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OXIDATIVE STRESS AND ANTIOXIDANT DEFENSE MECHANISMS IN HUMAN PHYSIOLOGY: A MOLECULAR REVIEW

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Abstract

Oxidative stress is now recognized as a major factor that links metabolic disruption, cell damage, aging, and long-term disease. Reactive oxygen and nitrogen species (ROS/RNS) are normally involved in routine cell signaling, such as immune responses, cell growth, blood vessel control, and metabolic regulation. These molecules become harmful when their levels rise beyond what antioxidant defenses can manage. When this occurs, they gradually damage lipids, proteins, and DNA, disrupt organelle activity, and contribute to cell malfunction. In the past decade, and particularly from 2021 to 2025, research has grown rapidly in areas such as redox signaling, mitochondrial function, environmental sources of oxidative stress, and potential antioxidant treatments. This review brings together established knowledge and recent findings, covering the chemistry of ROS/RNS, their internal and external sources, their molecular effects, the body's antioxidant defense systems, links to disease, current biomarkers, and developing therapeutic strategies.

INTRODUCTION

Oxidative stress occurs when the production of reactive oxygen and nitrogen species becomes greater than the body's ability to neutralize them (1). Under normal conditions, these molecules help regulate redox signaling and influence processes such as cell survival, immune activity, new blood vessel formation, and energy metabolism (2). For instance, hydrogen peroxide functions as a signaling molecule that affects protein phosphorylation and the activity of transcription factors involved in growth (3). Nitric oxide also supports essential functions, including the relaxation of blood vessels and communication between nerve cells. These examples show that reactive species can be useful when present in controlled amounts.

Problems develop when their levels rise beyond what antioxidant systems can handle. Excess reactive molecules begin to chemically modify lipids, proteins, and DNA, leading to disturbed cellular balance and impaired function (4). This imbalance is involved in a wide range of conditions, including cardiovascular disease, type 2 diabetes, obesity-related metabolic disorders, Alzheimer's disease, cancer, infertility, chronic kidney disease, and long-standing inflammation (5). The overall oxidative burden increases with age as mitochondrial performance declines and natural antioxidant defenses weaken (6). Environmental factors such as polluted air, cigarette smoke, ultraviolet radiation, heavy metals, alcohol use, and diets high in fat further add to this burden, making oxidative stress a common risk factor across different groups (7).

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Recent studies show that oxidative stress is not only a byproduct of disease but can also play a central role in triggering and advancing many disorders (FIGURE. 1). New tools in redox proteomics, mitochondrial genomics, and large-scale biomarker analysis have helped clarify how small changes in redox balance influence key decisions about cell survival, repair, and death. These insights have shifted therapeutic efforts toward targeting oxidative pathways, either by strengthening antioxidant defenses or by reducing the formation of reactive species at their sources. A clear understanding of these mechanisms is important for developing treatments that are both precise and effective.

2. Reactive oxygen and nitrogen species (ROS/RNS)

Reactive oxygen and nitrogen species are highly reactive molecules that arise from routine metabolic activity as well as from harmful stimuli. Their effects depend on their chemistry, how quickly they react, how long they persist, and where in the cell they are produced.

Superoxide ($O_2^{\bullet -}$) is the main ROS formed during mitochondrial respiration and through the activity of NADPH oxidases in many tissues (8). Although it is less reactive than other oxidants, it is rapidly converted into hydrogen peroxide, which can cross membranes more easily and plays a role in redox signaling.

Hydrogen peroxide (H_2O_2) acts as a signaling molecule when kept at low, controlled levels. At higher concentrations, it can interact with metal ions and form hydroxyl radicals, making it both useful and potentially harmful depending on its abundance (9). Hydroxyl radicals ($^{\bullet}OH$) are the most reactive of the ROS. They form primarily through Fenton reactions and immediately attack DNA, proteins, and lipids. Because there are no enzymatic systems to neutralize them, their formation poses a major risk to cell structure (10). Nitric oxide ($NO^{\bullet}$) is a reactive nitrogen species that serves important signaling functions, including regulating blood vessel tone and communication within the nervous system (11). When nitric oxide reacts with superoxide, however, it forms peroxynitrite ($ONOO^-$), a strong oxidant capable of damaging lipids, proteins, and mitochondria (12).

Overall, ROS and RNS can support normal physiology or contribute to tissue injury. Their impact depends on how much is produced, where they are generated, and the capacity of available antioxidant defenses (FIGURE. 1).

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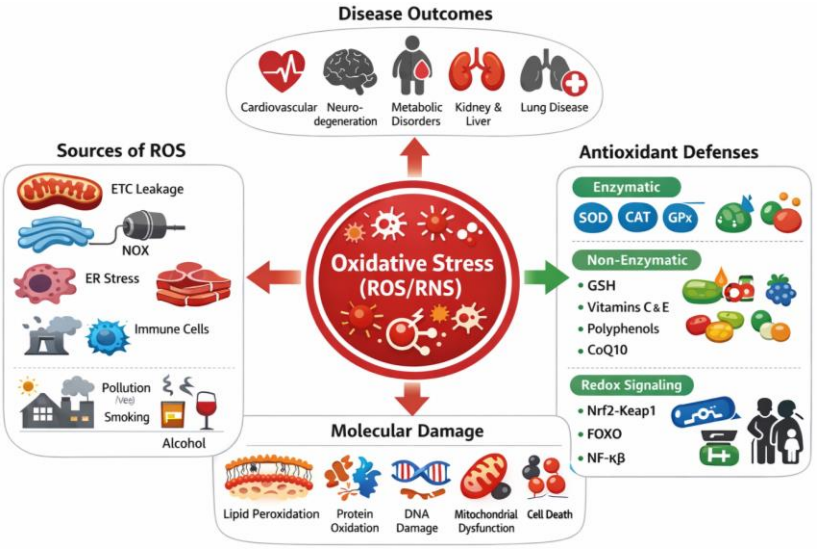

Figure 1. Overview of oxidative stress, its sources, molecular consequences, antioxidant defense systems, disease outcomes, and therapeutic strategies. ROS = reactive oxygen species; RNS = reactive nitrogen species.

3. Sources of oxidative stress

Oxidative stress arises from both metabolic activity and **exogenous** environmental exposures. Together, these sources contribute to fluctuations in redox balance throughout the lifespan.

3.1 Endogenous sources

3.1.1 Mitochondria

Mitochondria are the main internal source of reactive oxygen species. During oxidative phosphorylation, a small fraction of electrons, typically about 1-3%, escapes from the electron transport chain, most often at complexes I and III, and reduces oxygen to form superoxide (13). In healthy cells, this leakage is limited and quickly neutralized. When mitochondria become impaired due to aging, excess metabolic demand, or mutations in mitochondrial DNA, electron leakage increases and leads to higher ROS production (FIGURE. 2). Sustained mitochondrial ROS generation can damage mitochondrial membranes, lower ATP output, and promote additional oxidative leakage, creating a cycle in which damage fuels further dysfunction (14). This process is closely linked to the development of neurodegenerative diseases, cardiovascular problems, and metabolic disorders.

3.1.2 NADPH Oxidases (NOX Enzymes)

NOX deliberately produces ROS to support immune defense and cell signaling. While essential for microbial killing, excessive or prolonged NOX activity can cause oxidative damage in vascular,

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kidney, and metabolic tissues. NOX2 mediates inflammation-related oxidative bursts, whereas NOX4 is mainly involved in endothelial and renal oxidative stress (15).

3.1.3 Endoplasmic Reticulum Stress

The endoplasmic reticulum regulates protein folding and calcium homeostasis. Disulfide bond formation generates hydrogen peroxide, and accumulation of misfolded proteins activates the unfolded protein response, further increasing ROS. Chronic ER stress is linked to metabolic syndrome, obesity, and type 2 diabetes (16).

