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Review Article

Natural Products as Antioxidants: Molecular Mechanisms of Free Radical Scavenging, Redox Signaling, and Therapeutic Potential: A Review

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ABSTRACT

Reactive oxygen and nitrogen species are continuously generated in living systems as byproducts of mitochondrial respiration, immune activation, and exposure to environmental stressors. When their production outpaces the capacity of cellular antioxidant defenses, the resulting oxidative stress damages lipids, proteins, and nucleic acids and contributes to the pathogenesis of cardiovascular disease, cancer, neurodegeneration, and aging. Natural products derived from plants, algae, and other dietary sources represent a structurally diverse reservoir of antioxidant molecules-including polyphenols, carotenoids, vitamins, and organosulfur compounds-that counteract oxidative damage through both direct free radical scavenging and indirect modulation of endogenous defense pathways. This review synthesizes current understanding of the biochemical mechanisms by which natural antioxidants act, including hydrogen atom transfer and electron transfer reactions characteristic of phenolic compounds, singlet oxygen quenching by carotenoids, and activation of the Nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1)-Antioxidant Response Element (ARE) pathway. It also examines more complex and at times contradictory evidence from clinical intervention trials, the phenomenon of pro-oxidant behavior at high concentrations, and the persistent challenge of poor bioavailability that limits translation of *in vitro* antioxidant activity into clinical benefit. Methodological considerations in antioxidant capacity assays are discussed, and priorities for future mechanistic and clinical research are outlined.

Keywords: Free radicals, Reactive oxygen species, Natural antioxidants, Polyphenols, Oxidative stress, Nrf2.

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INTRODUCTION

Free radicals are atoms, ions, or molecules that possess one or more unpaired electrons in their outer orbital, a configuration that confers high chemical reactivity and a propensity to abstract electrons or hydrogen atoms from neighboring biomolecules (Juan *et al*., 2021). In biological systems, the most relevant free radicals and related non-radical oxidants are collectively termed Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), and they include the superoxide anion, hydrogen peroxide, the hydroxyl radical, singlet oxygen, nitric oxide, and peroxynitrite. These species are not simply unwanted byproducts of metabolism; at physiological concentrations they participate in cell signaling, immune defense against pathogens, and regulation of vascular tone (Lobo *et al*., 2010). Oxidative stress arises when the production of ROS and RNS exceeds the neutralizing capacity of the cell's antioxidant defenses, tipping the redox balance toward a state in which lipids, proteins, and DNA accumulate oxidative damage.

To counteract this damage, aerobic organisms have evolved a layered antioxidant defense network composed of enzymatic systems such as superoxide dismutase, catalase, and glutathione peroxidase, together with smaller non-enzymatic molecules such as glutathione, uric acid, and the dietary Vitamins C and E (Ighodaro and Akinloye, 2018). When endogenous synthesis or regeneration of these defenses is insufficient relative to oxidative load-as may occur with aging, chronic disease, smoking, or other environmental exposures-exogenous antioxidants obtained from the diet assume particular physiological importance. Plants, algae, fungi, and other natural sources synthesize an extraordinarily diverse array of secondary metabolites, many of which possess antioxidant activity *in vitro* and have attracted sustained scientific and commercial interest as "natural antioxidants," both as components of a health-promoting diet and as candidate therapeutic or nutraceutical agents (Myhrstad and Wolk, 2023; Rahaman *et al*., 2023).

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Interest in natural antioxidants has also been driven in part by concerns over the long-term safety of synthetic antioxidants used in the food and pharmaceutical industries, prompting comparative evaluations of natural versus synthetic compounds across multiple disease contexts, including cellular senescence and aging (Ebrahimirad *et al*., 2025). However, as this review will discuss, the assumption that a compound's natural origin guarantees a favorable benefit-risk profile is not consistently supported by clinical evidence, and the translation of promising *in vitro* and preclinical mechanistic data into demonstrable human health benefit has proven considerably more difficult than early enthusiasm suggested.

This review focuses specifically on the biochemical and molecular mechanisms by which natural products exert antioxidant effects. After outlining the chemistry of free radical generation and the molecular targets of oxidative damage, the review describes the body's endogenous antioxidant defenses as a frame of reference, then examines in detail the principal mechanistic classes by which natural antioxidants act: direct radical scavenging by polyphenols and carotenoids, the chain-breaking and regenerative chemistry of vitamins C and E, and indirect modulation of redox-sensitive signaling pathways such as Nrf2-Keap1-ARE. The review then considers the role of natural antioxidants in cardiovascular disease, cancer, and neurodegeneration; the phenomenon of context-dependent pro-oxidant activity and its clinical implications; bioavailability constraints; and methodological issues in antioxidant capacity measurement, before concluding with priorities for future research.

Chemistry of Free Radicals and Oxidative Stress

The reduction of molecular oxygen to water is thermodynamically favorable and proceeds through a series of one-electron steps that generate progressively more reactive intermediates. The first of these, the superoxide anion, is produced when electrons "leak" from the mitochondrial electron transport chain, predominantly at complexes I and III, and reduce molecular oxygen prematurely; under normal conditions this affects a small fraction, generally cited as well under two percent, of the electron flux through the chain (Juan *et al*., 2021). Superoxide is also generated deliberately by NADPH oxidase enzymes during immune cell activation and by xanthine oxidase and other oxidoreductases. Superoxide dismutase rapidly converts superoxide into hydrogen peroxide, which is comparatively stable and able to diffuse across membranes, but which becomes dangerous in the presence of reduced transition metals (Figure 1).

