Title: Oxidative Stress and Antioxidant Therapeutic Mechanisms

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Abstract

Oxidative stress is now understood as a disturbance in the cellular redox balance, involving the accumulation of reactive oxygen, nitrogen, and other reactive species beyond the capacity of antioxidant defenses, with effects that range from essential redox signaling to harmful oxidative damage. Reactive oxygen and nitrogen species are generated from both endogenous metabolic processes and exogenous environmental factors. While controlled levels of oxidative stress contribute to cellular signaling and homeostasis, excessive oxidative damage can lead to pathological conditions, including cardiovascular diseases, diabetes, neurodegenerative disorders, inflammatory conditions, and cancer. To counteract oxidative damage, body employs a complex antioxidant defense system, comprising endogenous enzymatic and non-enzymatic mechanisms, as well as exogenous dietary antioxidants. Therefore, understanding the regulatory pathways and mechanisms of antioxidants is essential for exploring their role in disease prevention, aging, and immune function. This review provides a comprehensive analysis of oxidative stress, its impact on cellular function, and its involvement in disease pathogenesis. Furthermore, it discusses current therapeutic intervention mechanisms, including dietary strategies, pharmacological antioxidants, and clinical trials evaluating antioxidant efficacy. Finally, emerging research directions, such as novel antioxidant compounds, gene therapy, and personalized antioxidant treatments, are highlighted as potential avenues for future exploration.

Keywords: Oxidative stress, antioxidants, reactive oxygen species, disease pathogenesis, therapeutic targets.

List of abbreviations

4-HNE, 4-hydroxynonenal; ACOX, acyl-CoA oxidase; AD, Alzheimer's disease; AGEs, advanced glycation end-products; ALS, amyotrophic lateral sclerosis; AP-1, ctivator protein-1; APOE, apolipoprotein E; ARE, antioxidant response element; Aβ, amyloid-beta; CAT, catalases; CoQ10, coenzyme Q10; CVDs, Cardiovascular diseases; DAMPs, damage-associated molecular patterns; DAO, d-amino acid oxidase; DTDH, dynamic thiol/disulfide homeostasis; EMT, epithelial-mesenchymal transition; EPR, electron paramagnetic resonance; ER, endoplasmic reticulum; ERO1, ER oxidoreductin 1; ETC, electron transport chain; FC, flow cytometry; FDA, Food and Drug Administration; FSP1, ferroptosis inhibitory protein 1; GCL, glutamate-cysteine ligase; GPx, glutathione peroxidases; GR, glutathione reductase; GSH, glutathione; GSSG, glutathione disulfide; IBD, inflammatory bowel disease; IDF, International Diabetes Federation; IL-6, interleukin-6; Keap1, Kelch-like ECH-associated protein 1; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; MDA, Malondialdehyde; MPO, myeloperoxidase; MPT, mitochondrial permeability transition; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κ light chain-enhancer of activated B cells; NOS, nitric oxide synthase; Nox, NADPH oxidase; NRF2, nuclear factor erythroid 2-related factor 2; OxLDL, oxidized-LDL; PAOX, polyamine oxidase; PARP-1, poly (ADP-ribose) polymerase-1; PD, Parkinson's disease; PDI, Protein disulfide isomerase; PHD, prolyl hydroxylase domain; PHGPx, phospholipid hydroperoxidase glutathione peroxidase; Prx, peroxiredoxins; PUFAs, polyunsaturated fatty acids; RA, rheumatoid arthritis; RBS, reactive bromine species; RCS, reactive chlorine species; RCTs, randomized clinical trials; RNS, reactive nitrogen species; ROS, reactive oxygen species; RS, reactive species; RSeS, reactive selenium species; RSS, reactive sulfur species; SLE, systemic lupus erythematosus; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; Tregs, regulatory T cells; Trx,

thioredoxin; TrxR, thioredoxin reductase; UV, ultraviolet; WGCNA, weighted gene co-expression network analysis; XO, xanthine oxidase

Contents

1 Introduction

Oxidative stress plays a crucial role in cellular physiology, influencing both normal biological processes and disease pathogenesis (Afrose, Alfonso-Sánchez, & McClements, 2025; Gorrini, Harris, & Mak, 2013; Hybertson, Gao, Bose, & McCord, 2011; Kimball, Johnson, & Carlson, 2021; van der Pol, van Gilst, Voors, & van der Meer, 2019). It arises from an imbalance between reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates using antioxidant systems (Brieger, Schiavone, Miller, & Krause, 2012). While ROS serves essential signaling functions at physiological levels, excessive accumulation leads to oxidative damage, impacting lipids, proteins, and DNA. This damage has been implicated in various chronic diseases, including cardiovascular diseases, neurodegenerative disorders, and cancer.

To counteract oxidative stress, biological systems have evolved intricate antioxidant defense mechanisms. Antioxidants are molecules that neutralize ROS, preventing cellular damage. They are broadly classified into enzymatic antioxidants, such as superoxide dismutase (SOD),

catalases (CAT), glutathione peroxidases (GPx), and peroxiredoxins (Prx), and non-enzymatic antioxidants, including vitamins (e.g., vitamin C and vitamin E), glutathione (GSH), and coenzyme Q10 (CoQ10) (Gulcin, 2025). The study of antioxidants has a long and rich history, marked by significant discoveries that have shaped our understanding of redox biology and therapeutic strategies for oxidative stress-related diseases. Figure 1 provides a historical timeline of key milestones in antioxidant research, showcasing landmark discoveries such as the identification of CAT in 1900, the discovery of key antioxidant vitamins (A, C, and E), and the characterization of essential antioxidant enzymes like SOD, GPx, and Prx. These milestones have provided fundamental insights into the mechanisms of oxidative stress and antioxidant defense, paving the way for current and future research (Fig. 1).

While many insights into the biological effects of antioxidants have been derived from *in vitro* and animal studies, translation to human health requires evidence from well-designed clinical trials. To address this, we discuss key clinical trial findings in a later section of this review, providing an integrated perspective from basic research to clinical applications.

2 Overview of oxidative stress

2.1 Reactive species

ROS are a diverse group of reactive molecules derived from molecular oxygen and represent a key subset of reactive species (RS). They are produced through redox reactions or electronic excitation and exhibit higher reactivity than molecular oxygen (O_2). Intracellular ROS play a critical role in redox signaling and post-translational modifications, making them significant indicators of oxidative stress (Matsui, et al., 2020; Helmut Sies, Berndt, & Jones, 2017). Beyond ROS, other RS contribute to intracellular oxidative signaling and stress, including reactive nitrogen species (RNS), reactive sulfur species (RSS), reactive chlorine species (RCS), reactive

bromine species (RBS), and reactive selenium species (RSeS) (Fig. 2). It is important to recognize that these terms serve as general categories, as the identification of individual RS compounds remains challenging (Halliwell & Gutteridge, 2015; Helmut Sies, 2015, 2020).

Some RS exist as free radicals, characterized by one or more unpaired electrons. Examples include superoxide anion ($•O_2^-$), hydroxyl radical (•OH), carbonate radical ($CO_3•^-$), carbon dioxide radical ($CO_2•^-$), peroxyl radical (ROO•), and alkoxyl radical (RO•) in ROS (Halliwell, 2006); nitric oxide (NO•) and nitrogen dioxide ($NO_2•$) in RNS; sulfhydryl radical (HS•), thiyl radical (RS•), and persulfide radical (RSS•) in RSS (Iciek, Bilska-Wilkosz, Kozdrowicki, & G órny, 2022; Lau & Pluth, 2019); chlorine atom (Cl•) and dichlorine radical ($Cl_2•^-$) in RCS (Lei, Lei, Westerhoff, Zhang, & Yang, 2021); atomic bromine (Br•) and dibromine radical ($Br_2•^-$) in RBS (Guo, et al., 2023). Non-radical RS include hydrogen peroxide (H_2O_2), organic hydroperoxide (ROOH), singlet oxygen ($^1O_2$), ozone (O_3), hypobromous acid (HOBr), and hypochlorous acid (HOCl) in ROS (Phaniendra, Jestadi, & Periyasamy, 2015); nitrate (NO_3^-), nitrite (NO_2^-), nitroxyl anion (NO^-), peroxynitrite ($ONOO^-$), and nitrosoperoxycarbonate ($ONOOCO_2^-$) in RNS, along with various hypohalites, RSS, and RSeS (Gilbert, Newton, Hettiaratchi, & Pluth, 2022).

The reactivity and stability of RS vary considerably. Among them, the hydroxyl radical (•OH) has the highest reactivity, allowing it to rapidly interact with a broad range of biomolecules. In contrast, hydrogen peroxide (H_2O_2) is relatively stable. However, when H_2O_2 interacts with specific cysteine residues in proteins, forming sulfonic acid, the reaction rate constant can increase significantly. Other species, including nitrite (NO_2^-), nitrate (NO_3^-), and ozone (O_3), demonstrate intermediate reactivity levels (Halliwell & Gutteridge, 2015).

Although initially regarded as harmful byproducts of mitochondrial respiration, research over the past five decades has uncovered the functional roles of RS in cellular processes. In particular, ROS function as crucial signaling molecules that regulate a variety of pathways and play an essential role in immunology. In neutrophils, ROS burst products are instrumental in the eradication of invading microorganisms (Dahlgren & Karlsson, 1999). Despite extensive research on this function, it remains a topic of ongoing debate and may not be fully explored. This topic will be discussed in more detail in the following section.

2.2 Sources of oxidative stress

Similar to pH, the redox state within a cell maintains a dynamic balance. However, this balance is inherently imperfect, as cells are constantly exposed to RS, which often act as oxidants and lead to oxidative stress. These oxidants can originate from both exogenous and endogenous sources.

Exogenous sources include drugs, air pollutants, toxicants, pro-oxidized diets, ultraviolet (UV) light, photosensitizers, and ionizing radiation (Davies, 2016) (Fig. 2). On the other hand, intracellular oxidants primarily arise from two major endogenous sources. The first is the mitochondrial electron transport chain (ETC) during aerobic respiration (Murphy, 2009). Within the ETC, complexes I (NADH: ubiquinone oxidoreductase) and III (cytochrome bc1 complex; ubiquinol: cytochrome c oxidoreductase) are the main producers of superoxide anion ($\bullet O_2^-$) and H_2O_2. These reactive species are released into the mitochondrial matrix and intermembrane space, contributing to distinct biological functions (Brand, 2016; Murphy, 2009). The second key source is the family of transmembrane NADPH oxidases (Noxs) (Bromberg & Pick, 1984; Magnani, et al., 2017). This family comprises seven members (Nox1, Nox2, Nox3, Nox4, Nox5, Duox1, and Duox2), each localized in different subcellular compartments and

capable of locally generating oxidants. These enzymes transfer electrons across biological membranes, reducing oxygen to $\bullet O_2^-$. Superoxide anion is rapidly converted into H_2O_2 via spontaneous dismutation or enzymatic reactions catalyzed by mitochondrial and cytosolic superoxide dismutases (SODs). H_2O_2 can then react with transition metals, such as iron(II) sulfate in the Fenton reaction, producing highly reactive hydroxyl radicals (•OH) that damage DNA, lipids, and other biomolecules (Imlay, Chin, & Linn, 1988).

Other organelles and enzymes also contribute to intracellular oxidant production, notably the endoplasmic reticulum (ER), peroxisomes, and SOD enzymes (SOD1-SOD3) (Antonenkov, Grunau, Ohlmeier, & Hiltunen, 2010; Helmut Sies & Jones, 2020; Y. Wang, Branicky, Noë, & Hekimi, 2018). In the ER, oxidative protein folding generates ROS as a byproduct. Protein disulfide isomerase (PDI) catalyzes the formation of disulfide bonds in substrate proteins, while ER oxidoreductin 1 (ERO1) reoxidizes the CXXC catalytic motifs of PDI by transferring electrons from reduced thiols to $\bullet O_2$, leading to H_2O_2 production (Konno, Melo, Chambers, & Avezov, 2021). ER stress is also linked to increased ROS levels (Bhandary, Marahatta, Kim, & Chae, 2012). Peroxisomes contribute to oxidant generation through various enzymes, including acyl-CoA oxidases (ACOX1-ACOX3), polyamine oxidase (PAOX), and d-amino acid oxidase (DAO), which produce H_2O_2, $\bullet O_2^-$, or nitric oxide (NO•) as metabolic byproducts (Antonenkov, et al., 2010; Fransen, Nordgren, Wang, & Apanasets, 2012). Additionally, SOD enzymes catalyze the conversion of $\bullet O_2^-$ into H_2O_2, serving as crucial components of the intracellular antioxidant defense system (Fridovich, 1997).

2.3 Impact of oxidative stress

Oxidative stress arises from an imbalance between oxidants and antioxidants within cells. This imbalance is bidirectional, as different oxidant concentrations lead to varying degrees of

oxidative stress. At physiological levels (low concentrations), oxidants function as signaling molecules with specific targets, playing essential roles in redox signaling. This type of oxidative eustress is crucial for fundamental biological processes such as cell proliferation, growth, differentiation, stress adaptation, and immune responses (Hong, Boiti, Vallone, & Foulkes, 2024). In contrast, excessive oxidant levels result in oxidative distress, causing irreversible damage to non-specific biomacromolecules, impairing their functions, and contributing to pathological conditions such as inflammation and, ultimately, cell death (Helmut Sies, 2019; Helmut Sies, et al., 2022). Understanding the dual role of ROS, both as regulatory molecules and potential sources of cellular damage, is vital for unraveling the complex interplay between cellular metabolism, oxidative stress, and the regulation of biological processes.