3.1.4 Peroxisomes

Peroxisomes break down very-long-chain fatty acids through β-oxidation, and this process produces hydrogen peroxide as a normal by-product. Under typical conditions, catalase inside the peroxisome removes this oxidant. However, when peroxisomes become overloaded or impaired, hydrogen peroxide can escape into the cytoplasm (17). This leakage may increase mitochondrial oxidative stress because of the close functional interaction between the two organelles.

3.1.5 Immune cell activation

Neutrophils and macrophages produce high amounts of reactive oxygen species during respiratory bursts that help eliminate pathogens. Although this response is essential for host defense, long-term or repeated activation, as seen in autoimmune conditions or ongoing inflammation, can cause oxidative damage to nearby tissues (18).

3.2 Exogenous sources

3.2.1 Ultraviolet radiation and ionizing radiation

Ultraviolet (UV) radiation enters the skin and promotes ROS formation through photochemical reactions involving photosensitizing molecules. These reactions generate singlet oxygen and hydroxyl radicals, which contribute to photoaging and increase the risk of skin cancer (19). Ionizing radiation produces a similar effect by causing radiolysis of water, leading to the formation of ROS and RNS that injure DNA and cellular membranes.

3.2.2 Cigarette smoke and air pollution

Cigarette smoke contains very high levels of free radicals and reactive chemicals. When inhaled, these compounds expose lung tissue and the bloodstream to oxidants that damage lipids and proteins. Air pollution, especially fine particulate matter (PM2.5), also triggers inflammatory reactions that increase ROS production in both the respiratory tract and the cardiovascular system (20).

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3.2.3 Alcohol, drugs, and environmental toxicants

Excessive alcohol consumption elevates oxidative burden through microsomal ethanol oxidation and cytochrome P450-dependent ROS production (21). Environmental toxicants such as pesticides, industrial solvents, and heavy metals (e.g., cadmium and lead) also provoke oxidative stress by disrupting mitochondrial function and depleting antioxidants (22).

3.2.4 Diet and lifestyle factors

High-fat diets place extra strain on mitochondria and promote lipid peroxidation. Processed foods add to the oxidative burden because they often contain oxidized lipids formed during high-temperature cooking. Chronic psychological stress also activates the hypothalamic-pituitary-adrenal (HPA) axis, raising cortisol levels and increasing ROS production (23). Low physical activity further contributes by lowering the expression of endogenous antioxidant enzymes.

4. Molecular consequences of oxidative stress

Oxidative stress initiates a range of biochemical and structural changes that interfere with normal cellular activity. The severity of this damage is shaped by the specific reactive species involved, how long cells are exposed, and which cellular compartments are affected (24).

4.1 Lipid peroxidation

Lipid peroxidation is an early and damaging effect of oxidative stress, particularly targeting polyunsaturated fatty acids in cell membranes (25). It begins when reactive species remove a hydrogen atom from a fatty acid, forming lipid radicals that react with oxygen to generate peroxyl radicals, propagating a chain reaction. This process produces reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which can modify proteins and DNA, disrupt signaling, and impair mitochondrial function (26).

4.2 Protein oxidation

Proteins are also major targets of oxidative injury. Reactive species can introduce carbonyl groups, alter disulfide bonds, or even break peptide chains, all of which distort normal protein structure. These changes can lower enzyme activity, impair receptor interactions, weaken structural integrity, and promote abnormal protein aggregation (27).

4.3 DNA and RNA damage

Oxidative stress also affects genetic material. It can modify DNA bases, most notably forming 8-oxo-2'-deoxyguanosine, and can cause both single- and double-strand breaks (28). Mitochondrial DNA is particularly exposed because it lacks histone protection and has limited repair capacity. When this damage accumulates, it can drive cancer development, contribute to mitochondrial disorders, and promote cellular aging (29).

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4.4 Mitochondrial dysfunction

ROS exposure disrupts mitochondrial membrane potential, impairs respiratory chain enzymes, and can open the mitochondrial permeability transition pore, leading to organelle dysfunction. Damaged mitochondria generate additional ROS, creating a feedback loop that amplifies oxidative stress and promotes apoptosis (30).

4.5 Activation of cell death pathways

Excessive oxidative stress triggers different forms of cell death based on its severity. Moderate, persistent stress often induces apoptosis, while severe damage can cause necrosis. Oxidative imbalance also disrupts autophagy, and extensive lipid peroxidation can initiate ferroptosis, an iron-dependent pathway linked to tissue injury and neurodegeneration (31).

5. Antioxidant defense mechanisms

Human physiology depends on an integrated antioxidant defense system that keeps reactive species in check. This network combines enzymatic antioxidants, small-molecule (non-enzymatic) antioxidants, and redox-responsive signaling pathways. Together, they regulate cellular redox balance, limit oxidative injury, and maintain normal physiological function (32).

5.1 Enzymatic antioxidants

Enzymatic antioxidants form the body's primary defense against reactive oxygen species. These enzymes convert unstable oxidants into less reactive products, helping prevent the spread of oxidative reactions that would otherwise damage cellular structures (33).

5.1.1 Superoxide dismutase (SOD)

Superoxide dismutases convert superoxide radicals into hydrogen peroxide, which other antioxidant enzymes then degrade. Humans express three forms: SOD1 (cytosol), SOD2 (mitochondria), and SOD3 (extracellular). SOD2 is especially important, as mitochondria are the main source of superoxide; reduced SOD2 activity increases mitochondrial oxidative stress, leading to energy deficits, neurodegeneration, and cardiomyopathy (34).

5.1.2 Catalase (CAT)

Catalase converts hydrogen peroxide into water and oxygen, preventing its transformation into highly reactive hydroxyl radicals. Located mainly in peroxisomes, reduced catalase activity allows H_2O_2 to accumulate and diffuse into the cytosol, causing oxidative damage in organs like the liver and kidneys (35).

5.1.3 Glutathione Peroxidase (GPx)

Glutathione peroxidases detoxify hydrogen peroxide and lipid peroxides using reduced glutathione (GSH). GPx4 is particularly important for limiting lipid peroxidation and preventing ferroptosis,

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with reduced activity linked to neurodegeneration, ischemia-reperfusion injury, cancer, diabetes, impaired fertility, and cardiovascular disease (36).

5.1.4 Glutathione Reductase (GR)

Glutathione reductase regenerates reduced glutathione (GSH) from GSSG using NADPH, maintaining antioxidant defenses. A shift toward GSSG disrupts redox balance and weakens the cell's ability to counter oxidative stress (37).

5.1.5 Thioredoxin (TRX) and Thioredoxin Reductase (TrxR)

The thioredoxin system plays a major role in maintaining redox-sensitive proteins in their reduced state. Thioredoxin reduces oxidized cysteine residues in proteins, while thioredoxin reductase regenerates reduced TRX using NADPH. Dysregulation of this system contributes to cancer development and inflammatory diseases (38).

5.2 Non-enzymatic antioxidants

Non-enzymatic antioxidants include vitamins, minerals, metabolic compounds, and dietary phytochemicals that directly neutralize ROS or regenerate other antioxidants.

5.2.1 Glutathione (GSH)

Glutathione, the most abundant cellular antioxidant, regulates redox balance, detoxifies hydrogen peroxide and foreign compounds, and maintains protein thiols. Low GSH levels increase susceptibility to oxidative damage, contributing to aging, liver injury, neurodegeneration, and immune dysfunction (39).

5.2.2 Vitamin C (Ascorbic Acid)

Vitamin C is a water-soluble antioxidant that directly scavenges reactive oxygen species and helps restore oxidized vitamin E to its active form. Through these actions, it protects the cytosol, mitochondria, and plasma from oxidative injury. Insufficient dietary intake lowers antioxidant capacity and heightens susceptibility to oxidative stress (40).

