



Review

Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease: Insights into Pathophysiology and Treatment

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Abstract: Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory loss. Increasing evidence highlights oxidative stress as a pivotal contributor to AD pathogenesis, closely associated with hallmark features such as amyloid- β ($A\beta$) plaque accumulation, tau hyperphosphorylation, and synaptic dysfunction. This review aims to elucidate the mechanisms by which oxidative stress contributes to AD and to evaluate emerging therapeutic strategies targeting oxidative damage. Methods: We conducted an extensive literature search using PubMed and Google Scholar for studies published between 1994 and 2024. This narrative review integrates findings from in vitro, in vivo, and clinical studies focusing on oxidative stress, mitochondrial dysfunction, and their roles in AD to provide a comprehensive overview of the current research landscape. Results: ROS and RNS levels are significantly elevated in aging and AD-affected brains, leading to oxidative damage to lipids, proteins, and DNA, which compromises neuronal function and structure. Mitochondrial dysfunction plays a key role by amplifying ROS production, impairing ATP synthesis, and accelerating neurodegeneration. Oxidative stress also interacts with central AD pathologies, including $A\beta$ aggregation, tau hyperphosphorylation, and synaptic dysfunction, creating a vicious cycle of neuronal injury. Although traditional antioxidant therapies have shown limited efficacy in clinical settings, often due to poor bioavailability, limited BBB penetration, and systemic distribution, novel strategies such as mitochondrial-targeted antioxidants and combination therapies have demonstrated improved outcomes in preclinical models. Conclusions: Oxidative stress plays a multifaceted role in the progression of AD, necessitating comprehensive therapeutic approaches. Future treatments should focus on targeting multiple aspects of oxidative stress, particularly mitochondrial dysfunction, to enhance clinical outcomes and slow neurodegeneration in AD patients.

Keywords: Alzheimer's disease; oxidative stress; mitochondrial dysfunction; antioxidant; reactive oxygen species



Academic Editor: Magda Tsolaki

Received: 13 March 2025

Revised: 31 March 2025

Accepted: 26 May 2025

Published: 3 June 2025

Citation: Alkhalifa, A.E.; Alkhalifa, O.; Durdanovic, I.; Ibrahim, D.R.; Maragkou, S. Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease: Insights into Pathophysiology and Treatment. *J. Dement. Alzheimer's Dis.* **2025**, *2*, 17. <https://doi.org/10.3390/jdad2020017>

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that significantly impacts the elderly population and primarily manifests as cognitive impairment, memory loss, and compromised daily activities [1]. Globally, AD stands as the foremost cause of dementia accounting for 60–80% of all cases, and is the sixth leading cause of

death among Americans aged 65 and older [2]. Approximately 6.7 million Americans currently live with AD, while worldwide cases are exceeding 55 million with a highly likely projection to almost triple of this number by 2050 [3]. This escalating prevalence, along with an aging global demographic, underscores the formidable challenge AD presents to healthcare systems worldwide [4].

AD is marked by two primary neuropathological hallmarks: the extracellular deposition of A β peptides forming diffuse and neuritic plaques and the intracellular accumulation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau proteins. [5,6]. These core features are widespread across the brain, inducing neuronal atrophy and synaptic loss, ultimately leading to neurodegeneration [6,7]. While these hallmarks are fundamental to understanding AD, they are part of a more complex pathogenesis. The development of AD also involves a broader spectrum of pathophysiological changes, including neuroinflammation, blood–brain barrier (BBB) dysfunction, mitochondrial dysfunction, and OS [8–10]. These core features are integrated through interconnected hypotheses, such as the amyloidogenic cascade, tauopathy, neurovascular dysfunction, and the impacts of OS and neuroinflammation [9,11]. Each of these hypotheses is integrated through various mechanistic relationships, suggesting a multifaceted and interconnected approach, which are crucial for fully understanding and addressing the progression of AD [12]. According to these core hypotheses, OS emerges as a central element in the pathophysiology of AD, particularly as it bridges several core hypotheses including amyloid cascade, tau protein, inflammation, and metal ions, as shown in Figure 1 [13,14]. Extensive research, including studies by Butterfield's group, has documented extensive oxidative damage in AD brains, linking it to the marked accumulation of A β and NFTs [15–17]. This oxidative damage is particularly detrimental due to the brain's unique vulnerability to OS. The brain's high oxygen demand, which accounts for 20% of the total body consumption, is coupled with its abundance of peroxidation-sensitive lipids and cerebrospinal fluid that poorly binds to iron and heightens the brain's vulnerability to oxidative damage [18]. Moreover, the brain's antioxidant defense mechanisms play a role in its higher susceptibility to OS and neurodegeneration [19]. This environment can lead to neuronal damage through several mechanisms such as increased intracellular calcium, excitotoxicity, and the breakdown of cellular components including lipids, proteins, and DNA [20,21].

Mitochondrial dysfunction is a crucial factor in AD's progression, evidenced by the reduced number and impaired functionality of mitochondria, highly due to defects in the electron transport chain (ETC) enzymes [17,22]. This mitochondrial impairment fosters ROS accumulation and further OS, disrupting calcium homeostasis and signal transduction, ultimately contributing to synaptic loss and neurodegeneration [23,24]. The complex interplay between reactive species and cellular antioxidant defenses underscores the importance of understanding their sources, regulation, and effects. This knowledge is crucial for developing therapeutic strategies to mitigate OS-related damage in various diseases, including AD [25]. Despite the central role of OS in AD pathology, current therapies predominantly target other aspects of the disease.

