2026 Volume: 02 Issue: 05 www.ijrpa.com ISSN 2456-9995 Research Article

International Journal Research Publication Analysis

Page: 01-13

BIOCHEMICAL MECHANISMS OF ANTIOXIDANTS IN PREVENTING CELLULAR DAMAGE

[1]Dr. Bsabana, [2]Dr. Umamaheswari R., [3]Deepikaa R.

[1]Assistant professor, Department of Biochemistry, Dr. MGR Janaki college for women, Adyar Chennai 28.

[2]Assistant Professor Department of Chemistry C. Kandaswami Naidu College for Women Cuddalore- 607001.

[3]M. Sc. Medical Biochemistry University of Madras.

Article Received: 08 April 2026
Article Revised: 28 April 2026
Published on: 18 May 2026

***Corresponding Author: Dr. Bsabana**
Assistant professor, Department of Biochemistry, Dr. MGR Janaki college for women, Adyar Chennai 28.

DOI: https://doi-doi.org/101555/ijrpa.9803

ABSTRACT

Reactive oxygen species (ROS) and free radicals are continuously generated as byproducts of normal cellular metabolism, yet their unchecked accumulation drives oxidative stress — a central pathological mechanism in aging, cancer, cardiovascular disease, neurodegeneration, and diabetes. Antioxidants constitute a multi-tiered biochemical defense system that neutralizes ROS through diverse mechanisms including free radical scavenging, metal ion chelation, enzymatic detoxification, and transcriptional regulation of cytoprotective genes. This review comprehensively examines the molecular mechanisms by which both endogenous and exogenous antioxidants prevent oxidative damage to proteins, lipids, and DNA. We discuss the roles of enzymatic antioxidants (superoxide dismutase, catalase, glutathione peroxidase), small-molecule antioxidants (vitamins C and E, glutathione, coenzyme Q10), and dietary phytochemicals (polyphenols, carotenoids, flavonoids). Special attention is given to the Nrf2/Keap1 signaling axis as a master regulator of antioxidant gene expression, the interplay between redox signaling and cellular homeostasis, and the context-dependence of antioxidant activity. Clinical implications for supplementation strategies and the emerging concept of the 'antioxidant paradox' are also addressed.

KEYWORDS: reactive oxygen species, free radicals, oxidative stress, Nrf2, glutathione, superoxide dismutase, polyphenols, lipid peroxidation, cellular protection, redox signaling.

1. INTRODUCTION

Living organisms exist in a state of continuous biochemical tension between the generation of reactive oxygen species (ROS) and the capacity of antioxidant defense systems to neutralize them. ROS — a collective term encompassing superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and singlet oxygen ($^1O_2$) — are inevitable byproducts of aerobic metabolism, produced primarily at the mitochondrial electron transport chain during oxidative phosphorylation.

Under physiological conditions, moderate ROS levels fulfill critical signaling functions, participating in immune defense, cellular proliferation, apoptosis regulation, and redox-sensitive gene expression. However, when ROS production exceeds the cell's antioxidant capacity — a state termed oxidative stress — these highly reactive molecules inflict indiscriminate damage on all classes of biological macromolecules.

The biomedical significance of oxidative stress is profound. Oxidative damage to DNA can induce strand breaks, base modifications, and chromosomal instability that promote carcinogenesis. Lipid peroxidation disrupts membrane integrity and generates toxic aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). Protein oxidation leads to structural unfolding, loss of enzymatic activity, and aberrant protein aggregation linked to neurodegenerative conditions including Alzheimer's and Parkinson's disease.

Antioxidants represent an evolutionarily ancient and biochemically diverse set of molecules that combat these damaging processes through multiple complementary mechanisms. This review provides a detailed examination of those mechanisms at the molecular and cellular level, with the goal of illuminating both the complexity of antioxidant biology and its therapeutic implications.

