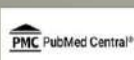
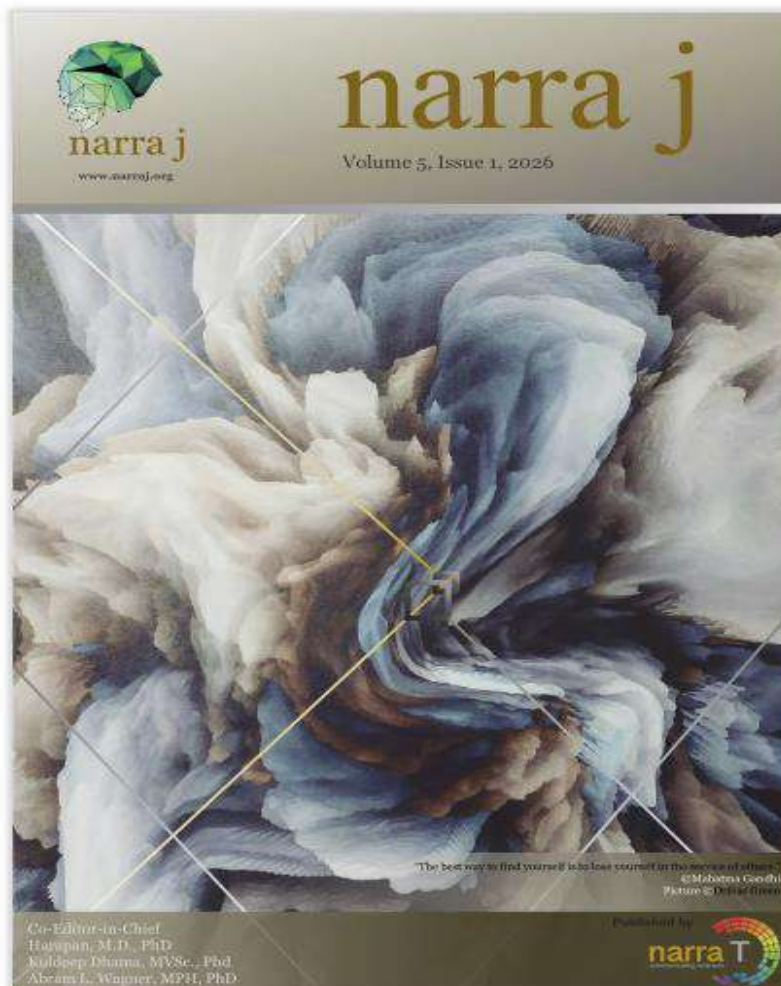


NARRA J

Vol. 6 No. 1 (2026): April 2026



This is an open-access article, content on this site is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License except where otherwise noted. Platform by OJS / PKP.

Published by Narra Sains Indonesia

e-ISSN: 2807-2618

NARRA J SINTA 1

https://sinta.kemdiktisaintek.go.id/journals/?q=narra_j



NARRA J

Google Scholar Website Editor URL

PT Narra Sains Indonesia

P-ISSN : | E-ISSN : 28072618

S1 Accredited

Garuda Indexed

3,69
Impact

25
H5-index

3.693
Citations 5yr

3.697
Citations

Previous **1** Next

Page 1 of 1 | Total Records 1

LINK JURNAL

<https://narraj.org/main/issue/view/22>

ORIGINAL ARTICLE

Delayed percentage attenuation ratio (DPAR) on multiphase CT as a quantitative predictor of early response in hepatocellular carcinoma

Yana Supriatna, Rifki Bachtiar, Muhammad Y. Makaraeng, Arif Budiman



Knowledge, attitudes, and practices related to the intergenerational cycle of malnutrition among adolescent girls: A school-based cross-sectional study

Tirumalasetti L. Varshitha, Sarada Vadlamani, Chaitanya Gujjalapudi, Manasa R. Venkata, Payala Vijayalakshmi

e2993



Multi-stakeholder perspectives on cervical cancer screening implementation in Indonesia: A qualitative study of cervical screening barriers in Banda Aceh

Febrina Yolanda, Tgk. Puspa Dewi, Sarah I. Nainggolan, Munawar Munawar, Munizar Munizar, Rijal Bulqini, Rachmad Suhandi, Rusnaidi



Development and evaluation of a synthetic Cu-Zn-reinforced biphasic calcium phosphate scaffold for periodontal bone repair

Devina Novelia, Theophani O. Cahyadi, Natasya MP. Sidharta, Mora Octavia, Evi UM. Situmorang, Daniel Edbert



Neurocognitive consequences of occupational heavy metal exposure among electronic waste sorting workers in Thailand

Wanwan, Deenthaip Komulkeo, Ananai Thathathakul

e2994

Patient experience, satisfaction, and adherence: Mediating roles of communication and outcome quality among geriatrics

Stepvia Stepvia, Juan AG. Silimalar, Oscar Jayanagara

e3015



Determinants of intrauterine device use among reproductive-age women in a province implementing Islamic Sharia law in Indonesia: An application of the theory of planned behavior

Dean R. Purnama, Tgk. Puspa Dewi, Rusnaldi Rusnaldi, Niken A. Utami, Rizka Aditya, Rachmad Suhandu

e3025



Loving-kindness moderates the association between neuroticism and anxiety symptoms among Thai older adults

Moe P. Phyu, Justin DeMaranville, Peerasak Lertrakarnnon, Danny Wedding, Nahathai Wongpakaran, Tinakon Wongpakaran

e3012



Enhancing neuromuscular recovery after sciatic nerve injury using stem cell therapy: Evidence from a preliminary preclinical study

Cut R. Firlana, Dessy R. Emril, Dedy Syahrizal, Cynthia R. Sartika, Nova D. Lestari, Yopie A. Habibie



SHORT COMMUNICATION

Predicting early in-hospital mortality in acute hemorrhagic stroke: Implications for improving stroke care and health outcomes in low-income settings

Shefina P. Harnold, Syahrul Syahrul, Imran Imran, Nasrul Musadir, Muhammad Yani



Evaluating serum cyclooxygenase-2 and vascular endothelial growth factor as biomarkers for endometriosis severity in reproductive-age women

Aga Aslam, Rajuddin Rajuddin, Munizar Munizar, Rusnaldi Rusnaldi, Hasanuddin Hasanuddin



Relationship between serum CA125, prolactin and cortisol levels with disease stage and pain level in endometriosis patients

Teuku A. Fasha, Rajuddin Rajuddin, Tgk. Puspa Dewi, Rusnaldi Rusnaldi, Munizar Munizar

e2988



REVIEW ARTICLE

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

Meutia A. Faradilla, Karina S. Anastasya, Deasyka Yastani, Yohana Yohana, Endrico X. Tungka, Suweino Suweino



Biomarkers for diagnosis, disease progression, and therapeutic response in psoriasis vulgaris: A mini-review

Sarah Q. Edwar, Yudo Irawan, Windy K. Budianti, Endi Novlanto, Eylene M. Fitri



Editorial Team

Editor in Chief



Harapan Harapan
Medical Research Unit, School of Medicine
Universitas Syiah Kuala, Indonesia
Scopus ID : [55844857500](#)

Co-Editor in Chief



Kuldeep Dhama
NAAS Associate, Principal Scientist
ICAR-Indian Veterinary Research Institute, India
Scopus ID : [6507396956](#)



Abram L. Wagner
School of Public Health
University of Michigan, USA
Scopus ID : [56178049300](#)

Editorial Board



Ruth Müller
Department of Biomedical Sciences
Institute of Tropical Medicine, Belgium
Scopus ID : [25653255200](#)



Herman Kosasih

Indonesia Research Partnership on Infectious Disease
INA-RESPOND, Indonesia
Scopus ID : [6507043017](#)



Mahir Gachabayov

School of Medicine
New York Medical College, USA
Scopus ID : [56626010400](#)



Santi Martini

Faculty of Public Health
Universitas Airlangga, Indonesia
Scopus ID : [57162600900](#)



Slobodan Janković

Faculty of Medical Sciences
University of Kragujevac, Serbia
Scopus ID : [7101906319](#)



Arief Budi Witarto

Department of Biochemistry and Molecular Biology
Indonesian Defense University, Indonesia
Scopus ID : [6507004235](#)



Morteza Arab-Zozani

Social Determinants of Health Research Center
Birjand University of Medical Sciences (BUMS), Iran
Scopus ID : [57210284593](#)



Dina Nur Anggraini Ningrum
Department of Public Health
Universitas Negeri Semarang, Indonesia
Scopus ID : [57195329470](#)



Talha Bin Emran
Department of Pharmacy
BGC Trust University Bangladesh, Bangladesh
Scopus ID : [55325267100](#)



Ferry Efendi
Faculty of Nursing
Universitas Airlangga, Indonesia
Scopus ID : [55301269100](#)



Raymond Pranata
Department of Cardiology and Vascular Medicine
Universitas Pelita Harapan, Indonesia
Scopus ID : [57201973901](#)



Tauseef Ahmad
School of Public Health
Zhejiang University, China
Scopus ID : [57214283386](#)



Lalu Muhammad Irham
Department of Toxicology
Universitas Ahmad Dahlan, Indonesia
Scopus ID : [57195464918](#)

Bukti Submission dan Review

Workflow **Publication**

Submission Review Copyediting Production

Submission Files

[Q Search](#)

 19170	meutia, Oxidative Stress as a Converging Mechanism of Aging.docx	12 January 2026	Manuscript
 19174	Layouted - 3042.docx	13 January 2026	Manuscript

[Download All Files](#)

Pre-Review Discussions

[Add discussion](#)

Name	From	Last Reply	Replies	Closed
"This revised manuscript follows the Narra J template."	meutia	-	0	<input type="checkbox"/>
	2026-01-12 20:12			

Workflow **Publication**

Submission **Review** Copyediting Production

Round 1

Round 1 Status

Submission accepted.

Notifications

[Narra] Decision on Your Manuscript Submission to Narra J	2026-01-30 19:15
[Narra] Editor Decision	2026-02-18 07:12
[Narra] Editor Decision	2026-03-12 10:44

Reviewer's Attachments		Q Search	
 19263	, 3042-Manuscript-19181-1-4-20260113 (1).docx	28	January 2026
 19266	, Recommendations.docx	29	January 2026

Revisions		Q Search		Upload File	
▶  19273	Revised Manuscript, REVISI1_3042-19263-1-5-20260128.docx	31	January 2026	Revised Manuscript	
▶  19319	Revised Manuscript, REVISI2_3042-Revised Manuscript-19317-1-18-20260204.docx	4	February 2026	Revised Manuscript	

3042 / Faradilla et al. / Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to the Library


Workflow
Publication

Submission
Review
Copyediting
Production

Copyediting Discussions Add discussion

Name	From	Last Reply	Replies	Closed
<i>No Items</i>				

Copyedited Q Search

 19376	3042-Correct-Proof.docx	24	February 2026	Correct Proof
---	-------------------------	----	---------------	---------------

Workflow

Publication

Submission

Review

Copyediting

Production

Production Discussions

[Add discussion](#)

Name	From	Last Reply	Replies	Closed
Final Proofread Requested	productioneditor	-	0	<input type="checkbox"/>
Your article is published	productioneditor	-	0	<input type="checkbox"/>

[Narra] Editor Decision External Inbox x



Narra J <admin@narraj.org>
to me ▾

Thu, Mar 12, 10:44 AM ☆ ☹️ ↶ ⋮

Dear Drs Meutia A. Faradilla, Karina S. Anastasya, Deasyka Yastani, Yohana Yohana, Endrico X. Tungka, Suweino Suweino:

Thank you for submitting your manuscript to Narra J.

I am pleased to inform you that your manuscript entitled "Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets" has been **officially accepted both scientifically and editorially in Narra J.**

Your accepted manuscript will now be transferred to our Production Department. A proof will be created, which you will be asked to review. If additional information is required during the production process, we will contact you directly.

Please note that this communication is not the Letter of Acceptance (LoA). The official LoA will be issued by the Narra J Finance Department. The Finance Department will send your invoice via the Odoo platform using the email address admin@narraj.org.

We appreciate your submission to Narra J and hope you will consider us again in the future.

Editor-In-Chief - Narra J

[Narra] New notification from Narra J External Inbox x



Narra J <admin@narraj.org>
to me ▾

Mon, Feb 2, 4:26 PM ☆ ☹️ ↶ ⋮

You have a new notification from Narra J:

You have been added to a discussion titled "Evidence of Figure Development" regarding the submission "2026_Oxidative Stress as a Converging Mechanism of Aging and Neurodegeneration: From Molecular Pathways to Therapeutic Targets".

Link: <https://narraj.org/main/authorDashboard/submission/3042>

Narra J Editorial Office

Editor-In-Chief - Narra J

[Narra] New notification from Narra J External Inbox x



Narra J <admin@narraj.org>
to me ▾

Wed, Feb 4, 11:38 AM ☆ ☹️ ↶ ⋮

You have a new notification from Narra J:

You have been added to a discussion titled "Further substantial revision is required" regarding the submission "2026_Oxidative Stress as a Converging Mechanism of Aging and Neurodegeneration: From Molecular Pathways to Therapeutic Targets".

Link: <https://narraj.org/main/authorDashboard/submission/3042>

Narra J Editorial Office

Editor-In-Chief - Narra J

[Narra] Editor Decision External Inbox x



Narra J <admin@narraj.org>
to me ▾

Feb 18, 2026, 7:12 AM ☆ 😊 ↶ ⋮

Dear Drs Meutia Atika Faradilla:

Thank you for submitting your manuscript to Narra J.

I am pleased to inform you that your manuscript entitled "2026_Oxidative Stress as a Converging Mechanism of Aging and Neurodegeneration: From Molecular Pathways to Therapeutic Targets" has been **accepted scientifically** in Narra J.

Your accepted manuscript will now be transferred to our Production Department. A proof will be created, which you will be asked to review. If additional information is required during the production process, we will contact you directly.

Please note that this communication is not the Letter of Acceptance (LoA). The official LoA will be issued by the Narra J Finance Department. The Finance Department will send your invoice via the Odoo platform using the email address admin@narraj.org.

We appreciate your submission to Narra J and hope you will consider us again in the future.

Editor-In-Chief - Narra J

[Narra] New notification from Narra J External Inbox x



Narra J <admin@narraj.org>
to me ▾

Mon, Jan 12, 8:23 PM ☆ 😊 ↶ ⋮

You have a new notification from Narra J:

You have been added to a discussion titled "Update on Scopus Indexing and APC Reduction" regarding the submission "Oxidative Stress as a Converging Mechanism of Aging and Neurodegeneration: From Molecular Pathways to Therapeutic Targets".

Link: <https://narraj.org/main/authorDashboard/submission/3042>

Narra J Editorial Office

Editor-In-Chief - Narra J

Oxidative stress_review article

by Meutia Faradilla

Submission date: 31-Jan-2026 09:30AM (UTC+0700)

Submission ID: 2867453421

File name: ss_as_a_converging_mechanism_of_aging_and_neurodegeneration.docx (6.71M)

Word count: 6648

Character count: 45333

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders (NDDs), most notably Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (1). Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor that is biological aging (2). Oxidative stress represents a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of neuronal vulnerability and decline. Within the network of aging-related mechanisms, oxidative stress functions as a central converging mechanism linking normal physiological aging to pathological neurodegeneration (3). Rather than being a mere product of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems (4). Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins (5).

Classical theories, such as Harman's Free Radical Theory of Aging, have historically attributed aging to random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival (6). The Central Nervous System (CNS) is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden. At the heart of this vulnerability lies the mitochondrion (7). As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses (8).

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance (9). The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid β in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation (10). This review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. We dissect the molecular origins of ROS, the age-associated erosion of antioxidant defenses, and the convergence of these pathways on protein aggregation and neuronal loss. Furthermore, we explore the historical pitfalls of broad-spectrum antioxidant therapies and advocate for a paradigm shift toward targeted modulation of redox-sensitive circuits rather than non-specific scavenging. Although oxidative stress has been widely implicated in aging and neurodegeneration, existing literature often examines these mechanisms independently. Few reviews integrate mitochondrial dysfunction, proteostatic collapse, neuroinflammation, and redox signaling into a unified framework. Although oxidative stress has

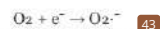
been widely implicated in aging and neurodegeneration, existing literature often examines these mechanisms independently. Few reviews integrate mitochondrial dysfunction, proteostatic collapse, neuroinflammation, and redox signaling into a unified framework. This article addresses this gap by synthesizing multi-level evidence to clarify how redox imbalance acts as a converging driver of neuronal decline.

Molecular mechanisms of oxidative stress

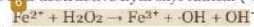
Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including AD, PD and ALS. Although these disorders are clinically distinct, they share biological aging as a common risk factor, indicating that age-related cellular processes actively contribute to neuronal degeneration(11). Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology(12). Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular defense systems, leading to damage of DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function(3)(8). The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration(13).

Molecular origins of reactive species

ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During oxidative phosphorylation, electron leakage occurs most notably at Complex I (NADH dehydrogenase) and Complex III (ubiquinone-cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O₂), forming the superoxide anion (O₂⁻), as described by the reaction(14):



Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H₂O₂), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe²⁺) or cuprous copper (Cu⁺), generating the highly reactive and destructive hydroxyl radical (-OH) (15):



The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression(16)(17).

Mitochondrial ROS Generation

Mitochondria are central to cellular energy production through oxidative phosphorylation, but they are also the primary source of reactive oxygen species (ROS). During oxidative phosphorylation, electrons are transferred through the mitochondrial electron transport chain, and some electrons leak at Complex I and Complex III. This leakage leads to the partial reduction of molecular oxygen, producing superoxide anions (O₂⁻). These superoxides are then converted into hydrogen peroxide (H₂O₂), which, in turn, can form hydroxyl radicals (-OH) through Fenton reactions, further amplifying oxidative stress(18). This ROS production becomes self-perpetuating in aging and neurodegenerative diseases, as damaged mitochondria generate more ROS, worsening mitochondrial dysfunction. This creates a vicious cycle where oxidative damage to cellular structures such as lipids, proteins, and DNA intensifies cellular dysfunction, accelerating the progression of diseases like Alzheimer's and Parkinson's. Moreover, mitochondrial damage can reduce ATP production, impeding cellular functions and contributing to neuronal degeneration(5).

Lipid Peroxidation and Membrane Vulnerability

Oxidative stress also leads to lipid peroxidation, a process in which ROS attack the polyunsaturated fatty acids in cellular membranes. Lipid peroxidation generates highly reactive secondary products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which can diffuse across the cell and interact with other cellular components. These lipid peroxidation products disrupt the structural integrity of neuronal membranes, impairing the fluidity and function of the lipid bilayer(19). This damage compromises membrane-bound proteins, receptors, and ion channels, leading to disturbances in cellular signaling, neurotransmission, and overall neuronal efficiency. In neurodegenerative diseases, this membrane vulnerability accelerates neuronal damage and contributes to synaptic dysfunction. For instance, in Alzheimer's disease, lipid peroxidation can facilitate the aggregation of amyloid-beta (A β), further exacerbating the pathological cycle. The **10**-rich membranes of neurons make them particularly susceptible to oxidative damage, reinforcing **the progression of diseases like AD and PD(20)**.

Proteostasis Collapse

Proteostasis is essential for maintaining **cellular homeostasis by** regulating **protein synth¹⁸**, **folding, and degradation**. However, oxidative stress disrupts proteostasis, leading to **the accumulation of damaged and misfolded proteins**. ROS can induce oxidative modifications such as carbonylation and nitration on proteins, altering their structure and function. These misfolded proteins are typically targeted for degradation by the **18**osome or autophagy pathways. However, **oxidative stress** impairs these systems, leading to **the accumulation of toxic protein aggregates**. In neurodegenerative diseases like Alzheimer's and Parkinson's, this collapse of proteostasis is particularly detrimental. **For example, in Alzheimer's disease, amyloid-beta (A β)** accumulates and forms plaques, while in Parkinson's disease, α -synuclein forms Lewy bodies. These protein aggregates not only disrupt cellular function but also impair synaptic plasticity, damage mitochondria, and promote neuroinflammation. The accumulation of misfolded proteins creates a positive feedback loop that exacerbates oxidative stress, mitochondrial dysfunction, and cellular damage(21).

Redox Inflammatory Crosstalk

Oxidative stress and neuroinflammation are intimately connected, with ROS playing a crucial role **1** activating **redox-sensitive transcription factors** like **NF- κ B, NF- κ B**, once activated by ROS, **translocates to the nucleus and initiates²** the expression of proinflammatory cytokines such as **IL-1 β , IL-6, and TNF- α** . These cytokines **activate microglia, the resident immune cells of the brain**, which further increase ROS production and promote inflammation. Chronic neuroinflammation exacerbates neuronal damage by impairing synaptic function, disrupting calcium homeostasis, and sensitizing neurons to excitotoxicity. This inflammatory response becomes self-perpetuating under conditions of sustained oxidative stress, where proinflammatory cytokines further exacerbate ROS production, leading to a cycle of oxidative injury and **2**inflammation. This crosstalk between oxidative stress and inflammation is a critical driver of **neurodegenerative diseases³** like Alzheimer's and Parkinson's, where inflammation amplifies the damage caused by ROS, **leading to** progressive **neuronal death and dysfunction** (22).

Autophagy and Mitophagy Failure

Autophagy and mitophagy are vital cellular processes for maintaining cellular integrity by degrading damaged proteins and organelles. In neurons, where turnover is limited due to the lack of cell division, the efficient functioning of autophagic pathways is critical for long-term survival. However, oxidative stress compromises the integrity of these pathways. ROS can damage the lysosomal system, which is responsible for the final stages of autophagic degradation, impairing its function(23). As a result, damaged proteins and dysfunctional organelles accumulate within neurons, further exacerbating cellular stress. In particular, mitophagy, the selective removal of damaged mitochondria, is essential to protect cells from oxidative damage. However, oxidative stress impairs mitophagy by disrupting the PINK1/Parkin pathway, which is responsible for marking damaged mitochondria for degradation. The failure to clear dysfunctional mitochondria allows them to persist

and continue generating ROS, perpetuating mitochondrial dysfunction and oxidative stress. This accumulation of damaged mitochondria, often referred to as “zombie mitochondria,” further disrupts cellular function, leading to energy depletion and contributing to the neurodegenerative processes observed in diseases like Parkinson's(24).

Antioxidant defense

Enzymatic vanguard: The first line of redox control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain(25). Because superoxide is highly reactive and short lived, its rapid conversion into hydrogen peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology(26). At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (46) and glutathione peroxidase (GPx) assume decisive roles (27)(28). By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation a species widely regarded as the most destructive ROS due to its indiscriminate reactivity (16). This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised whether due to genetic variation, post-translational alterations, or age-related functional decline the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage(29).

Non-enzymatic buffers and thiol-based redox modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione (GSH) playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond (29) capacity of enzymatic systems. By donating electrons, GSH neutralizes reactive species and is converted into its oxidized form, glutathione disulfide (GSSG). Consequently, the balance between reduced and oxidized glutathione (the GSH/GSSG ratio) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain (30). Evidence from aging studies consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation (31).

Regulatory control and the Nrf2 axis

The effectiveness of antioxidant defenses within the CNS is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of cellular stress responses. Under basal conditions, Nrf2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding SOD, GPx, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands(32). With advancing age, however, the responsiveness of the Nrf2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative

cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a "redox vulnerability gap," wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders(33).

Oxidative stress in aging: The "hardwiring" of senescence

The modified free radical theory of aging

Harman's Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by reactive oxygen species (ROS). While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury (34). Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled(35). However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu, commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline (36).

Accumulation of macromolecular damage in the aging brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between reactive oxygen species (ROS) production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function(37). Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency (38).

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin-proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress (21). Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2'-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration (39).

Oxidative stress in neurodegenerative diseases

Alzheimer's disease: Oxidative stress as a self-reinforcing pathological loop

In Alzheimer's disease, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through interconnected, self-reinforcing loops that involve amyloid-beta (A β) accumulation, mitochondrial dysfunction, and Tau pathology. Soluble A β ligomers display redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of reactive oxygen species (ROS). This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further A β aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment (40). As shown in figure 1, the pathological process begins with the accumulation of A β within neuronal mitochondria further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular energy balance. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in Alzheimer's disease(41).

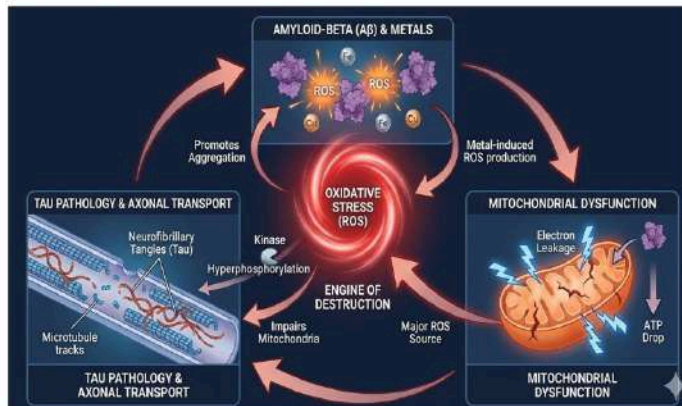


Figure 1. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction, illustrating the roles of amyloid-beta, metals, tau pathology, and mitochondrial dysfunction in Alzheimer's disease. The illustration was generated using BioRender, which was used to visualize the key mechanisms of oxidative stress and neuronal damage in AD pathology.

Parkinson's disease: Selective vulnerability to oxidative stress

Parkinson's disease illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons(42).

As shown in figure 2, the pathological process of parkinson's disease begins with mitochondrial dysfunction, which further amplifies oxidative injury. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1–Parkin–mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress(43). Loss of DJ-1–mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in Parkinson's disease [36].

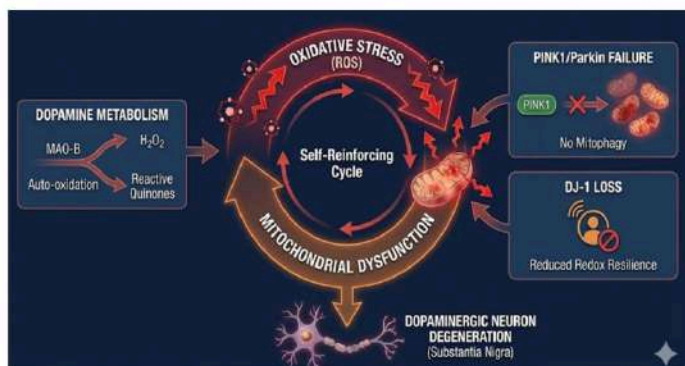


Figure 2. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction in Parkinson's disease, illustrating how dopamine metabolism, PINK1/Parkin failure, and DJ-1 loss contribute to dopaminergic neuron degeneration in the substantia nigra. The illustration was generated using BioRender to visualize the key mechanisms of oxidative stress and mitochondrial impairment in Parkinson's pathology

The converging pathways: Inflammation and autophagy

Oxidative stress represents an early destabilizing force in neuronal homeostasis, yet its most destructive effects emerge through its capacity to activate downstream pathological pathways (45). Rather than acting as an isolated insult, sustained redox imbalance orchestrates a broader cellular collapse by engaging neuroinflammatory signaling and disrupting intracellular quality-control mechanisms. Among these, chronic inflammation and autophagy impairment stand out as convergent pathways that transform transient oxidative disturbances into irreversible neurodegenerative trajectories (46).

The oxidative inflammatory axis: From redox imbalance to neurotoxicity

In the central nervous system, oxidative stress and inflammation are intimately intertwined, forming a self-amplifying pathological circuit. Microglia, the brain's resident immune cells, are uniquely positioned at the interface between neuronal metabolism and immune surveillance. Under physiological conditions, microglia maintain synaptic integrity and respond transiently to injury. However, persistent oxidative stress alters this homeostatic role, pushing microglia toward a chronically activated, proinflammatory phenotype (47).

ROS-mediated activation of proinflammatory signaling

Reactive oxygen species function as potent second messengers capable of activating redox-sensitive transcription factors. Among these, nuclear factor kappa-light-chain-enhancer of

activated B cells (NF- κ B) plays a central role in translating oxidative cues into inflammatory gene expression. Elevated ROS levels promote the dissociation of NF- κ B from its cytoplasmic inhibitors, allowing its translocation into the nucleus. Once activated, NF- κ B drives the transcription of a broad spectrum of proinflammatory mediators, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). These cytokines exert pleiotropic effects within the neural microenvironment. Beyond recruiting additional immune responses, they directly impair synaptic function, disrupt neuronal calcium homeostasis, and sensitize neurons to excitotoxic injury. Importantly, this inflammatory signaling is not a short-lived response but becomes sustained under conditions of chronic oxidative stress, reshaping the neural milieu into one that favors degeneration rather than repair (48).

Self-perpetuating cycle of ROS and inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders(49).

Autophagy and mitophagy failure: Breakdown of cellular quality control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival(50).

Lysosomal dysfunction and autophagic arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal (4-HNE) that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure(24).

Mitophagy failure and energetic collapse

Among autophagic processes, the selective removal of damaged mitochondria, known as mitophagy, is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as "zombie mitochondria," remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure. As ATP levels decline, energy-dependent processes including ion homeostasis, axonal transport, and synaptic transmission become unsustainable. Ultimately, this convergence

of oxidative damage, autophagy impairment, and bioenergetic collapse pushes neurons toward apoptotic or necrotic death(51). Figure 3 illustrate the central role of oxidative stress in neurodegenerative diseases such as Alzheimer's and Parkinson's. It highlights key mechanisms including mitochondrial ROS generation, proteostasis collapse, neuroinflammation, and defective autophagy, all contributing to cellular damage. The figure 3 below shows how oxidative stress promotes synaptic dysfunction and cognitive decline by driving the accumulation of toxic proteins like amyloid- β and tau in Alzheimer's and neuronal loss in Parkinson's. Additionally, it emphasizes therapeutic targets, such as Nrf2 activators (e.g., dimethyl fumarate), mitochondria-targeted antioxidants (e.g., MitoQ), and proteostasis and autophagy enhancers (e.g., rapamycin, SS-31, Urolithin A), which aim to mitigate oxidative damage and restore cellular function.

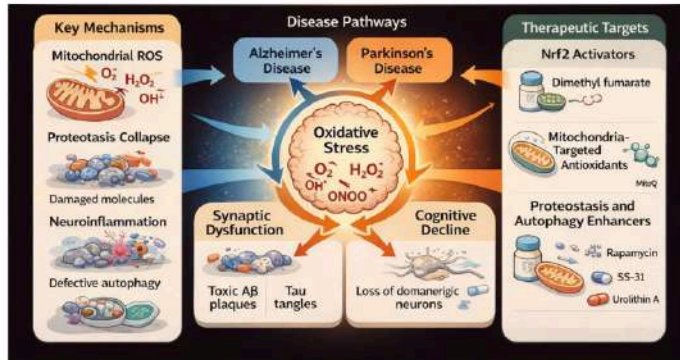


Figure 3. The journey from molecular origins (ROS) through cellular damage (mitochondria/inflammation) to clinical disease (AD/PD), while proposing a shift toward precision medicine and targeted therapies. The illustration was generated using BioRender.

Therapeutic targets and clinical implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However, decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated(52).

1 nrf2 pathway activation: Reinforcing endogenous redox resilience

Nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing Nrf2 to escape degradation and translocate into the nucleus. There, Nrf2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, Nrf2 activation enhances intrinsic redox resilience by strengthening the cell's capacity to respond to future oxidative challenges(32). While Nrf2 activation is beneficial in protecting against oxidative stress, chronic activation can have limitations. Continuous Nrf2 activation may inadvertently

promote tumorigenesis by aiding the survival of damaged cells, which may facilitate cancer progression. The activation of the pathway in non-cancerous tissues should, therefore, be carefully regulated. In terms of activating Nrf2, there are two primary categories: electrophilic and non-electrophilic activators. Electrophilic activators, such as sulforaphane, directly modify KEAP1, leading to the activation of Nrf2. However, these compounds can cause unintended damage due to their reactivity, potentially affecting cellular structures beyond their target. On the other hand, non-electrophilic activators, such as bardoxolone methyl, activate Nrf2 without directly altering KEAP1, which offers a safer profile with fewer side effects but may have lower potency.

Conventional antioxidants have shown limited efficacy in neurodegenerative

Conventional antioxidant therapies have demonstrated limited benefit⁴² in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal reactive oxygen species (ROS). This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, SS-31 (elamipretide) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis⁵³. Table 1 compares MitoQ and SS-31, both targeting mitochondria. MitoQ accumulates via membrane potential to scavenge ROS, while SS-31 stabilizes cardiolipin to prevent ROS. Both show preclinical efficacy in neurodegenerative diseases. MitoQ failed in Parkinson's trials but is used for vascular health, while SS-31 is FDA-approved for Barth Syndrome but failed in heart failure trials^{54–60}.

Table 1. Comparative Summary of MitoQ and SS-31 (54–60)

Feature	MitoQ (Mitoquinone Mesylate)	SS-31 (Elamipretide)
Primary Mechanism	Electrophoretic accumulation driven by mitochondrial membrane potential.	Potential-independent uptake; targets and stabilizes cardiolipin in the inner membrane.
Antioxidant Action	Redox-active ubiquinone moiety directly scavenges radicals and is regenerated by Complex II.	Structural stabilization of cristae/supercomplexes to prevent electron leakage and ROS formation.
Physical Impact	Can cause mitochondrial swelling and depolarization at high concentrations due to its alkyl chain.	Acts as "mitochondrial armor," protecting against membrane fragmentation and structural decay.
Preclinical Evidence	Robust protection in Alzheimer's (3xTg-AD), Parkinson's (MPTP), and Huntington's disease (HD) models.	Consistent success in AD, PD, HD, and brain injury models, improving dynamics and synaptic health.
Clinical Status	Failed PD trials (no clinical effect on UPDRS). Currently used as a dietary supplement for vascular health.	FDA Approved (Sept 2025) for Barth Syndrome. Failed trials in heart failure and primary mitochondrial myopathy.

Lifestyle interventions and hormetic redox adaptation

Lifestyle interventions, such as physical exercise and caloric restriction, activate endogenous antioxidant defenses through a process known as hormesis. Hormesis refers to the phenomenon where low-level, transient oxidative stress triggers adaptive protective responses within cells. When applied in moderation, physical exercise and mild caloric restriction induce controlled oxidative stress that enhances cellular resilience(61). These interventions improve mitochondrial efficiency by promoting better ATP production and reducing the production of excess ROS, stimulate autophagy for the clearance of damaged proteins and organelles, and upregulate antioxidant signaling pathways such as the Nrf2 pathway, which 23ances the cell's ability to combat oxidative damage. Additionally, they boost the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which support neuronal growth, survival, and synaptic plasticity, playing a crucial role in brain health(62).

32 However, it is important to note that the beneficial effects of hormesis are dose-dependent. When physical exercise or caloric restriction exceeds a certain threshold, it can shift from an adaptive to a maladaptive stress response. Prolonged or excessive exercise, for example, can lead to chronic oxidative stress, resulting in mitochondrial dysfunction, muscle damage, and an increase in inflammatory markers. Similarly, prolonged caloric restriction may impair cellular homeostasis, weaken the immune system, and exacerbate metabolic dysfunction. These maladaptive responses may overwhelm the body's protective mechanisms, leading to cellular damage rather than the intended health benefits. Therefore, while moderate exercise and caloric restriction can enhance redox balance and improve health outcomes, extreme or prolonged levels of these stressors may cause harm, highlighting the importance of balance in these lifestyle interventions(63).

Therapeutic potential and clinical translation

Pharmacological activation of Nrf2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach. By inducing mild electrophilic stress, it activates Nrf2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other Nrf2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive Nrf2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress(32).

Challenges and future directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in Alzheimer's disease (AD) and Parkinson's disease (PD) has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnect between compelling preclinical data and disappointing clinical outcomes highlights a critical "translational gap" that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

Table 2. Comparative Summary between Mechanisms of oxidative stress, Their roles in AD vs. PD and Potential therapeutic interventions

(1,1,1,3,3,11,19,24,33,42,42-44,46,46,52,52)

Mechanisms of Oxidative Stress	Role in Alzheimer's Disease (AD)	Role in Parkinson's Disease (PD)	Potential Therapeutic Interventions
Mitochondrial Dysfunction	Mitochondrial dysfunction leads to bioenergetic failure, impairing synaptic plasticity and contributing to neuronal damage.	Mitochondrial dysfunction in dopaminergic neurons accelerates ROS production and contributes to neuronal loss.	Mitochondria-targeted antioxidants (e.g., MitoQ, SS31) that help reduce ROS and restore mitochondrial function.
Lipid Peroxidation	Oxidative damage to membrane lipids leads to neuronal damage and loss of synaptic function.	Lipid peroxidation exacerbates dopaminergic neuron death and disrupts membrane integrity.	Use of lipid antioxidants like alpha-lipoic acid or other peroxyl scavengers to prevent oxidative damage.
Proteostasis Collapse	Proteostasis collapse contributes to the accumulation of amyloid β and tau, which disrupt neuronal function.	Accumulation of misfolded proteins, such as α -synuclein, leads to dopaminergic dysfunction.	Proteostasis regulators, such as proteasome activators or autophagy enhancers (e.g., rapamycin, spermidine).
Neuroinflammation	Chronic neuroinflammation amplifies the amyloid plaque formation and accelerates disease progression.	Neuroinflammation in microglia worsens dopaminergic neuron death and amplifies ROS production.	Anti-inflammatory agents targeting NF- κ B or microglial activation (e.g., minocycline, curcumin).
Redox-Imbalance (ROS and RNS)	ROS accumulation damages cellular structures (DNA, lipids, proteins) and triggers apoptosis.	ROS generation through dopamine metabolism leads to neuronal damage and contributes to cell death.	Nrf2 activators (e.g., dimethyl fumarate), which boost cellular antioxidant defenses and help restore redox homeostasis.
Autophagy and Mitophagy Failure	Impaired autophagy leads to the accumulation of damaged proteins, exacerbating neurodegeneration.	Deficient mitophagy results in the accumulation of dysfunctional mitochondria, contributing to neurodegeneration.	Autophagy enhancers (e.g., rapamycin) and mitophagy activators (e.g., Urolithin A, PINK1 activators) to clear damaged organelles.

Temporal mismatch: Treating too late in the disease course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather

than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles(64).

Bioavailability and blood brain barrier limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood-brain barrier (BBB), while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets(65). Even when compounds successfully cross the BBB, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery such as nanoparticle-based carriers, mitochondria-targeted molecules, and ligand-mediated transport systems represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects(66).