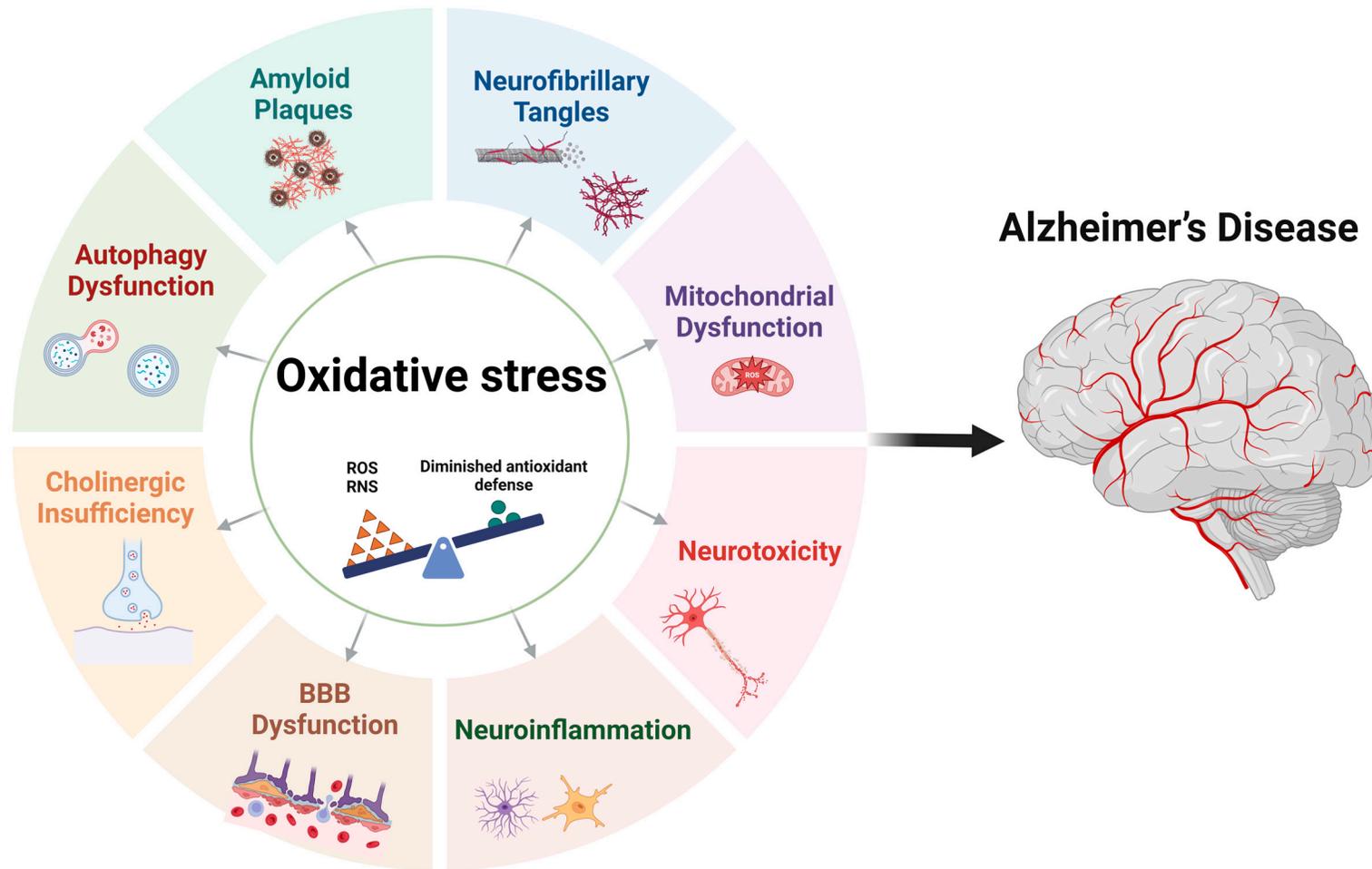


Figure 1. The central role of oxidative stress in Alzheimer’s disease pathogenesis. Oxidative stress, caused by the imbalance between reactive oxygen/nitrogen species and antioxidant defense systems, is shown at the center, emphasizing its contribution to multiple pathological processes of AD. These include mitochondrial dysfunction, amyloid plaque formation, tau hyperphosphorylation, excitotoxicity, neuroinflammation, BBB breakdown, cholinergic dysfunction, and impaired autophagy. Arrows illustrate the mechanistic overlap and reinforcing feedback loops, highlighting oxidative stress as a critical therapeutic target.

Recent therapeutic advances have been particularly noteworthy in highlighting this growing health concern. In particular, the U.S. Food and Drug Administration (FDA) has granted accelerated approval of monoclonal antibodies Aducanumab and Lecanemab, reflecting the general urgency for therapeutic strategies for AD [26]. These monoclonal antibodies target amyloid-beta peptides implicated in AD pathology and are designed to modify disease progression, contrasting with traditional symptomatic treatments such as acetylcholinesterase inhibitors and N-methyl-D-aspartate antagonists like memantine [27]. The emergence of these therapies highlights a shift towards more targeted approaches that address the underlying mechanisms of AD, reflecting the ongoing need for a comprehensive and multidimensional strategy in combating this pervasive disease.

Despite growing evidence showing OS as an essential factor in the development and progression of AD, the exact mechanisms and interactions between OS and AD pathology remain unclear. Additionally, clinical trials applying antioxidant therapies have yielded inconsistent and often disappointing results. This review aims to provide a comprehensive exploration of the intricate roles played by OS and mitochondrial dysfunction in AD pathophysiology. We will delve into the multifaceted interactions between oxidative damage and the key pathological features of AD, such as A β plaques, tau hyperphosphorylation, and synaptic dysfunction. Furthermore, we will assess how mitochondrial dysfunction exacerbates disease progression and contributes to neurodegeneration. By synthesizing current research findings, this review seeks to improve our understanding of the mechanisms underlying AD and the dual role that ROS plays in both neuronal health and disease. In addition, we will highlight recent advancements in antioxidant therapies and innovative strategies targeting OS, offering promising avenues for the development of effective treatments for AD.

2. Materials and Methods

In preparing this comprehensive review, we conducted an extensive search of the PubMed and Google Scholar databases for articles published between 1994 and 2024. Our search incorporated key terms such as oxidative stress, mitochondrial dysfunction, and Alzheimer's disease, aiming to capture a wide range of studies that explored these factors in AD. Unlike systematic reviews that adhere to strict inclusion and exclusion criteria, our approach included diverse research perspectives covering *in vitro*, *in vivo*, and clinical studies to provide a more holistic understanding of how oxidative stress and mitochondrial dysfunction contribute to pathology. We prioritized research articles that offered meaningful insights into these mechanisms, while still allowing for a broad representation of the current research landscape on AD. Some earlier or less widely supported theories were excluded to maintain focus on findings with sustained scientific relevance or recent advancements in the field.

3. Oxidative Stress

OS arises from an imbalance between the production of ROS and reactive nitrogen species (RNS), and the cell's capacity to neutralize these reactive intermediates or repair the damage they cause [28,29]. This imbalance, often associated with mitochondrial dysfunction, can result in significant harm to cellular components such as lipids, proteins, polysaccharides, DNA and RNA [30]. High ROS levels lead to free radical damage, specifically to cell membranes and DNA, compromising cellular function and survival. Consequently, the resulting DNA oxidation can affect gene transcription and replication, while the RNA oxidation primarily results in strand breaks and ribosomal dysfunction [31,32]. Lipid peroxidation, particularly that of unsaturated fatty acids, produces compounds like isoprostanes, MDA, and 4-hydroxynonenal (HNE), which impair cellular membrane integration and

protein functions [33,34]. The resulting oxidative damage to mitochondrial components can exacerbate ROS production, damage mitochondrial DNA, and trigger various cell death mechanisms, including apoptosis, necrosis, autophagy, and ferroptosis. These processes involve pathways associated with redox-sensitive proteins such as Thioredoxin-1 (Trx-1), Apoptosis Signal-regulating Kinase 1 (ASK-1), and the p53 pathway, which activates proapoptotic genes [35–38]. This can create a vicious cycle where OS damages biomolecules, which in turn, further amplifies ROS production [39].

