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Chemistry of Dietary Antioxidants and Their Role in Oxidative Stress Modulation: A Comprehensive Review

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Abstract

Oxidative stress results from an imbalance between the generation of reactive oxygen and nitrogen species and the capacity of biological antioxidant systems to neutralize or repair their damaging effects. Although reactive species are essential for cellular signaling and host defense, their excessive or dysregulated production can promote lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, inflammation, and cellular senescence. Dietary antioxidants represent a chemically diverse group of vitamins, carotenoids, polyphenols, sulfur-containing compounds, minerals, and other bioactive molecules that contribute to redox homeostasis. Their biological effects cannot be explained solely by direct radical scavenging. Contemporary evidence indicates that dietary antioxidants can modulate endogenous antioxidant defenses, redox-sensitive transcription factors, inflammatory signaling, mitochondrial function, metal homeostasis, and cellular adaptive responses. This review examines the chemical characteristics of major dietary antioxidants and relates their molecular structures to antioxidant mechanisms. Particular attention is given to electron- and hydrogen-atom transfer, metal chelation, lipid-phase protection, glutathione metabolism, nuclear factor erythroid 2-related factor 2 (Nrf2), nuclear factor-κB (NF-κB), and mitochondrial redox regulation. The review also discusses the bioavailability, metabolism, food matrix interactions, gut microbiota transformation, and concentration-dependent antioxidant/pro-oxidant behaviour of dietary phytochemicals. Current evidence suggests that the physiological activity of many dietary antioxidants arises more from modulation of endogenous defense and redox signaling than from sustained direct scavenging of free radicals in vivo. Understanding the relationship between chemical structure, metabolism, bioavailability, and molecular signaling is therefore essential for translating antioxidant chemistry into effective nutritional strategies for maintaining health and reducing oxidative-stress-associated disease risk.

Keywords: dietary antioxidants; oxidative stress; reactive oxygen species; polyphenols; flavonoids; carotenoids; vitamin C; vitamin E; Nrf2; redox signaling; bioavailability; phytochemicals

1. Introduction

Oxidation-reduction reactions are fundamental to biological energy production, cellular signaling, immune responses, and metabolic regulation. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are continuously generated during normal metabolism, particularly through mitochondrial electron transport, enzymatic reactions, inflammatory responses, and exposure to environmental stressors. At physiological concentrations, these

species participate in signaling processes; however, excessive or inadequately controlled production can disturb redox homeostasis and cause oxidative damage.

Oxidative stress is therefore better understood as a disturbance of cellular redox regulation rather than simply the presence of free radicals. ROS include superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), singlet oxygen ($^1O_2$), and lipid-derived radicals, whereas RNS include nitric oxide (NO•), nitrogen dioxide (NO_2•), and peroxynitrite ($ONOO^-$). The biological consequences depend on the concentration, localization, duration, and chemical reactivity of these species [1].

The antioxidant defense system consists of enzymatic (Superoxide dismutases, catalase) and non-enzymatic components. Because humans cannot synthesize several key non-enzymatic antioxidants *de novo*, they must be obtained through the diet. Dietary antioxidants have thus garnered immense interest in nutritional science and pharmacology as potential modulators of chronic inflammatory and degenerative diseases.

The observation that diets rich in fruits, vegetables, and whole grains are associated with reduced incidence of cardiovascular disease, several cancers, and neurodegenerative conditions has motivated decades of research into dietary antioxidants as a mechanistic explanation for this protection. Dietary antioxidants are commonly defined as exogenous compounds, obtained from plant and, to a lesser extent, animal foods, that are capable of delaying, preventing, or removing oxidative damage to a target molecule. This definition, however, has proven chemically and biologically more complicated than initially assumed. Many compounds classified as dietary antioxidants on the basis of in vitro radical-scavenging assays reach the systemic circulation at nanomolar to low-micromolar concentrations, far below those required to scavenge radicals stoichiometrically in vivo, and undergo extensive first-pass metabolism that alters their chemical reactivity. Furthermore, several dietary antioxidants exhibit pro-oxidant behaviour under certain conditions, and large randomized controlled trials of antioxidant supplementation have repeatedly failed to reproduce the benefits suggested by observational studies, in some cases revealing increased risk.

This review integrates the chemistry of major dietary antioxidants with their biological mechanisms, emphasizing how molecular structure determines redox behaviour, bioavailability, metabolism, and cellular activity. This review addresses the following specific objectives:

1. To relate the molecular and structural chemistry of major classes of dietary antioxidants (vitamins C and E, carotenoids, polyphenols, organosulfur compounds, and emerging compounds such as ergothioneine and sulforaphane) to their principal redox mechanisms.
2. To evaluate the relative contribution of direct radical-scavenging mechanisms (HAT, SET, SPLET, metal chelation) versus indirect mechanisms (Nrf2/Keap1/ARE signaling, NF-κB modulation, mitochondrial redox regulation) to the physiological activity of dietary antioxidants in vivo.
3. To examine how bioavailability, first-pass metabolism, food matrix interactions, and gut microbiota transformation determine whether in vitro antioxidant capacity translates into biological effect.