Specifically, Ferrous iron (Fe^{2+}) reacts with hydrogen peroxide in the Fenton reaction to generate the hydroxyl radical, among the most reactive and indiscriminately damaging species in biology; superoxide can additionally regenerate Fe^{2+} from Fe^{3+}, sustaining this cycle through the Haber-Weiss reaction (Juan *et al*., 2021). Nitric oxide, produced by nitric oxide synthase enzymes, can combine with superoxide to form peroxynitrite, a potent oxidizing and nitrating species implicated in protein tyrosine nitration. Beyond these endogenous sources, exogenous exposures including ionizing radiation, ultraviolet light, tobacco smoke, air pollution, and various xenobiotics and their metabolites contribute substantially to the total cellular oxidant burden (Juan *et al*., 2021).

It is important to emphasize that ROS and RNS are not intrinsically pathological. At low, tightly regulated concentrations they function as second messengers, modulating transcription factors, kinases, and phosphatases through reversible oxidation of reactive cysteine residues, and they are essential to processes such as pathogen killing by phagocytes and physiological angiogenic and proliferative signaling. Oxidative stress is therefore best understood not as the mere presence of ROS,

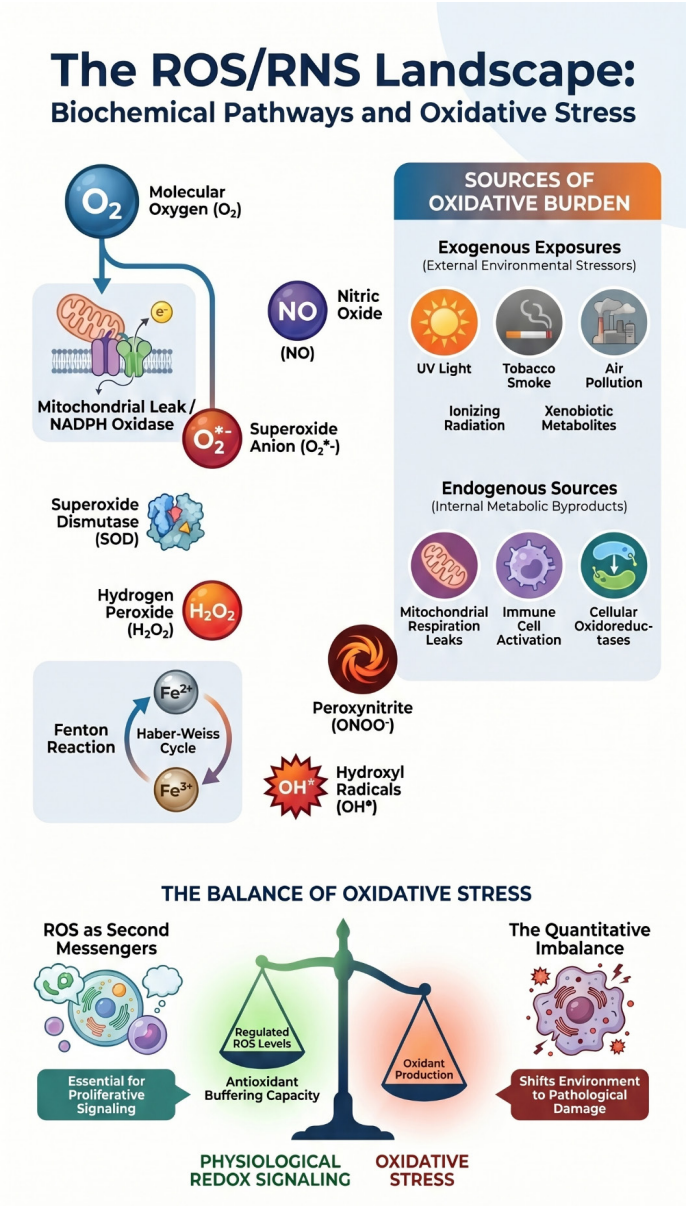


Figure 1: Oxidative Stress and Biochemical Pathways.