At the molecular level, OS involves various molecules and free radicals derived from molecular oxygen, including free radicals such as superoxide and hydroxyl radicals ($\text{OH}\bullet$), as well as non-radical species like hydrogen peroxide (H_2O_2) [40]. Although H_2O_2 is a weaker oxidant, its longer lifespan and ability to diffuse across cell membranes allow it to travel relatively long distances within the cell, contributing significantly to OS. Free radicals are chemical species with an unpaired electron in their outer shell, making them highly reactive [41]. Molecular oxygen in its ground state is a bi-radical with two unpaired electrons sharing the same spin, making it relatively unreactive [28]. However, when one of these electrons is excited, it changes its spin, allowing the oxygen molecule to react readily with other electron pairs, particularly those involving double bonds. This reaction produces singlet oxygen, a highly potent oxidant [25]. The reduction of oxygen by one electron generates relatively stable intermediates, leading to the formation of an $\text{O}_2^{\bullet-}$ [28,42]. This anion is a precursor to most reactive oxygen species (ROS) and a key player in OS chain reactions. $\text{O}_2^{\bullet-}$ is a precursor to many ROS and plays a crucial role in OS chain reactions. However, antioxidants primarily function to neutralize $\text{O}_2^{\bullet-}$ by donating electrons, preventing its participation in reactions that generate highly reactive species such as $\text{OH}\bullet$. In contrast, $\text{OH}\bullet$ are typically formed through the Fenton reaction, where $\text{O}_2^{\bullet-}$ facilitates the reduction of transition metals (e.g., Fe^{3+} to Fe^{2+}), which then catalyze the conversion of H_2O_2 into $\text{OH}\bullet$ as shown in Figure 2 [40,42]. This process is catalyzed by reduced transition metals, which can be re-reduced by $\text{O}_2^{\bullet-}$, hence further perpetuating the cycle [29,42]. $\text{O}_2^{\bullet-}$ can also react with other radicals, such as nitric oxide ($\text{NO}\bullet$), and form peroxynitrite (ONOO^-), an extremely potent oxidant driving reactive RNS [25,43].

$\text{O}_2^{\bullet-}$ is primarily produced by mitochondria and regulated by both enzymatic and non-enzymatic processes [44,45]. Within the ETC, certain components can leak electrons to oxygen, leading to the formation of $\text{O}_2^{\bullet-}$, particularly at Complexes I and III. In Complex I (Nicotinamide Adenine Dinucleotide Phosphate (NADPH): ubiquinone oxidoreductase), electrons can escape during the transfer from NADH to ubiquinone, resulting in the one-electron reduction of oxygen to superoxide, predominantly releasing superoxide into the mitochondrial matrix. In Complex III (Ubiquinol: cytochrome c oxidoreductase), during the Q cycle, semiquinone intermediates can donate single electrons to oxygen, forming superoxide that can be released into both the mitochondrial matrix and the intermembrane space [45,46]. Key enzymatic sources of $\text{O}_2^{\bullet-}$ include NADPH oxidases in various cell membranes, cytochrome P450 enzymes, and H_2O_2 -dependent oxygenases [40,47]. Another source is the conversion of xanthine dehydrogenase to xanthine oxidase [48]. Non-enzymatic production occurs via direct oxygen transfer by reduced coenzymes or prosthetic groups like flavin or iron–sulfur clusters or by xenobiotics after enzymatic reduction [49,50].

Mitochondria also employ several mechanisms to mitigate ROS and regulate the steady-state concentration of $\text{O}_2^{\bullet-}$ [51]. Superoxide dismutase (SOD) enzymes dismutate $\text{O}_2^{\bullet-}$ to H_2O_2 , which is further reduced to water [50,51]. Mitochondrial SOD (MnSOD or SOD2) eliminates $\text{O}_2^{\bullet-}$ in the matrix or inner membrane, while copper–zinc SOD (SOD1) functions in the cytoplasm [52]. Cytochrome c in the intermembrane space reduces superoxide anions, regenerating oxygen [53]. Moreover, ubiquinol (QH2) acts as a reducing

agent, detoxifying various peroxides [54]. Mitochondria also has DNA repair enzymes to correct oxidative damage, maintaining genetic integrity [25].

Fenton Reaction and ROS Amplification in Alzheimer's Disease

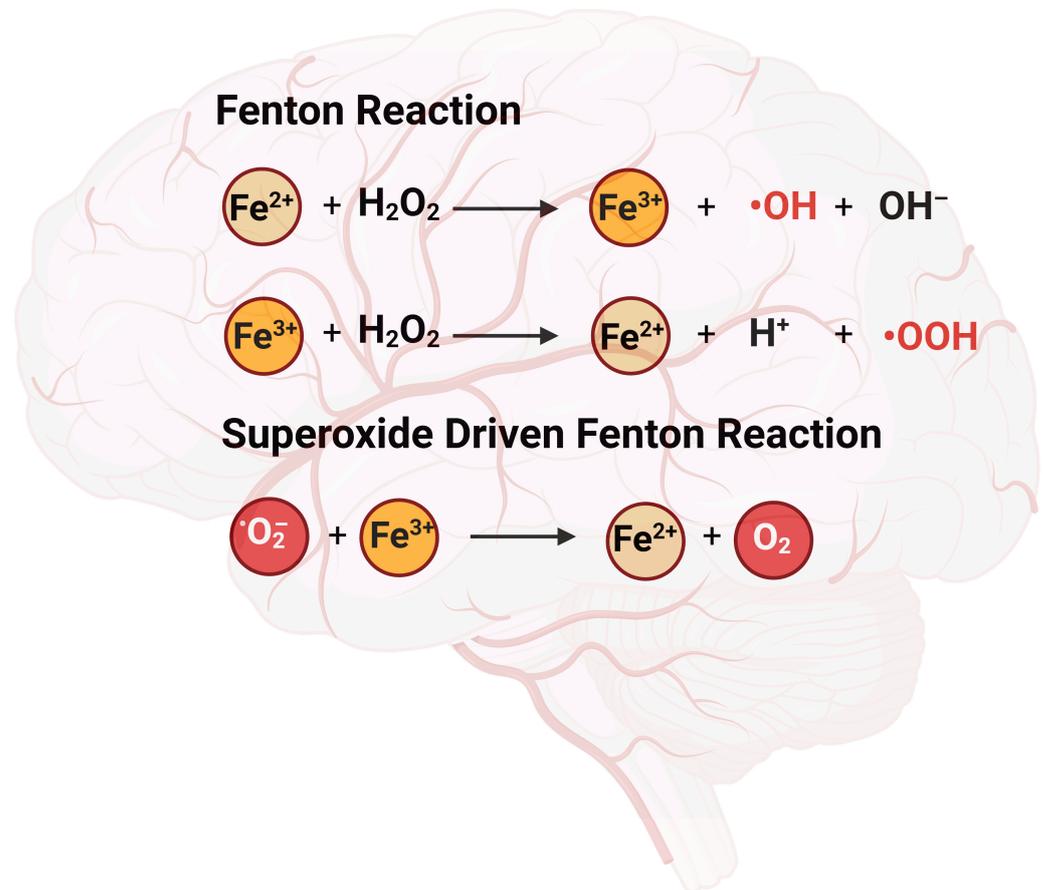


Figure 2. This schematic illustrates the classical Fenton reaction, where ferrous iron (Fe^{2+}) reacts with hydrogen peroxide (H_2O_2) to produce highly reactive hydroxyl radicals ($\cdot\text{OH}$) and hydroxide ions (OH^-). Additionally, the reaction of ferric iron (Fe^{3+}) with H_2O_2 generates hydroperoxyl radicals ($\cdot\text{OOH}$) and protons, contributing further to oxidative stress. Superoxide anion ($\text{O}_2\cdot^-$) can reduce Fe^{3+} back to Fe^{2+} , thereby sustaining the redox cycle and amplifying reactive oxygen species (ROS) production. These radicals cause extensive damage to lipids, proteins, and DNA, playing a critical role in the progression of Alzheimer's disease.