4. To critically assess the discrepancy between observational dietary evidence and randomized controlled trial evidence on antioxidant supplementation, and to identify methodological limitations that constrain current interpretation of antioxidant research.

1.1 Methodology:

This is a narrative review with a structured literature search strategy, rather than a formal systematic review; no PRISMA flow diagram or dual-reviewer screening process was used. Literature was identified through searches of PubMed, Scopus, and Web of Science for records published between 2004 and 2022, using combinations of the search terms "dietary antioxidants," "oxidative stress," "reactive oxygen species," "polyphenols," "flavonoids," "Nrf2," "Keap1," "bioavailability," and "antioxidant supplementation trials." Given the breadth of chemistry, physiology, and clinical evidence covered, source selection for mechanistic sections was guided by relevance and citation frequency within the field, while sections addressing clinical outcomes prioritized large-scale randomized controlled trials and systematic reviews/meta-analyses over single observational studies. This approach is consistent with standard practice for narrative reviews synthesizing evidence across chemistry, molecular biology, and clinical nutrition.

2. Oxidative Stress: Chemical and Biological Basis

2.1 Reactive Oxygen and Nitrogen Species

The superoxide anion radical (O_2•−) is generated primarily by one-electron reduction of molecular oxygen at complexes I and III of the mitochondrial electron transport chain, and by the NADPH oxidase (NOX) family of enzymes during immune activation. Superoxide is a moderately reactive, short-lived species that is rapidly converted to hydrogen peroxide (H_2O_2) by superoxide dismutases. Hydrogen peroxide is uncharged, membrane-permeant, and comparatively long-lived, properties that allow it to act as a diffusible signaling molecule that oxidizes redox-sensitive cysteine thiols on target proteins. In the presence of reduced transition metals, particularly ferrous iron, hydrogen peroxide undergoes the Fenton reaction to generate the hydroxyl radical (•OH), among the most reactive species known in biology, which reacts indiscriminately and at diffusion-limited rates with nucleic acids, lipids, and proteins.

Reactive nitrogen species arise chiefly from nitric oxide (•NO), produced by nitric oxide synthases. Nitric oxide itself has important vasodilatory and signaling functions, but its rapid reaction with superoxide yields peroxynitrite (ONOO−), a potent oxidizing and nitrating species capable of modifying tyrosine residues, lipids, and DNA bases. The balance between nitric oxide bioavailability and superoxide flux is therefore a key determinant of vascular redox status, and its disruption is central to endothelial dysfunction in cardiovascular disease.

2.2 Endogenous Antioxidant Defense Systems

Cells possess a layered enzymatic and non-enzymatic defense network. The superoxide dismutases convert superoxide to hydrogen peroxide, which is subsequently detoxified by catalase and by the glutathione peroxidase (GPx) and peroxiredoxin (PRDX) systems, both of which depend on reducing equivalents supplied by glutathione and thioredoxin, respectively, ultimately regenerated by NADPH. Glutathione S-transferases conjugate electrophilic

oxidation products for excretion. This enzymatic network is transcriptionally coordinated by the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which under basal conditions is bound by Kelch-like ECH-associated protein 1 (Keap1) and targeted for proteasomal degradation. Oxidation or electrophilic modification of reactive cysteine residues on Keap1 disrupts this interaction, allowing Nrf2 to translocate to the nucleus and activate transcription of antioxidant response element (ARE)-containing genes, including those encoding SOD, catalase, GPx, heme oxygenase-1, and glutathione biosynthetic enzymes. This pathway constitutes the principal mechanism by which many dietary compounds augment endogenous antioxidant capacity indirectly rather than by acting as stoichiometric radical scavengers themselves [2]. Figure 1 shows generation and detoxification of reactive oxygen and nitrogen species.

