidants administered at high doses bypass this natural regulatory environment. Consequently, they may disrupt finely tuned redox signaling systems rather than restore balance [7]. Given these concerns, there is a growing need to critically re-evaluate the long-term safety of antioxidant supplementation. This review synthesizes mechanistic, preclinical, and clinical evidence to clarify the toxicological risks associated with chronic use and to inform more judicious public health and clinical recommendations.

2. Conceptual Framework: Why Antioxidants Can Be Harmful

Far from being uniformly detrimental, reactive oxygen and nitrogen species (ROS/RNS) play indispensable physiological roles [8]. At controlled levels, they function as second messengers that regulate cell proliferation, immune activation, host defense, apoptosis, and metabolic adaptation. Redox signaling enables cells to respond appropriately to stress, repair damage, and maintain homeostasis [9]. Excessive antioxidant intake can dampen these essential signaling pathways, a phenomenon conceptualized through hormesis-the idea that low levels of oxidative stress trigger beneficial adaptive responses that are blunted when antioxidants are provided in excess [10]. Moreover, several antioxidants can act as pro-oxidants under certain biochemical conditions [11]. For instance, vitamin C can catalyze free radical formation in iron-rich environments, and β-carotene can degrade into reactive aldehydes when exposed to high oxygen tension. High-dose antioxidants may also influence mitochondrial electron transport, modify redox-sensitive transcription factors (such as Nrf2 and NF-κB), and alter phase I/II drug-metabolizing enzymes, thereby affecting cellular bioenergetics and drug interactions [12]. Collectively, these mechanisms illustrate how supplementation can inadvertently exacerbate pathology rather than alleviate it.

3. Preclinical Evidence of Toxicity

3.1 Pro-oxidant Activity and Genotoxicity

A significant body of preclinical research demonstrates that antioxidants can shift toward pro-oxidant behavior under specific biochemical conditions [13]. In vitro, high concentrations of vitamin C can react with catalytic iron or copper to generate hydrogen peroxide and hydroxyl radicals, producing measurable oxidative DNA damage [14]. Similar effects have been documented in vivo: rodents supplemented with megadose vitamin C under iron-overload conditions exhibit increased lipid peroxidation and oxidative injury. β-carotene, another widely consumed antioxidant, undergoes oxidative cleavage in high-oxygen environments, generating reactive aldehydes and epoxides capable of damaging nucleic acids and cell membranes [15]. These genotoxic products provide a plausible mechanistic explanation for some of the harmful outcomes observed in human trials, particularly in smokers and individuals with chronically inflamed tissues.

3.2 Tumor Promotion in Certain Contexts

Preclinical cancer models consistently show that antioxidants can facilitate tumor growth when malignant or premalignant cells are already present [16]. In mouse models of melanoma, lung cancer, and chemically induced carcinogenesis, antioxidant supplementation reduces oxidative stress within tumor cells, inadvertently supporting their survival and proliferation [17]. By dampening ROS-mediated apoptosis and weakening ROS-dependent immune detection, antioxidants may create a microenvironment that favors tumor progression. Increased tumor multiplicity and accelerated metastatic spread in antioxidant-treated animals highlight the risk of disrupting the natural oxidative defenses that constrain early-stage cancer cells [18].

3.3 Interference with Adaptive Responses

Physiological stressors such as exercise, fasting, and caloric restriction rely on transient ROS bursts to activate adaptive pathways, including mitochondrial biogenesis, antioxidant enzyme induction, and improved insulin signaling [19]. Rodent studies repeatedly show that chronic high-dose supplementation with vitamins C and E blunts these beneficial adaptations. Animals receiving antioxidants alongside exercise training demonstrate reduced mitochondrial enzyme activity, impaired glucose uptake, and diminished endurance capacity, suggesting that excessive antioxidant buffering disrupts essential hormetic signaling [20].

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3.4 Developmental and Reproductive Toxicity

Several antioxidants exhibit toxic effects during gestation or reproductive development when administered at high doses [21]. Retinoids (vitamin A derivatives) are well-established teratogens in animal models, causing craniofacial, cardiac, and neurologic malformations even within a narrow window of excess. Selenium toxicity is likewise documented in rodents, with high intake producing embryotoxicity, reduced litter size, and impaired postnatal growth [22]. These findings reinforce the principle that micronutrients with critical developmental roles also have narrow safety margins, and that supplementation during pregnancy requires strict dose regulation.

4. Clinical and Epidemiological Evidence

4.1 Increased Cancer Risk in Specific Populations

Perhaps the most robust clinical signal comes from randomized trials of β-carotene in smokers, where supplementation increased lung cancer incidence and mortality [23]. These findings have been replicated across multiple studies and represent a clear example of population-specific harm. Other trials examining high-dose vitamin E showed variable effects on cancer endpoints, with some analyses suggesting increased prostate cancer incidence in certain cohorts receiving supranutritional alpha-tocopherol [24].