2. Generation and Chemistry of Reactive Oxygen Species

2.1 Endogenous Sources of ROS

The mitochondrial electron transport chain is the predominant intracellular source of ROS, accounting for up to 90% of cellular superoxide production. During oxidative phosphorylation, electrons leak from complexes I and III and react directly with molecular oxygen to form superoxide ($O_2^{\bullet -}$). Additional enzymatic sources include NADPH oxidase (NOX) enzymes in phagocytes and endothelial cells, xanthine oxidase in ischemia-reperfusion injury, cytochrome P450 enzymes in the endoplasmic reticulum, and lipoxygenases and cyclooxygenases during arachidonic acid metabolism.

2.2 The Fenton and Haber–Weiss Reactions

Fenton reaction: The most chemically destructive ROS is the hydroxyl radical (•OH), produced primarily through the iron-catalyzed Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\bullet}OH + OH^-$$

Superoxide can reduce Fe^{3+} back to Fe^{2+}, perpetuating the cycle. The overall process (Haber–Weiss reaction) produces •OH from H_2O_2 and $O_2{\bullet}^-$. Because •OH has an extraordinarily short half-life (~10^{-9} seconds) and reacts at nearly diffusion-limited rates, it damages molecules at the site of its generation. This is why metal chelation is a key antioxidant strategy.

2.3 Oxidative Targets

- DNA: Base oxidation (8-oxo-dG), strand breaks, crosslinks
- Lipids: Polyunsaturated fatty acid peroxidation cascade producing MDA, 4-HNE
- Proteins: Carbonylation, disulfide bond formation, methionine oxidation, nitrosylation
- Carbohydrates: Glycation and advanced glycation end-product (AGE) formation

3. Enzymatic Antioxidant Defense Systems

The enzymatic arm of the antioxidant defense system represents the first and most potent line of cellular protection. These enzymes catalyze the rapid conversion of ROS to less reactive species with remarkable efficiency, operating in a coordinated network within specific subcellular compartments.

3.1 Superoxide Dismutase (SOD)

Superoxide dismutase catalyzes the disproportionation of superoxide into hydrogen peroxide and molecular oxygen:

$$2\ O_2{\bullet}^- + 2H^+ \rightarrow H_2O_2 + O_2$$

Three SOD isoforms exist in mammals, distinguished by their metal cofactors and subcellular localization: MnSOD (SOD2) resides in the mitochondrial matrix, where the bulk of superoxide is produced and is considered essential for life — SOD2 knockout mice die shortly after birth from cardiomyopathy. CuZnSOD (SOD1) is found in the cytosol and mitochondrial intermembrane space. Extracellular SOD (SOD3) is secreted and protects the extracellular matrix and vascular endothelium.

3.2 Catalase

Catalase, located predominantly in peroxisomes, decomposes hydrogen peroxide — the product of SOD — to water and oxygen with extraordinary efficiency (kcat ~10^7 mol/s):

$$\mathbf{2\ H_2O_2 \rightarrow 2\ H_2O + O_2}$$

Catalase contains a heme prosthetic group and follows a two-step ping-pong mechanism. Its peroxidatic activity (oxidizing small organic substrates using H_2O_2) also contributes to cellular detoxification. Catalase activity is highest in the liver, kidney, and red blood cells — tissues with high oxidative metabolic activity.

3.3 Glutathione Peroxidase (GPx)

Glutathione peroxidase (GPx) reduces both H_2O_2 and organic hydroperoxides (including lipid hydroperoxides, ROOH) using glutathione (GSH) as the electron donor:

$$\mathbf{H_2O_2 + 2\ GSH \rightarrow GSSG + 2\ H_2O}$$

Of the eight GPx isoforms in humans, GPx1 (cytosolic) and GPx4 (phospholipid hydroperoxide GPx, PHGPx) are particularly critical. GPx4 is unique in its ability to reduce phospholipid hydroperoxides directly within membranes, making it the primary defense against lipid peroxidation. Importantly, most GPx isoforms require selenium as a catalytic cofactor in the form of selenocysteine (Sec), explaining why dietary selenium deficiency is associated with oxidative pathology.