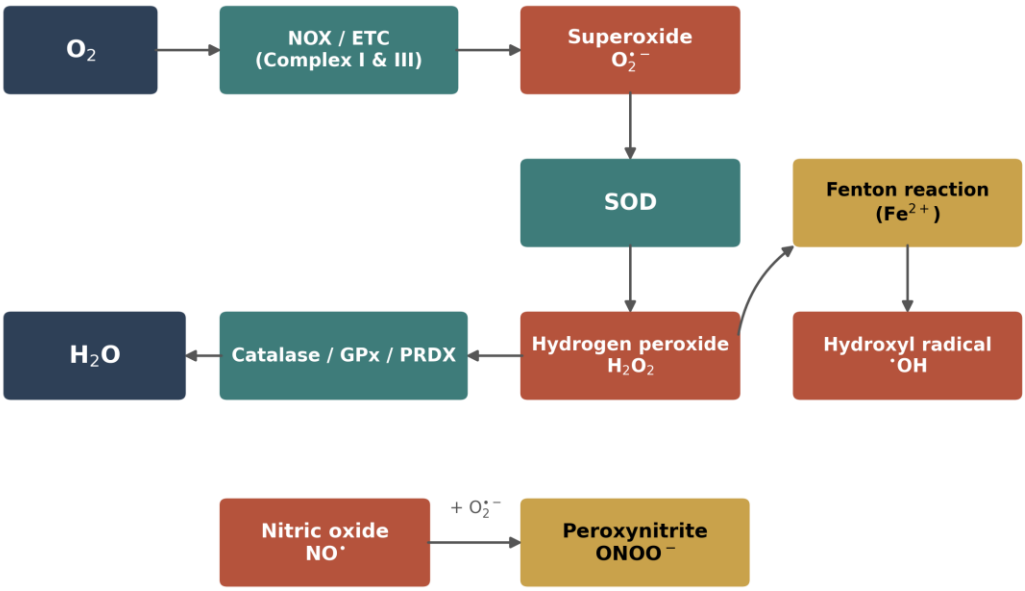

Figure 1. Generation and detoxification of reactive oxygen and nitrogen species.

2.3 Biomarkers of Oxidative Stress

Because RONS are short-lived, oxidative stress is typically assessed indirectly through stable end products of oxidative damage or through the status of antioxidant defenses. Commonly used biomarkers include malondialdehyde and F2-isoprostanes as indices of lipid peroxidation, 8-hydroxy-2'-deoxyguanosine as a marker of oxidative DNA damage, protein carbonyls as a marker of protein oxidation, and the ratio of reduced to oxidized glutathione (GSH:GSSG) as an index of cellular redox status. Total antioxidant capacity assays, such as the oxygen radical absorbance capacity (ORAC), the ferric reducing antioxidant power (FRAP), and the Trolox equivalent antioxidant capacity (TEAC) assays, are frequently used to characterize the in vitro antioxidant activity of foods and isolated compounds, but their translational relevance is limited [3]. Table 1 lists common biomarkers used to assess oxidative stress.

Table 1. Common biomarkers used to assess oxidative stress

Biomarker	Biological target	What it measures	Notes
Malondialdehyde (MDA)	Lipid peroxidation	End product of polyunsaturated fatty acid peroxidation	Widely used but subject to assay-specific artifacts
F2-isoprostanes	Lipid peroxidation	Prostaglandin-like compounds formed by free-radical peroxidation of arachidonic acid	Considered a more specific lipid peroxidation marker than MDA
8-hydroxy-2'-deoxyguanosine (8-OHdG)	DNA oxidation	Oxidative modification of guanine bases	Reflects oxidative DNA damage/repair balance
Protein carbonyls	Protein oxidation	Carbonyl groups introduced by oxidative modification of amino acid side chains	General, non-specific marker of protein oxidative damage
GSH:GSSG ratio	Cellular redox status	Ratio of reduced to oxidized glutathione	Reflects overall intracellular reducing capacity

3. Chemical Classification of Dietary Antioxidants

Dietary antioxidants can broadly be divided into several chemically distinct groups on the basis of their core structural scaffold: phenolic compounds, carotenoids, vitamin C, vitamin E, organosulfur compounds, and a heterogeneous group of trace-element-dependent cofactors and nitrogenous compounds. Table 2 listed different classes of dietary antioxidants, their characteristic and redox related action.

Table 2: Chemical classification of Dietary Antioxidants

Class	Representative compounds	Major chemical characteristic	Principal redox-related action
Vitamin C	Ascorbic acid	Enediol lactone	Electron/H-atom donation; antioxidant recycling
Vitamin E	α-Tocopherol	Chromanol ring + hydrophobic tail	Lipid radical trapping
Carotenoids	β-Carotene, lycopene, lutein	Conjugated polyene chain	Radical quenching; singlet oxygen quenching
Flavonoids	Quercetin, catechins, anthocyanins	Polyphenolic aromatic skeleton	H-atom/electron transfer; metal chelation; signaling
Phenolic acids	Caffeic, ferulic, gallic acids	Aromatic ring + phenolic groups	Radical stabilization; metal interaction
Stilbenes	Resveratrol	Polyphenolic stilbene structure	Redox signaling; enzyme modulation

Curcuminoids	Curcumin	Conjugated diarylheptanoid	Redox modulation; signaling
Organosulfur compounds	Sulforaphane, allicin	Electrophilic sulfur functionality	Nrf2 activation; thiol modification
Selenium compounds	Selenium-containing amino acids	Redox-active selenium	Glutathione peroxidase-dependent defense
Ergothioneine	Ergothioneine	Sulfur-containing histidine derivative	Redox buffering and cellular protection

The chemical diversity of these compounds is directly related to their differing solubility, redox potential, localization, metabolism, and biological activity.

