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REVIEW ARTICLE

Oxidative Stress: Molecular Mechanisms, Role in Pathology, and Therapeutic Implications

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Abstract

Oxidative stress is a biological state caused by an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant system's capacity to maintain redox homeostasis. This imbalance can damage vital biomolecules, including proteins, lipids, and DNA, and can initiate cellular signaling pathways involved in metabolic dysfunction, inflammation, and apoptosis. ROS originate from various endogenous sources, such as mitochondria and oxidase enzymes, as well as exogenous factors like pollution, radiation, and heavy metals. This article provides a

comprehensive review of the molecular mechanisms of oxidative stress, covering ROS types, biomolecular damage pathways, and the activation of redox-sensitive signals such as Nrf2, NF-κB, and MAPK. Cellular defense mechanisms against ROS, including enzymatic and non-enzymatic antioxidant systems, are also described. Oxidative stress is implicated in numerous chronic diseases, including neurological disorders, cardiovascular disease, diabetes mellitus, cancer, infertility, liver disease, and aging. Therapeutic strategies studied to counteract oxidative stress include redox-sensitive pharmaceuticals, lifestyle modifications, and antioxidant supplementation. Despite extensive research, antioxidant supplementation in clinical trials has produced inconsistent results, and in some cases, excessive intake has been associated with adverse effects, underscoring the complexity of modulating oxidative stress in therapy. Ongoing issues and debates persist regarding clinical efficacy, the risks of over-supplementation, and the need for personalized treatment approaches. This review also highlights potential future research directions, including the development of tailored interventions based on individual redox status and the use of oxidative stress biomarkers as more precise tools for therapeutic and diagnostic evaluation.

Keywords: Oxidative stress, ROS, Antioxidant, Disease, Redox therapy

Introduction

A biological condition known as oxidative stress is brought on by an imbalance between the body's antioxidant system's capacity to eliminate reactive oxygen species (ROS) and their creation [1]. ROS are chemically reactive molecules that contain oxygen, such as superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), and are characterized by having one or more unpaired electrons, which makes them highly reactive [2]. The body naturally produces this chemical as a byproduct of several metabolic processes, most notably cellular respiration in the mitochondria [3]. ROS function as intracellular signals at low concentrations and are involved in a number of physiological processes, including immunological responses, cell proliferation, signal transduction, and gene regulation [4]. However, an accumulation of reactive species occurs when the quantity of ROS surpasses the body's antioxidant system's capacity, leading to oxidative stress and other types of cell damage [5].

Oxidative stress has drawn a lot of attention in clinical and biological research because of its important involvement in a number of pathological disorders. According to scientific evidence, oxidative stress plays a role in the pathophysiology of several chronic and degenerative diseases, such as cancer [6], diabetes mellitus [7], cardiovascular disease [8], neurodegenerative diseases (like Parkinson's and Alzheimer's) [9], reproductive disorders [10], liver disease [11], and aging itself [12]. In this regard, ROS serve as both causal agents that encourage the destruction of significant macromolecules, including lipids, proteins, and nucleic acids, as well as byproducts

of cellular diseases [13]. Damage to these molecules results in tissue and cellular malfunction, which can hasten the course of a disease. Globally, oxidative stress-related conditions contribute significantly to morbidity and mortality. For example, cardiovascular diseases—many of which have oxidative stress as a key pathological driver—account for approximately 17.9 million deaths per year worldwide, representing 32% of all global deaths, according to the World Health Organization 2023 [14].

According to clinical research, oxidative stress also contributes to the aggravation of the chronic inflammatory process that underlying a number of degenerative and metabolic diseases [15]. ROS can trigger signaling pathways including NF-κB and MAPK, which in turn trigger the production of pro-oxidative enzymes, pro-inflammatory cytokines, and chemokines, all of which worsen tissue damage [16]. However, cells also include an antioxidant system, which includes both enzymatic (such glutathione peroxidase, catalase, and superoxide dismutase) and non-enzymatic (like vitamin C, vitamin E, glutathione, flavonoids, and carotenoids) components [17]. This system works to keep cells' redox balance and stop ROS from building up too much. The Nrf2-Keap1 pathway must be activated in order to respond to oxidative stress by triggering the production of genes that are protective and antioxidant. For readers seeking

additional background on redox biology, recent reviews provide detailed discussions of redox signaling networks, cellular antioxidant regulation, and ROS measurement techniques [18].

Oxidative stress is a key target in the scientific and therapeutic development of intervention and therapy techniques for a number of disorders. The use of antioxidant supplements to reduce the effects of oxidative stress has been extensively researched in clinical studies, animal models, and nutraceutical applications [19-21]. However, depending on the disease type, stage of development, antioxidant form and dosage, and physiological state of the individual, the outcomes of this strategy are frequently variable. Despite extensive research, antioxidant supplementation in clinical trials has produced inconsistent results, and in some cases, excessive intake has been linked to adverse effects, underscoring the complexity of oxidative stress modulation in therapy. This highlights the necessity for a thorough understanding of oxidative stress mechanisms to design more individualized and effective treatment strategies.

This review article aims to comprehensively review the molecular mechanisms of oxidative stress, starting from the sources of ROS formation, types of ROS, to signaling pathways involved in cell damage. Additionally, the antioxidant defense system, the role of oxidative stress in different diseases, and the potential for currently being researched treatments and intervention tactics are discussed. It is anticipated that this article will offer a thorough understanding and serve as a helpful scientific reference in oxidative stress research and clinical practice by including several discoveries from the most recent literature.

Literature search strategy

A comprehensive literature search was conducted using three major scientific databases: PubMed**,** Scopus, and Web of Science, covering the period from January 2000 to March 2024. The objective was to identify peer-reviewed articles related to the molecular mechanisms of oxidative stress, its pathological roles, and therapeutic implications. To maximize retrieval of relevant literature, a combination of controlled vocabulary (Medical Subject Headings, MeSH) and free-text keywords was used, applying Boolean operators “AND” and “OR” to refine the search. The search strategy included terms such as *oxidative stress*, *reactive oxygen species*, *free radicals*, *molecular mechanisms*, *pathology*, *therapeutics*, and *antioxidants*. For example, the PubMed search string applied was: (“oxidative stress” [MeSH Terms] OR “oxidative stress”[All Fields]) AND (“reactive oxygen species”[MeSH Terms] OR “ROS”[All Fields] OR “free radicals”[All Fields]) AND (“molecular mechanisms”[All Fields] OR “pathology”[All Fields] OR “therapeutics”[All Fields] OR “antioxidants”[MeSH Terms]). Equivalent search queries were adapted for Scopus and Web of Science. Additionally, reference lists of included articles were manually screened to identify any relevant studies that were not captured during the initial search.

Studies were selected based on predefined inclusion criteria, which consisted of: (i) peer-reviewed journal articles published between January 2000 and March 2024, (ii) investigations addressing the molecular mechanisms of oxidative stress, its role in specific diseases, or antioxidant defense systems and therapeutic strategies, (iii) publications in English or with available English translations, and (iv) both original research and review articles deemed relevant to the topic. The exclusion criteria included: Conference abstracts without full text, non-English publications without translation, editorials or letters lacking primary or secondary data, and studies unrelated to oxidative stress in the context of molecular mechanisms, pathology, or therapeutic implications.

From each eligible study, key data were extracted, including bibliographic details (author, year, and journal), study type (original research, clinical trial, review), biological context (disease model, cell type, organism), and major findings related to reactive oxygen species, molecular pathways, antioxidant systems, and therapeutic approaches. Quantitative outcomes such as effect sizes, hazard ratios, or relative risk values were recorded when available. The extracted information was synthesized narratively, emphasizing common mechanisms, consensus findings, and points of scientific debate. No formal meta-analysis was performed due to the heterogeneity of study designs and outcome measures.