2.3.1 Intracellular targets

Oxidative stress influences multiple signaling pathways that regulate cell survival, metabolism, and stress responses, with significant cross-talk and mutual regulation among these pathways (Fig. 3). The NRF2 (nuclear factor erythroid 2-related factor 2) pathway is a primary defense mechanism against oxidative stress. Under basal conditions, NRF2 is sequestered by Keap1 (Kelch-like ECH-associated protein 1) and targeted for degradation. However, ROS oxidizes critical cysteine residues in Keap1, leading to NRF2 stabilization and nuclear translocation, where it binds to sMaf and activates antioxidant gene expression. The NF-κB pathway, on the other hand, is closely linked to inflammatory responses. ROS activate IKK, leading to the phosphorylation and degradation of IκB, which allows NF-κB to translocate to the nucleus and promote the expression of immune and survival-related genes (Gloire, Legrand-Poels, & Piette, 2006; S. Mitchell, Vargas, & Hoffmann, 2016; Schröfelbauer, Polley, Behar, Ghosh, & Hoffmann, 2012; Zandi, Rothwarf, Delhase, Hayakawa, & Karin, 1997). The HIF-1α pathway is also sensitive to oxidative stress, as ROS inhibit prolyl hydroxylase domain (PHD) enzymes,

stabilizing HIF-1α and enhancing the expression of hypoxia-responsive genes (Appelhoff, et al., 2004; P. Lee, Chandel, & Simon, 2020; Pouysségur & Mechta-Grigoriou, 2006). Additionally, the AMPK and FoxO pathways function as metabolic sensors, activated by ROS-induced energy stress, and contribute to antioxidant defenses by promoting mitochondrial biogenesis and stress adaptation (Dansen, et al., 2009; Eijkelenboom & Burgering, 2013; Emerling, et al., 2009; Hinchy, et al., 2018; Klotz & Steinbrenner, 2017; Soh, Hardy, & Zur Nieden, 2021). The AP-1 pathway, activated via MAPKs in response to oxidative stimuli, plays a role in regulating cell proliferation, differentiation, and apoptosis (Engelberg, Klein, Martinetto, Struhl, & Karin, 1994; Hong, et al., 2024). Furthermore, p53 acts as a redox-sensitive transcription factor, responding to oxidative stress by modulating DNA repair, apoptosis, and antioxidant gene expression (Abbas, et al., 2010; B. Liu, Chen, & St Clair, 2008). Their redox regulation mainly involves cysteine signaling and is indirectly affected by other transcription factors and post-translational modifications caused by oxidative stress, which are summarized in Table 1. The balance among these pathways determines cellular outcomes, with their coordinated regulation being critical for maintaining redox homeostasis and preventing oxidative stress-related diseases.

Table 1. Mechanisms of transcriptional regulation in cellular signaling by oxidative stress.

Transcriptional factors	Mechanisms	References
NRF2 (nuclear factor erythroid 2-related factor 2)	Under oxidative stress conditions, ROS oxidize the cysteine residues in Keap1, weakening the binding affinity between Keap1 and Nrf2. As a result, Nrf2 is released, preventing ubiquitination and degradation, which enhances its stability. Nrf2 then translocates to the nucleus, where it associates with sMaf and binds	

	to the antioxidant response element (ARE), leading to the activation of antioxidant and phase II enzyme gene expression.	
NF-κB (nuclear factor-κ light chain-enhancer of activated B cells)	Under normal conditions, NF-κB binds to the inhibitory protein IκB, keeping it inactive. However, ROS produced during oxidative stress activate IκB kinase (IKK), resulting in the phosphorylation and degradation of the IκB protein. This release of NF-κB allows its translocation to the nucleus, where it binds to DNA and initiates the transcription of inflammatory and anti-apoptotic genes.	(Gloire, et al., 2006; S. Mitchell, et al., 2016; Schröfelbauer, et al., 2012; Zandi, et al., 1997)
HIF (hypoxia-inducible factor)	Oxidative stress inhibits prolyl hydroxylase domain (PHD) activity, preventing the degradation of HIF-1α. This results in the accumulation of HIF-1α, which activates the transcription factor HIF-1, initiating the expression of hypoxia-responsive genes.	(Appelhoff, et al., 2004; P. Lee, et al., 2020; Pouyssé gur & Mechta-Grigoriou, 2006)
ERR (estrogen-related receptor)	ERR functions as a redox sensor and regulator of ROS signaling, exerting both antioxidant and pro-oxidant effects.	(Scholtes & Giguère, 2021; Vernier, et al., 2020)
FoxO (forkhead box O transcription factor)	FoxO acts as a sensor of oxidative stress. Under normal conditions, FoxO remains inactive, but upon	(Eijkelenboom & Burgering,

	oxidative stress, it is activated, undergoes nuclear translocation, and becomes transcriptionally active. Additionally, FoxO regulates the expression of genes encoding antioxidant proteins, such as catalase, MnSOD, and Prx, thereby contributing to the regulation of the cellular redox state.	2013; Klotz & Steinbrenner, 2017; Soh, et al., 2021)
PGC1α (peroxisome proliferator-activated receptor-γ co-activator 1α)	When cells are exposed to oxidative stress, PGC-1α is directly regulated by FoxO or post-translationally modified by SIRT1 and AMPK, which promotes its expression. Concurrently, PGC-1α activates the mitochondrial antioxidant gene program, thereby protecting cells from damage induced by excessive oxidative stress.	(Rius-Pérez, Torres-Cuevas, Millán, Ortega Á, & Pérez, 2020)
p53 (cellular tumour antigen p53)	Multiple cysteine residues of p53 are sensitive to redox modifications. Oxidation of these residues reduces its binding affinity to specific DNA sequences, thereby affecting its transcriptional activity. ROS can also trigger the phosphorylation of p53 by activating various kinases, including p38 MAPK, ATM, and ERK, which influence the stability and activity of p53. Additionally, ROS can oxidize specific cysteine residues in MDM2, a major negative regulator of p53, disrupting its interaction with p53. Furthermore, p53 can transactivate antioxidant genes	(Abbas, et al., 2010; B. Liu, et al., 2008)

	to help maintain intracellular ROS levels within physiological limits.	
AP-1 (activator protein-1)	AP-1 factors are activated by environmental stressors such as toxins and UV radiation. The precise redox regulation of AP-1 activation is crucial for maintaining cellular homeostasis, and dysregulation of AP-1 function has been implicated in various pathological conditions, including cancer, inflammation, and neurodegenerative diseases.	(Engelberg, et al., 1994; Hong, et al., 2024)

Note: Keap1, Kelch-like ECH-associated protein 1-nuclear factor; ARE, antioxidant response element; IKK, IκB kinase; p38 MAPK, p38 mitogen-activated protein kinase; SIRT1, sirtuin 1; ATM, ataxia telangiectasia mutated; ERK, extracellular signal-regulated kinase; Prx, peroxiredoxins.

2.3.2 Impact on cellular functions and metabolism

The effects of oxidative stress on cell function depend on the severity, duration, and type of cells or tissues exposed to it. Mild oxidative stress can stimulate cell proliferation. Studies have shown that low levels of oxidative stress, typically induced by adding low concentrations of H_2O_2 to primary cultures of various cell types, can promote cell proliferation and DNA synthesis (Sigaud, Evelson, & González-Flecha, 2005; von Bülow, et al., 2024). As the level of oxidative stress increases and oxidative damage accumulates, however, cells shift from proliferative responses to activating adaptive mechanisms, such as enhancing antioxidant defenses, to mitigate further damage. Moderate oxidative stress affects cell migration and adhesion by disrupting the cytoskeleton and impairing cell barrier function (Boardman, Aryal, Miller, & Waters, 2004; Hurd, DeGennaro, & Lehmann, 2012; Quintá, et al., 2016).

Elevated intracellular oxidative stress also impacts ion metabolism. It damages ion channel proteins, ion pumps, and ion-binding proteins, reducing their activity. This leads to the loss of K^+ from cells, abnormal accumulation of Na^+ and Ca^{2+}, and alterations in intracellular and extracellular osmotic pressure, ultimately resulting in cellular dysfunction. High intracellular calcium levels can also trigger mitochondrial permeability transition (MPT) and collapse of the membrane potential. Furthermore, oxidative stress can damage cell membranes and organelles, causing them to rupture, and can target storage and transport proteins like caeruloplasmin and Fe-S proteins. This release of bound Fe^{2+} and Cu^{2+} increases pro-oxidant levels both inside and outside the cells, further contributing to oxidative damage (Halliwell & Gutteridge, 2015). Additionally, oxidative stress converts LDL cholesterol into its atherogenic form, oxidized-LDL (OxLDL). This transformation is crucial for initiating and amplifying the inflammatory response, recruiting leukocytes to the affected site, and playing a significant role in atherosclerosis progression by activating smooth muscle cells and reducing •NO bioavailability (X. Yang, et al., 2017). Moreover, abnormal production of H_2O_2 can lead to the erroneous activation of signaling pathways. This aberrant activation of stress signaling pathways contributes to disease development, as observed in diabetic complications (Evans, Goldfine, Maddux, & Grodsky, 2002).

2.3.3 Oxidative stress-induced damage and cell death pathways

Excessive oxidative stress in cells, surpassing their adaptive capacity, leads to damage to DNA, lipids, and proteins. Oxidants can directly damage DNA by causing oxidative modifications to DNA bases or 2-deoxyribose, as well as inducing strand breakage. They can also indirectly promote nuclear DNA fragmentation by disrupting Ca^{2+} metabolism, resulting in abnormal increases in intracellular calcium levels, which activate Ca^{2+}-dependent endonucleases.

Additionally, oxidative stress can damage mitochondrial DNA (Cadet & Davies, 2017; Melegh, Bock, Gáti, & Méhes, 1996; Yakes & Van Houten, 1997).

Oxidative stress also targets the carbon-carbon double bonds in lipid molecules within unsaturated fatty acid side chains of biological membranes, generating carbon radicals. These radicals react with oxygen to form peroxyl radicals, which then attack adjacent fatty acid side chains, generating more carbon radicals that continue to react with oxygen. This perpetuates a chain reaction, driving lipid peroxidation. Lipid peroxidation products can compromise membrane fluidity and integrity (Higdon, Diers, Oh, Landar, & Darley-Usmar, 2012). Furthermore, oxidative stress damages cellular proteins by causing irreversible effects, such as loss of function, conformational changes, and fragmentation through the direct destruction of peptide bonds or oxidation of amino acid side chains. It can also lead to reversible protein modifications, such as the oxidation of cysteine thiol groups to form disulfide bonds. Moreover, DNA mutations caused by oxidative stress can result in subsequent protein damage (Davies, 2016; Dotan, Lichtenberg, & Pinchuk, 2004; Fedorova, Bollineni, & Hoffmann, 2014; Halliwell & Gutteridge, 2015; McAdam, Brem, & Karran, 2016; Helmut Sies, et al., 2017).

Severe oxidative stress can lead to various forms of cell death, including programmed apoptosis, autophagic cell death, and unprogrammed ferroptosis or necrosis (Dixon, et al., 2012). Oxidative stress affects mitochondria by triggering MPT, releasing apoptosis-inducing factors like cytochrome C into the cytoplasm, or upregulating death receptors (e.g., Fas) and their ligands (e.g., FasL). This activation initiates the caspase cascade, triggering apoptotic pathways (Ott, Gogvadze, Orrenius, & Zhivotovsky, 2007). ROS can also regulate transcription factors, such as NF-κB and AP-1, which drive the transcription of pro-apoptotic genes and further promote apoptosis (Cabaner, et al., 1999; Chandra, Samali, & Orrenius, 2000; C. N. Kim, et al.,

1999; Stridh, Kimland, Jones, Orrenius, & Hampton, 1998). Oxidative stress primarily induces autophagic cell death through the lysosomal pathway. Chronic oxidative stress damages lysosomal membranes, preventing fusion with autophagic vacuoles containing damaged cellular components. This leads to the release of lysosomal enzymes, worsening cell damage, and initiating autophagic cell death (Brunk, Dalen, Roberg, & Hellquist, 1997; Y. Chen, McMillan-Ward, Kong, Israels, & Gibson, 2008; Kiffin, Bandyopadhyay, & Cuervo, 2006; H. Liu, et al., 2018; Scherz-Shouval, et al., 2007).

When oxidative stress exceeds a critical threshold, the cell's antioxidant defense mechanisms are overwhelmed. This leads to damage to cell membranes and organelles, lysosomal rupture, and loss of mitochondrial function, ultimately triggering necrosis. In necrosis, cell contents leak out, inducing an inflammatory response and causing damage to neighboring cells. Ferroptosis, a distinct form of cell death, is characterized by the loss of intracellular GPx4 activity and the accumulation of iron-dependent lipid peroxides, ultimately resulting in cell membrane rupture and death (Ahola & Langer, 2024; Dixon, et al., 2012; W. S. Yang & Stockwell, 2016). Ferroptosis is a ROS- and iron-dependent regulated cell death pathway . Studies have shown that ROS-induced autophagy can increase intracellular iron levels, promoting ferroptosis through the transferrin receptor (Park & Chung, 2019).

