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Oxidative Stress and Vitamins

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Abstract

Oxidative stress, resulting from the excessive production of free radicals and reactive oxygen species (ROS) or the inadequacy of an organism's antioxidant defense mechanisms in living systems, can cause permanent damage to cellular lipids, proteins, and DNA. This plays a significant role in the pathogenesis of many chronic diseases, particularly cancer, diabetes, cardiovascular diseases, and neurodegenerative disorders such as Alzheimer's and Parkinson's disease. However, low to moderate levels of physiological ROS production (oxidative estrous stress) are critical for maintaining cellular signaling, immune responses, and redox homeostasis.

Primary antioxidant vitamins (vitamin C, vitamin E, and vitamin A/carotenoids) stand out due to their ability to directly scavenge reactive species, interrupt lipid peroxidation chain reactions, and activate cellular antioxidant gene expression pathways such as Nrf2. Vitamin C functions as a direct scavenger in aqueous environments, while vitamin E provides protection within cell membranes. Furthermore, these vitamins create a synergistic defense network by regenerating each other from their oxidized forms. However, despite strong protective evidence from in vitro studies and animal models, clinical trials have revealed a complex picture known in the literature as the “antioxidant paradox.”.

Current clinical and epidemiological evidence demonstrates that holistic dietary patterns rich in natural phytochemicals and vitamins, such as the Mediterranean diet and the DASH diet, are significantly more effective and safer in reducing oxidative stress and systemic inflammation biomarkers (CRP, IL-6, TNF-α) than isolated and high-dose synthetic supplements. Furthermore, understanding nutrigenomics and the disease-specific molecular mechanisms underlying various pathologies makes it possible to develop antioxidant strategies tailored to individuals' genetic profiles.

This review article aims to identify both the beneficial and harmful aspects of oxidative stress, discuss the therapeutic potential of primary antioxidant vitamins and pro-oxidant risks in light of current clinical findings, and comprehensively present next-generation disease prevention strategies emphasizing lifestyle changes, validation of reliable biomarkers, and modern nutrigenomic approaches rather than relying on a single nutritional supplement.

Keywords: Oxidative stress; Antioxidant vitamins; Free radical

Oksidatif Stres ve Vitaminler

Özet

Canlı sistemlerde serbest radikallerin ve reaktif oksijen türlerinin (ROS) aşırı üretimi veya organizmanın antioksidan savunma mekanizmalarının yetersizliği sonucu ortaya çıkan oksidatif stres, hücresel lipitlere, proteinlere ve DNA'ya kalıcı hasar verebilir. Bu durum, özellikle kanser, diyabet, kardiyovasküler hastalıklar, Alzheimer ve Parkinson hastalığı gibi nörodejeneratif bozukluklar olmak üzere birçok kronik hastalığın patogenezinde önemli bir rol oynar. Bununla birlikte, düşük ve orta seviyelerde fizyolojik ROS üretimi (oksidatif östrese), hücresel sinyal iletimi, bağışıklık tepkileri ve redoks homeostazının korunması için kritik öneme sahiptir.

Birincil antioksidan vitaminler (C vitamini, E vitamini ve A vitamini/karotenoidler), reaktif türleri doğrudan temizleme, lipid peroksidasyon zincir reaksiyonlarını kesme ve Nrf2 gibi hücresel antioksidan gen ekspresyon yollarını aktive etme yetenekleri nedeniyle öne çıkmaktadır. C vitamini sulu ortamlarda doğrudan temizleyici olarak işlev görürken, E vitamini hücre zarları içinde koruma sağlar. Dahası, bu vitaminler oksitlenmiş formlarından birbirlerini yeniden üreterek sinerjik bir savunma ağı oluştururlar. Ancak, in vitro çalışmalar ve hayvan modellerinden elde edilen güçlü koruyucu kanıtlara rağmen, klinik araştırmalar literatürde “antioksidan paradoksu” olarak bilinen karmaşık bir tabloyu ortaya koymuştur.