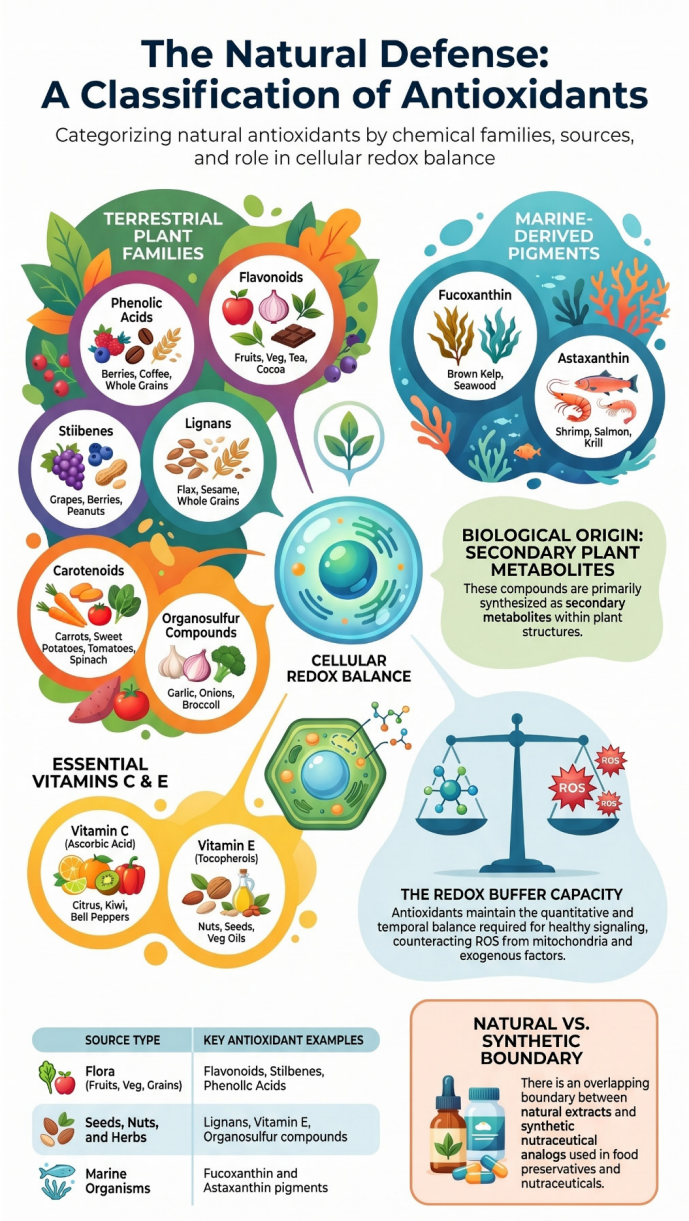


Figure 2: Classification of Natural Antioxidants.

but as a quantitative and temporal imbalance in which oxidant production overwhelms the buffering capacity of antioxidant systems, shifting redox-sensitive signaling toward a damaging rather than adaptive outcome.

Molecular Targets of Oxidative Damage

Lipid Peroxidation

Polyunsaturated fatty acids within membrane phospholipids are particularly vulnerable to oxidative attack because the bis-allylic hydrogens flanking their carbon-carbon double bonds are weakly bound and easily abstracted by free radicals. Once a lipid radical forms, it reacts with molecular oxygen to generate a lipid peroxyl radical, which can abstract a hydrogen atom from an adjacent fatty acid, propagating a self-sustaining chain reaction unless intercepted by a chain-breaking antioxidant (Ayala *et al.*, 2014). The breakdown of lipid hydroperoxides yields reactive aldehydes, most notably malondialdehyde and 4-hydroxy-2-nonenal, which are themselves electrophilic and capable of forming covalent adducts with proteins and DNA. These aldehydes function as both biomarkers of oxidative stress and as signaling molecules in their own right, with 4-hydroxy-2-nonenal in particular implicated in altered energy metabolism and mitochondrial dysfunction in neurodegenerative disease models (Ayala *et al.*, 2014).

Protein Oxidation

Oxidative modification of proteins can occur through direct oxidation of susceptible amino acid side chains, formation of carbonyl groups, or secondary modification by reactive lipid peroxidation products such as 4-hydroxy-2-nonenal, a process referred to as protein lipoxidation. These modifications frequently impair enzymatic activity, promote protein misfolding and aggregation, and mark damaged proteins for degradation; cumulative protein carbonylation is a well-established correlate of oxidative stress and is elevated in aging tissues and in several chronic diseases (Lobo *et al.*, 2010).

Nucleic Acid Damage

Hydroxyl radicals and other oxidants react with the bases and deoxyribose backbone of DNA, generating a spectrum of lesions of which 8-oxo-7,8-dihydro-2′-deoxyguanosine is the most extensively studied; this adduct is mutagenic, promoting G:C to T:A transversions if left unrepaired, and elevated levels are associated with increased cancer risk (Juan *et al.*, 2021). Mitochondrial DNA is especially susceptible given its proximity to the electron transport chain and comparatively limited repair capacity relative to nuclear DNA, a vulnerability thought to contribute to the accumulation of mitochondrial dysfunction with age.

Endogenous Antioxidant Defense Systems

The cellular antioxidant defense grid is conventionally organized into tiers based on the stage at which a given component intervenes in the lifecycle of a free radical (Ighodaro and Akinloye, 2018). First-line, or preventive, defenses suppress the formation of radicals or rapidly neutralize the most dangerous species before they propagate damage; the principal enzymes in this category are superoxide dismutase, catalase, and glutathione peroxidase. Cytosolic copper-zinc superoxide dismutase and mitochondrial manganese superoxide dismutase catalytically convert superoxide into hydrogen peroxide and molecular oxygen, after which catalase, concentrated in peroxisomes, and selenium-dependent glutathione peroxidase decompose hydrogen peroxide into water, the latter using glutathione as an electron donor (Ighodaro and Akinloye, 2018).

Second-line, or scavenging, defenses include the small-molecule chain breakers Vitamin E, Vitamin C, glutathione, and uric acid, which intercept radicals that escape the first-line enzymatic

systems, while metal-binding proteins such as transferrin and ceruloplasmin sequester free iron and copper to prevent Fenton-type chemistry (Ighodaro and Akinloye, 2018). Third-line defenses comprise repair systems, including DNA repair enzymes and proteases that degrade oxidatively damaged proteins, while a proposed fourth line involves adaptive signaling that upregulates the broader defense network in response to oxidative challenge, a function substantially mediated by the Nrf2-Keap1-ARE pathway discussed in Section 7. Natural product antioxidants intersect with this entire defense grid: some act as direct chemical surrogates for the second-line scavengers, while others act indirectly by inducing the expression of first-line enzymes or fourth-line adaptive responses.

Natural Products as Antioxidants: Scope and Classification

The term "natural antioxidant" encompasses a chemically heterogeneous group of compounds obtained from fruits, vegetables, whole grains, nuts, seeds, herbs, and marine organisms, most of which are secondary plant metabolites rather than products of primary metabolism (Myhrstad and Wolk, 2023). These phytochemicals are generally classified by chemical structure into several major families, including phenolic acids, flavonoids, stilbenes, lignans, carotenoids, and organosulfur compounds, alongside the classical antioxidant vitamins C and E and a growing list of marine-derived pigments such as fucoxanthin and astaxanthin (Table 1, Figure 2) (Rahaman *et al*., 2023).