3 Antioxidant defense systems

While both exogenous and endogenous oxidants constantly induce oxidative stress, cells have developed antioxidant defense systems. These systems primarily function to regulate RS levels within the cell, minimizing the damage caused by oxidative stress.

3.1 Sources and types of antioxidants

Like oxidants, antioxidants can be produced endogenously or obtained from external sources. Endogenous antioxidants are mainly classified into enzymatic antioxidants and non-enzymatic ROS scavengers (Fig. 2b). Additionally, certain molecules act to sequester pro-oxidative transition metal ions, preventing them from reacting and generating oxidants during transport (Halliwell, 2024; Jones & Sies, 2015).

3.1.1 Enzymatic antioxidants

Enzymatic antioxidants play a crucial role in the human body's defense against oxidative stress. Key enzymatic antioxidants include SOD, Prx, GPx, and CAT. SOD is the primary enzyme responsible for maintaining normal intracellular levels of superoxide anion ($\bullet O_2^-$). In mammals, three types of SOD exist, each located in different subcellular compartments: Cu/ZnSOD (also known as SOD1) is mainly found in the cytoplasm, with some in the mitochondrial membrane space; MnSOD (also known as SOD2) is predominantly found in the mitochondrial matrix; and EC-SOD (also known as SOD3) is the only form present in the extracellular matrix and body fluids . SOD catalyzes the dismutation of superoxide, converting $\bullet O_2^-$ into molecular oxygen and hydrogen peroxide. While H_2O_2 is an oxidant, its chemical reactivity is significantly lower than that of $\bullet O_2^-$, thus minimizing intracellular superoxide levels . Additionally, SODs help prevent the formation of the more reactive peroxynitrite ($ONOO^-$), while preserving physiologically important •NO (H. J. Forman & H. Zhang, 2021). Prxs are key regulators of hydrogen peroxide levels in cells and serve as peroxidases (Rhee, Woo, Kil, & Bae, 2012). These enzymes contain cysteine residues in their active sites, which act as the catalytic core (Halliwell & Gutteridge, 2015). The number of cysteine residues varies among different Prxs, with two cysteine residues being the most common. The cysteine residue reacts with hydrogen peroxide, forming a cysteine sulfinic acid (-SOH) intermediate, which is then converted to water. In the 2-Cys peroxiredoxin, the -SOH intermediate reacts with another thiol group to form a

disulfide bond, which is subsequently reduced by thioredoxin reductase (TrxR) with the help of thioredoxin (Trx). Prxs also interact rapidly with peroxynitrite (Amponsah, et al., 2021; Rhee & Woo, 2020). Moreover, GPx reduce hydrogen peroxide by utilizing GSH as a hydrogen donor, converting H_2O_2 to water and oxidizing GSH to glutathione disulfide (GSSG) (Halliwell & Gutteridge, 2015). The GPx family consists of four main members (GPx1-GPx4), each distributed across different tissues. Among these, GPx4, or phospholipid hydroperoxidase glutathione peroxidase (PHGPx), is crucial for regulating lipid peroxidation. GPx4 also plays a critical role in preventing ferroptosis .

In contrast to Prx and GPx, CAT directly catalyzes the dismutation of hydrogen peroxide into water and oxygen, without generating any byproducts (Hansberg, 2022). CAT is found in all organs, with the highest concentrations in the liver. While most CAT is located in peroxisomes, it is also present in mitochondria and cytoplasm in certain organelles, excluding red blood cells. The active site of mammalian CAT consists of a heme group, with each subunit containing a ferric heme and a bound NADPH molecule, which facilitates the decomposition of hydrogen peroxide (Díaz, Loewen, Fita, & Carpena, 2012; Fita & Rossmann, 1985; Goyal & Basak, 2010; Halliwell & Gutteridge, 2015; Tsiftsoglou, Tsamadou, & Papadopoulou, 2006).

3.1.2 Non-enzymatic ROS scavengers

Non-enzymatic ROS scavengers play a crucial role in the antioxidant defense system by acting as "sacrificial agents." They react with oxidants first, preventing more critical molecules from being damaged. GSH is the primary component of non-enzymatic ROS scavengers. It is synthesized in the cytoplasm of all animal cells and can be transported to the mitochondria and nucleus. GSH serves as a substrate in the GPx-mediated removal of hydrogen peroxide and participates in various antioxidant processes. It can also directly react with various oxidants

such as ONOOH, HOCl, and •OH. Given its relatively high concentration in cells (millimolar levels), GSH is highly effective at rapidly scavenging oxidants. Oxidized GSH (GSSG) can be reduced back to its active form by glutathione reductase (GR), using NADPH as an electron donor, thus maintaining a high GSH-to-GSSG ratio in cells (Flohé, et al., 2022; Giustarini, Milzani, Dalle-Donne, & Rossi, 2023; Halliwell & Gutteridge, 2015).

In addition to GSH, other molecules like CoQ10 (also known as ubiquinone), plasmalogens, and urate also play important antioxidant roles. CoQ10 can be reduced to its antioxidant form, ubiquinol ($CoQ10H_2$), by ferroptosis inhibitory protein 1 (FSP1), a glutathione-independent ferroptosis suppressor. Ubiquinol is highly effective at scavenging free radicals, directly neutralizing them and preventing lipid peroxidation. In this way, CoQ10 helps inhibit ferroptosis and protects cells from oxidative damage (Bersuker, et al., 2019; X. Chen, et al., 2021; Xin Chen, et al., 2021; Doll, et al., 2019). The ether bonds in plasmalogens can capture and neutralize free radicals, preventing lipid oxidation in cell membranes, thereby maintaining membrane integrity and function (Lessig & Fuchs, 2009). Urate, the final product of purine metabolism, scavenges $•O_2^-$, •OH, and NO_3^-, and interacts with other antioxidant systems, such as SOD and ascorbic acid, to enhance its antioxidant function (Crotty, Ascherio, & Schwarzschild, 2017; Halliwell & Gutteridge, 2015; Sevanian, Davies, & Hochstein, 1991). Moreover, due to the pro-oxidative properties of Fe^{2+}, Cu^{2+}, heme, and heme proteins, certain endogenous molecules are produced to store these ions or keep them in a non-redox-active form, minimizing ROS generation and allowing for their safe transport in the body. For example, transferrin and lactoferrin bind to Fe^{2+}, ceruloplasmin binds to Cu^{2+}, and transferrin/lactoferrin also bind hemoglobin/heme (Halliwell & Gutteridge, 1990; Halliwell & Gutteridge, 2015).

3.1.3 Exogenous dietary antioxidants

In addition to endogenous antioxidants, there are also molecules with antioxidant effects found in the diet, considered exogenous sources of the antioxidant defense system. These include vitamins E (VitE), C (VitC), and A (VitA, a mixture of retinol, retinal, retinoic acid, carotenoids, and β-carotene), flavonoids, polyphenols, and others. VitE and VitC are essential vitamins in the human diet. VitE refers to a group of eight monophenols, with α-tocopherol being the most important form for the human body. VitE plays a crucial role in lipid peroxidation reactions by donating its hydrogen to peroxide free radicals, generating lipid hydroperoxides and vitamin E free radicals (VitE•). This process inhibits the formation of carbon-centered radicals and delays the chain reaction of lipid peroxidation. VitC, known as ascorbate, is an essential vitamin that acts as an important cofactor, directly reducing various free radicals and thus quenching oxidative damage. Additionally, VitC can regenerate the active form of VitE by reducing VitE•, enhancing VitE's ability to inhibit lipid peroxidation. Carotenoids, which include xanthophylls (oxygen-containing) and carotenes (hydrocarbons without oxygen), are found in both animal and plant foods. These compounds act as scavengers and quenchers of singlet molecular oxygen and ROS. Provitamin A carotenoids, such as β-carotene, can be converted into VitA in the human intestine through the enzyme beta-carotene monooxygenase type 1. While VitA is not a direct antioxidant, it indirectly regulates the expression of various genes involved in mediating the body's antioxidant responses (Blaner, Shmarakov, & Traber, 2021). Polyphenols, including flavonoids, have strong antioxidant properties *in vitro*, but in the gastrointestinal tract, they are metabolized into compounds with lower ROS-scavenging abilities (Halliwell, 2008; Zhor, et al., 2023). Additionally, melatonin, a hormone regulated by circadian rhythms and primarily released by the pineal gland, has been increasingly recognized for its free radical scavenging capabilities. It plays roles in protecting against liver injury, promoting reproductive health, and acting as an anti-inflammatory agent (Megha, et al., 2024; Mortezaee & Khanlarkhani, 2018; L. Wang, Wang, & Choi, 2022; Yong, et al., 2021). However, melatonin also functions as a pro-

oxidant in tumor cells, inhibiting tumor growth, which presents an apparent paradox (Florido, et al., 2022). Further studies are needed to clarify this dual role. Furthermore, minerals like zinc, copper, and selenium contribute to enhancing antioxidant defenses and improving immune function (Allen & Klevay, 1994; Bjørklund, et al., 2022; Jarosz, Olbert, Wyszogrodzka, Mł yniec, & Librowski, 2017).

3.2 Regulation of antioxidant pathways

Antioxidant defense in cells is regulated through a series of antioxidant pathways. Transcription factors such as NRF2, AP-1, NF-κB, HIF, FoxOs, PGC-1α, P53, and AMPK, while serving as targets of oxidative stress, also play critical roles in activating the transcription of downstream antioxidant genes and regulating the cellular redox state (!!! INVALID CITATION !!! ; Budanov, 2014; Glorieux, et al., 2016; Hayes, Dinkova-Kostova, & Tew, 2020; Klotz, et al., 2015; X.-N. Li, et al., 2009; H. Lu, et al., 2015; Q. Ma, 2013; Maillet & Pervaiz, 2012; Morgan & Liu, 2011; Soriano, et al., 2009; St-Pierre, et al., 2006; Valle, Alvarez-Barrientos, Arza, Lamas, & Monsalve, 2005) (Table 2). Among these, NRF2 is considered the central regulator of the antioxidant defense system in cells, as it governs a broad array of antioxidant and detoxification genes (Hayes & Dinkova-Kostova, 2014; Q. Ma, 2013). These transcription factors also interact with one another, forming a complex regulatory network that coordinates the antioxidant stress response, metabolism, and cell survival. For instance, there exists a negative feedback loop between NRF2 and NF-κB. Activation of NRF2 can inhibit NF-κB activity, while NF-κB activation can suppress NRF2 by promoting the expression of Keap1 (W. Gao, et al., 2021; Sivandzade, Prasad, Bhalerao, & Cucullo, 2019). Furthermore, AMPK activates PGC-1α and FoxO, enhancing the expression of downstream antioxidant genes (X.-N. Li, et al., 2009) (Fig. 4).

Table 2. Transcriptional regulation of antioxidant genes.

Transcriptional Factors	Target antioxidant genes	Reference
NRF2	*GPX2, PRDX1, PRDX6, GCLC, GCLM, G6PD, SRXN1, NQO1, TXN, PRDX1, HMOX1, GSTM1, GPX4*	(Cuadrado, et al., 2019; Hayes & Dinkova-Kostova, 2014; Hayes, et al., 2020; Q. Ma, 2013; Mulcahy & Gipp, 1995)
AP-1	*SOD1, GCLM, SRXN1, FTH1, GSTP1*	(Hayes, et al., 2020; Soriano, et al., 2009)
NF-κB	*SOD2, SOD1, FTH1, TXN, GSTP1, NQO1, HMOX1, GPX1*	(Hayes, et al., 2020; Morgan & Liu, 2011)
HIF	*GCLM, GLS1, SLC7A11*	(Hayes, et al., 2020; H. Lu, et al., 2015)
FoxOs	*CAT, SOD2, PRDX*	(Hayes, et al., 2020; Klotz, et al., 2015)

PGC1α	*PRDX3, PRDX5, SOD2, TXN2, GCLM*	(Hayes, et al., 2020; St-Pierre, et al., 2006; Valle, et al., 2005)
P53	*GPX1, SOD2, GLS2*	(Budanov, 2014; Hayes, et al., 2020; Maillet & Pervaiz, 2012)

Note: GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modifier subunit; G6DP, Glucose-6-phosphate dehydrogenase; SRXN1, Sulfiredoxin-1; FTH1, Ferritin Heavy Chain 1; GSTP1, Glutathione S-transferase pi 1; NQO1, NAD(P)H quinone oxidoreductase 1; HMOX1, heme oxygenase 1; SLC7A11, solute carrier family 7 member 11.

4 Oxidative stress in disease

4.1 Oxidative stress and disease pathogenesis

ROS and RNS are natural byproducts of cellular metabolism. In low to moderate amounts, both ROS and RNS play crucial roles in various physiological processes, such as pathogen defense, wound healing, and tissue repair . However, the excessive generation of ROS and RNS can lead to oxidative stress, disrupting homeostasis and causing significant oxidative damage to tissues (Ushio-Fukai, et al., 2021).

4.2 Mechanisms of oxidative damage in diseases

Organisms continuously strive to maintain optimal levels of ROS and RNS necessary for normal physiological functions. However, excessive production of ROS and RNS can overwhelm the antioxidant defense system, reducing the activity of antioxidant enzymes and depleting non-enzymatic antioxidants. This imbalance impairs the overall defense, making it unable to neutralize the excess free radicals. Excessive ROS and RNS are typically produced in conditions of hyperoxia, inflammation, or when the antioxidant defense system is weak or compromised, ultimately disrupting the homeostasis of the entire biological system (Hajam, et al., 2022). This surplus of ROS and RNS leads to damage to DNA, lipids, and proteins, ultimately causing cell death. ROS can interact with nucleic acids by attacking the nitrogenous bases and the sugar-phosphate backbone, inducing single- and double-stranded DNA breaks, which are linked to various oxidative stress-related diseases.