ROS production sources

The regular metabolic activity of aerobic organisms results in the constant production of ROS in their cells [2]. However, oxidative stress may result from an excessive buildup of ROS if the antioxidant system is unable to counteract it [22]. ROS sources can be broadly divided into two groups: Exogenous (originating from outside environmental stimuli) and endogenous (originating from within the cell or body) [23]. It can be seen in **Figure 1**. These two sources work together to raise the oxidative burden in biological systems, which could eventually compromise the integrity and functionality of cells (**Table 1**).

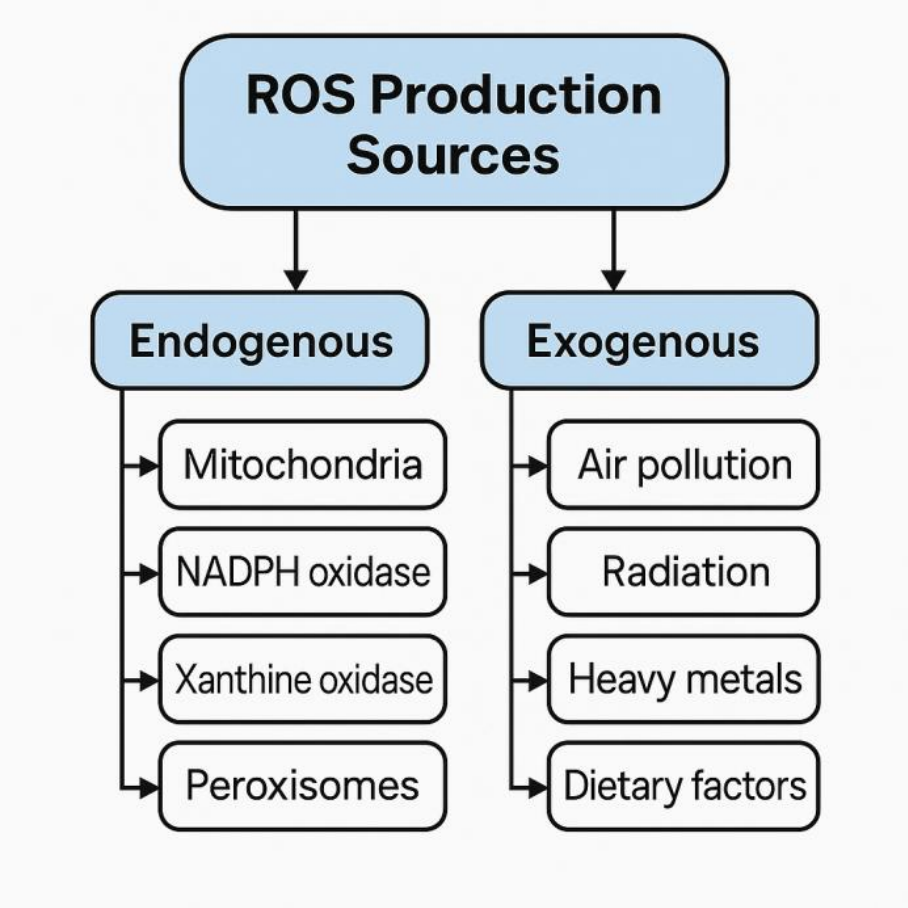

Figure 1 ROS production sources, categorized into endogenous (internal) and exogenous (external) origins.

Table 1 Sources of ROS production.

Category	Source	Examples/Enzymes/Processes	Information
Endogenous	Mitochondria	Electron transport chain (ETC)	Electron leakage from complexes I & III forms superoxide ($O_2^{\bullet-}$)
	NADPH oxidase (NOX)	Neutrophils, macrophages, endothelial cells	Produces $O_2^{\bullet-}$ as part of the immune and inflammatory response
	Xanthine oxidase	Purine catabolism (hypoxanthine → uric acid)	Production of $O_2^{\bullet-}$ and H_2O_2 increases during ischemia-reperfusion
	Peroxisomes	β-oxidation of fatty acids, acyl-CoA oxidase	Produces H_2O_2; neutralized by catalase, but can be excessive during metabolic stress
	Other metabolic	Cytochrome P450, monoamine oxidase, prostaglandin synthase	Produce ROS during certain metabolic processes

Category	Source	Examples/Enzymes/Processes	Information
	enzymes		
Exogenous	Air pollution	O_3, NO_2, PM2.5	Systemic inflammatory and ROS activation; associated with heart and lung disease
	Radiation	UV, X-rays, gamma rays	Ionization of water produces •OH; UV also activates NOX
	Heavy metal	Fe^{2+}, Cu^{2+}, Cd^{2+}, As^{3+}	Induces ROS via Fenton reaction; disrupts antioxidant system
	Pesticide	Paraquat	Disrupt mitochondria, increase ROS production
	Cigarette smoke	>4,000 chemical compounds	Contains pro-oxidants; damages lung and vascular tissue
	Alcohol	Metabolism by ADH and CYP2E1	Increase ROS, especially in the liver
	Bad diet	Diet high in saturated fat, low in antioxidants	Triggers metabolic inflammation and ROS; linked to insulin resistance and premature aging

Endogenous sources

Physiologically, ROS are created as a byproduct of mitochondrial energy metabolism, mostly as a result of electron transport chain (ETC) activity [24]. Water is created during this process when electrons are moved from NADH and $FADH_2$ to molecular oxygen [24]. Superoxide anions ($O_2^{\bullet -}$) are created when a tiny percentage of electrons leak, particularly in complexes I and III of the transport chain [25]. The enzyme superoxide dismutase (SOD) can transform this superoxide into hydrogen peroxide (H_2O_2), which can subsequently undergo further metabolism or, in some cases, undergo the Fenton reaction to produce hydroxyl radicals (•OH) [26]. Increased metabolic activity or dysfunctional mitochondria can produce more ROS and oxidative stress, which can lead to a number of clinical disorders, including cardiomyopathies and neurodegenerative illnesses [27].

The relative contribution of mitochondria compared with NADPH oxidase (NOX) to ROS production varies between diseases: In neurodegenerative diseases such as Alzheimer's and Parkinson's, mitochondrial ROS are dominant due to bioenergetic failure and accumulation of misfolded proteins, whereas in vascular diseases like hypertension, NOX-derived ROS play a larger role by promoting endothelial dysfunction and vascular remodeling [28-30].

Another enzyme involved in purine catabolism, xanthine oxidase, also generates ROS during the conversion of hypoxanthine to xanthine and xanthine to uric acid [31]. The by-products of this reaction include superoxide and H_2O_2. Xanthine oxidase is a key target in the treatment of ischemia and reperfusion injury because its activity rises dramatically during both situations [32].

The peroxisome is another endogenous source; it is a cellular organelle involved in the metabolism of amino acids and the β-oxidation of fatty acids [33]. The production of H_2O_2 occurs in peroxisomes when enzymes such acyl-CoA oxidase are active [34]. The catalase enzyme, which peroxisomes possess to detoxify H_2O_2, can be compromised by high metabolic circumstances, leading to oxidative stress [35]. Furthermore, it is known that a number of enzymes, including prostaglandin synthase, monoamine oxidase, and cytochrome P450, generate ROS while they are active [36].

Exogenous sources

Environmental factors are a significant contributor to the creation of ROS in addition to internal causes [37]. Both directly and by activating inflammatory pathways, exposure to air pollutants like ozone (O_3), nitrogen dioxide (NO_2), and particulate matter (PM 2.5) can increase the generation of ROS [38]. Through systemic oxidative stress processes,

long-term exposure to air pollution has been associated with an increased risk of cardiovascular disease, respiratory disease, and premature aging [39].