4. Chemistry of Major Dietary Antioxidants

4.1 Vitamin C

Ascorbic acid is a water-soluble antioxidant abundant in fruits and vegetables. Its antioxidant activity is associated with its enediol structure, which facilitates electron donation and formation of relatively stable oxidation products. The oxidation of ascorbate proceeds through the ascorbyl radical and ultimately dehydroascorbic acid. Because of this reversible redox chemistry, vitamin C can participate in antioxidant recycling and help regenerate oxidized vitamin E.

Vitamin C is particularly important in aqueous biological compartments, where it can react with several reactive species and protect biomolecules from oxidative modification. However, its behavior is concentration-dependent. Under particular conditions involving transition metals, high concentrations of ascorbate can contribute to oxidative chemistry rather than simply suppressing it [4]. Therefore, antioxidant behavior must be interpreted in relation to chemical environment, dose, and metal availability.

4.2 Vitamin E

Vitamin E refers to a family of tocopherols and tocotrienols, of which α-tocopherol is particularly important biologically. Its amphipathic structure consists of a chromanol head group and hydrophobic side chain.

The chromanol hydroxyl group donates a hydrogen atom to lipid radicals:

LOO• + TocOH → LOOH + TocO•

The resulting tocopheroxyl radical is resonance stabilized and can subsequently be reduced by other antioxidants, particularly vitamin C.

Vitamin E therefore acts primarily within lipid-rich environments and biological membranes. Its importance lies in interrupting lipid peroxidation chain reactions, thereby limiting propagation of oxidative damage through cellular membranes [5].

4.3 Carotenoids

Carotenoids are lipophilic pigments characterized by extended conjugated double-bond systems. β-Carotene, lycopene, lutein, zeaxanthin, β-cryptoxanthin, and astaxanthin are

important dietary representatives. Their conjugated systems allow carotenoids to interact with excited-state oxygen and free radicals. A major mechanism is physical quenching of singlet oxygen through energy transfer. The efficiency of this process is influenced by the length and configuration of the conjugated system.

Carotenoids also demonstrate context-dependent antioxidant and pro-oxidant properties. At elevated oxygen tension or under conditions favoring radical formation, some carotenoids may undergo oxidative cleavage and produce reactive metabolites. Current evidence consequently views carotenoids as regulators of redox homeostasis rather than simply as radical scavengers [6].

4.4 Polyphenols

Polyphenols represent one of the largest and chemically diverse groups of dietary antioxidants. Major subclasses include flavonoids, phenolic acids, stilbenes, lignans, tannins, and related compounds. Their antioxidant chemistry is strongly influenced by the number and position of hydroxyl groups, conjugation, resonance stabilization, glycosylation, methylation, and metal-binding capacity.

A simplified hydrogen atom transfer reaction can be represented as:

ArOH + R• → ArO• + RH

The phenoxyl radical formed is stabilized by resonance, making hydrogen donation thermodynamically favorable for appropriately substituted phenols.

Important dietary polyphenols include quercetin, kaempferol, catechins, epigallocatechin gallate, anthocyanins, chlorogenic acid, caffeic acid, ferulic acid, curcumin, and resveratrol. However, the direct antioxidant capacity measured in chemical assays should not automatically be equated with physiological activity. Polyphenols undergo extensive intestinal, hepatic, and microbial metabolism. The metabolites reaching tissues may differ substantially from the parent compounds [7].

5. Mechanism of Antioxidant Action

Dietary antioxidants generally operate as "primary" (chain-breaking) or "secondary" (preventative) antioxidants. Primary antioxidants intercept radical species directly.