4.3 Neurodegenerative diseases

4.3.1 Oxidative stress as a central driver of neurodegeneration

Neurodegenerative diseases are characterized by the progressive loss of selectively vulnerable neurons, affecting millions of people worldwide (Sahoo, et al., 2022). Aging is the primary risk factor for most of these diseases (Hou, et al., 2019), which can be classified based on their clinical features, including Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (ALS) (Dugger & Dickson, 2017). While studies suggest that ROS are not direct triggers of these diseases, they may contribute to disease progression through oxidative damage and interactions with mitochondria (Teleanu, et al., 2022). Increasing evidence underscores the central role of mitochondria in the pathogenesis of neurodegenerative diseases (M. T. Lin & Beal, 2006), Mitochondrial dysfunction is a major source of ROS in neurodegenerative diseases, contributing to disease progression. Mitochondria generate the majority of cellular energy through the ETC, but ETC dysfunction

leads to electron leakage and excessive superoxide radical formation, exacerbating oxidative stress and cellular damage. These radicals are rapidly converted to other ROS, such as hydrogen peroxide and hydroxyl radicals, further exacerbating oxidative damage.

In addition to mitochondrial dysfunction, activated glial cells are a significant source of ROS in neurodegenerative diseases. Misfolded protein aggregates, such as amyloid-beta (Aβ), tau protein, and α-synuclein, as well as damage-associated molecular patterns (DAMPs) released from injured neurons, rapidly activate microglia and astrocytes. Activated microglia and astrocytes generate significant bursts of ROS through activation of the Nox pathway (Simpson & Oliver, 2020). Elevated ROS subsequently enhance activation of inflammatory signaling cascades, notably through NF-κB and MAPK pathways, thereby intensifying cytokine release and sustaining chronic neuroinflammation. Recent studies have further demonstrated that ROS activate the NLRP3 inflammasome pathway by facilitating the autocleavage of procaspase-1 into active caspase-1, which subsequently promotes maturation and secretion of pro-inflammatory cytokines IL-1β (C. Han, et al., 2020; Pang, et al., 2021). This self-amplifying oxidative-inflammatory cascade significantly exacerbates neuronal damage.

In PD, pathological α-synuclein aggregates specifically bind to Toll-like receptor 4 (TLR4) on glial cell surfaces, activating downstream MyD88-dependent NF-κB signaling pathways, enhanced ROS production and increased secretion of inflammatory cytokines such as TNF-α and IL-6 (Heidari, Yazdanpanah, & Rezaei, 2022; Trudler, Farfara, & Frenkel, 2010). Excessive ROS production can damage cellular components, including lipids, proteins, and DNA. In the brain, which has a high oxygen consumption and lipid-rich environment, lipid peroxidation is a primary consequence of oxidative stress (Jelinek, Jurajda, & Duris, 2021). Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), byproducts of lipid peroxidation,

are highly reactive and form adducts with proteins and DNA, leading to cellular dysfunction and apoptosis. Oxidative stress contributes to the aggregation of amyloid-β plaques and tau tangles, further promoting neuronal injury in AD (R. Bai, Guo, Ye, Xie, & Xie, 2022). These damaged proteins often lose their functional activity and accumulate as protein aggregates, a hallmark of several neurodegenerative diseases. Additionally, oxidative stress induces DNA damage, particularly in the form of single-strand breaks. The activation of poly (ADP-ribose) polymerase-1 (PARP-1) in response to DNA damage can lead to energy depletion and cell death, exacerbating the development of AD and PD (Kam, et al., 2018; Martire, Mosca, & d'Erme, 2015).

At the molecular level, oxidative insults drive neurodegeneration through interconnected mechanisms. APOE4 allele, a major genetic risk factor for AD, impair cholesterol trafficking, leading to increased membrane oxidation and facilitate the localization and activity of β-secretase in lipid rafts, which accelerates Aβ production (S. I. Lee, et al., 2021). Copper-bound Aβ peptides further exacerbate oxidative stress by generating ROS through Fenton reactions. These radicals can damage both the Aβ peptide itself and surrounding biomolecules, contributing to neuronal injury and disease progression in AD. ALS-linked SOD1 mutants lose their normal superoxide dismutase activity and instead gain toxic properties, leading to mitochondrial dysfunction, fragmentation, and impaired axonal transport in motor neurons (J. Liu, et al., 2004). Multiple sclerosis lesions feature oxidized myelin basic protein epitopes that activate $CD8^+$ T cell cross-reactivity, perpetuating demyelination through inflammation-oxidation synergy (Clarkson, et al., 2023). These interlocking mechanisms position oxidative stress as both a universal driver and disease-specific amplifier of neurodegeneration.

4.3.2 Oxidative stress and antioxidant pathway impairment in neurodegenerative disorders

To counteract oxidative stress, cells rely on a complex network of antioxidant defense systems. But in various neurodegenerative diseases, this antioxidant defense system is commonly impaired, rendering neurons particularly vulnerable to oxidative damage and accelerating disease progression. For example, AD patients had lower intracellular and extracellular blood GSH and lower brain GSH (J. J. Chen, et al., 2022). Disruption of GSH metabolism pathways substantially aggravates neurodegeneration.

Dysregulation of the NRF2-ARE signaling pathway has also emerged as a critical mechanism underlying impaired antioxidant defenses (S. Liu, Pi, & Zhang, 2022). Under physiological conditions, elevated ROS levels trigger nuclear translocation of NRF2, activating downstream antioxidant gene expression to counteract oxidative stress (Shaw & Chattopadhyay, 2020). NRF2 is predominantly retained in the cytoplasm of neurons in AD, resulting in reduced nuclear translocation and insufficient activation of antioxidant gene expression, despite ongoing oxidative stress (Ramsey, et al., 2007). Activation of NRF2, particularly in astrocytes, enhances glutathione secretion, which protects motor neurons and delays disease onset and progression in ALS mouse models (Vargas, Johnson, Sirkis, Messing, & Johnson, 2008).

Mechanisms underlying oxidative stress in neurodegenerative diseases were illustrated in Fig. 5. Targeting oxidative stress through antioxidants and mitochondrial protectors offers a promising therapeutic approach. Ongoing research into the molecular mechanisms underlying oxidative damage will continue to enhance our understanding and guide the development of effective treatments for neurodegenerative diseases.

4.4. Other diseases

4.4.1 Inflammatory diseases

Oxidative stress plays a central role in the onset and progression of inflammatory diseases by acting as both a trigger and an amplifier of chronic inflammation. ROS function as key signaling molecules that regulate immune responses, but excessive ROS levels can lead to sustained inflammation and tissue damage. One of the primary mechanisms through which oxidative stress promotes inflammation is the activation of NF-κB and MAPK pathways, which drive the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β (Sharma, Khan, & Tirpude, 2023). This oxidative-inflammatory feedback loop is particularly evident in diseases such as rheumatoid arthritis (RA), where excessive ROS production in RA joints, leads to persistent joint inflammation and destruction (Jing, et al., 2023).

In addition to direct cytokine signaling, ROS-induced mitochondrial dysfunction plays a pivotal role in inflammatory diseases. Oxidative damage to mitochondrial DNA (mtDNA) and proteins disrupts normal cellular metabolism, leading to the release of damage-associated molecular patterns (DAMPs) that further activate immune cells (Grazioli & Pugin, 2018). This process is especially relevant in inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (M. Ma, Jiang, & Zhou, 2024), where increased ROS levels contribute to intestinal epithelial barrier dysfunction and uncontrolled immune activation via the NLRP3 inflammasome (Faas & de Vos, 2020; Zeng, et al., 2024). The breakdown of this barrier allows microbial translocation, further intensifying the inflammatory response and perpetuating chronic intestinal damage. Similar mechanisms are observed in systemic lupus erythematosus (SLE), where oxidative stress contributes to the pathogenesis of SLE by causing inflammatory

and cellular defects, triggering an aggressive autoimmune attack, and reducing DNA methylation (Yan, Chen, & Xia, 2023).

Another key aspect of oxidative stress in inflammation is its role in immune cell dysregulation. ROS influence naïve $CD4^+$ T cell towards a Th2 phenotype and alter cytokine response of terminally differentiated T cells (Abimannan, et al., 2016). Suggesting altering intracellular ROS might be a potential way to target differentiated T cells in autoimmune disorders. In psoriasis, oxidative stress activates keratinocytes, leading to aberrant NF-κB and STAT3 signaling, which amplifies IL-17 and IL-22-driven inflammation in the skin (Sudha Yalamarthi, et al., 2022).

4.4.2 Cancer

Cancer is fundamentally a disease of uncontrolled proliferation by transformed cells, subject to evolution by natural selection, and is the second-leading cause of death worldwide (Sonkin, Thomas, & Teicher, 2024). ROS-induced DNA damage can lead to replication stress, which promotes genome instability and paves the way for tumor development through the accumulation of additional pro-carcinogenic changes (Z. Chen, et al., 2015; Popovici, et al., 2022). Oxidative stress plays a crucial role in the initiation of cancer by inducing DNA damage, genomic instability, and chronic inflammation. ROS can directly damage DNA, leading to mutations that affect both tumor suppressor genes and oncogenes. Tumor suppressor genes such as TP53, RB, p21, and p16 play crucial roles in DNA damage repair and cellular responses to oxidative stress. ROS-induced DNA damage can trigger mutations in these tumor suppressors, potentially impairing their protective functions and promoting cancer development (Vafa, et al., 2002; Vurusaner, Poli, & Basaga, 2012). Additionally, oxidative stress impairs the DNA repair machinery, thereby contributing to the accumulation of mutations. The tumor

microenvironment is also shaped by oxidative stress, as ROS can modulate immune cell infiltration and function. For example, high oxidative stress in glioblastoma is associated with increased M2-like pro-tumoral macrophages and reduced natural killer cell infiltration (X. Liang, et al., 2024).

Oxidative stress also significantly impacts cancer therapy, contributing to both drug resistance and potential therapeutic strategies. Many chemotherapeutic agents and radiotherapy function by generating excessive ROS to induce cancer cell death. However, cancer cells often develop resistance by upregulating antioxidant defense mechanisms, such as the activation of Nrf2, leading to increased production of GSH and SOD (Zhou, et al., 2023). On the other hand, targeting oxidative stress has emerged as a potential therapeutic strategy. The induction of ferroptosis, a ROS-dependent form of cell death (X. Jiang, Stockwell, & Conrad, 2021), has shown promise in overcoming therapy resistance in certain cancers, including lung cancer (Z. Wu, et al., 2025) and breast cancer (Qi, et al., 2022). Combining ferroptosis and other cell death pathway inducers with existing therapies may offer new avenues for improving treatment outcomes.

Overall, oxidative stress serves as a double-edged sword in cancer biology, driving tumor initiation and progression while also presenting therapeutic vulnerabilities. A deeper understanding of how ROS influences different cancer types will be essential for developing more effective, targeted therapeutic interventions.

4.4.3 Cardiovascular diseases

Cardiovascular diseases (CVDs) encompass a group of disorders that affect the heart and blood vessels, including cerebrovascular disease, coronary heart disease, congestive heart failure, and

rheumatic heart disease. CVDs remain the leading cause of death globally, with 523 million people affected and approximately 10 million deaths attributed to these conditions (Coronado, Melvin, Bell, & Zhao, 2022). The primary behavioral risk factor for CVDs is an unhealthy diet. Studies have shown that maintaining a healthy dietary pattern can significantly contribute to the prevention of CVDs (Chareonrungrueangchai, Wongkawinwoot, Anothaisintawee, & Reutrakul, 2020). Oxidative stress plays a central role in the pathology of atherosclerotic cardiovascular diseases (Henry Jay Forman & Hongqiao Zhang, 2021). In freshly isolated human plaques, about 20% of cholesteryl linoleate (Ch18:2) was found to be oxidized, while this oxidation was absent in normal arteries (Suarna, Dean, May, & Stocker, 1995). Additionally, the concentration of HNE-modified low-density lipoprotein (LDL) was observed to be 50% higher in the plasma of patients with atherosclerosis compared to healthy individuals (Salomon, et al., 2000).

Under normal conditions, ROS and RNS are produced in small amounts in the heart by enzymes such as NADPH oxidases, nitric oxide synthase (NOS), and xanthine oxidase (XO), where they play essential roles in regulating cell cycle homeostasis, excitation-contraction coupling, and cellular function (Ng, et al., 2023). However, increased oxidative stress is recognized as a common underlying cause of cardiovascular diseases. It is triggered by factors such as inflammation, matrix remodeling, myocardial fibrosis, neurohumoral activation, and cardiomyocyte apoptosis, all of which contribute to the progression of cardiovascular conditions. The Nox family of proteins (NADPH oxidases) is a key ROS-generating enzyme involved in atherogenesis. Judkins et al. demonstrated that Nox2 promotes superoxide production and reduces nitric oxide bioavailability (Judkins, et al., 2010). Comparing $ApoE^{-/-}$ mice with $Nox2^{-/y}$ $ApoE^{-/-}$ mice, a 50% reduction in atherosclerotic plaque area and a significant decrease in ROS production in the aorta were observed. Additionally, oxidative stress-related

biomarkers, including myeloperoxidase (MPO), advanced glycation end-products (AGEs), and NADPH oxidases (e.g., sNox2-dp), serve as important signaling molecules that reflect pathobiological changes in heart failure (Arshi, Chen, Ikram, Zillikens, & Kavousi, 2023; Daiber, et al., 2021; Ng, et al., 2023; Sultan, et al., 2021).