5.2.3 Vitamin E (α-Tocopherol)

Vitamin E is a lipid-soluble antioxidant that defends cellular membranes by stopping the propagation of lipid peroxidation reactions. It protects phospholipids and lipoproteins from free-radical damage, preserving membrane stability. Low vitamin E levels increase the likelihood of oxidative injury in lipid-rich tissues (41).

5.2.4 Carotenoids and Flavonoids

Carotenoids like β-carotene and lycopene neutralize singlet oxygen, while flavonoids stabilize reactive species and enhance Nrf2 signaling. Diets rich in colorful fruits and vegetables are linked to lower oxidative stress (42).

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5.2.5 Coenzyme Q10 (Ubiquinone)

CoQ10 supports mitochondrial electron transport and acts as a lipid-soluble antioxidant, stabilizing mitochondria and ATP production. Supplementation can reduce oxidative stress in cardiovascular and metabolic disorders (43).

5.3 Redox-sensitive transcriptional regulation

Cells adapt to oxidative challenges through transcription factors that regulate antioxidant gene expression.

5.3.1 The Nrf2-Keap1 Pathway

Nrf2 (nuclear factor erythroid 2-related factor 2) is the key regulator of the cellular antioxidant response. Normally bound to Keap1 and degraded, Nrf2 is released when oxidative stress oxidizes Keap1 cysteines (FIGURE. 2). It then translocates to the nucleus, binds antioxidant response elements (AREs), and activates genes for detoxification, redox balance, and phase II metabolism (44). Enhancing Nrf2 limits oxidative damage in cardiovascular, metabolic, and neurodegenerative diseases, and can be stimulated by compounds like sulforaphane, curcumin, and synthetic agents.

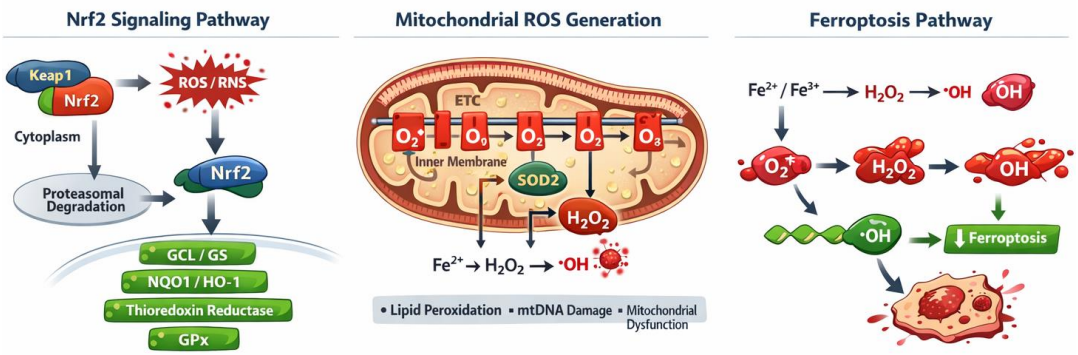

Figure 2. Oxidative stress activates Nrf2, inducing antioxidant genes. Mitochondrial electron leakage produces ROS, causing lipid, DNA, and mitochondrial damage. Ferroptosis occurs when lipid peroxides accumulate due to GPx4/GSH inactivation or iron overload.

5.3.2 NF-κB and AP-1 Pathways

NF-κB and AP-1, although primarily known for roles in inflammation, are also responsive to changes in cellular redox status. Elevated ROS levels activate these transcription factors, leading to increased expression of cytokines and adhesion molecules. When activation becomes persistent, it drives chronic inflammation and contributes to progressive tissue damage (45).

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5.3.3 FOXO transcription factors

FOXO transcription factors regulate genes involved in antioxidant responses, DNA repair, and cellular longevity. Their activity rises during oxidative stress as a compensatory mechanism. Reduced FOXO function has been linked to age-related declines in antioxidant capacity and impaired stress resilience (46).

5.4 Metal-binding and detoxification proteins

Transition metals such as iron and copper can accelerate ROS formation through Fenton-type reactions, making their regulation crucial for maintaining redox balance. Ferritin safely stores iron, transferrin transports it in the bloodstream, and ceruloplasmin binds copper, all limiting the potential for oxidative damage. Disruption of metal homeostasis has been linked to neurodegenerative diseases, cardiovascular dysfunction, and metabolic disorders (47).

5.5 Cross-Talk Among Antioxidant Systems

Antioxidant defenses operate as an interconnected system. Superoxide dismutase converts superoxide into hydrogen peroxide, which is then removed by catalase and glutathione peroxidase. Glutathione helps regenerate oxidized antioxidants and supports continuous detoxification. The transcription factor Nrf2 strengthens this network by increasing the expression of major antioxidant and detoxifying enzymes. Together, these mechanisms stabilize redox balance when metabolic activity or environmental exposure increases oxidant production (48, 49).

Table 1. Summary of oxidative stress mechanisms, antioxidant defenses, disease associations, and therapeutic strategies.

Category	Key Components / Examples	Effects / Mechanisms	Associated Diseases / Conditions	Therapeutic Strategies	References
Sources of ROS/RNS	Endogenous: Mitochondria (ETC leakage), NADPH oxidases (NOX), ER stress, peroxisomes, immune cells Exogenous: UV, ionizing radiation, cigarette smoke, pollutants, alcohol, high-fat diet	Overproduction of ROS/RNS, oxidative damage to biomolecules	Cardiovascular, neurodegenerative, metabolic, liver, kidney, reproductive disorders	Reduce exposure, lifestyle modification, antioxidant intake	13-23, 78

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Molecular Consequences	Lipid peroxidation, protein oxidation, DNA & mt DNA damage, mitochondrial dysfunction, apoptosis, ferroptosis	Disruption of membranes, protein function, genome integrity, organelle dysfunction, cell death	Aging, cancer, neurodegeneration, metabolic syndrome	Antioxidants, ferroptosis inhibitors, mitochondrial support	24-31
Antioxidant Defenses	Enzymatic: SOD, CAT, GPx, GR, Trx/TrxR Non-enzymatic: GSH, vitamins C & E, polyphenols, CoQ10 Redox Signaling: Nrf2-Keap1, FOXO, NF-κB	Scavenge ROS/RNS, regenerate oxidized antioxidants, maintain redox homeostasis	Deficiency contributes to cardiovascular, metabolic, neurological, liver, kidney disorders	Nrf2 activators (sulforaphane, curcumin, resveratrol), glutathione precursors (NAC, SAMe), polyphenols	32-49, 114-115
Disease Associations	Cardiovascular, metabolic/endocrine, neurodegenerative, renal, liver, pulmonary, reproductive, immune/inflammatory disorders, cancer, aging	ROS-induced molecular damage and chronic inflammation	Hypertension, diabetes, Alzheimer's, Parkinson's, CKD, NAFLD, COPD, infertility, autoimmune diseases, cancer	Targeted antioxidant therapy, redox-modulating drugs, lifestyle interventions	50-97, 116-118
Therapeutic Strategies	Nrf2 activation, mitochondrial biogenesis (PGC-1α/AMPK/SIRT1), ferroptosis modulators (GPx4, deferoxamine, ferrostatin-1), anti-inflammatory	Reduce ROS production, enhance endogenous defenses, repair oxidative damage, restore	All diseases associated with oxidative stress	Pharmacological antioxidants, diet/lifestyle interventions, exercise, probiotics, nanoparticles	113-154

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	biologics (anti-TNFα, anti-IL6, JAK/STAT inhibitors), mitochondria-targeted gene therapy, nanomedicine, microbiome modulation	mitochondrial function, modulate inflammation		, gene therapy	

6. Oxidative stress in human disease

Oxidative stress plays a key role in many diseases. Reactive oxygen and nitrogen species can cause damage, worsen existing problems, and increase long-term tissue injury, influencing how quickly a disease develops and how severe it becomes (50). The next sections outline how redox imbalance affects major physiological systems.