The paradox of reductive stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. Reactive oxygen species are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction. This concept challenges the simplistic view that "more antioxidants are better" and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease(67).

The need for redox biomarkers and patient stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status in vivo. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism(68).

Toward a systems-level therapeutic strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways(69). In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system(70).

Conclusion

This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy, collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.

Acknowledgments

The authors gratefully acknowledge the Department of Biochemistry, Faculty of Medicine, Trisakti University, for its continuous academic support and supportive environment during the development of this review. We also sincerely thank the researchers and scholars whose work has contributed to the advancement of knowledge in the field of oxidative stress, aging, and neurodegeneration. Their contributions provided essential scientific insights that informed and strengthened this manuscript.

7 Competing interests

All authors declare that there are no conflicts of interest related to this work.

Funding

This study received no external funding.

Underlying data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

33 Declaration of artificial intelligence use

During the preparation of this manuscript, the authors made limited use of artificial intelligence-based tools as a supporting aid for language editing and improvement of sentence clarity. These tools were used only to assist in refining grammar and readability. All scientific content, interpretations, critical analyses, and conclusions presented in this manuscript were developed, reviewed, and finalized by the authors. The use of AI did not influence the scientific substance of the work and does not replace the authors' intellectual contribution or responsibility.

Oxidative stress_review article

ORIGINALITY REPORT

12%	8%	10%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	1%
2	redefininghomeopathy.com Internet Source	1%
3	Ghulam Md Ashraf, Md. Habibur Rahman, Karri V. V. S. Narayana Reddy, Chenmala Karthika, Ali T. Zari, Gowthamarajan Kuppusamy. "Therapeutic Potential of Natural Products in Neurodegenerative Disorders", CRC Press, 2026 Publication	1%
4	Trideva Sastri Koduru. "Nucleic Acids and Precision Therapies for Neuroprotection", CRC Press, 2026 Publication	1%
5	worldwidescience.org Internet Source	1%
6	D Gupta, T Saleh, Y Moustafa, AJ Gow. "The Toxicology of Reactive Oxygen and Nitrogen Species (RONS)", Elsevier BV, 2026 Publication	1%
7	jurnal.stis.ac.id Internet Source	<1%
8	www.researchsquare.com Internet Source	<1%
9	pmc.ncbi.nlm.nih.gov Internet Source	<1%
10	Chinmay Pal. "Mitochondria-targeting by small molecules against Alzheimer's disease:	<1%

A mechanistic perspective", *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 2025

Publication

11 Abhishek Tiwari, Varsha Tiwari. "Exploring the Synthesis, Ethnopharmacology, and Therapeutic Applications of Bioactive Polyphenols", CRC Press, 2026

Publication

12 Chenchen Song, Kesong Zhu, Yafei Zhuang, Hongyu Jia, Aimei Liu. "Nrf2: the key target for antagonizing the toxicity of deoxynivalenol", *Toxicon*, 2026

Publication

13 George Țocu, Bogdan Ioan Ștefănescu, Loredana Stavăr Matei, Lavinia Țocu. "Phagocyte NADPH Oxidase NOX2-Derived Reactive Oxygen Species in Antimicrobial Defense: Mechanisms, Regulation, and Therapeutic Potential—A Narrative Review", *Antioxidants*, 2025

Publication

14 pureadmin.uhi.ac.uk

Internet Source

15 v3r.esp.org

Internet Source

16 Peter J. Adhihetty, Isabella Irrcher, Anna-Maria Joseph, Vladimir Ljubicic, David A. Hood. "Plasticity of Skeletal Muscle Mitochondria in Response to Contractile Activity", *Experimental Physiology*, 2003

Publication

17 www.dovepress.com

Internet Source

18 Devendra Kumar, Shraddha Manish Gupta, Nagendra Singh Chauhan, Kamal Shah.

"Alzheimer's Disease - Diagnosis, Molecular Targets, and Therapeutic Modalities", CRC Press, 2025

Publication

19 Etan Eigner, Yacov Reisman, Nicola Fazza, Ameer Nsair, Valentin Shabataev, Ariel Zisman. "Review of techniques and approaches for ectopic reservoir placement in inflatable penile implant", Canadian Journal of Urology, 2025

Publication

20 Gino A Kurian, Srijan Jayaraman, Eren Rose Gino. "Strategic Targeting of Mitochondria: Bridging Biology and Therapy for Health Benefits", Cell Biochemistry and Biophysics, 2025

Publication

21 lansbury.bwh.harvard.edu

Internet Source

22 www.benthamscience.com

Internet Source

23 www.coursehero.com

Internet Source

24 Wang, G.. "Protein adducts of malondialdehyde and 4-hydroxynonenal contribute to trichloroethene-mediated autoimmunity via activating Th17 cells: Dose- and time-response studies in female MRL+/+ mice", Toxicology, 20120226

Publication

25 www.benchchem.com

Internet Source

26 www.frontiersin.org

Internet Source

27 Michael Aschner, Lucio G. Costa. "The Role of Glia in Neurotoxicity", CRC Press, 2019

28 Ruijing Li, Weili Yang, Lijuan Zheng, Xingxue Yan, Cuihua Liu, Yaodong Zhang, Jitong Li. "Gastrodin alleviates alcohol-induced developmental and neurotoxic effects in zebrafish larvae by suppressing ferroptosis via regulating the Nrf2/GPX4 signaling pathway", *Toxicology and Applied Pharmacology*, 2026

Publication

29 Sokol, Anna Magdalena, Malgorzata Eliza Sztolsztener, Michal Wasilewski, Eva Heinz, and Agnieszka Chacinska. "Mitochondrial protein translocases for survival and wellbeing", *FEBS Letters*, 2014.

Publication

30 bcmd8.bcm.edu
Internet Source

31 coek.info
Internet Source

32 Cui Zhang, Hao Qi, Dongjing Jia, Jingting Zhao et al. "Cognitive impairment in Alzheimer's disease FAD4T mouse model: Synaptic loss facilitated by activated microglia via C1qA", *Life Sciences*, 2024

Publication

33 Samuel Bruchfeld, Therese Djärv, Gabriel Riva, Johan Israelsson, Anders Bremer, Kristofer Årestedt, Joel Ohm. "Aetiology of in-hospital cardiac arrest and long-term survival after the first 30days: insights from the Swedish registry for cardiopulmonary resuscitation", *Resuscitation*, 2026

Publication

34 curis.ku.dk
Internet Source

35	www.ecronicon.com Internet Source	<1%
36	Kishore KumarS. Narasimhan, Deepthy Jayakumar, Kalaiselvi Periandavan. "Perspective Chapter: Nrf2 at the Realm of Antioxidant Protection in Cardiovascular Systems", IntechOpen, 2025 Publication	<1%
37	Taha Ghantabpour, Saba Parvaneh, Houman Parsaie, Tina Ramzani Gilani, Marzieh Sadat Tabaei, Fardin Amidi. "Overview of the effects of astaxanthin on the male reproductive system focusing on mechanism underling its action", European Journal of Pharmacology, 2025 Publication	<1%
38	skindeep.skinonline.org Internet Source	<1%
39	www.detoxmetals.com Internet Source	<1%
40	www.gethealthspan.com Internet Source	<1%
41	Bhupendra Gopalbhai Prajapati, Rishabha Malviya, Himanshu Paliwal, Sonali Sundram. "Macular Degeneration - A Progressive Retinal Disorder", Apple Academic Press, 2026 Publication	<1%
42	link.springer.com Internet Source	<1%
43	www.researchgate.net Internet Source	<1%
44	"Tackling the Concussion Epidemic", Springer Science and Business Media LLC, 2022 Publication	<1%

45

Hosakatte Niranjana Murthy. "Bioactive Compounds in Edible Flowers", CRC Press, 2026

Publication

<1%

46

Manoj Tukaram Kamble, Nopadon Pirarat, Balasaheb Ramdas Chavan, Seema Vijay Medhe. "Phytobiotics for Sustainable Aquaculture - Innovations, Benefits, and Future Perspectives", CRC Press, 2026

Publication

<1%

Exclude quotes Off

Exclude matches Off

Exclude bibliography Off



Review Article

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

Meutia A. Faradilla¹, Karina S. Anastasya², Deasyka Yastani¹, Yohana Yohana¹, Endrico X. Tungka¹ and Suweino Suweino¹

¹Department of Biochemistry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia; ²Department of Nutrition, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

*Corresponding author: meutia.atika@trisakti.ac.id

Abstract

Aging is the primary risk factor for major neurodegenerative disorders, yet the precise molecular links between biological aging and progressive neuronal loss remain complex. Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, has emerged as a central converging mechanism driving both processes. This review aims to synthesize current evidence demonstrating how chronic redox imbalance drives cellular senescence and neuronal vulnerability through mitochondrial dysfunction, lipid peroxidation, and oxidative protein damage. These insights underscore how sustained oxidative insults promote the misfolding and aggregation of disease-defining proteins, including amyloid-beta in Alzheimer's disease and α -synuclein in Parkinson's disease, thereby amplifying neuroinflammation, synaptic dysfunction, and bioenergetic failure. Furthermore, antioxidant-based therapeutic strategies are critically reassessed, highlighting a paradigm shift from non-specific radical scavenging toward targeted modulation of endogenous defense systems, particularly NRF2 signaling and mitochondria-directed antioxidants. By integrating molecular mechanisms with translational perspectives, this review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Keywords: Oxidative stress, aging, neurodegeneration, mitochondria, reactive oxygen species

Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders, most notably Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor that is biological aging [2]. Oxidative stress represents a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of neuronal vulnerability and decline. Within the network of aging-related mechanisms, oxidative stress functions as a central converging mechanism linking normal physiological aging to pathological neurodegeneration [3]. Rather than being a mere byproduct



of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems [4]. Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins [5].

Classical theories, such as Harman's Free Radical Theory of Aging [6], have historically attributed aging to the random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival [7]. The central nervous system is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden [8]. At the heart of this vulnerability lies the mitochondrion [9]. As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses [10].

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance [11]. The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid-beta in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation [12]. Although oxidative stress is widely recognized as a hallmark of biological aging and neurodegeneration, existing literature frequently addresses mitochondrial dysfunction, proteostatic failure, neuroinflammation, and redox signaling in isolation. This review addresses this gap by integrating molecular, cellular, and translational evidence to clarify how redox imbalance functions as a convergent driver of neuronal dysfunction and loss in Alzheimer's and Parkinson's diseases. The molecular sources of reactive oxygen species, age-related declines in antioxidant capacity, and the convergence of these processes on protein aggregation and neurodegeneration are synthesized. Finally, the limitations of broad-spectrum antioxidant strategies are discussed, and a conceptual shift toward targeted modulation of redox-sensitive pathways, rather than non-specific scavenging, is proposed.

Molecular mechanisms of oxidative stress

Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including AD, PD, and ALS. Although these disorders are clinically distinct, they share biological aging as a common risk factor, indicating that age-related cellular processes actively contribute to neuronal degeneration [13]. Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology [14]. Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular defense systems, leading to damage to DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function [8]. The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration [15].

Molecular origins of reactive species

ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During

oxidative phosphorylation, electron leakage occurs most notably at Complex I (nicotinamide adenine dinucleotide reduced (NADH) dehydrogenase) and Complex III (ubiquinone–cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O_2), forming the superoxide anion ($O_2^{\cdot-}$), as described by the reaction $O_2 + e^- \rightarrow O_2^{\cdot-}$ [16].

Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H_2O_2), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe^{2+}) or cuprous copper (Cu^+), generating the highly reactive and destructive hydroxyl radical ($\cdot OH$): $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$ [17].

The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression [18].

Mitochondrial ROS generation

Mitochondria are central to cellular energy production through oxidative phosphorylation, but they are also the primary source of ROS. During oxidative phosphorylation, electrons are transferred through the mitochondrial electron transport chain, and some electrons leak at Complex I and Complex III. This leakage leads to the partial reduction of molecular oxygen, producing superoxide anions ($O_2^{\cdot-}$). These superoxides are then converted into hydrogen peroxide, which, in turn, can form hydroxyl radicals ($\cdot OH$) through Fenton reactions, further amplifying oxidative stress [19]. This ROS production becomes self-perpetuating in aging and neurodegenerative diseases, as damaged mitochondria generate more ROS, worsening mitochondrial dysfunction. This creates a vicious cycle where oxidative damage to cellular structures such as lipids, proteins, and DNA intensifies cellular dysfunction, accelerating the progression of diseases like AD and PD. Moreover, mitochondrial damage can reduce ATP production, impeding cellular functions and contributing to neuronal degeneration [5].

Lipid peroxidation and membrane vulnerability

Oxidative stress also leads to lipid peroxidation, a process in which ROS attack the polyunsaturated fatty acids in cellular membranes. Lipid peroxidation generates highly reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which can diffuse across the cells and interact with other cellular components [20]. These lipid peroxidation products disrupt the structural integrity of neuronal membranes, impairing the fluidity and function of the lipid bilayer [21]. This damage compromises membrane-bound proteins, receptors, and ion channels, leading to disturbances in cellular signaling, neurotransmission, and overall neuronal efficiency. In neurodegenerative diseases, this membrane vulnerability accelerates neuronal damage and contributes to synaptic dysfunction. For instance, in AD, lipid peroxidation can facilitate the aggregation of amyloid-beta, further exacerbating the pathological cycle [20]. The lipid-rich membranes of neurons make them particularly susceptible to oxidative damage, reinforcing the progression of diseases like AD and PD [20].

Proteostasis collapse

Proteostasis is essential for maintaining cellular homeostasis by regulating protein synthesis, folding, and degradation. However, oxidative stress disrupts proteostasis, leading to the accumulation of damaged and misfolded proteins. ROS can induce oxidative modifications such as carbonylation and nitration on proteins, altering their structure and function [22]. These misfolded proteins are typically targeted for degradation by the proteasome or autophagy pathways. However, oxidative stress impairs these systems, leading to the accumulation of toxic protein aggregates [23]. In neurodegenerative diseases like AD and PD, this collapse of proteostasis is particularly detrimental. For example, in AD, amyloid-beta accumulates and forms plaques, while in PD, α -synuclein forms Lewy bodies. These protein aggregates not only disrupt cellular function but also impair synaptic plasticity, damage mitochondria, and promote

neuroinflammation [23]. The accumulation of misfolded proteins creates a positive feedback loop that exacerbates oxidative stress, mitochondrial dysfunction, and cellular damage [11].

Redox inflammatory crosstalk

Oxidative stress and neuroinflammation are intimately connected, with ROS playing a crucial role in activating redox-sensitive transcription factors like nuclear factor kappa B (NF- κ B). NF- κ B, once activated by ROS, translocates to the nucleus and initiates the expression of proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α [24]. These cytokines activate microglia, the resident immune cells of the brain, which further increase ROS production and promote inflammation [25]. Chronic neuroinflammation exacerbates neuronal damage by impairing synaptic function, disrupting calcium homeostasis, and sensitizing neurons to excitotoxicity. This inflammatory response becomes self-perpetuating under conditions of sustained oxidative stress, where proinflammatory cytokines further exacerbate ROS production, leading to a cycle of oxidative injury and inflammation [24]. This crosstalk between oxidative stress and inflammation is a critical driver of neurodegenerative diseases like AD and PD, where inflammation amplifies the damage caused by ROS, leading to progressive neuronal death and dysfunction [24].

Autophagy and mitophagy failure

Autophagy and mitophagy are vital cellular processes for maintaining cellular integrity by degrading damaged proteins and organelles. In neurons, where turnover is limited due to the lack of cell division, the efficient functioning of autophagic pathways is critical for long-term survival. However, oxidative stress compromises the integrity of these pathways. ROS can damage the lysosomal system, which is responsible for the final stages of autophagic degradation, impairing its function [26]. As a result, damaged proteins and dysfunctional organelles accumulate within neurons, further exacerbating cellular stress. In particular, mitophagy, the selective removal of damaged mitochondria, is essential to protect cells from oxidative damage. However, oxidative stress impairs mitophagy by disrupting the PINK1/Parkin pathway, which is responsible for marking damaged mitochondria for degradation [27]. The failure to clear dysfunctional mitochondria allows them to persist and continue generating ROS, perpetuating mitochondrial dysfunction and oxidative stress. This accumulation of damaged mitochondria, often referred to as “zombie mitochondria,” further disrupts cellular function, leading to energy depletion and contributing to the neurodegenerative processes observed in diseases like PA [27].

Antioxidant defense

Enzymatic vanguard: The first line of redox control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain [28]. Because superoxide is highly reactive and short-lived, its rapid conversion into hydrogen peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology [29]. At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (CAT) and glutathione peroxidase assume decisive roles [30,31]. By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation, a species widely regarded as the most destructive ROS due to its indiscriminate reactivity [18]. This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised, whether due to genetic variation,

post-translational alterations, or age-related functional decline, the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage [32].

Non-enzymatic buffers and thiol-based redox modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond the capacity of enzymatic systems. By donating electrons, glutathione neutralizes reactive species and is converted into its oxidized form, glutathione disulfide. Consequently, the balance between reduced and oxidized glutathione (the ratio of glutathione to glutathione disulfide) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain [33]. Evidence consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event [34]. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function [24]. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation [35].

Regulatory control and the NRF2 axis

The effectiveness of antioxidant defenses within the central nervous system is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2-related factor 2 (NRF2), a master regulator of cellular stress responses. Under basal conditions, NRF2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding superoxide dismutases, glutathione peroxidase, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands [36]. With advancing age, however, the responsiveness of the NRF2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a “redox vulnerability gap”, wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders [37].

Oxidative stress in aging: Molecular mechanism of senescence

The modified free radical theory of aging

Harman's Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by ROS [38]. While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury [39]. Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled [40]. However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu, commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes

aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline [41].

Accumulation of macromolecular damage in the aging brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between ROS production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function [42]. Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency [43].

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin–proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress [22]. Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2'-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration [44].

Oxidative stress in neurodegenerative diseases

Alzheimer's disease (AD): Oxidative stress as a self-reinforcing pathological loop

In AD, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through interconnected, self-reinforcing loops that involve amyloid-beta accumulation, mitochondrial dysfunction, and Tau pathology (**Figure 1**). Soluble amyloid-beta oligomers have redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of ROS [13]. This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further amyloid-beta aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment [45]. As shown in **Figure 1**, the pathological process begins with the accumulation of amyloid-beta within neuronal mitochondria, which further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular energy balance [10]. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport [1]. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in AD [46].

Parkinson's disease (PA): Selective vulnerability to oxidative stress

PA illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and

impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons [47].

As shown in **Figure 2**, the pathological process of PA begins with mitochondrial dysfunction, which further amplifies oxidative injury. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1–Parkin–mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress [48]. Loss of DJ-1–mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in PD [36].

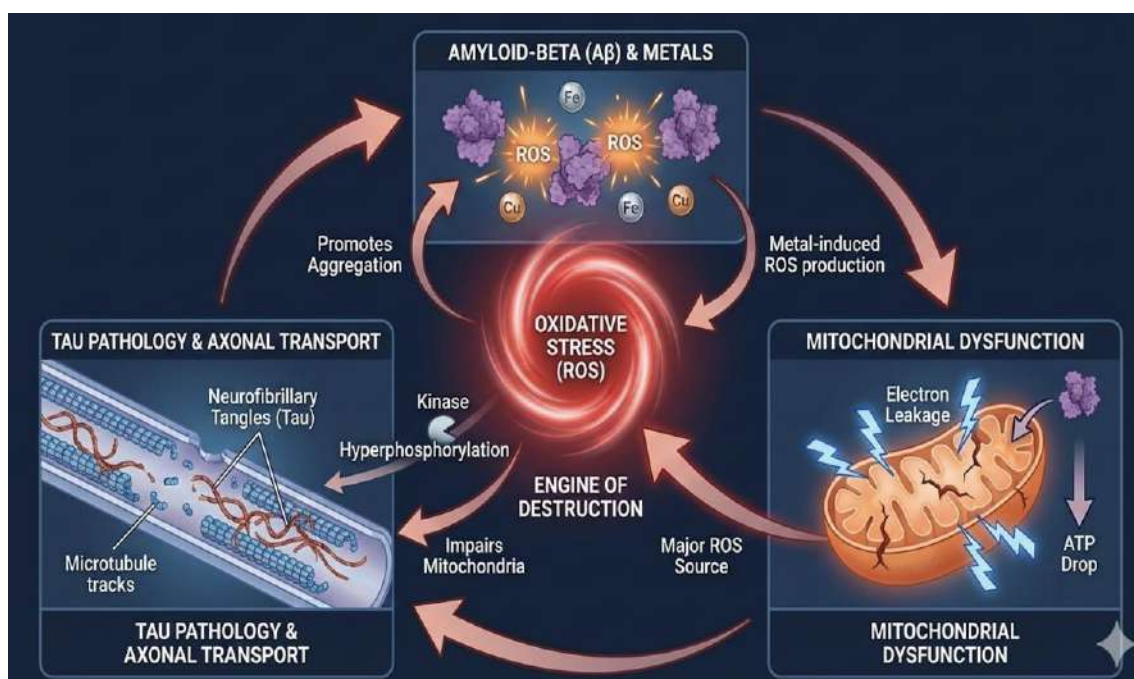


Figure 1. Key mechanisms of oxidative stress and neuronal damage in Alzheimer's disease (AD) pathology. Self-reinforcing cycle of oxidative stress and mitochondrial dysfunction, illustrating the roles of amyloid-beta, metals, tau pathology, and mitochondrial dysfunction in AD. The figure is generated using BioRender.

Self-perpetuating cycle of ROS and inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation [50]. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders [50].

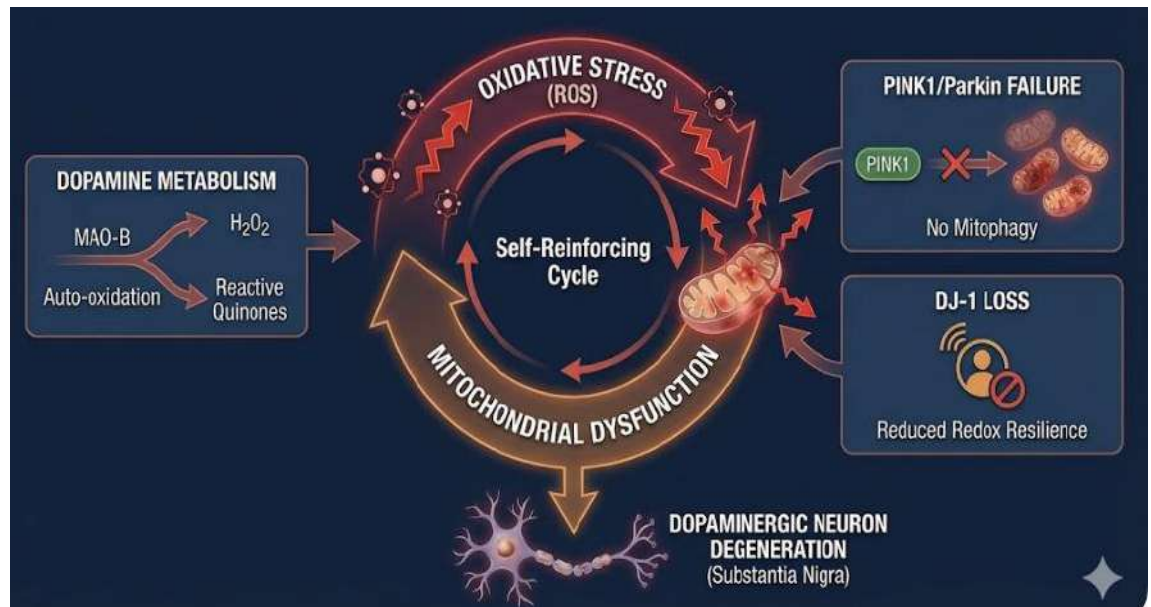


Figure 2. Key mechanisms of oxidative stress and mitochondrial impairment in Parkinson's disease (PD) pathology. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction in PD, illustrating how dopamine metabolism, PINK1/Parkin failure, and DJ-1 loss contribute to dopaminergic neuron degeneration in the substantia nigra. The figure is generated using BioRender.

Autophagy and mitophagy failure: Breakdown of cellular quality control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival [51].

Lysosomal dysfunction and autophagic arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure [27].

Mitophagy failure and energetic collapse

Among autophagic processes, the selective removal of damaged mitochondria is known as mitophagy. It is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage [3]. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as “zombie mitochondria,” remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure [52]. As ATP levels decline, energy-dependent processes, including ion homeostasis, axonal transport, and synaptic transmission, become unsustainable. Ultimately, this convergence of oxidative damage, autophagy impairment, and bioenergetic

collapse pushes neurons toward apoptotic or necrotic death [53]. The central roles of oxidative stress in neurodegenerative diseases such as AD and PD are illustrated in **Figure 3**. It highlights key mechanisms, including mitochondrial ROS generation, proteostasis collapse, neuroinflammation, and defective autophagy, all contributing to cellular damage. **Figure 3** also shows how oxidative stress promotes synaptic dysfunction and cognitive decline by driving the accumulation of toxic proteins like amyloid-beta and tau in AD and neuronal loss in PD. Additionally, it emphasizes therapeutic targets, such as NRF2 activators (e.g., dimethyl fumarate), mitochondria-targeted antioxidants (e.g., MitoQ), and proteostasis and autophagy enhancers (e.g., rapamycin, SS-31, Urolithin A), which aim to mitigate oxidative damage and restore cellular function.

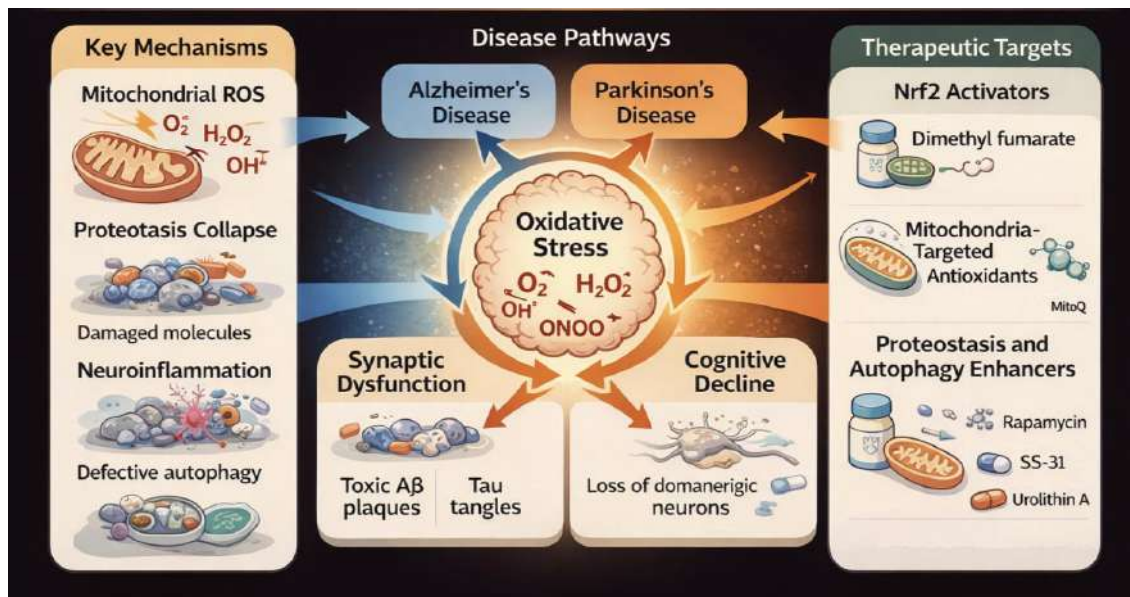


Figure 3. Schematic overview illustrating the continuum from the molecular origins of reactive oxygen species (ROS) through cellular damage—encompassing mitochondrial dysfunction and neuroinflammation—to clinical manifestations of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. The figure also highlights the emerging shift toward precision medicine and targeted therapeutic strategies. The illustration was created using BioRender.

Therapeutic targets and clinical implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However, decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated [31].

NRF2 pathway activation: Reinforcing endogenous redox resilience

NRF2 serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, NRF2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation [37]. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing NRF2 to escape degradation and translocate into the nucleus. There, NRF2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, NRF2 activation enhances intrinsic redox

resilience by strengthening the cell's capacity to respond to future oxidative challenges [36]. While NRF2 activation is beneficial in protecting against oxidative stress, chronic activation can have limitations. Continuous NRF2 activation may inadvertently promote tumorigenesis by aiding the survival of damaged cells, which may facilitate cancer progression. The activation of the pathway in non-cancerous tissues should, therefore, be carefully regulated. In terms of activating NRF2, activators can be classified into two primary categories, which include electrophilic and non-electrophilic types. Electrophilic activators, such as sulforaphane, directly modify KEAP1, leading to the activation of NRF2 [53]. However, these compounds can cause unintended damage due to their reactivity, potentially affecting cellular structures beyond their target. On the other hand, non-electrophilic activators, such as bardoxolone methyl, activate NRF2 without directly altering KEAP1, which offers a safer profile with fewer side effects but may have lower potency [37].

Conventional antioxidants have shown limited efficacy in neurodegenerative

Conventional antioxidant therapies have demonstrated limited benefit in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal ROS. This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, elamipretide (SS-31) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis [54]. Comparison of mitochondria-targeted antioxidants MitoQ and SS-31 is summarized in Table 1 [25,55–60].

Table 1. Comparative summary of mitochondria-targeted antioxidants MitoQ and SS-31

Feature	Mitoquinone mesylate (MitoQ)	Elamipretide (SS-31)
Primary mechanism	Electrophoretic accumulation driven by mitochondrial membrane potential.	Potential-independent uptake; targets and stabilizes cardiolipin in the inner membrane.
Antioxidant action	Redox-active ubiquinone moiety directly scavenges radicals and is regenerated by Complex II.	Structural stabilization of cristae/supercomplexes to prevent electron leakage and ROS formation.
Physical impact	It can cause mitochondrial swelling and depolarization at high concentrations due to its alkyl chain.	Acts as "mitochondrial armor," protecting against membrane fragmentation and structural decay.
Preclinical evidence	Robust protection in Alzheimer's, Parkinson's, and Huntington's disease models.	Consistent success in Alzheimer's, Parkinson's, Huntington's disease, and brain injury models, improving dynamics and synaptic health.
Clinical status	Failed PD trials (no clinical effect on UPDRS). Currently used as a dietary supplement for vascular health.	FDA approved (Sept 2025) for Barth syndrome. Failed trials in heart failure and primary mitochondrial myopathy.

Lifestyle interventions and hormetic redox adaptation

Lifestyle interventions, such as physical exercise and caloric restriction, activate endogenous antioxidant defenses through a process known as hormesis. Hormesis refers to the phenomenon where low-level, transient oxidative stress triggers adaptive protective responses within cells. When applied in moderation, physical exercise and mild caloric restriction induce controlled oxidative stress that enhances cellular resilience [61]. These interventions improve mitochondrial efficiency by promoting better ATP production and reducing the production of excess ROS, stimulate autophagy for the clearance of damaged proteins and organelles, and upregulate antioxidant signaling pathways such as the Nrf2 pathway, which enhances the cell's ability to combat oxidative damage. Additionally, they boost the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which support neuronal growth, survival, and synaptic plasticity, playing a crucial role in brain health [62].

However, it is important to note that the beneficial effects of hormesis are dose-dependent. When physical exercise or caloric restriction exceeds a certain threshold, it can shift from an adaptive to a maladaptive stress response. Prolonged or excessive exercise, for example, can lead to chronic oxidative stress, resulting in mitochondrial dysfunction, muscle damage, and an increase in inflammatory markers. Similarly, prolonged caloric restriction may impair cellular homeostasis, weaken the immune system, and exacerbate metabolic dysfunction. These maladaptive responses may overwhelm the body's protective mechanisms, leading to cellular damage rather than the intended health benefits. Therefore, while moderate exercise and caloric restriction can enhance redox balance and improve health outcomes, extreme or prolonged levels of these stressors may cause harm, highlighting the importance of balance in these lifestyle interventions [63].

Therapeutic potential and clinical translation

Pharmacological activation of NRF2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach [64]. By inducing mild electrophilic stress, it activates NRF2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other NRF2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive NRF2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress [36].

Challenges and future directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in AD and PD has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnect between compelling preclinical data and disappointing clinical outcomes highlights a critical “translational gap” that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

Table 2. Comparative summary between mechanisms of oxidative stress, their roles in Alzheimer's disease (AD) vs. Parkinson's disease (PD) and potential therapeutic interventions

Mechanisms of oxidative stress	Role in Alzheimer's disease (AD)	Role in Parkinson's disease (PD)	Potential therapeutic interventions
Mitochondrial dysfunction	Mitochondrial dysfunction leads to bioenergetic failure, impairing synaptic plasticity and contributing to neuronal damage.	Mitochondrial dysfunction in dopaminergic neurons accelerates ROS production and contributes to neuronal loss.	Mitochondria-targeted antioxidants (e.g., MitoQ, SS31) that help reduce ROS and restore mitochondrial function.
Lipid peroxidation	Oxidative damage to membrane lipids leads to neuronal damage and loss of synaptic function.	Lipid peroxidation exacerbates dopaminergic neuron death and disrupts membrane integrity.	Use of lipid antioxidants like alpha-lipoic acid or other peroxyl scavengers to prevent oxidative damage.
Proteostasis collapse	Proteostasis collapse contributes to the accumulation of amyloid-beta and tau, which disrupt neuronal function.	Accumulation of misfolded proteins, such as α -synuclein, leads to dopaminergic dysfunction.	Proteostasis regulators, such as proteasome activators or autophagy enhancers (e.g., rapamycin, spermidine).

Mechanisms of oxidative stress	Role in Alzheimer's disease (AD)	Role in Parkinson's disease (PD)	Potential therapeutic interventions
Neuroinflammation	Chronic neuroinflammation amplifies the amyloid plaque formation and accelerates disease progression.	Neuroinflammation in microglia worsens dopaminergic neuron death and amplifies ROS production.	Anti-inflammatory agents targeting NF- κ B or microglial activation (e.g., minocycline, curcumin).
Redox-Imbalance (ROS and RNS)	ROS accumulation damages cellular structures (DNA, lipids, proteins) and triggers apoptosis.	ROS generation through dopamine metabolism leads to neuronal damage and contributes to cell death.	Nrf2 activators (e.g., dimethyl fumarate), which boost cellular antioxidant defences and help restore redox homeostasis.
Autophagy and mitophagy failure	Impaired autophagy leads to the accumulation of damaged proteins, exacerbating neurodegeneration.	Deficient mitophagy results in the accumulation of dysfunctional mitochondria, contributing to neurodegeneration.	Autophagy enhancers (e.g., rapamycin) and mitophagy activators (e.g., Urolithin A, PINK1 activators) to clear damaged organelles.

Temporal mismatch: Treating too late in the disease course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred [66,67]. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure [68]. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles [69].

Bioavailability and blood-brain barrier limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood-brain barrier, while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets [70]. Even when compounds successfully cross the blood-brain barrier, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery, such as nanoparticle-based carriers, mitochondria-targeted molecules, and ligand-mediated transport systems, represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects [71].

Paradox of reductive stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. ROS are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction [23]. This concept challenges the simplistic view that “more antioxidants are better” and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS

indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease [72].

Need for redox biomarkers and patient stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status in vivo. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism [73].

Toward a systems-level therapeutic strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways [74]. In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system [75].

Conclusion

This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy, collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.

Acknowledgments

The authors gratefully acknowledge the Department of Biochemistry, Faculty of Medicine, Trisakti University, for its continuous academic support and supportive environment during the development of this review. We also sincerely thank the researchers and scholars whose work has contributed to the advancement of knowledge in the field of oxidative stress, aging, and neurodegeneration. Their contributions provided essential scientific insights that informed and strengthened this manuscript.

Competing interests

All authors declare that there are no conflicts of interest related to this work.

Funding

This study received no external funding.

Underlying data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

This study employed the artificial intelligence (AI) tools Gemini Pro and ChatGPT to support manuscript writing, including language refinement (improving grammar, sentence structure, and overall readability) and technical writing assistance (providing suggestions for structuring complex technical descriptions more effectively). All AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were made solely by the authors.

How to cite

Faradilla MA, Anastasya KS, Yastani D, *et al.* Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets. *Narra J* 2026; 6 (1): e3042 - <http://doi.org/10.52225/narra.v6i1.3042>.

References

1. Rostagno A, Ghiso J. Alzheimer's disease pathogenic mechanisms: Linking redox homeostasis and mitochondria-associated metabolic pathways through nuclear factor erythroid 2-related factor 2 (Nrf2). *Antioxidants* 2025;14(7):812.
2. Tenchov R, Sasso JM, Wang X, *et al.* Aging hallmarks and progression and age-related diseases: A landscape view of research advancement. *ACS Chem Neurosci* 2023;15(1):1-30.
3. Spina E, Ferrari RR, Pellegrini E, *et al.* Mitochondrial alterations, oxidative stress, and therapeutic implications in alzheimer's disease: A narrative review. *Cells* 2025;14(3):229.
4. Jurcau MC, Jurcau A, Diaconu RG. Oxidative stress in the pathogenesis of neurodegenerative diseases. *Stresses* 2024;4(4):827-849.
5. Xu X, Pang Y, Fan X. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. *Signal Transduct Target Ther* 2025;10(1):190.
6. Harman D. Free radical theory of aging. *Mutat Res* 1992;275:257-266.
7. Harman D. Free radical theory of aging: An update: Increasing the functional life span. *Ann N Y Acad Sci* 2006;1067(1):10-21.
8. Watts ME, Pocock R, Claudianos C. Brain energy and oxygen metabolism: Emerging role in normal function and disease. *Front Mol Neurosci* 2018;11:216.
9. Tripathi K, Ben-Shachar D. Mitochondria in the central nervous system in health and disease: The puzzle of the therapeutic potential of mitochondrial transplantation. *Cells* 2024;13(5):410.
10. Stefanatos R, Sanz A. The role of mitochondrial ROS in the aging brain. *FEBS Lett* 2018;592(5):743-758.
11. Kuzu OF, Granerud LJT, Saatcioglu F. Navigating the landscape of protein folding and proteostasis: from molecular chaperones to therapeutic innovations. *Signal Transduct Target Ther* 2025;10(1):358.
12. Hu C, Lin M, Wang C, *et al.* Current understanding of protein aggregation in neurodegenerative diseases. *Int J Mol Sci* 2025;26(21):10568.
13. Tchekalarova J, Tzoneva R. Oxidative stress and aging as risk factors for alzheimer's disease and parkinson's disease: The role of the antioxidant melatonin. *Int J Mol Sci* 2023;24(3):3022.
14. Hou Y, Dan X, Babbar M, *et al.* Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol* 2019;15(10):565-581.
15. Neyra Chauca JM, Vázquez VanDyck M, Espinoza Santana A, *et al.* Oxidative stress, neuroinflammation, and microvascular damage in neurodegenerative diseases: Mechanistic insights and therapeutic approaches 2025;10(11):1-14.
16. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat Rev Mol Cell Biol* 2020;21(7):363-383.
17. Fujii J, Homma T, Osaki T. Superoxide radicals in the execution of cell death. *Antioxidants* 2022;11(3):501.
18. Liu S, Liu J, Wang Y, *et al.* Oxidative stress: Signaling pathways, biological functions, and disease. *MedComm* 2025;6(7):e70268.