5.1 Direct Radical Mechanism

5.1.1 Hydrogen Atom Transfer (HAT)

The antioxidant ($ArOH$) donates a hydrogen atom to a free radical ($R^{\cdot}$), neutralizing it. The resulting antioxidant radical ($ArO^{\cdot}$) is stabilized by resonance and lacks the reactivity to propagate the chain.

$$R^{\cdot} + ArOH \rightarrow RH + ArO^{\cdot}$$

5.1.2 Single Electron Transfer (SET)

The antioxidant yields an electron to the free radical, forming a radical cation. This mechanism is governed by the ionization potential of the antioxidant.

$$R^{\cdot} + ArOH \rightarrow R^{-} + ArOH^{\cdot +}$$

5.1.3 Sequential Proton Loss Electron Transfer (SPLET)

In sequential proton loss electron transfer (SPLET), the antioxidant first deprotonates, and the resulting phenolate anion then transfers an electron.

$$ArOH \rightarrow ArO^{-} + H^{+}$$

$$ArO^{-} + R^{\cdot} \rightarrow ArO^{\cdot} + R^{-}$$

The mechanism that predominates for a given antioxidant-radical pair depends on the bond dissociation enthalpy of the relevant O–H bond, the ionization potential of the antioxidant, the solvent polarity, and the pH of the medium, with HAT generally favored in non-polar environments and SET-PT/SPLET favored in polar, protic environments where the phenol is substantially deprotonated [8].

5.2 Metal Chelation (Secondary Antioxidant Action)

The Fenton reaction between hydrogen peroxide and free ferrous or cuprous ions is a major source of the highly reactive hydroxyl radical in vivo, sequestration of redox-active transition metals constitutes an important, chemically distinct antioxidant mechanism. Ortho-dihydroxyl (catechol) and ortho-trihydroxyl (gallate) arrangements on flavonoid B-rings, and the carbonyl-hydroxyl arrangements found in many phenolic acids, form stable bidentate chelates with Fe^{2+}, Fe^{3+}, and Cu^{2+}, removing these ions from redox cycling. This mechanism is kinetically distinct from, and additive to, direct radical scavenging, and is particularly relevant in the gastrointestinal lumen and in tissues with local iron overload [8].

5.3 Indirect antioxidant activity

The therapeutic evaluation of dietary antioxidants focused entirely on direct, stoichiometric radical scavenging. However, the localized concentration of dietary antioxidants *in vivo* is often too low to outcompete abundant endogenous antioxidants for direct ROS neutralization. Indirect antioxidant activity involves stimulation of endogenous cellular defense systems.

This mechanism is particularly important for dietary polyphenols and electrophilic phytochemicals. Rather than chemically neutralizing every ROS molecule, they can alter redox-sensitive signaling pathways and induce antioxidant and detoxification enzymes.

5.3.1 The Keap1-Nrf2-ARE Pathway

The Nrf2–Keap1 pathway represents one of the most important examples. Under basal conditions, Keap1 promotes Nrf2 degradation. Electrophilic or oxidative modification of critical Keap1 cysteine residues can impair this process, allowing Nrf2 to accumulate and enter the nucleus. Nrf2 then promotes transcription of antioxidant and cytoprotective genes through antioxidant response elements. This pathway regulates enzymes involved in glutathione synthesis, detoxification, NADPH generation, and cellular redox protection. The Nrf2 pathway provides a conceptual bridge between antioxidant chemistry and cellular adaptation [2].

Several dietary compounds can influence Nrf2 signaling, including sulforaphane, curcumin, flavonoids, phenolic compounds, and certain carotenoid-derived metabolites. Sulforaphane is

particularly interesting because it is an electrophilic isothiocyanate derived from glucoraphanin in cruciferous vegetables. Its electrophilic center can react with protein thiols and influence Keap1-dependent regulation of Nrf2.

Nrf2 activation increases expression of several cytoprotective systems, including enzymes involved in glutathione metabolism and phase II detoxification. Thus, the antioxidant effect of some dietary phytochemicals is mediated by induction of endogenous defenses rather than direct ROS scavenging.

5.3.2 Redox-Sensitive Signaling Pathways

Beyond the Nrf2-ARE axis, dietary antioxidants influence other redox-sensitive transcription factors, notably nuclear factor kappa B (NF-κB), whose activation by oxidative stimuli drives expression of pro-inflammatory cytokines and adhesion molecules. Polyphenols such as resveratrol, curcumin, and epigallocatechin gallate have been shown to attenuate NF-κB activation and to modulate components of the mitogen-activated protein kinase (MAPK) cascades, linking antioxidant chemistry to anti-inflammatory outcomes that are mechanistically intertwined with, but not reducible to, redox chemistry alone [9].

Oxidative stress and inflammation are closely interconnected. ROS can activate inflammatory signaling pathways, while activated immune cells generate additional ROS and RNS. NF-κB is a major transcription factor regulating inflammatory mediators. Figure 2 shows a self-amplifying feedback loop between oxidative stress and inflammation. Dietary polyphenols and carotenoids can influence NF-κB signaling through several mechanisms, including modulation of kinase activity, oxidative status, and upstream inflammatory mediators.