6.1 Cardiovascular disorders

The cardiovascular system is especially sensitive to oxidative stress because it continuously faces mechanical strain, lipid oxidation, and low-grade inflammation. Elevated ROS disrupts endothelial signaling, impairs nitric-oxide-mediated vasodilation, and promotes the oxidation of lipoproteins that drive atherosclerotic plaque formation. Persistent oxidative stress also contributes to vascular stiffening, hypertension, and the deterioration of cardiac muscle seen in heart failure **(51)**.

6.1.1 Endothelial Dysfunction

Endothelial cells play a central role in controlling blood vessel tone, platelet behavior, and local

inflammatory activity (52). Under normal conditions, endothelial nitric oxide synthase (eNOS) produces nitric oxide (NO), which supports steady vasodilation and helps maintain vascular balance. When superoxide levels rise, it reacts quickly with NO to form peroxynitrite, lowering the amount of NO available for signaling. As NO declines, vessels lose their ability to relax properly, vascular resistance increases, and platelets become more prone to sticking to the vessel wall (53).

6.1.2 Atherosclerosis

Atherosclerosis is driven in large part by oxidative mechanisms. Low-density lipoprotein (LDL) becomes oxidized within the subendothelial space, generating oxLDL that is readily taken up by macrophage scavenger receptors and promotes the formation of foam cells **(54)**. The presence of oxLDL activates inflammatory signaling, encourages smooth-muscle cell migration and proliferation, and increases the likelihood that plaques will become unstable. Mitochondrial DNA damage within

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endothelial cells adds to this process by weakening mitochondrial respiration and increasing ROS production (**55**). Recent work published between 2022 and 2025 suggests that targeting mitochondrial ROS can slow the earliest stages of plaque development.

6.1.3 Hypertension

ROS activate the angiotensin II pathway, causing vasoconstriction, sodium retention, and vascular smooth muscle growth. NOX1 and NOX2 further increase superoxide production, contributing to arterial stiffness. People with hypertension often show higher oxidative markers such as MDA, F2-isoprostanes, and oxidized proteins (56).

6.1.4 Heart failure

In heart failure, ongoing oxidative stress impairs calcium cycling, damages mitochondria, and triggers apoptosis, leading to cardiac remodeling and fibrosis. ROS also oxidize contractile proteins, reducing heart function. While antioxidant therapies show mixed results, Nrf2-targeted strategies are being explored to limit oxidative damage (57).

6.2 Metabolic and endocrine disorders

Metabolic diseases involve profound redox disruptions due to nutrient excess, chronic inflammation, and endocrine dysfunction.

6.2.1 Diabetes mellitus (Type 1 and Type 2)

Hyperglycemia drives excessive ROS production through several interconnected mechanisms, including mitochondrial overload, activation of protein kinase C, increased flux through the polyol pathway, and the formation of advanced glycation end-products (AGEs). These redox disturbances reduce β-cell survival, impair insulin release, and promote insulin resistance in peripheral tissues. Oxidative injury to DNA and lipids shows a strong association with major diabetic complications such as retinopathy, nephropathy, and neuropathy. Recent findings from 2021-2024 indicate that ferroptosis, an iron-dependent, lipid peroxidation-driven cell death pathway, contributes significantly to diabetic cardiomyopathy and renal dysfunction (**58**).

6.2.2 Obesity and metabolic syndrome

Adipose tissue enlargement creates a chronic inflammatory setting in which resident macrophages generate ROS. At the same time, mitochondrial dysfunction within adipocytes increases oxidant production, contributing to insulin resistance. Pro-inflammatory cytokines such as TNF-α and IL-6, which are elevated in obesity, further stimulate NADPH oxidases and intensify oxidative stress. This redox imbalance interferes with adiponectin signaling, weakening its protective anti-inflammatory and insulin-sensitizing actions (**59**).

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6.2.3 Thyroid Dysfunction

The thyroid gland naturally generates large amounts of hydrogen peroxide during hormone synthesis. Under normal conditions, antioxidant enzymes keep this oxidant in check, but when these defenses are insufficient, excess H_2O_2 can damage thyroid cells and promote autoimmune thyroiditis, hypothyroidism, and Graves' disease. Elevated oxidative stress markers are frequently reported in both hyperthyroid and hypothyroid patients, highlighting the sensitivity of thyroid tissue to redox imbalance (60).

6.3 Neurodegenerative disorders

The brain consumes approximately 20% of the body's oxygen, contains high levels of polyunsaturated fatty acids, and has relatively low antioxidant levels, making it extremely vulnerable to oxidative injury (61).

6.3.1 Alzheimer's disease

Amyloid-β (Aβ) peptides promote oxidative stress by interacting with transition metals and disrupting mitochondrial membranes. These interactions drive lipid peroxidation, protein oxidation, impaired glucose metabolism, and loss of synaptic function. Elevated levels of 4-HNE and protein carbonyls appear early in Alzheimer's disease and are considered key oxidative biomarkers. Mitochondrial fragmentation and reduced cytochrome-c-oxidase activity further intensify oxidative injury and accelerate neuronal dysfunction (62).

6.3.2 Parkinson's disease

Oxidative stress is deeply involved in the loss of dopaminergic neurons. As dopamine breaks down, it forms hydrogen peroxide, and the excess iron in the substantia nigra can react with it to produce even more damaging radicals. Problems in mitochondrial complex I allow superoxide to escape, pushing neurons toward programmed cell death. Oxidative changes also make α-synuclein more likely to clump together, which further harms mitochondria and reinforces the cycle of neuronal injury (63).

6.3.3 Amyotrophic lateral sclerosis (ALS)

SOD1 mutations are linked to inherited ALS. Altered SOD1 fails to clear superoxide, misfolds, and stresses mitochondria and the ER. Activated microglia add ROS and RNS, further damaging motor neurons and accelerating their loss (64).

6.3.4 Stroke and ischemia-reperfusion injury

Oxidative stress is a major factor in the loss of dopaminergic neurons. As dopamine breaks down, it naturally forms hydrogen peroxide, and the buildup of iron in the substantia nigra helps convert this into even more reactive molecules. When mitochondrial complex I is not working properly, extra superoxide escapes and pushes neurons toward apoptosis. Oxidative changes also make α-

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synuclein more likely to clump together, creating a harmful cycle that damages mitochondria and increases nerve cell injury (65).

6.4 Chronic kidney disease (CKD)

The kidneys are especially vulnerable to oxidative stress because they contain many mitochondria, work at a very high energy rate, and constantly filter substances from the blood. In chronic kidney disease, excess ROS from damaged mitochondria and ongoing inflammation gradually injure kidney cells. Over time, this oxidative strain contributes to the steady loss of functioning nephrons (66).

6.4.1 Glomerular damage

In CKD, elevated ROS induce structural changes in the glomerular basement membrane, including thickening, crosslinking of proteins, and increased permeability. These changes contribute to proteinuria, a key indicator of glomerular injury. Oxidation of podocyte proteins disrupts cytoskeletal stability, accelerating podocyte detachment and glomerulosclerosis (66).

6.4.2 Tubular injury

Tubular epithelial cells use a lot of energy, which makes them especially sensitive to oxidative stress. When ROS levels rise, their mitochondria begin to swell, ATP drops, and cell-death pathways such as caspase activation are triggered. Recent work from 2022-2025 also shows that ferroptosis contributes significantly to tubular injury, since this form of cell death depends on iron buildup and lipid damage (67).

6.4.3 Renal fibrosis

ROS and RNS stimulate pathways like TGF-β/Smad that drive the kidneys to produce too much extracellular matrix. Over time, this buildup thickens and scars the tissue, leading to interstitial fibrosis. Once this scarring becomes long-standing, the kidneys lose function, and the damage cannot be reversed (68).