Both ionizing (like X-rays and gamma) and non-ionizing (like ultraviolet) radiation contribute to the production of ROS [40]. Radiation can ionize water molecules, resulting in the production of extremely reactive hydroxyl radicals [41]. For instance, NOX enzymes in the skin can be activated by UV radiation, resulting in ROS that cause DNA mutations and raise the risk of skin cancer [42].

The production of ROS can be accelerated by heavy metals like iron (Fe^{2+}), copper (Cu^{2+}), cadmium (Cd^{2+}), and arsenic (As^{3+}) through Fenton and redox processes [43]. These metals can worsen oxidative stress by increasing ROS and inhibiting the action of antioxidant enzymes by substituting necessary cofactors.

Alcohol, cigarette smoke, and pesticides are additional exogenous sources [37]. It is well known that pesticides like paraquat increase the generation of ROS by interfering with mitochondrial activity [44]. Numerous pro-oxidant chemicals included in cigarette smoke harm blood vessels and lung tissue [45]. The enzymes CYP2E1 and alcohol dehydrogenase can enhance the buildup of ROS, particularly in the liver, as a result of alcohol's metabolism [46].

ROS can also rise as a result of a diet heavy in saturated fat and deficient in antioxidants [47]. A diet heavy in fat and glucose triggers metabolic processes that generate too many ROS, resulting in chronic inflammation and insulin resistance [48]. On the other hand, the oxidative load can be decreased by eating a diet high in antioxidant-rich foods like fruits and vegetables [49].

Types of reactive species and their reactive properties

Various reactive chemicals that have a high potential to cause oxidative damage to biological structures accumulate during oxidative stress [1]. These molecules are often separated into 2 major categories: Reactive nitrogen species (RNS) and reactive oxygen species (ROS) (**Table 2**). Even though these molecules are produced normally, excessive levels or deregulation of their activity can upset cellular homeostasis and play a role in a number of pathological diseases.

Table 2 Characteristics and biological effects of reactive oxygen and nitrogen species.

Types of molecules	Group	Chemical properties	Source of formation	Main biological effects	Physiological role	Pathological role
$O_2^{\bullet-}$ (Superoxide)	ROS	Free radicals, moderate reactivity	Mitochondria (ETC), NOX	Precursors of H_2O_2 and $ONOO^-$, mild DNA/protein damage	Small cellular redox signals	Converting to another, more dangerous ROS
H_2O_2 (Hydrogen peroxide)	ROS	Non-radical, stable, easily diffused	SOD, peroxisome	Acts as a signal or precursor of hydroxyl radicals	Redox regulation, protein modification	Increased oxidative stress, precursor of Fenton reaction
•OH (Hydroxyl radical)	ROS	Free radicals are very reactive, short life span	Fenton reaction ($Fe^{2+} + H_2O_2$)	Extensive and non-specific damage to lipids, proteins, and DNA	No physiological role	One of the most damaging ROS, triggering mutations, necrosis
$^1O_2$ (Singlet oxygen)	ROS	Non-radical excitability, highly	Photochemistry (UV)	Lipid peroxidation, membrane damage	No physiological role	Triggers structural damage due to UV radiation

Types of molecules	Group	Chemical properties	Source of formation	Main biological effects	Physiological role	Pathological role
		reactive				
NO• (Nitric oxide)	RNS	Free radicals, high diffusion	Nitric oxide synthase (NOS)	Vasodilation, neurotransmission, immunomodulation	Vascular regulation, nervous system signals	Reaction with $O_2•^-$ forms $ONOO^-$, disrupting mitochondria
$ONOO^-$ (Peroxynitrite)	RNS	Non-radical, highly reactive	$NO• + O_2•^-$	Protein nitration (nitrotyrosine), lipid oxidation, DNA damage	No physiological role	Causes nitro-oxidative stress, multi-target damage

Reactive Oxygen Species (ROS)

ROS are oxygen-derived compounds or molecular fragments that are highly reactive chemically because they contain unpaired electrons [50]. ROS are classified as either non-radicals (containing no unpaired electrons but yet being reactive) or free radicals (having one unpaired electron) [4].

The $O_2•^-$, which is created when an electron is transferred to an oxygen molecule, is one of the most prevalent ROS [29]. Although superoxide is not as reactive as other ROS, it can serve as a precursor to more harmful ROS [51]. Superoxide is changed into H_2O_2 by the action of the enzyme SOD [52]. As a more stable and non-radical chemical that can permeate cell membranes, hydrogen peroxide has the potential to have systemic effects [53]. Despite not being particularly harmful directly, H_2O_2 can react with transition metal ions like Fe^{2+} through the Fenton reaction to create hydroxyl radicals (•OH), which are among the most hazardous and reactive ROS due to their ability to target nearly all biomolecules without discrimination [54].

Furthermore, the O_2 molecule can also exist in an excited form called singlet oxygen ($^1O_2$), which has a different electron configuration than its ground state [55]. Photochemical reactions, particularly when exposed to ultraviolet light, can produce singlet oxygen [56]. This molecule can lead to lipid peroxidation, which compromises the integrity of cell membranes, and it is extremely reactive to double bonds [57]. Singlet oxygen and hydroxyl radicals are extremely reactive, which quickly damages biomolecules like lipids, proteins, and DNA [50].

Reactive Nitrogen Species (RNS)

Reactive nitrogen species (RNS), which are reactive molecules containing nitrogen, are another component of oxidative stress in addition to ROS [37]. This group's primary molecule is nitric oxide (NO•), a free radical generated by the nitric oxide synthase (NOS) enzyme [58]. At the physiological level, NO• plays crucial roles in the immune system, neurotransmission, and vascular control [59]. On the other hand, an oxidative environment with too much NO• can combine with superoxide to generate peroxynitrite ($ONOO^-$) [60]. Peroxynitrite is a very reactive substance that can oxidize lipids, damage DNA, and titrate tyrosine groups in proteins to create nitrotyrosine [61]. RNS can also cause protein nitrosylation, which disrupts vital enzymes and mitochondrial function [62].

ROS and RNS frequently cooperate to cause oxidative damage [36]. For instance, active macrophages in chronic inflammatory circumstances can effectively create peroxynitrite by producing superoxide and NO• at the same time [60]. Nitro-oxidative stress, which results from this, is more harmful than the effects of ROS or RNS alone.

Chemical and biological characteristics

In general, these species' longevity, diffusion capability, and target specificity all affect how reactive they are. Despite their brief lifespan, hydroxyl radicals can do a great deal of harm because of their high reactivity [50]. The redox alteration of protein cysteine residues allows H_2O_2 to act as a signaling molecule and has a longer lifespan [63]. Even though they are produced quickly, singlet oxygen and peroxynitrite

have extremely harmful local effects [1]. The redox state of the cell microenvironment and the availability of transition metal ions both influence this reactivity [64].

Excess ROS and RNS can cause oxidative stress, protein malfunction, genetic mutations, lipid peroxidation, activation of inflammatory pathways, and cell death in pathological settings by upsetting redox equilibrium [65]. As a result, knowing these kinds of reactive species is essential for locating possible therapy targets and creating targeted intervention plans. The types of ROS and their relationship with RNS can be seen in **Figure 2**.