Güncel klinik ve epidemiyolojik kanıtlar, izole ve yüksek dozlu sentetik takviyelerden ziyade, Akdeniz diyeti ve DASH diyeti gibi doğal fitokimyasallar ve vitaminler açısından zengin bütünsel beslenme modellerinin, oksidatif stres ve sistemik inflamasyon biyobelirteçlerini (CRP, IL-6, TNF-α) azaltmada önemli ölçüde daha etkili ve güvenli olduğunu göstermektedir. Dahası, besin-gen etkileşimlerinin (nutrigenomik) ve çeşitli patolojilerin altında yatan hastalığa özgü moleküler mekanizmaların anlaşılması, bireylerin genetik profillerine göre uyarlanmış antioksidan stratejilerinin geliştirilmesini mümkün kılmaktadır.

Bu derleme makalesi, oksidatif stresin hem yararlı hem de zararlı yönlerini tanımlamayı, güncel klinik bulgular ışığında birincil antioksidan vitaminlerin terapötik potansiyelini ve pro-oksidan risklerini tartışmayı ve tek bir besin takviyesine dayanmak yerine yaşam tarzı değişikliklerini, güvenilir biyobelirteçlerin doğrulanmasını ve modern nutrigenomik yaklaşımları vurgulayan yeni nesil hastalık önleme stratejilerini kapsamlı bir şekilde sunmayı amaçlamaktadır.

Anahtar kelimeler: Oksidatif stress; Antioksidan vitaminler; Serbest radikal

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INTRODUCTION

In living systems, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are continuously generated as natural by-products of fundamental metabolic processes such as cellular respiration, as well as through the influence of external factors including radiation and environmental pollution (1-2). At low to moderate levels, these free radicals remain within a physiological range referred to as "oxidative eustress," where they function as critical second messengers involved in vital biological processes such as immune responses, cellular signal transduction, gene expression, and defense against pathogens (3-5). However, when the delicate balance between free radical production and the organism's capacity to detoxify them is disrupted in favor of oxidants, oxidative stress (or oxidative distress) occurs. This condition leads to irreversible damage to cellular macromolecules such as lipids, proteins, and DNA, thereby contributing to the underlying pathogenesis of many contemporary chronic diseases, including cancer, cardiovascular diseases, diabetes, aging, and neurodegenerative disorders such as Alzheimer's and Parkinson's disease (1,3).

The human body utilizes a complex and multilayered antioxidant defense network to limit the deleterious effects of ROS without interfering with essential cellular signaling processes. One of the most important components of this system is low–molecular weight primary antioxidant vitamins (vitamin C, vitamin E, and vitamin A/carotenoids), which must be obtained exogenously through the diet. Acting within different cellular compartments, these vitamins interrupt free radical chain reactions and function synergistically to maintain redox homeostasis. Numerous studies have investigated the antioxidant properties of vitamins such as vitamin E, vitamin C, and carotenoids and their effects on human health (1,3,6). In light of current evidence, the effects of these essential vitamins on oxidative stress and human health are mediated through distinct mechanisms. Vitamin C (ascorbic acid), a water-soluble vitamin, directly scavenges ROS in the cytoplasm and extracellular fluids. Beyond acting solely as a scavenger, it also regenerates vitamin E from its oxidized radical form by reducing it back to its active state (redox recycling), thereby substantially enhancing the overall cellular antioxidant capacity (1,3).

However, recent molecular studies indicate that vitamin C possesses a dual nature. While it acts as a potent antioxidant at normal physiological doses, at pharmacologically high concentrations and in the presence of transition metals such as iron, it can behave as a pro-oxidant by generating hydrogen peroxide through the "Fenton reaction." This property is currently being investigated as a promising strategy for selectively targeting cancer cells (2,7).

Vitamin E (tocopherols and tocotrienols), a fat-soluble antioxidant located in lipid-rich environments such as cell membranes and lipoproteins, prevents ROS from attacking polyunsaturated fatty acids. Vitamin E is considered one of the most effective components in terminating the lipid peroxidation chain reaction, which is a major trigger of processes such as atherosclerosis and neuronal cell death (3,8,9).

Vitamin A and carotenoids (e.g., β-carotene and lycopene) are highly effective in stabilizing singlet oxygen and peroxyl radicals by absorbing unpaired electrons, primarily due to their conjugated double-bond systems. In addition to protecting tissues exposed to high levels of oxygen and light such as the eye and skin from oxidative damage, they regulate the expression of specific genes related to apoptosis, cellular differentiation, and immune responses through retinoic acid receptors (10-12).