6.4.4 Uremic toxins and oxidative stress

As kidney function declines, waste products like indoxyl sulfate and p-cresol sulfate begin to build up in the blood. These compounds activate NADPH oxidase and lower the activity of natural antioxidant enzymes. Over time, this creates a harmful cycle, more toxins lead to more ROS, and the rising oxidative stress causes even greater toxin accumulation (69).

6.5 Liver diseases

The liver plays a central role in metabolism, detoxification, and lipid regulation, making it particularly susceptible to oxidative insults.

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6.5.1 Non-alcoholic fatty liver disease (NAFLD)

NAFLD develops when too much fat builds up inside liver cells, usually because of obesity or insulin resistance. As the liver tries to burn these fats, the mitochondria become overloaded, and this causes more ROS to leak out. These reactive molecules damage lipids, and the resulting byproducts activate Kupffer cells, setting off inflammation that can progress into NASH (70).

6.5.2 Alcoholic liver disease

Excess alcohol intake boosts the activity of **CYP2E1**, an enzyme in the liver known to generate large amounts of ROS. As CYP2E1 breaks down alcohol, it releases hydrogen peroxide and superoxide, which damage mitochondrial membranes and weaken cellular energy production. Alcohol also makes the gut more permeable, allowing more endotoxin to enter the bloodstream. When this endotoxin reaches the liver, it activates Kupffer cells, leading them to release inflammatory cytokines and additional ROS. Together, these processes worsen liver inflammation and injury (71).

6.5.3 Viral Hepatitis and fibrosis

Chronic hepatitis B and C infections place the liver under constant immune pressure, which increases oxidative stress. The excess ROS can damage DNA and lipids, and they also activate hepatic stellate cells, the main drivers of liver scarring (72). As fibrosis progresses, liver function gradually declines.

6.6 Respiratory disorders

The lungs are directly exposed to environmental oxidants such as cigarette smoke, pollutants, and airborne toxins.

6.6.1 Chronic obstructive pulmonary disease (COPD)

Cigarette smoke contains thousands of radicals, including nitric oxide, semiquinone, and peroxynitrite generators. These compounds harm epithelial cells, inactivate antiproteases, and spoil mucociliary clearance. ROS also stimulates NF-κB, leading to airway remodeling and chronic inflammation (73).

6.6.2 Asthma

Asthma is marked by airway inflammation, tightening of the bronchial muscles, and excess mucus. Immune cells such as eosinophils and neutrophils release ROS, which intensifies inflammation and makes the airways constrict more easily. Oxidative stress can also weaken the effects of corticosteroids by altering the glucocorticoid receptor, making treatment less effective (74).

6.6.3 Pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) develops when fibroblasts grow uncontrollably, and too much connective tissue builds up in the lungs. Reactive oxygen species (ROS) contribute by causing

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epithelial cells to die and by pushing fibroblasts into an overactive, scar-producing state through TGF-β signaling (75). Research also shows that when mitochondria in alveolar type II cells stop working properly, they generate large amounts of ROS, which further drives the disease process.

6.7 Reproductive health and fertility

Oxidative stress exerts profound effects on both male and female reproductive function.

6.7.1 Male fertility

Sperm cells contain large amounts of polyunsaturated fats but have limited antioxidant defenses, making them highly vulnerable to oxidative stress (76). Elevated ROS can damage membrane lipids, impair mitochondrial function in the midpiece, and cause DNA fragmentation, leading to reduced sperm motility and viability (77). Oxidative stress is estimated to contribute to nearly 30-40% of unexplained male infertility cases and is commonly associated with infections, smoking, varicocele, and environmental exposures (78).

6.7.2 Female Fertility

Oxidative stress impairs ovarian function by reducing egg quality, disrupting maturation, and affecting embryo development. Age-related increases in mitochondrial ROS and conditions such as endometriosis further compromise fertility. While low ROS levels support early implantation, excessive ROS can impair implantation and increase miscarriage risk (79).

6.7.3 Pregnancy complications

Several pregnancy-related disorders involve redox imbalance. In preeclampsia, placental hypoxia and re-oxygenation generate excess ROS that damage maternal endothelium, while in gestational diabetes, hyperglycemia-driven ROS disrupt placental nutrient transfer. Oxidative stress is also linked to preterm birth through inflammation-induced weakening of fetal membranes, and emerging evidence suggests antioxidant-based therapies may reduce recurrent pregnancy loss (80).

6.8 Immune and inflammatory disorders

Oxidative stress is closely tied to how the immune system works. Small, controlled amounts of ROS help immune cells kill pathogens, but when ROS levels stay high for too long, they disrupt normal immune signaling. This imbalance can push the immune system toward chronic inflammation and contribute to the development of inflammatory diseases (81).

6.8.1 Autoimmune diseases

Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis show consistently higher levels of oxidative stress. These conditions involve ongoing inflammation, which increases ROS production and places extra pressure on antioxidant defenses (82).

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Rheumatoid Arthritis (RA)

Synovial macrophages and neutrophils produce abundant ROS during inflammation. These oxidants damage chondrocytes and degrade cartilage matrix proteins, accelerating joint destruction. Peroxynitrite-mediated nitration of proteins has been observed in synovial fluid of RA patients, indicating intense nitrosative stress (83).

Systemic Lupus Erythematosus (SLE)

Oxidative damage to DNA and lipids creates altered molecules that the immune system can mistakenly recognize as new antigens, contributing to autoantibody formation in SLE. Mitochondria-derived ROS released during the formation of neutrophil extracellular traps also add to this immune activation and help sustain the autoimmune cycle (84).

Multiple Sclerosis (MS)

Activated microglia in MS produce reactive oxygen and nitrogen species, which injure myelin and oligodendrocytes. This oxidative stress plays a direct role in axonal degeneration and can worsen neurological symptoms (85).

6.8.2 Chronic inflammation

Chronic inflammation involves sustained ROS production, which activates redox-sensitive transcription factors like NF-κB and AP-1. This boosts pro-inflammatory cytokines, increases adhesion molecules, and impairs tissue repair, sustaining a persistent inflammatory state that drives chronic disease (86).

6.8.3 Immune suppression and dysregulation

While low to moderate levels of ROS help initiate normal immune responses, excessive oxidative stress can undermine immunity by damaging T-cell receptors, disrupting antigen presentation, and triggering apoptosis in lymphocytes (87).

6.9 Oxidative stress and cancer Biology

Cancer development is closely linked to redox biology. Reactive oxygen species shape multiple stages of tumorigenesis, including initiation, promotion, and progression, yet excessive ROS can also overwhelm malignant cells and restrict their survival (88).

6.9.1 DNA damage and mutagenesis

Chronic oxidative stress leads to DNA base damage, strand breaks, and epigenetic changes. One common lesion, 8-oxo-dG, can mispair with adenine and generate point mutations that contribute to oncogenesis. When ROS levels remain elevated, DNA repair systems become overwhelmed, allowing mutations to persist and accumulate over time (89).

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6.9.2 Redox regulation of oncogenes and tumor suppressors

ROS regulate key cancer signaling pathways by modulating tumor suppressors and oncogenic cascades. They can alter p53 activity, activate MAPK/ERK to promote proliferation, and oxidatively inactivate PTEN, enhancing PI3K/Akt signaling. Redox balance thus critically shapes tumor behavior (90).

6.9.3 Tumor microenvironment (TME)

The tumor microenvironment exhibits elevated oxidative stress due to hypoxia, inflammatory infiltration, metabolic reprogramming, and increased NADPH oxidase activity, prompting cancer cells to upregulate antioxidant defenses such as Nrf2 signaling. This redox adaptation allows malignant cells to tolerate higher ROS levels than normal cells and contributes to chemotherapy resistance (91).