3.4 Thioredoxin and Glutaredoxin Systems

Thioredoxin (Trx) and thioredoxin reductase (TrxR) form a NADPH-dependent disulfide reductase system that reduces oxidized protein thiols, regulates transcription factors (including NF-κB and AP-1), and supports DNA synthesis via ribonucleotide reductase. Glutaredoxins (Grxs) use glutathione as their reductant and specialize in reversing protein S-glutathionylation — a key redox post-translational modification. Together, these systems maintain the cytoplasmic redox balance and protect critical cysteine residues in regulatory proteins.

3.5 Glutathione Reductase (GR) and the GSSG/GSH Cycle

Glutathione reductase regenerates reduced glutathione (GSH) from oxidized glutathione (GSSG) using NADPH as a reductant. This NADPH is supplied by the pentose phosphate

pathway (PPP) via glucose-6-phosphate dehydrogenase (G6PD). Genetic deficiency of G6PD — the most common enzymopathy worldwide — impairs this regeneration, leaving red blood cells vulnerable to hemolytic anemia under oxidative challenge.

4. Small-Molecule Non-Enzymatic Antioxidants

4.1 Glutathione (GSH): The Master Intracellular Antioxidant

Glutathione (γ-L-glutamyl-L-cysteinyl-glycine) is the most abundant low-molecular-weight thiol in mammalian cells, present at concentrations of 1–10 mM in the cytosol. Its antioxidant function is mediated by the thiol (-SH) group of cysteine, which acts as the electron donor. GSH operates as a direct free radical scavenger, a cofactor for GPx and glutaredoxins, a substrate for glutathione S-transferases (GSTs) in xenobiotic detoxification, and a direct reducer of ascorbyl and tocopheryl radicals, regenerating these vitamins.

GSH is synthesized in two ATP-dependent steps catalyzed by glutamate-cysteine ligase (GCL, the rate-limiting enzyme) and glutathione synthetase (GS). Its intracellular synthesis is upregulated by oxidative stress through Nrf2-mediated transcription of GCL subunit genes.

4.2 Ascorbic Acid (Vitamin C)

Ascorbate (the reduced form of vitamin C) is a potent water-soluble antioxidant that functions through sequential one-electron transfer reactions. It donates electrons to neutralize superoxide, hydroxyl radicals, singlet oxygen, and peroxyl radicals. A key biochemical role is the regeneration of α-tocopherol (vitamin E): ascorbate reduces the tocopheroxyl radical back to tocopherol at the membrane–cytosol interface, completing the lipophilic–hydrophilic antioxidant network.

Ascorbyl radical (semidehydroascorbate) formed in this process is relatively unreactive and is reduced back to ascorbate by NADH-dependent semidehydroascorbate reductase, or undergoes disproportionation to ascorbate and dehydroascorbate. The latter is reduced back to ascorbate by GSH-dependent dehydroascorbate reductase. This recycling network ensures that limited dietary ascorbate is used with high efficiency.

4.3 α-Tocopherol (Vitamin E)

Alpha-tocopherol is the principal lipid-soluble antioxidant in biological membranes. Its chromanol head group donates a hydrogen atom from the phenolic -OH to lipid peroxyl radicals (LOO•), interrupting the chain-propagation step of lipid peroxidation:

LOO• + α-Toc-OH → LOOH + α-Toc-O•

The resulting tocopheroxyl radical (α-Toc-O•) is stabilized by resonance delocalization within the chromanoxyl ring, preventing it from participating in further damaging reactions. It is subsequently reduced back to α-tocopherol by ascorbate or ubiquinol ($CoQ10H_2$). Vitamin E is particularly important in protecting mitochondrial membranes, the endoplasmic reticulum, and plasma membranes from oxidative damage.

4.4 Coenzyme Q10 (Ubiquinol/Ubiquinone)

Coenzyme Q10 (CoQ10) cycles between its oxidized (ubiquinone), semiquinone, and fully reduced (ubiquinol, $CoQ10H_2$) forms. Ubiquinol is a potent membrane-bound antioxidant that regenerates vitamin E, scavenges peroxyl radicals, and prevents lipid peroxidation within inner mitochondrial membranes. Given its central role in both electron transport and antioxidant defense, CoQ10 deficiency is associated with mitochondrial myopathy and cardiomyopathy.