Despite their strong protective profiles at the mechanistic level, the role of these vitamins in disease prevention presents a complex picture known

in the literature as the "antioxidant paradox" (8). Although isolated and megadose vitamin supplementation has shown promising results in in vitro settings, large-scale clinical trials investigating their role in the prevention of chronic diseases in humans (e.g., the SELECT and ATBC trials) have generally failed to demonstrate beneficial effects and, in some cases, have even reported an increased disease risk (3,8). For instance, high-dose β-carotene supplementation has been shown to oxidize under the high oxygen pressure present in the lungs of smokers, leading to the formation of pro-oxidant degradation products that may promote carcinogenesis (13). Similarly, synthetic vitamin E supplementation has been reported not only to fail in reducing prostate cancer risk but also to contribute to an increased risk (14). These findings provide strong evidence that non-physiological high doses may disrupt beneficial ROS signalling pathways or convert antioxidants into pro-oxidant agents (3,8,15).

In light of these findings, current health strategies have shifted away from isolated megadose supplementation toward holistic plant-based dietary patterns—such as the Mediterranean diet in which nutrients interact synergistically to stimulate antioxidant gene expression pathways such as NRF2, as well as toward the emerging field of nutrigenomics, which investigates the specific effects of vitamins on gene expression (8,16). This review aims to define the physiological and pathological dual nature of oxidative stress, critically evaluate the molecular mechanisms through which vitamins E, C, and A, along with carotenoids, contribute to the protection of human health in light of current clinical evidence, and comprehensively present emerging dietary and therapeutic perspectives guided by modern redox biology that may help overcome the "antioxidant paradox."

Literature Search Strategy

The literature search for this review article was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed using the electronic databases PubMed/MEDLINE, Web of Science, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. The search was limited to studies published in English, while no specific restriction was applied regarding the year of publication in order to include both historical and the most up-to-date evidence relevant to the topic.

Measurement of Antioxidant Capacity

The measurement of the Total Antioxidant Capacity (TAC) of foods is conducted to evaluate the overall ability of a food matrix to neutralize free radicals, reduce metal ions, or prevent oxidative damage. Because antioxidants in foods operate via a variety of complex mechanisms (such as radical scavenging, hydrogen donation, or metal chelation), measuring TAC cannot be accurately achieved with a single method. Instead, a combination of in vitro techniques is typically recommended to get a comprehensive profile (17).

The measurement of the total antioxidant capacity (TAC) of foods is performed to evaluate the ability of a food matrix to neutralize free radicals and prevent oxidative damage. Because antioxidants operate through different mechanisms, TAC cannot be accurately assessed using a single method; instead, a combination of various in vitro techniques is employed. The most commonly used approaches are spectrometric assays that measure color or fluorescence changes resulting from the reaction of radicals or metal complexes with antioxidants (e.g., DPPH, ABTS, ORAC, FRAP, CUPRAC). In addition, electrochemical techniques and chromatographic methods that separate individual components (such as GC and HPLC) are also frequently used (18).

One of the most important challenges specific to food analysis is that conventional liquid extraction methods often overlook macromolecular (insoluble) antioxidants bound to dietary fibers. To overcome this limitation, the QUENCHER method was developed, which completely bypasses the extraction step and allows radicals to react directly with the solid–liquid surface of the food matrix.

Although these assays are invaluable for the preliminary screening of food components, the scientific community emphasizes that the concept of "total antioxidant capacity" measured under laboratory conditions has significant limitations (19). In vitro TAC values cannot be directly translated into in vivo health benefits or clinical outcomes because they do not account for factors such as the

bioavailability, metabolism of antioxidant molecules in the human body, or the organism's endogenous enzymatic defense systems (18).

Primary Antioxidant Vitamins and Oxidative Stress

Oxidative stress is a physiological condition that arises when there is an imbalance between the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) and the body's antioxidant defense systems (3). While low levels of ROS are essential for normal cellular signaling, pathogen destruction, and immune defense (a state known as oxidative eustress), excessive ROS levels (oxidative distress) lead to the oxidative damage of vital biomolecules, including lipids, proteins, and DNA (3,15). This cellular damage is a common denominator in aging and the pathogenesis of chronic conditions such as cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders (3). To combat this, the body relies on an intricate antioxidant defense network comprising endogenous enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase) and low-molecular-weight exogenous antioxidants obtained primarily from the diet (20,21). The primary antioxidant vitamins Vitamin C, Vitamin E, and Vitamin A (along with its precursors, carotenoids) play crucial roles in maintaining this redox homeostasis (7).