6.9.4 Ferroptosis in cancer

Ferroptosis is a regulated form of cell death driven by iron-dependent lipid peroxidation. Many cancers evade this process by suppressing ferroptotic pathways. Strategies that promote ferroptosis, such as inhibiting GPx4 or reducing glutathione availability, are being explored as promising therapeutic approaches in oncology (92).

6.10 Aging and longevity

Aging is characterized by progressive physiological decline, much of which is linked to cumulative oxidative damage accumulated over decades.

6.10.1 Mitochondrial Free Radical Theory of Aging

First introduced in the 1950s, the mitochondrial free radical theory of aging proposes that ROS progressively damage mitochondrial DNA, weakening respiratory chain function and increasing ROS leakage in a self-amplifying cycle. Although recent research reveals a more complex picture, mitochondrial oxidative stress continues to be recognized as a key contributor to the biology of aging (93).

6.10.2 Cellular senescence

Senescent cells are characterized by elevated ROS levels, mitochondrial dysfunction, and the development of a senescence-associated secretory phenotype (SASP). The SASP consists of pro-inflammatory cytokines, chemokines, and proteases that further amplify oxidative stress and contribute to tissue dysfunction. As these senescent cells accumulate, they promote age-related diseases and impair normal tissue regeneration (94).

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6.10.3 Telomere attrition

Oxidative stress accelerates telomere loss by preferentially oxidizing the guanine-rich sequences within telomeric DNA. When telomeres become critically short, cells enter senescence or undergo apoptosis, contributing to the broader process of cellular aging (95).

6.10.4 Stem cell exhaustion

Adult stem cells depend on tightly controlled ROS levels. Excess ROS reduces stem cell self-renewal capacity and differentiation potential. This decline contributes to impaired wound healing, reduced immune function, and frailty in older adults (96).

6.10.5 Longevity and antioxidant pathways

Longevity-related pathways such as FOXO, AMPK, and the sirtuins regulate antioxidant gene expression, support mitochondrial biogenesis, and enhance DNA repair capacity. Their activation lowers oxidative burden and is associated with increased lifespan in both animal models and humans (97).

7. Biomarkers and assessment of oxidative stress

Accurately assessing oxidative stress is important for evaluating disease risk, monitoring treatment responses, and studying redox biology. Available biomarkers can indicate ROS or RNS activity, antioxidant defense status, or oxidative damage to cellular components. Because each marker captures only part of the redox landscape, panels of multiple biomarkers are typically used to obtain a more complete assessment.

7.1 Biomarkers of lipid peroxidation

Lipid peroxidation generates a variety of reactive aldehydes and breakdown products useful for assessing oxidative stress (98).

7.1.1 Malondialdehyde (MDA)

MDA is a commonly used marker of lipid peroxidation. It reacts with thiobarbituric acid to produce TBARS, which can be measured in plasma, urine, and tissue samples. Higher MDA levels have been linked to conditions such as cardiovascular disease, diabetes, obesity, and neurodegenerative disorders. Despite its frequent use, the TBARS method is not highly specific, so more accurate techniques like HPLC or LC-MS are often recommended for confirmation (99).

7.1.2 4-Hydroxynonenal (4-HNE)

4-HNE is generated as a result of the peroxidation of omega-6 fatty acids. Once formed, it readily reacts with proteins to create covalent adducts, which can disrupt normal cellular processes. Assessing 4-HNE–protein adducts is considered a more specific and reliable marker of oxidative

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damage compared with TBARS. Elevated levels of 4-HNE have been reported in several pathological conditions, including Alzheimer's disease, alcoholic liver disease, and atherosclerosis (100).

7.1.3 F2-Isoprostanes

F2-isoprostanes are widely regarded as the most reliable biomarkers for assessing lipid peroxidation. They are generated through the non-enzymatic oxidation of arachidonic acid and can be quantified with high accuracy using mass spectrometry. In contrast to MDA, isoprostanes show greater specificity and stability and can be consistently detected in biological samples such as plasma, urine, and tissues (101).

7.2 Biomarkers of protein oxidation

Proteins undergo oxidative modifications that serve as robust indicators of cellular oxidative stress.

7.2.1 Protein carbonyls

Protein carbonylation represents an irreversible form of protein modification that arises either from direct attack by reactive oxygen species or from secondary reactions with lipid-derived aldehydes such as 4-HNE. Levels of protein carbonyls are known to rise in association with aging, diabetes, renal failure, and various inflammatory disorders. These modifications are commonly assessed using DNPH derivatization, followed by analysis through spectrophotometric methods or immunoblotting (102).

7.2.2 Advanced oxidation protein products (AOPPs)

Advanced oxidation protein products (AOPPs) are generated when proteins undergo oxidation by chlorinated oxidants released from neutrophils during inflammatory responses. Their concentrations are notably increased in chronic kidney disease, where higher levels have been shown to correlate with the severity of the condition. In addition to serving as markers of oxidative damage, AOPPs can stimulate NADPH oxidase activity, thereby promoting further oxidative stress (103).

7.2.3 Nitrotyrosine and protein nitration

Nitrotyrosine is produced when tyrosine residues in proteins are modified by peroxynitrite or related reactive nitrogen species. The detection of nitrotyrosine is commonly used as evidence of nitrosative stress and has been associated with a range of pathological conditions, including cardiovascular diseases, sepsis, and impaired immune function (104).

7.3 Biomarkers of DNA and RNA oxidation

Nucleic acids are highly susceptible to oxidative modification, which can lead to mutations and impaired cellular function.

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7.3.1 8-Hydroxy-2-deoxyguanosine (8-oxo-dG)

8-oxo-dG is formed through the oxidative modification of guanine bases in DNA and is among the most commonly applied markers for assessing DNA oxidative damage. Increased levels of urinary 8-oxo-dG have been linked to a higher risk of cancer and are also associated with smoking, exposure to radiation, and various metabolic disorders (105).

7.3.2 DNA strand breaks and comet Assay

The alkaline comet assay is used to detect both single- and double-strand DNA breaks that arise as a result of oxidative stress. This technique has been extensively employed in fields such as toxicology, reproductive biology, and environmental health research (106).

7.3.3 RNA oxidation (8-oxo-G)

RNA is more susceptible to oxidative damage than DNA because of its single-stranded nature. The oxidized nucleoside 8-oxo-G is commonly used as an indicator of RNA oxidation and has been found at increased levels in neurodegenerative disorders, including Alzheimer's disease and amyotrophic lateral sclerosis (107).

7.4 Measurement of antioxidant capacity

Assessing antioxidant defenses is as important as quantifying oxidative damage. These measurements reflect the body's capacity to neutralize ROS/RNS.

7.4.1 Total antioxidant capacity (TAC)

Total antioxidant capacity (TAC) assays measure the combined activity of enzymatic and non-enzymatic antioxidants in blood or tissues, using methods such as FRAP, ORAC, and TEAC. Reduced TAC has been observed in metabolic syndrome, diabetes, cardiovascular diseases, and aging, but these assays do not reveal individual antioxidant levels or activities (108).

7.4.2 Enzymatic antioxidant activity assays

Common assays for antioxidant enzymes assess cellular defense mechanisms: superoxide dismutase activity measures superoxide conversion, catalase assays monitor hydrogen peroxide breakdown, and glutathione peroxidase/reductase assays evaluate glutathione metabolism, collectively revealing impairments in major enzymatic antioxidant pathways (109).

7.4.3 Glutathione levels (GSH/GSSG Ratio)

The balance between reduced and oxidized glutathione, expressed as the GSH/GSSG ratio, is commonly applied to evaluate the cellular redox state. A lower ratio reflects heightened oxidative stress and has been associated with diseases including cancer, liver disorders, aging, and neurodegenerative conditions. Alterations in this ratio can signal a move toward an oxidative

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environment at an early phase, even before clear structural or molecular damage becomes evident (110).