4.5 Uric Acid

Uric acid, the end-product of purine catabolism in humans (due to loss of uricase activity during primate evolution), is one of the most abundant antioxidants in human plasma. It effectively scavenges peroxynitrite ($ONOO^-$), singlet oxygen, and hydroxyl radicals, and chelates iron and copper ions. The paradoxically high uric acid levels in humans compared to other mammals may have evolved as a compensatory antioxidant mechanism following loss of endogenous ascorbate synthesis.

5. Dietary Phytochemical Antioxidants

5.1 Polyphenols: Structure-Activity Relationships

Polyphenols are a structurally diverse class of plant secondary metabolites characterized by one or more phenolic rings bearing multiple hydroxyl groups. Their antioxidant potency derives from the ability of these -OH groups to donate hydrogen atoms to free radicals, with the resulting phenoxyl radical being stabilized by resonance and intramolecular hydrogen bonding. Key structural determinants of antioxidant activity include the number and position of hydroxyl groups, the degree of conjugation, and the presence of a catechol (ortho-dihydroxyphenyl) moiety.

5.1.1 Flavonoids

Flavonoids — the largest polyphenol subclass — include flavonols (quercetin, kaempferol), flavones, flavanones, catechins (found in green tea), anthocyanins, and isoflavones. Quercetin

is among the most studied flavonoids; its high radical-scavenging capacity reflects the 3,4-catechol group on the B ring, the 2,3 double bond conjugated with the 4-keto group, and the 3-OH and 5-OH groups on the C and A rings. Beyond direct scavenging, flavonoids chelate iron and copper, inhibit pro-oxidant enzymes (xanthine oxidase, lipoxygenase, NADPH oxidase), and activate Nrf2-mediated antioxidant gene transcription.

5.1.2 Resveratrol

Resveratrol (3,4′,5-trihydroxystilbene), found in grape skins, red wine, and peanuts, exhibits antioxidant activity through free radical scavenging and activation of sirtuins (SIRT1), which deacetylate and activate Nrf2. Resveratrol upregulates the expression of SOD, catalase, GPx, and heme oxygenase-1 (HO-1). It also inhibits NF-κB, a redox-sensitive transcription factor that promotes pro-inflammatory and pro-oxidant gene expression.

5.1.3 Curcumin

Curcumin (diferuloylmethane), the principal bioactive component of turmeric (Curcuma longa), is a bis-α,β-unsaturated β-diketone with dual antioxidant activity. It scavenges ROS directly via its phenolic groups and acts as a potent inducer of the Nrf2/HO-1 pathway, upregulating phase II detoxification enzymes and antioxidant proteins. The Michael acceptor capability of its enone system allows covalent modification of Keap1 cysteine residues, liberating Nrf2 for nuclear translocation.

5.2 Carotenoids

Carotenoids are C40 polyene pigments characterized by an extended conjugated double-bond system that makes them highly effective quenchers of singlet oxygen ($^1O_2$) and scavengers of peroxyl radicals, particularly in lipid environments. β-Carotene quenches singlet oxygen via physical energy transfer: the excitation energy of $^1O_2$ is absorbed by the carotenoid's polyene chain and released as heat, regenerating the carotenoid in its ground state. Lycopene (found in tomatoes) and astaxanthin have particularly high singlet oxygen quenching rates. Lutein and zeaxanthin concentrate in the macular region of the retina, where they filter high-energy blue light and quench ROS to protect against age-related macular degeneration.

5.3 Organosulfur Compounds

Sulforaphane (from cruciferous vegetables) and allicin (from garlic) are potent Nrf2 activators. Sulforaphane is an isothiocyanate that modifies Keap1 cysteines directly, triggering Nrf2 nuclear accumulation and a broad transcriptional antioxidant response. This

indirect mechanism — inducing cellular antioxidant defenses rather than directly scavenging ROS — makes sulforaphane particularly effective at sustained cytoprotection.