The complex interplay between ROS and RNS with cellular antioxidant defenses is important for understanding the sources, regulation, and mechanisms of action of these reactive species [29]. Figure 3 illustrates how mitochondrial dysfunction leads to ROS production, highlighting the role of ETC and its implications in OS and AD.

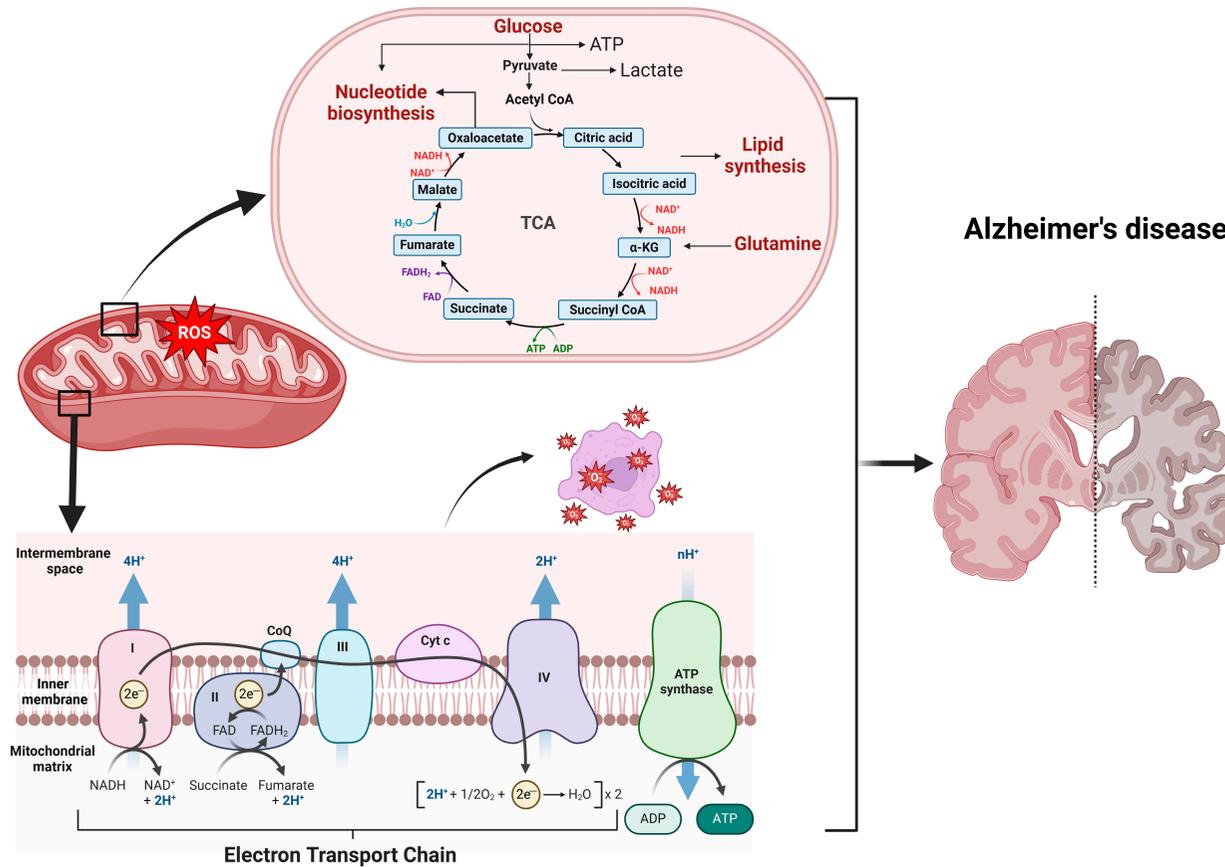


Figure 3. The relationship between mitochondrial dysfunction, OS, and AD. At the core of cellular metabolism, mitochondria generate energy through the electron transport chain (ETC), a series of protein complexes embedded in the inner mitochondrial membrane. The ETC facilitates the transfer of electrons from NADH and flavin adenine dinucleotide (FADH₂) through complexes I to IV, culminating in the reduction of oxygen to water and the synthesis of ATP via ATP synthase. During this process, ROS are generated as by-products. Excessive ROS production, as indicated in the figure, leads to OS, damaging cellular components such as lipids, proteins, and DNA. This oxidative damage is particularly detrimental to neuronal cells, contributing to the pathogenesis of AD. The schematic highlights how metabolic intermediates like glucose and pyruvate fuel the tricarboxylic acid (TCA) cycle, producing substrates for the ETC. However, dysregulation in these pathways exacerbates ROS production, ultimately promoting neurodegenerative processes associated with AD, as depicted by the brain image showing areas affected by the disease.

4. Oxidative Stress in Alzheimer's Disease

Brain membrane phospholipids rich in polyunsaturated fatty acids are particularly susceptible to free radical attacks, leading to lipid peroxidation—a prominent feature in AD [25,55]. The brain is highly susceptible to oxidative stress due to its significant energy demand, high oxygen consumption, and elevated mitochondrial activity [14]. Neuronal cells contain high levels of lipids and iron, with the latter being found in A β and NFT deposits, catalyzing H₂O₂ into OH• by the Fenton reaction. The Fenton reaction is an oxidation process in which iron salts, particularly ferrous ions (Fe²⁺), catalyze the oxidation of organic substrates with H₂O₂. This reaction produces highly reactive OH•, which are potent inducers of OS. Fenton reaction forms a self-propagating loop, as the free radicals generated exacerbate oxidative damage to cellular components, promoting A β plaque formation and accelerating ROS production [25,39,56].

Biometals such as iron, zinc, and copper play critical roles in A β aggregation and neurodegeneration, with copper exacerbating OS as a potent mediator of OH• found in elevated levels in amyloid plaques [25]. Elevated levels of oxidative damage markers are found in individuals with symptoms of preclinical Alzheimer's disease (PCAD), amnesic mild cognitive impairment (aMCI), and AD [40].

Markers of protein oxidation, such as protein carbonyls (PCs), are elevated in AD-affected brain regions rich in A β -peptide senile plaques [40]. Furthermore, lipid peroxidation markers, including protein-conjugated HNE, F₂-isoprostanes, and F₄-isoprostanes, are increased in patients diagnosed with AD, aMCI, and particularly in the hippocampus of patients with PCAD [57]. Elevated 3-nitrotyrosine (3-NT) levels indicate damage by ONOO— and the biomarker 8-hydroxy-deoxyguanosine (8-OHdG) reflects oxidative damage to both nuclear and mitochondrial DNA [58,59].

The consequences of oxidative and nitrosative damage include disrupted glucose metabolism, loss of ion gradients, impaired action potentials, and calcium imbalance [57]. OS also affects protein function and can impair critical enzymes like glutamine synthetase (GS) and creatine kinase, which are reduced in AD pathology. This reduction is linked to altered glutamate concentrations, increased excitotoxicity, and decreased energy metabolism [60].