19. Mailloux RJ. An update on mitochondrial reactive oxygen species production. *Antioxidants* 2020;9(6):472.
20. Valgimigli L. Lipid peroxidation and antioxidant protection. *Biomolecules* 2023;13(9):1291.
21. Wang B, Wang Y, Zhang J, *et al.* ROS-induced lipid peroxidation modulates cell death outcome: mechanisms behind apoptosis, autophagy, and ferroptosis. *Arch Toxicol* 2023;97(6):1439-1451.
22. Sonninen TM, Goldsteins G, Laham-Karam N, *et al.* Proteostasis disturbances and inflammation in neurodegenerative diseases. *Cells* 2020;9(10):2183.
23. Ulfig A, Jakob U. Cellular oxidants and the proteostasis network: Balance between activation and destruction. *Trends Biochem Sci* 2024;49(9):761-774.
24. Bellanti F, Coda ARD, Trecca MI, *et al.* Redox imbalance in inflammation: The interplay of oxidative and reductive stress. *Antioxidants* 2025;14(6):656.
25. Şerban M, Toader C, Covache-Busuioc RA. The redox revolution in brain medicine: Targeting oxidative stress with ai, multi-omics and mitochondrial therapies for the precision eradication of neurodegeneration. *Int J Mol Sci* 2025;26(15):7498.
26. Doblado L, Lueck C, Rey C, *et al.* Mitophagy in human diseases. *Int J Mol Sci* 2021;22(8):3903.
27. Du M, Yu Y, Wang J, *et al.* Autophagy-lysosome pathway dysfunction in neurodegeneration and cancer: Mechanisms and therapeutic opportunities. *Int J Mol Sci* 2025;27(1):366.
28. Jomova K, Alomar SY, Alwasel SH, *et al.* Several lines of antioxidant defense against oxidative stress: Antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch Toxicol* 2024;98(5):1323-1367.
29. Gulcin İ. Antioxidants: a comprehensive review. *Arch Toxicol* 2025;99(5):1893-1997.
30. Gusti AM, Qusti SY, Alshammari EM, *et al.* Antioxidants-related superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione-S-transferase (GST), and nitric oxide synthase (NOS) gene variants analysis in an obese population: a preliminary case-control study. *Antioxidants* 2021;10(4):595.
31. Ashok A, Andrabi SS, Mansoor S, *et al.* Antioxidant therapy in oxidative stress-induced neurodegenerative diseases: role of nanoparticle-based drug delivery systems in clinical translation. *Antioxidants* 2022;11(2):408.
32. Alhaj Sulaiman A, Katanaev VL. Beyond antioxidants: How redox pathways shape cellular signaling and disease outcomes. *Antioxidants* 2025;14(9):1142.
33. Chakravorty S, Malvi A, Chaturvedi A, *et al.* Glutathione—the master antioxidant. *Int J Med Res Pharm Sci* 2020;7(2):1-11.
34. Wadhwa R, Gupta R, Maurya PK. Oxidative stress and accelerated aging in neurodegenerative and neuropsychiatric disorder. *Curr Pharm Des* 2018;24(40):4711-4725.
35. Moustapha A. Neurodegenerative diseases: Potential effect of glutathione. in: Dulce bagatini m, editor. *Glutathione Syst Oxid Stress Health Dis* 2020;2(5):92240.
36. Mayer C, Riera-Ponsati L, Kauppinen S, *et al.* Targeting the NRF2 pathway for disease modification in neurodegenerative diseases: Mechanisms and therapeutic implications. *Front Pharmacol* 2024;15:1437939.
37. Bitra VR, Moshapa F, Adiukwu PC, *et al.* Nrf2-mediated signaling as a therapeutic target in alzheimer's disease. *Open Neurol J* 2024;18(1):e1874205X319474.
38. Harman D. Aging: A Theory based on free radical and radiation chemistry. *J Gerontol* 1956;11(3):298-300.
39. Pomatto LCD, Davies KJA. Adaptive homeostasis and the free radical theory of ageing. *Free Radic Biol Med* 2018;124:420-430.
40. Li B, Ming H, Qin S, *et al.* Redox regulation: mechanisms, biology and therapeutic targets in diseases. *Signal Transduct Target Ther* 2025;10(1):72.
41. Płóciniczak A, Bukowska-Olech E, Wysocka E. The complexity of oxidative stress in human age-related diseases—a review. *Metabolites* 2025;15(7):479.
42. Abdelhamid RF, Nagano S. Crosstalk between oxidative stress and aging in neurodegeneration disorders. *Cells* 2023;12(5):753.
43. Chandimali N, Bak SG, Park EH, *et al.* Free radicals and their impact on health and antioxidant defenses: A review. *Cell Death Discov* 2025;11(1):19.
44. Tripathi D, Oldenburg DJ, Bendich AJ. Oxidative and glycation damage to mitochondrial dna and plastid dna during plant development. *Antioxidants* 2023;12(4):891.
45. Boccardi V, Mancinetti F, Mecocci P. Oxidative stress, advanced glycation end products (AGEs), and neurodegeneration in alzheimer's disease: A metabolic perspective. *Antioxid Basel Switz* 2025;14(9):1044.

46. Alkhalifa AE, Alkhalifa O, Durdanovic I, *et al.* Oxidative stress and mitochondrial dysfunction in alzheimer's disease: Insights into pathophysiology and treatment. *J Dement Alzheimer's Dis* 2025;2(2):17.
47. Watanabe H, Dijkstra JM, Nagatsu T. Parkinson's disease: Cells succumbing to lifelong dopamine-related oxidative stress and other bioenergetic challenges. *Int J Mol Sci* 2024;25(4):2009.
48. Henrich MT, Oertel WH, Surmeier DJ, *et al.* Mitochondrial dysfunction in Parkinson's disease – a key disease hallmark with therapeutic potential. *Mol Neurodegener* 2023;18(1):83.
49. Skou LD, Johansen SK, Okarmus J, *et al.* Pathogenesis of DJ-1/PARK7-Mediated parkinson's disease. *Cells* 2024;13(4):296.
50. Shi X. Targeting NOX2 to combat oxidative stress and neuroinflammation and provide neuroprotection in neurodegeneration. 2024. Available from: <http://www.uni-heidelberg.de/mydata.html>. Accessed: 25 December 2025.
51. Kulkarni A, Chen J, Maday S. Neuronal autophagy and intercellular regulation of homeostasis in the brain. *Curr Opin Neurobiol* 2018;51:29-36.
52. Ramsey CL. Biologically structured water (BSW)-a review (Part 1): structured water (SW) properties, BSW and redox biology, BSW and bioenergetics. *J Basic Appl Sci* 2023;19:174-201.
53. Champilas N, Fang EF, Palikaras K. Mitophagy and neuroinflammation: A compelling interplay. *Curr Neuropharmacol* 2023;21(7):1477-1481.
54. Apostolova N, Victor VM. Molecular strategies for targeting antioxidants to mitochondria: Therapeutic Implications. *Antioxid Redox Signal* 2015;22(8):686-729.
55. Broome SC, Whitfield J, Janssens K, *et al.* MitoQ supplementation does not impact redox responses to acute exercise in skeletal muscle of older individuals. *Redox Biol* 2025;88:103927.
56. Pin F, Huot JR, Bonetto A. The mitochondria-targeting agent MitoQ improves muscle atrophy, weakness and oxidative metabolism in C26 tumor-bearing mice. *Front Cell Dev Biol* 2022;10:861622.
57. Zhou J, Shen R, Makale EC, *et al.* SS31 confers cerebral protection by reversing mitochondrial dysfunction in early brain injury following subarachnoid hemorrhage, via the Nrf2-and PGC-1 α -dependent pathways. *Neurochem Res* 2023;48(5):1580-1595.
58. Li M, Kong D, Meng L, *et al.* Discovery of novel SS-31 (d-Arg-dimethylTyr-Lys-Phe-NH₂) derivatives as potent agents to ameliorate inflammation and increase mitochondrial ATP synthesis. *RSC Adv* 2024;14(41):29789-29799.
59. Jiang Q, Yin J, Chen J, *et al.* Mitochondria-targeted antioxidants: A step towards disease treatment. *Oxid Med Cell Longev* 2020;2020(1):8837893.
60. Wadan AHS, Shaaban AH, El-Sadek MZ, *et al.* Mitochondrial-based therapies for neurodegenerative diseases: A review of the current literature. *Naunyn Schmiedebergs Arch Pharmacol* 2025;398(9):11357-11386.
61. Singh AK, Sinha JK, Seetharam RN. The potential of intermittent fasting in age-related diseases and precision anti-aging therapeutics. London: Academic Press; 2025.
62. Bevere M, Di Cola G, Santangelo C, *et al.* Redox-based disruption of cellular hormesis and promotion of degenerative pathways: perspectives on aging processes. *J Gerontol Ser A* 2022;77(11):2195-2206.
63. Mehdi MM, Solanki P, Singh P. Oxidative stress, antioxidants, hormesis and calorie restriction: The current perspective in the biology of aging. *Arch Gerontol Geriatr* 2021;95:104413.
64. Linker RA, Haghikia A. Dimethyl fumarate in multiple sclerosis: Latest developments, evidence and place in therapy. *Ther Adv Chronic Dis* 2016;7(4):198-207.
65. Toader C, Tataru CP, Munteanu O, *et al.* Decoding neurodegeneration: A review of molecular mechanisms and therapeutic advances in alzheimer's, parkinson's, and ALS. *Int J Mol Sci* 2024;25(23):12613.
66. Colom-Cadena M, Spires-Jones T, Zetterberg H, *et al.* The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. *Alzheimers Res Ther* 2020;12(1):21.
67. Dejanovic B, Sheng M, Hanson JE. Targeting synapse function and loss for treatment of neurodegenerative diseases. *Nat Rev Drug Discov* 2024;23(1):23-42.
68. Manful CF, Fordjour E, Subramaniam D, *et al.* Antioxidants and reactive oxygen species: Shaping human health and disease outcomes. *Int J Mol Sci* 2025;26(15):7520.
69. Velikic G, Supic G, Maric DL, *et al.* Neurodegeneration as ecosystem failure: A new paradigm for prevention and treatment. *Int J Mol Sci* 2025;26(22):11207.
70. Niazi SK. Non-invasive drug delivery across the blood-brain barrier: A prospective analysis. *Pharmaceutics* 2023;15(11):2599.
71. Vargas R, Martinez-Martinez N, Lizano-Barrantes C, *et al.* Advancing through the blood-brain barrier: Mechanisms, challenges and drug delivery strategies. *Admet Dmpk* 2025;13(5):2988.

72. Pérez-Torres I, Guarner-Lans V, Rubio-Ruiz ME. Reductive Stress in Inflammation-associated diseases and the pro-oxidant effect of antioxidant agents. *Int J Mol Sci* 2017;18(10):2098.
73. Şerban M, Toader C, Covache-Busuioc RA. The redox revolution in brain medicine: Targeting oxidative stress with ai, multi-omics and mitochondrial therapies for the precision eradication of neurodegeneration. *Int J Mol Sci* 2025;26(15):7498.
74. Zhang W, Xiao D, Mao Q, *et al.* Role of neuroinflammation in neurodegeneration development. *Signal Transduct Target Ther* 2023;8(1):267.
75. Hein ZM, Karikalan B, Gopalakrishna PK, *et al.* Toward a unified framework in molecular neurobiology of alzheimer's disease: Revisiting the pathophysiological hypotheses. *Mol Neurobiol* 2026;63(1):282.

REKAP SUBMISSION

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets **Jurnal Narra J Vo. 6 No.1 April 2026**

No	Tahap	Tanggal	Kegiatan / Dokumen
1	Submission	12 Januari 2026	meutia, Oxidative Stress as a Converging Mechanism of Aging.docx
2	Submission	13 Januari 2026	Layouted - 3042.docx
3	Pre-Review Discussion	12 Januari 2026	"This revised manuscript follows the Narra J template."
4	Reviewer's Attachment	28 Januari 2026	3042-Manuscript-19181-1-4-20260113 (1).docx
5	Reviewer's Attachment	29 Januari 2026	Recommendations
6	Revision 1	31 Januari 2026	Revisi manuskrip
10	Revision 2	4 Februari 2026	Revisi Manuskrip
11	Notification	12 Maret 2026	Editor Decision
12	Copyediting	24 Februari 2026	3042-Correct-Proof.docx
13	Production	2 Maret 2026	Final Proofread Requested
14	PUBLISHED 	13 Maret 2026	Your article is published

[Narra] Editor Decision

2026-03-12 10:44

Dear Drs Meutia A. Faradilla, Karina S. Anastasya, Deasyka Yastani, Yohana Yohana, Endrico X. Tungka, Suweino Suweino:

Thank you for submitting your manuscript to Narra J.

I am pleased to inform you that your manuscript entitled "Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets" has been **officially accepted both scientifically and editorially in Narra J.**

Your accepted manuscript will now be transferred to our Production Department. A proof will be created, which you will be asked to review. If additional information is required during the production process, we will contact you directly.

Please note that this communication is not the Letter of Acceptance (LoA). The official LoA will be issued by the Narra J Finance Department. The Finance Department will send your invoice via the Odoo platform using the email address admin@narraj.org.

We appreciate your submission to Narra J and hope you will consider us again in the future.

Editor-In-Chief - Narra J

[Narra] Decision on Your Manuscript Submission to Narra J

2026-01-30 19:15

Meutia Atika Faradilla:

Thank you for submitting your manuscript entitled "2026_Oxidative Stress as a Converging Mechanism of Aging and Neurodegeneration: From Molecular Pathways to Therapeutic Targets" to Narra J. It has been reviewed by experts in the field and we have reached a decision that **Revisions Required** before further processes.

Please revise the manuscript according to the reviewers' comments and upload the revised file within 10 days. Any revisions should be clearly highlighted using the "Track Changes" function in Microsoft Word, so that changes are easily visible to the editors and reviewers. **Please provide response to each comment/suggestion from the reviewers and editor directly in the manuscript file by replaying the comment directly.** If the comments/suggestions are provided in the separated page, please provide a cover letter consisting the author's response for each comment/suggestion.

Do not hesitate to contact us if you have any questions regarding the revision of your manuscript or if you need more time. We look forward to hearing from you soon.

Notifications

[Narra] Editor Decision

2026-02-18 07:12

Dear Drs Meutia Atika Faradilla:

Thank you for submitting your manuscript to Narra J.

I am pleased to inform you that your manuscript entitled "2026_Oxidative Stress as a Converging Mechanism of Aging and Neurodegeneration: From Molecular Pathways to Therapeutic Targets" has been **accepted scientifically in Narra J.**

Your accepted manuscript will now be transferred to our Production Department. A proof will be created, which you will be asked to review. If additional information is required during the production process, we will contact you directly.

Please note that this communication is not the Letter of Acceptance (LoA). The official LoA will be issued by the Narra J Finance Department. The Finance Department will send your invoice via the Odoo platform using the email address admin@narraj.org.

We appreciate your submission to Narra J and hope you will consider us again in the future.

Messages

Note

From

Dear Authors

productioneditor
2026-03-02 00:34

The proof of your article, to be published in Narra J, is attached to this e-mail as a PDF file.

We will do everything possible to get your article published quickly and accurately; to do this we need your cooperation. Please respond promptly (48 hours), even if you have no corrections: the sooner we hear from you, the sooner your corrected article will appear online. Please note that any delay in returning your corrections could result in a delay in publication and that any significant changes to the article as accepted for publication will only be considered at this stage with the permission of the Editor.

Please note that proof corrections can now be annotated on-screen, which allows you to mark directly in the PDF file, and upload it through the system.

Please use this proof for checking the typesetting, editing, completeness and correctness of the text, tables and figures.

This is the last opportunity to make corrections before the final publication of your article.

In addition, we kindly ask that any references that are still missing be completed and that all authors accept the ORCID authorization request sent to the author email address to activate their ORCID ID.

Kind regards,
Narra J Editorial Office
(CA)

Your article is published



Participants

Production Editor (productioneditor)

Meutia Atika Faradilla (meutia)

Messages	
Note	From
<p>Your article is now published. If you have correction, please let us know within 24 hours. After 24 hours, further corrections need to be submitted as a corrigendum. Your article can be downloaded from here: https://narraj.org/main/issue/view/22. Please share the link of the article to your groups, colleagues and social media to increase the possibility your article being cited in the future.</p> <p>Thank you for trusting Narra J to publish your work.</p> <p>Sharp! Narra J (CA)</p>	<p>productioneditor 2026-03-13 22:10</p>

"This revised manuscript follows the Narra J template."

Review Article

Oxidative Stress as a Converging Mechanism of Aging and Neurodegeneration: From Molecular Pathways to Therapeutic Targets

Meutia Atika Faradilla¹, Karina Shasri Anastasya², Deasyka Yastani¹, Yohana¹, Endrico Xavieres Tungka¹, Suweino¹

¹ Department of Biochemistry, Faculty of Medicine, Trisakti University, Jakarta, Indonesia

² Department of Nutritional, Faculty of Medicine, Trisakti University, Jakarta, Indonesia

*Corresponding author: meutia.atika@trisakti.ac.id

Abstract

Aging is the primary risk factor for major neurodegenerative disorders, yet the precise molecular intertwining between biological aging and neuronal loss remains complex. Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, has emerged as a fundamental converging mechanism driving both processes. This review synthesizes current evidence delineating how chronic redox imbalance drives cellular senescence and neuronal vulnerability through mitochondrial dysfunction, lipid peroxidation, and oxidative protein damage. We highlight how sustained oxidative insults promote the misfolding and aggregation of disease-defining proteins, including amyloid- β in Alzheimer's disease and α -synuclein in Parkinson's disease, thereby amplifying neuroinflammation, synaptic dysfunction, and bioenergetic failure. Furthermore, we critically reassess antioxidant-based therapeutic strategies, emphasizing a paradigm shift away from non-specific radical scavenging toward targeted modulation of endogenous defense systems, particularly Nrf2 signaling and mitochondria-directed antioxidants. By integrating molecular mechanisms with translational perspectives, this review positions redox modulation as a promising avenue to delay aging-associated neurodegenerative progression rather than merely alleviating downstream pathology.

Keywords: Oxidative Stress; Aging; Neurodegeneration; Mitochondria; Reactive Oxygen Species (ROS); Nrf2

Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders (NDDs), most notably Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS)[1]. Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor is biological aging [2]. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of



neuronal vulnerability and decline. Within the network of aging-related mechanisms, oxidative stress has emerged as a pivotal molecular bridge linking normal physiological aging to pathological neurodegeneration[3]. Rather than being a mere byproduct of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems[4]. Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins[5].

Classical theories, such as Harman's Free Radical Theory of Aging, have historically attributed aging to random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival[6]. The Central Nervous System (CNS) is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden. At the heart of this vulnerability lies the mitochondrion[7]. As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses[8].

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance[9]. The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid beta in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation [10]. This article critically examines the dual role of oxidative stress as both a driver of physiological aging and a catalyst for pathological neurodegeneration. We dissect the molecular origins of ROS, the age associated erosion of antioxidant defenses, and the convergence of these pathways on protein aggregation and neuronal loss. Furthermore, we explore the historical pitfalls of broad spectrum antioxidant therapies and advocate for a paradigm shift toward targeted modulation of redox-sensitive circuits rather than non-specific scavenging.

1. Molecular Mechanisms of Oxidative Stress

Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Although these disorders are clinically distinct, they share biological aging as a common risk factor, indicating that age-related cellular processes actively contribute to neuronal degeneration[11]. Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology[12]. Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular

defense systems, leading to damage of DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function[3][8]. The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration[13].

2.1 Molecular Origins of Reactive Species

To understand the progression of neurodegeneration, it is essential to trace the molecular origins of reactive oxygen species (ROS). ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During oxidative phosphorylation, electron leakage occurs most notably at Complex I (NADH dehydrogenase) and Complex III (ubiquinone–cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O₂), forming the superoxide anion (O₂^{•-}), as described by the reaction[14]:



Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H₂O₂), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe²⁺) or cuprous copper (Cu⁺), generating the highly reactive and destructive hydroxyl radical (•OH)[15]:



The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression[16][17].

2.2 Antioxidant Defense

a. Enzymatic Vanguard: The First Line of Redox Control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain[18]. Because superoxide is highly reactive and short lived, its rapid conversion into hydrogen peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology[19]. At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from

signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (CAT) and glutathione peroxidase (GPx) assume decisive roles[20][21]. By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation a species widely regarded as the most destructive ROS due to its indiscriminate reactivity [16]. This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised whether due to genetic variation, post-translational alterations, or age-related functional decline the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage[22].

b. Non-Enzymatic Buffers and Thiol-Based Redox Modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione (GSH) playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond the capacity of enzymatic systems. By donating electrons, GSH neutralizes reactive species and is converted into its oxidized form, glutathione disulfide (GSSG). Consequently, the balance between reduced and oxidized glutathione (the GSH/GSSG ratio) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain[23]. Evidence from aging studies consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation[24].

c. Regulatory Control and the Nrf2 Axis

The effectiveness of antioxidant defenses within the CNS is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of cellular stress responses. Under basal conditions, Nrf2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding SOD, GPx, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands. With advancing age, however, the responsiveness of the Nrf2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a “redox vulnerability gap,” wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders.

3. Oxidative Stress in Aging: The "Hardwiring" of Senescence

3.1. The Modified Free Radical Theory of Aging

Harman's Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by reactive oxygen species (ROS). While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury [25]. Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled [26]. However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu, commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline [27].

3.2. Accumulation of Macromolecular Damage in the Aging Brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between reactive oxygen species (ROS) production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function [28]. Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency [29].

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin–proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress [30]. Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2'-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration [31].

4. Oxidative Stress in Neurodegenerative Diseases

4.1. Alzheimer's Disease: Oxidative Stress as a Self-Reinforcing Pathological Loop

In Alzheimer's disease, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through interconnected, self-reinforcing loops that involve amyloid-beta ($A\beta$) accumulation, mitochondrial dysfunction, and Tau pathology. Soluble $A\beta$ oligomers display redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of reactive oxygen species (ROS). This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further $A\beta$ aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment [32]. The accumulation of $A\beta$ within neuronal mitochondria further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular energy balance. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in Alzheimer's disease[33].

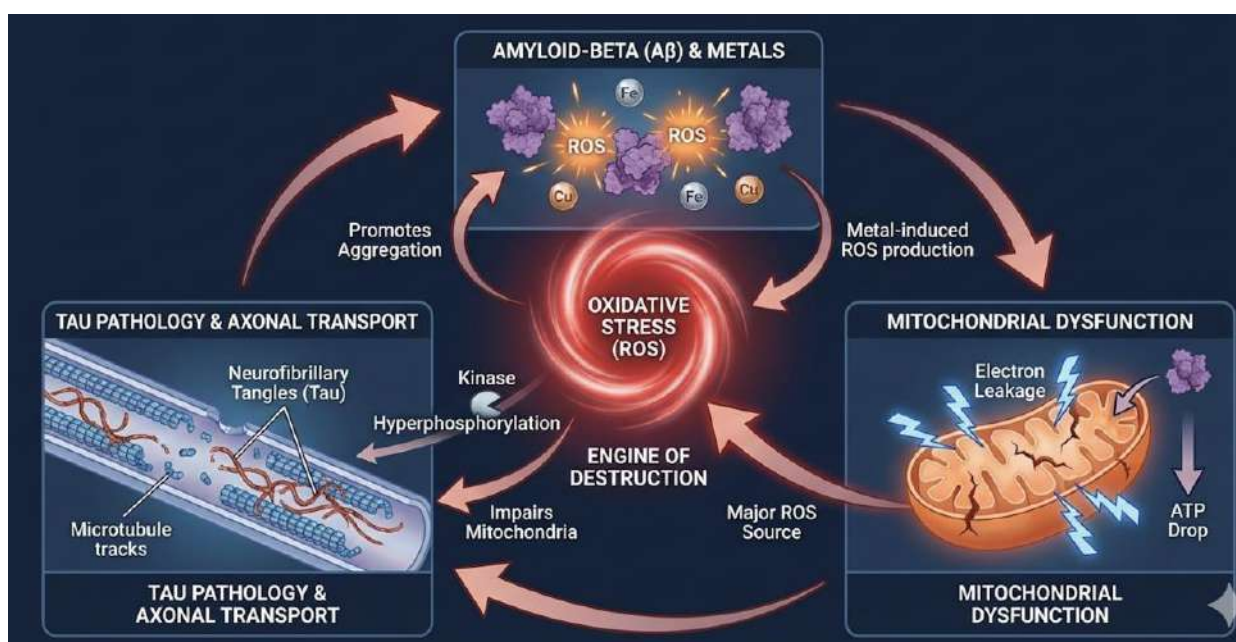


Figure 1. The self reinforcing oxidative loop in alzheimer's disease

4.2. Parkinson's Disease: Selective Vulnerability to Oxidative Stress

Parkinson's disease illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons[34].

Mitochondrial dysfunction further amplifies oxidative injury in parkinson's disease. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1–Parkin–mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress[35]. Loss of DJ-1–mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in Parkinson's disease [36].

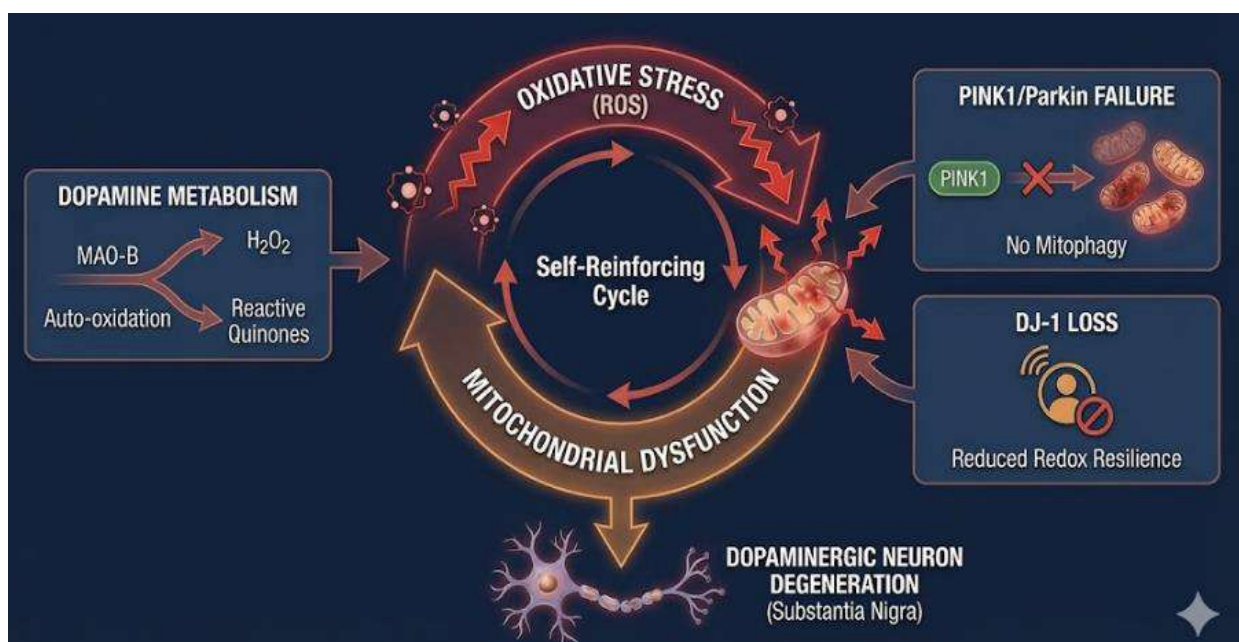


Figure 2. the transition from healthy redox homeostasis maintained by antioxidant defenses and hormesis to a pathological state driven by mitochondrial dysfunction, neuroinflammation, and lipid peroxidation. This pathway ultimately leads to the desolate landscape of neurodegeneration, characterized by protein aggregation (such as Amyloid- β and α -synuclein) and autophagy failure in Alzheimer's and Parkinson's diseases.

5. The Converging Pathways: Inflammation and Autophagy

Oxidative stress represents an early destabilizing force in neuronal homeostasis, yet its most destructive effects emerge through its capacity to activate downstream pathological pathways[37]. Rather than acting as an isolated insult, sustained redox imbalance orchestrates a broader cellular collapse by engaging neuroinflammatory signaling and disrupting intracellular quality-control mechanisms. Among these, chronic inflammation and autophagy impairment stand out as convergent pathways that transform transient oxidative disturbances into irreversible neurodegenerative trajectories[38].

5.1. The Oxidative Inflammatory Axis: From Redox Imbalance to Neurotoxicity

In the central nervous system, oxidative stress and inflammation are intimately intertwined, forming a self-amplifying pathological circuit. Microglia, the brain's resident immune cells, are uniquely positioned at the interface between neuronal metabolism and immune surveillance. Under physiological conditions, microglia maintain synaptic integrity and respond transiently to injury. However, persistent

oxidative stress alters this homeostatic role, pushing microglia toward a chronically activated, proinflammatory phenotype[39].

ROS-Mediated Activation of Proinflammatory Signaling

Reactive oxygen species function as potent second messengers capable of activating redox-sensitive transcription factors. Among these, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) plays a central role in translating oxidative cues into inflammatory gene expression. Elevated ROS levels promote the dissociation of NF- κ B from its cytoplasmic inhibitors, allowing its translocation into the nucleus. Once activated, NF- κ B drives the transcription of a broad spectrum of proinflammatory mediators, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). These cytokines exert pleiotropic effects within the neural microenvironment. Beyond recruiting additional immune responses, they directly impair synaptic function, disrupt neuronal calcium homeostasis, and sensitize neurons to excitotoxic injury. Importantly, this inflammatory signaling is not a short-lived response but becomes sustained under conditions of chronic oxidative stress, reshaping the neural milieu into one that favors degeneration rather than repair [40].

The Self Perpetuating Cycle of ROS and Inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders[41].

5.2. Autophagy and Mitophagy Failure: Breakdown of Cellular Quality Control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival[42].

Lysosomal Dysfunction and Autophagic Arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal (4-HNE) that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This

accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure[43].

Mitophagy Failure and Energetic Collapse

Among autophagic processes, the selective removal of damaged mitochondria known as mitophagy is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as “zombie mitochondria,” remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure. As ATP levels decline, energy-dependent processes including ion homeostasis, axonal transport, and synaptic transmission become unsustainable. Ultimately, this convergence of oxidative damage, autophagy impairment, and bioenergetic collapse pushes neurons toward apoptotic or necrotic death[44].

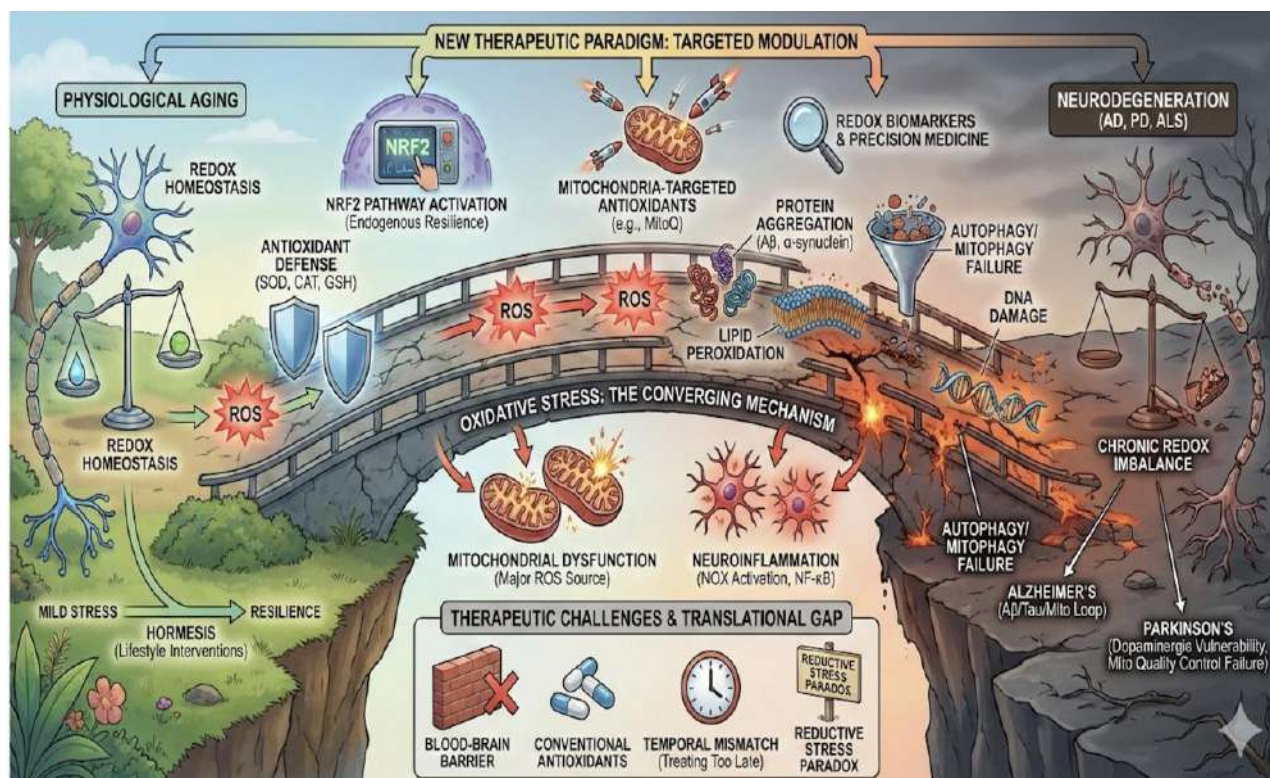


Figure 3. the journey from molecular origins (ROS) through cellular damage (mitochondria/inflammation) to clinical disease (AD/PD), while proposing a shift toward precision medicine and targeted therapies.

6. Therapeutic Targets and Clinical Implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However,

decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated[45].

6.1. Nrf2 Pathway Activation: Reinforcing Endogenous Redox Resilience

Nuclear factor erythroid 2–related factor 2 (Nrf2) serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing Nrf2 to escape degradation and translocate into the nucleus. There, Nrf2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, Nrf2 activation enhances intrinsic redox resilience by strengthening the cell’s capacity to respond to future oxidative challenges[46].

6.2 Conventional antioxidants have shown limited efficacy in neurodegenerative.

Conventional antioxidant therapies have demonstrated limited benefit in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal reactive oxygen species (ROS). This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, SS-31 (elamipretide) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis[47].

6.3. Lifestyle Interventions and Hormetic Redox Adaptation

Lifestyle interventions such as physical exercise and caloric restriction activate endogenous antioxidant defenses through hormesis, a process in which low-level, transient oxidative stress induces adaptive protective responses. These interventions enhance mitochondrial efficiency, stimulate autophagy, and upregulate antioxidant signaling pathways, while also increasing neurotrophic factors such as brain-derived neurotrophic factor (BDNF). Importantly, hormetic benefits are dose-dependent, as excessive or prolonged stress may exacerbate oxidative damage rather than confer protection.Mitochondria-Targeted Antioxidants[48].

Therapeutic Potential and Clinical Translation

Pharmacological activation of Nrf2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach. By inducing mild electrophilic stress, it activates Nrf2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other Nrf2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive Nrf2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress[46].

7. Challenges and Future Directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in Alzheimer's disease (AD) and Parkinson's disease (PD) has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnect between compelling preclinical data and disappointing clinical outcomes highlights a critical "translational gap" that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

7.1. Temporal Mismatch: Treating Too Late in the Disease Course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles[49].

7.2. Bioavailability and Blood Brain Barrier Limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood-brain barrier (BBB), while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets[50]. Even when compounds successfully cross the BBB, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery such as nanoparticle-based carriers, mitochondria-targeted

molecules, and ligand-mediated transport systems represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects[51].

7.3. The Paradox of Reductive Stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. Reactive oxygen species are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction. This concept challenges the simplistic view that “more antioxidants are better” and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease[52].

7.4. The Need for Redox Biomarkers and Patient Stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status *in vivo*. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism[53].

7.5. Toward a Systems-Level Therapeutic Strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways[54]. In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system[55].

Conclusion

Oxidative stress represents a central, unifying mechanism that bridges physiological aging and pathological neurodegeneration. Through sustained redox imbalance, reactive

oxygen species progressively damage cellular macromolecules, disrupt mitochondrial function, impair proteostasis, and perpetuate neuroinflammation, ultimately undermining neuronal integrity and network function. The limited success of conventional antioxidant therapies underscores a critical insight: neurodegeneration arises not from excessive ROS alone, but from the failure of redox regulation. Future therapeutic strategies must therefore shift from indiscriminate radical scavenging toward precise modulation of endogenous defense systems. Approaches that restore mitochondrial quality control, preserve autophagic flux, and activate adaptive pathways such as Nrf2 offer a more rational framework for intervention. By reframing aging as a modifiable redox-driven process, targeted redox modulation may delay the onset and progression of neurodegenerative diseases, extending neural healthspan rather than merely treating symptoms.

Acknowledgments

The authors gratefully acknowledge the Department of Biochemistry, Faculty of Medicine, Trisakti University, for its continuous academic support and supportive environment during the development of this review. We also sincerely thank the researchers and scholars whose work has contributed to the advancement of knowledge in the field of oxidative stress, aging, and neurodegeneration. Their contributions provided essential scientific insights that informed and strengthened this manuscript.

Competing interests

All authors declare that there are no conflicts of interest related to this work.

Underlying data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

During the preparation of this manuscript, the authors made limited use of artificial intelligence–based tools as a supporting aid for language editing and improvement of sentence clarity. These tools were used only to assist in refining grammar and readability. All scientific content, interpretations, critical analyses, and conclusions presented in this manuscript were developed, reviewed, and finalized by the authors. The use of AI did not influence the scientific substance of the work and does not replace the authors' intellectual contribution or responsibility.