6. The Nrf2/Keap1/ARE Signaling Axis

The Nrf2 (Nuclear factor erythroid 2-related factor 2) transcription factor is the master regulator of the cellular antioxidant response. Under basal conditions, Nrf2 is bound to its cytoplasmic repressor Keap1 (Kelch-like ECH-associated protein 1), which serves as a substrate adaptor for a Cul3-based E3 ubiquitin ligase, targeting Nrf2 for proteasomal degradation with a half-life of approximately 20 minutes.

6.1 Activation Mechanism

Keap1 functions as an electrophile and oxidant sensor through a set of highly reactive cysteine residues (particularly Cys151, Cys273, and Cys288) that form the 'cysteine code.' Oxidation or covalent modification of these thiols (by ROS, electrophilic compounds, or natural inducers like sulforaphane) causes conformational changes in Keap1 that disrupt its interaction with the DLG and ETGE motifs in the Neh2 domain of Nrf2. Released from Keap1-mediated degradation, Nrf2 accumulates, translocates to the nucleus, and heterodimerizes with small Maf proteins.

6.2 Antioxidant Response Element (ARE) Target Genes

The Nrf2/sMaf heterodimer binds to antioxidant response elements (AREs) — consensus sequence 5′-TGACTCAGC-3′ — in the promoters of over 200 cytoprotective genes, including:

- Phase II detoxifying enzymes: NQO1, GSTs, UGTs, SULTs
- Glutathione synthesis and metabolism: GCL (GCLC, GCLM subunits), GSS, GPx2
- Thioredoxin system: TXN1, TXNRD1
- Heme oxygenase-1 (HO-1): generates cytoprotective biliverdin, CO, and ferritin
- Ferritin: sequesters iron, preventing Fenton chemistry
- Sulfiredoxin and sestrin: repair overoxidized peroxiredoxins

The breadth of Nrf2's transcriptional program explains why pharmacological Nrf2 activation (e.g., with sulforaphane, dimethyl fumarate, bardoxolone methyl) is being investigated as a therapeutic strategy in a wide range of oxidative stress-related diseases.

7. Summary of Key Antioxidant Mechanisms

Table 1. Principal biochemical mechanisms by which antioxidants prevent cellular oxidative damage.

Mechanism	Description	Key Antioxidants
Free Radical Scavenging	Direct donation of hydrogen atoms or electrons to neutralize reactive oxygen species	Vitamin C, Vitamin E, Polyphenols, Carotenoids
Metal Chelation	Binding of transition metals (Fe^{2+}, Cu^{2+}) to prevent Fenton reaction catalysis	EDTA, Quercetin, Desferrioxamine, Phytic Acid
Enzyme Activation	Upregulation of endogenous antioxidant enzymes via Nrf2 pathway signaling	Sulforaphane, Curcumin, Resveratrol
Singlet Oxygen Quenching	Physical or chemical deactivation of excited singlet oxygen molecules	β-Carotene, Lycopene, Zeaxanthin
Lipid Peroxidation Inhibition	Chain-breaking activity within lipid bilayers to prevent oxidative cascade	α-Tocopherol (Vitamin E), CoQ10

8. Classification of Antioxidants

Table 2. Classification of major antioxidant categories, representative examples, primary cellular targets, and bioavailability.

Category	Examples	Primary Target	Bioavailability
Enzymatic	SOD, Catalase, GPx	Intracellular ROS	Endogenous
Vitamin-based	Vitamins C, E, A	Aqueous & lipid phases	Dietary/Supplemental
Polyphenolic	Quercetin, Resveratrol, Curcumin	Membrane & cytosol	Variable (5–20%)
Carotenoids	β-Carotene, Lycopene, Lutein	Lipid membranes	Fat-soluble
Thiols	Glutathione, N-Acetylcysteine	Cytoplasmic ROS	High (intracellular)
Minerals	Selenium, Zinc, Manganese	Enzyme cofactors	Dietary

9. Lipid Peroxidation and Its Prevention

Lipid peroxidation of polyunsaturated fatty acids (PUFAs) in biological membranes is one of the most destructive oxidative processes. The reaction proceeds as a free radical chain reaction in three phases:

Initiation: A •OH or LOO• abstracts a bisallylic hydrogen from a PUFA, generating a lipid radical (L•).