4.2 All-Cause Mortality Meta-Analyses

Meta-analyses of RCTs have reported small but statistically significant increases in all-cause mortality associated with high doses of certain antioxidant vitamins, particularly vitamin E and beta-carotene, though results vary by dose threshold, form, and trial quality [25]. These pooled findings have prompted caution regarding indiscriminate long-term use of high-dose antioxidant pills [26].

4.3 Interaction with Cancer Therapies

Antioxidant supplements may reduce the efficacy of chemotherapy and radiotherapy by protecting malignant cells from therapy-induced oxidative damage mechanistic concerns supported by observational reports and, on occasion, clinical evidence of impaired treatment response [27]. Oncology guidelines often advise against routine antioxidant supplement use during active cytotoxic treatment unless clinically indicated and supervised [28].

4.4 Metabolic and Cardiovascular Outcomes

Large RCTs testing antioxidant vitamins for cardiovascular prevention have largely failed to demonstrate benefit; a few studies reported neutral to adverse outcomes [29]. In type 2 diabetes and metabolic syndrome cohorts, antioxidant supplementation has sometimes failed to improve clinical endpoints and in some cases attenuated pharmacologic therapy effects, raising safety questions in those taking multiple agents.

4.5 Reproductive and Developmental Outcomes in Humans

High intakes of vitamin A (as retinol or retinoids) are teratogenic in humans; international guidelines warn against high-dose vitamin A supplementation in pregnancy [30]. Selenium toxicity (selenosis) is documented in areas of excessive environmental exposure, and supplementation trials emphasize narrow margins of safety.

5. Mechanisms Underlying Toxicity

The mechanisms underlying toxicity are multifaceted and largely depend on dose, cellular context, and individual susceptibility [31]. A key pathway involves disruption of hormetic redox signaling, whereby excessive antioxidant exposure suppresses physiological reactive oxygen species (ROS) required for normal stress adaptation, cellular signaling, and immune responses. In addition, certain compounds can exhibit pro-oxidant behavior, particularly in the presence of transition metals such as iron and copper, leading to enhanced ROS generation [32]. High antioxidant levels may also protect malignant or pre-malignant cells from ROS-mediated apoptosis, thereby reducing immune surveillance and facilitating tumor survival. Alterations in phase I and phase II drug-metabolizing enzymes further contribute to toxicity by modifying drug clearance and increasing the risk of adverse drug interactions [33]. At elevated local concentrations, oxidative DNA damage and genomic instability may occur. Furthermore, interference with mitochondrial electron transport chains can promote uncoupling, impair ATP generation, and compromise cellular bioenergetics [34]. Genetic polymorphisms in antioxidant enzymes, including GPX1 and SOD2, alongside baseline nutritional status, significantly influence individual vulnerability to these toxic effects.

6. Determinants of Toxicological Risk

The toxicological profile of antioxidant supplementation varies widely across individuals and contexts, underscoring that risk is neither uniform nor easily generalized [35]. Dose remains the most influential determinant: supraphysiologic intakes, particularly of synthetic or isolated compounds such as high-dose

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alpha-tocopherol or β-carotene, are far more likely to disrupt redox signaling than moderate, food-based intakes [36]. Chemical form also matters, as different isoforms exhibit distinct biological activities and metabolic fates; for example, mixed tocopherols may behave differently from isolated alpha-tocopherol, and natural carotenoids differ from synthetic forms in oxidative stability [37].

Duration and timing of exposure amplify or mitigate risk [38]. Chronic, lifelong supplementation may accumulate subtle metabolic effects that do not manifest in short-term trials. Critical life stages-pregnancy, early childhood, and periods of immune compromise-may heighten vulnerability to excess [39]. Host factors strongly modify outcomes: smoking status dramatically increases β-carotene-related carcinogenic risk, while pre-existing cancer, metabolic disease, or genetic polymorphisms in antioxidant enzymes (such as variants in GSTM1, SOD2, or GPX1) alter susceptibility to both benefit and harm [40]. Co-exposures further shape toxicity. Iron overload, heavy metal exposure, environmental pollutants, and certain medications can convert antioxidants into pro-oxidant agents or alter their metabolism [41]. Poor supplement quality, contamination with heavy metals or adulterants, and inaccurate labeling introduce additional unpredictability. Together, these determinants emphasize the need for individualized, context-aware risk assessment.

CONCLUSION

Long-term antioxidant supplementation carries inherent toxicological risks that challenge the perception of antioxidants as universally beneficial. Evidence from preclinical studies and human trials demonstrates context-dependent harms, including increased cancer incidence in high-risk groups, interference with cancer therapies, metabolic disruption, and potential increases in all-cause mortality at excessive doses. A prudent, evidence-informed strategy-favoring dietary sources, individualized assessment, and calibrated dosing-is essential to ensure safe and effective use. Strengthened regulation and rigorous research are critical to refining guidance and minimizing harm as supplement use continues to grow.

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