References

- [1] A. Rostagno and J. Ghiso, "Alzheimer's Disease Pathogenic Mechanisms: Linking Redox Homeostasis and Mitochondria-Associated Metabolic Pathways Through Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)," *Antioxidants*, vol. 14, no. 7, p. 812, July 2025, doi: 10.3390/antiox14070812.
- [2] R. Tenchov, J. M. Sasso, X. Wang, and Q. A. Zhou, "Aging hallmarks and progression and age-related diseases: a landscape view of research advancement," *ACS Chem. Neurosci.*, vol. 15, no. 1, pp. 1–30, 2023.
- [3] E. Spina *et al.*, "Mitochondrial Alterations, Oxidative Stress, and Therapeutic Implications in Alzheimer's Disease: A Narrative Review," *Cells*, vol. 14, no. 3, p. 229, Feb. 2025, doi: 10.3390/cells14030229.
- [4] M.-C. Jurcau, A. Jurcau, and R.-G. Diaconu, "Oxidative Stress in the Pathogenesis of Neurodegenerative Diseases," *Stresses*, vol. 4, no. 4, pp. 827–849, Dec. 2024, doi: 10.3390/stresses4040055.
- [5] X. Xu, Y. Pang, and X. Fan, "Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 190, June 2025, doi: 10.1038/s41392-025-02253-4.
- [6] D. Harman, "Free Radical Theory of Aging: An Update: Increasing the Functional Life Span," *Ann. N. Y. Acad. Sci.*, vol. 1067, no. 1, pp. 10–21, May 2006, doi: 10.1196/annals.1354.003.

- [7] K. Tripathi and D. Ben-Shachar, "Mitochondria in the Central Nervous System in Health and Disease: The Puzzle of the Therapeutic Potential of Mitochondrial Transplantation," *Cells*, vol. 13, no. 5, p. 410, Feb. 2024, doi: 10.3390/cells13050410.
- [8] R. Stefanatos and A. Sanz, "The role of mitochondrial ROS in the aging brain," *FEBS Lett.*, vol. 592, no. 5, pp. 743–758, Mar. 2018, doi: 10.1002/1873-3468.12902.
- [9] O. F. Kuzu, L. J. T. Granerud, and F. Saaticioglu, "Navigating the landscape of protein folding and proteostasis: from molecular chaperones to therapeutic innovations," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 358, Oct. 2025, doi: 10.1038/s41392-025-02439-w.
- [10] C. Hu, M. Lin, C. Wang, and S. Zhang, "Current Understanding of Protein Aggregation in Neurodegenerative Diseases," *Int. J. Mol. Sci.*, vol. 26, no. 21, p. 10568, Oct. 2025, doi: 10.3390/ijms262110568.
- [11] J. Tchekalarova and R. Tzoneva, "Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin," *Int. J. Mol. Sci.*, vol. 24, no. 3, p. 3022, Feb. 2023, doi: 10.3390/ijms24033022.
- [12] Y. Hou *et al.*, "Ageing as a risk factor for neurodegenerative disease," *Nat. Rev. Neurol.*, vol. 15, no. 10, pp. 565–581, Oct. 2019, doi: 10.1038/s41582-019-0244-7.
- [13] J. M. Neyra Chauca *et al.*, "Oxidative Stress, Neuroinflammation, and Microvascular Damage in Neurodegenerative Diseases: Mechanistic Insights and Therapeutic Approaches," Nov. 10, 2025. doi: 10.20944/preprints202511.0551.v1.
- [14] H. Sies and D. P. Jones, "Reactive oxygen species (ROS) as pleiotropic physiological signalling agents," *Nat. Rev. Mol. Cell Biol.*, vol. 21, no. 7, pp. 363–383, July 2020, doi: 10.1038/s41580-020-0230-3.
- [15] J. Fujii, T. Homma, and T. Osaki, "Superoxide Radicals in the Execution of Cell Death," *Antioxidants*, vol. 11, no. 3, p. 501, Mar. 2022, doi: 10.3390/antiox11030501.
- [16] S. Liu, J. Liu, Y. Wang, F. Deng, and Z. Deng, "Oxidative Stress: Signaling Pathways, Biological Functions, and Disease," *MedComm*, vol. 6, no. 7, p. e70268, July 2025, doi: 10.1002/mco2.70268.
- [17] Z. Z. Chong and N. Souayah, "Oxidative Stress: Pathological Driver in Chronic Neurodegenerative Diseases," *Antioxidants*, vol. 14, no. 6, p. 696, June 2025, doi: 10.3390/antiox14060696.
- [18] K. Jomova, S. Y. Alomar, S. H. Alwasel, E. Nepovimova, K. Kuca, and M. Valko, "Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants," *Arch. Toxicol.*, vol. 98, no. 5, pp. 1323–1367, May 2024, doi: 10.1007/s00204-024-03696-4.
- [19] I. Gulcin, "Antioxidants: a comprehensive review," *Arch. Toxicol.*, vol. 99, no. 5, pp. 1893–1997, May 2025, doi: 10.1007/s00204-025-03997-2.
- [20] S. Anwar *et al.*, "Exploring Therapeutic Potential of Catalase: Strategies in Disease Prevention and Management," *Biomolecules*, vol. 14, no. 6, p. 697, June 2024, doi: 10.3390/biom14060697.
- [21] M. E. Pereira, J. V. De Souza, G. G. Gomar, I. L. Kruk, and C. S. Oliveira, "Glutathione peroxidase activity in Alzheimer's disease patients: A systematic review and meta-analysis," *J. Alzheimer's Dis.*, vol. 106, no. 3, pp. 842–857, Aug. 2025, doi: 10.1177/13872877251346981.
- [22] A. Alhaj Sulaiman and V. L. Katanaev, "Beyond Antioxidants: How Redox Pathways Shape Cellular Signaling and Disease Outcomes," *Antioxidants*, vol. 14, no. 9, p. 1142, Sept. 2025, doi: 10.3390/antiox14091142.
- [23] S. Chakravorty, A. Malvi, A. Chaturvedi, K. Sonkusare, and N. Dave, "Glutathione—the master antioxidant," *Int J Med Res Pharm Sci*, vol. 7, no. 2, pp. 1–11, 2020.
- [24] A. Moustapha, "Neurodegenerative Diseases: Potential Effect of Glutathione," in *Glutathione System and Oxidative Stress in Health and Disease*, M. Dulce Bagatini, Ed., IntechOpen, 2020. doi: 10.5772/intechopen.92240.
- [25] L. C. D. Pomatto and K. J. A. Davies, "Adaptive homeostasis and the free radical theory of ageing," *Free Radic. Biol. Med.*, vol. 124, pp. 420–430, Aug. 2018, doi: 10.1016/j.freeradbiomed.2018.06.016.
- [26] B. Li *et al.*, "Redox regulation: mechanisms, biology and therapeutic targets in diseases," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 72, Mar. 2025, doi: 10.1038/s41392-024-02095-6.
- [27] A. Płóciniczak, E. Bukowska-Olech, and E. Wysocka, "The Complexity of Oxidative Stress in Human Age-Related Diseases—A Review," *Metabolites*, vol. 15, no. 7, p. 479, July 2025, doi: 10.3390/metabo15070479.
- [28] R. F. Abdelhamid and S. Nagano, "Crosstalk between Oxidative Stress and Aging in Neurodegeneration Disorders," *Cells*, vol. 12, no. 5, p. 753, Feb. 2023, doi: 10.3390/cells12050753.
- [29] N. Chandimali *et al.*, "Free radicals and their impact on health and antioxidant defenses: a review," *Cell Death Discov.*, vol. 11, no. 1, p. 19, Jan. 2025, doi: 10.1038/s41420-024-02278-8.
- [30] T.-M. Sonninen, G. Goldsteins, N. Laham-Karam, J. Koistinaho, and Š. Lehtonen, "Proteostasis Disturbances and Inflammation in Neurodegenerative Diseases," *Cells*, vol. 9, no. 10, p. 2183, Sept. 2020, doi: 10.3390/cells9102183.

- [31] D. Tripathi, D. J. Oldenburg, and A. J. Bendich, "Oxidative and Glycation Damage to Mitochondrial DNA and Plastid DNA during Plant Development," *Antioxidants*, vol. 12, no. 4, p. 891, Apr. 2023, doi: 10.3390/antiox12040891.
- [32] V. Boccardi, F. Mancinetti, and P. Mecocci, "Oxidative Stress, Advanced Glycation End Products (AGEs), and Neurodegeneration in Alzheimer's Disease: A Metabolic Perspective," *Antioxid. Basel Switz.*, vol. 14, no. 9, p. 1044, Aug. 2025, doi: 10.3390/antiox14091044.
- [33] A. E. Alkhalifa, O. Alkhalifa, I. Durdanovic, D. R. Ibrahim, and S. Maragkou, "Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease: Insights into Pathophysiology and Treatment," *J. Dement. Alzheimer's Dis.*, vol. 2, no. 2, p. 17, 2025.
- [34] H. Watanabe, J. M. Dijkstra, and T. Nagatsu, "Parkinson's Disease: Cells Succumbing to Lifelong Dopamine-Related Oxidative Stress and Other Bioenergetic Challenges," *Int. J. Mol. Sci.*, vol. 25, no. 4, p. 2009, Feb. 2024, doi: 10.3390/ijms25042009.
- [35] M. T. Henrich, W. H. Oertel, D. J. Surmeier, and F. F. Geibl, "Mitochondrial dysfunction in Parkinson's disease – a key disease hallmark with therapeutic potential," *Mol. Neurodegener.*, vol. 18, no. 1, p. 83, Nov. 2023, doi: 10.1186/s13024-023-00676-7.
- [36] L. D. Skou, S. K. Johansen, J. Okarmus, and M. Meyer, "Pathogenesis of DJ-1/PARK7-Mediated Parkinson's Disease," *Cells*, vol. 13, no. 4, p. 296, Feb. 2024, doi: 10.3390/cells13040296.
- [37] U. C. Dash *et al.*, "Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications," *Acta Pharm. Sin. B*, vol. 15, no. 1, pp. 15–34, Jan. 2025, doi: 10.1016/j.apsb.2024.10.004.
- [38] C. Toader *et al.*, "Decoding Neurodegeneration: A Review of Molecular Mechanisms and Therapeutic Advances in Alzheimer's, Parkinson's, and ALS," *Int. J. Mol. Sci.*, vol. 25, no. 23, p. 12613, Nov. 2024, doi: 10.3390/ijms252312613.
- [39] M. A. Guzmán-Ruiz *et al.*, "Microglia in physiological conditions and the importance of understanding their homeostatic functions in the arcuate nucleus," *Front. Immunol.*, vol. 15, p. 1392077, Sept. 2024, doi: 10.3389/fimmu.2024.1392077.
- [40] Y. Li *et al.*, "Oxidative stress of mitophagy in neurodegenerative diseases: Mechanism and potential therapeutic targets," *Arch. Biochem. Biophys.*, vol. 764, p. 110283, Feb. 2025, doi: 10.1016/j.abb.2024.110283.
- [41] X. Shi, "Targeting NOX2 to combat oxidative stress and neuroinflammation and provide neuroprotection in neurodegeneration," 2024.
- [42] A. Kulkarni, J. Chen, and S. Maday, "Neuronal autophagy and intercellular regulation of homeostasis in the brain," *Curr. Opin. Neurobiol.*, vol. 51, pp. 29–36, Aug. 2018, doi: 10.1016/j.conb.2018.02.008.
- [43] M. Du, Y. Yu, J. Wang, and C. Ji, "Autophagy–Lysosome Pathway Dysfunction in Neurodegeneration and Cancer: Mechanisms and Therapeutic Opportunities," *Int. J. Mol. Sci.*, vol. 27, no. 1, p. 366, Dec. 2025, doi: 10.3390/ijms27010366.
- [44] N. Charmpilas, E. F. Fang, and K. Palikaras, "Mitophagy and Neuroinflammation: A Compelling Interplay," *Curr. Neuropharmacol.*, vol. 21, no. 7, pp. 1477–1481, July 2023, doi: 10.2174/1570159X20666220628153632.
- [45] A. Ashok, S. S. Andrabi, S. Mansoor, Y. Kuang, B. K. Kwon, and V. Labhsetwar, "Antioxidant Therapy in Oxidative Stress-Induced Neurodegenerative Diseases: Role of Nanoparticle-Based Drug Delivery Systems in Clinical Translation," *Antioxidants*, vol. 11, no. 2, p. 408, Feb. 2022, doi: 10.3390/antiox11020408.
- [46] C. Mayer, L. Riera-Ponsati, S. Kauppinen, H. Klitgaard, J. T. Erler, and S. N. Hansen, "Targeting the NRF2 pathway for disease modification in neurodegenerative diseases: mechanisms and therapeutic implications," *Front. Pharmacol.*, vol. 15, p. 1437939, July 2024, doi: 10.3389/fphar.2024.1437939.
- [47] N. Apostolova and V. M. Victor, "Molecular Strategies for Targeting Antioxidants to Mitochondria: Therapeutic Implications," *Antioxid. Redox Signal.*, vol. 22, no. 8, pp. 686–729, Mar. 2015, doi: 10.1089/ars.2014.5952.
- [48] M. M. Mehdi, P. Solanki, and P. Singh, "Oxidative stress, antioxidants, hormesis and calorie restriction: The current perspective in the biology of aging," *Arch. Gerontol. Geriatr.*, vol. 95, p. 104413, July 2021, doi: 10.1016/j.archger.2021.104413.
- [49] G. Velikic *et al.*, "Neurodegeneration as Ecosystem Failure: A New Paradigm for Prevention and Treatment," *Int. J. Mol. Sci.*, vol. 26, no. 22, p. 11207, Nov. 2025, doi: 10.3390/ijms262211207.
- [50] S. K. Niazi, "Non-Invasive Drug Delivery across the Blood–Brain Barrier: A Prospective Analysis," *Pharmaceutics*, vol. 15, no. 11, p. 2599, Nov. 2023, doi: 10.3390/pharmaceutics15112599.
- [51] R. Vargas *et al.*, "Advancing through the blood-brain barrier: mechanisms, challenges and drug delivery strategies," *Admet Dmpk*, vol. 13, no. 5, p. 2988, 2025, doi: 10.5599/admet.2988.
- [52] I. Pérez-Torres, V. Guarner-Lans, and M. E. Rubio-Ruiz, "Reductive Stress in Inflammation-Associated Diseases and the Pro-Oxidant Effect of Antioxidant Agents," *Int. J. Mol. Sci.*, vol. 18, no. 10, p. 2098, Oct. 2017, doi: 10.3390/ijms18102098.

- [53] M. Şerban, C. Toader, and R.-A. Covache-Busuioc, “The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration,” *Int. J. Mol. Sci.*, vol. 26, no. 15, p. 7498, Aug. 2025, doi: 10.3390/ijms26157498.
- [54] W. Zhang, D. Xiao, Q. Mao, and H. Xia, “Role of neuroinflammation in neurodegeneration development,” *Signal Transduct. Target. Ther.*, vol. 8, no. 1, p. 267, July 2023, doi: 10.1038/s41392-023-01486-5.
- [55] Z. M. Hein *et al.*, “Toward a Unified Framework in Molecular Neurobiology of Alzheimer’s Disease: Revisiting the Pathophysiological Hypotheses,” *Mol. Neurobiol.*, vol. 63, no. 1, p. 282, Jan. 2026, doi: 10.1007/s12035-025-05602-0.

Comprehensive Recommendations for Enhancing the Oxidative Stress, Aging, and Neurodegeneration Review Article

Abstract Enhancement

1. Linguistic Precision

- The abstract is generally well-written, but consistency in tense can be improved.
 - “This review synthesizes...” is preferable to “This review aimed to synthesize...”
- Suggested refinements:
 - “Oxidative stress has emerged as a fundamental mechanism...” → “Oxidative stress functions as a central converging mechanism...”
 - “This review highlights...” → “These insights underscore...”

2. Conceptual Clarity

- The scope is clear but can be made more explicit:
 - “This review examines oxidative stress...” → “This review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases.”
- Avoid broad terms like “major role”; specify mechanisms (mitochondrial dysfunction, proteostasis failure, neuroinflammation).

Introduction Improvement

1. Strengthen Scientific Context

- The introduction provides strong background, but the opening can be more impactful:
 - Suggested opening: “Oxidative stress represents a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression.”

2. Add a Research Gap Paragraph

Suggested paragraph to add at the end of the introduction:

“Although oxidative stress has been widely implicated in aging and neurodegeneration, existing literature often examines these mechanisms independently. Few reviews integrate mitochondrial dysfunction, proteostatic collapse, neuroinflammation, and redox signaling into a unified

framework. This article addresses this gap by synthesizing multi-level evidence to clarify how redox imbalance acts as a converging driver of neuronal decline.”

Materials and Methods (for narrative reviews)

If the manuscript is intended for a peer-reviewed journal, consider adding:

- Databases searched (e.g., PubMed, Scopus).
- Keywords used.
- Inclusion/exclusion criteria for selected studies.
- Timeframe of literature search.
- Any quality-assessment approach (if applicable).

This strengthens transparency and methodological rigor.

Main Body / Results Section Enhancement

1. Data Organization

- The manuscript is rich in detail; organization can be improved by:
 - Adding clearer subheadings such as:
 - “Mitochondrial ROS Generation”
 - “Lipid Peroxidation and Membrane Vulnerability”
 - “Proteostasis Collapse”
 - “Redox-Inflammatory Crosstalk”
 - “Autophagy and Mitophagy Failure”
- Consider adding summary diagrams illustrating:
 - The oxidative stress loop in Alzheimer’s disease
 - The dopaminergic vulnerability pathway in Parkinson’s disease

2. Mechanistic Clarity

- Mechanisms are well described; however, linking them explicitly to disease progression strengthens the narrative.
- Example refinement:
 - “Oxidative stress disrupts proteostasis” → “Oxidative stress disrupts proteostasis by impairing the ubiquitin–proteasome system and autophagy, leading to toxic protein accumulation characteristic of AD and PD.”

Therapeutic Targets Section Enhancement

1. Nrf2 Pathway

- Well explained; consider adding:

- Limitations of chronic Nrf2 activation
- Differences between electrophilic vs. non-electrophilic activators

2. Mitochondria-Targeted Antioxidants

- Strengthen by briefly comparing:
 - MitoQ vs. SS-31 mechanisms
 - Evidence from preclinical vs. clinical studies

3. Hormetic Interventions

- Clarify dose-dependency:
 - “Excessive exercise or prolonged caloric restriction may shift from adaptive to maladaptive stress.”

Conclusion Refinement

Suggested improved conclusion paragraph:

“This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy, collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.”

Final Recommendations for Publication Readiness

- Already included:
 - Ethical approval
 - Funding statement
 - Conflict of interest declaration
- Recommended additions:
 - Ensure references follow the journal’s required format (Vancouver, APA, etc.).
 - Add ORCID IDs for all authors.
 - Include a graphical abstract summarizing:
 - Key mechanisms
 - Disease pathways
 - Therapeutic targets
 - Consider adding a summary table comparing:
 - Mechanisms of oxidative stress
 - Their roles in AD vs. PD
 - Potential therapeutic interventions

REVISI 1

Review Article

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

Meutia A. Faradilla¹, Karina S. Anastasya², Deasyka Yastani¹, Yohana Yohana¹, Endrico X. Tungka¹ and Suweino Suweino¹

¹Department of Biochemistry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia; ²Department of Nutritional, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

Meutia Atika Faradilla · 0009-0006-1216-5891
karina shasri anastahya (0000-0002-4539-8812)

*Corresponding author: meutia.atika@trisakti.ac.id

Abstract

Aging is the primary risk factor for specify mechanism neurodegenerative disorders, yet the precise molecular intertwining between biological aging and neuronal loss remains complex. Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, has emerged as a fundamental converging mechanism driving both processes. This review aimed to synthesize current evidence delineating how chronic redox imbalance drives cellular senescence and neuronal vulnerability through mitochondrial dysfunction, lipid peroxidation, and oxidative protein damage. These insights underscore how sustained oxidative insults promote the misfolding and aggregation of disease-defining proteins, including amyloid β in Alzheimer's disease and α -synuclein in Parkinson's disease, thereby amplifying neuroinflammation, synaptic dysfunction, and bioenergetic failure. Furthermore, we critically reassess antioxidant based therapeutic strategies, emphasizing a paradigm shift away from non-specific radical scavenging toward targeted modulation of endogenous defense systems, particularly Nrf2 signaling and mitochondria directed antioxidants. By integrating molecular mechanisms with translational perspectives, this review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Keywords: Oxidative stress, aging, neurodegeneration, mitochondria, reactive oxygen species (ROS)

Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders (NDDs), most notably Alzheimer's disease (AD),



Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (1). Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor that is biological aging (2). Oxidative stress represents a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of neuronal vulnerability and decline. Within the network of aging-related mechanisms, Oxidative stress functions as a central converging mechanism linking normal physiological aging to pathological neurodegeneration (3). Rather than being a mere byproduct of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems (4). Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins (5).

Classical theories, such as Harman's Free Radical Theory of Aging, have historically attributed aging to random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival (6). The Central Nervous System (CNS) is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden. At the heart of this vulnerability lies the mitochondrion (7). As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses (8).

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance (9). The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid β in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation (10). This review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. We dissect the molecular origins of ROS, the age associated erosion of antioxidant defenses, and the convergence of these pathways on protein aggregation and neuronal loss. Furthermore, we explore the historical pitfalls of broad-spectrum antioxidant therapies and advocate for a paradigm shift toward targeted modulation of redox-sensitive circuits rather than non-specific scavenging. Although oxidative stress has been widely implicated in aging and neurodegeneration, existing literature often examines these mechanisms independently. Few reviews integrate mitochondrial dysfunction, proteostatic collapse, neuroinflammation, and redox signaling into a unified framework. Although oxidative stress has been widely implicated in aging and neurodegeneration, existing literature often examines these mechanisms independently. Few reviews integrate mitochondrial dysfunction, proteostatic collapse, neuroinflammation, and redox signaling into a unified framework. This article addresses this gap by synthesizing multi-level evidence to clarify how redox imbalance acts as a converging driver of neuronal decline.

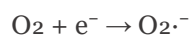
Molecular mechanisms of oxidative stress

Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including AD, PD and ALS. Although these disorders are clinically distinct, they share

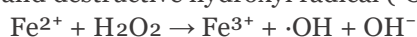
biological aging as a common risk factor, indicating that age-related cellular processes actively contribute to neuronal degeneration(11). Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology(12). Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular defense systems, leading to damage of DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function(3)(8). The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration(13).

Molecular origins of reactive species

ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During oxidative phosphorylation, electron leakage occurs most notably at Complex I (NADH dehydrogenase) and Complex III (ubiquinone–cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O₂), forming the superoxide anion (O₂^{·-}), as described by the reaction(14):



Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H₂O₂), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe²⁺) or cuprous copper (Cu⁺), generating the highly reactive and destructive hydroxyl radical (·OH) (15):



The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression(16)(17).

Mitochondrial ROS Generation

Mitochondria are central to cellular energy production through oxidative phosphorylation, but they are also the primary source of reactive oxygen species (ROS). During oxidative phosphorylation, electrons are transferred through the mitochondrial electron transport chain, and some electrons leak at Complex I and Complex III. This leakage leads to the partial reduction of molecular oxygen, producing superoxide anions (O₂^{·-}). These superoxides are then converted into hydrogen peroxide (H₂O₂), which, in turn, can form hydroxyl radicals (·OH) through Fenton reactions, further amplifying oxidative stress(18). This ROS production becomes self-perpetuating in aging and neurodegenerative diseases, as damaged mitochondria generate more ROS, worsening mitochondrial dysfunction. This creates a vicious cycle where oxidative damage to cellular structures such as lipids, proteins, and DNA intensifies cellular dysfunction, accelerating the progression of diseases like Alzheimer's and Parkinson's. Moreover, mitochondrial damage can reduce ATP production, impeding cellular functions and contributing to neuronal degeneration(5).

Lipid Peroxidation and Membrane Vulnerability

Oxidative stress also leads to lipid peroxidation, a process in which ROS attack the polyunsaturated fatty acids in cellular membranes. Lipid peroxidation generates highly reactive secondary products such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which can diffuse across the cell and interact with other cellular components. These lipid peroxidation products disrupt the structural integrity of neuronal membranes, impairing the fluidity and function of the lipid bilayer(19). This damage compromises membrane-bound proteins, receptors, and

ion channels, leading to disturbances in cellular signaling, neurotransmission, and overall neuronal efficiency. In neurodegenerative diseases, this membrane vulnerability accelerates neuronal damage and contributes to synaptic dysfunction. For instance, in Alzheimer's disease, lipid peroxidation can facilitate the aggregation of amyloid-beta ($A\beta$), further exacerbating the pathological cycle. The lipid-rich membranes of neurons make them particularly susceptible to oxidative damage, reinforcing the progression of diseases like AD and PD(20).

Proteostasis Collapse

Proteostasis is essential for maintaining cellular homeostasis by regulating protein synthesis, folding, and degradation. However, oxidative stress disrupts proteostasis, leading to the accumulation of damaged and misfolded proteins. ROS can induce oxidative modifications such as carbonylation and nitration on proteins, altering their structure and function. These misfolded proteins are typically targeted for degradation by the proteasome or autophagy pathways. However, oxidative stress impairs these systems, leading to the accumulation of toxic protein aggregates. In neurodegenerative diseases like Alzheimer's and Parkinson's, this collapse of proteostasis is particularly detrimental. For example, in Alzheimer's disease, amyloid-beta ($A\beta$) accumulates and forms plaques, while in Parkinson's disease, α -synuclein forms Lewy bodies. These protein aggregates not only disrupt cellular function but also impair synaptic plasticity, damage mitochondria, and promote neuroinflammation. The accumulation of misfolded proteins creates a positive feedback loop that exacerbates oxidative stress, mitochondrial dysfunction, and cellular damage(21).

Redox Inflammatory Crosstalk

Oxidative stress and neuroinflammation are intimately connected, with ROS playing a crucial role in activating redox-sensitive transcription factors like NF- κ B. NF- κ B, once activated by ROS, translocates to the nucleus and initiates the expression of proinflammatory cytokines such as IL- 1β , IL-6, and TNF- α . These cytokines activate microglia, the resident immune cells of the brain, which further increase ROS production and promote inflammation. Chronic neuroinflammation exacerbates neuronal damage by impairing synaptic function, disrupting calcium homeostasis, and sensitizing neurons to excitotoxicity. This inflammatory response becomes self-perpetuating under conditions of sustained oxidative stress, where proinflammatory cytokines further exacerbate ROS production, leading to a cycle of oxidative injury and inflammation. This crosstalk between oxidative stress and inflammation is a critical driver of neurodegenerative diseases like Alzheimer's and Parkinson's, where inflammation amplifies the damage caused by ROS, leading to progressive neuronal death and dysfunction (22).

Autophagy and Mitophagy Failure

Autophagy and mitophagy are vital cellular processes for maintaining cellular integrity by degrading damaged proteins and organelles. In neurons, where turnover is limited due to the lack of cell division, the efficient functioning of autophagic pathways is critical for long-term survival. However, oxidative stress compromises the integrity of these pathways. ROS can damage the lysosomal system, which is responsible for the final stages of autophagic degradation, impairing its function(23). As a result, damaged proteins and dysfunctional organelles accumulate within neurons, further exacerbating cellular stress. In particular, mitophagy, the selective removal of damaged mitochondria, is essential to protect cells from oxidative damage. However, oxidative stress impairs mitophagy by disrupting the PINK1/Parkin pathway, which is responsible for marking damaged mitochondria for degradation. The failure to clear dysfunctional mitochondria allows them to persist

and continue generating ROS, perpetuating mitochondrial dysfunction and oxidative stress. This accumulation of damaged mitochondria, often referred to as “zombie mitochondria,” further disrupts cellular function, leading to energy depletion and contributing to the neurodegenerative processes observed in diseases like Parkinson's(24).

Antioxidant defense

Enzymatic vanguard: The first line of redox control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain(25). Because superoxide is highly reactive and short lived, its rapid conversion into hydrogen peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology(26). At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (CAT) and glutathione peroxidase (GPx) assume decisive roles (27)(28). By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation a species widely regarded as the most destructive ROS due to its indiscriminate reactivity (16). This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised whether due to genetic variation, post-translational alterations, or age-related functional decline the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage(29).

Non-enzymatic buffers and thiol-based redox modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione (GSH) playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond the capacity of enzymatic systems. By donating electrons, GSH neutralizes reactive species and is converted into its oxidized form, glutathione disulfide (GSSG). Consequently, the balance between reduced and oxidized glutathione (the GSH/GSSG ratio) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain (30). Evidence from aging studies consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation (31).

Regulatory control and the Nrf2 axis

The effectiveness of antioxidant defenses within the CNS is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2–related factor 2 (Nrf2), a master regulator of cellular stress responses. Under basal conditions, Nrf2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding SOD, GPx, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands(32). With advancing age, however, the responsiveness of the Nrf2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative

cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a “redox vulnerability gap,” wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders(33).

Oxidative stress in aging: The "hardwiring" of senescence

The modified free radical theory of aging

Harman’s Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by reactive oxygen species (ROS). While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury (34). Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled(35). However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu, commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline (36).

Accumulation of macromolecular damage in the aging brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between reactive oxygen species (ROS) production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function(37). Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency (38).

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin–proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress (21). Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2'-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration (39).

Oxidative stress in neurodegenerative diseases

Alzheimer’s disease: Oxidative stress as a self-reinforcing pathological loop

In Alzheimer’s disease, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through

interconnected, self-reinforcing loops that involve amyloid-beta ($A\beta$) accumulation, mitochondrial dysfunction, and Tau pathology. Soluble $A\beta$ oligomers display redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of reactive oxygen species (ROS). This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further $A\beta$ aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment (40). As shown in figure 1, the pathological process begins with the accumulation of $A\beta$ within neuronal mitochondria further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular energy balance. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in Alzheimer's disease(41).

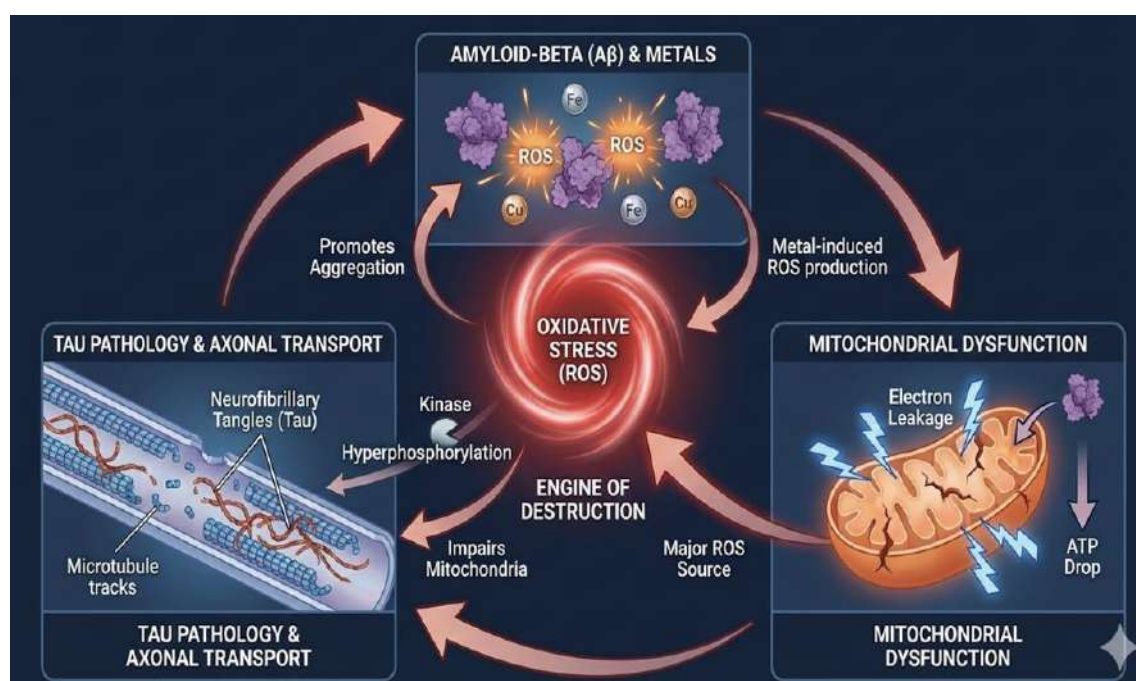


Figure 1. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction, illustrating the roles of amyloid-beta, metals, tau pathology, and mitochondrial dysfunction in Alzheimer's disease. The illustration was generated using BioRender, which was used to visualize the key mechanisms of oxidative stress and neuronal damage in AD pathology.

Parkinson's disease: Selective vulnerability to oxidative stress

Parkinson's disease illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons(42).

As shown in figure 2, the pathological process of parkinson's disease begins with mitochondrial dysfunction, which further amplifies oxidative injury. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1-

Parkin-mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress(43). Loss of DJ-1-mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in Parkinson's disease [36].

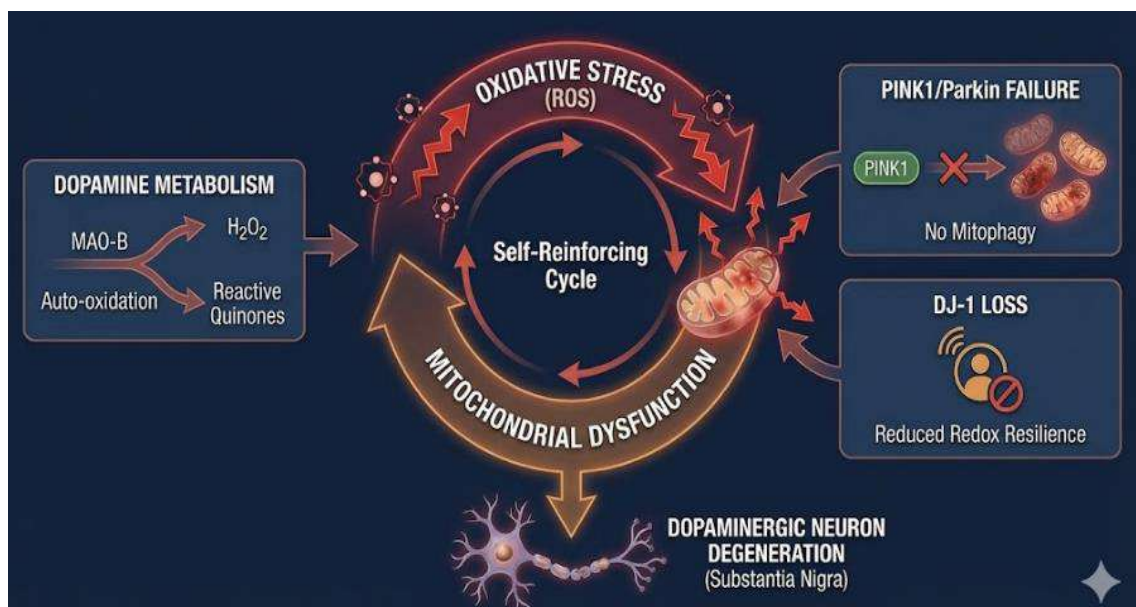


Figure 2. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction in Parkinson's disease, illustrating how dopamine metabolism, PINK₁/Parkin failure, and DJ-1 loss contribute to dopaminergic neuron degeneration in the substantia nigra. The illustration was generated using BioRender to visualize the key mechanisms of oxidative stress and mitochondrial impairment in Parkinson's pathology

The converging pathways: Inflammation and autophagy

Oxidative stress represents an early destabilizing force in neuronal homeostasis, yet its most destructive effects emerge through its capacity to activate downstream pathological pathways (45). Rather than acting as an isolated insult, sustained redox imbalance orchestrates a broader cellular collapse by engaging neuroinflammatory signaling and disrupting intracellular quality-control mechanisms. Among these, chronic inflammation and autophagy impairment stand out as convergent pathways that transform transient oxidative disturbances into irreversible neurodegenerative trajectories (46).

The oxidative inflammatory axis: From redox imbalance to neurotoxicity

In the central nervous system, oxidative stress and inflammation are intimately intertwined, forming a self-amplifying pathological circuit. Microglia, the brain's resident immune cells, are uniquely positioned at the interface between neuronal metabolism and immune surveillance. Under physiological conditions, microglia maintain synaptic integrity and respond transiently to injury. However, persistent oxidative stress alters this homeostatic role, pushing microglia toward a chronically activated, proinflammatory phenotype (47).

ROS-mediated activation of proinflammatory signaling

Reactive oxygen species function as potent second messengers capable of activating redox-sensitive transcription factors. Among these, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) plays a central role in translating oxidative cues into inflammatory gene expression. Elevated ROS levels promote the dissociation of NF-κB from its cytoplasmic inhibitors, allowing its translocation into the nucleus. Once activated, NF-κB drives the transcription of a broad spectrum of proinflammatory mediators, including interleukin-1β (IL-

1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). These cytokines exert pleiotropic effects within the neural microenvironment. Beyond recruiting additional immune responses, they directly impair synaptic function, disrupt neuronal calcium homeostasis, and sensitize neurons to excitotoxic injury. Importantly, this inflammatory signaling is not a short-lived response but becomes sustained under conditions of chronic oxidative stress, reshaping the neural milieu into one that favors degeneration rather than repair (48).

Self-perpetuating cycle of ROS and inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders(49).

Autophagy and mitophagy failure: Breakdown of cellular quality control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival(50).

Lysosomal dysfunction and autophagic arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal (4-HNE) that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure(24).

Mitophagy failure and energetic collapse

Among autophagic processes, the selective removal of damaged mitochondria, known as mitophagy, is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as “zombie mitochondria,” remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure. As ATP levels decline, energy-dependent processes including ion homeostasis, axonal transport, and synaptic transmission become unsustainable. Ultimately, this convergence of oxidative damage, autophagy impairment, and bioenergetic collapse pushes neurons toward apoptotic or necrotic death(51). Figure 3 illustrate the central role of oxidative stress in neurodegenerative diseases such as Alzheimer's and Parkinson's. It highlights key mechanisms including mitochondrial ROS generation, proteostasis collapse, neuroinflammation, and

defective autophagy, all contributing to cellular damage. The figure 3 below shows how oxidative stress promotes synaptic dysfunction and cognitive decline by driving the accumulation of toxic proteins like amyloid- β and tau in Alzheimer's and neuronal loss in Parkinson's. Additionally, it emphasizes therapeutic targets, such as Nrf2 activators (e.g., dimethyl fumarate), mitochondria-targeted antioxidants (e.g., MitoQ), and proteostasis and autophagy enhancers (e.g., rapamycin, SS-31, Urolithin A), which aim to mitigate oxidative damage and restore cellular function.