Vitamin C (Ascorbic Acid) Vitamin C is a highly effective, water-soluble antioxidant that operates mainly in aqueous cellular environments, such as the cell cytosol and extracellular fluids. Antioxidant Mechanism: It directly scavenges various ROS, including hydroxyl radicals, superoxide, and hydrogen peroxide. Beyond direct scavenging, Vitamin C plays an essential synergistic role by recycling oxidized Vitamin E (the -tocopheryl radical) back into its active, non-radical form, thereby restoring the cell's lipid defense mechanisms (1,3).

Pro-oxidant Risks: At pharmacological (very high) doses, particularly in the presence of unbound transition metals like iron (Fe) or copper (Cu), Vitamin C can exhibit pro-oxidant properties. It reduces these metals, which subsequently react with hydrogen peroxide via the Fenton reaction to generate highly destructive hydroxyl radicals (2,3).

Vitamin E (-Tocopherol) Vitamin E is the principal lipid-soluble antioxidant and is strategically anchored within cell membranes and lipoproteins. Antioxidant Mechanism: Its primary function is to protect polyunsaturated fatty acids (PUFAs) from free radical attacks. When a lipid peroxyl radical forms, Vitamin E donates a hydrogen atom to halt the destructive chain reaction of lipid peroxidation, converting itself into a relatively stable -tocopheryl radical (3,22).

Clinical Limitations: Despite its potent molecular mechanism, clinical trials using high-dose Vitamin E supplements (such as the CHAOS and HOPE studies for cardiovascular disease, and the SELECT trial for prostate cancer) have largely failed to demonstrate significant preventive benefits. In the SELECT trial, supplementation with synthetic Vitamin E (all-rac--tocopheryl acetate) actually increased the risk of developing prostate cancer, underscoring that supra-nutritional doses can disrupt normal physiological processes and act as pro-oxidants (3,15).

Vitamin A and Carotenoids (e.g., -Carotene) Carotenoids are lipid-soluble plant pigments that serve as precursors to Vitamin A (retinol), which is vital for immune function, cellular differentiation, and epithelial barrier integrity. Antioxidant Mechanism: Carotenoids possess conjugated double bonds that allow them to absorb unpaired electrons and efficiently quench singlet oxygen ($^1O_2$), protecting tissues from light-induced and oxygen-induced damage. They also scavenge peroxyl and hydroxyl radicals (3,23). The Pro-oxidant Danger in Smokers: The behavior of -carotene is highly dependent on the cellular environment (specifically the partial pressure of oxygen). In the large-scale ATBC and CARET trials, heavy smokers given high-dose -carotene supplements experienced an unexpected increase in lung cancer incidence and mortality. In the radical-rich, high-oxygen environment of a smoker's lung, -carotene undergoes auto-oxidation, forming destructive pro-oxidant metabolites (like -apocarotenals) that impair retinoic acid signaling pathways and promote cellular proliferation (3,23).

The "Antioxidant Paradox" The relationship between primary antioxidant vitamins and oxidative stress highlights what is known in scientific literature as the "antioxidant paradox". While diets rich in these

vitamins (such as the Mediterranean diet) are consistently linked to reduced chronic disease risk due to the synergistic interaction of multiple nutrients, isolated high-dose supplementation often fails. Mega-doses of isolated vitamins can: Interfere with the beneficial signaling roles of ROS (such as immune defense against pathogens, vasodilation, and exercise adaptation). Fail to reach the specific subcellular compartments where oxidative damage actually occurs. Convert into pro-oxidants under specific physiological conditions, exacerbating tissue damage and disease progression (8,15).

Therefore, modern nutritional science emphasizes that maintaining redox balance is best achieved through a diverse, plant-based diet containing a matrix of synergistic antioxidants, rather than through high-dose single-vitamin supplementation (8).

Antioxidant Vitamins in the Prevention of Chronic Diseases

Oxidative stress, which results from the excessive production of free radicals and the insufficient capacity of the organism's antioxidant defense system, is considered one of the fundamental pathogenic mechanisms underlying many chronic diseases, including cardiovascular diseases, cancer, diabetes, neurodegenerative disorders, and cellular aging (1,3). In this context, primary antioxidant vitamins such as vitamin C, vitamin E, and carotenoids the precursors of vitamin A play an important role in the prevention of chronic diseases due to their potential to neutralize free radicals and limit cellular damage (12).