4.4.4 Diabetes and metabolic syndrome

Diabetes is a chronic disease that results from either insufficient insulin production by the pancreas or the body's inability to effectively utilize the insulin it produces. Hyperglycemia is a common consequence of uncontrolled diabetes and can cause significant damage to various body systems, particularly the nerves and blood vessels. According to the International Diabetes Federation (IDF), an estimated 536.6 million adults, representing 9.2% of the global population, are affected by diabetes. Additionally, 6.7 million people under the age of 60 die each year due to diabetes, and it is projected to become the leading cause of disability and mortality by 2030 (Gambale, et al., 2022). There are three main types of diabetes: type 1, type 2, and gestational diabetes. Type 1 diabetes is characterized by a deficiency in insulin production and is classified as a chronic autoimmune disease (DiMeglio, Evans-Molina, & Oram, 2018). Type 2 diabetes is marked by insulin resistance and initial hyperinsulinemia, followed by a gradual decline in the ability of pancreatic β-cells to produce insulin. The complex interplay between β-cell dysfunction and insulin resistance contributes to the progression of type 2 diabetes (Ahmad, Lim, Lamptey, Webb, & Davies, 2022). Gestational diabetes is diagnosed during the second or third trimester of pregnancy and is distinct from overt diabetes before pregnancy or other forms of diabetes that may arise during pregnancy (Committee, 2023). Women with gestational diabetes face a higher risk of complications during pregnancy and childbirth, as well as an increased risk of developing type 2 diabetes later in life (Johns, Denison, Norman, & Reynolds, 2018).

Elevated levels of ROS play a significant role in diabetes by acting as secondary messengers that regulate the biological functions of proteins such as NRF2, PKC, IKKβ, and Keap1. ROS achieve this by interacting with the cysteine residues of these proteins, influencing their activity and contributing to the disease pathology (David, Rifkin, Rabbani, & Ceradini, 2017; Evans, et al., 2002; P. Zhang, et al., 2020).

5 Role of antioxidants in health

The antioxidants play a number of roles in human health. Antioxidants contribute to health maintenance by reducing oxidative stress. They help: 1) Prevent cardiovascular diseases by lowering LDL oxidation, inflammation, and supporting vascular health. 2) Prevent neurodegenerative diseases by decreasing neuronal oxidative damage and slowing the progression of AD and PD. 3) Prevent diabetes by reducing oxidative stress in β-cells and improving insulin sensitivity. 4) Delay aging by minimizing cumulative oxidative damage and enhancing healthspan. 5) Prevent infections by boosting immune cell function and reducing pathogen survival. Core mechanisms of these impacts include antioxidants neutralizing free radicals, protecting DNA, proteins, and lipids from oxidative damage (Fig. 6).

5.1 Prevention of chronic diseases

It is widely acknowledged that oxidative stress is a common underlying factor in many chronic diseases, despite their multifactorial origins (Jomova, et al., 2023). Both enzymatic and non-enzymatic antioxidants play a vital role in alleviating and preventing the harmful effects of oxidative stress. Through their combined actions, antioxidants help protect against chronic conditions such as diabetes, cardiovascular diseases, and neurodegenerative disorders (Sen & Chakraborty, 2011).

5.1.1 Neurodegenerative diseases

Mitochondrial dysfunction, inflammation, and oxidative stress are key factors linked to neurodegenerative diseases, leading to growing interest in antioxidants as potential treatments. Dietary antioxidants have shown promise in managing and potentially curing these conditions (Bakir, et al., 2020). Sulforaphane (1-isothiocyanato-4-(methylsulfinyl)butane), found primarily in cruciferous vegetables like cabbage and broccoli, is known for its anti-apoptotic, anti-inflammatory, and antioxidant properties (Schepici, Bramanti, & Mazzon, 2020). Research has shown that sulforaphane regulates the Nrf2 pathway, helping protect against oxidative stress-induced neurotoxicity in rat models (Mizuno, et al., 2011). Additionally, sulforaphane has been found to promote neurogenesis and increase the WNT signal and brain-derived neurotrophic factor level (Z. Han, Xu, Li, & Zhao, 2017). Macroalgae polyphenols derived from marine sources have also gained attention for their promising antioxidant effects (Lomartire & Gonçalves, 2023). Studies by Alghazwi et al. highlighted the neuroprotective properties of macroalgae polyphenols, showing their ability to inhibit Aβ aggregation and reduce $A\beta_{1-42}$-induced cytotoxicity in PC12 cells (Alghazwi, Smid, Karpiniec, & Zhang, 2019). It may help alleviate $A\beta_{1-42}$ neurotoxicity in Alzheimer's disease. Furthermore, lipophilic antioxidants such as CoQ10, carotenoids, VitA, and VitE are gaining recognition as both preventive and therapeutic interventions for neurodegenerative diseases. These antioxidants have demonstrated neuroprotective effects in various cellular and animal studies (Chang, Cheng, Chiang, & Chen, 2018).

5.1.2 Diabetes

Diabetes mellitus is a major global public health concern. Recent evidence suggests that cellular redox imbalances lead to oxidative stress, which plays a crucial role in the onset and progression

of diabetes and its complications by regulating key signaling pathways involved in β-cell dysfunction and insulin resistance (P. Zhang, et al., 2020). Given the complex relationship between oxidative stress and diabetes, various approaches have been explored to improve the health of diabetic patients, particularly through dietary antioxidant supplements, such as enzymatic antioxidant-like mimics, VitC, and VitE (Johansen, Harris, Rychly, & Ergul, 2005). Studies indicate that early management, through lifestyle changes and an antioxidant-rich diet, can help prevent complications in patients with type 2 diabetes (Ganjifrockwala, Joseph, & George, 2017).

Astaxanthin, a potent natural antioxidant found in marine organisms, has been shown to protect β-cells and may be beneficial in treating diabetes (Kanwugu, Glukhareva, Danilova, & Kovaleva, 2022). It has been found that astaxanthin significantly reduces RS production in high glucose-exposed proximal tubular epithelial cells (Y. J. Kim, Kim, & Yokozawa, 2009). Astaxanthin treatment has also been reported to ameliorate redox balance by increasing the concentration or activity of antioxidant enzymes such as GPx, SOD, and CAT (Kanwugu, et al., 2022; Toprak & Dedeoğlu, 2022). Catalpol, an iridoid glucoside derived from the Chinese herb *Rehmannia glutinosa*, also exhibits antioxidative properties and has shown beneficial effects in managing diabetes and its complications (Bhattamisra, Koh, Lim, Choudhury, & Pandey, 2021). In one study, 40 mM of catalpol increased insulin secretion in response to high-glucose stimulation by elevating the expression of p-IRS1 and p-AKT in pancreatic INS-1E cells (Elhassan, Candasamy, Ching, Heng, & Bhattamisra, 2021).

Polyphenols, origin from natural plants, are also relevant to antioxidant mechanisms that enhance antidiabetic therapy by reducing oxidative stress, preserving β-cell function, and improving insulin sensitivity (Krawczyk, Burzynska-Pedziwiatr, Wozniak, & Bukowiecka-

Matusiak, 2023). Resveratrol, a polyphenol found in certain plants, has been shown to protect pancreatic islets against oxidative stress when administered to db/db mice. It also improved glucose tolerance in these mice and reduced urinary 8-OHdG levels (Y. E. Lee, et al., 2012). Gyeong-Min et al. demonstrated that resveratrol ameliorates diabetes-related metabolic changes through the AMPK signaling pathway (Do, et al., 2012). Curcumin, another well-known antioxidant found in turmeric, acts both as a direct antioxidant to scavenge reactive species and as an indirect antioxidant by covalently modifying cysteine residues of Keap1 to inhibit the Keap1-NRF2 interaction (Jiménez-Osorio, González-Reyes, & Pedraza-Chaverri, 2015). Dietary curcumin has been shown to significantly improve diabetes in animal models by reducing hepatic NF-κB activity and improving glycemic control in diabetic mice (Weisberg, Leibel, & Tortoriello, 2008).

5.1.3 Cardiovascular diseases

Oxidative stress plays a critical role in the pathogenesis of cardiovascular diseases. Physical exercise, along with lifestyle changes, is considered the primary non-pharmacological treatment for cardiovascular conditions (Sharifi-Rad, et al., 2020; N. N. Wu, et al., 2019). Antioxidant supplements, such as VitE, have been shown to reduce cardiovascular mortality, but they do not significantly impact overall mortality from the women's health comprehensive study (I. M. Lee, et al., 2005). In recent years, plant-derived antioxidant molecules have garnered increasing attention for their potential therapeutic benefits in both disease prevention and treatment (Sharifi-Rad, et al., 2020). Several clinical trials support the beneficial effects of polyphenols on the cardiovascular system (Jomova, et al., 2023).

Apigenin (4',5,7-trihydroxyflavone), a naturally occurring dietary flavonoid found abundantly in fruits and vegetables, exerts both antioxidant and anticancer functions. It has been shown to

be beneficial in the treatment of hypertension, stroke, ischemia/reperfusion-induced myocardial injury, atherosclerosis, and diabetic cardiomyopathy. Apigenin also offers protection against drug-induced cardiotoxicity (Thomas, Jha, Jha, Sadek, & Ojha, 2023). One glycoside subtype of apigenin, Apigenin-7-O-β-D-(-6"-p-coumaroyl)-glucopyranoside, has demonstrated a neuroprotective effect in a cerebral ischemia/reperfusion model. This compound protects against cerebrovascular diseases by activating the Keap-1 independent of NRF2 signaling pathway (Cai, et al., 2016; J. Wang, et al., 2020).

5.2 Cancer

The unique role of antioxidants in tumor prevention has drawn increasing attention due to their ability to counteract one of the key driving forces of carcinogenesis-oxidative stress. Pharmacological antioxidants and dietary compounds exhibit considerable promise in chemoprevention. They prevent DNA damage, mutations, and the activation of signaling pathways that lead to tumor development. VitE and VitC have demonstrated efficacy in reducing tumor burden and preventing the development of malignant skin tumors in female mice with chronically UVB-damaged skin (Alleva, et al., 2012). N-acetylcysteine (NAC), a precursor of glutathione, has been found to overcome NF1 loss-driven resistance to PI3Kα inhibition and reverse the glycolytic phenotype in breast cancer (Auf der Maur, et al., 2023). Polyphenols such as curcumin (Ameer, Mohamed, Elzubair, Sharif, & Ibrahim, 2024), resveratrol (Nadile, Retsidou, Gioti, Beloukas, & Tsiani, 2022), and epigallocatechin gallate (Almatroodi, et al., 2020) have shown promise in inhibiting cancer cell growth and modulating gene expression related to cell death and proliferation. Furthermore, clinical observations have indicated that populations with high dietary intake of antioxidant-rich foods favorable effects on lung cancer prevention (J. Yang, Qian, Na, & Zhao, 2023). While these associations are

influenced by multiple factors, they underscore the potential role of antioxidant-based strategies in public health-level cancer prevention.

However, the role of antioxidants in cancer prevention is not universally beneficial. In some cases, antioxidants have even accelerated tumor growth or reduced survival (Dastmalchi, et al., 2020; Diao, et al., 2016; Wiel, et al., 2019). It has been shown that long-term supplementation with the antioxidants N-acetylcysteine and vitamin E promotes KRAS-driven lung cancer metastasis (Wiel, et al., 2019). The effectiveness of antioxidants appears to depend on factors such as the type of antioxidant, timing of administration, cancer type, and the underlying genetic context of the tumor.

5.3. Aging and Longevity

5.3.1 Theories of aging and oxidative stress

The aging process refers to the gradual changes that occur in an organism, increasing the likelihood of debility, disease, and death. Among the various biological theories of aging, the oxidative damage theory is one of the most extensively studied (Sivakanesan, 2018). According to this theory, age-related declines in physiological functions are a result of the progressive accumulation of oxidative damage to macromolecules. This damage builds up over time, correlating with age and having a direct impact on an organism's lifespan (Michael T. Lin & Flint Beal, 2003). Reducing oxidative damage could potentially slow down the aging process.

5.3.2 Role in extending lifespan

Human lifespan has significantly increased over the past century, though the rate of this increase has slowed in recent years. Consequently, scientists continue to explore methods to enhance longevity. Research has shown that both dietary and genetic interventions can slow the aging

process in mammals (Michael T. Lin & Flint Beal, 2003). One of the few known interventions that can decelerate aging is caloric restriction. Studies have demonstrated that caloric restriction reduces mitochondrial ROS generation in mice and rats (Michael T. Lin & Flint Beal, 2003; Sohal & Weindruch, 1996). It has also been shown to decrease heart 8-hydroxy-2′-deoxyguanosine in mitochondrial DNA, although it does not have the same effect on nuclear DNA. In humans, a 2-year clinical trial led by Leanne Redman and colleagues explored the impact of caloric restriction on aging and health. The study revealed that a 15% reduction in caloric intake over two years resulted in an average weight loss of 8.7 kg. Participants in the treatment group showed a 10% reduction in sleeping metabolic rate, a biomarker for decreased aging, as well as lower levels of ROS and thyroid hormone T3 (Leong, 2018; Redman, et al., 2018). Caloric restriction is also recognized as one of the most effective interventions for reducing the incidence and progression of various cancers, including limiting tumor growth and metastasis, such as from the breast to the lung (Pomatto-Watson, et al., 2021).