It is worth noting that the boundary between "natural" and "synthetic" antioxidants is not always sharp in practice, since many compounds first isolated from natural sources are now produced synthetically at scale for use as food preservatives or nutraceutical ingredients, and several comparative reviews have evaluated whether such natural-identical or fully synthetic analogs retain equivalent biological activity and safety profiles relative to their plant-derived counterparts (Ebrahimirad *et al*., 2025). The sections that follow examine the specific chemical mechanisms underlying the antioxidant activity of the major natural product classes.

Molecular Mechanisms of Free Radical Scavenging by Natural Products

Polyphenols

Polyphenols are characterized by one or more aromatic rings bearing hydroxyl substituents, a structural feature that underlies their capacity to neutralize free radicals through three principal, and sometimes competing, chemical pathways: Hydrogen Atom Transfer (HAT), Single-Electron Transfer (SET), and Sequential Proton-Loss Electron Transfer (SPLET) (Sadowska and Bartosz, 2024). In the HAT mechanism, a free radical abstracts a hydrogen atom directly from a phenolic hydroxyl group, converting the aggressive radical into a more stable, non-reactive species while generating a relatively stabilized phenoxyl radical on the polyphenol. In the SET mechanism, the polyphenol instead donates a single electron to the radical; in aqueous or polar environments, the phenolic proton may first dissociate, after which the resulting phenolate anion donates an electron via the SPLET pathway, which is often kinetically favored over direct SET once deprotonation has occurred (Sadowska and Bartosz, 2024).

The relative importance of these mechanisms and the overall potency of a given polyphenol depend strongly on its substitution pattern. An ortho-dihydroxy, or catechol, arrangement on the aromatic B-ring is a particularly important structural determinant because the resulting phenoxyl radical is stabilized by intramolecular hydrogen bonding and resonance delocalization across the catechol moiety; conjugation between the aromatic rings and any C2-C3 double bond further extends this stabilization (Sadowska and Bartosz, 2024). Glycosylation, by contrast, tends to reduce antioxidant potency relative to the corresponding free aglycone, since the sugar moiety can sterically hinder access to the reactive hydroxyl groups and is not itself redox-active. These structure-activity relationships explain why closely related flavonoids, such as quercetin and its glycosides rutin and quercitrin, can differ substantially in radical-scavenging efficiency despite sharing the same core flavonoid skeleton.

Beyond direct radical scavenging, many polyphenols, including phenolic acids and flavonoids, possess a secondary antioxidant mechanism through metal chelation: the ortho-hydroxyl and carbonyl groups present in many of these structures can bind redox-active transition metals such as ferrous iron and cuprous copper, sequestering them in a form unable to catalyze Fenton-type generation of the hydroxyl radical (Rahaman *et al*., 2023). This dual capacity-direct scavenging combined with metal chelation-helps explain why polyphenol-rich extracts often outperform single-mechanism synthetic antioxidants in complex biological matrices, where transition metal catalysis of oxidative damage is a significant contributor to overall oxidative burden.

Carotenoids

Carotenoids are lipophilic pigments built from a long chain of conjugated double bonds, a structural feature that confers their characteristic color and underlies their principal antioxidant function: the quenching of singlet oxygen, an excited and highly reactive non-radical form of molecular oxygen generated during photo-oxidative reactions and certain enzymatic processes (Black *et al*., 2020). Quenching can occur through a physical mechanism, in which excitation energy is transferred from singlet oxygen to the carotenoid, which subsequently dissipates the absorbed energy harmlessly as heat while the carotenoid itself remains largely intact and available for further quenching cycles, or through a chemical mechanism, in which the carotenoid

reacts directly with singlet oxygen or with peroxyl radicals and is consumed in the process (Black *et al*., 2020).

Different carotenoids favor these two pathways to different extents and with different efficiencies; lycopene, for example, has been reported to undergo more chemical quenching, while β-carotene favors the physical pathway, and the two carotenoids appear capable of protecting one another against oxidative degradation when present together. Critically, the antioxidant behavior of carotenoids is highly context-dependent: at high local oxygen tension or high carotenoid concentration, the carotenoid-derived radical cations and breakdown products that form during quenching can themselves act as pro-oxidants, a property with direct clinical relevance discussed further in Section 10 in relation to lung cancer chemoprevention trials (Black *et al*., 2020).

Vitamin C and Vitamin E: A Chain-Breaking Antioxidant Network

α-Tocopherol, the most biologically active form of vitamin E, resides within the lipid bilayer of cellular membranes and lipoproteins, where its chromanol hydroxyl group readily donates a hydrogen atom to lipid peroxyl radicals, intercepting the propagation phase of the lipid peroxidation chain reaction roughly a thousand times faster than peroxyl radicals react with adjacent polyunsaturated fatty acids (Linus Pauling Institute, 2026). This reaction converts α-tocopherol into a resonance-stabilized tocopheroxyl radical that, left unchecked, could itself propagate oxidative damage or be further oxidized to inactive tocopherylquinone. Ascorbic acid, which is water-soluble and concentrated in the cytosol and extracellular fluid, complements this lipid-phase defense by directly scavenging aqueous-phase radicals and, importantly, by donating an electron to regenerate the tocopheroxyl radical back to active α-tocopherol, being itself oxidized to the relatively unreactive dehydroascorbate in the process (Linus Pauling Institute, 2026).