Carotenoids have been reported to influence both Nrf2-related antioxidant signaling and NF-κB-associated inflammatory pathways. This interaction creates a potentially important feedback loop:

Oxidative stress → inflammatory signaling → ROS generation → cellular damage

Dietary phytochemicals may disrupt this cycle by simultaneously strengthening antioxidant defenses and reducing excessive inflammatory signaling.

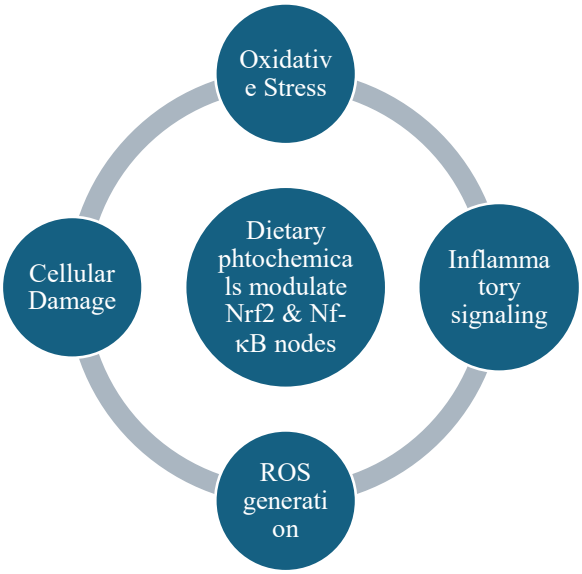

Figure 2. Self-amplifying feedback loop between oxidative stress and inflammation

5.3.3 Mitochondrial Redox Regulation

Mitochondria are both major producers and targets of ROS. Oxidative modification of mitochondrial proteins, membrane lipids, mitochondrial DNA, and respiratory-chain components can impair energy production and increase further ROS generation.

Dietary antioxidants may influence mitochondrial redox status through several mechanisms like direct radical scavenging, preservation of membrane integrity, modulation of mitochondrial antioxidant enzymes, regulation of mitochondrial biogenesis, activation of Nrf2, modulation of inflammatory signaling, regulation of apoptosis. However, mitochondrial ROS also act as signaling molecules. Therefore, excessive suppression of mitochondrial ROS may interfere with physiological adaptations, including those associated with exercise [10].

5.3.4 Antioxidants, Glutathione and Redox Recycling

Glutathione (GSH) is one of the major intracellular reducing agents. The GSH/GSSG couple is an important determinant of cellular redox status [11].

Glutathione peroxidases use GSH to reduce hydrogen peroxide and lipid hydroperoxides:

$2\ GSH + H_2O_2 \rightarrow GSSG + 2\ H_2O$

Glutathione reductase subsequently regenerates GSH using NADPH.

Dietary antioxidants can interact with this system at multiple levels. Vitamin C can participate in antioxidant recycling, while phytochemicals can induce enzymes involved in GSH synthesis and regeneration. Thus, dietary antioxidant action should be considered within a network rather than as isolated molecular reactions.

6. Bioavailability and Metabolism: The Critical Determinants

One of the major limitations in antioxidant research is the assumption that the chemical activity of a purified compound directly predicts its biological effect. After ingestion, dietary antioxidants undergo digestion, absorption, metabolism, conjugation, transport, and

elimination. A defining challenge in translating the in vitro chemistry into biological relevance is the substantial mismatch between the antioxidant potency of dietary compounds as measured in cell-free assays and their behavior after ingestion. Polyphenols are particularly extensively transformed through glucuronidation, sulfation, methylation, and microbial metabolism.

Many polyphenols reach the colon, where gut microorganisms generate smaller phenolic metabolites that may be absorbed and contribute to systemic activity. Consequently, the compound measured in a chemical antioxidant assay may not be the compound responsible for biological effects in humans [12]. Recent evidence further indicates substantial inter-individual variation in polyphenol metabolism. Differences in gut microbiota, genetics, age, sex, body composition, physiological status, and lifestyle can influence circulating metabolites and potentially modify biological responses. Carotenoids require dietary fat for efficient micellar solubilization and intestinal absorption, and their bioavailability is further influenced by food matrix, degree of processing, and competition among carotenoid species for shared absorption and transport pathways. These pharmacokinetic realities mean that a compound's rank order of potency in a cell-free chemical assay cannot be assumed to predict its rank order of physiological antioxidant effect [7].

This supports the emerging concept of personalized antioxidant nutrition, in which the biological response to a food-derived antioxidant depends on the individual's metabolic phenotype.

7. Food Matrix and Synergistic Effects

Dietary antioxidants are rarely consumed as isolated compounds. Fruits, vegetables, whole grains, legumes, nuts, seeds, spices, tea, coffee, and other foods contain complex mixtures of antioxidants and other bioactive constituents. The food matrix can influence solubility, absorption, intestinal metabolism, stability, cellular uptake and interaction with other nutrients.