Oxidative stress plays a particularly critical role in the development of cardiovascular diseases. In the early stages of atherosclerosis, endothelial dysfunction and the oxidation of low-density lipoprotein (LDL) into its oxidized form (oxLDL) represent key pathogenic mechanisms. Vitamin E, a potent fat-soluble antioxidant, inhibits lipid peroxidation in cell membranes and lipoproteins, thereby reducing the oxidation of LDL and potentially slowing the progression of atherosclerotic plaque formation (24,25). Vitamin C, a water-soluble antioxidant, supports antioxidant capacity by reducing the oxidized form of vitamin E back to its active state, while also promoting vasodilation by increasing nitric oxide (NO) bioavailability in endothelial cells (1,3).

Similarly, oxidative stress can trigger the carcinogenesis process through DNA damage and genomic instability (1). Antioxidant vitamins, particularly vitamin C, vitamin E, and carotenoids, may exert potential protective effects against tumor development by scavenging reactive oxygen species and modulating cellular signaling pathways (23). However, a phenomenon described in the literature as the "antioxidant paradox" has also been reported. While the protective effects of physiologically relevant dietary antioxidant vitamins have been demonstrated, some clinical studies have indicated that high-dose β-carotene supplementation may increase the risk of lung cancer, particularly in smokers (26).

Oxidative stress also plays a critical role in the pathogenesis of neurodegenerative diseases (27). Brain tissue is highly susceptible to oxidative damage due to its high oxygen consumption, rich lipid content, and relatively low antioxidant capacity. In Alzheimer's disease, the relationship between oxidative damage and amyloid-β plaque accumulation is particularly notable. Vitamins E and C have been reported to exert neuroprotective effects by protecting neuronal cells against lipid peroxidation and free radical-induced damage, with the potential to slow disease progression (28).

Oxidative stress also plays a pivotal role in the development of diabetes and its associated complications. Chronic hyperglycemia overstimulates cellular metabolic pathways, leading to the excessive generation of reactive oxygen species, which contributes to the development of microvascular complications such as neuropathy, nephropathy, and retinopathy. Antioxidant vitamins have been suggested to mitigate oxidative stress, suppress inflammatory processes, and exert beneficial effects on insulin resistance (29).

One of the areas with the strongest clinical evidence for antioxidant vitamin supplementation is eye health. The Age-Related Eye Disease Study (AREDS) demonstrated that a combination of vitamin C, vitamin E, β-carotene (or lutein/zeaxanthin), and zinc significantly reduced the risk of progression to advanced age-related macular degeneration (AMD) (30).

Overall, the literature indicates that the source and dosage of antioxidant vitamins are critical factors in chronic disease prevention. Diets rich in fruits, vegetables, and whole grains provide not only natural antioxidant vitamins but also a variety of bioactive compounds that collectively reduce oxidative stress biomarkers. In contrast, some large-scale clinical trials have reported that high-dose isolated vitamin supplementation often fails to confer the expected protective effects against chronic diseases and, in certain cases, may disrupt redox balance and exert pro-oxidant effects (3,8,11).

In conclusion, while antioxidant vitamins play important molecular and physiological roles in the prevention of chronic diseases, current scientific evidence indicates that this protective effect is more safely and effectively achieved through balanced, plant-based dietary patterns in which diverse food components act synergistically, rather than through high-dose supplementation (8,11).

The Antioxidant Paradox

Antioxidants provide cellular protection by neutralizing free radicals at physiological doses; however, when administered at high or pharmacological doses, they can exhibit pro-oxidant properties under certain conditions (1,3,31). In particular, the presence of transition metals such as iron and copper or specific cellular microenvironments has been reported to facilitate the pro-oxidant activity of antioxidants (3). This phenomenon, described as the "antioxidant paradox," demonstrates that antioxidants can exert not only protective but also harmful or therapeutic effects depending on context and dosage (3,8,15). Recent studies indicate that this dual activity may be associated at the cellular level with mechanisms that can both promote cancer progression and, in specific circumstances, be harnessed for therapeutic strategies targeting cancer cells (15,32).