This Vitamin C-mediated regeneration of Vitamin E illustrates a broader principle relevant to natural antioxidants generally: many act not as isolated, single-use scavengers but as nodes within an interconnected antioxidant network, in which glutathione can in turn help regenerate ascorbate from dehydroascorbate, and NADPH-dependent enzymes ultimately restore reduced glutathione from its oxidized form. The practical implication is that the antioxidant efficacy of any one dietary compound *in vivo* cannot be fully understood in isolation from the broader redox status and micronutrient availability of the organism consuming it.

Natural Products as Modulators of Endogenous Defense: Redox Signaling Mechanisms

The Nrf2-Keap1-ARE Pathway

Many natural products exert antioxidant effects not by directly scavenging radicals stoichiometrically but by inducing the cell's own adaptive antioxidant machinery, most prominently through activation of the transcription factor Nrf2. Under basal conditions, Nrf2 is bound in the cytoplasm by its repressor protein Keap1, which targets Nrf2 for continuous ubiquitination and proteasomal degradation, keeping cellular Nrf2 levels low (Paunkov *et al*., 2019). Keap1 contains numerous reactive cysteine residues that act as sensors of electrophilic and oxidative stress; when these cysteines are covalently modified or oxidized, Keap1 undergoes a conformational change that disrupts its ability to target Nrf2 for degradation, allowing Nrf2 to accumulate, translocate to the nucleus, heterodimerize with small Maf proteins, and bind antioxidant response elements in the promoters of cytoprotective genes, including those encoding glutathione-synthesizing enzymes, NAD(P)H quinone oxidoreductase 1, and heme oxygenase-1 (Paunkov *et al*., 2019).

Numerous natural products are capable of triggering this pathway by virtue of their own electrophilic reactivity toward the Keap1 cysteine sensors. Sulforaphane, an isothiocyanate generated from glucoraphanin upon mechanical disruption of cruciferous vegetables such as broccoli, is considered among the most potent dietary Nrf2 activators identified to date, while curcumin, resveratrol, and various other polyphenols have also been shown to engage this pathway, generally through analogous electrophilic or redox-modifying chemistry directed at Keap1 (Paunkov *et al*., 2019). Because Nrf2 activation upregulates the endogenous first-line and second-line defenses described in Section 4 rather than simply consuming the inducing compound itself, this mechanism is, in principle, catalytic and self-amplifying in a way that direct stoichiometric radical scavenging is not.

This Nrf2-inducing property of dietary phytochemicals has attracted particular interest in the context of neurodegenerative disease, where impaired Nrf2 signaling has been implicated in the pathology of Alzheimer's disease. A recent review summarizing evidence published between 2018 and 2023 concluded that a range of natural antioxidants can restore or enhance Nrf2-mediated cytoprotection in cellular and animal models of Alzheimer's disease, supporting the therapeutic rationale for this pathway, while also noting that the evidence base to date remains predominantly preclinical, derived from *in vitro* systems and animal models rather than confirmatory human trials (Sidiropoulou *et al*., 2023).

SIRT1/PGC-1α and Mitochondrial Biogenesis: The Case of Resveratrol

Resveratrol, a stilbene found in grapes and red wine, has been extensively investigated for a proposed mechanism in which it activates the NAD+-dependent deacetylase sirtuin 1 (SIRT1), which in turn deacetylates and activates the transcriptional coactivator PGC-1α, a master regulator of mitochondrial biogenesis and oxidative metabolism. Subsequent work identified that resveratrol can promote binding between the upstream kinase

LKB1 and SIRT1, leading to LKB1-mediated phosphorylation of SIRT1 that enhances its deacetylase activity toward PGC-1α and increases mitochondrial biogenesis and respiratory capacity in cultured cells (Huang *et al*., 2021).

This mechanism, however, illustrates how the molecular pharmacology of natural products can be more contested than is often conveyed in popular accounts. A careful reevaluation of the resveratrol-SIRT1-PGC-1α model found that feeding rodents resveratrol at doses used in earlier studies had no detectable effect on skeletal muscle mitochondrial protein content, and that experimentally increasing SIRT1 activity in muscle cells, rather than promoting mitochondrial biogenesis, in some conditions reduced PGC-1α coactivator activity and mitochondrial protein levels, an outcome opposite to the originally proposed model (Higashida *et al*., 2013). The authors of that reevaluation concluded that the relationship between SIRT1 activity and PGC-1α-driven mitochondrial biogenesis is considerably more complex and context-dependent than initially described, and that high concentrations of resveratrol can promote mitochondrial biogenesis through SIRT1-independent activation of AMP-activated protein kinase rather than through the originally proposed SIRT1 pathway (Higashida *et al*., 2013).

This example is presented not to dismiss resveratrol's biological activity, which is supported by a substantial body of cell-signaling data, but to illustrate a recurring theme in natural product pharmacology: An *in vitro* or single-model mechanistic finding, however mechanistically elegant, does not always generalize cleanly across cell types, tissues, doses, and species, and apparently contradictory results across studies often reflect genuine biological context-dependence rather than simple experimental error. This caution is directly relevant to the broader translational challenges discussed in Section 10.