Antioxidants may also interact synergistically. For example, vitamin C can participate in regeneration of vitamin E, while combinations of polyphenols and carotenoids may influence different cellular compartments. Therefore, the antioxidant activity of a whole food cannot always be predicted by adding the antioxidant capacities of its individual constituents.

8. The Antioxidant Paradox: Pro-oxidant Effect and Hormesis

An important contemporary concept is that antioxidant compounds can display pro-oxidant behavior under certain conditions. Polyphenols containing catechol or other redox-active structures can undergo oxidation to quinones. These reactions may generate ROS or electrophilic products capable of modifying cellular proteins. Similarly, carotenoids can undergo oxidative cleavage, particularly under conditions of high oxidative stress or elevated oxygen concentration. Such products may have biological signaling functions but may also contribute to oxidative chemistry [14].

This apparent contradiction does not necessarily represent a weakness of dietary antioxidants. Controlled mild oxidative or electrophilic stress can activate adaptive pathways such as Nrf2. This phenomenon is often described as **hormesis**, in which a low-intensity stressor stimulates cellular defense mechanisms. Thus, the biological effects of dietary antioxidants may arise

from a combination of direct antioxidant activity, electrophilic signaling, metabolic transformation, and adaptive stress responses [13].

9. Evidence from Human Studies

Observational research consistently associates diets rich in fruits, vegetables, whole grains, nuts, legumes, and other plant foods with favorable health outcomes. However, translating these associations into evidence for isolated antioxidant supplements has proven considerably more difficult.

Large randomized evidence has not established that antioxidant supplementation universally prevents disease or mortality. A large systematic review of randomized trials involving 78 trials and approximately 297,000 participants found no simple universal benefit of antioxidant supplementation on mortality outcomes [15]. This distinction is crucial. A diet rich in antioxidant-containing foods is not equivalent to taking high-dose antioxidant supplements.

Whole foods contain mixtures of vitamins, minerals, fiber, polyphenols, carotenoids, and other compounds that interact with metabolism and the gut microbiome. Furthermore, the dose and chemical form of an isolated supplement may differ substantially from dietary exposure. Therefore, current evidence supports dietary patterns rich in diverse plant foods more strongly than indiscriminate high-dose antioxidant supplementation.

10. Emerging Dietary Antioxidants

10.1 Ergothioneine

Ergothioneine is a sulfur-containing amino-acid derivative obtained primarily from dietary sources such as mushrooms and certain microorganisms. Its chemistry enables it to participate in cellular redox buffering, and it is transported into cells through a specific transporter, suggesting that it may have physiological functions beyond nonspecific radical scavenging [16].

10.2 Sulforaphane

Sulforaphane is generated from glucoraphanin in cruciferous vegetables. Its electrophilic isothiocyanate group provides a strong chemical basis for modification of protein thiols, particularly within redox-sensitive signaling systems. Nrf2 activation is considered a major validated mechanism [17].

10.3 Microbiota-derived antioxidant metabolites

Increasing evidence indicates that microbial metabolites derived from dietary polyphenols may contribute to biological activity. This changes the traditional concept of antioxidants from “food compounds acting directly in tissues” to a more complex model involving:

Food compound → digestion → microbial transformation → host metabolism → active metabolite → cellular signaling

The microbiome therefore represents an important determinant of antioxidant efficacy [12].

11. Limitations of Current Antioxidant Research

Several methodological challenges continue to affect the interpretation of antioxidant research.

First, chemical antioxidant assays such as DPPH, ABTS, FRAP, and ORAC measure properties under artificial experimental conditions and may not reproduce cellular environments. Second, antioxidant concentrations used in cell culture experiments may exceed physiologically achievable concentrations. Third, the parent dietary compound may not be the predominant circulating or tissue form. Fourth, oxidative stress biomarkers differ in specificity and biological interpretation. Fifth, individual variation in absorption and metabolism can produce substantially different responses to the same dietary exposure. Finally, oxidative stress is highly compartmentalized. A reduction in total plasma oxidative markers does not necessarily indicate improved mitochondrial, nuclear, or intracellular redox homeostasis. These limitations emphasize the need for pharmacokinetic studies, metabolomics, redox proteomics, validated biomarkers, and well-designed randomized controlled trials.