7.5 Redox-sensitive imaging techniques

Modern imaging technologies permit visualization of oxidative stress in real time.

7.5.1 Fluorescent probes

Reactive oxygen species-sensitive probes, including DCFH-DA and MitoSOX, are used to monitor intracellular hydrogen peroxide and superoxide, respectively. These fluorescent probes allow the assessment of oxidative changes in real time within living cells (111).

7.5.2 MRI and PET imaging

Recent advances in imaging have led to the development of MRI contrast agents and PET tracers that are designed to target oxidative stress-related biomarkers, including 8-oxo-dG and peroxynitrite. These imaging tools are being increasingly applied in research on cancer and neurodegenerative diseases to visualize oxidative processes in vivo (112).

8. Therapeutic strategies targeting oxidative stress

Therapeutic strategies against oxidative stress aim to reduce reactive species, enhance antioxidant defenses, or repair oxidative damage. Recent studies (2021-2025) highlight advances in activating endogenous protective pathways, pharmacological antioxidants, and targeted redox-based therapies.

8.1 Enhancing endogenous antioxidant systems

Endogenous antioxidant systems constitute the primary line of cellular defense against oxidative stress, and strengthening these intrinsic pathways represents a more physiologically appropriate therapeutic strategy than relying on direct antioxidant supplementation (113).

8.1.1 Activation of the Nrf2-Keap1 Pathway

Nrf2 is a key regulator of cellular antioxidant defenses, promoting enzymes like those for glutathione synthesis, NQO1, HO-1, thioredoxin reductase, and glutathione peroxidase to protect against oxidative stress. Natural compounds such as sulforaphane, curcumin, resveratrol, and quercetin activate Nrf2, enhancing antioxidant capacity and reducing inflammation (114).

8.1.2 Upregulating mitochondrial biogenesis

Mitochondrial dysfunction drives pathological ROS, while promoting mitochondrial biogenesis, regulated by PGC-1α, AMPK, and SIRT1, enhances energy metabolism, and limits oxidative stress. Strategies activating these pathways, including exercise mimetics, metformin, resveratrol, and NAD^+ boosters, reduce oxidative damage in models of metabolic and neurodegenerative diseases (115).

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8.1.3 Anti-inflammatory regulation

Chronic inflammation is a sustained source of reactive oxygen species, and therefore, limiting inflammatory signaling can indirectly lower oxidative stress. Pharmacological agents that inhibit NF-κB activity, along with cytokine-targeted biologics such as anti-TNF-α therapies, have been shown to confer significant redox-related benefits by reducing inflammation-driven oxidative damage (116).

8.2 Exogenous antioxidant supplementation

Exogenous antioxidants originate from dietary sources, nutritional supplements, or pharmacological compounds. While early clinical studies reported inconsistent outcomes, more recent research suggests that these agents can be beneficial when applied in a targeted and context-specific manner.

8.2.1 Vitamin-based antioxidants

Vitamin C (Ascorbic Acid)

Vitamin C acts as a broad-spectrum antioxidant by neutralizing multiple reactive oxygen species and by restoring vitamin E to its reduced, active form. High-dose vitamin C has been investigated in clinical settings, including sepsis, as an adjunct in cancer therapy, and in the management of cardiovascular disease (117).

Vitamin E (α-Tocopherol)

Vitamin E plays an important role in protecting lipid membranes from oxidative damage. Clinical studies have reported beneficial effects of vitamin E supplementation in conditions such as non-alcoholic fatty liver disease and male infertility (118).

Vitamin A and Carotenoids

Carotenoids, including β-carotene, lutein, and lycopene, act as antioxidants by quenching singlet oxygen and thereby limiting oxidative damage. Their protective effects are particularly relevant for tissues exposed to high oxidative stress, such as the skin and the eyes (119).

8.2.2 Polyphenols and flavonoids

Dietary polyphenols contribute to antioxidant defense by scavenging free radicals and by stimulating the expression of antioxidant-related genes. Compounds such as resveratrol, quercetin, and epigallocatechin gallate (EGCG) from green tea have been associated with protective effects in aging, cardiovascular health, inflammation, viral infections, neurodegeneration, and cancer (120).

8.2.3 Glutathione and related molecules

Direct oral supplementation with glutathione is limited by poor absorption. In contrast, several precursor and supportive compounds can effectively increase endogenous glutathione availability. N-acetylcysteine enhances glutathione synthesis, lipoic acid contributes to the regeneration of glutathione as well as vitamins C and E, and S-adenosylmethionine supports redox-related

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methylation processes. Among these agents, N-acetylcysteine has demonstrated therapeutic benefits in conditions such as respiratory diseases, acetaminophen toxicity, and certain psychiatric disorders (121).

8.2.4 Omega-3 fatty acids

Omega-3 fatty acids exert antioxidant-related effects by reducing inflammatory signaling, supporting mitochondrial function, and lowering markers of oxidative stress in cardiovascular and metabolic diseases (122). In addition, these fatty acids have been shown to enhance the expression of antioxidant-related genes in both hepatic and neural tissues.

8.3 Pharmacological redox-modulating drugs

Pharmaceutical progress increasingly focuses on drugs that impact ROS production or improve antioxidant response pathways.

8.3.1 Mitochondria-targeted antioxidants

Omega-3 fatty acids exert antioxidant-related effects by reducing inflammatory signaling, supporting mitochondrial function, and lowering markers of oxidative stress in cardiovascular and metabolic diseases (123).

8.3.2 NOX enzyme inhibitors

Because NADPH oxidases are major ROS producers in tissues, NOX-specific inhibitors have become promising therapeutic candidates. These drugs reduce vascular inflammation, kidney injury, and fibrosis in experimental models (124).

8.3.3 Ferroptosis modulators

Ferroptosis is an iron-dependent, lipid peroxidation-driven cell death involved in cancer, neurodegeneration, and organ injury. Therapeutic strategies include enhancing GPx4 activity, chelating iron with deferoxamine, and inhibiting lipid peroxidation with agents like ferrostatin-1 (FIGURE. 2). Targeted ferroptosis modulators are emerging in precision redox therapies (125).

8.3.4 Anti-inflammatory and cytokine-targeting drugs

Inflammatory signaling can intensify oxidative stress, and therefore, targeting inflammation provides an indirect means of reducing redox imbalance. Biologic therapies that block interleukin-6, tumor necrosis factor-α, or components of the JAK/STAT pathway are widely used in autoimmune and inflammatory diseases and have been shown to confer secondary benefits by limiting inflammation-driven oxidative damage (126).

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8.4.1 Antioxidant nanoparticles

Several types of nanoparticles display intrinsic antioxidant properties. Cerium oxide nanoparticles can cycle between Ce^{3+} and Ce^{4+} oxidation states, allowing them to scavenge superoxide and hydrogen peroxide. Selenium nanoparticles provide a bioavailable source of selenium that supports glutathione peroxidase activity, while gold nanoparticles can be engineered to carry antioxidant compounds for targeted delivery. Collectively, these nanomaterial-based systems have shown neuroprotective, cardioprotective, and anti-inflammatory effects in experimental studies (127).

8.4.2 Nano-delivery of antioxidant drugs

Nanocarrier systems, including liposomes, polymeric nanoparticles, dendrimers, and micelles, are used to improve drug stability and enable more targeted delivery. For instance, nanoparticles loaded with N-acetylcysteine have been shown to enhance brain penetration and protect neurons from oxidative damage. Formulating curcumin into nanoparticles markedly increases its bioavailability compared with the free compound (128).

8.5 Lifestyle and dietary interventions

Lifestyle factors play a major role in regulating oxidative stress. Evidence shows that a balanced diet, limited exposure to oxidative agents, and healthy daily habits help maintain redox balance.