Marine-Derived Natural Antioxidants

Brown seaweeds and microalgae represent a comparatively underexploited source of structurally distinctive natural antioxidants, of which the xanthophyll carotenoid fucoxanthin is among the best characterized. Fucoxanthin and its principal metabolite fucoxanthinol have demonstrated radical-scavenging and singlet-oxygen-quenching activity *in vitro* that is comparable to, or in some assays exceeds, that of α-tocopherol, with particularly strong activity reported against the hydroxyl radical (Peng *et al*., 2011). As with many dietary carotenoids and polyphenols, however, the bioavailability of fucoxanthin in humans following ingestion of whole seaweed is reported to be low, and co-administration with dietary lipids has been proposed as a strategy to improve its intestinal absorption (Peng *et al*., 2011). Other marine pigments, including the carotenoid astaxanthin from microalgae and crustaceans and the phlorotannins found in brown algae cell walls, have likewise been investigated for antioxidant and associated anti-inflammatory activity, broadening the natural antioxidant landscape beyond terrestrial plant sources and underscoring marine biodiversity as a continuing source of candidate compounds for future research.

Natural Antioxidants and Human Disease: Mechanistic Links

Cardiovascular Disease

Oxidative modification of Low-Density Lipoprotein (LDL) particles within the arterial wall is considered an early and important step in atherogenesis, promoting uptake by macrophage scavenger receptors and foam cell formation, while endothelial dysfunction driven in part by NADPH oxidase-derived superoxide and the consequent loss of nitric oxide bioavailability contributes to impaired vasodilation and a pro-inflammatory vascular phenotype. Dietary antioxidants, including ascorbate and α-tocopherol, have been proposed to counter these processes by directly limiting LDL oxidation and by supporting endothelial nitric oxide synthase function, with ascorbate appearing more consistently effective than α-tocopherol across several mechanistic studies. Polyphenol-rich foods and beverages have similarly been associated with improved measures of endothelial function in observational and short-term mechanistic studies, lending biological plausibility to epidemiological associations between fruit and vegetable consumption and reduced cardiovascular risk (Lobo *et al*., 2010; Rahaman *et al*., 2023).

Cancer

The relationship between reactive oxygen species, natural antioxidants, and cancer is markedly more complex than a simple protective paradigm would suggest. Chronic oxidative stress can promote carcinogenesis through mutagenic DNA damage and activation of pro-proliferative signaling pathways, providing a rationale for antioxidant chemoprevention; however, established cancer cells frequently exhibit an altered redox state, with both elevated basal ROS production and a correspondingly upregulated antioxidant capacity that supports survival and proliferation. In this setting, several natural polyphenols have been reported to act preferentially as pro-oxidants within malignant cells, exploiting their distinct redox vulnerabilities to trigger oxidative stress-mediated apoptosis, a phenomenon that runs counter to the classical view of these compounds as uniformly protective antioxidants. Systematic comparative work evaluating both natural and synthetic antioxidants across disease contexts, including processes closely linked to carcinogenesis such as cellular senescence, has emphasized that the directionality and magnitude of a given compound's effect is highly dependent on cell type, concentration, and the prevailing redox environment rather than being a fixed, intrinsic property of the molecule (Ebrahimirad *et al*., 2025).

Neurodegenerative Disease

The central nervous system is considered especially vulnerable to oxidative injury owing to its high oxygen consumption, abundant polyunsaturated lipid content, and comparatively modest endogenous antioxidant enzyme activity relative to other tissues. Oxidative stress and impaired Nrf2-mediated antioxidant signaling have been implicated in the pathophysiology of Alzheimer's disease, motivating substantial preclinical investigation of natural Nrf2-activating compounds, including various flavonoids, sulforaphane, and curcumin, for their capacity to restore antioxidant gene expression and limit neuronal oxidative damage in cellular and animal models (Sidiropoulou *et al*., 2023). As with the cancer literature discussed above, the strength of preclinical mechanistic evidence in this area considerably exceeds the current strength of confirmatory clinical evidence, a gap discussed further in the following section.

The Antioxidant Paradox: Pro-Oxidant Effects and Lessons from Clinical Trials

A substantial body of epidemiological evidence has associated diets rich in fruits and vegetables with reduced risk of cardiovascular disease and certain cancers, observations that motivated large-scale randomized clinical trials testing whether isolated, high-dose supplementation with specific natural antioxidants could replicate these benefits in high-risk populations. The results of these trials have been sobering and have substantially reshaped how the field interprets *in vitro* and mechanistic antioxidant data.

In the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, more than 29,000 Finnish male smokers were randomized to receive α-tocopherol, β-carotene, both, or neither; contrary to the study's protective hypothesis, participants who received β-carotene supplementation showed a significantly increased incidence of lung cancer and an increase in total mortality relative to those who did not (ATBC Cancer Prevention Study Group, 1994). A similar and even larger effect was observed in the Beta-Carotene and Retinol Efficacy Trial (CARET), which enrolled smokers and asbestos-exposed workers and was terminated ahead of schedule after an interim analysis found a statistically significant increase in lung cancer incidence and overall mortality among participants receiving combined β-carotene and retinyl palmitate supplementation compared with placebo (Omenn *et al*., 1996).

These findings are most plausibly explained by the context-dependent, concentration-sensitive chemistry of carotenoid radical reactions described in Section 6.2: at the high tissue concentrations achieved with supplementation, and potentially under the high local oxidative and pro-oxidant conditions associated with cigarette smoke exposure in the lung, β-carotene oxidation products may behave as pro-oxidants and pro-carcinogens rather than as protective antioxidants, particularly in already at-risk tissue (Black *et al*., 2020). This body of evidence does not indicate that dietary β-carotene from food sources is harmful; rather, it demonstrates that the biological behavior of an isolated phytochemical administered at supraphysiological doses to a specific at-risk population cannot be reliably predicted from epidemiological associations with

Table 1: Summarizes the principal classes, representative compounds, common sources, and primary mechanism of action discussed in detail in subsequent sections.