Propagation: L• reacts with O_2 to form a lipid peroxyl radical (LOO•), which abstracts hydrogen from adjacent PUFA molecules, propagating the chain. Each initiation event can generate hundreds of lipid peroxide molecules before termination.

Termination: Two radical species react to form non-radical products, or a chain-breaking antioxidant (α-tocopherol, $CoQ10H_2$) intercepts LOO•.

The toxic aldehydes produced — principally 4-HNE and MDA — form adducts with DNA, proteins, and lipids. 4-HNE modifies histidine, cysteine, and lysine residues of proteins, impairing their function and creating neo-epitopes recognized by the immune system. MDA forms DNA adducts (M1dG) that are mutagenic. Antioxidants prevent lipid peroxidation by neutralizing initiating radicals (vitamin C, polyphenols), breaking the chain reaction within membranes (vitamin E, CoQ10), or reducing lipid hydroperoxides before they decompose to aldehydes (GPx4).

10. Protection of DNA Against Oxidative Damage

Among the most well-characterized oxidative DNA lesions is 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG), formed by hydroxyl radical attack on guanine. 8-oxo-dG is highly mutagenic — it mispairs with adenine during DNA replication, causing G→T transversions. The MutM/OGG1 DNA glycosylase recognizes and excises 8-oxo-dG in the base excision repair (BER) pathway. Antioxidants protect against 8-oxo-dG formation primarily by suppressing the intracellular free iron pool (preventing Fenton chemistry) and by maintaining adequate levels of GSH and ascorbate.

In addition to base modifications, ROS cause single- and double-strand breaks (SSBs/DSBs), DNA-protein crosslinks, and abasic sites. These lesions, if unrepaired, activate DNA damage response kinases (ATM, ATR), trigger cell cycle arrest, and — if damage is irreparable — initiate apoptosis or promote senescence. The accumulation of unrepaired oxidative DNA damage is a cardinal feature of aging and is mechanistically linked to carcinogenesis through mutational activation of oncogenes and inactivation of tumor suppressor genes.

11. Redox Signaling and the Antioxidant Paradox

A critical conceptual development in the field has been the recognition that ROS are not merely toxic byproducts but essential second messengers in redox signaling. H_2O_2, in particular, at low concentrations mediates reversible oxidation of cysteine residues in tyrosine

phosphatases (e.g., PTP1B), kinases, and transcription factors, regulating pathways including PI3K/Akt, MAPK, and NF-κB. This redox signaling underpins physiological processes such as insulin signal transduction, immune activation, and stem cell differentiation.

This understanding gives rise to the 'antioxidant paradox': wholesale suppression of ROS by high-dose exogenous antioxidants can be detrimental. Clinical trials of high-dose β-carotene supplementation in smokers (ATBC, CARET trials) paradoxically increased lung cancer incidence. High-dose vitamin E supplementation increased all-cause mortality in some meta-analyses. These findings likely reflect disruption of physiological ROS signaling and potential pro-oxidant activity of antioxidants at supraphysiological concentrations.

This paradox highlights that the therapeutic goal should not be the elimination of ROS but the restoration of redox homeostasis — the proper balance between ROS generation and antioxidant neutralization. Dietary antioxidants that work through Nrf2 induction (sulforaphane, resveratrol) or mitochondria-targeted antioxidants (MitoQ, SkQ1) represent more nuanced strategies that bolster endogenous defenses without globally suppressing redox signaling.