A prominent example of this paradoxical activity is associated with vitamin C. Under normal conditions, ascorbic acid acts as a potent antioxidant; however, in environments containing free iron or copper ions, it can trigger the Fenton reaction, leading to the formation of hydrogen peroxide and highly reactive hydroxyl radicals (3). The pro-oxidant effects of pharmacological doses of vitamin C have been proposed to selectively target tumor cells in certain types of cancer (2). High-dose vitamin C administration can induce excessive reactive oxygen species production, particularly in cancer cells, depleting cellular antioxidant defenses such as glutathione and cysteine, and generating intense oxidative stress (32). This process can disrupt NAD^+ biosynthesis, impair energy-producing pathways such as glycolysis and the tricarboxylic acid cycle, and ultimately lead to cancer cell death via apoptosis or necrosis (32).

Another significant example of the antioxidant paradox involves vitamin E and N-acetylcysteine (NAC). Large-scale clinical studies have shown that high-dose antioxidant supplementation does not always confer protective effects (33,34). For instance, the SELECT trial reported that synthetic vitamin E supplementation increased the risk of prostate cancer (33). Similarly, high-dose vitamin E and the potent antioxidant NAC have been suggested to accelerate tumor growth and metastasis in certain contexts, such as lung cancer (35,36). Cancer cells require a certain level of antioxidant defense for survival, and enhancement of this defense may protect cells from oxidative stress-induced damage. Moreover, these antioxidants have been shown to reduce cellular free heme levels, thereby stabilizing the transcription factor BACH1, which can promote glycolysis and facilitate lung cancer metastasis (3).

Dietary Antioxidants vs. Supplementation: Clinical and Biological Differences

Findings related to β-carotene represent one of the most striking examples of the antioxidant paradox. Although β-carotene functions as a potent antioxidant and a provitamin A source under physiological conditions, unexpected outcomes have been observed when administered as a high-dose supplement, particularly in smokers. Large randomized controlled trials investigating lung cancer prevention, such as the ATBC and CARET studies, reported that heavy smokers and individuals with asbestos exposure who received approximately 20–30 mg/day of β-carotene supplementation exhibited a significantly higher incidence and mortality of lung cancer compared to the placebo group (33,34). The underlying mechanism of this paradoxical effect is thought to be related to the intense oxidative stress and free radical burden

induced by cigarette smoke in the pulmonary microenvironment.

Current epidemiological and toxicological evidence indicates that physiologically relevant β-carotene intake from natural dietary sources, such as fruits and vegetables, is safe and protective for the general population. However, international authorities, including the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA), emphasize that high-dose isolated β-carotene supplementation should be avoided, particularly in smokers (37).

The fundamental differences between antioxidants obtained naturally through diet and those administered as supplements in the form of pills or capsules lie in their bioavailability, dosage, cellular effects, and capacity to prevent disease (1,2). Antioxidants consumed through natural plant-based sources such as fruits, vegetables, and grains function synergistically with other vitamins, phytochemicals, and dietary fibers present in the food matrix (8). A well-balanced diet provides not only molecules that directly scavenge free radicals but also essential cofactor minerals such as zinc, manganese, iron, copper, and selenium required for the body's endogenous antioxidant enzyme systems, including superoxide dismutase and catalase. In contrast, supplements generally contain isolated high doses of one or a few antioxidants and cannot replicate this complex synergistic balance found in natural foods (8).

Dietary antioxidants are present at physiological levels and contribute to the maintenance of cellular redox balance by neutralizing free radicals. However, isolated antioxidants administered at high or "megadose" levels through supplementation (e.g., high-dose vitamin C or E) may disrupt this delicate equilibrium. Many molecules that act as potent antioxidants in vitro can, under conditions of high doses or in the presence of transition metals, exert the opposite effect and become pro-oxidant agents that induce cellular damage (19).

Epidemiological studies indicate that plant-based dietary patterns, including the consumption of fresh fruits, vegetables, whole grains, and adherence to the Mediterranean diet, significantly reduce the risk of cancer, cardiovascular diseases, neurodegenerative disorders, and diabetes (8). However, large-scale, long-term clinical trials have demonstrated that isolated, high-dose antioxidant supplementation is largely ineffective in preventing these chronic diseases and in mitigating oxidative damage (3,8).