Class	Representative compounds	Common dietary/natural sources	Primary antioxidant mechanism
Phenolic acids	Gallic acid, caffeic acid, ferulic acid, chlorogenic acid	Coffee, fruits, whole grains, vegetables	Hydrogen Atom Transfer (HAT) from phenolic -OH; metal chelation
Flavonoids	Quercetin, kaempferol, catechins, anthocyanins	Onions, tea, berries, citrus, cocoa	HAT / Single-Electron Transfer (SET) / Sequential Proton-Loss Electron Transfer (SPLET); metal chelation
Stilbenes	Resveratrol, pterostilbene	Grapes, red wine, peanuts, berries	Direct radical scavenging; SIRT1/ PGC-1α activation; Nrf2 induction
Carotenoids	β-carotene, lycopene, lutein, astaxanthin, fucoxanthin	Carrots, tomatoes, leafy greens, marine algae	Singlet oxygen quenching (physical and chemical); peroxyl radical scavenging
Vitamins	Ascorbic acid (Vitamin C), α-tocopherol (Vitamin E)	Citrus fruit, peppers; vegetable oils, nuts, seeds	Aqueous-phase (C) and lipid-phase (E) chain-breaking scavenging; mutual regeneration
Organosulfur compounds	Sulforaphane, allicin	Cruciferous vegetables (broccoli), garlic	Indirect antioxidant action via Keap1 cysteine modification and Nrf2/ARE activation

Table 2: Summarizes the mechanistic basis and principal limitations of these four widely used assays.

Assay	Underlying mechanism	Radical/probe	Principal limitation
DPPH	Electron/hydrogen transfer (mixed)	Stable synthetic DPPH• radical	Non-physiological radical; steric hindrance affects reaction with bulky polyphenols
ABTS/TEAC	Single electron transfer	$ABTS^{\bullet+}$ cation radical	Non-physiological radical; reaction kinetics vary with sample matrix
FRAP	Single electron transfer (reducing power)	Ferric-TPTZ complex	Measures reducing capacity, not direct radical scavenging; pH-dependent
ORAC	Hydrogen atom transfer	Peroxyl radical (AAPH-generated)	Biologically relevant radical but lengthy protocol; sensitive to assay conditions

whole-food consumption patterns or from *in vitro* antioxidant capacity data alone.

A related and more general lesson, applicable beyond carotenoids, is that many natural polyphenols exhibit dose-dependent dual antioxidant and pro-oxidant behavior, particularly in the presence of transition metal ions or under high local concentrations achievable with concentrated extracts or supplements but not typically reached through ordinary dietary intake. Comparative reviews juxtaposing natural and synthetic antioxidants across multiple disease models have consistently emphasized that neither category can be assumed categorically safe or effective, and that rigorous, context-specific evaluation is required before extrapolating mechanistic or *in vitro* findings to clinical recommendations (Ebrahimirad *et al.*, 2025). For practicing clinicians and the public, the most defensible current interpretation of this evidence base favors dietary patterns rich in diverse whole foods over high-dose isolated antioxidant supplementation, particularly in populations, such as smokers, identified as being at elevated risk in the relevant clinical trials.

Bioavailability and Translational Challenges

A persistent obstacle in translating the antioxidant activity of natural products from the test tube to the clinic is poor oral bioavailability. Most dietary polyphenols undergo limited intestinal absorption, extensive first-pass metabolism by intestinal and hepatic phase II enzymes, and rapid renal excretion of their conjugated metabolites, such that the circulating concentrations achieved after typical dietary intake are often one to several orders of magnitude lower than the concentrations used to demonstrate antioxidant activity *in vitro* (Rahaman *et al.*, 2023). The same constraint applies to many marine carotenoids; fucoxanthin, for instance, despite showing strong radical-scavenging and singlet-oxygen-quenching activity in cell-free systems, is absorbed poorly from whole seaweed unless co-administered with dietary lipid to facilitate micellar solubilization (Peng *et al.*, 2011).

This bioavailability gap has two important implications for interpreting the natural antioxidant literature. First, *in vitro* antioxidant capacity, however rigorously measured, should not be assumed to predict physiological efficacy at achievable dietary or even moderate supplemental doses. Second, much of the benefit historically attributed to direct radical scavenging by ingested polyphenols may in practice be mediated by alternative mechanisms that do not require high systemic concentrations of the parent compound, including modulation of the gut microbiota, generation of bioactive microbial metabolites, and the catalytic, gene-inductive Nrf2 signaling mechanism described in Section 7.1, which does not require the inducing compound to persist at high concentration to sustain its downstream antioxidant gene expression effects.

Methods for Evaluating Antioxidant Capacity

Antioxidant activity is most commonly quantified *in vitro* using one of several spectrophotometric or fluorometric assays that differ fundamentally in their underlying chemistry. The DPPH and ABTS (Trolox equivalent antioxidant capacity, or TEAC) assays both rely on the reduction of a stable, colored synthetic radical by the test antioxidant and are valued for their speed and simplicity, while the Ferric Reducing Antioxidant Power (FRAP) assay instead measures the capacity of a sample to reduce a ferric-ligand complex, reflecting general reducing power rather than direct radical quenching (Schaich *et al.*, 2015). The Oxygen Radical Absorbance Capacity (ORAC) assay differs mechanistically from all three in that it measures protection of a fluorescent probe against a biologically generated peroxyl radical via a hydrogen atom transfer mechanism, which is often considered more physiologically relevant than the electron-transfer chemistry underlying DPPH, ABTS, and FRAP (Table 2).