12. Clinical Implications and Disease Contexts

12.1 Cardiovascular Disease

Oxidative modification of low-density lipoprotein (LDL) by reactive oxygen species and nitrogen species is a pivotal early step in atherogenesis, triggering foam cell formation and plaque development. Antioxidants — particularly vitamin E, polyphenols in olive oil, and flavonoids in dark chocolate and tea — are associated with reduced cardiovascular risk in observational studies, though large randomized trials have been inconsistent, likely due to the paradox discussed above.

12.2 Neurodegenerative Diseases

The brain is particularly vulnerable to oxidative damage owing to its high oxygen consumption, abundant polyunsaturated lipids, and relatively low catalase activity. In Alzheimer's disease, oxidative stress drives amyloid-β aggregation and tau hyperphosphorylation. In Parkinson's disease, dopaminergic neurons in the substantia nigra exhibit depleted GSH, elevated iron, and damaged mitochondria. Nrf2 activators and mitochondria-targeted antioxidants are under active clinical investigation for neuroprotection.

12.3 Diabetes and Metabolic Syndrome

Hyperglycemia generates ROS through multiple mechanisms: mitochondrial overload, advanced glycation end-product (AGE) formation, polyol pathway flux, and activation of protein kinase C. Oxidative stress in diabetes damages insulin-producing beta cells, promotes insulin resistance, and drives the microvascular complications of diabetic nephropathy, retinopathy, and neuropathy. Alpha-lipoic acid — a dithiolane compound that regenerates GSH, vitamins C and E, and CoQ10 — is clinically approved in several countries for diabetic neuropathy.

12.4 Cancer

The relationship between antioxidants and cancer is bidirectional and context-dependent. In normal cells, antioxidants prevent the oxidative DNA damage that initiates carcinogenesis. However, established tumor cells with elevated ROS also rely on antioxidant defenses (particularly Nrf2 and GSH) to survive oxidative stress and resist chemotherapy. This has led to the counterintuitive therapeutic strategy of exploiting pro-oxidant or antioxidant depletion approaches in cancer — for example, using BSO (buthionine sulfoximine) to inhibit GSH synthesis and sensitize tumors to oxidative damage.

13. Conclusions and Future Directions

The biochemistry of antioxidant protection is characterized by extraordinary complexity, redundancy, and context-dependence. Multiple overlapping mechanisms — enzymatic catalysis, small-molecule scavenging, metal chelation, chain-breaking activity, and transcriptional gene regulation — collectively maintain redox homeostasis across the diverse chemical environments of subcellular compartments.

Key emerging themes include: (1) the role of Nrf2 as a therapeutic target for oxidative stress-related diseases; (2) the importance of redox signaling as a physiological process that must be preserved rather than eliminated; (3) subcellular targeting of antioxidants (mitochondria-directed antioxidants) as a strategy for improving therapeutic efficacy; (4) the gut microbiome's role in polyphenol bioavailability and biotransformation; and (5) the genetic polymorphisms in antioxidant enzymes (MnSOD Ala16Val, GPx1 Pro197Leu) that contribute to individual variation in oxidative stress susceptibility.

Future therapeutic strategies will likely move away from simplistic supplementation with high-dose single antioxidants toward nuanced, targeted approaches that enhance endogenous

antioxidant capacity, preserve redox signaling, and are tailored to the specific oxidative mechanisms driving individual diseases.

REFERENCES

1. Sies H, Berndt C, Jones DP. Oxidative stress. Annu Rev Biochem. 2017;86:715–748.
2. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;408(6809):239–247.
3. Itoh K, et al. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem Biophys Res Commun. 1997;236(2):313–322.
4. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J. 2009;417(1):1–13.
5. Halliwell B, Gutteridge JMC. Free Radicals in Biology and Medicine. 5th ed. Oxford University Press; 2015.
6. Valko M, et al. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol. 2007;39(1):44–84.
7. Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. Biochim Biophys Acta. 2013;1830(5):3289–3303.
8. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79(5):727–747.
9. Bjelakovic G, et al. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA. 2007;297(8):842–857.
10. Dixon SJ, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060–1072.