8.5.1 Diet and antioxidant-rich foods

Diets rich in fruits, vegetables, whole grains, nuts, and legumes supply important antioxidants, polyphenols, and minerals. Key dietary sources include vitamin C from citrus fruits, berries, and peppers; vitamin E from nuts, seeds, and vegetable oils; carotenoids from carrots, tomatoes, and leafy greens; and polyphenols from berries, green tea, and cocoa. Studies published between 2021 and 2024 indicate that Mediterranean and plant-forward dietary patterns are associated with lower levels of oxidative stress markers and inflammation (129).

8.5.2 Reduction of dietary oxidants

Highly processed, fried, or charred foods contain oxidized lipids and advanced glycation end-products (AGEs), which contribute to increased oxidative stress. Limiting the consumption of these foods has been shown to reduce systemic reactive oxygen species production (130).

8.5.3 Alcohol and smoking reduction

Alcohol metabolism generates ROS through CYP2E1, while cigarette smoke introduces thousands of oxidants into the bloodstream. Reducing or eliminating these exposures dramatically decreases oxidative load, improves endothelial function, and enhances antioxidant capacity (131).

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8.6 Exercise and redox biology

Exercise influences oxidative stress in a balanced and generally beneficial manner. Although short bouts of physical activity temporarily increase reactive oxygen species, this brief rise serves as a hormetic signal that enhances antioxidant defenses and supports long-term cellular adaptation (132).

8.6.1 Acute exercise and ROS production

During physical activity, skeletal muscle increases oxygen use and mitochondrial electron transport, which leads to a short-term rise in reactive oxygen species. These molecules function as signaling mediators that promote mitochondrial biogenesis, improve insulin sensitivity, and activate the expression of antioxidant-related genes (133).

8.6.2 Exercise-induced antioxidant adaptation

Regular moderate exercise increases the expression of antioxidant enzymes such as SOD1, SOD2, and GPx, enhances catalase activity, and supports mitochondrial quality control. It also activates the Nrf2 pathway, leading to improved cellular defense capacity and reduced baseline oxidative stress (134).

8.6.3 Overtraining and oxidative damage

Excessive high-intensity training without adequate recovery can increase oxidative damage to muscle proteins, lipids, and mitochondria. This imbalance may contribute to fatigue, impaired performance, and persistent inflammation. Therefore, maintaining a balanced training approach is important for preserving redox homeostasis (135).

8.7 Microbiome and oxidative stress

The gut microbiome plays an important and evolving role in systemic oxidative balance.

8.7.1 Microbiota-derived antioxidants

Gut microbiota generate short-chain fatty acids (SCFAs), vitamins, and polyphenol metabolites that help support the body's antioxidant defenses. SCFAs, including butyrate, can decrease inflammation and enhance mitochondrial efficiency (136).

8.7.2 Dysbiosis and increased ROS

Dysbiosis, an imbalance in gut microbiota, can contribute to oxidative stress through multiple mechanisms, including increased intestinal permeability, translocation of lipopolysaccharides (LPS), activation of immune responses, and ROS production by pathogenic bacteria. This microbial imbalance has been linked to metabolic disorders, neurodegenerative diseases, and inflammatory bowel conditions (137).

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8.7.3 Microbiome-targeting therapeutics

Therapeutic strategies to address gut-related oxidative stress include the use of probiotics to help restore redox balance, prebiotics to promote the growth of beneficial microbes, fecal microbiota transplantation (FMT) for severe dysbiosis, and polyphenol-rich diets that can reshape the microbiota and lower oxidative stress markers. These interventions influence host redox status by modulating gut-derived metabolites (138).

9. Future directions in redox biology (2025 and beyond)

Research on oxidative stress has progressed considerably over the past decade. Future advances are expected from combining molecular redox biology with precision medicine, artificial intelligence, and novel therapeutic technologies. Despite this progress, important gaps remain in our understanding of ROS and RNS dynamics and their contributions to human diseases.

9.1 Precision redox medicine

A key future objective is the personalization of antioxidant therapy. Many current antioxidant approaches have limited success in clinical trials because oxidative stress differs significantly between individuals (139). Precision redox medicine could involve genetic profiling of antioxidant enzyme polymorphisms, mitochondrial genomic screening, assessment of lifestyle and environmental exposures, and the use of redox-based biomarker panels to guide therapy (140). This strategy would enable clinicians to design interventions tailored to each patient's specific redox profile.

9.2 Single-cell redox profiling

Traditional methods for measuring oxidative stress rely on bulk tissue analysis, which can obscure differences between individual cells. Advances such as single-cell transcriptomics and redox proteomics now enable the assessment of ROS levels, antioxidant gene expression, and mitochondrial function at the single-cell level. These technologies are essential for studying diseases with high cellular heterogeneity, including cancer, neurodegenerative conditions, and autoimmune disorders (141).

9.3 Advanced redox imaging

Next-generation imaging techniques are being developed to visualize oxidative stress in vivo. These include ROS-sensitive PET tracers, real-time MRI contrast agents, and two-photon redox ratio imaging. Such tools have the potential to enable clinicians to non-invasively monitor treatment responses and track disease progression (142).

9.4 Redox-based drug development

Targeted modulation of specific oxidants, rather than broad antioxidant therapy, is emerging as a promising strategy. Examples include selective NOX isoform inhibitors, which reduce ROS production in disease models (143); ferroptosis-targeting agents that modulate GPX4 and related pathways to control oxidative stress (144); mitochondrial ROS blockers such as MitoTEMPO and

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MitoQ (145); and redox-activated prodrugs designed to respond to oxidative microenvironments (146). Advances in understanding redox-sensitive signaling proteins, including Keap1 (147), PTEN (48), FOXO (149), and p53, are expected to accelerate drug discovery in this area (150).

9.5 Nanotechnology and gene therapy

Future therapeutic approaches may integrate nanomedicine and gene-editing technologies. Examples include CRISPR-based correction of antioxidant enzyme mutations, such as editing regulators of Nrf2 to enhance antioxidant responses (151); nanoparticles designed to deliver Nrf2 activators to the brain and improve antioxidant delivery across biological barriers (152); and mitochondria-targeted gene therapies aimed at restoring electron transport chain function. These advanced strategies have the potential to reverse oxidative damage rather than merely managing it (153).

9.6 Microbiome-redox axis

Gut microbes influence systemic oxidative balance. Future studies may explore antioxidant-producing probiotics, microbial metabolites affecting mitochondrial ROS, and personalized microbiome interventions, offering potential therapies for metabolic, neurological, and inflammatory diseases (154).

10. General discussion

Oxidative stress links key physiological processes to chronic diseases. While ROS and RNS are essential at normal levels, excessive production causes molecular damage, inflammation, and organ dysfunction. Their complex, localized, and transient signaling makes measurement and therapy challenging. Many non-specific antioxidant trials failed, but targeted antioxidants, pathway-specific modulators, nanomedicine, and lifestyle interventions offer more precise strategies. Effective therapies must also consider interactions with inflammation, metabolism, mitochondria, and genetics.

11. Conclusion

Oxidative stress is central to human physiology, affecting signaling, metabolism, immunity, and aging. When dysregulated, it contributes to cardiovascular, metabolic, neurodegenerative, hepatic, renal, respiratory, and reproductive diseases. Recent research (2021-2025) emphasizes preventing excessive ROS and enhancing endogenous antioxidant defenses.

Effective strategies include redox-targeted drugs, mitochondria-focused therapies, Nrf2 activation, anti-inflammatory treatments, antioxidant-rich diets, structured exercise, microbiome modulation, and nanotechnology-based delivery. Advances in precision redox medicine promise individualized therapies, integrating diagnostics, molecular interventions, and lifestyle measures to reduce oxidative damage and support long-term health.

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