5.4 Immune function

5.4.1 Antioxidants in immune response

The immune response is intricately linked to oxidative stress. ROS, RNS, and other RS play pivotal roles in immunity. In addition to initiating cytotoxic reactions to defend against pathogens, redox reactions also regulate and shape the immune response, influencing both the initiation and termination of cellular restorative processes. Redox-activated signaling events help ensure immune responses occur at the correct spatial and temporal (Gostner, Becker, Fuchs, & Sucher, 2013). During immune-inflammatory responses, redox changes are orchestrated by the actions of NF-κB, HIF1α, mTOR, PI3K/AKT, MAPK, AMPK, and PPARs. The survival and function of individual immune cells are influenced by both extracellular and intracellular levels of RS (G. Morris, Gevezova, Sarafian, & Maes, 2022).

Macrophages can be activated by ROS, cytokines, and NF-κB signaling pathways (Dorrington & Fraser, 2019; G. Morris, et al., 2022). When NF-κB is upregulated, it enhances the expression of proinflammatory chemokines and cytokines, HIF1α, and iNOS (254). These enzymes and signaling pathways are essential for maintaining macrophage M1 polarization and activation. However, M2 polarization is associated with increased fatty acid oxidation (Van den Bossche, O'Neill, & Menon, 2017).

The immune response is also regulated by cellular antioxidants, including NRF2, the HDL/ApoA1/PON1 complex, and the glutathione and thioredoxin systems. For example, the activity of GSH systems and GSH levels directly influence macrophage polarization and function (D. Morris, et al., 2013). Thioredoxin plays a critical role in modulating macrophage migration inhibitory factor, affecting the inflammatory status of macrophages (Son, et al., 2009). NRF2 further regulates macrophage by reducing the activity of proinflammatory cytokines, such as IL-1β and IL-6, thus exerting an anti-inflammatory effect (E. H. Kobayashi, et al., 2016). Fucoxanthin, a xanthophyll carotenoid, has been shown that reduces LPS-induced inflammation and oxidative stress by activating Nrf2 through the PI3K/AKT pathway in macrophages (M. B. Kim, Kang, Li, Park, & Lee, 2021).

In addition to endogenous antioxidant systems, numerous exogenous antioxidants, particularly dietary polyphenols, have been shown to modulate inflammatory responses through both direct and indirect mechanisms. For instance, epigallocatechin gallate can protect microglia from hypoxia-induced inflammation and oxidative stress via abrogating the NF-κB pathway (S. R. Kim, Seong, Kim, & Jung, 2022). By targeting signaling pathways like MAPK and NF-κB, epigallocatechin gallate reduced CSM-induced inflammatory chemokine interleukin (IL)-8

productions in cell model (Y. Liang, Ip, & Mak, 2019). These findings suggest that antioxidants can play a significant role in dampening inflammatory responses and may have therapeutic potential for diseases characterized by chronic inflammation.

Moderate oxidative stress serves as a mechanism for immune cells to eliminate pathogens; however, excessive oxidative stress may impair immune function. Antioxidants, including Vit C, Vit E, zinc, and selenium, play a crucial role in regulating immune responses, protecting immune cells from self-generated free radical damage, thereby sustaining normal immune function and enhancing resistance.

5.4.2 Prevention of infections

Free radicals are generated by various pathogenic agents and play a crucial role in establishing their virulence and pathogenicity by damaging the immune system's cells (Kaur, Kaur, & Kaur, 2018). Recent research emphasizes the significance of antioxidants in preventing infectious diseases. These antioxidants can be provided externally through foods or supplements, or endogenously produced by the body (Kaur, et al., 2018).

Dietary antioxidants, such as VitA, C, and E, have been shown to modulate the host’s resistance or susceptibility to infectious diseases. VitA is essential for modulating T helper cell differentiation, lymphocyte activation, and tissue-specific lymphocyte homing (Mora, Iwata, & von Andrian, 2008). High levels of VitC are associated with enhanced T cell proliferation, increased cytokine production, and improved immunoglobulin synthesis (Carr & Maggini, 2017). VitE helps improve immunocompetence by boosting resistance to bacterial infections, enhancing immune responses, and supporting cellular immunity through inflammatory cells.

Additionally, these antioxidants exhibit microbiocidal activity. VitC, in particular, is well-established in treating several bacterial infections (Hemilä, 2017).

The antimicrobial and antiviral effects of dietary components, such as grapes, berries, and walnuts, which are rich in phenolics and flavonoids, are well-documented. Interestingly, in infection-associated cancers, such as human papillomavirus-induced cervical cancer, hepatitis B virus-positive hepatocarcinoma, and helicobacter pylori-positive gastric cancer, high doses and long-term use of antioxidants may help prevent or delay carcinogenesis through redox-dependent molecular pathways (Ahn, et al., 2003; Andreone, et al., 2001; Correa, et al., 2000; De Luca, Kharaeva, & Korkina, 2015; J. Kim, et al., 2010).

6 Therapeutic interventions and clinical trials

6.1 Antioxidant supplementation

ROS is widely believed to cause or exacerbate various human pathologies, including neurodegenerative diseases, cancer, and many other ailments. Antioxidants are thought to counteract the harmful effects of ROS and prevent or treat oxidative stress-related diseases. Much research has been done on using antioxidant supplements to prevent and treat various diseases (Ashok, et al., 2022).

6.1.1 Evidence from clinical trials

In recent years, there has been a significant increase in clinical research focused on the therapeutic use of antioxidants for various diseases. These studies provide valuable insights into the potential benefits and limitations of antioxidant supplementation in managing chronic conditions. Table 3 summarizes the outcomes of several clinical trials that have explored the use of antioxidants in treating a range of diseases..

One of the most studied antioxidants in clinical trials is CoQ10, which has been investigated for its potential to treat conditions such as ALS, PD, and hypertension. However, trials involving CoQ10, such as those for ALS and PD, have shown limited or no significant benefits. On the other hand, CoQ10 did show some effects in hypertensive patients, such as increasing adiponectin levels (Bagheri Nesami, Mozaffari-Khosravi, Najarzadeh, & Salehifar, 2015). Curcumin, another widely studied antioxidant, demonstrated promising results in clinical trials for AD and ALS. Specifically, curcumin was associated with slowing cognitive decline in Alzheimer's patients (Baum, et al., 2008) and slowing disease progression in ALS patients (Chico, et al., 2018). These findings suggest that curcumin may have therapeutic potential for neurodegenerative diseases, particularly in reducing inflammation and oxidative damage.

Resveratrol has been the subject of several clinical trials investigating its effects on aging, diabetes, and cardiovascular diseases. Resveratrol supplementation showed positive results in reducing glucose levels in older adults,supporting the study of resveratrol for improving cardio-metabolic health in older adults in larger clinical trials (Anton, et al., 2014), improving endothelial function in chronic kidney disease patients (Gimblet, et al., 2024), and modulating neuro-inflammation in AD patients (Moussa, et al., 2017). Sulforaphane has also been studied for its therapeutic effects in conditions such as autism spectrum disorder, chronic kidney disease, and type 2 diabetes.

Despite the extensive research conducted on antioxidants, several areas remain underexplored, particularly in understanding the long-term effects and optimal dosages of these compounds. Furthermore, the exact mechanisms by which antioxidants exert their effects are still not fully understood, requiring more in-depth mechanistic studies. The variability in study designs,

antioxidant dosages, and patient demographics also highlights the need for more standardized trials to draw conclusive evidence.

Table 3. Clinical trials of antioxidants in diseases.

Antioxidants	**Disease**	**Route**	**Dosage**	**Follow up period**	**Outcome**	**References**
CoQ10	Amyotrophic lateral sclerosis	Oral	1800 or 2700 mg/day	9 months	No evidence of benefit	(Kaufmann, et al., 2009)
CoQ10	Parkinson disease	Oral	1200 or 2400 mg/day	16 months	No evidence of benefit	(Beal, et al., 2014)
CoQ10	Hypertensive	Oral	100 mg/day	12 weeks	Increasing adiponectin and pro-inflammatory factors	(Bagheri Nesami, et al., 2015)
Curcumin	Alzheimer disease	Oral	1 or 4 g/day	6 months	May decline the cognitive deterioration slowdown	(Baum, et al., 2008)
Curcumin	Amyotrophic lateral sclerosis	Oral	600 mg/day	6 months	Slowdown in disease progression	(Chico, et al., 2018)

Ebselen	Meniere's disease	Oral	200, 400, 600 mg/ twice daily	21 days	Improvements in low-frequency hearing	(Kil, Huang, Nguyen, Chandrasekhar, & Lambert, 2018)
GC4419	Oropharyngeal carcinoma	Intravenous infusion	30 mg or 90 mg/ day	6-7 weeks	Reduce the oral mucositis in patients	(Anderson, et al., 2016)
GSH	Parkinson disease	Intranasal	300 mg or 600 mg/day	3 months	Improving UPDRS scores	(Mischley, et al., 2015)
GSH	Parkinson disease	Intranasal	100 mg or 200 mg/day	3 months	The high-dose group demonstrated improvement in UPDRS score	(Mischley, Lau, Shankland, Wilbur, & Padowski, 2017)
Orgotein	Bladder cancer	Intramuscular injection	8 mg/day	NA	Reduce the acute radio-induced damage	(Sanchiz, et al., 1996)

Resveratrol	Aging	Oral	300 mg or 1000mg twice daily	12 weeks	Reduce the glucose levels.	(Anton, et al., 2014)
Resveratrol	Alzheimer disease	Oral	1 g/day	52 weeks	Resveratrol treatment attenuated declines in MMSE score, modulated neuro-inflammation	(Moussa, et al., 2017)
Resveratrol	Chronic kidney disease and diabetes	Oral	400 mg/day	6 weeks	Improved endothelial function in patients	(Gimblet, et al., 2024)
Resveratrol	Diabetic nephropathy	Oral	500 mg/day	90 days	Reduce albumin excretion	(Sattarinezhad, Roozbeh, Shirazi Yeganeh, Omrani, & Shams, 2019)

Resveratrol	Dilated cardiomyopathy	Oral	500 mg twice daily	12 months	NA	ClinicalTrials.gov ID: NCT01914081
Resveratrol	Friedreich ataxia	Oral	500 mg twice daily	24 weeks	NA	ClinicalTrials.gov ID: NCT03933163
Resveratrol	Hypertensive	Oral	300 mg/day	NA	NA	ClinicalTrials.gov ID: NCT02616822
Resveratrol	Metabolic Syndrome	Oral	1000 mg/ three times daily	3 weeks	NA	ClinicalTrials.gov ID: NCT02219906
Resveratrol	Nondialyzed chronic kidney disease	Oral	500 mg/day	4 weeks	No antioxidants or anti-inflammatory effects were observed in patients.	(Saldanha, et al., 2016)

Sulforaphane	Autism spectrum disorder	Oral	2.2 µmol/kg/day	15 weeks	There is no significant difference between the sulforaphane group and the placebo group, but a positive one.	(Zimmerman, et al., 2021)
Sulforaphane	Breast cancer	Oral	Once daily	12weeks	NA	ClinicalTrials.gov ID: NCT03934905
Sulforaphane	Chronic kidney disease	Oral	4 g/day	2 months	NA	ClinicalTrials.gov ID: NCT04608903
Sulforaphane	Chronic obstructive pulmonary disease	Oral	4.4 mg or 26.6 mg/day	4 weeks	No different among the groups	(Wise, et al., 2016)
Sulforaphane	Depression	Oral	NA	12 weeks	NA	ClinicalTrials.gov ID:

						NCT04246905
Sulforaphane	Type 2 diabetes	Oral	Once daily	12 weeks	Reduce fasting blood glucose and glycated hemoglobin in patients	(Axelsson, et al., 2017)
Vitamin C, vitamin E	Hypertension	Oral	1 g/day, 400 IU/day	8 weeks	Reduce blood pressure	(Rodrigo, Miranda-Merchak, Valenzuela Grau, Bachler, & Vergara, 2014)
Vitamin E	Diabetes	Oral	400 IU/day	8 weeks	Vitamin E decreases fasting blood sugar and insulin resistance	(Rafraf, Bazyun, Sarabchian, Safaeiyan, & Gargari, 2016)

Vitamin E, memantine	Alzheimer Disease	Oral	2000 IU/day, 20 mg/day	4 years	The Vitamin E group showed lower functional decline	(Dysken, et al., 2014)
Vitamin E, Selenium	Non-melanoma Skin Cancers	Oral	100 mg/day, 200 ug/day	6 years	NA	ClinicalTrials.gov ID: NCT00392561

6.1.2 Safety and efficacy concerns

While there is substantial evidence supporting the benefits of antioxidant supplements in managing chronic diseases associated with aging, cardiovascular diseases, and diabetes, it is important to recognize that excessively high doses of antioxidants may not always be beneficial. In fact, they can interfere with normal cellular signaling and essential cell functions (Milisav, Ribarič, & Poljsak, 2018). High doses of antioxidants can have detrimental effects on the human body. For instance, excessive daily β-carotene intake has been associated with an increased risk of lung cancer (Kordiak, Bielec, Jabłoński, & Pastuszak-Lewandoska, 2022), while high doses of vitamin E have been shown to cause serious bleeding events by impairing blood clotting after an injury (Abrol, et al., 2023). Although vitamin C is generally considered safe at high intake levels, it can cause gastrointestinal disturbances such as nausea and diarrhea (Jacob & Sotoudeh, 2002). Overall, the therapeutic use of small-molecule antioxidants has yielded unsatisfactory results, largely due to overly optimistic or incorrect assumptions about their mechanisms of action (H. J. Forman & H. Zhang, 2021).