5. Mitochondrial Dysfunction in Alzheimer's Disease

Mitochondria, the powerhouse of the cell, are pivotal in oxidative phosphorylation-driven energy production and generating adenosine triphosphate (ATP) [61]. This process makes them a significant source of reactive ROS due to ETC activity in the inner membrane [45]. A considerable amount of cellular H₂O₂ originates from mitochondria, primarily as a result of the dismutation of O₂•⁻ produced during electron leakage from the ETC. This makes mitochondria a major source of ROS, with both O₂•⁻ and H₂O₂ contributing to oxidative stress [45,62].

OS severely impacts proteins involved in mitochondrial ATP production and glycolysis [63]. Impaired cellular metabolism leads to increased ROS production, creating a vicious cycle of OS and increased cellular damage [64]. Reduced ATP levels cause heightened mitochondrial activity, further escalating ROS production and electron leakage from the ETC [65]. Additionally, ROS-induced ROS release (RIRR) amplifies this cycle, where initial ROS production triggers further ROS generation within mitochondria, exacerbating oxidative stress and cellular injury [51].

Mitochondrial dysfunction is evident early in AD and affects various aspects of mitochondrial function, including energy metabolism, calcium homeostasis, and the expression of mitochondrial DNA (mtDNA) [16]. Glucose metabolism, closely linked to cognitive function, is essential for monitoring AD progression [66]. In AD, energy metabolism genes,

such as those of the mitochondrial ETC, are decreased in the posterior cingulate cortex, a region affected early in the disease progression [67]. The reduced glucose metabolism in the AD brain is associated with decreased activity of mitochondrial ETC enzymes like pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase complex, and cytochrome oxidase [66,68]. This reduction correlates with clinical symptoms and is consistent with the presence of A β plaques. Furthermore, AD brains show elevated levels of mtDNA oxidation and mutations compared to age-matched controls, largely due to the proximity of mtDNA to ROS generation sites in the mitochondria and the absence of protective histone proteins [24,69,70]. These mutations compromise mitochondrial function and reduce mitochondrial numbers in affected neurons. The broader implications of DNA oxidation in AD pathogenesis, including both nuclear and mitochondrial contexts, are discussed in detail in the subsequent chapter [71]. Interestingly, mitochondrial size in AD brains is increased, which is attributed to impaired fusion and fission dynamics resulting from abnormal protein expression. Dihydrosphingosine phosphate lyase (DPL1) is a protein mainly expressed in the cytoplasm and is recruited to mitochondria during fission. DPL1 is increased in AD and may also interact with A β and phosphorylated tau, contributing to AD pathophysiology [72]. Therefore, excessive mitochondrial fission may enhance oxidative and nitrosative stress in AD pathology.

Calcium ions (Ca $_2^+$), an essential cellular signaling messenger, are dysregulated in AD, which consequently leads to neurons becoming more susceptible to neurodegeneration [73]. ROS produced from mitochondrial damage can disrupt calcium homeostasis and impair the endoplasmic reticulum's ability to buffer calcium, which is detrimental to cell signaling and survival [74]. Increased levels of calcium-related enzymes in AD patients further highlight this proposed mechanism of cellular dysregulation [73].

Mitochondria play a crucial role in cell death pathways. ROS can activate pro-apoptotic proteins like Bcl-2-associated X protein (Bax), leading to their translocation to the mitochondrial membrane [75]. This translocation facilitates the release of cytochrome c into the cytosol, triggering apoptotic pathways. Additionally, under conditions of elevated calcium levels and oxidative stress, the mitochondrial permeability transition pore (mPTP) can open, resulting in mitochondrial swelling, loss of membrane potential, and release of pro-apoptotic factors, culminating in cell death. The specific outcome apoptosis or necrosis is influenced by the extent of mPTP opening and the cell's energy status [76]. This translocation results in the formation of the mitochondrial membrane permeability transition pore, releasing cytochrome c and triggering cell death [77].

Although there is some controversy regarding these processes, the role of mitochondrial dysfunction in AD is evident [78]. The intricate interplay between mitochondrial dysfunction and OS underscores the importance of early detection and potential therapeutic strategies aimed at restoring mitochondrial function and mitigating oxidative damage in AD [65].

6. Oxidative Stress Impact on Cellular Functions

The impact of OS on cellular function is profound and multifaceted. Lipid peroxidation, for instance, damages cell membranes, affecting their fluidity and permeability [79]. This damage compromises the integrity and function of the cell membrane, leading to cellular instability. Similarly, protein oxidation can alter enzyme activities and disrupt protein-protein interactions, thereby interfering with critical cellular processes [80].

6.1. Protein Oxidation

In AD, ROS mediates protein oxidation such as lysine, arginine, proline, and threonine, which results in introducing hydroxyl groups or generating reactive protein-based

carbonyls and aldehydes in AD; these products are produced after oxidation for further cells' components (lipids, DNA, and sugars,) work in a loop cycle of protein oxidation [81]. This process also involves the cleavage of peptide bonds via the α -amidation pathway or the oxidation of glutamyl residues [40]. ROS can also interact with lipids, DNA, and sugars, producing reactive carbonyl derivatives and aldehydes that further react with proteins to form protein-bound carbonyls [40,81]. Measurement of protein carbonylation is a reliable indicator of oxidative damage linked to several OS conditions, aging, physiological disorders, and AD [82].

6.2. Lipid Oxidation

Lipid peroxidation, a crucial process in OS, results in the formation of several aldehyde by-products, including MDA, HNE, and acrolein [83]. Among these, HNE and MDA are the most abundant, while acrolein is highly reactive [84]. Elevated levels of HNE-histidine and glutathione-HNE adducts have been observed in AD brains [85]. Proteomic analysis has shown a significant increase in protein-bound HNE in these brains [84]. F2-isoprostanes (F2-IsoPs) and neuroprostanes are also significantly elevated in patients with MCI and late-stage AD [86]. Increased acrolein levels are found in the hippocampus and temporal cortex of AD patients, regions where OS is exceptionally high [87]. Due to its high reactivity, acrolein is both a marker of lipid peroxidation and an initiator of OS, forming adducts with proteins, lipids, and nucleic acids [84].

Lipid peroxidation occurs not only in the brains of MCI patients but also in those with preclinical AD, suggesting that oxidative damage may play an early role in the disease pathogenesis [84]. $A\beta$ induces lipid peroxidation of membranes, correlating strongly with the presence of antioxidant enzymes, amyloid plaques, and NFTs in AD brains [40]. OS breakdown products such as HNE, acrolein, MDA, and F2-isoprostanes are more prevalent in AD brains compared to age-matched controls. Particularly, HNE can modify proteins, inhibiting neuronal glucose and glutamate transporters, Na-K ATPases, and disrupting intracellular calcium signaling, ultimately triggering apoptotic mechanisms [40,88–91].