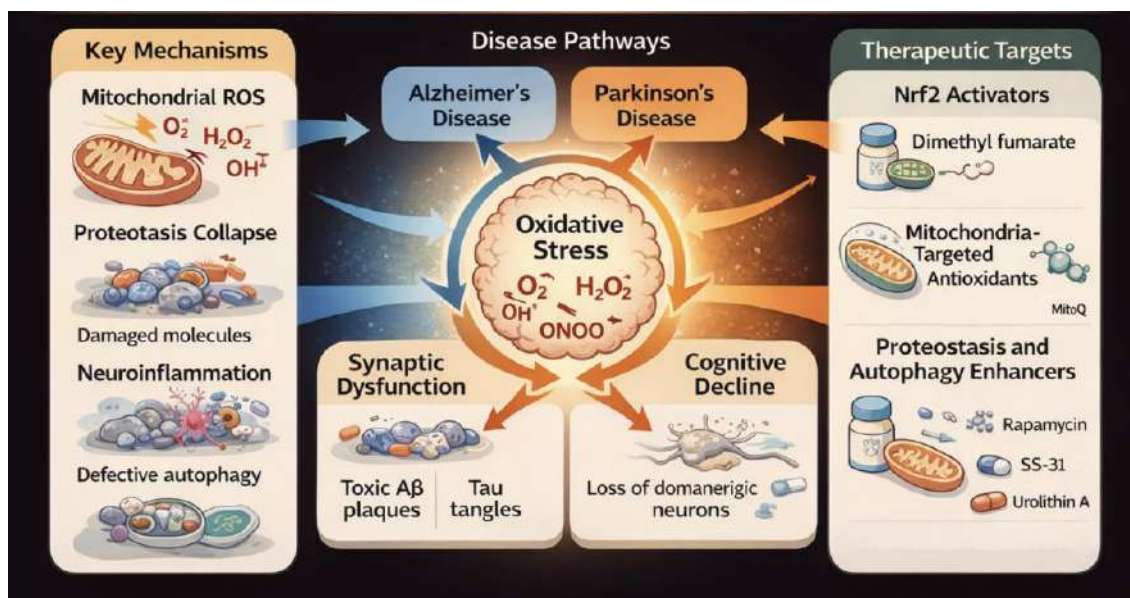


Figure 3. The journey from molecular origins (ROS) through cellular damage (mitochondria/inflammation) to clinical disease (AD/PD), while proposing a shift toward precision medicine and targeted therapies. The illustration was generated using BioRender.

Therapeutic targets and clinical implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However, decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated(52).

Nrf2 pathway activation: Reinforcing endogenous redox resilience

Nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing Nrf2 to escape degradation and translocate into the nucleus. There, Nrf2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, Nrf2 activation enhances intrinsic redox resilience by strengthening the cell's capacity to respond to future oxidative challenges(32). While Nrf2 activation is beneficial in protecting against oxidative stress, chronic activation can have limitations. Continuous Nrf2 activation may inadvertently promote tumorigenesis by aiding the survival of damaged cells, which may facilitate cancer progression. The activation of the pathway in non-cancerous tissues should, therefore, be carefully regulated. In terms of activating Nrf2, there are two primary categories: electrophilic and non-electrophilic activators. Electrophilic activators, such as sulforaphane, directly modify

KEAP1, leading to the activation of Nrf2. However, these compounds can cause unintended damage due to their reactivity, potentially affecting cellular structures beyond their target. On the other hand, non-electrophilic activators, such as bardoxolone methyl, activate Nrf2 without directly altering KEAP1, which offers a safer profile with fewer side effects but may have lower potency.

Conventional antioxidants have shown limited efficacy in neurodegenerative

Conventional antioxidant therapies have demonstrated limited benefit in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal reactive oxygen species (ROS). This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, SS-31 (elamipretide) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis(53). Table 1 compares MitoQ and SS-31, both targeting mitochondria. MitoQ accumulates via membrane potential to scavenge ROS, while SS-31 stabilizes cardiolipin to prevent ROS. Both show preclinical efficacy in neurodegenerative diseases. MitoQ failed in Parkinson's trials but is used for vascular health, while SS-31 is FDA-approved for Barth Syndrome but failed in heart failure trials.(54–60)

Table 1. Comparative Summary of MitoQ and SS-31 (54–60)

Feature	MitoQ (Mitoquinone Mesylate)	SS-31 (Elamipretide)
Primary Mechanism	Electrophoretic accumulation driven by mitochondrial membrane potential.	Potential-independent uptake; targets and stabilizes cardiolipin in the inner membrane.
Antioxidant Action	Redox-active ubiquinone moiety directly scavenges radicals and is regenerated by Complex II.	Structural stabilization of cristae/supercomplexes to prevent electron leakage and ROS formation.
Physical Impact	Can cause mitochondrial swelling and depolarization at high concentrations due to its alkyl chain.	Acts as "mitochondrial armor," protecting against membrane fragmentation and structural decay.
Preclinical Evidence	Robust protection in Alzheimer's (3xTg-AD), Parkinson's (MPTP), and Huntington's disease (HD) models.	Consistent success in AD, PD, HD, and brain injury models, improving dynamics and synaptic health.
Clinical Status	Failed PD trials (no clinical effect on UPDRS). Currently used as a dietary supplement for vascular health.	FDA Approved (Sept 2025) for Barth Syndrome. Failed trials in heart failure and primary mitochondrial myopathy.

Lifestyle interventions and hormetic redox adaptation

Lifestyle interventions, such as physical exercise and caloric restriction, activate endogenous antioxidant defenses through a process known as hormesis. Hormesis refers to the phenomenon where low-level, transient oxidative stress triggers adaptive protective responses within cells. When applied in moderation, physical exercise and mild caloric restriction induce controlled oxidative stress that enhances cellular resilience(61). These interventions improve mitochondrial

efficiency by promoting better ATP production and reducing the production of excess ROS, stimulate autophagy for the clearance of damaged proteins and organelles, and upregulate antioxidant signaling pathways such as the Nrf2 pathway, which enhances the cell's ability to combat oxidative damage. Additionally, they boost the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which support neuronal growth, survival, and synaptic plasticity, playing a crucial role in brain health(62).

However, it is important to note that the beneficial effects of hormesis are dose-dependent. When physical exercise or caloric restriction exceeds a certain threshold, it can shift from an adaptive to a maladaptive stress response. Prolonged or excessive exercise, for example, can lead to chronic oxidative stress, resulting in mitochondrial dysfunction, muscle damage, and an increase in inflammatory markers. Similarly, prolonged caloric restriction may impair cellular homeostasis, weaken the immune system, and exacerbate metabolic dysfunction. These maladaptive responses may overwhelm the body's protective mechanisms, leading to cellular damage rather than the intended health benefits. Therefore, while moderate exercise and caloric restriction can enhance redox balance and improve health outcomes, extreme or prolonged levels of these stressors may cause harm, highlighting the importance of balance in these lifestyle interventions(63).

Therapeutic potential and clinical translation

Pharmacological activation of Nrf2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach. By inducing mild electrophilic stress, it activates Nrf2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other Nrf2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive Nrf2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress(32).

Challenges and future directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in Alzheimer's disease (AD) and Parkinson's disease (PD) has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnect between compelling preclinical data and disappointing clinical outcomes highlights a critical "translational gap" that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

Table 2. Comparative Summary between Mechanisms of oxidative stress, Their roles in AD vs. PD and Potential therapeutic interventions

(1,1,1,3,3,11,19,24,33,42,42-44,46,46,52,52)

Mechanisms of Oxidative Stress	Role in Alzheimer's Disease (AD)	Role in Parkinson's Disease (PD)	Potential Therapeutic Interventions
Mitochondrial Dysfunction	Mitochondrial dysfunction leads to bioenergetic failure, impairing synaptic plasticity and	Mitochondrial dysfunction in dopaminergic neurons accelerates ROS production and	Mitochondria-targeted antioxidants (e.g., MitoQ, SS31) that help reduce ROS

Mechanisms of Oxidative Stress	Role in Alzheimer's Disease (AD)	Role in Parkinson's Disease (PD)	Potential Therapeutic Interventions
Lipid Peroxidation	contributing to neuronal damage. Oxidative damage to membrane lipids leads to neuronal damage and loss of synaptic function.	contributes to neuronal loss. Lipid peroxidation exacerbates dopaminergic neuron death and disrupts membrane integrity.	and restore mitochondrial function. Use of lipid antioxidants like alpha-lipoic acid or other peroxy scavengers to prevent oxidative damage.
Proteostasis Collapse	Proteostasis collapse contributes to the accumulation of amyloid β and tau, which disrupt neuronal function.	Accumulation of misfolded proteins, such as α -synuclein, leads to dopaminergic dysfunction.	Proteostasis regulators, such as proteasome activators or autophagy enhancers (e.g., rapamycin, spermidine).
Neuroinflammation	Chronic neuroinflammation amplifies the amyloid plaque formation and accelerates disease progression.	Neuroinflammation in microglia worsens dopaminergic neuron death and amplifies ROS production.	Anti-inflammatory agents targeting NF- κ B or microglial activation (e.g., minocycline, curcumin).
Redox-Imbalance (ROS and RNS)	ROS accumulation damages cellular structures (DNA, lipids, proteins) and triggers apoptosis.	ROS generation through dopamine metabolism leads to neuronal damage and contributes to cell death.	Nrf2 activators (e.g., dimethyl fumarate), which boost cellular antioxidant defenses and help restore redox homeostasis.
Autophagy and Mitophagy Failure	Impaired autophagy leads to the accumulation of damaged proteins, exacerbating neurodegeneration.	Deficient mitophagy results in the accumulation of dysfunctional mitochondria, contributing to neurodegeneration.	Autophagy enhancers (e.g., rapamycin) and mitophagy activators (e.g., Urolithin A, PINK1 activators) to clear damaged organelles.

Temporal mismatch: Treating too late in the disease course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles(64).

Bioavailability and blood brain barrier limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood–brain barrier (BBB), while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets(65). Even when compounds successfully cross the BBB, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery such as nanoparticle-based carriers, mitochondria-targeted molecules, and ligand-mediated transport systems represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects(66).

The paradox of reductive stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. Reactive oxygen species are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction. This concept challenges the simplistic view that “more antioxidants are better” and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease(67).

The need for redox biomarkers and patient stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status in vivo. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism(68).

Toward a systems-level therapeutic strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways(69). In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system(70).

Conclusion

This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy,

collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.

Acknowledgments

The authors gratefully acknowledge the Department of Biochemistry, Faculty of Medicine, Trisakti University, for its continuous academic support and supportive environment during the development of this review. We also sincerely thank the researchers and scholars whose work has contributed to the advancement of knowledge in the field of oxidative stress, aging, and neurodegeneration. Their contributions provided essential scientific insights that informed and strengthened this manuscript.

Competing interests

All authors declare that there are no conflicts of interest related to this work.

Funding

This study received no external funding.

Underlying data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

During the preparation of this manuscript, the authors made limited use of artificial intelligence–based tools as a supporting aid for language editing and improvement of sentence clarity. These tools were used only to assist in refining grammar and readability. All scientific content, interpretations, critical analyses, and conclusions presented in this manuscript were developed, reviewed, and finalized by the authors. The use of AI did not influence the scientific substance of the work and does not replace the authors' intellectual contribution or responsibility.

How to cite

Faradilla MA, Anastasya KS, Yastani D, *et al.* Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets. *Narra J* 2026; 6 (1): e3042 - [http://doi.org/10.52225/narra.v6i1.\[X\]](http://doi.org/10.52225/narra.v6i1.[X]).

References

1. Rostagno A, Ghiso J. Alzheimer's Disease Pathogenic Mechanisms: Linking Redox Homeostasis and Mitochondria-Associated Metabolic Pathways Through Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2). *Antioxidants* [Internet]. 2025 Jul 1 [cited 2026 Jan 2];14(7):812. Available from: <https://www.mdpi.com/2076-3921/14/7/812>
2. Tenchov R, Sasso JM, Wang X, Zhou QA. Aging hallmarks and progression and age-related diseases: a landscape view of research advancement. *ACS Chem Neurosci*. 2023;15(1):1–30.
3. Spina E, Ferrari RR, Pellegrini E, Colombo M, Poloni TE, Guaita A, *et al.* Mitochondrial Alterations, Oxidative Stress, and Therapeutic Implications in Alzheimer's Disease: A Narrative Review. *Cells* [Internet]. 2025 Feb 6 [cited 2026 Jan 2];14(3):229. Available from: <https://www.mdpi.com/2073-4409/14/3/229>
4. Jurcau MC, Jurcau A, Diaconu RG. Oxidative Stress in the Pathogenesis of Neurodegenerative Diseases. *Stresses* [Internet]. 2024 Dec 2 [cited 2026 Jan 2];4(4):827–49. Available from: <https://www.mdpi.com/2673-7140/4/4/55>
5. Xu X, Pang Y, Fan X. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. *Signal Transduct Target Ther* [Internet]. 2025 Jun 11 [cited 2026 Jan 2];10(1):190. Available from: <https://www.nature.com/articles/s41392-025-02253-4>

6. Harman D. Free Radical Theory of Aging: An Update: Increasing the Functional Life Span. *Ann N Y Acad Sci* [Internet]. 2006 May [cited 2026 Jan 2];1067(1):10–21. Available from: <https://nyaspubs.onlinelibrary.wiley.com/doi/10.1196/annals.1354.003>
7. Tripathi K, Ben-Shachar D. Mitochondria in the Central Nervous System in Health and Disease: The Puzzle of the Therapeutic Potential of Mitochondrial Transplantation. *Cells* [Internet]. 2024 Feb 27 [cited 2026 Jan 2];13(5):410. Available from: <https://www.mdpi.com/2073-4409/13/5/410>
8. Stefanatos R, Sanz A. The role of mitochondrial ROS in the aging brain. *FEBS Lett* [Internet]. 2018 Mar [cited 2026 Jan 2];592(5):743–58. Available from: <https://febs.onlinelibrary.wiley.com/doi/10.1002/1873-3468.12902>
9. Kuzu OF, Granerud LJT, Saatcioglu F. Navigating the landscape of protein folding and proteostasis: from molecular chaperones to therapeutic innovations. *Signal Transduct Target Ther* [Internet]. 2025 Oct 23 [cited 2026 Jan 2];10(1):358. Available from: <https://www.nature.com/articles/s41392-025-02439-w>
10. Hu C, Lin M, Wang C, Zhang S. Current Understanding of Protein Aggregation in Neurodegenerative Diseases. *Int J Mol Sci* [Internet]. 2025 Oct 30 [cited 2026 Jan 2];26(21):10568. Available from: <https://www.mdpi.com/1422-0067/26/21/10568>
11. Tchekalarova J, Tzoneva R. Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin. *Int J Mol Sci* [Internet]. 2023 Feb 3 [cited 2026 Jan 2];24(3):3022. Available from: <https://www.mdpi.com/1422-0067/24/3/3022>
12. Hou Y, Dan X, Babbar M, Wei Y, Hasselbalch SG, Croteau DL, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol* [Internet]. 2019 Oct [cited 2026 Jan 2];15(10):565–81. Available from: <https://www.nature.com/articles/s41582-019-0244-7>
13. Neyra Chauca JM, Vázquez VanDyck M, Espinoza Santana A, Robles Martínez GG, Romero Vega KA, García Quintana N, et al. Oxidative Stress, Neuroinflammation, and Microvascular Damage in Neurodegenerative Diseases: Mechanistic Insights and Therapeutic Approaches [Internet]. 2025 [cited 2026 Jan 2]. Available from: <https://www.preprints.org/manuscript/202511.0551/v1>
14. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat Rev Mol Cell Biol* [Internet]. 2020 Jul 15 [cited 2026 Jan 2];21(7):363–83. Available from: <https://www.nature.com/articles/s41580-020-0230-3>
15. Fujii J, Homma T, Osaki T. Superoxide Radicals in the Execution of Cell Death. *Antioxidants* [Internet]. 2022 Mar 4 [cited 2026 Jan 2];11(3):501. Available from: <https://www.mdpi.com/2076-3921/11/3/501>
16. Liu S, Liu J, Wang Y, Deng F, Deng Z. Oxidative Stress: Signaling Pathways, Biological Functions, and Disease. *MedComm*. 2025 Jul;6(7):e70268.
17. Chong ZZ, Souayah N. Oxidative Stress: Pathological Driver in Chronic Neurodegenerative Diseases. *Antioxidants* [Internet]. 2025 Jun 9 [cited 2026 Jan 2];14(6):696. Available from: <https://www.mdpi.com/2076-3921/14/6/696>
18. Mailloux RJ. An update on mitochondrial reactive oxygen species production. *Antioxidants*. 2020;9(6):472.
19. Wang B, Wang Y, Zhang J, Hu C, Jiang J, Li Y, et al. ROS-induced lipid peroxidation modulates cell death outcome: mechanisms behind apoptosis, autophagy, and ferroptosis. *Arch Toxicol*. 2023;97(6):1439–51.
20. Valgimigli L. Lipid peroxidation and antioxidant protection. *Biomolecules*. 2023;13(9):1291.
21. Sonninen TM, Goldsteins G, Laham-Karam N, Koistinaho J, Lehtonen Š. Proteostasis Disturbances and Inflammation in Neurodegenerative Diseases. *Cells* [Internet]. 2020 Sep 28 [cited 2026 Jan 2];9(10):2183. Available from: <https://www.mdpi.com/2073-4409/9/10/2183>
22. Bellanti F, Coda ARD, Trecca MI, Lo Buglio A, Serviddio G, Vendemiale G. Redox imbalance in inflammation: the interplay of oxidative and reductive stress. *Antioxidants*. 2025;14(6):656.
23. Doblado L, Lueck C, Rey C, Samhan-Arias AK, Prieto I, Stacchiotti A, et al. Mitophagy in human diseases. *Int J Mol Sci*. 2021;22(8):3903.
24. Du M, Yu Y, Wang J, Ji C. Autophagy–Lysosome Pathway Dysfunction in Neurodegeneration and Cancer: Mechanisms and Therapeutic Opportunities. *Int J Mol Sci* [Internet]. 2025 Dec 29 [cited 2026 Jan 2];27(1):366. Available from: <https://www.mdpi.com/1422-0067/27/1/366>
25. Jomova K, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch Toxicol*

- [Internet]. 2024 May [cited 2026 Jan 2];98(5):1323–67. Available from: <https://link.springer.com/10.1007/s00204-024-03696-4>
26. Gulcin İ. Antioxidants: a comprehensive review. *Arch Toxicol* [Internet]. 2025 May [cited 2026 Jan 2];99(5):1893–997. Available from: <https://link.springer.com/10.1007/s00204-025-03997-2>
 27. Anwar S, Alrumaihi F, Sarwar T, Babiker AY, Khan AA, Prabhu SV, et al. Exploring Therapeutic Potential of Catalase: Strategies in Disease Prevention and Management. *Biomolecules* [Internet]. 2024 Jun 14 [cited 2026 Jan 2];14(6):697. Available from: <https://www.mdpi.com/2218-273X/14/6/697>
 28. Pereira ME, De Souza JV, Gomar GG, Kruk IL, Oliveira CS. Glutathione peroxidase activity in Alzheimer's disease patients: A systematic review and meta-analysis. *J Alzheimer's Dis* [Internet]. 2025 Aug [cited 2026 Jan 2];106(3):842–57. Available from: <https://journals.sagepub.com/doi/10.1177/13872877251346981>
 29. Alhaj Sulaiman A, Katanaev VL. Beyond Antioxidants: How Redox Pathways Shape Cellular Signaling and Disease Outcomes. *Antioxidants* [Internet]. 2025 Sep 22 [cited 2026 Jan 2];14(9):1142. Available from: <https://www.mdpi.com/2076-3921/14/9/1142>
 30. Chakravorty S, Malvi A, Chaturvedi A, Sonkusare K, Dave N. Glutathione—the master antioxidant. *Int J Med Res Pharm Sci*. 2020;7(2):1–11.
 31. Moustapha A. Neurodegenerative Diseases: Potential Effect of Glutathione. In: Dulce Bagatini M, editor. *Glutathione System and Oxidative Stress in Health and Disease* [Internet]. IntechOpen; 2020 [cited 2026 Jan 2]. Available from: <https://www.intechopen.com/books/glutathione-system-and-oxidative-stress-in-health-and-disease/neurodegenerative-diseases-potential-effect-of-glutathione>
 32. Mayer C, Riera-Ponsati L, Kauppinen S, Klitgaard H, Erler JT, Hansen SN. Targeting the NRF2 pathway for disease modification in neurodegenerative diseases: mechanisms and therapeutic implications. *Front Pharmacol* [Internet]. 2024 Jul 25 [cited 2026 Jan 2];15:1437939. Available from: <https://www.frontiersin.org/articles/10.3389/fphar.2024.1437939/full>
 33. Bitra VR, Moshapa F, Adiukwu PC, Rapaka D. Nrf2-Mediated Signaling as a Therapeutic Target in Alzheimer's Disease. *Open Neurol J* [Internet]. 2024 Jun 21 [cited 2026 Jan 2];18(1):e1874205X319474. Available from: <https://openneurologyjournal.com/VOLUME/18/ELOCATOR/e1874205X319474/>
 34. Pomatto LCD, Davies KJA. Adaptive homeostasis and the free radical theory of ageing. *Free Radic Biol Med* [Internet]. 2018 Aug [cited 2026 Jan 2];124:420–30. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0891584918310645>
 35. Li B, Ming H, Qin S, Nice EC, Dong J, Du Z, et al. Redox regulation: mechanisms, biology and therapeutic targets in diseases. *Signal Transduct Target Ther* [Internet]. 2025 Mar 7 [cited 2026 Jan 2];10(1):72. Available from: <https://www.nature.com/articles/s41392-024-02095-6>
 36. Plóciniczak A, Bukowska-Olech E, Wysocka E. The Complexity of Oxidative Stress in Human Age-Related Diseases—A Review. *Metabolites* [Internet]. 2025 Jul 15 [cited 2026 Jan 2];15(7):479. Available from: <https://www.mdpi.com/2218-1989/15/7/479>
 37. Abdelhamid RF, Nagano S. Crosstalk between Oxidative Stress and Aging in Neurodegeneration Disorders. *Cells*. 2023 Feb 27;12(5):753.
 38. Chandimali N, Bak SG, Park EH, Lim HJ, Won YS, Kim EK, et al. Free radicals and their impact on health and antioxidant defenses: a review. *Cell Death Discov* [Internet]. 2025 Jan 24 [cited 2026 Jan 2];11(1):19. Available from: <https://www.nature.com/articles/s41420-024-02278-8>
 39. Tripathi D, Oldenburg DJ, Bendich AJ. Oxidative and Glycation Damage to Mitochondrial DNA and Plastid DNA during Plant Development. *Antioxidants* [Internet]. 2023 Apr 6 [cited 2026 Jan 2];12(4):891. Available from: <https://www.mdpi.com/2076-3921/12/4/891>
 40. Boccardi V, Mancinetti F, Mecocci P. Oxidative Stress, Advanced Glycation End Products (AGEs), and Neurodegeneration in Alzheimer's Disease: A Metabolic Perspective. *Antioxid Basel Switz*. 2025 Aug 25;14(9):1044.
 41. Alkhalifa AE, Alkhalifa O, Durdanovic I, Ibrahim DR, Maragkou S. Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease: Insights into Pathophysiology and Treatment. *J Dement Alzheimer's Dis*. 2025;2(2):17.
 42. Watanabe H, Dijkstra JM, Nagatsu T. Parkinson's Disease: Cells Succumbing to Lifelong Dopamine-Related Oxidative Stress and Other Bioenergetic Challenges. *Int J Mol Sci* [Internet]. 2024 Feb 7 [cited 2026 Jan 2];25(4):2009. Available from: <https://www.mdpi.com/1422-0067/25/4/2009>
 43. Henrich MT, Oertel WH, Surmeier DJ, Geibl FF. Mitochondrial dysfunction in Parkinson's disease – a key disease hallmark with therapeutic potential. *Mol Neurodegener* [Internet].

- 2023 Nov 11 [cited 2026 Jan 2];18(1):83. Available from: <https://molecularneurodegeneration.biomedcentral.com/articles/10.1186/s13024-023-00676-7>
44. Skou LD, Johansen SK, Okarmus J, Meyer M. Pathogenesis of DJ-1/PARK7-Mediated Parkinson's Disease. *Cells* [Internet]. 2024 Feb 6 [cited 2026 Jan 2];13(4):296. Available from: <https://www.mdpi.com/2073-4409/13/4/296>
 45. Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, et al. Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. *Acta Pharm Sin B* [Internet]. 2025 Jan [cited 2026 Jan 2];15(1):15–34. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2211383524004040>
 46. Toader C, Tataru CP, Munteanu O, Serban M, Covache-Busuioc RA, Ciurea AV, et al. Decoding Neurodegeneration: A Review of Molecular Mechanisms and Therapeutic Advances in Alzheimer's, Parkinson's, and ALS. *Int J Mol Sci* [Internet]. 2024 Nov 24 [cited 2026 Jan 2];25(23):12613. Available from: <https://www.mdpi.com/1422-0067/25/23/12613>
 47. Guzmán-Ruiz MA, Guerrero Vargas NN, Ramírez-Carreto RJ, González-Orozco JC, Torres-Hernández BA, Valle-Rodríguez M, et al. Microglia in physiological conditions and the importance of understanding their homeostatic functions in the arcuate nucleus. *Front Immunol* [Internet]. 2024 Sep 4 [cited 2026 Jan 2];15:1392077. Available from: <https://www.frontiersin.org/articles/10.3389/fimmu.2024.1392077/full>
 48. Li Y, Zhang W, Zhang Q, Li Y, Xin C, Tu R, et al. Oxidative stress of mitophagy in neurodegenerative diseases: Mechanism and potential therapeutic targets. *Arch Biochem Biophys* [Internet]. 2025 Feb [cited 2026 Jan 2];764:110283. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0003986124004053>
 49. Shi X. Targeting NOX2 to combat oxidative stress and neuroinflammation and provide neuroprotection in neurodegeneration. 2024;
 50. Kulkarni A, Chen J, Maday S. Neuronal autophagy and intercellular regulation of homeostasis in the brain. *Curr Opin Neurobiol* [Internet]. 2018 Aug [cited 2026 Jan 2];51:29–36. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0959438818300011>
 51. Charmpilas N, Fang EF, Palikaras K. Mitophagy and Neuroinflammation: A Compelling Interplay. *Curr Neuropharmacol* [Internet]. 2023 Jul [cited 2026 Jan 2];21(7):1477–81. Available from: <https://www.eurekaselect.com/206466/article>
 52. Ashok A, Andrabi SS, Mansoor S, Kuang Y, Kwon BK, Labhasetwar V. Antioxidant Therapy in Oxidative Stress-Induced Neurodegenerative Diseases: Role of Nanoparticle-Based Drug Delivery Systems in Clinical Translation. *Antioxidants* [Internet]. 2022 Feb 17 [cited 2026 Jan 2];11(2):408. Available from: <https://www.mdpi.com/2076-3921/11/2/408>
 53. Apostolova N, Victor VM. Molecular Strategies for Targeting Antioxidants to Mitochondria: Therapeutic Implications. *Antioxid Redox Signal* [Internet]. 2015 Mar 10 [cited 2026 Jan 2];22(8):686–729. Available from: <http://www.liebertpub.com/doi/10.1089/ars.2014.5952>
 54. Broome SC, Whitfield J, Janssens K, Hawley JA. MitoQ supplementation does not impact redox responses to acute exercise in skeletal muscle of older individuals. *Redox Biol*. 2025;103927.
 55. Pin F, Huot JR, Bonetto A. The mitochondria-targeting agent MitoQ improves muscle atrophy, weakness and oxidative metabolism in C26 tumor-bearing mice. *Front Cell Dev Biol*. 2022;10:861622.
 56. Şerban M, Toader C, Covache-Busuioc RA. The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration. *Int J Mol Sci* [Internet]. 2025 Aug 3 [cited 2026 Jan 2];26(15):7498. Available from: <https://www.mdpi.com/1422-0067/26/15/7498>
 57. Zhou J, Shen R, Makale EC, Zhong W, Chen Z, Huang Q. SS31 confers cerebral protection by reversing mitochondrial dysfunction in early brain injury following subarachnoid hemorrhage, via the Nrf2-and PGC-1 α -dependent pathways. *Neurochem Res*. 2023;48(5):1580–95.
 58. Li M, Kong D, Meng L, Wang Z, Bai Z, Wu G. Discovery of novel SS-31 (d-Arg-dimethylTyr-Lys-Phe-NH₂) derivatives as potent agents to ameliorate inflammation and increase mitochondrial ATP synthesis. *RSC Adv*. 2024;14(41):29789–99.
 59. Jiang Q, Yin J, Chen J, Ma X, Wu M, Liu G, et al. Mitochondria-targeted antioxidants: a step towards disease treatment. *Oxid Med Cell Longev*. 2020;2020(1):8837893.
 60. Wadan AHS, Shaaban AH, El-Sadek MZ, Mostafa SA, Moshref AS, El-Hussein A, et al. Mitochondrial-based therapies for neurodegenerative diseases: a review of the current literature. *Naunyn Schmiedebergs Arch Pharmacol* [Internet]. 2025 Sep [cited 2026 Jan

2];398(9):11357–86. Available from: <https://link.springer.com/10.1007/s00210-025-04014-0>

61. Kyriazis M. Hormesis and adaptive responses: intermittent fasting-induced stress resistance and disease resilience. In: *The Potential of Intermittent Fasting in Age-related Diseases and Precision Anti-aging Therapeutics*. Elsevier; 2026. p. 213–27.
62. Bevere M, Di Cola G, Santangelo C, Grazioli E, Marramiero L, Pignatelli P, et al. Redox-based disruption of cellular hormesis and promotion of degenerative pathways: perspectives on aging processes. *J Gerontol Ser A*. 2022;77(11):2195–206.
63. Mehdi MM, Solanki P, Singh P. Oxidative stress, antioxidants, hormesis and calorie restriction: The current perspective in the biology of aging. *Arch Gerontol Geriatr* [Internet]. 2021 Jul [cited 2026 Jan 2];95:104413. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0167494321000753>
64. Velikic G, Supic G, Maric DL, Puletic M, Ovcak Kos M, Vojvodic D, et al. Neurodegeneration as Ecosystem Failure: A New Paradigm for Prevention and Treatment. *Int J Mol Sci* [Internet]. 2025 Nov 20 [cited 2026 Jan 2];26(22):11207. Available from: <https://www.mdpi.com/1422-0067/26/22/11207>
65. Niazi SK. Non-Invasive Drug Delivery across the Blood–Brain Barrier: A Prospective Analysis. *Pharmaceutics* [Internet]. 2023 Nov 7 [cited 2026 Jan 2];15(11):2599. Available from: <https://www.mdpi.com/1999-4923/15/11/2599>
66. Vargas R, Martinez-Martinez N, Lizano-Barrantes C, Pacheco-Molina JA, García-Montoya E, Pérez-Lozano P, et al. Advancing through the blood-brain barrier: mechanisms, challenges and drug delivery strategies. *Admet Dmpk*. 2025;13(5):2988.
67. Pérez-Torres I, Guarner-Lans V, Rubio-Ruiz ME. Reductive Stress in Inflammation-Associated Diseases and the Pro-Oxidant Effect of Antioxidant Agents. *Int J Mol Sci* [Internet]. 2017 Oct 5 [cited 2026 Jan 2];18(10):2098. Available from: <https://www.mdpi.com/1422-0067/18/10/2098>
68. Şerban M, Toader C, Covache-Busuioc RA. The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration. *Int J Mol Sci* [Internet]. 2025 Aug 3 [cited 2026 Jan 2];26(15):7498. Available from: <https://www.mdpi.com/1422-0067/26/15/7498>
69. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. *Signal Transduct Target Ther* [Internet]. 2023 Jul 12 [cited 2026 Jan 2];8(1):267. Available from: <https://www.nature.com/articles/s41392-023-01486-5>
70. Hein ZM, Karikalan B, Gopalakrishna PK, Dhevi K, Alkatiri A, Hussan F, et al. Toward a Unified Framework in Molecular Neurobiology of Alzheimer’s Disease: Revisiting the Pathophysiological Hypotheses. *Mol Neurobiol* [Internet]. 2026 Jan [cited 2026 Jan 2];63(1):282. Available from: <https://link.springer.com/10.1007/s12035-025-05602-0>

REVISI 2

Review Article

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

Meutia A. Faradilla¹, Karina S. Anastasya², Deasyka Yastani¹, Yohana Yohana¹, Endrico X. Tungka¹ and Suweino Suweino¹

¹Department of Biochemistry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia; ²Department of Nutritional, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

*Corresponding author: meutia.atika@trisakti.ac.id

Abstract

Aging is the primary risk factor for major neurodegenerative disorders, yet the precise molecular links between biological aging and progressive neuronal loss remain complex. Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, has emerged as a central converging mechanism driving both processes. This review aims to synthesize current evidence demonstrating how chronic redox imbalance drives cellular senescence and neuronal vulnerability through mitochondrial dysfunction, lipid peroxidation, and oxidative protein damage. These insights underscore how sustained oxidative insults promote the misfolding and aggregation of disease-defining proteins, including amyloid-beta in Alzheimer's disease and α -synuclein in Parkinson's disease, thereby amplifying neuroinflammation, synaptic dysfunction, and bioenergetic failure. Furthermore, antioxidant based therapeutic strategies are critically reassessed, highlighting a paradigm shift from non-specific radical scavenging toward targeted modulation of endogenous defense systems, particularly NRF2 signaling and mitochondria-directed antioxidants. By integrating molecular mechanisms with translational perspectives, this review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Keywords: Oxidative stress, aging, neurodegeneration, mitochondria, reactive oxygen species

Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders, most notably Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor that is biological aging [2]. Oxidative stress represents



a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of neuronal vulnerability and decline. Within the network of aging-related mechanisms, oxidative stress functions as a central converging mechanism linking normal physiological aging to pathological neurodegeneration [3]. Rather than being a mere byproduct of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems [4]. Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins [5].

Classical theories, such as Harman's Free Radical Theory of Aging[6][1](X), have historically attributed aging to random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival [7]. The central nervous system is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden[8]. At the heart of this vulnerability lies the mitochondrion [9]. As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses [10].

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance [11]. The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid-beta in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation [12]. Although oxidative stress is widely recognized as a hallmark of biological aging and neurodegeneration, existing literature frequently addresses mitochondrial dysfunction, proteostatic failure, neuroinflammation, and redox signaling in isolation. This review addresses this gap by integrating molecular, cellular, and translational evidence to clarify how redox imbalance functions as a convergent driver of neuronal dysfunction and loss in Alzheimer's and Parkinson's diseases. The molecular sources of reactive oxygen species, age-related declines in antioxidant capacity, and the convergence of these processes on protein aggregation and neurodegeneration are synthesized. Finally, the limitations of broad-spectrum antioxidant strategies are discussed, and a conceptual shift toward targeted modulation of redox-sensitive pathways, rather than non-specific scavenging, is proposed.

Molecular mechanisms of oxidative stress

Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including AD, PD and ALS. Although these disorders are clinically distinct, they share biological aging as a common risk factor, indicating that age-related cellular processes actively contribute to neuronal degeneration [13]. Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology [14]. Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular defense systems, leading to damage of DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function [8]. The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand

and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration [15].

Molecular origins of reactive species

ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During oxidative phosphorylation, electron leakage occurs most notably at Complex I (nicotinamide adenine dinucleotide reduced (NADH) dehydrogenase) and Complex III (ubiquinone–cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O_2), forming the superoxide anion ($O_2^{\cdot-}$), as described by the reaction $O_2 + e^- \rightarrow O_2^{\cdot-}$ [16].

Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H_2O_2), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe^{2+}) or cuprous copper (Cu^+), generating the highly reactive and destructive hydroxyl radical ($\cdot OH$): $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$ [17]:

The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression [18].

Mitochondrial ROS generation

Mitochondria are central to cellular energy production through oxidative phosphorylation, but they are also the primary source of ROS. During oxidative phosphorylation, electrons are transferred through the mitochondrial electron transport chain, and some electrons leak at Complex I and Complex III. This leakage leads to the partial reduction of molecular oxygen, producing superoxide anions ($O_2^{\cdot-}$). These superoxides are then converted into hydrogen peroxide, which, in turn, can form hydroxyl radicals ($\cdot OH$) through Fenton reactions, further amplifying oxidative stress [19]. This ROS production becomes self-perpetuating in aging and neurodegenerative diseases, as damaged mitochondria generate more ROS, worsening mitochondrial dysfunction. This creates a vicious cycle where oxidative damage to cellular structures such as lipids, proteins, and DNA intensifies cellular dysfunction, accelerating the progression of diseases like AD and PD. Moreover, mitochondrial damage can reduce ATP production, impeding cellular functions and contributing to neuronal degeneration [5].

Lipid peroxidation and membrane vulnerability

Oxidative stress also leads to lipid peroxidation, a process in which ROS attack the polyunsaturated fatty acids in cellular membranes. Lipid peroxidation generates highly reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which can diffuse across the cells and interact with other cellular components [20]. These lipid peroxidation products disrupt the structural integrity of neuronal membranes, impairing the fluidity and function of the lipid bilayer [21]. This damage compromises membrane-bound proteins, receptors, and ion channels, leading to disturbances in cellular signaling, neurotransmission, and overall neuronal efficiency. In neurodegenerative diseases, this membrane vulnerability accelerates neuronal damage and contributes to synaptic dysfunction. For instance, in AD, lipid peroxidation can facilitate the aggregation of amyloid-beta, further exacerbating the pathological cycle [20]. The lipid-rich membranes of neurons make them particularly susceptible to oxidative damage, reinforcing the progression of diseases like AD and PD [20].

Proteostasis collapse

Proteostasis is essential for maintaining cellular homeostasis by regulating protein synthesis, folding, and degradation. However, oxidative stress disrupts proteostasis, leading to the accumulation of damaged and misfolded proteins. ROS can induce oxidative modifications such as carbonylation and nitration on proteins, altering their structure and function [22]. These

misfolded proteins are typically targeted for degradation by the proteasome or autophagy pathways. However, oxidative stress impairs these systems, leading to the accumulation of toxic protein aggregates[23]. In neurodegenerative diseases like AD and PD, this collapse of proteostasis is particularly detrimental. For example, in AD, amyloid-beta accumulates and forms plaques, while in PD, α -synuclein forms Lewy bodies. These protein aggregates not only disrupt cellular function but also impair synaptic plasticity, damage mitochondria, and promote neuroinflammation[23]. The accumulation of misfolded proteins creates a positive feedback loop that exacerbates oxidative stress, mitochondrial dysfunction, and cellular damage [1][11].