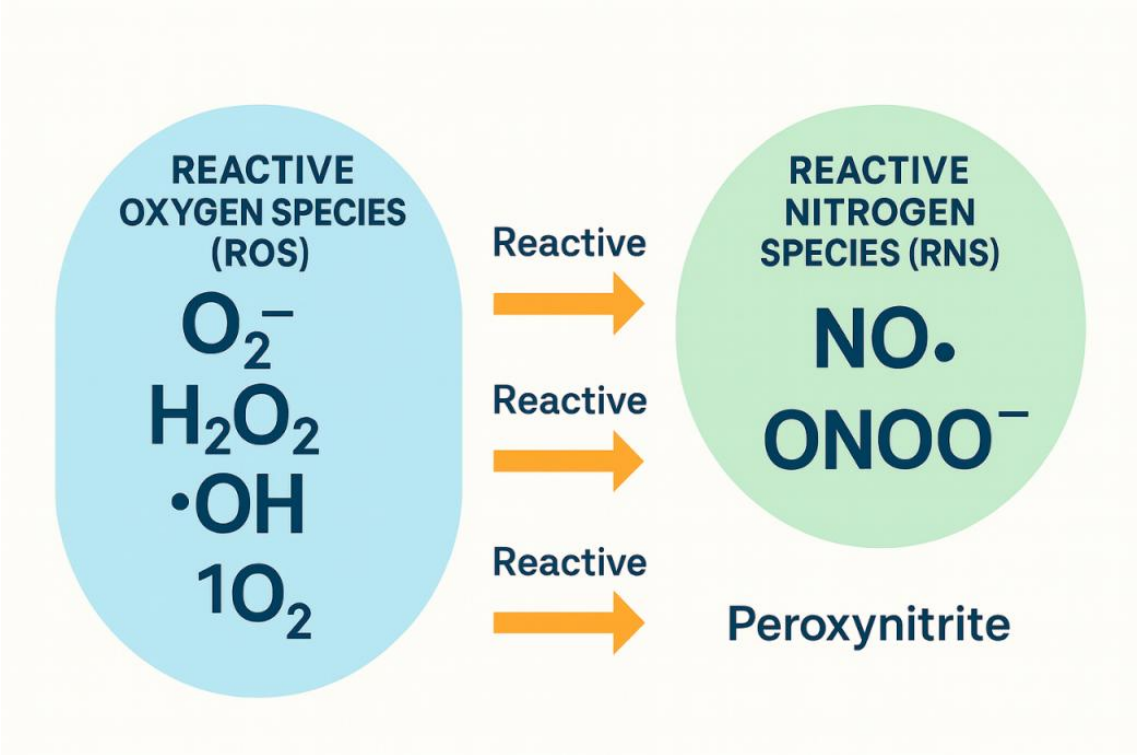

Figure 2 Key reactive oxygen species (ROS) and reactive nitrogen species (RNS), along with their interactions leading to oxidative stress and peroxynitrite formation.

Molecular mechanisms of oxidative stress

Increases in ROS or a reduction in the body's antioxidant system's capabilities cause oxidative stress [66]. ROS are produced by a number of cellular metabolic processes under normal conditions, particularly in the mitochondrial electron transport chain [4]. Complexes I and III release electrons that combine with molecular oxygen to create O_2•$^-$, which SOD subsequently transforms into H_2O_2 [29]. Catalase or glutathione peroxidase can then transform hydrogen peroxide into water [67]. However, hydroxyl radicals (•OH), which are extremely reactive and harmful ROS, will develop if H_2O_2 interacts with metal ions like Fe^{2+} in the Fenton reaction [68].

Numerous biological macromolecules can be attacked by excessive ROS. One of the most important types of harm brought on by hydroxyl radicals is lipid peroxidation [69]. Cell membrane phospholipids' unsaturated fatty acids are harmed by this process, which also produces harmful aldehydes including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) and compromises the fluidity and integrity of the membrane [69]. This substance is reactive and can increase damage by forming covalent connections with DNA and proteins. Furthermore, ROS oxidize protein amino acid residues like cysteine, methionine, and tyrosine, which can alter a protein's structure, enzymatic activity, or cause non-functional proteins to aggregate [70]. The production of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a sign of oxidative DNA damage, indicates that DNA is also a target of ROS

[71]. This may result in excessive activation of DNA repair systems, cell cycle arrest, or genetic alterations.

Excessive exposure to ROS also causes the activation of several cellular signaling pathways involved in inflammation, cell death, and adaptability [72]. The Nrf2-Keap1 pathway, which controls the expression of antioxidant genes, is one of the main adaptive mechanisms [73]. In order to trigger the production of antioxidant genes including SOD, HO-1, and glutathione S-transferase, Nrf2 is liberated from Keap1 and moved to the cell nucleus during oxidative stress [74]. On the other hand, ROS also trigger the NF-κB pathway, which contributes to the inflammatory response by promoting the production of adhesion molecules, chemokines, and proinflammatory cytokines [75]. The regulation of proliferation, differentiation, and apoptosis is influenced by the activation of MAPK (mitogen-activated protein kinase), which includes p38, ERK, and JNK [76]. Even though the PI3K/Akt pathway is typically prosurvival, ROS can also alter it, which, depending on the situation, can change the ratio of cell death to growth [77].

Prolonged oxidative stress can trigger the apoptosis pathway, which is a type of planned cell death [78]. Caspases 9 and 3 are apoptosis executors that are activated when ROS triggers the release of cytochrome c from mitochondria into the cytosol [79]. As a survival strategy, oxidative stress can also trigger autophagy, which is the breakdown and recycling of damaged cellular components, in addition to apoptosis [80]. Nevertheless, in severe circumstances, excessive autophagy may be a factor in type II cell death, also known as autophagic cell death [81]. An illustration of molecular oxidative stress is shown in **Figure 3**.

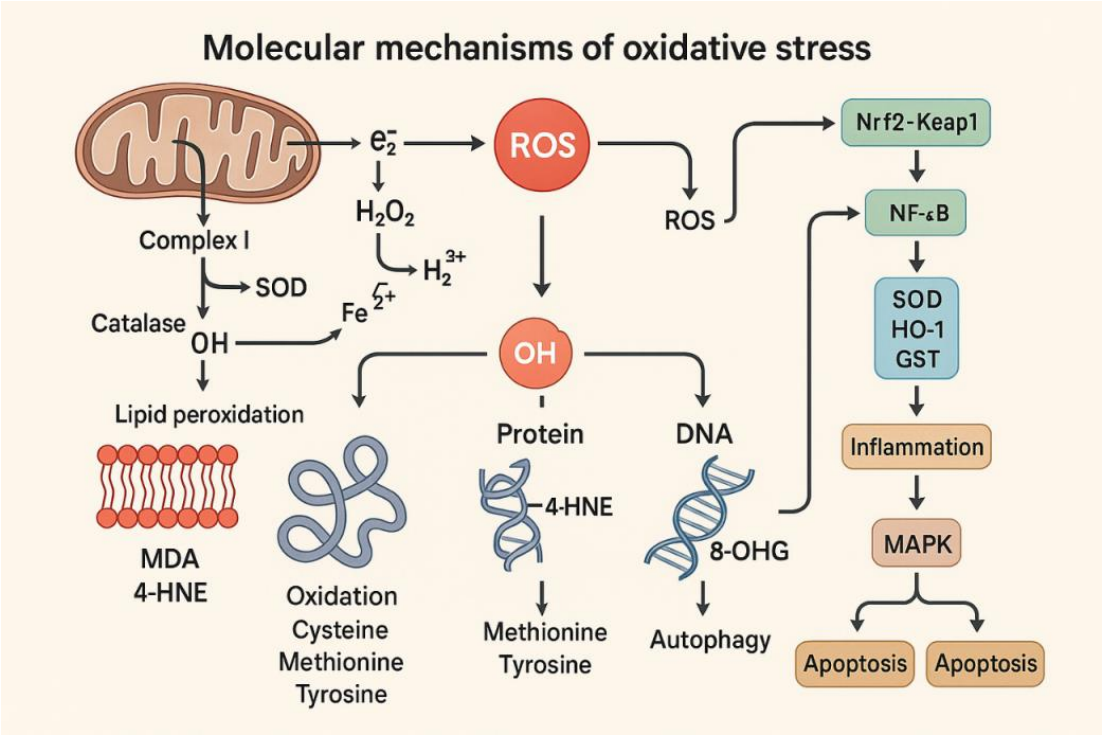

Figure 3 Molecular pathways and cellular targets involved in oxidative stress-induced damage.