The first evidence of $A\beta$ -induced lipid peroxidation was demonstrated using electron paramagnetic resonance (EPR) methods [92]. $A\beta$ addition to synaptosomes led to a rapid loss of the EPR signal, indicating lipid-centered free radical formation [14,92]. Subsequent studies using a murine model of mutant presenilin-1 (PS-1) supported these findings, showing oxidative damage in the brain [93]. A proposed mechanism involves the $A\beta$ 42 peptide, which in its oligomeric form can integrate into the lipid bilayer of neuronal membranes, adopting an α -helical structure [89,94,95]. This conformation contributes to oxidative damage and neurotoxicity [89]. The interaction between specific amino acid residues within the peptide, such as the sulfur atom of methionine and the oxygen atom of isoleucine, facilitates one-electron oxidation, generating free radicals that propagate lipid peroxidation [15]. This process leads to the formation of lipid peroxy radicals and lipid hydroperoxides which together contribute to the OS observed in AD [83,96].

6.3. DNA Oxidation

OS significantly impacts DNA integrity in AD, contributing to its pathogenesis and disease progression [40,97]. ROS, particularly $OH\bullet$, can cause various forms of DNA damage, including strand breaks, DNA–DNA and DNA–protein cross-linking, and the formation of oxidized base adducts [98,99]. These modifications can lead to mutations, and altered protein synthesis affects various stages in protein synthesis such as hydroxylation, protein carbonylation, and nitration [40,99,100]. One of the most prominent markers of oxidative DNA damage is 8-OH-guanosine, which forms when ROS reacts with guanine [101]. Due to its low oxidation potential, guanine is readily oxidized and forms several by-products,

including 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua) and 7,8-dihydro-8-oxoguanine (8-OHG) [70,102]. ROS attack on DNA leads to more than 20 oxidized base adducts [103]. The most common oxidative DNA damage includes single-strand breaks (SSBs) and double-strand breaks (DSBs), with DSBs being more toxic and capable of altering gene transcription [104]. SSBs occur due to the breakdown of the DNA sugar-phosphate backbone following ROS oxidation, while DSBs can result in changes in the transcription of gene promoters near break sites [103,104].

The capacity to repair DNA damage is compromised in AD [105]. Studies indicate a decline in the efficiency of the base excision repair (BER) pathway and other DNA repair mechanisms [105,106]. This impairment is evidenced by reduced recruitment of repair proteins such as p53-binding protein 1 (53BP1) to sites of damage and lower levels of critical proteins involved in double-strand break (DSB) repair, including DNA PKcs and the MRN complex [107,108]. Elevated levels of γ H2AX, a marker of DSBs, have been found in the neurons and astrocytes of AD patients, indicating persistent DNA damage [109].

7. Neurobiological Implications

7.1. Oxidative Stress and A β Plaques

The formation of A β plaques is intricately linked to OS, with A β peptides, particularly A β 42, prone to aggregation and forming insoluble fibrils that deposit as plaques in the brain [110]. OS enhances the production and aggregation of A β [111]. ROS can induce the expression of amyloid precursor protein (APP) and influence the activity of secretases that process APP, favoring the production of amyloidogenic A β fragments [43]. Moreover, A β itself can generate ROS, creating a vicious cycle where OS promotes A β production, and A β , in turn, generates more ROS [111]. This self-propagating loop exacerbates oxidative damage and plaque formation, with biometals like iron, copper, and zinc in amyloid plaques further accelerating ROS production through Fenton reactions [111].

Further compounding this issue, A β has been shown to enhance ROS production and cause mitochondrial dysfunction, exacerbating OS [95,112]. Research indicates that brain regions with higher A β expression exhibit more significant levels of protein oxidation and lipid peroxidation than the cerebellum, which has relatively low levels of A β [113]. Amyloid plaques predominantly contain A β with a methionine sulfoxide modification, suggesting that lipid peroxidation is an early event in neurodegeneration [114]. When incorporated into lipid bilayer membranes, A β induces OS, leading to lipid peroxidation and subsequent damage to nucleic acids and proteins [95,115]. Proteins are mainly subjected to oxidative damage, which can result in irreversible structural modifications such as unfolding, aggregation, and the disassociation of subunits, ultimately leading to functional loss [116].

In both AD patients and transgenic mice models, A β has been shown to interact with the mitochondrial enzyme A β -binding alcohol dehydrogenase (ABAD), causing mitochondrial dysfunction, increased ROS production, and eventual apoptosis [116,117]. Apoptosis, a primary mode of cell death in AD progression, is closely associated with elevated oxidative and nitrosative stress (OS&NS), as observed in AD models [28]. Treatment of fibroblasts derived from AD patients with the A β peptide leads to the oxidation of proteins such as vimentin and heat shock protein 60 (HSP60), which have been implicated in apoptotic regulation. Similarly, neuroblastoma cells treated with A β (1–42) show increased oxidation of proteins involved in apoptosis regulation, including glutaredoxin-1 (GRX-1) and TRX-1 [118]. Furthermore, increased levels of the pro-apoptotic protein p53 and its oxidized form have been detected in the AD brain, further contributing to increased apoptosis [119,120]. Overall, the induction of A β significantly contributes to the heightened oxidative status observed in AD.

7.2. Oxidative Stress and Tau Hyperphosphorylation

Tau protein is critical in stabilizing microtubules and ensuring smooth neuronal signal transmission [121]. Numerous studies have demonstrated that OS contributes to the hyperphosphorylation of tau proteins [122]. The peroxidation end product Carbonyl-4-HNE has been identified as a key factor in the accumulation of hyperphosphorylated tau [123]. However, the exact relationship between tau hyperphosphorylation and OS remains unclear. In animal studies, exposure to OS-inducing compounds has been shown to increase the activity of glycogen synthase kinase 3 β (GSK3 β), a Ser/Thr kinase that hyperphosphorylates tau proteins, thereby exacerbating disease pathology [123,124]. Besides GSK3 β , OS also influences other kinases, promoting tau hyperphosphorylation [123]. Additional research has indicated that OS reduces peptidyl-prolyl cis-trans isomerase 1 (Pin1) in AD brains [124]. Pin1 is crucial for the dephosphorylation of tau proteins [122]. The decrease in antioxidant molecules like GSH and the use of buthionine sulfoximine further contribute to increased tau hyperphosphorylation under OS conditions. [123]. Moreover, OS can directly induce tau hyperphosphorylation by affecting protein phosphatase 2A (PP2A) [123]. Under OS, GSK3 β activity is heightened while PP2A activity is diminished, activating the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway, leading to apoptosis [123,124].

Studies show that low doses of GSK-3 β inhibitors protect neuron cells from OS-induced apoptosis, while higher doses can have the opposite effect [125]. Increased GSK-3 β and the p25 activator of cyclin-dependent kinase five halts mitochondrial movement in neurons, but GSK-3 β inhibition reverses axonal transport disruption caused by Tau overexpression [126,127]. ROS-mimicking mitochondrial OS promotes Tau phosphorylation by increasing GSK-3 β activity [128].

Overall, OS, mitochondrial dysfunction, and A β involvement are interconnected with Tau pathology, and Tau pathology also induces OS and mitochondrial damage, partly by modulating A β toxicity [50].