12. Future Perspectives

Future research should move beyond the simplistic concept of "antioxidants versus free radicals." Several priorities are particularly important. Detailed analysis of molecular structure, redox potential, electrophilicity, metal-binding ability, and membrane partitioning can help identify compounds with predictable biological activities. Studies should evaluate metabolites and conjugated forms rather than focusing exclusively on parent compounds. Differences in gut microbiota, genetic background, metabolic phenotype, and lifestyle should be incorporated into nutritional intervention studies. Future clinical studies should use validated markers of lipid oxidation, protein oxidation, DNA oxidation, glutathione status, redox signaling, and inflammatory pathways rather than relying on a single nonspecific marker. Greater emphasis should be placed on dietary patterns and whole foods rather than isolated antioxidant supplements. Combining metabolomics, lipidomics, proteomics, transcriptomics, microbiome analysis, and redox biology may clarify the molecular pathways through which dietary antioxidants influence health.

13. Conclusion

Dietary antioxidants represent a chemically diverse network of compounds whose biological effects extend far beyond direct radical scavenging. Their antioxidant properties arise from structural features such as phenolic hydroxyl groups, conjugated double bonds, electrophilic centers, metal-binding sites, and favorable redox potentials. Vitamin C primarily contributes to aqueous-phase redox chemistry and antioxidant recycling, vitamin E protects lipid membranes, carotenoids participate in singlet oxygen and radical quenching, and polyphenols exert a combination of direct chemical and indirect signaling effects. The emerging understanding of dietary antioxidant biology emphasizes Nrf2-mediated cytoprotection, glutathione metabolism, mitochondrial regulation, inflammatory signaling, and interactions with the gut microbiota. Importantly, antioxidant activity is context-dependent and may shift toward pro-oxidant or signaling functions depending on concentration, oxygen tension, metal availability, chemical structure, and metabolic transformation. The strongest conceptual shift is therefore from viewing dietary antioxidants as simple "free-radical scavengers" toward recognizing them as modulators of cellular redox homeostasis. Their physiological effects depend on the interaction

between chemistry, bioavailability, metabolism, food matrix, microbiota, and host biology. Future research integrating chemical biology with nutritional science and precision medicine will be essential for translating antioxidant chemistry into evidence-based dietary strategies.

Declarations

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References

1. Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol. 2015;4:180-183.
2. Lu MC, Ji JA, Jiang ZY, You QD. The Keap1-Nrf2-ARE pathway as a potential preventive and therapeutic target: an update. Med Res Rev. 2016;36(5):924-963.
3. Graille M, Wild P, Sauvain JJ, Hemmendinger M, Guseva Canu I, Hopf NB. Urinary 8-OHdG as a biomarker for oxidative stress: a systematic literature review and meta-analysis. Int J Mol Sci. 2020;21(11):3743.
4. Timoshnikov VA, Kobzeva TV, Polyakov NE, Kontoghiorghes GJ. Redox interactions of vitamin C and iron: inhibition of the pro-oxidant activity by deferiprone. Int J Mol Sci. 2020;21(11):3967.
5. Traber MG, Atkinson J. Vitamin E, antioxidant and nothing more. Free Radic Biol Med. 2007;43(1):4-15.
6. Black HS, Boehm F, Edge R, Truscott TG. The benefits and risks of certain dietary carotenoids that exhibit both anti- and pro-oxidative mechanisms—a comprehensive review. Antioxidants (Basel). 2020;9(3):264.
7. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79(5):727-747.
8. Leopoldini M, Russo N, Toscano M. The molecular basis of working mechanism of natural polyphenolic antioxidants. Food Chem. 2011;125(2):288-306.
9. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol. 2006;71(10):1397-1421.
10. Cheng Z, Schmelz EM, Liu D, Hulver MW. Targeting mitochondrial alterations to prevent type 2 diabetes—evidence from studies of dietary redox-active compounds. Mol Nutr Food Res. 2014;58(8):1739-1749.
11. Aoyama K, Nakaki T. Glutathione in cellular redox homeostasis: association with the excitatory amino acid carrier 1 (EAAC1). Molecules. 2015;20(5):8742-8758.
12. Duda-Chodak A, Tarko T, Satora P, Sroka P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review. Eur J Nutr. 2015;54(3):325-341.
13. Son TG, Camandola S, Mattson MP. Hormetic dietary phytochemicals. Neuromolecular Med. 2008;10(4):236-246.
14. Babich H, Schuck AG, Weisburg JH, Zuckerbraun HL. Research strategies in the study of the pro-oxidant nature of polyphenol nutraceuticals. J Toxicol. 2011;2011:467305.
15. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database Syst Rev. 2012;3:CD007176.

16. Ey J, Schömig E, Taubert D. Dietary sources and antioxidant effects of ergothioneine. J Agric Food Chem. 2007;55(16):6466-6474.
17. Ruhee RT, Suzuki K. The integrative role of sulforaphane in preventing inflammation, oxidative stress and fatigue: a review of a potential protective phytochemical. Antioxidants (Basel). 2020;9(6):521.