Antioxidant system

Cells in aerobic species depend on a sophisticated antioxidant system to preserve redox balance and guard against ROS damage. Enzymatic and non-enzymatic elements of this system cooperate to detoxify ROS and restore oxidized biomolecules [82]. The chemical underpinning of many disease processes, oxidative stress, is brought on by an imbalance between ROS and the antioxidant system's capacity (**Table 3**). Therefore, the presence and management of the antioxidant system is particularly crucial to maintain cellular homeostasis. Recent debates have emerged over whether dietary antioxidants or endogenous antioxidant defenses play a more decisive role in maintaining

redox homeostasis. While epidemiological data support the benefits of diets rich in antioxidant compounds, large randomized controlled trials (RCTs) often fail to show consistent disease-preventive effects from supplementation alone. This discrepancy suggests that endogenous antioxidant enzyme regulation—such as Nrf2-mediated upregulation of SOD, GPx, and catalase—may have a stronger protective role than relying solely on exogenous supplementation. Furthermore, excessive supplementation in individuals with already optimal antioxidant status could disrupt physiological ROS signaling and cause unintended pro-oxidant effects.

Table 3 Cellular antioxidant systems.

Category	Component	Working mechanism	Location/Specifications	Main biological roles
Enzymatic antioxidants	Superoxide dismutase (SOD)	Converting $O_2^{\bullet-}$ to H_2O_2 and O_2	SOD1 (cytoplasm), SOD2 (mitochondrial), SOD3 (extracellular)	First line of defense against superoxide
	Catalase	Decompose H_2O_2 into H_2O and O_2	Peroxisomes	Rapid detoxification of H_2O_2, important in high metabolic tissues
	Glutathione peroxidase (GPx)	Reducing H_2O_2 and lipid peroxides with GSH	Cytoplasm, mitochondria	Protection of cell membranes, preventing lipid peroxidation
	Glutathione reductase (GR)	Reducing GSSG to GSH with NADPH	Cytoplasm	Maintaining the GSH/GSSG ratio for redox homeostasis
Non-enzymatic antioxidants	Glutathione (GSH)	Neutralizes ROS and peroxides; involved in detoxification and S-glutathionylation	Cytoplasm	Major cellular antioxidant; indicator of redox status
	Vitamin C (ascorbic acid)	Neutralizes free radicals; regenerates vitamin E	Intracellular and extracellular fluids	Water-soluble redox protection; maintaining endothelial function
	Vitamin E (α-tocopherol)	Inhibits lipid peroxidation in membranes	Lipid membrane	Protection of membrane phospholipids; synergistic with vitamin C
	Carotenoids (β-carotene, lycopene)	Capturing ROS, especially singlet oxygen	Lipophilic membranes and tissues	Natural lipophilic antioxidant; prevents oxidative damage
	Polyphenols (flavonoids, resveratrol)	ROS/RNS scavenger; modulates antioxidant gene expression	Nucleus, cytoplasm	Redox and anti-inflammatory activity; modulates cell signaling
Genetic regulation	Nrf2-Keap1 pathway	Nrf2 activation triggers antioxidant gene expression via ARE elements	Cytoplasm → Cell nucleus	Long-term adaptive regulation of antioxidants; a potential therapeutic target
	Nrf2 target gene	HO-1, NQO1, SOD1, GPx, xenobiotic detoxification enzymes	Various tissues	Increases cell defense capacity against chronic oxidative stress

Enzymatic antioxidants

The primary defense against ROS is provided by enzymatic antioxidant components, which are made up of 3 primary enzymes: Glutathione peroxidase (GPx), catalase, and SOD.

$O_2•^-$ is dismutated into H_2O_2 and oxygen by the enzyme SOD [26]. Based on their location and cofactors, SOD1 (Cu/Zn-SOD) is found in the cytosol, SOD2 (Mn-SOD) is found in the mitochondria, and SOD3 is found in the extracellular space [83]. It must be broken down right away since the H_2O_2 generated by SOD action is less reactive but still has the potential to be harmful [84].

The enzyme catalase, which is widely distributed in peroxisomes, converts H_2O_2 into oxygen and water [85]. This enzyme is highly effective at lowering H_2O_2 buildup and has a high catalytic capacity, particularly in situations involving acute oxidative stress [35]. Catalase is crucial for detoxifying ROS in organs with high metabolic activity, such the liver [84].

Glutathione peroxidase (GPx) uses reduced glutathione (GSH) as a substrate and contributes to the breakdown of lipid hydroperoxides and H_2O_2 [86]. This enzyme aids in preventing damage to cell membranes and lipid peroxidation [84]. The cellular redox cycle is maintained throughout this process by oxidizing GSH to glutathione disulfide (GSSG), which is subsequently reduced once again by the enzyme glutathione reductase (GR) using NADPH as an electron donor [87].

Non-enzymatic antioxidants

Small molecules known as non-enzymatic antioxidants can directly absorb or neutralize ROS without the need for enzyme activity [88]. A number of non-enzymatic antioxidants, both endogenous and exogenous, are crucial for preserving redox equilibrium.

The main non-enzymatic antioxidant in cells is GSH [89]. GSH is a tripeptide with thiol groups on cysteine residues that can lower lipid peroxides and H_2O_2. It also aids in maintaining protein structure by means of the S-glutathionylation process [90]. One important measure of oxidative stress and redox state in cells is the GSH/GSSG ratio [91].

Ascorbic acid, also known as vitamin C, is a water-soluble antioxidant that efficiently eliminates free radicals from the extracellular space and cytoplasm [92]. It also contributes to endothelial function maintenance and vitamin E renewal [93]. In the meantime, membrane phospholipids are shielded from lipid peroxidation by vitamin E (α-tocopherol), a lipophilic antioxidant [94]. The durability of cell membranes depends on the vitamins C and E working in concert [92].

Furthermore, fruits, vegetables, and medicinal plants include polyphenols (including flavonoids, catechins, and resveratrol) and carotenoids (like beta-carotene and lycopene) that have strong antioxidant activity [95]. These substances have the ability to alter redox signaling pathways and antioxidant gene expression in addition to directly neutralizing ROS [4].

Genetic regulation by the Nrf2-Keap1 pathway

Apart from the actual existence of antioxidant molecules, controlling their expression is equally essential. The nuclear factor erythroid 2-related factor 2–Kelch-like ECH-associated protein 1 (Nrf2-Keap1) pathway is a crucial mechanism in controlling the antioxidant system [96]. In the cytoplasm, Nrf2 attaches itself to Keap1 and is broken down by proteasomes under normal conditions [97]. However, Keap1 changes at its cysteine residues under oxidative stress, which prevents it from marking Nrf2 for destruction [18]. Consequently, Nrf2 builds up and moves into the nucleus, where it attaches itself to target gene promoters' antioxidant response elements (AREs) [98].

Enzymatic antioxidants

The primary defense against ROS is provided by enzymatic antioxidant components, which are made up of 3 primary enzymes: Glutathione peroxidase (GPx), catalase, and SOD.