Redox inflammatory crosstalk

Oxidative stress and neuroinflammation are intimately connected, with ROS playing a crucial role in activating redox-sensitive transcription factors like nuclear factor kappa B (NF- κ B). NF- κ B, once activated by ROS, translocate to the nucleus and initiates the expression of proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α [24]. These cytokines activate microglia, the resident immune cells of the brain, which further increase ROS production and promote inflammation[25]. Chronic neuroinflammation exacerbates neuronal damage by impairing synaptic function, disrupting calcium homeostasis, and sensitizing neurons to excitotoxicity. This inflammatory response becomes self-perpetuating under conditions of sustained oxidative stress, where proinflammatory cytokines further exacerbate ROS production, leading to a cycle of oxidative injury and inflammation[24]. This crosstalk between oxidative stress and inflammation is a critical driver of neurodegenerative diseases like AD and PD, where inflammation amplifies the damage caused by ROS, leading to progressive neuronal death and dysfunction [24].

Autophagy and mitophagy failure

Autophagy and mitophagy are vital cellular processes for maintaining cellular integrity by degrading damaged proteins and organelles. In neurons, where turnover is limited due to the lack of cell division, the efficient functioning of autophagic pathways is critical for long-term survival. However, oxidative stress compromises the integrity of these pathways. ROS can damage the lysosomal system, which is responsible for the final stages of autophagic degradation, impairing its function [26]. As a result, damaged proteins and dysfunctional organelles accumulate within neurons, further exacerbating cellular stress. In particular, mitophagy, the selective removal of damaged mitochondria, is essential to protect cells from oxidative damage. However, oxidative stress impairs mitophagy by disrupting the PINK1/Parkin pathway, which is responsible for marking damaged mitochondria for degradation[27]. The failure to clear dysfunctional mitochondria allows them to persist and continue generating ROS, perpetuating mitochondrial dysfunction and oxidative stress. This accumulation of damaged mitochondria, often referred to as “zombie mitochondria,” further disrupts cellular function, leading to energy depletion and contributing to the neurodegenerative processes observed in diseases like PA [27].

Antioxidant defence

Enzymatic vanguard: The first line of redox control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain [28]. Because superoxide is highly reactive and short lived, its rapid conversion into hydrogen peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology [29]. At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (CAT) and glutathione peroxidase assume decisive roles [30], [31]. By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation a species widely regarded as the most destructive

ROS due to its indiscriminate reactivity [18]. This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised whether due to genetic variation, post-translational alterations, or age-related functional decline the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage [32].

Non-enzymatic buffers and thiol-based redox modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond the capacity of enzymatic systems. By donating electrons, glutathione neutralizes reactive species and is converted into its oxidized form, glutathione disulfide. Consequently, the balance between reduced and oxidized glutathione (the ratio of glutathione-to-glutathione disulfide) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain [33]. Evidence from aging studies consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event [34]. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function [24]. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation [35].

Regulatory control and the NRF2 axis

The effectiveness of antioxidant defenses within the central nervous system is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2–related factor 2 (NRF2), a master regulator of cellular stress responses. Under basal conditions, NRF2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding superoxide dismutases, glutathione peroxidase, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands [36]. With advancing age, however, the responsiveness of the NRF2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a “redox vulnerability gap”, wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders [37].

Oxidative stress in aging: Molecular Mechanism of senescence

The modified free radical theory of aging

Harman's Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by ROS [38]. While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury [39]. Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled [40]. However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu,

commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline [41].

Accumulation of macromolecular damage in the aging brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between ROS production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function [42]. Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency [43].

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin–proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress [22]. Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2'-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration [44].

Oxidative stress in neurodegenerative diseases

Alzheimer's disease (AD): Oxidative stress as a self-reinforcing pathological loop

In AD, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through interconnected, self-reinforcing loops that involve amyloid-beta accumulation, mitochondrial dysfunction, and Tau pathology (Figure 1). Soluble amyloid-beta oligomers has redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of ROS[13]. This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further amyloid-beta aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment [45]. As shown in Figure 1, the pathological process begins with the accumulation of amyloid-beta within neuronal mitochondria further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular energy balance[10]. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport[1]. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in AD [46].

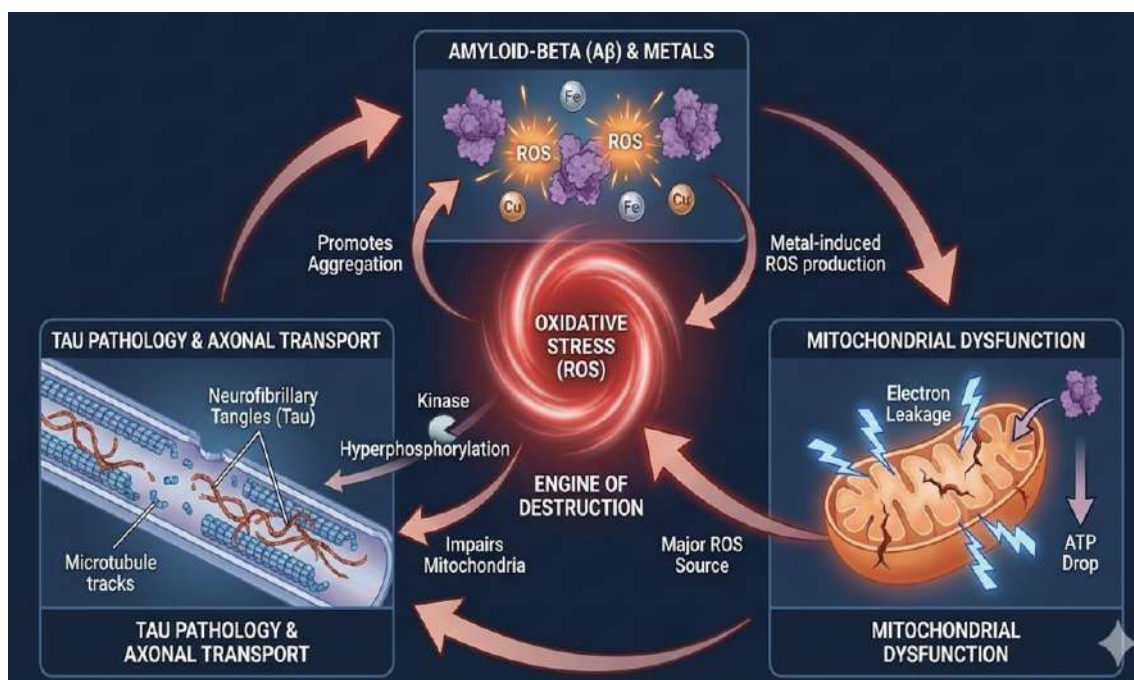


Figure 1. Key mechanisms of oxidative stress and neuronal damage in Alzheimer's disease (AD) pathology. Self-reinforcing cycle of oxidative stress and mitochondrial dysfunction, illustrating the roles of amyloid-beta, metals, tau pathology, and mitochondrial dysfunction in AD. The figure is generated using BioRender.

Parkinson's disease (PA): Selective vulnerability to oxidative stress

PA illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons [47].

As shown in **Figure 2**, the pathological process of PA begins with mitochondrial dysfunction, which further amplifies oxidative injury. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1–Parkin–mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress [48]. Loss of DJ-1–mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in PD [36].

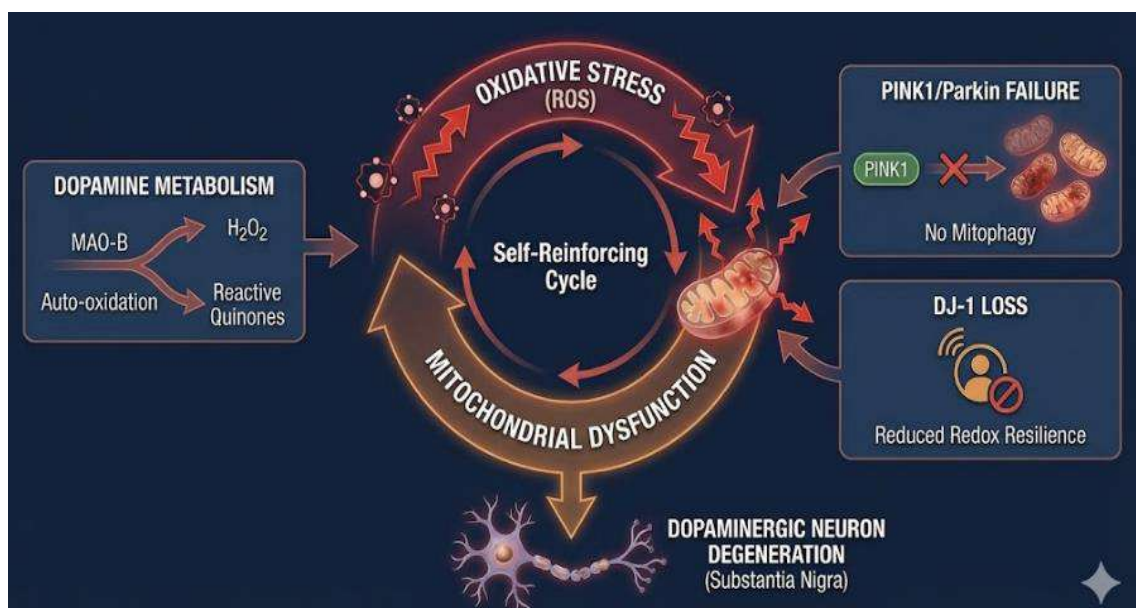


Figure 2. Key mechanisms of oxidative stress and mitochondrial impairment in Parkinson's disease (PD) pathology. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction in PD, illustrating how dopamine metabolism, PINK1/Parkin failure, and DJ-1 loss contribute to dopaminergic neuron degeneration in the substantia nigra. The figure is generated using BioRender.

Converging pathways: Inflammation and autophagy

Oxidative stress represents an early destabilizing force in neuronal homeostasis, yet its most destructive effects emerge through its capacity to activate downstream pathological pathways [50]. Rather than acting as an isolated insult, sustained redox imbalance orchestrates a broader cellular collapse by engaging neuroinflammatory signaling and disrupting intracellular quality-control mechanisms. Among these, chronic inflammation and autophagy impairment stand out as convergent pathways that transform transient oxidative disturbances into irreversible neurodegenerative trajectories [51].

The oxidative inflammatory axis: From redox imbalance to neurotoxicity

In the central nervous system, oxidative stress and inflammation are intimately intertwined, forming a self-amplifying pathological circuit. Microglia, the brain's resident immune cells, are uniquely positioned at the interface between neuronal metabolism and immune surveillance. Under physiological conditions, microglia maintain synaptic integrity and respond transiently to injury. However, persistent oxidative stress alters this homeostatic role, pushing microglia toward a chronically activated, proinflammatory phenotype [52].

ROS-mediated activation of proinflammatory signaling

Reactive oxygen species function as potent second messengers capable of activating redox-sensitive transcription factors. Among these, nuclear factor kappa light chain enhancer of activated B cells (NF- κ B) plays a central role in translating oxidative cues into inflammatory gene expression. Elevated ROS levels promote the dissociation of NF- κ B from its cytoplasmic inhibitors, allowing its translocation into the nucleus. Once activated, NF- κ B drives the transcription of a broad spectrum of proinflammatory mediators, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor α (TNF- α). These cytokines exert pleiotropic effects within the neural microenvironment. Beyond recruiting additional immune responses, they directly impair synaptic function, disrupt neuronal calcium homeostasis, and sensitize neurons to excitotoxic injury. Importantly, this inflammatory signaling is not a short-lived response but becomes sustained under conditions of chronic oxidative stress, reshaping the neural milieu into one that favors degeneration rather than repair [53].

Self-perpetuating cycle of ROS and inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation[54]. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders [54].

Autophagy and mitophagy failure: Breakdown of cellular quality control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival [55].

Lysosomal dysfunction and autophagic arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure [27].

Mitophagy failure and energetic collapse

Among autophagic processes, the selective removal of damaged mitochondria, known as mitophagy, is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage[3]. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as “zombie mitochondria,” remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure[56]. As ATP levels decline, energy-dependent processes including ion homeostasis, axonal transport, and synaptic transmission become unsustainable. Ultimately, this convergence of oxidative damage, autophagy impairment, and bioenergetic collapse pushes neurons toward apoptotic or necrotic death [57]. The central roles of oxidative stress in neurodegenerative diseases such as AD and PD are illustrated in [Figure 3](#). It highlights key mechanisms including mitochondrial ROS generation, proteostasis collapse, neuroinflammation, and defective autophagy, all contributing to cellular damage. The [Figure 3](#) also shows how oxidative stress promotes synaptic dysfunction and cognitive decline by driving the accumulation of toxic proteins like amyloid- β and tau in AD and neuronal loss in PD. Additionally, it emphasizes therapeutic targets, such as NRF2 activators (e.g., dimethyl fumarate), mitochondria-targeted antioxidants (e.g., MitoQ), and proteostasis and autophagy enhancers (e.g., rapamycin, SS-31, Urolithin A), which aim to mitigate oxidative damage and restore cellular function.

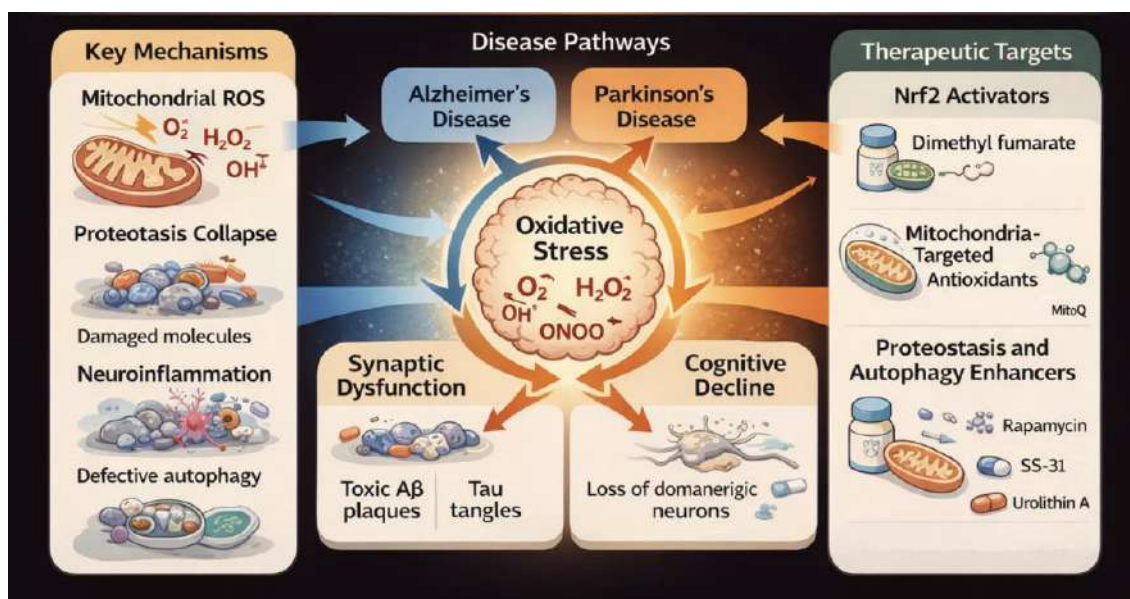


Figure 3. Schematic overview illustrating the continuum from the molecular origins of reactive oxygen species (ROS) through cellular damage—encompassing mitochondrial dysfunction and neuroinflammation—to clinical manifestations of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. The figure also highlights the emerging shift toward precision medicine and targeted therapeutic strategies. The illustration was created using BioRender.

Therapeutic targets and clinical implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However, decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated [31].

NRF2 pathway activation: Reinforcing endogenous redox resilience

NRF2 serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, NRF2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation [37]. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing NRF2 to escape degradation and translocate into the nucleus. There, NRF2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, NRF2 activation enhances intrinsic redox resilience by strengthening the cell's capacity to respond to future oxidative challenges [36]. While NRF2 activation is beneficial in protecting against oxidative stress, chronic activation can have limitations. Continuous NRF2 activation may inadvertently promote tumorigenesis by aiding the survival of damaged cells, which may facilitate cancer progression. The activation of the pathway in non-cancerous tissues should, therefore, be carefully regulated. In terms of activating NRF2, there are two primary categories: electrophilic and non-electrophilic activators. Electrophilic activators, such as sulforaphane, directly modify KEAP1, leading to the activation of NRF2 [57]. However, these compounds can cause unintended damage due to their reactivity, potentially affecting cellular structures beyond their target. On the other hand, non-electrophilic activators, such as bardoxolone methyl, activate NRF2 without directly altering KEAP1, which offers a safer profile with fewer side effects but may have lower potency [37].

Conventional antioxidants have shown limited efficacy in neurodegenerative

Conventional antioxidant therapies have demonstrated limited benefit in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal ROS. This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, elamipretide (SS-31) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis [58]. Comparison of mitochondria-targeted antioxidants MitoQ and SS-31 are summarized in Table 1 [25], [59], [60], [61], [62], [63], [64].

Table 1. Comparative summary of mitochondria-targeted antioxidants MitoQ and SS-31

Feature	Mitoquinone mesylate (MitoQ)	Elamipretide (SS-31)
Primary mechanism	Electrophoretic accumulation driven by mitochondrial membrane potential.	Potential-independent uptake; targets and stabilizes cardiolipin in the inner membrane.
Antioxidant action	Redox-active ubiquinone moiety directly scavenges radicals and is regenerated by Complex II.	Structural stabilization of cristae/supercomplexes to prevent electron leakage and ROS formation.
Physical impact	Can cause mitochondrial swelling and depolarization at high concentrations due to its alkyl chain.	Acts as "mitochondrial armor," protecting against membrane fragmentation and structural decay.
Preclinical evidence	Robust protection in Alzheimer', Parkinson's, and Huntington's disease models.	Consistent success in Alzheimer', Parkinson's, Huntington's disease and brain injury models, improving dynamics and synaptic health.
Clinical status	Failed PD trials (no clinical effect on UPDRS). Currently used as a dietary supplement for vascular health.	FDA approved (Sept 2025) for Barth syndrome. Failed trials in heart failure and primary mitochondrial myopathy.

Lifestyle interventions and hormetic redox adaptation

Lifestyle interventions, such as physical exercise and caloric restriction, activate endogenous antioxidant defenses through a process known as hormesis. Hormesis refers to the phenomenon where low-level, transient oxidative stress triggers adaptive protective responses within cells. When applied in moderation, physical exercise and mild caloric restriction induce controlled oxidative stress that enhances cellular resilience [65]. These interventions improve mitochondrial efficiency by promoting better ATP production and reducing the production of excess ROS, stimulate autophagy for the clearance of damaged proteins and organelles, and upregulate antioxidant signaling pathways such as the Nrf2 pathway, which enhances the cell's ability to combat oxidative damage. Additionally, they boost the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which support neuronal growth, survival, and synaptic plasticity, playing a crucial role in brain health [66].

However, it is important to note that the beneficial effects of hormesis are dose-dependent. When physical exercise or caloric restriction exceeds a certain threshold, it can shift from an adaptive to a maladaptive stress response. Prolonged or excessive exercise, for example, can lead to chronic oxidative stress, resulting in mitochondrial dysfunction, muscle damage, and an increase in inflammatory markers. Similarly, prolonged caloric restriction may impair cellular homeostasis, weaken the immune system, and exacerbate metabolic dysfunction. These maladaptive responses may overwhelm the body's protective mechanisms, leading to cellular damage rather than the intended health benefits. Therefore, while moderate exercise and caloric restriction can enhance redox balance and improve health outcomes, extreme or prolonged levels of these stressors may cause harm, highlighting the importance of balance in these lifestyle interventions [67].

Therapeutic potential and clinical translation

Pharmacological activation of NRF2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach[68]. By inducing mild electrophilic stress, it activates NRF2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other NRF2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive NRF2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress [36].

Challenges and future directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in AD and PD has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnect between compelling preclinical data and disappointing clinical outcomes highlights a critical “translational gap” that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

Table 2. Comparative summary between mechanisms of oxidative stress, their roles in Alzheimer's disease (AD) vs. Parkinson's disease (PD) and potential therapeutic interventions [1], [1], [1], [3], [3], [13], [21], [27], [31], [31], [37], [47], [47], [48], [49], [51], [51]

Mechanisms of oxidative stress	Role in Alzheimer's disease (AD)	Role in Parkinson's disease (PD)	Potential therapeutic interventions
Mitochondrial dysfunction	Mitochondrial dysfunction leads to bioenergetic failure, impairing synaptic plasticity and contributing to neuronal damage.	Mitochondrial dysfunction in dopaminergic neurons accelerates ROS production and contributes to neuronal loss.	Mitochondria-targeted antioxidants (e.g., MitoQ, SS31) that help reduce ROS and restore mitochondrial function.
Lipid peroxidation	Oxidative damage to membrane lipids leads to neuronal damage and loss of synaptic function.	Lipid peroxidation exacerbates dopaminergic neuron death and disrupts membrane integrity.	Use of lipid antioxidants like alpha-lipoic acid or other peroxy scavengers to prevent oxidative damage.
Proteostasis collapse	Proteostasis collapse contributes to the accumulation of amyloid β and tau, which disrupt neuronal function.	Accumulation of misfolded proteins, such as α -synuclein, leads to dopaminergic dysfunction.	Proteostasis regulators, such as proteasome activators or autophagy enhancers (e.g., rapamycin, spermidine).
Neuroinflammation	Chronic neuroinflammation amplifies the amyloid plaque formation and accelerates disease progression.	Neuroinflammation in microglia worsens dopaminergic neuron death and amplifies ROS production.	Anti-inflammatory agents targeting NF- κ B or microglial activation (e.g., minocycline, curcumin).
Redox-Imbalance (ROS and RNS)	ROS accumulation damages cellular structures (DNA, lipids, proteins) and triggers apoptosis.	ROS generation through dopamine metabolism leads to neuronal damage and contributes to cell death.	Nrf2 activators (e.g., dimethyl fumarate), which boost cellular antioxidant defences and help restore redox homeostasis.
Autophagy and mitophagy failure	Impaired autophagy leads to the accumulation of	Deficient mitophagy results in the	Autophagy enhancers (e.g., rapamycin) and

damaged proteins, exacerbating neurodegeneration.	accumulation of dysfunctional mitochondria, contributing to neurodegeneration.	mitophagy activators (e.g., Urolithin A, PINK1 activators) to clear damaged organelles.
---	--	---

Temporal mismatch: Treating too late in the disease course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred[69], [70]. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure[71]. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles [72].

Bioavailability and blood brain barrier limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood–brain barrier, while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets [73]. Even when compounds successfully cross the blood–brain barrier, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery such as nanoparticle-based carriers, mitochondria-targeted molecules, and ligand-mediated transport systems represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects [74].

Paradox of reductive stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. ROS are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction[23]. This concept challenges the simplistic view that “more antioxidants are better” and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease [75].

Need for redox biomarkers and patient stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status *in vivo*. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to

benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism [76].

Toward a systems-level therapeutic strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways [77]. In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system [78].

Conclusion

This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy, collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.

Acknowledgments

The authors gratefully acknowledge the Department of Biochemistry, Faculty of Medicine, Trisakti University, for its continuous academic support and supportive environment during the development of this review. We also sincerely thank the researchers and scholars whose work has contributed to the advancement of knowledge in the field of oxidative stress, aging, and neurodegeneration. Their contributions provided essential scientific insights that informed and strengthened this manuscript.

Competing interests

All authors declare that there are no conflicts of interest related to this work.

Funding

This study received no external funding.

Underlying data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

During the preparation of this work, authors utilized specifically Gemini Pro and ChatGPT Pro, to support the conceptualization, planning, and refinement phases of the manuscript. The application of these tools was strictly limited to specific capacities, starting with conceptualization and ideation, where the AI models were employed to brainstorm initial research frameworks, organize the logical flow of arguments, and suggest structural outlines. Regarding visual design strategy, AI tools were utilized solely for design optimization to analyze draft layouts and provide feedback on visual clarity and color accessibility. Authors explicitly confirm that no generative AI tools were used to create, generate, or manipulate the final

images, as all figures and diagrams were manually constructed using BioRender.com to ensure compliance with scientific accuracy and copyright standards. Additionally, the tools were used for linguistic refinement to enhance the readability, grammatical accuracy, and stylistic consistency of the written text.

How to cite

Faradilla MA, Anastasya KS, Yastani D, *et al.* Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets. Narra J 2026; 6 (1): e3042 - [http://doi.org/10.52225/narra.v6i1.\[X\]](http://doi.org/10.52225/narra.v6i1.[X]).

References

- [1] A. Rostagno and J. Ghiso, "Alzheimer's Disease Pathogenic Mechanisms: Linking Redox Homeostasis and Mitochondria-Associated Metabolic Pathways Through Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)," *Antioxidants*, vol. 14, no. 7, p. 812, Jul. 2025, doi: 10.3390/antiox14070812.
- [2] R. Tenchov, J. M. Sasso, X. Wang, and Q. A. Zhou, "Aging hallmarks and progression and age-related diseases: a landscape view of research advancement," *ACS Chem. Neurosci.*, vol. 15, no. 1, pp. 1–30, 2023.
- [3] E. Spina *et al.*, "Mitochondrial Alterations, Oxidative Stress, and Therapeutic Implications in Alzheimer's Disease: A Narrative Review," *Cells*, vol. 14, no. 3, p. 229, Feb. 2025, doi: 10.3390/cells14030229.
- [4] M.-C. Jurcau, A. Jurcau, and R.-G. Diaconu, "Oxidative Stress in the Pathogenesis of Neurodegenerative Diseases," *Stresses*, vol. 4, no. 4, pp. 827–849, Dec. 2024, doi: 10.3390/stresses4040055.
- [5] X. Xu, Y. Pang, and X. Fan, "Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 190, Jun. 2025, doi: 10.1038/s41392-025-02253-4.
- [6] D. Harman, "Free radical theory of aging," *Mutat. Res.*, vol. 275, no. 3–6, pp. 257–266, 1992.
- [7] D. Harman, "Free Radical Theory of Aging: An Update: Increasing the Functional Life Span," *Ann. N. Y. Acad. Sci.*, vol. 1067, no. 1, pp. 10–21, May 2006, doi: 10.1196/annals.1354.003.
- [8] M. E. Watts, R. Pocock, and C. Claudianos, "Brain energy and oxygen metabolism: emerging role in normal function and disease," *Front. Mol. Neurosci.*, vol. 11, p. 216, 2018.
- [9] K. Tripathi and D. Ben-Shachar, "Mitochondria in the Central Nervous System in Health and Disease: The Puzzle of the Therapeutic Potential of Mitochondrial Transplantation," *Cells*, vol. 13, no. 5, p. 410, Feb. 2024, doi: 10.3390/cells13050410.
- [10] R. Stefanatos and A. Sanz, "The role of mitochondrial ROS in the aging brain," *FEBS Lett.*, vol. 592, no. 5, pp. 743–758, Mar. 2018, doi: 10.1002/1873-3468.12902.
- [11] O. F. Kuzu, L. J. T. Granerud, and F. Saatcioglu, "Navigating the landscape of protein folding and proteostasis: from molecular chaperones to therapeutic innovations," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 358, Oct. 2025, doi: 10.1038/s41392-025-02439-w.
- [12] C. Hu, M. Lin, C. Wang, and S. Zhang, "Current Understanding of Protein Aggregation in Neurodegenerative Diseases," *Int. J. Mol. Sci.*, vol. 26, no. 21, p. 10568, Oct. 2025, doi: 10.3390/ijms262110568.
- [13] J. Tchekalarova and R. Tzoneva, "Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin," *Int. J. Mol. Sci.*, vol. 24, no. 3, p. 3022, Feb. 2023, doi: 10.3390/ijms24033022.
- [14] Y. Hou *et al.*, "Ageing as a risk factor for neurodegenerative disease," *Nat. Rev. Neurol.*, vol. 15, no. 10, pp. 565–581, Oct. 2019, doi: 10.1038/s41582-019-0244-7.
- [15] J. M. Neyra Chauca *et al.*, "Oxidative Stress, Neuroinflammation, and Microvascular Damage in Neurodegenerative Diseases: Mechanistic Insights and Therapeutic Approaches," Nov. 10, 2025. doi: 10.20944/preprints202511.0551.v1.
- [16] H. Sies and D. P. Jones, "Reactive oxygen species (ROS) as pleiotropic physiological signalling agents," *Nat. Rev. Mol. Cell Biol.*, vol. 21, no. 7, pp. 363–383, Jul. 2020, doi: 10.1038/s41580-020-0230-3.
- [17] J. Fujii, T. Homma, and T. Osaki, "Superoxide Radicals in the Execution of Cell Death," *Antioxidants*, vol. 11, no. 3, p. 501, Mar. 2022, doi: 10.3390/antiox11030501.
- [18] S. Liu, J. Liu, Y. Wang, F. Deng, and Z. Deng, "Oxidative Stress: Signaling Pathways, Biological Functions, and Disease," *MedComm*, vol. 6, no. 7, p. e70268, Jul. 2025, doi: 10.1002/mco2.70268.

- [19] R. J. Mailloux, "An update on mitochondrial reactive oxygen species production," *Antioxidants*, vol. 9, no. 6, p. 472, 2020.
- [20] L. Valgimigli, "Lipid peroxidation and antioxidant protection," *Biomolecules*, vol. 13, no. 9, p. 1291, 2023.
- [21] B. Wang *et al.*, "ROS-induced lipid peroxidation modulates cell death outcome: mechanisms behind apoptosis, autophagy, and ferroptosis," *Arch. Toxicol.*, vol. 97, no. 6, pp. 1439–1451, 2023.
- [22] T.-M. Sonninen, G. Goldsteins, N. Laham-Karam, J. Koistinaho, and Š. Lehtonen, "Proteostasis Disturbances and Inflammation in Neurodegenerative Diseases," *Cells*, vol. 9, no. 10, p. 2183, Sep. 2020, doi: 10.3390/cells9102183.
- [23] A. Ulfig and U. Jakob, "Cellular oxidants and the proteostasis network: balance between activation and destruction," *Trends Biochem. Sci.*, 2024.
- [24] F. Bellanti, A. R. D. Coda, M. I. Trecca, A. Lo Buglio, G. Serviddio, and G. Vendemiale, "Redox imbalance in inflammation: the interplay of oxidative and reductive stress," *Antioxidants*, vol. 14, no. 6, p. 656, 2025.
- [25] M. Şerban, C. Toader, and R.-A. Covache-Busuioc, "The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration," *Int. J. Mol. Sci.*, vol. 26, no. 15, p. 7498, Aug. 2025, doi: 10.3390/ijms26157498.
- [26] L. Doblado *et al.*, "Mitophagy in human diseases," *Int. J. Mol. Sci.*, vol. 22, no. 8, p. 3903, 2021.
- [27] M. Du, Y. Yu, J. Wang, and C. Ji, "Autophagy–Lysosome Pathway Dysfunction in Neurodegeneration and Cancer: Mechanisms and Therapeutic Opportunities," *Int. J. Mol. Sci.*, vol. 27, no. 1, p. 366, Dec. 2025, doi: 10.3390/ijms27010366.
- [28] K. Jomova, S. Y. Alomar, S. H. Alwasel, E. Nepovimova, K. Kuca, and M. Valko, "Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants," *Arch. Toxicol.*, vol. 98, no. 5, pp. 1323–1367, May 2024, doi: 10.1007/s00204-024-03696-4.
- [29] Í. Gulcin, "Antioxidants: a comprehensive review," *Arch. Toxicol.*, vol. 99, no. 5, pp. 1893–1997, May 2025, doi: 10.1007/s00204-025-03997-2.
- [30] A. M. Gusti, S. Y. Qusti, E. M. Alshammari, E. A. Toraih, and M. S. Fawzy, "Antioxidants-related superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione-S-transferase (GST), and nitric oxide synthase (NOS) gene variants analysis in an obese population: a preliminary case-control study," *Antioxidants*, vol. 10, no. 4, p. 595, 2021.
- [31] A. Ashok, S. S. Andrabi, S. Mansoor, Y. Kuang, B. K. Kwon, and V. Labhassetwar, "Antioxidant Therapy in Oxidative Stress-Induced Neurodegenerative Diseases: Role of Nanoparticle-Based Drug Delivery Systems in Clinical Translation," *Antioxidants*, vol. 11, no. 2, p. 408, Feb. 2022, doi: 10.3390/antiox11020408.
- [32] A. Alhaj Sulaiman and V. L. Katanaev, "Beyond Antioxidants: How Redox Pathways Shape Cellular Signaling and Disease Outcomes," *Antioxidants*, vol. 14, no. 9, p. 1142, Sep. 2025, doi: 10.3390/antiox14091142.
- [33] S. Chakravorty, A. Malvi, A. Chaturvedi, K. Sonkusare, and N. Dave, "Glutathione—the master antioxidant," *Int J Med Res Pharm Sci*, vol. 7, no. 2, pp. 1–11, 2020.
- [34] R. Wadhwa, R. Gupta, and P. K. Maurya, "Oxidative stress and accelerated aging in neurodegenerative and neuropsychiatric disorder," *Curr. Pharm. Des.*, vol. 24, no. 40, pp. 4711–4725, 2018.
- [35] A. Moustapha, "Neurodegenerative Diseases: Potential Effect of Glutathione," in *Glutathione System and Oxidative Stress in Health and Disease*, M. Dulce Bagatini, Ed., IntechOpen, 2020. doi: 10.5772/intechopen.92240.
- [36] C. Mayer, L. Riera-Ponsati, S. Kauppinen, H. Klitgaard, J. T. Erler, and S. N. Hansen, "Targeting the NRF2 pathway for disease modification in neurodegenerative diseases: mechanisms and therapeutic implications," *Front. Pharmacol.*, vol. 15, p. 1437939, Jul. 2024, doi: 10.3389/fphar.2024.1437939.
- [37] V. R. Bitra, F. Moshapa, P. C. Adiukwu, and D. Rapaka, "Nrf2-Mediated Signaling as a Therapeutic Target in Alzheimer's Disease," *Open Neurol. J.*, vol. 18, no. 1, p. e1874205X319474, Jun. 2024, doi: 10.2174/011874205X319474240611070113.
- [38] D. Harman, "Aging: A Theory Based on Free Radical and Radiation Chemistry," *J. Gerontol.*, vol. 11, no. 3, pp. 298–300, Jul. 1956, doi: 10.1093/geronj/11.3.298.
- [39] L. C. D. Pomatto and K. J. A. Davies, "Adaptive homeostasis and the free radical theory of ageing," *Free Radic. Biol. Med.*, vol. 124, pp. 420–430, Aug. 2018, doi: 10.1016/j.freeradbiomed.2018.06.016.

- [40] B. Li *et al.*, “Redox regulation: mechanisms, biology and therapeutic targets in diseases,” *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 72, Mar. 2025, doi: 10.1038/s41392-024-02095-6.
- [41] A. Plóciniczak, E. Bukowska-Olech, and E. Wysocka, “The Complexity of Oxidative Stress in Human Age-Related Diseases—A Review,” *Metabolites*, vol. 15, no. 7, p. 479, Jul. 2025, doi: 10.3390/metabo15070479.
- [42] R. F. Abdelhamid and S. Nagano, “Crosstalk between Oxidative Stress and Aging in Neurodegeneration Disorders,” *Cells*, vol. 12, no. 5, p. 753, Feb. 2023, doi: 10.3390/cells12050753.
- [43] N. Chandimali *et al.*, “Free radicals and their impact on health and antioxidant defenses: a review,” *Cell Death Discov.*, vol. 11, no. 1, p. 19, Jan. 2025, doi: 10.1038/s41420-024-02278-8.
- [44] D. Tripathi, D. J. Oldenburg, and A. J. Bendich, “Oxidative and Glycation Damage to Mitochondrial DNA and Plastid DNA during Plant Development,” *Antioxidants*, vol. 12, no. 4, p. 891, Apr. 2023, doi: 10.3390/antiox12040891.
- [45] V. Boccardi, F. Mancinetti, and P. Mecocci, “Oxidative Stress, Advanced Glycation End Products (AGEs), and Neurodegeneration in Alzheimer’s Disease: A Metabolic Perspective,” *Antioxid. Basel Switz.*, vol. 14, no. 9, p. 1044, Aug. 2025, doi: 10.3390/antiox14091044.
- [46] A. E. Alkhalifa, O. Alkhalifa, I. Durdanovic, D. R. Ibrahim, and S. Maragkou, “Oxidative Stress and Mitochondrial Dysfunction in Alzheimer’s Disease: Insights into Pathophysiology and Treatment,” *J. Dement. Alzheimer’s Dis.*, vol. 2, no. 2, p. 17, 2025.
- [47] H. Watanabe, J. M. Dijkstra, and T. Nagatsu, “Parkinson’s Disease: Cells Succumbing to Lifelong Dopamine-Related Oxidative Stress and Other Bioenergetic Challenges,” *Int. J. Mol. Sci.*, vol. 25, no. 4, p. 2009, Feb. 2024, doi: 10.3390/ijms25042009.
- [48] M. T. Henrich, W. H. Oertel, D. J. Surmeier, and F. F. Geibl, “Mitochondrial dysfunction in Parkinson’s disease – a key disease hallmark with therapeutic potential,” *Mol. Neurodegener.*, vol. 18, no. 1, p. 83, Nov. 2023, doi: 10.1186/s13024-023-00676-7.
- [49] L. D. Skou, S. K. Johansen, J. Okarmus, and M. Meyer, “Pathogenesis of DJ-1/PARK7-Mediated Parkinson’s Disease,” *Cells*, vol. 13, no. 4, p. 296, Feb. 2024, doi: 10.3390/cells13040296.
- [50] U. C. Dash *et al.*, “Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications,” *Acta Pharm. Sin. B*, vol. 15, no. 1, pp. 15–34, Jan. 2025, doi: 10.1016/j.apsb.2024.10.004.
- [51] C. Toader *et al.*, “Decoding Neurodegeneration: A Review of Molecular Mechanisms and Therapeutic Advances in Alzheimer’s, Parkinson’s, and ALS,” *Int. J. Mol. Sci.*, vol. 25, no. 23, p. 12613, Nov. 2024, doi: 10.3390/ijms252312613.
- [52] M. A. Guzmán-Ruiz *et al.*, “Microglia in physiological conditions and the importance of understanding their homeostatic functions in the arcuate nucleus,” *Front. Immunol.*, vol. 15, p. 1392077, Sep. 2024, doi: 10.3389/fimmu.2024.1392077.
- [53] Y. Li *et al.*, “Oxidative stress of mitophagy in neurodegenerative diseases: Mechanism and potential therapeutic targets,” *Arch. Biochem. Biophys.*, vol. 764, p. 110283, Feb. 2025, doi: 10.1016/j.abb.2024.110283.
- [54] X. Shi, “Targeting NOX2 to combat oxidative stress and neuroinflammation and provide neuroprotection in neurodegeneration,” 2024.
- [55] A. Kulkarni, J. Chen, and S. Maday, “Neuronal autophagy and intercellular regulation of homeostasis in the brain,” *Curr. Opin. Neurobiol.*, vol. 51, pp. 29–36, Aug. 2018, doi: 10.1016/j.conb.2018.02.008.
- [56] C. L. Ramsey, “Biologically structured water (BSW)—a review (Part 1): structured water (SW) properties, BSW and redox biology, BSW and bioenergetics,” *J. Basic Appl. Sci.*, vol. 19, pp. 174–201, 2023.
- [57] N. Charmpilas, E. F. Fang, and K. Palikaras, “Mitophagy and Neuroinflammation: A Compelling Interplay,” *Curr. Neuropharmacol.*, vol. 21, no. 7, pp. 1477–1481, Jul. 2023, doi: 10.2174/1570159X20666220628153632.
- [58] N. Apostolova and V. M. Victor, “Molecular Strategies for Targeting Antioxidants to Mitochondria: Therapeutic Implications,” *Antioxid. Redox Signal.*, vol. 22, no. 8, pp. 686–729, Mar. 2015, doi: 10.1089/ars.2014.5952.
- [59] S. C. Broome, J. Whitfield, K. Janssens, and J. A. Hawley, “MitoQ supplementation does not impact redox responses to acute exercise in skeletal muscle of older individuals,” *Redox Biol.*, p. 103927, 2025.
- [60] F. Pin, J. R. Huot, and A. Bonetto, “The mitochondria-targeting agent MitoQ improves muscle atrophy, weakness and oxidative metabolism in C26 tumor-bearing mice,” *Front. Cell Dev. Biol.*, vol. 10, p. 861622, 2022.