Despite promising preclinical results, many small-molecule antioxidants have shown disappointing outcomes in clinical trials (H. J. Forman & H. Zhang, 2021). Current evidence does not support the idea that antioxidants can effectively prevent cancer. In 2022, the US Preventive Services Task Force recommended against the use of beta-carotene or vitamin E supplements for preventing cardiovascular diseases or cancer (Mangione, et al., 2022; O'Connor, et al., 2022). Furthermore, studies have demonstrated that vitamin E supplementation could increase the risk of prostate cancer (Klein, et al., 2011), and there are indications that antioxidant supplements may interfere with chemotherapy, potentially reducing its efficacy (Wieland, et al., 2021).

One key factor behind the limited effectiveness of antioxidants in clinical settings is their low effective biological concentration. Another concern is the potential for nonspecific effects. While NRF2 activation and the induction of antioxidant enzymes are beneficial, some NRF2 activators may also influence other signaling pathways, disrupting related biological processes.. For example, sulforaphane can suppress the inflammatory response by inhibiting NF-κB and inflammasome activation (Greaney, Maier, Leppla, & Moayeri, 2016), It can also cause cell cycle arrest by inhibiting the PI3K–AKT and MAPK–ERK pathways (Roy, Srivastava, & Shankar, 2010). However, many of these nonspecific effects have only been investigated *in vitro*, with concentrations of sulforaphane exceeding 10 μM, a level that is unlikely to be achieved *in vivo*.

Moreover, the activation of NRF2 and the induction of antioxidant enzymes are not restricted to specific cells or organs, which may result in systemic side effects. For example, although NRF2 activation can prevent the initiation of cancer, it may paradoxically promote cancer progression under certain conditions (Le Gal, et al., 2015; Wiel, et al., 2019; Zou, et al., 2021).

The commercialization of antioxidant products containing small molecules that do not function as expected *in vivo* will ultimately lead to disappointment. These products are unlikely to provide benefits beyond what can be achieved through a diet rich in antioxidant enzyme-inducing nutrients. This realization poses a significant challenge to the development of effective therapeutics and may hinder the public's acceptance of truly effective antioxidant-based treatments (Henry Jay Forman & Hongqiao Zhang, 2021).

6.2 Dietary interventions

6.2.1 Role of diet in maintaining antioxidant levels

The Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes defines dietary antioxidants as substances found in food that can reduce the adverse effects of ROS and RNS on normal human physiological functions (Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference, 1998). These dietary antioxidants include Vit C, Vit E, carotenoids such as β-carotene, polyphenols, and essential minerals like zinc and selenium, among others. Primarily sourced from fruits and vegetables, these antioxidants play a key role in maintaining antioxidant levels in the body, decreasing ROS levels, preventing cellular damage, and contributing to overall metabolic health. Through these mechanisms, they help reduce the risk of chronic diseases (Bjørklund & Chirumbolo, 2017; Halliwell, 1996; Z. Liu, et al., 2018).

6.2.2 Examples of antioxidant-rich diets

The Mediterranean and Atlantic diets are among the most well-known examples of antioxidant-rich dietary patterns. These diets are abundant in fruits, vegetables, legumes, olive oil, and whole grains, providing essential vitamins (such as C, E, A, and B-12), minerals (including selenium, zinc, iron, and manganese), and polyphenols. These components are crucial for

maintaining antioxidant levels and supporting immune function. The Mediterranean diet has garnered widespread attention for its health benefits. Numerous studies have shown that it can reduce the risk of cardiovascular disease, metabolic syndrome, diabetes, certain cancers, and even depression (Martínez-González, Gea, & Ruiz-Canela, 2019; Martini, 2019). Additionally, it is associated with a lower risk of sudden cardiac death, particularly in women (Bertoia, et al., 2014). The Atlantic diet, based on the traditional eating patterns of northern Portugal and northwest Spain, includes more potatoes, dairy, and red meat compared to the Mediterranean diet. Recent studies have indicated that a 6-month intervention based on the Atlantic diet significantly reduces the risk of incident cases of metabolic syndrome (Cambeses-Franco, et al., 2024). Other research suggests that the Atlantic diet may help alleviate depression and promote longevity (Carballo-Casla, et al., 2024; Carballo-Casla, et al., 2023). Notably, olive oil, a key component of both the Mediterranean and Atlantic diets, has been shown to lower the risk of cardiovascular disease and is associated with reduced mortality from both total and cause-specific factors (Guasch-Ferré, et al., 2022). Polyphenols, which are soluble compounds found in fruits, vegetables, red wine, and tea, are especially prevalent in the Mediterranean diet. Key polyphenols such as resveratrol, catechins, and curcumin, contribute to the antioxidant properties of these diets.

6.3 Pharmacological agents

6.3.1 FDA-approved antioxidant drugs

Despite the promising potential of antioxidants in the treatment of various diseases, their approval by the U.S. Food and Drug Administration (FDA) remains limited. The primary obstacle is the lack of conclusive evidence from randomized clinical trials (RCTs) demonstrating the consistent efficacy of antioxidant therapies. This inconclusive evidence has

hindered the widespread approval of antioxidant drugs by regulatory agencies like the FDA (Ghezzi, Jaquet, Marcucci, & Schmidt, 2017).

Despite these challenges, there are a few FDA-approved antioxidant drugs, though they are relatively limited in scope. Medihoney® is the only antioxidant product specifically cleared by the FDA for wound healing. It is used to manage oxidative stress in wounds, promoting the healing process (314). Another notable FDA-approved antioxidant drug is Radicava ORS (Edaravone), which is used in the treatment of ALS and ischemic stroke (Y. Y. Ma, et al., 2024; Pattee, et al., 2023). Table 4 below summarizes the FDA-approved antioxidant drugs currently available, including those approved for various indications ranging from chronic diseases like multiple sclerosis and rheumatoid arthritis to advanced primary cutaneous T-cell lymphoma treatments.

Table 4. List of FDA-approved antioxidant drugs.

Drug	**Sponsor**	**Indication**	**Regulatory Status**
AEOL 10150	Aeolus Pharmaceuticals Inc.	Idiopathic Pulmonary Fibrosis	FDA orphan drug designation (2015)
Allopurinol	Burroughs Wellcome	Adult patients with signs and symptoms of primary or secondary gout	FDA-Approved (1966)
Antabuse (Disulfiram)	Odyssey Pharmaceuticals, Inc.	Alcoholism	FDA-Approved (1951)

Ascor (Ascorbic acid injection)	McGuff Pharmaceuticals Inc.	Scurvy	FDA-Approved (2017)
Auranofin	Ctr for Discovery & Innovation in Parasitic Diseas	Rheumatoid arthritis	FDA-Approved (1985)
Bafiertam (Monomethyl fumarate)	Banner Life Sciences, LLC	Multiple sclerosis	FDA-Approved (2013)
Bucillamine	Revive Therapeutics Ltd.	Ischemia-reperfusion injury during liver transplantation	FDA orphan drug designation (2022)
Coreg (Carvedilol)	GlaxoSmithKline	Mild to severe chronic heart failure	FDA-Approved (1995)
Halfan (Halofantrine)	SmithKline Beecham	Malaria	FDA-Approved (1992)
INOmax (Nitric oxide)	INO Therapeutics, Inc.,	Hypoxic respiratory failure in premature neonates	FDA-Approved (1999)
Lodoxamide tromethamine	Alcon Laboratories, Inc.	Vernal keratoconjunctivitis	FDA-Approved (1993)

Medihoney wound gel	Derma Sciences, Inc.	Acute and chronic wounds and burns	FDA-Cleared (2007)
Mirapex (Pramipexole)	Pharmacia & Upjohn, Inc.	Signs and symptoms of idiopathic Parkinson's disease	FDA-Approved (1997)
PSX-514 (Ultra-pure epigallocatechin gallate)	PharmassêtX	Pouchitis	FDA orphan drug designation (2024)
Radicava ORS (Edaravone)	Mitsubishi Tanabe Pharma America, Inc.	Amyotrophic lateral sclerosis	FDA-Approved (2022)
Rucosopasem manganese	Galera Therapeutics, Inc.	Pancreatic cancer	FDA orphan drug designation (2023)
Skyclarys (Omaveloxolone)	Biogen Idec Inc.	Friedreich’s ataxia	FDA orphan drug designation (2023)
Solage (Mequinol 2%, Tretinoin 0.01%)	Bristol-Myers Squibb Pharmaceutical Research Institute	Solar lentigines	FDA-Approved (1999)
Tecfidera (Dimethyl fumarate)	Biogen Idec Inc.	Multiple sclerosis	FDA-Approved (2013)
TRENTAL (Pentoxifylline)	Upsher-Smith Laboratories, Inc.	Patients with intermittent claudication on the	FDA-Approved (1999)

		basis of chronic occlusive arterial disease of the limbs	
Uloric (Febuxostat)	Takeda Pharmaceuticals Inc.	Hyperuricemia in patients with gout	FDA-Approved (2009)
Vorasidenib	Voranigo，Servier Pharmaceuticals LLC	Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation	FDA-Approved (2024)
Vumerity (Diroximel fumarate)	Biogen Inc.	Multiple Sclerosis	FDA-Approved (2019)
Zolinza (Vorinostat)	Merck & Co., Inc	Advanced Primary Cutaneous T-Cell Lymphoma	FDA-Approved (2006)

7 Future research

Advancements in oxidative stress and antioxidant systems are paving the way for innovative therapies. Key areas of focus include the development of novel antioxidants, high-throughput screening for drug discovery, and gene therapy targeting metabolic pathways. Cutting-edge technologies such as AI-driven modeling, real-time ROS detection, and precision drug delivery systems are expected to revolutionize treatment for cancer, neurodegenerative disorders, and other oxidative stress-related diseases. Personalized medicine, leveraging genetic profiling and

targeted therapies, will further enhance therapeutic outcomes. These multidisciplinary approaches hold great promise for improving health and disease management (Fig. 7).

7.1 Advances in the detection and measurement of ROS

The detection and measurement of ROS have made significant strides in recent years, owing to advances in technology. Traditional methods, such as chemical fluorescence probes, have been complemented by more sophisticated techniques like high-throughput sensors and mass spectrometry for redox proteomics (Butterfield, Gu, Di Domenico, & Robinson, 2014; Q. Liu, et al., 2023; McDonagh, 2017). These advancements enable researchers to capture subtle variations in redox proteomics, crucial for understanding their role in various diseases. Looking ahead, the development of real-time and dynamic monitoring technologies will play a key role in early disease diagnosis and the advancement of personalized treatments (Abdesselem, et al., 2023). The ability to track ROS levels in real-time within living organisms could pave the way for more targeted and efficient therapeutic strategies. Additionally, the rise of single-cell analysis technologies has provided a breakthrough in understanding ROS dynamics at the individual cell or even the organelle level (K. Liu, et al., 2023; Pleskova, et al., 2023). This capability allows researchers to explore the heterogeneous responses of cells to oxidative stress, offering new insights into disease mechanisms and enabling more precise, cell-specific interventions in the treatment of conditions linked to ROS, such as cancer and neurodegenerative diseases. Currently, research into oxidative stress is focused on two main aspects: identifying more sensitive and disease-specific markers of oxidative stress, and refining technologies for more efficient and accurate measurement. These efforts are aimed at improving our ability to monitor oxidative stress levels in various conditions and develop more precise diagnostic tools.

In clinical and translational research, assessing oxidative stress involves a comprehensive approach that includes: (1) direct measurement of ROS levels, (2) detection of biomarkers for ROS-induced molecular damage and the stabilization of final reaction products, and (3) evaluating the antioxidant system (including enzymatic and nonenzymatic antioxidant activities, transcription factors, and total antioxidant capacity [TAC]). However, direct measurement of ROS remains challenging due to their rapid reactivity and short half-lives. While advanced systems like electron paramagnetic resonance (EPR) spectroscopy can measure ROS through their unpaired electron signals (Suzen, Gurer-Orhan, & Saso, 2017), these methods are expensive and difficult to reproduce in everyday clinical settings.

As a result, biomarkers for oxidative stress-induced damage are more commonly used to assess oxidative stress levels. Traditional biomarkers, such as 8-OHdG, MDA, and protein carbonyls (oxidative protein products), have been widely employed and generally show consistent trends with oxidative stress damage in various diseases (Dalle-Donne, Rossi, Giustarini, Milzani, & Colombo, 2003; Feng, Hu, Marnett, & Tang, 2006; Fenga, et al., 2017; Khelfi, 2024). More recently, novel oxidative stress biomarkers have been discovered and validated for specific diseases. For instance, dynamic thiol-disulfide homeostasis (DTDH) may serve as a potential biomarker for oxidative stress in autism, while serum free thiols have been identified as potential markers for schizophrenia spectrum disorders (Borkent, et al., 2023; Efe, Neşelioğlu, & Soykan, 2021). Advances in bioinformatics, machine learning, and public datasets have also facilitated large-scale identification of oxidative stress markers. For example, studies using weighted gene co-expression network analysis (WGCNA) and machine learning have identified CD63 as a biomarker for immune-related oxidative stress in diabetic nephropathy (M. Xu, et al., 2023). Furthermore, computational models and datasets now allow for the quantitative

evaluation of TAC within tissues and cells (J. Bai, Tan, An, & Xu, 2022; L. Liu, Cui, & Xu, 2020).