$O_2•^-$ is dismutated into H_2O_2 and oxygen by the enzyme SOD [26]. Based on their location and cofactors, SOD1 (Cu/Zn-SOD) is found in the cytosol, SOD2 (Mn-SOD) is found in the mitochondria, and SOD3 is found in the extracellular space [83]. It must be broken down right away since the H_2O_2 generated

by SOD action is less reactive but still has the potential to be harmful [84].

The enzyme catalase, which is widely distributed in peroxisomes, converts H_2O_2 into oxygen and water [85]. This enzyme is highly effective at lowering H_2O_2 buildup and has a high catalytic capacity, particularly in situations involving acute oxidative stress [35]. Catalase is crucial for detoxifying ROS in organs with high metabolic activity, such the liver [84].

Glutathione peroxidase (GPx) uses reduced glutathione (GSH) as a substrate and contributes to the breakdown of lipid hydroperoxides and H_2O_2 [86]. This enzyme aids in preventing damage to cell membranes and lipid peroxidation [84]. The cellular redox cycle is maintained throughout this process by oxidizing GSH to glutathione disulfide (GSSG), which is subsequently reduced once again by the enzyme glutathione reductase (GR) using NADPH as an electron donor [87].

Non-enzymatic antioxidants

Small molecules known as non-enzymatic antioxidants can directly absorb or neutralize ROS without the need for enzyme activity [88]. A number of non-enzymatic antioxidants, both endogenous and exogenous, are crucial for preserving redox equilibrium.

The main non-enzymatic antioxidant in cells is GSH [89]. GSH is a tripeptide with thiol groups on cysteine residues that can lower lipid peroxides and H_2O_2. It also aids in maintaining protein structure by means of the S-glutathionylation process [90]. One important measure of oxidative stress and redox state in cells is the GSH/GSSG ratio [91].

Ascorbic acid, also known as vitamin C, is a water-soluble antioxidant that efficiently eliminates free radicals from the extracellular space and cytoplasm [92]. It also contributes to endothelial function maintenance and vitamin E renewal [93]. In the meantime, membrane phospholipids are shielded from lipid peroxidation by vitamin E (α-tocopherol), a lipophilic antioxidant [94]. The durability of cell membranes depends on the vitamins C and E working in concert [92].

Furthermore, fruits, vegetables, and medicinal plants include polyphenols (including flavonoids, catechins, and resveratrol) and carotenoids (like beta-carotene and lycopene) that have strong antioxidant activity [95]. These substances have the ability to alter redox signaling pathways and antioxidant gene expression in addition to directly neutralizing ROS [4].

Genetic regulation by the Nrf2-Keap1 pathway

Apart from the actual existence of antioxidant molecules, controlling their expression is equally essential. The nuclear factor erythroid 2-related factor 2–Kelch-like ECH-associated protein 1 (Nrf2-Keap1) pathway is a crucial mechanism in controlling the antioxidant system [96]. In the cytoplasm, Nrf2 attaches itself to Keap1 and is broken down by proteasomes under normal conditions [97]. However, Keap1 changes at its cysteine residues under oxidative stress, which prevents it from marking Nrf2 for destruction [18]. Consequently, Nrf2 builds up and moves into the nucleus, where it attaches itself to target gene promoters' antioxidant response elements (AREs) [98].

Numerous protective and antioxidant genes, including HO-1 (heme oxygenase-1), NQO1 (NAD(P)H quinone dehydrogenase 1), SOD1, GPx, and other xenobiotic detoxifying enzymes, are expressed when Nrf2 is activated [99]. Nrf2 activity is critical for cellular tolerance to long-term oxidative stress and has become a prominent target in the development of pharmaceutical drugs aimed at improving endogenous redox defenses [100].

The role of oxidative stress in disease pathogenesis

Numerous chronic and degenerative diseases have been found to have oxidative stress as a key pathophysiological mechanism [1]. Excess ROS or an antioxidant system malfunction damages vital biomolecules like proteins, lipids, and DNA, impairing the function of cells and tissues [2]. Redox signaling pathway activation also sets off apoptosis, inflammatory reactions, and epigenetic modifications that promote the onset and spread of disease [101].

Neurodegenerative diseases

Oxidative stress is a primary cause of neuron damage in disorders like Parkinson's and Alzheimer's [102]. Lipid peroxidation and mitochondrial dysfunction are caused by the increased production of

ROS due to β-amyloid buildup in Alzheimer's disease [103]. ROS-induced inflammatory pathway activation worsens synaptic degeneration and initiates neuronal death [14]. In Parkinson's disease, the substantia nigra's breakdown of dopamine results in H_2O_2, which, if not efficiently neutralized by glutathione peroxidase or catalase, forms hydroxyl radicals that harm dopaminergic cells [104]. ROS-induced mitochondrial damage hastens the loss of neurons and the development of motor signs [105].

Cardiovascular disease

An important factor in atherosclerosis, hypertension, and cardiac insufficiency is oxidative stress [106]. ROS convert LDL to ox-LDL, a pro-inflammatory substance that aids in the development of atheromatous plaques in atherosclerosis [107]. Additionally, ROS increases immune cell recruitment and chronic inflammation by activating the expression of inflammatory cytokines and adhesion molecules (ICAM-1, VCAM-1) in vascular endothelium [108]. Endothelial dysfunction is exacerbated in hypertension by NADPH oxidase activation, which raises ROS in vascular smooth muscle cells and causes vasoconstriction, vascular remodeling, and decreased NO bioavailability [109]. Clinical evidence further supports this: In the Heart Outcomes Prevention Evaluation (HOPE) study, high oxidative stress markers correlated with greater incidence of myocardial infarction and cardiovascular death. However, vitamin E supplementation in this trial failed to significantly reduce primary cardiovascular events, suggesting that ROS in vascular disease are not uniformly suppressed by non-specific antioxidants, and that disease-specific sources like NOX may require targeted inhibition.

Diabetes mellitus

Chronic hyperglycemia in type 2 diabetes raises ROS via non-enzymatic protein glycation, the polyol pathway, and protein kinase C (PKC) activation [110]. Reduced insulin release is the result of ROS damaging pancreatic β cells, which are vulnerable to oxidative stress because they do not express antioxidant enzymes [111]. Oxidative stress aggravates insulin resistance at the peripheral level by activating inflammatory pathways (JNK, IKKβ/NF-κB) and interfering with insulin signaling [112]. Diabetes-related microvascular and macrovascular problems, including retinopathy, heart disease, and nephropathy, are also influenced by ROS [113].

Cancer

In carcinogenesis, oxidative stress has 2 aspects: It contributes to the development of cancer by causing DNA mutations, but if ROS levels get to a hazardous level, it can also stop tumor growth [6]. ROS damages DNA by causing strand breaks, adducts, and mutations in tumor suppressor genes like p53 [114]. Furthermore, ROS trigger pro-survival signaling pathways that promote angiogenesis, proliferation, and resistance to apoptosis, including PI3K/Akt, NF-κB, and MAPK [115]. Some cancer cells even alter the antioxidant system, such as by overexpressing glutathione or Nrf2, in order to survive in a very oxidative environment [116].

Infertility

Oxidative stress affects ovarian function and sperm quality in the reproductive system [117]. The sperm plasma membrane, which is rich in unsaturated fatty acids, can be harmed by too many ROS in males, which can result in reduced motility and sperm DNA breakage [118]. This can raise the possibility of genetic abnormalities in the embryo and decrease the success of fertilization. ROS disrupt oocyte maturation, embryo development, and implantation in females [119]. Local inflammation and chronic oxidative stress are also linked to endometriosis and polycystic ovarian syndrome (PCOS) [120].