- [61] J. Zhou, R. Shen, E. C. Makale, W. Zhong, Z. Chen, and Q. Huang, "SS31 confers cerebral protection by reversing mitochondrial dysfunction in early brain injury following subarachnoid hemorrhage, via the Nrf2-and PGC-1 α -dependent pathways," *Neurochem. Res.*, vol. 48, no. 5, pp. 1580–1595, 2023.
- [62] M. Li, D. Kong, L. Meng, Z. Wang, Z. Bai, and G. Wu, "Discovery of novel SS-31 (d-Arg-dimethylTyr-Lys-Phe-NH₂) derivatives as potent agents to ameliorate inflammation and increase mitochondrial ATP synthesis," *RSC Adv.*, vol. 14, no. 41, pp. 29789–29799, 2024.
- [63] Q. Jiang *et al.*, "Mitochondria-targeted antioxidants: a step towards disease treatment," *Oxid. Med. Cell. Longev.*, vol. 2020, no. 1, p. 8837893, 2020.
- [64] A.-H. S. Wadan *et al.*, "Mitochondrial-based therapies for neurodegenerative diseases: a review of the current literature," *Naunyn. Schmiedeberg's Arch. Pharmacol.*, vol. 398, no. 9, pp. 11357–11386, Sep. 2025, doi: 10.1007/s00210-025-04014-0.
- [65] M. Kyriazis, "Hormesis and adaptive responses: intermittent fasting-induced stress resistance and disease resilience," in *The Potential of Intermittent Fasting in Age-related Diseases and Precision Anti-aging Therapeutics*, Elsevier, 2026, pp. 213–227.
- [66] M. Bevere *et al.*, "Redox-based disruption of cellular hormesis and promotion of degenerative pathways: perspectives on aging processes," *J. Gerontol. Ser. A*, vol. 77, no. 11, pp. 2195–2206, 2022.
- [67] M. M. Mehdi, P. Solanki, and P. Singh, "Oxidative stress, antioxidants, hormesis and calorie restriction: The current perspective in the biology of aging," *Arch. Gerontol. Geriatr.*, vol. 95, p. 104413, Jul. 2021, doi: 10.1016/j.archger.2021.104413.
- [68] R. A. Linker and A. Haghikia, "Dimethyl fumarate in multiple sclerosis: latest developments, evidence and place in therapy," *Ther. Adv. Chronic Dis.*, vol. 7, no. 4, pp. 198–207, 2016.
- [69] M. Colom-Cadena *et al.*, "The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease," *Alzheimers Res. Ther.*, vol. 12, no. 1, p. 21, 2020.
- [70] B. Dejanovic, M. Sheng, and J. E. Hanson, "Targeting synapse function and loss for treatment of neurodegenerative diseases," *Nat. Rev. Drug Discov.*, vol. 23, no. 1, pp. 23–42, 2024.
- [71] C. F. Manful, E. Fordjour, D. Subramaniam, A. A. Sey, Lord Abbey, and R. Thomas, "Antioxidants and reactive oxygen species: shaping human health and disease outcomes," *Int. J. Mol. Sci.*, vol. 26, no. 15, p. 7520, 2025.
- [72] G. Velikic *et al.*, "Neurodegeneration as Ecosystem Failure: A New Paradigm for Prevention and Treatment," *Int. J. Mol. Sci.*, vol. 26, no. 22, p. 11207, Nov. 2025, doi: 10.3390/ijms262211207.
- [73] S. K. Niazi, "Non-Invasive Drug Delivery across the Blood–Brain Barrier: A Prospective Analysis," *Pharmaceutics*, vol. 15, no. 11, p. 2599, Nov. 2023, doi: 10.3390/pharmaceutics15112599.
- [74] R. Vargas *et al.*, "Advancing through the blood-brain barrier: mechanisms, challenges and drug delivery strategies," *Admet Dmpk*, vol. 13, no. 5, p. 2988, 2025, doi: 10.5599/admet.2988.
- [75] I. Pérez-Torres, V. Guarner-Lans, and M. E. Rubio-Ruiz, "Reductive Stress in Inflammation-Associated Diseases and the Pro-Oxidant Effect of Antioxidant Agents," *Int. J. Mol. Sci.*, vol. 18, no. 10, p. 2098, Oct. 2017, doi: 10.3390/ijms18102098.
- [76] M. Şerban, C. Toader, and R.-A. Covache-Busuioc, "The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration," *Int. J. Mol. Sci.*, vol. 26, no. 15, p. 7498, Aug. 2025, doi: 10.3390/ijms26157498.
- [77] W. Zhang, D. Xiao, Q. Mao, and H. Xia, "Role of neuroinflammation in neurodegeneration development," *Signal Transduct. Target. Ther.*, vol. 8, no. 1, p. 267, Jul. 2023, doi: 10.1038/s41392-023-01486-5.
- [78] Z. M. Hein *et al.*, "Toward a Unified Framework in Molecular Neurobiology of Alzheimer's Disease: Revisiting the Pathophysiological Hypotheses," *Mol. Neurobiol.*, vol. 63, no. 1, p. 282, Jan. 2026, doi: 10.1007/s12035-025-05602-0.

PROOFREAD

Review Article

Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets

Meutia A. Faradilla¹, Karina S. Anastasya², Deasyka Yastani¹, Yohana Yohana¹, Endrico X. Tungka¹ and Suweino Suweino¹

¹Department of Biochemistry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia; ²Department of Nutrition, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

*Corresponding author: meutia.atika@trisakti.ac.id

Abstract

Aging is the primary risk factor for major neurodegenerative disorders, yet the precise molecular links between biological aging and progressive neuronal loss remain complex. Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, has emerged as a central converging mechanism driving both processes. This review aims to synthesize current evidence demonstrating how chronic redox imbalance drives cellular senescence and neuronal vulnerability through mitochondrial dysfunction, lipid peroxidation, and oxidative protein damage. These insights underscore how sustained oxidative insults promote the misfolding and aggregation of disease-defining proteins, including amyloid-beta in Alzheimer's disease and α -synuclein in Parkinson's disease, thereby amplifying neuroinflammation, synaptic dysfunction, and bioenergetic failure. Furthermore, antioxidant-based therapeutic strategies are critically reassessed, highlighting a paradigm shift from non-specific radical scavenging toward targeted modulation of endogenous defense systems, particularly NRF2 signaling and mitochondria-directed antioxidants. By integrating molecular mechanisms with translational perspectives, this review integrates molecular, cellular, and translational evidence to explain how oxidative stress links biological aging to neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

Keywords: Oxidative stress, aging, neurodegeneration, mitochondria, reactive oxygen species



Introduction

The unprecedented expansion of the elderly demographic worldwide has been paralleled by a dramatic rise in neurodegenerative disorders, most notably Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [1]. Although these conditions present with distinct clinical manifestations and hallmark protein signatures, they converge upon a common and arguably central risk factor that is biological aging [2]. Oxidative stress represents a fundamental biological process that becomes progressively dysregulated with aging, driving neuronal vulnerability and neurodegenerative disease progression. This observation suggests that the molecular processes governing senescence do not serve merely as a passive backdrop, but rather act as active drivers of neuronal vulnerability and decline. Within the network of aging-related mechanisms, oxidative stress functions as a central converging mechanism linking normal physiological aging to pathological neurodegeneration [3]. Rather than being a mere byproduct of metabolic activity, oxidative stress represents a failure of redox homeostasis, a state in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the capacity of cellular detoxification and repair systems [4]. Crucially, while basal ROS levels play indispensable roles in signal transduction and cellular adaptation, chronic elevations beyond physiological thresholds instigate cumulative structural damage to DNA, membrane lipids, and functional proteins [5].

Classical theories, such as Harman's Free Radical Theory of Aging [6], have historically attributed aging to the random accumulation of oxidative damage. However, contemporary research has refined this perspective to emphasize that oxidative stress disrupts regulated redox-sensitive signaling pathways, thereby destabilizing fundamental processes essential for neuronal survival [7]. The central nervous system is uniquely susceptible to this form of dysregulation. Although the brain constitutes only about 2% of total body mass, it consumes roughly 20% of basal oxygen, reflecting a metabolic intensity that predisposes it to disproportionate oxidative burden [8]. At the heart of this vulnerability lies the mitochondrion [9]. As the primary source of intracellular ROS generation, mitochondria are paradoxically both the generators and principal victims of oxidative insult. In the aging brain, progressive mitochondrial compromise precipitates a bioenergetic crisis, impairing neuronal capacity to sustain ionic gradients, neurotransmission, and synaptic plasticity. Moreover, damaged electron transport chains become leakier, generating excessive ROS that further tax dwindling antioxidant defenses [10].

This bioenergetic imbalance is intimately linked to the collapse of proteostasis, the constellation of cellular systems that govern protein folding, trafficking, and degradation. Oxidative modifications such as carbonylation and nitration render proteins prone to misfolding while simultaneously inhibiting the ubiquitin proteasome system and autophagy lysosomal pathways responsible for their clearance [11]. The resultant molecular gridlock fosters the accumulation of neurotoxic aggregates, including amyloid-beta in AD and alpha-synuclein in PD. In turn, these aggregates destabilize redox balance, creating a synergistic feedback loop in which protein aggregation exacerbates oxidative stress, and oxidative stress accelerates aggregation [12]. Although oxidative stress is widely recognized as a hallmark of biological aging and neurodegeneration, existing literature frequently addresses mitochondrial dysfunction, proteostatic failure, neuroinflammation, and redox signaling in isolation. This review addresses this gap by integrating molecular, cellular, and translational evidence to clarify how redox imbalance functions as a convergent driver of neuronal dysfunction and loss in Alzheimer's and Parkinson's diseases. The molecular sources of reactive oxygen species, age-related declines in antioxidant capacity, and the convergence of these processes on protein aggregation and neurodegeneration are synthesized. Finally, the limitations of broad-spectrum antioxidant strategies are discussed, and a conceptual shift toward targeted modulation of redox-sensitive pathways, rather than non-specific scavenging, is proposed.

Molecular mechanisms of oxidative stress

Global population aging has been accompanied by a marked increase in neurodegenerative diseases, including AD, PD, and ALS. Although these disorders are clinically distinct, they share biological aging as a common risk factor, indicating that age-related cellular processes actively

contribute to neuronal degeneration [13]. Among the molecular pathways involved, oxidative stress has emerged as a central converging mechanism linking physiological aging with neurodegenerative pathology [14]. Oxidative stress arises when the production of reactive oxygen and nitrogen species exceeds the capacity of cellular defense systems, leading to damage to DNA, lipids, and proteins. While low levels of reactive species are essential for normal cellular signaling, sustained elevations disrupt redox homeostasis and impair neuronal function [8]. The central nervous system is particularly susceptible to oxidative injury due to its high metabolic demand and disproportionate oxygen consumption, making oxidative stress a critical driver of age-related neurodegeneration [15].

Molecular origins of reactive species

ROS are primarily generated as metabolic byproducts of aerobic respiration, with the mitochondrial electron transport chain (ETC) serving as the principal intracellular source. During oxidative phosphorylation, electron leakage occurs most notably at Complex I (nicotinamide adenine dinucleotide reduced (NADH) dehydrogenase) and Complex III (ubiquinone–cytochrome c reductase). This leakage results in the partial reduction of molecular oxygen (O_2), forming the superoxide anion ($O_2^{\cdot-}$), as described by the reaction $O_2 + e^- \rightarrow O_2^{\cdot-}$ [16].

Superoxide is rapidly dismutated into the more stable hydrogen peroxide (H_2O_2), which can diffuse across cellular membranes and function as a signaling molecule. However, the pathogenic potential of oxidative stress markedly increases in the presence of transition metals. Through the Fenton reaction, hydrogen peroxide reacts with ferrous iron (Fe^{2+}) or cuprous copper (Cu^+), generating the highly reactive and destructive hydroxyl radical ($\cdot OH$): $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$ [17].

The oxidative burden within the brain is not exclusively of mitochondrial origin. Several enzymatic systems contribute significantly to intracellular ROS production, including the NADPH oxidase (NOX) family, peroxisomes, and cytochrome P450 enzymes. In the context of neurodegeneration, the activation of NOX enzymes in microglia is recognized as a major driver of neuroinflammation. This process creates a toxic synergy between oxidative stress and immune activation, amplifying neuronal damage and accelerating neurodegenerative progression [18].

Mitochondrial ROS generation

Mitochondria are central to cellular energy production through oxidative phosphorylation, but they are also the primary source of ROS. During oxidative phosphorylation, electrons are transferred through the mitochondrial electron transport chain, and some electrons leak at Complex I and Complex III. This leakage leads to the partial reduction of molecular oxygen, producing superoxide anions ($O_2^{\cdot-}$). These superoxides are then converted into hydrogen peroxide, which, in turn, can form hydroxyl radicals ($\cdot OH$) through Fenton reactions, further amplifying oxidative stress [19]. This ROS production becomes self-perpetuating in aging and neurodegenerative diseases, as damaged mitochondria generate more ROS, worsening mitochondrial dysfunction. This creates a vicious cycle where oxidative damage to cellular structures such as lipids, proteins, and DNA intensifies cellular dysfunction, accelerating the progression of diseases like AD and PD. Moreover, mitochondrial damage can reduce ATP production, impeding cellular functions and contributing to neuronal degeneration [5].

Lipid peroxidation and membrane vulnerability

Oxidative stress also leads to lipid peroxidation, a process in which ROS attack the polyunsaturated fatty acids in cellular membranes. Lipid peroxidation generates highly reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which can diffuse across the cells and interact with other cellular components [20]. These lipid peroxidation products disrupt the structural integrity of neuronal membranes, impairing the fluidity and function of the lipid bilayer [21]. This damage compromises membrane-bound proteins, receptors, and ion channels, leading to disturbances in cellular signaling, neurotransmission, and overall neuronal efficiency. In neurodegenerative diseases, this membrane vulnerability accelerates neuronal damage and contributes to synaptic dysfunction. For instance, in AD, lipid peroxidation can facilitate the aggregation of amyloid-beta, further exacerbating the pathological cycle [20]. The

lipid-rich membranes of neurons make them particularly susceptible to oxidative damage, reinforcing the progression of diseases like AD and PD [20].

Proteostasis collapse

Proteostasis is essential for maintaining cellular homeostasis by regulating protein synthesis, folding, and degradation. However, oxidative stress disrupts proteostasis, leading to the accumulation of damaged and misfolded proteins. ROS can induce oxidative modifications such as carbonylation and nitration on proteins, altering their structure and function [22]. These misfolded proteins are typically targeted for degradation by the proteasome or autophagy pathways. However, oxidative stress impairs these systems, leading to the accumulation of toxic protein aggregates [23]. In neurodegenerative diseases like AD and PD, this collapse of proteostasis is particularly detrimental. For example, in AD, amyloid-beta accumulates and forms plaques, while in PD, α -synuclein forms Lewy bodies. These protein aggregates not only disrupt cellular function but also impair synaptic plasticity, damage mitochondria, and promote neuroinflammation [23]. The accumulation of misfolded proteins creates a positive feedback loop that exacerbates oxidative stress, mitochondrial dysfunction, and cellular damage [22].

Redox inflammatory crosstalk

Oxidative stress and neuroinflammation are intimately connected, with ROS playing a crucial role in activating redox-sensitive transcription factors like nuclear factor kappa B (NF- κ B). NF- κ B, once activated by ROS, translocates to the nucleus and initiates the expression of proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α [24]. These cytokines activate microglia, the resident immune cells of the brain, which further increase ROS production and promote inflammation [25]. Chronic neuroinflammation exacerbates neuronal damage by impairing synaptic function, disrupting calcium homeostasis, and sensitizing neurons to excitotoxicity. This inflammatory response becomes self-perpetuating under conditions of sustained oxidative stress, where proinflammatory cytokines further exacerbate ROS production, leading to a cycle of oxidative injury and inflammation [24]. This crosstalk between oxidative stress and inflammation is a critical driver of neurodegenerative diseases like AD and PD, where inflammation amplifies the damage caused by ROS, leading to progressive neuronal death and dysfunction [24].

Autophagy and mitophagy failure

Autophagy and mitophagy are vital cellular processes for maintaining cellular integrity by degrading damaged proteins and organelles. In neurons, where turnover is limited due to the lack of cell division, the efficient functioning of autophagic pathways is critical for long-term survival. However, oxidative stress compromises the integrity of these pathways. ROS can damage the lysosomal system, which is responsible for the final stages of autophagic degradation, impairing its function [26]. As a result, damaged proteins and dysfunctional organelles accumulate within neurons, further exacerbating cellular stress. In particular, mitophagy, the selective removal of damaged mitochondria, is essential to protect cells from oxidative damage. However, oxidative stress impairs mitophagy by disrupting the PINK1/Parkin pathway, which is responsible for marking damaged mitochondria for degradation [27]. The failure to clear dysfunctional mitochondria allows them to persist and continue generating ROS, perpetuating mitochondrial dysfunction and oxidative stress. This accumulation of damaged mitochondria, often referred to as “zombie mitochondria,” further disrupts cellular function, leading to energy depletion and contributing to the neurodegenerative processes observed in diseases like PA [27].

Antioxidant defense

Enzymatic vanguard: The first line of redox control

The first layer of cellular antioxidant defense is formed by a tightly coordinated system of enzymatic antioxidants that operate in a sequential and highly regulated manner. Superoxide dismutases (SODs) act as primary responders by rapidly neutralizing superoxide radicals, which are predominantly produced through electron leakage from the mitochondrial respiratory chain [28]. Because superoxide is highly reactive and short-lived, its rapid conversion into hydrogen

peroxide constitutes a crucial protective mechanism rather than a simple chemical reaction. However, hydrogen peroxide occupies a dual role within neuronal physiology [29]. At low concentrations, it functions as a diffusible second messenger involved in synaptic plasticity and signal transduction. Yet, when allowed to accumulate, it becomes a latent threat, particularly in metal-rich neural environments where iron and copper are abundant. To prevent this transition from signaling molecule to cytotoxic precursor, downstream enzymes such as catalase (CAT) and glutathione peroxidase assume decisive roles [30], [31]. By decomposing hydrogen peroxide into water and molecular oxygen, these enzymes effectively terminate the oxidative cascade before it can culminate in hydroxyl radical formation, a species widely regarded as the most destructive ROS due to its indiscriminate reactivity [18]. This enzymatic cascade is not simply redundant; instead, it represents an evolutionarily refined system built to maintain redox stability under stress. When any component of this network is compromised, whether due to genetic variation, post-translational alterations, or age-related functional decline, the balance of redox control can be disrupted. As a result, neurons become particularly vulnerable to oxidative damage [32].

Non-enzymatic buffers and thiol-based redox modulation

Alongside enzymatic antioxidants, cells rely on a broad network of non-enzymatic redox buffers, with glutathione playing a central and indispensable role. As the most abundant intracellular thiol antioxidant, glutathione functions as a dynamic redox reservoir that buffers oxidative fluctuations beyond the capacity of enzymatic systems. By donating electrons, glutathione neutralizes reactive species and is converted into its oxidized form, glutathione disulfide. Consequently, the balance between reduced and oxidized glutathione (the ratio of glutathione to glutathione disulfide) serves as a sensitive marker of cellular redox status. In neurons, which possess limited tolerance to oxidative stress, even subtle changes in this ratio may indicate early metabolic strain [33]. Evidence consistently shows a gradual decline in glutathione levels, suggesting that neurodegeneration is preceded by a slow weakening of intrinsic redox buffering rather than an abrupt oxidative event [34]. Beyond direct antioxidant activity, glutathione supports detoxification processes and modulates redox-sensitive protein thiols, thereby influencing gene regulation, mitochondrial stability, and synaptic function [24]. Loss of glutathione therefore reflects not only diminished antioxidant protection but a broader breakdown in redox regulation [35].

Regulatory control and the NRF2 axis

The effectiveness of antioxidant defenses within the central nervous system is ultimately governed at the transcriptional level. Central to this regulation is the nuclear factor erythroid 2-related factor 2 (NRF2), a master regulator of cellular stress responses. Under basal conditions, NRF2 is sequestered in the cytoplasm; however, in the presence of oxidative stress, it translocates to the nucleus and initiates the expression of a broad repertoire of antioxidant and cytoprotective genes, including those encoding superoxide dismutases, glutathione peroxidase, catalase, and glutathione synthesis enzymes. In youthful and healthy neural tissue, this inducible system provides a remarkable degree of plasticity, enabling neurons to adapt rapidly to fluctuating redox demands [36]. With advancing age, however, the responsiveness of the NRF2 pathway becomes progressively attenuated. This decline does not necessarily reflect a complete loss of function, but rather a diminished sensitivity to oxidative cues. As a result, the antioxidant response becomes delayed or insufficient, allowing ROS production to outpace detoxification. This age-associated regulatory failure creates what can be described as a “redox vulnerability gap”, wherein neurons persist under conditions of chronic, low-grade oxidative stress. Over time, this imbalance promotes cumulative macromolecular damage, mitochondrial dysfunction, and inflammatory signaling hallmarks that converge to drive the initiation and progression of neurodegenerative disorders [37].

Oxidative stress in aging: Molecular mechanism of senescence

The modified free radical theory of aging

Harman's Free Radical Theory of Aging, introduced in 1956, initially proposed that aging results from the gradual accumulation of oxidative damage to essential biomolecules caused by ROS [38]. While this concept laid the foundation for modern aging research, it has since evolved beyond the idea of random and irreversible molecular injury [39]. Current perspectives recognize ROS not only as damaging agents but also as critical regulators of physiological redox signaling. In young and healthy cells, redox balance is tightly controlled [40]. However, this regulatory capacity declines with age, leading to a state of chronic, low-grade oxidative stress. This persistent redox imbalance subtly disrupts cellular signaling pathways and promotes a pro-inflammatory milieu, commonly referred to as inflammaging. In this framework, oxidative stress contributes to aging not merely through direct macromolecular damage, but by driving immune dysregulation and sustained inflammatory signaling. The modified Free Radical Theory therefore reframes aging as a systemic failure of redox homeostasis, in which oxidative stress and inflammation interact to accelerate functional decline [41].

Accumulation of macromolecular damage in the aging brain

The aging brain is particularly susceptible to oxidative damage due to its high oxygen consumption, lipid-rich composition, and limited regenerative capacity. Over time, an imbalance between ROS production and antioxidant defenses leads to the gradual accumulation of damage to lipids, proteins, and nucleic acids, ultimately compromising neuronal structure and function [42]. Lipid peroxidation represents an early and amplifying form of oxidative injury in neurons. Neuronal membranes are rich in polyunsaturated fatty acids, which are highly vulnerable to oxidative attack. This process generates reactive secondary products such as 4-hydroxynonenal and malondialdehyde, which persist longer than primary radicals and diffuse across cellular compartments. These byproducts disrupt membrane integrity, impair receptor signaling, and interfere with synaptic transmission, thereby reducing neuronal efficiency [43].

Proteins are also major targets of oxidative stress. Oxidative modifications promote protein misfolding and aggregation, a process that is especially harmful in post-mitotic neurons. With aging, the efficiency of proteostatic systems, including the ubiquitin–proteasome pathway and autophagy, progressively declines. As a result, damaged proteins accumulate and form insoluble aggregates that disrupt intracellular transport and synaptic maintenance, further exacerbating cellular stress [22]. Oxidative damage to DNA, particularly mitochondrial DNA, adds another layer of vulnerability. Located near the electron transport chain and lacking robust protective and repair mechanisms, mitochondrial DNA is highly prone to oxidative lesions such as 8-hydroxy-2'-deoxyguanosine. These mutations impair mitochondrial gene expression and energy production, increasing electron leakage and ROS generation. This establishes a self-perpetuating cycle in which oxidative damage and mitochondrial dysfunction reinforce one another, accelerating neuronal aging and degeneration [44].

Oxidative stress in neurodegenerative diseases

Alzheimer's disease (AD): Oxidative stress as a self-reinforcing pathological loop

In AD, oxidative stress is no longer viewed as a secondary consequence of neuronal damage but rather as a central driver of disease progression. It operates through interconnected, self-reinforcing loops that involve amyloid-beta accumulation, mitochondrial dysfunction, and Tau pathology (**Figure 1**). Soluble amyloid-beta oligomers have redox-active properties and readily interact with neuronal membranes and redox-active metals such as iron and copper, triggering localized production of ROS [13]. This pro-oxidative microenvironment damages surrounding cellular components while simultaneously promoting further amyloid-beta aggregation, creating a bidirectional interaction between amyloid pathology and oxidative stress that contributes to early synaptic impairment [45]. As shown in **Figure 1**, the pathological process begins with the accumulation of amyloid-beta within neuronal mitochondria, which further intensifies oxidative injury by disrupting the electron transport chain, particularly cytochrome c oxidase, resulting in reduced ATP synthesis and increased electron leakage. These changes enhance mitochondrial ROS generation, induce mitochondrial DNA damage, and progressively compromise cellular

energy balance [10]. In parallel, oxidative stress modulates Tau pathology by activating stress-responsive kinases that promote Tau hyperphosphorylation, leading to microtubule destabilization and impaired axonal transport [1]. Aggregated Tau subsequently worsens mitochondrial dysfunction and oxidative imbalance. Together, these interdependent mechanisms place oxidative stress at the center of a pathological network that links amyloid toxicity, bioenergetic failure, and cytoskeletal disruption in AD [46].

Parkinson's disease (PA): Selective vulnerability to oxidative stress

PA illustrates how intrinsic metabolic characteristics render specific neuronal populations highly vulnerable to oxidative stress. Degeneration of dopaminergic neurons in the substantia nigra pars compacta arises from the convergence of dopamine metabolism, mitochondrial dysfunction, and impaired antioxidant defenses. Dopamine itself contributes to oxidative burden through enzymatic degradation by monoamine oxidase B, which generates hydrogen peroxide, as well as through spontaneous auto-oxidation that produces reactive quinones capable of damaging proteins and mitochondrial enzymes. This persistent oxidative environment selectively stresses dopaminergic neurons [47].

As shown in **Figure 2**, the pathological process of PA begins with mitochondrial dysfunction, which further amplifies oxidative injury. Genes implicated in familial PD, including PINK1, Parkin, and DJ-1, play critical roles in mitochondrial quality control and redox regulation. Under normal conditions, damaged mitochondria are removed via PINK1–Parkin-mediated mitophagy, limiting excessive reactive oxygen species production. Disruption of this system allows dysfunctional, ROS-generating mitochondria to accumulate, intensifying oxidative stress [48]. Loss of DJ-1-mediated redox sensing further reduces neuronal resilience. Together, these mechanisms establish a self-reinforcing cycle in which oxidative stress and mitochondrial failure drive selective dopaminergic neurodegeneration in PD [36].

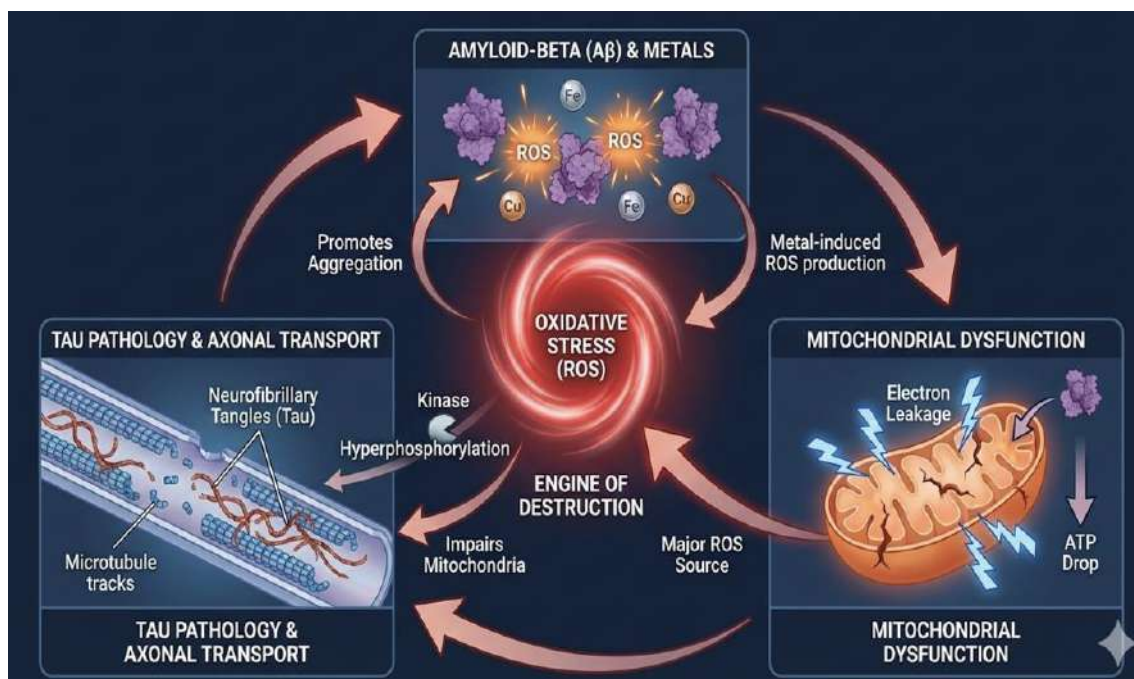


Figure 1. Key mechanisms of oxidative stress and neuronal damage in Alzheimer's disease (AD) pathology. Self-reinforcing cycle of oxidative stress and mitochondrial dysfunction, illustrating the roles of amyloid-beta, metals, tau pathology, and mitochondrial dysfunction in AD. The figure is generated using BioRender.

Self-perpetuating cycle of ROS and inflammation

Once neuroinflammation is established, it further amplifies oxidative stress through the activation of enzymatic sources of reactive oxygen species. Proinflammatory cytokines promote the activation of microglial NADPH oxidase 2 (NOX2), an enzyme complex specifically dedicated

to regulated ROS generation. Unlike mitochondrial ROS, which are produced as byproducts of cellular metabolism, NOX2-derived ROS are intentionally generated as part of immune signaling. Under conditions of sustained activation, however, this response becomes maladaptive. Elevated ROS levels inflict additional damage on neuronal membranes, proteins, and mitochondria, leading to the release of danger-associated molecular patterns that further stimulate microglial activation [54]. This feedback loop establishes a self-perpetuating cycle in which oxidative stress and inflammation reinforce one another, progressively spreading neuronal injury and contributing to the chronic and progressive nature of neurodegenerative disorders [54].

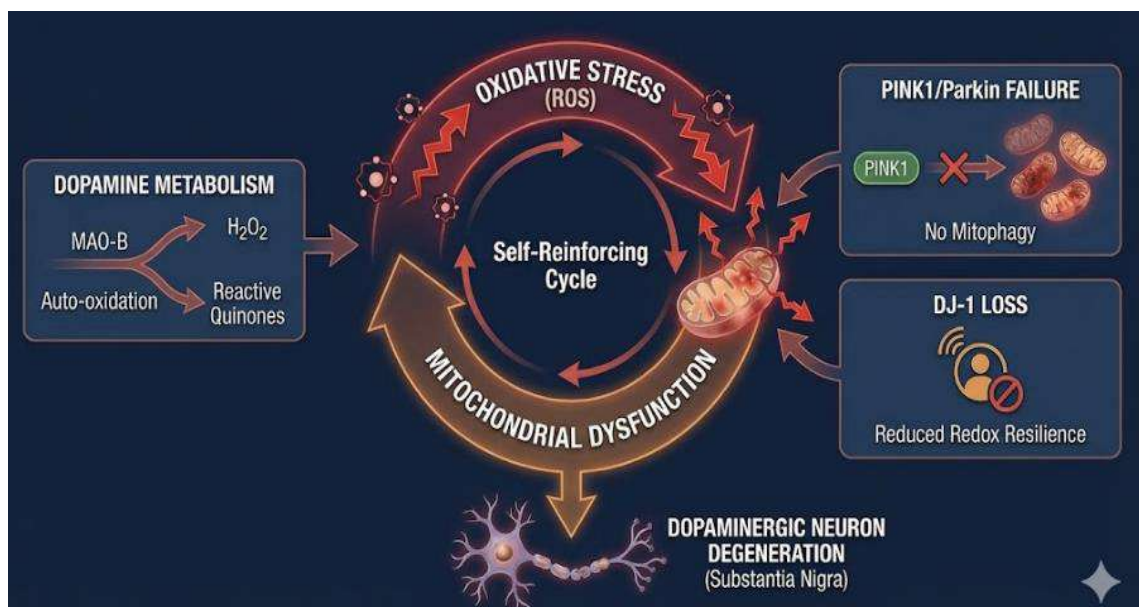


Figure 2. Key mechanisms of oxidative stress and mitochondrial impairment in Parkinson's disease (PD) pathology. The self-reinforcing cycle of oxidative stress and mitochondrial dysfunction in PD, illustrating how dopamine metabolism, PINK1/Parkin failure, and DJ-1 loss contribute to dopaminergic neuron degeneration in the substantia nigra. The figure is generated using BioRender.

Autophagy and mitophagy failure: Breakdown of cellular quality control

While inflammation accelerates extracellular and intercellular damage, oxidative stress simultaneously undermines the intracellular systems responsible for maintaining neuronal integrity. Autophagy, the primary pathway for degrading aggregated proteins and dysfunctional organelles, is particularly vulnerable to redox dysregulation. In post-mitotic cells such as neurons, where damaged components cannot be diluted through cell division, the integrity of autophagic flux is essential for long-term survival [55].

Lysosomal dysfunction and autophagic arrest

Effective autophagy depends on intact lysosomal function. However, oxidative stress generates lipid peroxidation products such as 4-hydroxynonenal that covalently modify lysosomal membranes and hydrolytic enzymes. These modifications compromise lysosomal acidity and enzymatic efficiency, impairing the final stages of autophagic degradation. As autophagic flux slows, damaged proteins and organelles accumulate within neurons, placing additional stress on already compromised cellular systems. This accumulation not only disrupts intracellular trafficking and synaptic maintenance but also amplifies oxidative stress by allowing ROS-generating structures to persist. Thus, lysosomal dysfunction represents a critical bottleneck where oxidative damage translates into widespread cellular failure [27].

Mitophagy failure and energetic collapse

Among autophagic processes, the selective removal of damaged mitochondria is known as mitophagy. It is of particular importance in neurodegeneration. Mitochondria are both the primary producers and principal targets of ROS. Under normal conditions, the PINK1/Parkin

pathway identifies dysfunctional mitochondria and targets them for autophagic clearance, preventing excessive ROS leakage [3]. Oxidative stress, however, disrupts this quality-control system. Damage to PINK1/Parkin signaling impairs mitochondrial tagging and clearance, allowing dysfunctional mitochondria to accumulate. These organelles, often described as “zombie mitochondria,” remain metabolically active enough to generate ROS but fail to produce adequate ATP. The persistence of such mitochondria exacerbates oxidative stress while simultaneously precipitating cellular energy failure [56]. As ATP levels decline, energy-dependent processes, including ion homeostasis, axonal transport, and synaptic transmission, become unsustainable. Ultimately, this convergence of oxidative damage, autophagy impairment, and bioenergetic collapse pushes neurons toward apoptotic or necrotic death [57]. The central roles of oxidative stress in neurodegenerative diseases such as AD and PD are illustrated in **Figure 3**. It highlights key mechanisms, including mitochondrial ROS generation, proteostasis collapse, neuroinflammation, and defective autophagy, all contributing to cellular damage. **Figure 3** also shows how oxidative stress promotes synaptic dysfunction and cognitive decline by driving the accumulation of toxic proteins like amyloid-beta and tau in AD and neuronal loss in PD. Additionally, it emphasizes therapeutic targets, such as NRF2 activators (e.g., dimethyl fumarate), mitochondria-targeted antioxidants (e.g., MitoQ), and proteostasis and autophagy enhancers (e.g., rapamycin, SS-31, Urolithin A), which aim to mitigate oxidative damage and restore cellular function.