7.3. Oxidative Stress and Glutamatergic Signaling and Synaptic Dysfunction

Neuronal pathology and neurotransmitter system dysfunction are critical factors in various neurodegenerative diseases, including AD [129,130]. While astrocytes play essential roles in regulating synaptic transmission, supplying nutrients to neurons, controlling vasodilation, maintaining BBB permeability, and responding to injury and immune challenges [131], glutamate, the primary excitatory neurotransmitter produced in neurons, plays a central role in synaptic function and brain plasticity. However, excessive glutamate contributes to neurodegenerative diseases, brain trauma, seizures, and cerebral ischemic injury [132–134].

Glutamate activates ionotropic receptors (NMDAR, AMPA, and kainate) and metabotropic receptors [135]. Although astrocytes are crucial for glutamate recycling, primarily through glutamate uptake mediated by glutamate aspartate transporter (GLAST or EAAT1) and glutamate transporter 1 (GLT-1 or EAAT2), neurons are the primary producers of glutamate. The enzyme GS, primarily found in astrocytes, converts glutamate to glutamine, which is recycled back to neurons [136,137]. Proper regulation of glutamate is essential for neuronal survival; low levels compromise neuron viability, while excess glutamate leads to excitotoxicity, characterized by increased intracellular calcium through heightened NMDAR activity, impairing synaptic function and causing neuronal cell death [74,137]. In AD, impaired glutamate homeostasis and NMDAR dysfunction contribute to OS exacerbation [138].

Synaptic dysfunction is a hallmark of AD, and glutamatergic neurons are particularly affected. Synapses, specialized neuronal regions for signaling, rely on precise mechanisms such as neurotransmitter biosynthesis, delivery, synaptic vesicle formation, receptor bind-

ing, and neurotransmitter removal [139]. Ca_2^+ is critical in mediating synaptic transmission by triggering synaptic vesicle release through voltage-gated calcium channels. [140]. Disruption in any step can severely impact synaptic function and cognitive abilities. In AD, progressive memory impairment is closely associated with synaptic dysfunction, mainly through the inhibition of long-term potentiation (LTP) and enhancement of long-term depression (LTD) in the hippocampus [141,142]. Glutamate plays a key role in synaptic plasticity, including LTP, which is crucial for learning and memory formation [143]. LTP strengthens synapses by increasing the efficiency of glutamatergic signaling, whereas LTD weakens synapses [144]. In AD, impaired glutamatergic signaling reduces the capacity for LTP and enhances LTD, contributing to memory deficits and cognitive decline [145].

Extensive research indicates a direct relationship between OS and synaptic dysfunction in AD [138,146]. ROS, $\text{A}\beta$, and phosphorylated tau independently and synergistically affect NMDAR activity, which is crucial for excitatory synaptic transmission and plasticity [147,148]. $\text{A}\beta$ reduces surface NMDA receptors, triggers NMDA-mediated calcium influx, and induces excitotoxicity, exacerbating OS and impairing neuronal function [149,150]. Memantine targets non-synaptic NMDA receptors involved in excitotoxicity due to glutamate spillover [151,152]. Additionally, soluble $\text{A}\beta$ species promote AMPA receptor internalization, affecting synaptic plasticity and causing synaptic dysfunction and dendritic spine loss [153].

OS significantly impacts synaptic integrity and function, especially in synaptic membranes rich in polyunsaturated fatty acids, which are highly susceptible to lipid peroxidation, which changes the physical properties of cellular membranes and impairs the function of membrane-bound proteins [154,155]. Furthermore, $\text{A}\beta$ oligomers are particularly toxic to synapses, inducing OS by interacting with synaptic receptors and disrupting calcium homeostasis [156,157]. Excessive glutamate resulting from impaired astrocytic glutamate transporters overstimulates NMDA receptors, leading to a large influx of calcium into neurons [158]. Elevated intracellular calcium levels activate detrimental cellular events, including calcium-dependent enzymes like calpains, phospholipases, and nitric oxide synthase (NOS), which increase ROS production [158]. Together with the overwhelming damage to the antioxidant defenses that disrupt cellular processes in neurons, mitochondrial dysfunction also contributes to synaptic loss [159]. Mitochondrial dysfunction leads to decreased ATP production, which alters the function of ATP-dependent vesicular transporters responsible for packaging and releasing neurotransmitters into the synaptic cleft. This reduction in energy supply results in inefficient neurotransmitter release and decreased receptor binding affinity, causing diminished synaptic transmission over time [158].

7.4. Role of MAO-A and MAO-B in Alzheimer's Disease

Monoamine oxidases (MAO-A and MAO-B) are mitochondrial outer membrane enzymes that catalyze the oxidative deamination of monoamines, producing H_2O_2 as a byproduct [160,161]. Among them, MAO-B is the predominant isoform in the human brain, especially localized in astrocytes and serotonergic neurons [162]. In AD, MAO-B expression is significantly upregulated, particularly in the hippocampus and cerebral cortex [163]. A more than three-fold increase in active MAO-B has been detected in reactive astrocytes surrounding $\text{A}\beta$ plaques [164], contributing to excessive H_2O_2 production and further mitochondrial and neuronal damage [165].

The functional overexpression of MAO-B in AD is considered an early and sustained event that exacerbates pathological progression. Inhibiting MAO-B has thus emerged as a potential therapeutic strategy. Selegiline, an irreversible MAO-B inhibitor, demonstrated some cognitive benefits in clinical studies [166], while lazabemide, a reversible MAO-B

inhibitor, showed a 20–40% reduction in cognitive decline during phase 2 trials before its development was discontinued due to toxicity concerns [167].

Beyond redox imbalance, MAO-B is implicated in neurotransmitter dysregulation, particularly affecting dopaminergic, serotonergic, adrenergic, and cholinergic signaling systems essential for cognition [168]. It may also promote neuroinflammation, acting through cytokine-related mechanisms that worsen cognitive impairment [169]. Altered MAO-linked metabolites, such as homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), have been associated with dementia severity in both preclinical models and AD patients. Furthermore, elevated MAO-B activity in both brain tissue and platelets of AD patients correlates with cognitive decline and Mini-Mental State Examination (MMSE) scores, particularly in later disease stages [170]. This reinforces the potential of MAO-B as a biomarker and therapeutic target. Additionally, MAO-B overactivity has been linked to enhanced A β production, further tying it to the core pathology of AD.

In summary, MAO-B contributes to AD through multiple interconnected mechanisms, including ROS generation, neurotransmitter imbalance, neuroinflammation, and amyloidogenesis. Although MAO inhibitors have shown promise, further investigation is necessary to optimize their efficacy and safety for AD treatment.

8. Recent Advances in Alzheimer's Disease Therapeutics Targeting Oxidative Stress

Currently, the FDA-approved drugs for treating AD include galantamine, donepezil, memantine, rivastigmine, and the combination drug Namzaric (donepezil and memantine). Tacrine was the first drug approved for AD treatment, but it was later withdrawn due to hepatotoxicity [124,171]. Acetylcholinesterase inhibitors are beneficial in almost all stages of dementia, yet their efficacy in MCI and prodromal AD remains unproven [171]. Memantine is effective for moderate to severe AD, possibly by mitigating the glutamate-induced excitotoxicity, as it is an NMDA receptor antagonist, but does not significantly mitigate cognitive decline [171]. Recently, anti-amyloid- β antibodies, such as aducanumab, lecanemab, and gantenerumab, have also been included in the FDA-approved drugs and have garnered attention for AD treatment [26]. These monoclonal IgG1 antibodies target aggregated forms of A β , and growing clinical evidence supports the beneficial role of A β immunotherapy in improving AD conditions [172]. These medications, however, provide only symptomatic relief without halting disease progression or altering its outcomes [173].