Liver disease

Oxidative stress can affect the liver, a key metabolic organ, particularly in cases of drug toxicity, viral hepatitis, and non-alcoholic steatohepatitis (NASH) [121]. Hepatocyte fat buildup in NASH raises ROS and mitochondrial β-oxidation, which in turn causes lipid peroxidation and liver cell death [122]. ROS contributes to the activation of hepatic stellate cells in chronic hepatitis, which results in fibrosis [123]. Excessive ROS are also produced by drugs like paracetamol in high dosages through hazardous metabolites (NAPQI), which harm liver cells if glutathione is not quickly neutralized [124].

Aging

According to the free radical theory, oxidative damage builds up over time and has a role in both aging and the deterioration of organ function [125]. ROS that is continuously generated results in enzyme malfunction, mutations in mitochondrial DNA, and a reduction in the ability of cells to repair themselves [126]. Deterioration of endogenous antioxidants like SOD and GSH is another characteristic of aging [12]. This promotes the development of immunosenescence, sarcopenia, cognitive decline, and persistent low-grade inflammation [127].

Interventions against oxidative stress

The prevention and treatment of chronic diseases now heavily emphasize intervention strategies that target redox imbalance since oxidative stress is a crucial factor in many pathogenic processes. These interventions include lifestyle changes that promote the body's natural antioxidant defense mechanisms, more targeted pharmaceutical interventions on redox pathways, and nutraceutical methods through antioxidant supplementation (see **Figure 4**).

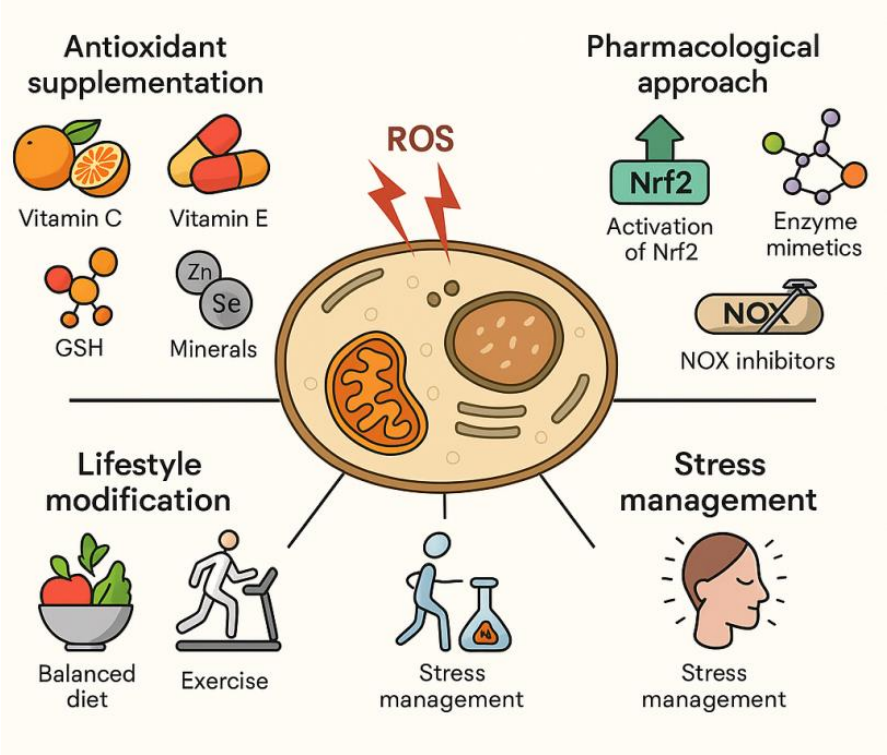

Figure 4 Cellular strategies and interventions to mitigate oxidative stress.

Antioxidant supplementation

The goal of antioxidant supplements is to boost the body's external antioxidant capacity, particularly in cases where endogenous processes are insufficient [128]. One water-soluble antioxidant that works well in absorbing ROS from both intracellular and external environments is vitamin C (ascorbic acid) [129]. This vitamin also helps to maintain the immune system and aids in the regeneration of vitamin E [130]. The lipophilic antioxidant vitamin E (α-tocopherol) has been utilized to treat degenerative and cardiovascular disorders by shielding cell membranes from lipid peroxidation [131].

Although its active form is poorly absorbed orally, GSH can be boosted by precursors like N-acetylcysteine (NAC), which also has hepatoprotective and mucolytic properties [132]. Antioxidant enzymes (GPx and SOD) also require minerals like zinc and selenium as cofactors [133]. Furthermore, natural plant-based substances like quercetin, EGCG, curcumin, and resveratrol have demonstrated potent antioxidant properties and the capacity to alter redox signaling pathways like Nrf2 and NF-κB [134].

Clinical evidence in people is still conflicting, despite the fact that numerous *in vitro* studies have demonstrated the advantages of antioxidant supplementation [135,136]. According to a number of studies, excessive antioxidant intake may interfere with regular redox signaling or be pro-oxidant in specific situations [137-139]. Consequently, the clinical state and redox status of the individual should be taken into consideration when designing these therapies.

One of the key reasons for the failure of antioxidant trials is the non-specificity of the intervention—antioxidants often fail to reach the cellular compartments where ROS are generated (e.g., mitochondria), and in some cases, they may quench beneficial ROS required for vascular tone regulation, immune defense, and metabolic signaling. Moreover, trial designs often overlook baseline antioxidant status, leading to ineffective or even harmful supplementation in individuals who are not truly deficient. Consequently, the clinical state and redox status of the individual should be taken into consideration when designing these therapies.

Pharmacological approach

The goal of pharmacological treatments for oxidative stress is to create more precise and regulated substances that target ROS or redox signaling pathways. A primary tactic is the Nrf2-Keap1 pathway activation, which controls the expression of endogenous antioxidant genes [73]. Dimethyl fumarate (DMF) and bardoxolone methyl are 2 examples of compounds that are known to activate Nrf2 and exhibit therapeutic advantages in chronic kidney disease and neurodegenerative illnesses [140].

Tempol, an analogue of SOD, and ebselen, an analogue of GPx, are examples of chemicals that replicate the activities of natural antioxidant enzymes [141]. Particularly in ischemia-reperfusion injury and stroke, this chemical exhibits promise in lowering ROS-induced tissue damage [142]. The primary ROS-generating enzyme in a number of inflammatory and cardiovascular disorders, NADPH oxidase (NOX), is also the target of several pharmaceutical treatments [143]. Apocynin and VAS2870 are two NOX inhibitors that are being developed as more specific antioxidative treatments [144].

Furthermore, edaravone and other reactive ROS-trapping drugs have shown encouraging results in the treatment of ischemic stroke and amyotrophic lateral sclerosis (ALS) [145]. The synergistic effects of pharmaceutical treatments and anti-inflammatory therapy in lowering systemic oxidative stress are also being investigated [146].

Lifestyle modification

One of the main tenets of long-term oxidative stress management is lifestyle modifications [147]. It has been demonstrated that a balanced diet, especially a Mediterranean diet high in unsaturated fatty acids, phytonutrients, and natural antioxidants, lowers oxidative stress indicators [148]. Frequent intake of whole grains, fruits, vegetables, and olive oil promotes redox equilibrium by lowering chronic inflammation and boosting the activity of endogenous antioxidant enzymes [149].

The body's antioxidant capacity has also been demonstrated to rise with moderate-to-frequent physical activity [150]. Chronic physical activity promotes redox system adaptability by increasing the expression of SOD, GPx, and other Nrf2 target enzymes, even if acute exercise can increase the production of ROS [151]. Additionally, exercise increases insulin sensitivity, mitochondrial activity, and tissue perfusion, all of which lower the risk of diseases linked to oxidative stress [152].