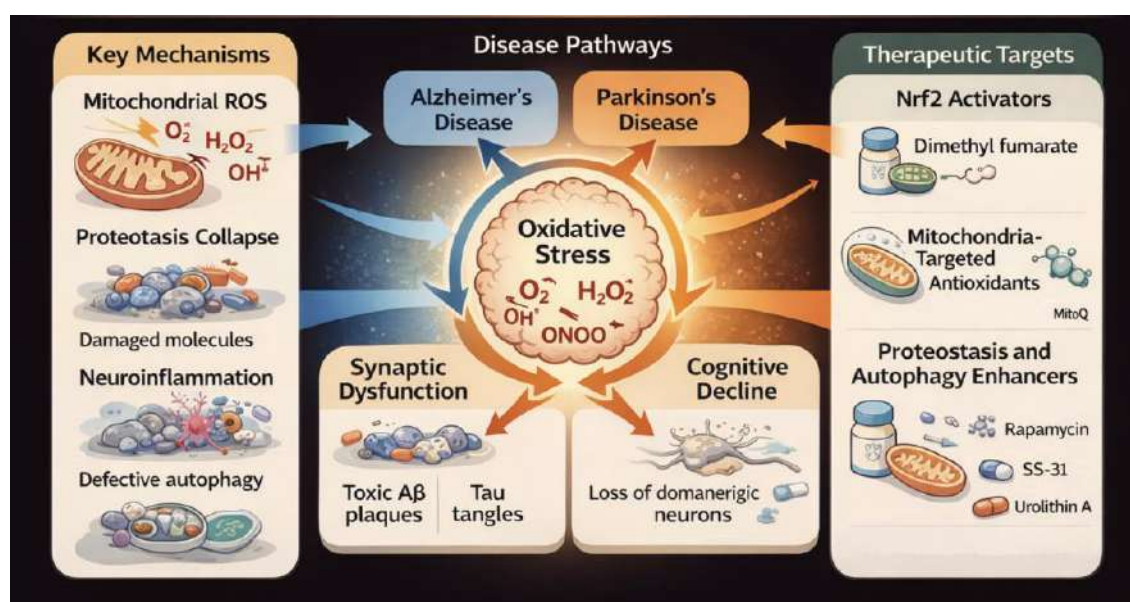


Figure 3. Schematic overview illustrating the continuum from the molecular origins of reactive oxygen species (ROS) through cellular damage—encompassing mitochondrial dysfunction and neuroinflammation—to clinical manifestations of neurodegenerative disorders, including Alzheimer’s disease and Parkinson’s disease. The figure also highlights the emerging shift toward precision medicine and targeted therapeutic strategies. The illustration was created using BioRender.

Therapeutic targets and clinical implications

The recognition of oxidative stress as a central driver of neurodegeneration has naturally positioned antioxidant-based strategies as attractive therapeutic candidates. However, decades of clinical experience have revealed the limitations of simplistic antioxidant supplementation. The emerging consensus is that effective intervention requires a shift away from indiscriminate radical scavenging toward targeted modulation of endogenous defense pathways, mitochondrial resilience, and adaptive stress responses. In this context, oxidative stress is no longer viewed merely as a pathological burden to be neutralized, but as a dysregulated signaling state that must be recalibrated [31].

NRF2 pathway activation: Reinforcing endogenous redox resilience

NRF2 serves as a central regulator of cellular antioxidant defense by coordinating a broad transcriptional program that maintains redox homeostasis and cytoprotection. Under physiological conditions, NRF2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (KEAP1) and targeted for proteasomal degradation [37]. Oxidative or electrophilic stress modifies key cysteine residues on KEAP1, allowing NRF2 to escape degradation and translocate into the nucleus. There, NRF2 binds antioxidant response elements and induces the expression of genes involved in antioxidant defense and detoxification, including heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and enzymes regulating glutathione metabolism. Rather than simply scavenging reactive oxygen species, NRF2 activation enhances intrinsic redox resilience by strengthening the cell's capacity to respond to future oxidative challenges [36]. While NRF2 activation is beneficial in protecting against oxidative stress, chronic activation can have limitations. Continuous NRF2 activation may inadvertently promote tumorigenesis by aiding the survival of damaged cells, which may facilitate cancer progression. The activation of the pathway in non-cancerous tissues should, therefore, be carefully regulated. In terms of activating NRF2, activators can be classified into two primary categories, which include electrophilic and non-electrophilic types. Electrophilic activators, such as sulforaphane, directly modify KEAP1, leading to the activation of NRF2 [57]. However, these compounds can cause unintended damage due to their reactivity, potentially affecting cellular structures beyond their target. On the other hand, non-electrophilic activators, such as bardoxolone methyl, activate NRF2 without directly altering KEAP1, which offers a safer profile with fewer side effects but may have lower potency[37].

Conventional antioxidants have shown limited efficacy in neurodegenerative

Conventional antioxidant therapies have demonstrated limited benefit in neurodegenerative diseases, largely because they fail to adequately target mitochondria, the main intracellular source of neuronal ROS. This shortcoming has driven the development of mitochondria-targeted antioxidants that preferentially accumulate within the mitochondrial matrix by utilizing the mitochondrial membrane potential. MitoQ, for example, couples a ubiquinone moiety to a triphenylphosphonium cation, enabling direct scavenging of mitochondrial ROS and protection of mitochondrial lipids, proteins, and DNA. Similarly, elamipretide (SS-31) exerts its effects by stabilizing cardiolipin in the inner mitochondrial membrane, thereby preserving electron transport efficiency and limiting ROS production at its origin. Collectively, these strategies reflect a paradigm shift from broad-spectrum antioxidant use toward targeted modulation of mitochondrial redox homeostasis [58]. Comparison of mitochondria-targeted antioxidants MitoQ and SS-31 is summarized in Table 1 [25], [59], [60], [61], [62], [63], [64].

Table 1. Comparative summary of mitochondria-targeted antioxidants MitoQ and SS-31

Feature	Mitoquinone mesylate (MitoQ)	Elamipretide (SS-31)
Primary mechanism	Electrophoretic accumulation driven by mitochondrial membrane potential.	Potential-independent uptake; targets and stabilizes cardiolipin in the inner membrane.
Antioxidant action	Redox-active ubiquinone moiety directly scavenges radicals and is regenerated by Complex II.	Structural stabilization of cristae/supercomplexes to prevent electron leakage and ROS formation.
Physical impact	It can cause mitochondrial swelling and depolarization at high concentrations due to its alkyl chain.	Acts as "mitochondrial armor," protecting against membrane fragmentation and structural decay.
Preclinical evidence	Robust protection in Alzheimer's, Parkinson's, and Huntington's disease models.	Consistent success in Alzheimer's, Parkinson's, Huntington's disease, and brain injury models, improving dynamics and synaptic health.
Clinical status	Failed PD trials (no clinical effect on UPDRS). Currently used as a dietary supplement for vascular health.	FDA approved (Sept 2025) for Barth syndrome. Failed trials in heart failure and primary mitochondrial myopathy.

Lifestyle interventions and hormetic redox adaptation

Lifestyle interventions, such as physical exercise and caloric restriction, activate endogenous antioxidant defenses through a process known as hormesis. Hormesis refers to the phenomenon where low-level, transient oxidative stress triggers adaptive protective responses within cells.

When applied in moderation, physical exercise and mild caloric restriction induce controlled oxidative stress that enhances cellular resilience [65]. These interventions improve mitochondrial efficiency by promoting better ATP production and reducing the production of excess ROS, stimulate autophagy for the clearance of damaged proteins and organelles, and upregulate antioxidant signaling pathways such as the Nrf2 pathway, which enhances the cell's ability to combat oxidative damage. Additionally, they boost the secretion of neurotrophic factors like brain-derived neurotrophic factor (BDNF), which support neuronal growth, survival, and synaptic plasticity, playing a crucial role in brain health [66].

However, it is important to note that the beneficial effects of hormesis are dose-dependent. When physical exercise or caloric restriction exceeds a certain threshold, it can shift from an adaptive to a maladaptive stress response. Prolonged or excessive exercise, for example, can lead to chronic oxidative stress, resulting in mitochondrial dysfunction, muscle damage, and an increase in inflammatory markers. Similarly, prolonged caloric restriction may impair cellular homeostasis, weaken the immune system, and exacerbate metabolic dysfunction. These maladaptive responses may overwhelm the body's protective mechanisms, leading to cellular damage rather than the intended health benefits. Therefore, while moderate exercise and caloric restriction can enhance redox balance and improve health outcomes, extreme or prolonged levels of these stressors may cause harm, highlighting the importance of balance in these lifestyle interventions [67].

Therapeutic potential and clinical translation

Pharmacological activation of NRF2 has therefore emerged as a promising therapeutic strategy in neurodegenerative disorders. Dimethyl fumarate, an approved treatment for multiple sclerosis, represents a clinically validated example of this approach [68]. By inducing mild electrophilic stress, it activates NRF2 signaling and confers neuroprotective and anti-inflammatory effects. Beyond fumarates, synthetic triterpenoids and other NRF2 activators are under investigation for their ability to restore redox homeostasis in aging and neurodegeneration. Nevertheless, clinical translation requires careful calibration. Chronic or excessive NRF2 activation may disrupt physiological redox signaling or promote maladaptive metabolic states. Thus, the therapeutic challenge lies not in maximal activation, but in restoring dynamic responsiveness to oxidative stress [36].

Challenges and future directions

Despite an increasingly robust molecular framework linking oxidative stress to neurodegenerative disease, clinical translation of antioxidant-based therapies in AD and PD has been largely underwhelming. Numerous trials, particularly those relying on conventional antioxidant supplementation, have failed to demonstrate consistent or meaningful clinical benefit. This disconnect between compelling preclinical data and disappointing clinical outcomes highlights a critical “translational gap” that extends beyond simple issues of drug efficacy. Rather than invalidating the role of oxidative stress in neurodegeneration, these failures underscore the complexity of redox biology in the human brain and reveal fundamental limitations in how antioxidant strategies have been conceptualized and implemented.

Table 2. Comparative summary between mechanisms of oxidative stress, their roles in Alzheimer's disease (AD) vs. Parkinson's disease (PD) and potential therapeutic interventions [1], [1], [1], [3], [3], [13], [21], [27], [31], [31], [37], [47], [47], [48], [49], [51], [51]

Mechanisms of oxidative stress	Role in Alzheimer's disease (AD)	Role in Parkinson's disease (PD)	Potential therapeutic interventions
Mitochondrial dysfunction	Mitochondrial dysfunction leads to bioenergetic failure, impairing synaptic plasticity and contributing to neuronal damage.	Mitochondrial dysfunction in dopaminergic neurons accelerates ROS production and contributes to neuronal loss.	Mitochondria-targeted antioxidants (e.g., MitoQ, SS31) that help reduce ROS and restore mitochondrial function.
Lipid peroxidation	Oxidative damage to membrane lipids leads to	Lipid peroxidation exacerbates dopaminergic	Use of lipid antioxidants like

	neuronal damage and loss of synaptic function.	neuron death and disrupts membrane integrity.	alpha-lipoic acid or other peroxy scavengers to prevent oxidative damage.
Proteostasis collapse	Proteostasis collapse contributes to the accumulation of amyloid-beta and tau, which disrupt neuronal function.	Accumulation of misfolded proteins, such as α -synuclein, leads to dopaminergic dysfunction.	Proteostasis regulators, such as proteasome activators or autophagy enhancers (e.g., rapamycin, spermidine).
Neuroinflammation	Chronic neuroinflammation amplifies the amyloid plaque formation and accelerates disease progression.	Neuroinflammation in microglia worsens dopaminergic neuron death and amplifies ROS production.	Anti-inflammatory agents targeting NF- κ B or microglial activation (e.g., minocycline, curcumin).
Redox-Imbalance (ROS and RNS)	ROS accumulation damages cellular structures (DNA, lipids, proteins) and triggers apoptosis.	ROS generation through dopamine metabolism leads to neuronal damage and contributes to cell death.	Nrf2 activators (e.g., dimethyl fumarate), which boost cellular antioxidant defences and help restore redox homeostasis.
Autophagy and mitophagy failure	Impaired autophagy leads to the accumulation of damaged proteins, exacerbating neurodegeneration.	Deficient mitophagy results in the accumulation of dysfunctional mitochondria, contributing to neurodegeneration.	Autophagy enhancers (e.g., rapamycin) and mitophagy activators (e.g., Urolithin A, PINK1 activators) to clear damaged organelles.

Temporal mismatch: Treating too late in the disease course

One of the most significant challenges lies in the timing of therapeutic intervention. Neurodegenerative diseases are characterized by long preclinical phases, during which molecular and cellular damage accumulates silently over years or even decades. By the time clinical symptoms emerge and patients are enrolled in trials, substantial neuronal loss and synaptic disintegration have already occurred [69], [70]. At this advanced stage, oxidative stress is no longer a primary driver but rather a downstream consequence of irreversible structural damage. Antioxidant therapy administered under these conditions is therefore unlikely to restore lost neurons or reverse established network failure [71]. This temporal mismatch suggests that antioxidant interventions may be more effective as preventive or early-stage strategies, rather than as treatments for symptomatic disease. Future clinical trials must therefore prioritize early diagnosis and intervention, potentially targeting individuals with prodromal disease or those identified as high-risk based on genetic, metabolic, or biomarker profiles [72].

Bioavailability and blood-brain barrier limitations

Another major obstacle is the limited bioavailability of many antioxidant compounds within the central nervous system. The blood-brain barrier, while essential for protecting neural tissue, poses a formidable challenge for drug delivery. Many antioxidants exhibit poor lipophilicity, rapid systemic clearance, or extensive peripheral metabolism, resulting in insufficient concentrations reaching neuronal targets [73]. Even when compounds successfully cross the blood-brain barrier, their intracellular distribution is often non-specific, failing to reach subcellular compartments such as mitochondria, where oxidative stress is most pronounced. This pharmacokinetic mismatch further diminishes therapeutic efficacy and helps explain the failure of broad-spectrum antioxidants in clinical trials. Advances in drug delivery, such as nanoparticle-based carriers, mitochondria-targeted molecules, and ligand-mediated transport systems, represent promising avenues for overcoming these limitations. However, their clinical translation will require rigorous evaluation of safety, specificity, and long-term effects [74].

Paradox of reductive stress

A less intuitive, yet increasingly recognized challenge is the phenomenon of reductive stress. While oxidative stress reflects an excess of reactive species, excessive antioxidant

supplementation can shift the redox balance in the opposite direction, suppressing physiological ROS signaling. ROS are not inherently pathological; at controlled levels, they play essential roles in synaptic plasticity, immune defense, and cellular adaptation. Overzealous scavenging of ROS can therefore impair normal signaling pathways, disrupt mitochondrial function, and paradoxically exacerbate cellular dysfunction [23]. This concept challenges the simplistic view that “more antioxidants are better” and highlights the need for precision in redox modulation. Therapeutic strategies must aim to restore redox homeostasis rather than eliminate ROS indiscriminately. This requires a nuanced understanding of individual redox states and the context-dependent roles of oxidative signaling in health and disease [75].

Need for redox biomarkers and patient stratification

Perhaps the most critical gap in current clinical approaches is the lack of reliable biomarkers to assess oxidative status in vivo. Neurodegenerative diseases are heterogeneous, and not all patients exhibit the same degree or pattern of redox dysregulation. Without biomarkers to stratify patients, antioxidant therapies are applied indiscriminately, diluting potential benefits within responsive subgroups. Future research must therefore focus on developing and validating biomarkers that reflect systemic and brain-specific oxidative stress, antioxidant capacity, and mitochondrial function. These may include circulating redox markers, imaging-based indicators of oxidative metabolism, or genetic and epigenetic signatures linked to redox regulation. Such biomarkers would enable precision medicine approaches, identifying individuals most likely to benefit from antioxidant or redox-modulating interventions and allowing therapies to be tailored in terms of timing, dosage, and mechanism [76].

Toward a systems-level therapeutic strategy

Looking forward, the field must move beyond reductionist strategies that target oxidative stress in isolation. Neurodegeneration arises from the convergence of redox imbalance, mitochondrial dysfunction, neuroinflammation, impaired autophagy, and synaptic failure. Effective therapies will likely need to engage multiple nodes within this network, either through combination treatments or through interventions that restore upstream regulatory control, such as Nrf2 signaling or mitochondrial quality control pathways [77]. In this context, antioxidant therapy should be reframed not as a standalone solution, but as one component of an integrated disease-modifying strategy. Bridging the translational gap will require early intervention, targeted delivery, biomarker-guided patient selection, and a deeper appreciation of redox biology as a dynamic and context-dependent system [78].

Conclusion

This review demonstrates that oxidative stress serves as a central, unifying mechanism linking biological aging to neurodegenerative disorders. Through sustained redox imbalance, ROS drive mitochondrial dysfunction, proteostatic failure, neuroinflammation, and impaired autophagy, collectively undermining neuronal integrity. The limited success of conventional antioxidants highlights the need for targeted redox modulation rather than indiscriminate radical scavenging. Strategies that enhance endogenous defenses, restore mitochondrial quality control, and activate adaptive pathways such as Nrf2 offer promising avenues for delaying neurodegenerative progression and extending neural healthspan.

Acknowledgments

The authors gratefully acknowledge the Department of Biochemistry, Faculty of Medicine, Trisakti University, for its continuous academic support and supportive environment during the development of this review. We also sincerely thank the researchers and scholars whose work has contributed to the advancement of knowledge in the field of oxidative stress, aging, and neurodegeneration. Their contributions provided essential scientific insights that informed and strengthened this manuscript.

Competing interests

All authors declare that there are no conflicts of interest related to this work.

Funding

This study received no external funding.

Underlying data

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of artificial intelligence use

This study employed the artificial intelligence (AI) tools Gemini Pro and ChatGPT to support manuscript writing, including language refinement (improving grammar, sentence structure, and overall readability) and technical writing assistance (providing suggestions for structuring complex technical descriptions more effectively). All AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were made solely by the authors.

How to cite

Faradilla MA, Anastasya KS, Yastani D, *et al.* Oxidative stress as a converging mechanism of aging and neurodegeneration: From molecular pathways to therapeutic targets. *Narra J* 2026; 6 (1): e3042 - [http://doi.org/10.52225/narra.v6i1.\[X\]](http://doi.org/10.52225/narra.v6i1.[X]).

References

- [1] A. Rostagno and J. Ghiso, "Alzheimer's Disease Pathogenic Mechanisms: Linking Redox Homeostasis and Mitochondria-Associated Metabolic Pathways Through Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)," *Antioxidants*, vol. 14, no. 7, p. 812, Jul. 2025, doi: 10.3390/antiox14070812.
- [2] R. Tenchov, J. M. Sasso, X. Wang, and Q. A. Zhou, "Aging hallmarks and progression and age-related diseases: a landscape view of research advancement," *ACS Chem. Neurosci.*, vol. 15, no. 1, pp. 1–30, 2023.
- [3] E. Spina *et al.*, "Mitochondrial Alterations, Oxidative Stress, and Therapeutic Implications in Alzheimer's Disease: A Narrative Review," *Cells*, vol. 14, no. 3, p. 229, Feb. 2025, doi: 10.3390/cells14030229.
- [4] M.-C. Jurcau, A. Jurcau, and R.-G. Diaconu, "Oxidative Stress in the Pathogenesis of Neurodegenerative Diseases," *Stresses*, vol. 4, no. 4, pp. 827–849, Dec. 2024, doi: 10.3390/stresses4040055.
- [5] X. Xu, Y. Pang, and X. Fan, "Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 190, Jun. 2025, doi: 10.1038/s41392-025-02253-4.
- [6] D. Harman, "Free radical theory of aging," *Mutat. Res.*, vol. 275, no. 3–6, pp. 257–266, 1992.
- [7] D. Harman, "Free Radical Theory of Aging: An Update: Increasing the Functional Life Span," *Ann. N. Y. Acad. Sci.*, vol. 1067, no. 1, pp. 10–21, May 2006, doi: 10.1196/annals.1354.003.
- [8] M. E. Watts, R. Pocock, and C. Claudianos, "Brain energy and oxygen metabolism: emerging role in normal function and disease," *Front. Mol. Neurosci.*, vol. 11, p. 216, 2018.
- [9] K. Tripathi and D. Ben-Shachar, "Mitochondria in the Central Nervous System in Health and Disease: The Puzzle of the Therapeutic Potential of Mitochondrial Transplantation," *Cells*, vol. 13, no. 5, p. 410, Feb. 2024, doi: 10.3390/cells13050410.
- [10] R. Stefanatos and A. Sanz, "The role of mitochondrial ROS in the aging brain," *FEBS Lett.*, vol. 592, no. 5, pp. 743–758, Mar. 2018, doi: 10.1002/1873-3468.12902.
- [11] O. F. Kuzu, L. J. T. Granerud, and F. Saatcioglu, "Navigating the landscape of protein folding and proteostasis: from molecular chaperones to therapeutic innovations," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 358, Oct. 2025, doi: 10.1038/s41392-025-02439-w.

- [12] C. Hu, M. Lin, C. Wang, and S. Zhang, "Current Understanding of Protein Aggregation in Neurodegenerative Diseases," *Int. J. Mol. Sci.*, vol. 26, no. 21, p. 10568, Oct. 2025, doi: 10.3390/ijms262110568.
- [13] J. Tchekalarova and R. Tzoneva, "Oxidative Stress and Aging as Risk Factors for Alzheimer's Disease and Parkinson's Disease: The Role of the Antioxidant Melatonin," *Int. J. Mol. Sci.*, vol. 24, no. 3, p. 3022, Feb. 2023, doi: 10.3390/ijms24033022.
- [14] Y. Hou *et al.*, "Ageing as a risk factor for neurodegenerative disease," *Nat. Rev. Neurol.*, vol. 15, no. 10, pp. 565–581, Oct. 2019, doi: 10.1038/s41582-019-0244-7.
- [15] J. M. Neyra Chauca *et al.*, "Oxidative Stress, Neuroinflammation, and Microvascular Damage in Neurodegenerative Diseases: Mechanistic Insights and Therapeutic Approaches," Nov. 10, 2025, doi: 10.20944/preprints202511.0551.v1.
- [16] H. Sies and D. P. Jones, "Reactive oxygen species (ROS) as pleiotropic physiological signalling agents," *Nat. Rev. Mol. Cell Biol.*, vol. 21, no. 7, pp. 363–383, Jul. 2020, doi: 10.1038/s41580-020-0230-3.
- [17] J. Fujii, T. Homma, and T. Osaki, "Superoxide Radicals in the Execution of Cell Death," *Antioxidants*, vol. 11, no. 3, p. 501, Mar. 2022, doi: 10.3390/antiox11030501.
- [18] S. Liu, J. Liu, Y. Wang, F. Deng, and Z. Deng, "Oxidative Stress: Signaling Pathways, Biological Functions, and Disease," *MedComm*, vol. 6, no. 7, p. e70268, Jul. 2025, doi: 10.1002/mco2.70268.
- [19] R. J. Mailloux, "An update on mitochondrial reactive oxygen species production," *Antioxidants*, vol. 9, no. 6, p. 472, 2020.
- [20] L. Valgimigli, "Lipid peroxidation and antioxidant protection," *Biomolecules*, vol. 13, no. 9, p. 1291, 2023.
- [21] B. Wang *et al.*, "ROS-induced lipid peroxidation modulates cell death outcome: mechanisms behind apoptosis, autophagy, and ferroptosis," *Arch. Toxicol.*, vol. 97, no. 6, pp. 1439–1451, 2023.
- [22] T.-M. Sonninen, G. Goldsteins, N. Laham-Karam, J. Koistinaho, and Š. Lehtonen, "Proteostasis Disturbances and Inflammation in Neurodegenerative Diseases," *Cells*, vol. 9, no. 10, p. 2183, Sep. 2020, doi: 10.3390/cells9102183.
- [23] A. Ulfig and U. Jakob, "Cellular oxidants and the proteostasis network: balance between activation and destruction," *Trends Biochem. Sci.*, 2024.
- [24] F. Bellanti, A. R. D. Coda, M. I. Trecca, A. Lo Buglio, G. Serviddio, and G. Vendemiale, "Redox imbalance in inflammation: the interplay of oxidative and reductive stress," *Antioxidants*, vol. 14, no. 6, p. 656, 2025.
- [25] M. Şerban, C. Toader, and R.-A. Covache-Busuioc, "The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration," *Int. J. Mol. Sci.*, vol. 26, no. 15, p. 7498, Aug. 2025, doi: 10.3390/ijms26157498.
- [26] L. Doblado *et al.*, "Mitophagy in human diseases," *Int. J. Mol. Sci.*, vol. 22, no. 8, p. 3903, 2021.
- [27] M. Du, Y. Yu, J. Wang, and C. Ji, "Autophagy–Lysosome Pathway Dysfunction in Neurodegeneration and Cancer: Mechanisms and Therapeutic Opportunities," *Int. J. Mol. Sci.*, vol. 27, no. 1, p. 366, Dec. 2025, doi: 10.3390/ijms27010366.
- [28] K. Jomova, S. Y. Alomar, S. H. Alwasel, E. Nepovimova, K. Kuca, and M. Valko, "Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants," *Arch. Toxicol.*, vol. 98, no. 5, pp. 1323–1367, May 2024, doi: 10.1007/s00204-024-03696-4.
- [29] Í. Gulcin, "Antioxidants: a comprehensive review," *Arch. Toxicol.*, vol. 99, no. 5, pp. 1893–1997, May 2025, doi: 10.1007/s00204-025-03997-2.
- [30] A. M. Gusti, S. Y. Qusti, E. M. Alshammari, E. A. Toraih, and M. S. Fawzy, "Antioxidants-related superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), glutathione-S-transferase (GST), and nitric oxide synthase (NOS) gene variants analysis in an obese population: a preliminary case-control study," *Antioxidants*, vol. 10, no. 4, p. 595, 2021.
- [31] A. Ashok, S. S. Andrabi, S. Mansoor, Y. Kuang, B. K. Kwon, and V. Labhasetwar, "Antioxidant Therapy in Oxidative Stress-Induced Neurodegenerative Diseases: Role of Nanoparticle-Based Drug Delivery Systems in Clinical Translation," *Antioxidants*, vol. 11, no. 2, p. 408, Feb. 2022, doi: 10.3390/antiox11020408.
- [32] A. Alhaj Sulaiman and V. L. Katanaev, "Beyond Antioxidants: How Redox Pathways Shape Cellular Signaling and Disease Outcomes," *Antioxidants*, vol. 14, no. 9, p. 1142, Sep. 2025, doi: 10.3390/antiox14091142.
- [33] S. Chakravorty, A. Malvi, A. Chaturvedi, K. Sonkusare, and N. Dave, "Glutathione—the master antioxidant," *Int J Med Res Pharm Sci*, vol. 7, no. 2, pp. 1–11, 2020.

- [34] R. Wadhwa, R. Gupta, and P. K. Maurya, "Oxidative stress and accelerated aging in neurodegenerative and neuropsychiatric disorder," *Curr. Pharm. Des.*, vol. 24, no. 40, pp. 4711–4725, 2018.
- [35] A. Moustapha, "Neurodegenerative Diseases: Potential Effect of Glutathione," in *Glutathione System and Oxidative Stress in Health and Disease*, M. Dulce Bagatini, Ed., IntechOpen, 2020. doi: 10.5772/intechopen.92240.
- [36] C. Mayer, L. Riera-Ponsati, S. Kauppinen, H. Klitgaard, J. T. Erler, and S. N. Hansen, "Targeting the NRF2 pathway for disease modification in neurodegenerative diseases: mechanisms and therapeutic implications," *Front. Pharmacol.*, vol. 15, p. 1437939, Jul. 2024, doi: 10.3389/fphar.2024.1437939.
- [37] V. R. Bitra, F. Moshapa, P. C. Adiukwu, and D. Rapaka, "Nrf2-Mediated Signaling as a Therapeutic Target in Alzheimer's Disease," *Open Neurol. J.*, vol. 18, no. 1, p. e1874205X319474, Jun. 2024, doi: 10.2174/011874205X319474240611070113.
- [38] D. Harman, "Aging: A Theory Based on Free Radical and Radiation Chemistry," *J. Gerontol.*, vol. 11, no. 3, pp. 298–300, Jul. 1956, doi: 10.1093/geronj/11.3.298.
- [39] L. C. D. Pomatto and K. J. A. Davies, "Adaptive homeostasis and the free radical theory of ageing," *Free Radic. Biol. Med.*, vol. 124, pp. 420–430, Aug. 2018, doi: 10.1016/j.freeradbiomed.2018.06.016.
- [40] B. Li *et al.*, "Redox regulation: mechanisms, biology and therapeutic targets in diseases," *Signal Transduct. Target. Ther.*, vol. 10, no. 1, p. 72, Mar. 2025, doi: 10.1038/s41392-024-02095-6.
- [41] A. Plóciniczak, E. Bukowska-Olech, and E. Wysocka, "The Complexity of Oxidative Stress in Human Age-Related Diseases—A Review," *Metabolites*, vol. 15, no. 7, p. 479, Jul. 2025, doi: 10.3390/metabo15070479.
- [42] R. F. Abdelhamid and S. Nagano, "Crosstalk between Oxidative Stress and Aging in Neurodegeneration Disorders," *Cells*, vol. 12, no. 5, p. 753, Feb. 2023, doi: 10.3390/cells12050753.
- [43] N. Chandimali *et al.*, "Free radicals and their impact on health and antioxidant defenses: a review," *Cell Death Discov.*, vol. 11, no. 1, p. 19, Jan. 2025, doi: 10.1038/s41420-024-02278-8.
- [44] D. Tripathi, D. J. Oldenburg, and A. J. Bendich, "Oxidative and Glycation Damage to Mitochondrial DNA and Plastid DNA during Plant Development," *Antioxidants*, vol. 12, no. 4, p. 891, Apr. 2023, doi: 10.3390/antiox12040891.
- [45] V. Boccardi, F. Mancinetti, and P. Mecocci, "Oxidative Stress, Advanced Glycation End Products (AGEs), and Neurodegeneration in Alzheimer's Disease: A Metabolic Perspective," *Antioxid. Basel Switz.*, vol. 14, no. 9, p. 1044, Aug. 2025, doi: 10.3390/antiox14091044.
- [46] A. E. Alkhalifa, O. Alkhalifa, I. Durdanovic, D. R. Ibrahim, and S. Maragkou, "Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease: Insights into Pathophysiology and Treatment," *J. Dement. Alzheimer's Dis.*, vol. 2, no. 2, p. 17, 2025.
- [47] H. Watanabe, J. M. Dijkstra, and T. Nagatsu, "Parkinson's Disease: Cells Succumbing to Lifelong Dopamine-Related Oxidative Stress and Other Bioenergetic Challenges," *Int. J. Mol. Sci.*, vol. 25, no. 4, p. 2009, Feb. 2024, doi: 10.3390/ijms25042009.
- [48] M. T. Henrich, W. H. Oertel, D. J. Surmeier, and F. F. Geibl, "Mitochondrial dysfunction in Parkinson's disease – a key disease hallmark with therapeutic potential," *Mol. Neurodegener.*, vol. 18, no. 1, p. 83, Nov. 2023, doi: 10.1186/s13024-023-00676-7.
- [49] L. D. Skou, S. K. Johansen, J. Okarmus, and M. Meyer, "Pathogenesis of DJ-1/PARK7-Mediated Parkinson's Disease," *Cells*, vol. 13, no. 4, p. 296, Feb. 2024, doi: 10.3390/cells13040296.
- [50] U. C. Dash *et al.*, "Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications," *Acta Pharm. Sin. B*, vol. 15, no. 1, pp. 15–34, Jan. 2025, doi: 10.1016/j.apsb.2024.10.004.
- [51] C. Toader *et al.*, "Decoding Neurodegeneration: A Review of Molecular Mechanisms and Therapeutic Advances in Alzheimer's, Parkinson's, and ALS," *Int. J. Mol. Sci.*, vol. 25, no. 23, p. 12613, Nov. 2024, doi: 10.3390/ijms252312613.
- [52] M. A. Guzmán-Ruíz *et al.*, "Microglia in physiological conditions and the importance of understanding their homeostatic functions in the arcuate nucleus," *Front. Immunol.*, vol. 15, p. 1392077, Sep. 2024, doi: 10.3389/fimmu.2024.1392077.
- [53] Y. Li *et al.*, "Oxidative stress of mitophagy in neurodegenerative diseases: Mechanism and potential therapeutic targets," *Arch. Biochem. Biophys.*, vol. 764, p. 110283, Feb. 2025, doi: 10.1016/j.abb.2024.110283.
- [54] X. Shi, "Targeting NOX2 to combat oxidative stress and neuroinflammation and provide neuroprotection in neurodegeneration," 2024.

- [55] A. Kulkarni, J. Chen, and S. Maday, "Neuronal autophagy and intercellular regulation of homeostasis in the brain," *Curr. Opin. Neurobiol.*, vol. 51, pp. 29–36, Aug. 2018, doi: 10.1016/j.conb.2018.02.008.
- [56] C. L. Ramsey, "Biologically structured water (BSW)-a review (Part 1): structured water (SW) properties, BSW and redox biology, BSW and bioenergetics," *J. Basic Appl. Sci.*, vol. 19, pp. 174–201, 2023.
- [57] N. Charmpilas, E. F. Fang, and K. Palikaras, "Mitophagy and Neuroinflammation: A Compelling Interplay," *Curr. Neuropharmacol.*, vol. 21, no. 7, pp. 1477–1481, Jul. 2023, doi: 10.2174/1570159X20666220628153632.
- [58] N. Apostolova and V. M. Victor, "Molecular Strategies for Targeting Antioxidants to Mitochondria: Therapeutic Implications," *Antioxid. Redox Signal.*, vol. 22, no. 8, pp. 686–729, Mar. 2015, doi: 10.1089/ars.2014.5952.
- [59] S. C. Broome, J. Whitfield, K. Janssens, and J. A. Hawley, "MitoQ supplementation does not impact redox responses to acute exercise in skeletal muscle of older individuals," *Redox Biol.*, p. 103927, 2025.
- [60] F. Pin, J. R. Huot, and A. Bonetto, "The mitochondria-targeting agent MitoQ improves muscle atrophy, weakness and oxidative metabolism in C26 tumor-bearing mice," *Front. Cell Dev. Biol.*, vol. 10, p. 861622, 2022.
- [61] J. Zhou, R. Shen, E. C. Makale, W. Zhong, Z. Chen, and Q. Huang, "SS31 confers cerebral protection by reversing mitochondrial dysfunction in early brain injury following subarachnoid hemorrhage, via the Nrf2-and PGC-1 α -dependent pathways," *Neurochem. Res.*, vol. 48, no. 5, pp. 1580–1595, 2023.
- [62] M. Li, D. Kong, L. Meng, Z. Wang, Z. Bai, and G. Wu, "Discovery of novel SS-31 (d-Arg-dimethylTyr-Lys-Phe-NH₂) derivatives as potent agents to ameliorate inflammation and increase mitochondrial ATP synthesis," *RSC Adv.*, vol. 14, no. 41, pp. 29789–29799, 2024.
- [63] Q. Jiang *et al.*, "Mitochondria-targeted antioxidants: a step towards disease treatment," *Oxid. Med. Cell. Longev.*, vol. 2020, no. 1, p. 8837893, 2020.
- [64] A.-H. S. Wadan *et al.*, "Mitochondrial-based therapies for neurodegenerative diseases: a review of the current literature," *Naunyn. Schmiedebergs Arch. Pharmacol.*, vol. 398, no. 9, pp. 11357–11386, Sep. 2025, doi: 10.1007/s00210-025-04014-0.
- [65] M. Kyriazis, "Hormesis and adaptive responses: intermittent fasting-induced stress resistance and disease resilience," in *The Potential of Intermittent Fasting in Age-related Diseases and Precision Anti-aging Therapeutics*, Elsevier, 2026, pp. 213–227.
- [66] M. Bevere *et al.*, "Redox-based disruption of cellular hormesis and promotion of degenerative pathways: perspectives on aging processes," *J. Gerontol. Ser. A*, vol. 77, no. 11, pp. 2195–2206, 2022.
- [67] M. M. Mehdi, P. Solanki, and P. Singh, "Oxidative stress, antioxidants, hormesis and calorie restriction: The current perspective in the biology of aging," *Arch. Gerontol. Geriatr.*, vol. 95, p. 104413, Jul. 2021, doi: 10.1016/j.archger.2021.104413.
- [68] R. A. Linker and A. Haghikia, "Dimethyl fumarate in multiple sclerosis: latest developments, evidence and place in therapy," *Ther. Adv. Chronic Dis.*, vol. 7, no. 4, pp. 198–207, 2016.
- [69] M. Colom-Cadena *et al.*, "The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease," *Alzheimers Res. Ther.*, vol. 12, no. 1, p. 21, 2020.
- [70] B. Dejanovic, M. Sheng, and J. E. Hanson, "Targeting synapse function and loss for treatment of neurodegenerative diseases," *Nat. Rev. Drug Discov.*, vol. 23, no. 1, pp. 23–42, 2024.
- [71] C. F. Manful, E. Fordjour, D. Subramaniam, A. A. Sey, Lord Abbey, and R. Thomas, "Antioxidants and reactive oxygen species: shaping human health and disease outcomes," *Int. J. Mol. Sci.*, vol. 26, no. 15, p. 7520, 2025.
- [72] G. Velikic *et al.*, "Neurodegeneration as Ecosystem Failure: A New Paradigm for Prevention and Treatment," *Int. J. Mol. Sci.*, vol. 26, no. 22, p. 11207, Nov. 2025, doi: 10.3390/ijms262211207.
- [73] S. K. Niazi, "Non-Invasive Drug Delivery across the Blood–Brain Barrier: A Prospective Analysis," *Pharmaceutics*, vol. 15, no. 11, p. 2599, Nov. 2023, doi: 10.3390/pharmaceutics15112599.
- [74] R. Vargas *et al.*, "Advancing through the blood-brain barrier: mechanisms, challenges and drug delivery strategies," *Admet Dmpk*, vol. 13, no. 5, p. 2988, 2025, doi: 10.5599/admet.2988.
- [75] I. Pérez-Torres, V. Guarner-Lans, and M. E. Rubio-Ruiz, "Reductive Stress in Inflammation-Associated Diseases and the Pro-Oxidant Effect of Antioxidant Agents," *Int. J. Mol. Sci.*, vol. 18, no. 10, p. 2098, Oct. 2017, doi: 10.3390/ijms18102098.
- [76] M. Șerban, C. Toader, and R.-A. Covache-Busuioc, "The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the

Precision Eradication of Neurodegeneration,” *Int. J. Mol. Sci.*, vol. 26, no. 15, p. 7498, Aug. 2025, doi: 10.3390/ijms26157498.

- [77] W. Zhang, D. Xiao, Q. Mao, and H. Xia, “Role of neuroinflammation in neurodegeneration development,” *Signal Transduct. Target. Ther.*, vol. 8, no. 1, p. 267, Jul. 2023, doi: 10.1038/s41392-023-01486-5.
- [78] Z. M. Hein *et al.*, “Toward a Unified Framework in Molecular Neurobiology of Alzheimer’s Disease: Revisiting the Pathophysiological Hypotheses,” *Mol. Neurobiol.*, vol. 63, no. 1, p. 282, Jan. 2026, doi: 10.1007/s12035-025-05602-0.