7.2 Development of novel antioxidants and their mechanisms

Antioxidant therapy plays a major role in the treatment of ROS-related diseases accompanied by oxidative damage, inflammation, and cell death. The discovery and development of novel antioxidants is expected to make progress in addressing these diseases. Currently, many antioxidants are broad-spectrum, which, while effective at reducing ROS levels, lack the precision necessary for optimal therapeutic outcomes. These agents are not able to selectively target ROS in specific tissues or pathological conditions, which may result in the disruption of normal physiological processes. Therefore, there is increasing interest in designing targeted antioxidants, such as mitochondria-directed antioxidants, enzyme mimetics, and nanocarrier-based delivery systems, which can localize treatment to sites of excessive ROS generation. In the future, research is likely to focus on developing more specific and targeted antioxidants that can precisely modulate ROS levels within particular cellular environments, minimizing side effects while maximizing therapeutic efficacy.

Since a disease usually has multiple pathogenic factors, it is necessary to screen and develop multi-functional antioxidants that can target multiple molecular targets, or to combine antioxidants with drugs targeting other targets and disease pathways to achieve the best therapeutic effect (Brown, Cheung, Lee, Zhao, & Chait, 2002; H. Y. Zhang, Yang, & Tang, 2006).

7.3 Novel drug delivery system

Another problem faced by antioxidant therapy in clinical transformation and application is that due to poor solubility and uncontrollable stability of antioxidants in the human body, their ability to reach pathological sites is limited and their bioavailability is poor, making it difficult to exert therapeutic effects. Currently, the nanoparticle-based drug delivery systems have been widely studied to improve the precision and availability of antioxidant delivery (Ashok, et al., 2022). By encapsulating antioxidant drugs into nanocarriers to obtain NP-antioxidant, the active targeting and stability of antioxidants can be significantly improved. At the same time, the properties of nanoparticles also enable them to be enriched in pathological sites, thereby achieving precise release of antioxidants without the risk of rapid metabolism or clearance, which is a common problem with traditional antioxidants (R. Hu, et al., 2023; S. Li, Li, Xu, Saw, & Zhang, 2020; H. Xu, et al., 2022). This targeted delivery is especially beneficial in treating diseases where ROS plays a central role, such as diabetes, atherosclerosis, and liver diseases (Flores, et al., 2020; S. Li, et al., 2020; Pengju Zhang, et al., 2020).

In addition to nanoparticles, are also being explored to accommodate different antioxidant molecular structures and different pathological conditions (Binatti, et al., 2021; J. Liu, et al., 2022). For example, hydrogel carriers incorporating antioxidants can sustainably release antioxidants, effectively neutralizing ROS at the disease site. Furthermore, their porous structure facilitates cell replication and migration, facilitating tissue regeneration and repair (B. Hu, et al., 2024). Polymer-based drug delivery systems are also widely used in antioxidant therapy. Polymer materials exhibiting antioxidant properties have been developed by polymerizing antioxidant groups into the structure of polymersomes or polymeric micelles to achieve higher antioxidant effects. At the same time, by polymerizing some combined therapeutic drugs or imaging agents, more intelligent antioxidant delivery can be achieved (K. Y. Lee, et al., 2015; Yeo, Lee, Lee, & Kim, 2021). These delivery systems not only increase

the therapeutic potential of antioxidants but also allow for better tissue-specific targeting, which can significantly improve treatment outcomes.

7.4 High-throughput screening of antioxidants

In clinical settings, antioxidant-based therapeutic strategies have already shown significant promise in managing diseases such as atherosclerosis, chronic obstructive pulmonary disease, diabetic retinopathy, and various neurodegenerative diseases (Barnes, 2020; H. J. Forman & H. Zhang, 2021; J. Gao, Tao, & Jiang, 2023; M. Liang, et al., 2024; Morén, deSouza, Giraldo, & Uff, 2022). However, conventional antioxidant screening processes are often time-consuming and costly. As a result, the need for more efficient screening methods to identify antioxidants from both natural and synthetic sources is critical. The integration of advanced screening technologies can address this challenge, enabling researchers to identify potent antioxidants more rapidly and cost-effectively.

Moreover, current research increasingly employs a combination of advanced technologies to conduct high-throughput screening. Mass spectrometry has become a standard method for the qualitative analysis of antioxidants, providing accurate and detailed data (Hong, Wang, Barrow, Dunshea, & Suleria, 2021; Zeb, 2021). Moreover, high-volume, automated technologies such as 96-well microplates and microarray chip systems have been developed to improve throughput and increase screening efficiency (Musa, Abdullah, Kuswandi, & Hidayat, 2013; Sun, et al., 2019). Furthermore, online analysis systems enable automatic real-time screening of antioxidants, allowing for the simultaneous analysis of larger numbers of samples and improving the overall efficiency of the process (Y. Lu, Wu, Fang, Shaheen, & Wei, 2017; Z. Zhang, et al., 2022).

7.5 Individual variability in response to antioxidants

The response to antioxidants varies significantly across individuals, influenced by factors such as genetic background, immune status, and metabolic pathways. This variability underscores the importance of personalized treatment strategies when managing oxidative stress-related diseases (Margaritelis, Paschalis, Theodorou, Kyparos, & Nikolaidis, 2018). As we continue to progress in the field of antioxidant research, a primary focus will shift toward understanding these individual differences. By identifying how factors like genetic predisposition, immune function, and individual metabolic pathways contribute to the varied responses to antioxidants, researchers will be better equipped to develop tailored therapies.

This personalized approach is crucial because it recognizes that a one-size-fits-all solution may not be effective for everyone. For instance, the same antioxidant may have different effects on two individuals with distinct genetic profiles or immune responses. This is where precision medicine becomes indispensable. Personalized antioxidant therapies will not only optimize treatment efficacy but also minimize potential side effects, ensuring that each patient receives the most effective intervention based on their unique biological makeup. For healthcare providers, the ability to offer such tailored therapies could significantly improve the management of diseases like cancer, neurodegenerative conditions, and cardiovascular diseases, where oxidative stress plays a key role.

Furthermore, advances in genomics and epigenomics will be pivotal in the development of personalized antioxidant strategies. By studying genetic variations, researchers can uncover specific gene mutations or polymorphisms that influence how an individual responds to antioxidants. Similarly, epigenetic modifications, such as DNA methylation and histone modifications, could provide insights into how environmental factors, lifestyle choices, or

disease states affect the antioxidant response. This deeper understanding of genetic and epigenetic variations will help explain why certain populations respond more favorably to antioxidant treatments than others.

With these insights, the creation of personalized ROS regulation strategies will be possible, which may lead to more effective and individualized antioxidant interventions. Such advancements could significantly improve therapeutic outcomes by allowing healthcare providers to fine-tune antioxidant treatments for patients, ultimately optimizing their quality of life and enhancing disease management. The ability to match antioxidant therapies to specific genetic and epigenetic profiles represents the next frontier in treating oxidative stress-related conditions.

7.6 Antioxidant gene therapy

Another major strategy in combating oxidative stress-related diseases is enhancing the synthesis of endogenous antioxidant enzymes, along with the de novo synthesis of GSH through the NRF2 signaling pathway in cells (Henry Jay Forman & Hongqiao Zhang, 2021). This strategy has gained attention due to its potential to boost the body's natural defense mechanisms against oxidative damage.

Gene therapy holds significant promise in addressing oxidative stress-related diseases, particularly with the use of gene editing technologies such as CRISPR/Cas9. These cutting-edge tools allow for precise modifications of the genome, enabling the direct regulation of antioxidant enzyme genes that are implicated in ROS production. By targeting key antioxidant enzymes, gene therapy has the potential to enhance the cell’s intrinsic antioxidant capacity, making it an attractive therapeutic option for diseases driven by ROS imbalances. This includes

chronic conditions like cancer, cardiovascular diseases, and neurodegenerative disorders, where oxidative stress plays a pivotal role in disease progression. Gene therapy not only offers the possibility of correcting oxidative stress imbalances but also represents a more personalized, tailored approach to treatment by addressing the root cause of these diseases at the genetic level.

The potential of these strategies to restore the body's natural defenses against ROS opens up new therapeutic avenues that were previously unattainable. Moreover, these approaches could reduce the need for broad-spectrum antioxidant drugs, which often have limited precision and can lead to unwanted side effects. By targeting the source of oxidative stress directly through gene editing and enzyme replacement, these strategies could pave the way for more effective, personalized treatments that offer higher therapeutic efficacy and improved patient outcomes.

7.7 New strategy against RS downstream target therapy

In future therapeutic strategies targeting ROS, there is likely to be a paradigm shift from simply clearing ROS to modulating their role in cellular signal transduction. ROS are not only by-products of cellular metabolism but also play an essential role in regulating several critical signaling pathways, including those involved in cell proliferation, apoptosis, and inflammation. These pathways are integral to the development and progression of various diseases. By targeting these ROS-induced signaling pathways, it becomes possible to more precisely control disease processes, rather than just neutralizing ROS indiscriminately. This approach offers the potential for better therapeutic outcomes by fine-tuning the balance between ROS-mediated cellular responses and disease progression.

Moreover, combining antioxidant therapies with other treatment modalities, such as immunotherapy and targeted therapies, holds great promise for improving the effectiveness of

treatment. Cancer therapy, in particular, could benefit from this synergistic approach. ROS-induced signaling can contribute to tumor progression and resistance to treatment, so by modulating ROS levels alongside other therapies, it may be possible to overcome resistance mechanisms and optimize treatment responses. This combination therapy could enhance the overall therapeutic efficacy, particularly in complex diseases like cancer, where overcoming resistance to conventional treatments remains a major challenge. Such a multifaceted strategy could increase the success rate of treatments and improve clinical outcomes for patients, providing a more comprehensive approach to disease management.

The rapid advancement of big data technologies is also set to significantly impact the understanding and treatment of ROS-related diseases. Although challenges remain, the integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, will allow researchers to gain deeper insights into the complex ROS-related pathways that drive disease. This data-driven approach will help identify new biomarkers and therapeutic targets with greater accuracy and precision, enabling more personalized medicine approaches for oxidative stress-related conditions. Furthermore, the use of machine learning algorithms and AI-driven predictive models will aid in deciphering intricate disease mechanisms and optimizing treatment strategies. As data-sharing platforms and global collaborations continue to expand, the development of targeted interventions will become more efficient, ultimately facilitating the creation of more effective prevention and treatment strategies for ROS-associated diseases in the future.

8 Conclusion

Oxidative stress, resulting from an imbalance between the production of reactive oxygen and nitrogen species (ROS/RNS) and the body’s antioxidant defenses, is a critical factor in the

development of a wide range of diseases, including cardiovascular disorders, diabetes, neurodegenerative diseases, cancer, and inflammatory conditions. While ROS are essential in regulating cellular signaling and homeostasis, excessive oxidative damage disrupts cellular function, leading to pathological consequences. The body's antioxidant defense system, composed of both enzymatic and non-enzymatic mechanisms, plays a crucial role in mitigating this damage, while exogenous dietary antioxidants provide an additional layer of protection.

Despite the body's robust defense systems, the growing understanding of oxidative stress has highlighted the need for advanced therapeutic interventions, particularly in the form of pharmacological antioxidants, dietary strategies, and clinical trials. Current therapies show promise but often fall short in targeting specific ROS-induced damage in a way that maximizes therapeutic efficacy and minimizes side effects. Future research directions are increasingly focusing on developing novel antioxidants, enhancing drug delivery systems, and incorporating cutting-edge technologies such as high-throughput screening and gene therapy. Personalized treatments that consider individual variability in response to antioxidants could revolutionize the approach to managing oxidative stress-related diseases. The future of antioxidant-based therapies will likely see a shift from merely neutralizing ROS to modulating their role in cellular signaling, which could allow for more targeted and effective treatments. The integration of multi-omics data, artificial intelligence, and machine learning will further enable the discovery of novel biomarkers and therapeutic targets, paving the way for precision medicine. Ultimately, advances in antioxidant research and therapeutic strategies hold great promise for improving disease management, slowing aging processes, and enhancing overall health outcomes. As the field continues to evolve, it is crucial that we explore these emerging strategies to unlock the full potential of antioxidants in combating oxidative stress-related diseases.

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CRediT authorship contribution statement

Hengrui Liu: Conceptualization, Visualization, Writing – original draft, Writing – review and editing. **Yaqi Jiao**: Writing – original draft, Writing – review and editing. **Peng-Chao Wang**: Writing – original draft, Writing – review and editing. **Yingjie Chen**: Writing – original draft, Writing – review and editing. **Maokai Xu**: Writing – original draft. **Xiaojuan Zhang**: Visualization, Writing – original draft, Writing – review and editing, Supervision. **Xiaochun Zheng**: Writing – original draft, Writing – review and editing, Supervision. **Zhenshan Yang**: Conceptualization, Visualization, Writing – original draft, Writing – review and editing, Supervision.

Declaration of competing interests

The authors declare no competing interests.

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