However, psychological stress management is also crucial since long-term stress triggers the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, which both enhance the creation of ROS [153]. Numerous clinical research have demonstrated that relaxation practices including mindfulness, meditation, getting enough sleep, and social support can lower oxidative stress and cortisol levels [154-156].

Challenges and controversies in oxidative stress management

Therapeutic approaches that target oxidative stress still confront several major scientific and clinical obstacles, despite the fact that oxidative stress has been generally acknowledged as a contributing component in a variety of chronic degenerative and inflammatory disorders. The need to create context-based or

customized therapies that consider each patient's unique redox status and underlying disease, the inconsistent results of clinical studies on the use of antioxidants, and the possible pro-oxidative effects of excessive supplementation are some of the most important concerns.

Inconsistency of clinical evidence

The conflicting findings from clinical research on the use of antioxidants, particularly vitamins C, E, beta-carotene, and selenium, in preventing or curing chronic illnesses including diabetes, cancer, and heart disease, are among the primary points of contention [157]. Antioxidants have been shown to protect against oxidative stress in the majority of *in vitro* or animal experimental trials [17,158]. However, the outcomes of clinical trials on humans are frequently unsatisfactory or even indicate neutral to negative effects [84].

For instance, a number of extensive meta-analyses have demonstrated that taking high doses of vitamin E supplements not only does not lower mortality, but is rather linked to a higher chance of dying [159]. In contrast, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) found that beta-carotene supplementation actually raised the incidence of lung cancer in chronic smokers [160]. This demonstrates how theoretical advantages and real biological reactions in complicated individuals differ greatly, and how crucial it is to take into account how antioxidants interact with other elements including environmental exposures, genetic polymorphisms, and nutritional status.

Risks of over-supplementation and pro-oxidative effects

The usage of antioxidants in large dosages or long term can potentially generate pro-oxidative effects, meaning a scenario in which substances that are initially beneficial actually trigger oxidative stress [161]. This phenomenon happens when antioxidants, like vitamins C or E, interfere with redox signals that are necessary for regular cellular function or when they go through repeated redox reactions that result in semioxonium radicals [162].

Furthermore, ROS isn't necessarily bad. ROS are necessary for immunological defense, cell signaling, and proliferation control at the physiological level [163]. As a result, severe and non-specific suppression of ROS can interfere with redox equilibrium and regular biological functions, including wound healing and immune system function [1]. This supports the idea that ROS are crucial signaling molecules that need to be balancedly controlled rather than merely being "enemies" to be eliminated.

The need for personalized therapy

The requirement for context-based or customized therapy is highlighted by the failure of the "one-dose-fits-all" strategy in antioxidant therapy [164]. Not every person experiences oxidative stress to the same degree, and not every illness calls for the same redox strategy. The response to antioxidant supplementation may be influenced by genetic variability (e.g., polymorphisms in the SOD, GPx, or Nrf2 genes), dietary status, gender, age, and medical history [165].

Therefore, it is essential to establish antioxidant demands and the efficacy of therapy by evaluating an individual's redox status early on using biomarkers such the GSH/GSSG ratio, MDA (lipid peroxidation), or 8-OHdG (oxidative DNA damage) [166]. This strategy fosters the development of precision medicine in redox therapy, where the dose, kind of antioxidant, and duration of therapy are selected individually based on laboratory examination and the patient's clinical circumstances.

Future research perspectives

A pathological state known as oxidative stress is defined by an imbalance between the generation of ROS and the antioxidant system's ability to preserve redox equilibrium [84]. Numerous studies have demonstrated that oxidative stress is a key factor in the pathophysiology of a number of chronic illnesses, including as cancer [6], diabetes mellitus, cardiovascular disease [7], neurodegenerative disorders [8], and reproductive dysfunction [10]. The production of ROS, which harm vital biomolecules (DNA, lipids, and proteins), interference with redox signaling pathways, the start of inflammatory pathways, and cell death are some of the molecular mechanisms of oxidative stress [22]. As a result, comprehending these fundamental processes is crucial for developing preventative and treatment plans.

Interventions against oxidative stress have expanded along with the advancement of biomedical science. These include lifestyle changes, pharmaceutical strategies that target redox signaling pathways (such Nrf2-Keap1), and nutraceutical antioxidant supplements [167]. Clinical research on the efficacy of these therapies, however, has produced a wide range of findings [168]. The potential pro-oxidative consequences of prolonged supplementation, dose mismatch to individual redox status, and the complexity of ROS's role as vital physiological signaling molecules are some of the novel issues this presents. As a result, therapeutic strategies for oxidative stress must take into account factors including dose, target specificity, and customization according to each person's unique redox profile [169].

Nonetheless, additional research is required to fill in a variety of information gaps. One of these is the difficulty in finding precise and sensitive oxidative stress indicators for early identification, tracking the course of the disease, and assessing the effectiveness of treatment [170]. Furthermore, more research is still required to fully comprehend how ROS, the immune system, and epigenetics interact, particularly in the setting of chronic illnesses and multifactorial disorders. More focus must be placed on developing treatments that specifically target mitochondria because of their roles as a source of ROS and a regulator of cellular metabolism [171].

Future research should concentrate on creating a precision redox medicine strategy, which involves integrating proteomic, metabolomic, and genomic data to create medication that is customized to a patient's oxidative status in order to address these issues. Furthermore, further research must be done on novel natural and artificial bioactive substances that have the capacity to inhibit oxidative stress-induced pathogenic pathways, control the expression of protective genes, and have direct antioxidant effects. The best dosage parameters, the best time to administer medication, and the effects of lifestyle and environmental factors must all be taken into account in translational studies from *in vitro* and animal research to human clinical trials.

Conslusions

The biological state known as oxidative stress is brought on by an imbalance between the body's antioxidant system's capacity to neutralize reactive oxygen species (ROS) and its creation. Excessive ROS can harm vital biomolecules such as proteins, lipids, and DNA, leading to cell and tissue dysfunction. This dysfunction contributes to the pathophysiology of various chronic and degenerative diseases, including cancer, diabetes, cardiovascular disease, neurodegenerative disorders, and aging. By promoting chronic inflammation, ROS-activated signaling pathways such as NF-κB and MAPK further exacerbate these conditions. Although the body possesses both enzymatic and non-enzymatic antioxidant defense systems, severe oxidative stress can overwhelm their capabilities. Consequently, biomedical research has increasingly focused on therapeutic strategies aimed at alleviating oxidative stress, either by activating protective pathways like Nrf2-Keap1 or through antioxidant supplementation. However, numerous factors influence the efficacy of these interventions, and clinical outcomes remain inconsistent.

Future research should therefore prioritize the development of selective ROS pathway inhibitors—such as NOX isoform-specific blockers or mitochondrial-targeted antioxidants—to preserve beneficial ROS signaling while suppressing pathological sources; the identification of reliable oxidative stress biomarkers, including real-time redox imaging, plasma 8-OHdG, and protein carbonylation profiles, for early disease detection and therapy monitoring; the advancement of precision redox medicine by integrating genomic, metabolomic, and proteomic profiling to tailor antioxidant strategies to individual redox phenotypes; the exploration of combined interventions involving dietary modification, physical activity, and pharmacological modulation rather than relying on single-agent antioxidant therapy; and the investigation of epigenetic regulation of redox homeostasis to design long-term interventions that can reprogram cellular antioxidant capacity.

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Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI tools were used in the writing or preparation of this manuscript.

CRediT Author Statement

EM, ARK, RW, and AA drafted the manuscript. **RD, IM, SM, MS, and BWKW** revised and edited the manuscripts. **RZA, AOA, BPP, IM, and DAAK** participated in the preparation and critical checking of the manuscript. **ANMA, WY, MN, and SW** edited the references. All authors read and approved the final manuscript draft.

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