A critical evaluation of these methods concluded that the different assays frequently yield poorly correlated rankings of antioxidant capacity for the same set of samples, a discrepancy attributable to their distinct underlying chemistries, their use of non-physiological radicals or probes, and their sensitivity to assay conditions such as pH, solvent, and reaction time (Schaich *et al.*,

2015). This methodological heterogeneity means that antioxidant capacity values reported using a single assay should be interpreted cautiously, that comparisons across studies using different assays are often not directly valid, and that researchers reporting antioxidant capacity for a natural product extract are encouraged to employ more than one assay, ideally including at least one electron-transfer-based and one hydrogen-atom-transfer-based method, to obtain a more complete characterization.

FUTURE DIRECTIONS

Several priorities emerge from the gaps identified throughout this review. First, future clinical trials of natural antioxidants should move beyond single high-dose isolated compounds toward designs that better reflect realistic dietary exposure, whole-food matrices, or combinations of compounds that may act synergistically, given that the clearest clinical harms to date have arisen specifically from high-dose isolated supplementation in at-risk populations rather than from whole-food antioxidant intake. Second, greater mechanistic attention to dose-response relationships and the conditions under which a given natural antioxidant transitions from protective to pro-oxidant behavior is needed, since this transition appears to be a recurring and clinically consequential phenomenon rather than an isolated curiosity specific to β-carotene.

Third, addressing the bioavailability limitations described in Section 11 through delivery strategies such as nanoencapsulation, phospholipid complexation, or co-formulation with absorption-enhancing lipids represents an active area of investigation that may help reconcile the gap between promising *in vitro* mechanistic data and modest clinical effects observed to date. Fourth, given the mechanistic distinction between direct stoichiometric radical scavenging and catalytic, gene-inductive pathways such as Nrf2-Keap1-ARE activation, future research would benefit from more clearly distinguishing which mechanism is being invoked when a compound is described as a natural antioxidant, since the dosing, pharmacokinetic, and safety considerations relevant to each mechanism differ substantially. Finally, continued exploration of underutilized sources such as marine algae and other non-terrestrial organisms is likely to expand the structural diversity of candidate natural antioxidants available for future mechanistic and clinical study (Paunkov *et al*., 2019; Peng *et al*., 2011).

CONCLUSION

Natural products offer a chemically diverse and mechanistically rich source of antioxidant activity, acting through direct radical scavenging chemistries specific to each structural class-hydrogen atom transfer and electron transfer reactions in polyphenols, singlet oxygen quenching in carotenoids, and a cooperative chain-breaking network involving vitamins C and E-as well as through indirect activation of the cell's own adaptive antioxidant and cytoprotective machinery via pathways such as Nrf2-Keap1-ARE signaling. This mechanistic diversity provides a strong biochemical rationale for the long-observed association between antioxidant-rich dietary patterns and reduced risk of chronic disease.

At the same time, the evidence reviewed here underscores that this rationale does not translate uncritically into a recommendation for high-dose isolated antioxidant supplementation. Landmark clinical trials of β-carotene in smokers, the well-documented dose- and context-dependent pro-oxidant behavior of several carotenoids and polyphenols, and the persistent gap between *in vitro* antioxidant potency and *in vivo* bioavailability collectively argue for caution and specificity rather than blanket enthusiasm. Future progress in this field will depend on continued mechanistic dissection of how individual natural compounds engage specific molecular targets, more physiologically informed dosing in clinical research, and a clearer conceptual separation between natural products that act as direct chemical scavengers and those that act as inducers of the body's own endogenous antioxidant defenses.

ABBREVIATIONS

ROS: Reactive Oxygen Species; **RNS:** Reactive Nitrogen Species; **DNA:** Deoxyribonucleic Acid; **NADPH:** Nicotinamide Adenine Dinucleotide Phosphate (reduced form); **Fe^{2+}:** Ferrous Iron; **Fe^{3+}:** Ferric Iron; **LDL:** Low-Density Lipoprotein; **HAT:** Hydrogen Atom Transfer; **SET:** Single-Electron Transfer; **SPLET:** Sequential Proton-Loss Electron Transfer; **OH:** Hydroxyl Group; **SIRT1:** Sirtuin 1; **PGC-1α:** Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **Keap1:** Kelch-Like ECH-Associated Protein 1; **ARE:** Antioxidant Response Element; **Maf:** Musculoaponeurotic Fibrosarcoma; **NQO1:** NAD(P)H Quinone Oxidoreductase 1; **HO-1:** Heme Oxygenase-1; **SOD:** Superoxide Dismutase; **CAT:** Catalase; **GPx:** Glutathione Peroxidase; **GSH:** Reduced Glutathione; **LKB1:** Liver Kinase B1; **AMPK:** AMP-Activated Protein Kinase; **AAPH:** 2,2′-Azobis(2-amidinopropane) Dihydrochloride; **DPPH:** 2,2-Diphenyl-1-picrylhydrazyl; **ABTS:** 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic Acid); **TEAC:** Trolox Equivalent Antioxidant Capacity; **FRAP:** Ferric Reducing Antioxidant Power; **ORAC:** Oxygen Radical Absorbance Capacity; **TPTZ:** 2,4,6-Tris(2-pyridyl)-s-triazine; **ATBC:** Alpha-Tocopherol, Beta-Carotene Cancer Prevention; **CARET:** Beta-Carotene and Retinol Efficacy Trial; **α-Tocopherol:** Alpha-Tocopherol (Vitamin E); **β-Carotene:** Beta-Carotene; **NAD^+:** Nicotinamide Adenine Dinucleotide (oxidized form); **G:C:** Guanine:Cytosine Base Pair; **T:A:** Thymine:Adenine Base Pair.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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