While naturally occurring dietary antioxidants create a protective environment against cancer, the use of supplemental antioxidants can sometimes produce adverse outcomes. This phenomenon, described in the literature as the "antioxidant paradox," suggests that supplements may protect cancer cells, thereby potentially promoting tumor growth and metastasis (33).

From a bioavailability perspective, naturally consumed antioxidants offer distinct advantages. Many antioxidants, such as polyphenols found in green tea, red wine, and various fruits, are metabolized by the gut microbiota into biologically active compounds that can enter systemic circulation. In contrast, numerous antioxidants taken in isolated supplement form have been reported to exhibit limited in vivo bioavailability. Compounds that effectively scavenge free radicals in vitro often show restricted activity in human tissues, particularly in target organs such as the brain, and evidence for their efficient recycling within endogenous antioxidant systems is limited (3,8).

CONCLUSION

In conclusion, reactive oxygen (ROS) and nitrogen species (RNS), which are natural by-products of cellular metabolism, are essential at low concentrations for cellular signalling, gene expression, and immune responses (oxidative eustress). However, when their production exceeds the organism's antioxidant scavenging capacity, they cause irreversible damage to lipids, proteins, and DNA (oxidative distress), representing a key pathogenic mechanism underlying cancer, cardiovascular diseases, diabetes, and neurodegenerative disorders (3). In addition to the endogenous enzymatic defense systems developed by the body against such destructive damage (e.g., SOD, GPx, catalase), exogenous antioxidants obtained from the diet such as primary vitamins (C, E, A/carotenoids) and phenolic compounds play a critical complementary role in maintaining cellular redox homeostasis (1,11).

Nevertheless, potent free radical-scavenging data obtained in vitro have not always translated into positive outcomes in clinical studies, giving rise to the complex phenomenon described in the literature as the "antioxidant paradox." Large-scale epidemiological and clinical trials, including ATBC, CARET, and SELECT, have shown that synthetic antioxidant supplements administered in isolated form and at pharmacological (megadose) levels (e.g., β-carotene and vitamin E) are largely insufficient in preventing chronic diseases (3). More importantly, these molecules have been definitively shown to act as pro-oxidant agents under conditions of high risk such as in smokers or under elevated oxygen tension, suppressing beneficial ROS signalling and potentially accelerating tumour progression. On the other hand, this pro-oxidant property of high-dose antioxidants has also been leveraged in contemporary oncology research (e.g., pharmacological doses of vitamin C in thyroid cancer cells) as an innovative, targeted therapeutic strategy. By generating hydrogen peroxide and free radicals, high-dose vitamin C can selectively induce apoptosis and necrosis in cancer cells, while disrupting glycolysis and the tricarboxylic acid (TCA) cycle (1,23).

In light of current scientific consensus and clinical evidence, plant-based dietary patterns that harness the holistic power of the food matrix should replace isolated, high-dose vitamin supplements in the primary prevention of disease. Dietary patterns such as the Mediterranean and DASH diets, in which free antioxidants from natural foods and bound antioxidants linked to cellular macromolecules and dietary fibers simultaneously enter the digestive system, have been shown to create cellular synergy and are significantly more effective and safer than isolated supplements in reducing systemic inflammation and oxidative stress biomarkers (e.g., MDA, F2-isoprostanes, ox-LDL, hs-CRP) (11,38).

Future research directions should focus on the discovery of novel and validated biomarker panels capable of accurately quantifying local oxidative damage at the tissue level and establishing causal links to disease. Additionally, nutrigenomic approaches that investigate the influence of genetic variation and individual enzymatic differences on antioxidant metabolism, such as NRF2 activation, should be rapidly integrated into clinical practice (3,9). The fundamental medical paradigm for oxidative stress management should shift from indiscriminate administration of synthetic antioxidants toward personalized strategies tailored to an individual's genetic profile, incorporating diet, exercise, and other beneficial stressors that finely modulate cellular redox balance (3,8).

Ethics Committee Approval

This article is a review of previously published literature. Since it does not involve any studies with human participants or animals conducted by the author, ethical approval was not required.

Author Contributions

Conception - Cansu Can Figen; Design - Cansu Can Figen; Supervision - Cansu Can Figen; Literature Search - Cansu Can Figen; Writing - Cansu Can Figen; Critical Review - Cansu Can Figen.

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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