Emerging therapeutic developments include naturally occurring polyphenolic compounds that act as antioxidants and confer neuroprotection in AD [174]. In general, polyphenols have exhibited various biological activities against several human diseases [175,176]. They also potentially modulate gut dysbiosis [177]. When it comes to AD, polyphenols either reduce the production of ROS or enhance antioxidant release [175]. For instance, α -lipoic acid, a dithiol antioxidant compound, acts as a free radical scavenger and mitigates H₂O₂ or iron-induced pathologies by inhibiting ferroptosis. It reduces the iron required for converting H₂O₂ into OH \bullet via the Fenton reaction by forming chelates with iron. Additionally, it decreases brain calcium content and calpain activity, thereby preventing neuronal cell death [178].

Green tea polyphenols, rich in (-)-epigallocatechin-3-gallate (EGCG), scavenge free radicals, chelate metal ions, and inhibit the nuclear translocation of NF- κ B, alleviating OS and protecting against various AD-promoting factors [179]. Polyphenolic compounds can cross the BBB and promote neuroprotection [180]. In contrast, ROS have been found to disrupt the BBB by activating several signaling pathways, leading to tight junction activation, adherent junction modification, mitochondrial membrane pore activation, and cytoskeletal disorganization. This disruption results in BBB dysfunction and further exac-

erbrates other pathological conditions, including neuroinflammation, progressing to AD. Naturally occurring polyphenols such as stilbenes, flavanones, isoflavones, and phenolic acids act as antioxidants, mitigating BBB dysfunction associated with increased OS [181].

Since mitochondrial dysfunction is one primary source of free radicals, identifying antioxidants that act in mitochondria's proximity is crucial in ameliorating OS-induced AD. Antioxidants like coenzyme Q10, MitoQ, and dimebon are potent in alleviating mitochondrial dysfunction and associated oxidative damage, thereby reducing cognitive decline in AD patients [182]. Thus, polyphenols are considered potential therapeutic molecules for treating OS-induced AD. A summary of clinical trials assessing various compounds targeting OS in AD is presented in Table 1.

Aside from mitochondrial dysfunction, the contents of the inflammatory system can also impact AD's progression. ROS activates protein kinase C and the Mitogen-Activated Protein Kinase (MAPK) pathway, triggering the release of inflammatory cytokines and chemokines. These inflammatory cells synthesize free radicals, further stimulating other inflammatory mediators. Consequently, anti-inflammatory drugs can be employed to reduce OS-induced damage and prevent neurodegeneration. Tumor Necrosis Factor- α (TNF- α) is a significant stimulator of cytokines and other inflammatory mediators, leading to the abnormal cleavage of APP. TNF- α also stimulates the Nuclear Factor kappa B (NF κ B) pathway, producing A β . Inhibiting TNF- α in AD patients has been found to mitigate cognitive defects [183]. TNF- α inhibitors, such as etanercept, can reduce TNF- α -induced neuronal damage.

Table 1. Overview of clinical trials assessing the impact of various compounds on OS in AD.

NCT Number	The Intervention	Target/Outcome Measured	Status of the Study	Ref
NCT06797817	Tributylin	Cognitive function, blood markers (such as BDNF and GFAP), and gut health	Not Yet Recruiting	[184]
NCT01731093	AT-001	Serum and CSF selenium levels; isoprostanes in serum, urine, and CSF	Completed	[185]
NCT01388478	R-pramipexole	Cognitive performance, cerebral glucose metabolism (via PET scan), and oxidative stress (CSF isoprostane levels)	Completed	[186]
NCT01731093	Tebofortan	Cognitive and neuropsychiatric performance (N-BACE, MMSE, NPI-Q, CDR, GDS, Blessed scale), neurological status, and blood markers of inflammation and oxidative stress	Completed	[187]
NCT03630419	Mito-Food Plan, Cellular Repair Therapy	Inflammation, Mini-Mental State Exam, Montreal Cognitive Assessment	Completed	[188]

Table 1. *Cont.*

NCT Number	The Intervention	Target/Outcome Measured	Status of the Study	Ref
NCT04740580	Glycine plus N-acetylcysteine	Cognition, brain glucose uptake, inflammation, mitochondrial function, glutathione, key amino acids, oxidative stress, and BDNF	Recruiting	[189]
NCT00596024	Lutein/zeaxanthin	Oxidative damage markers	Terminated	[190]
NCT04430517	Nicotinamide Riboside	Cognition (RBANS), daily function (ADCS-ADL), mood (PHQ-9), neuropsychiatric symptoms (NPI-Q), brain NAD ⁺ /NADH ratio, CK/ATPase activity, and GSH levels	Recruiting	[191]
NCT05323812	Edaravone	Oxidative stress markers (8-OHdG/8-OHG), plasma uric acid, amyloid (A β 42, A β 40), phosphorylated tau, GFAP, NfL, t-tau, YKL-40, and NRG1 in plasma and CSF	Not Recruiting	[192]
NCT05977088	Transcranial Magnetic Stimulation	Cognition, mood, neuropsychiatric symptoms, neurotrophic factors (BDNF, GDNF), inflammation, oxidative stress, lipid and amino acid profiles, exosomes, and brain activity (EEG)	Recruiting	[193]
NCT05929924	Extra-Virgin Olive Oil	Blood metabolites and mRNA transcripts	Not Yet Recruiting	[194]
NCT06019117	Probiotic K10	Motor function (MDS-UPDRS), quality of life (PDQ-39, QOL), neuropsychiatric symptoms (NPI-Q), cognition (MMSE), and cortisol levels	Completed	[195]
NCT00090402	Fish Oil and Alpha Lipoic Acid	F2-isoprostane Level Urine F2-Isoprostanes, Mini-Mental State Exam (MMSE), ADL/IADL	Completed	[196]
NCT04213391	Sulforaphane	Cognition (ADAS-Cog, MMSE, MoCA, CIBIC-plus), daily function (ADCS-ADL), neuropsychiatric symptoms (NPI), oxidative stress, epigenetics, inflammation (cytokines/chemokines), metabolites, RNA expression, and gut microbiota	Unknown Status	[197]
NCT04559828	Pomace Olive Oil, High-Oleic Sunflower Oil	Release of proinflammatory markers TNF- α , IL-6 and IL-1 β by BV2 cells, redox markers	Completed	[198]
NCT04939792	Vitamin D3, L-cysteine	Blood levels of 25(OH)VD, TNF- α , HOMA-IR	Completed	[199]

While the table summarizes several compounds under investigation for their potential to mitigate OS in AD, certain treatments merit further discussion due to their unique mechanisms and advanced clinical testing stages.

Carvedilol, a nonselective β -blocker and α -1 blocker used for cardiovascular diseases, may also be effective in AD due to its ability to block harmful β -adrenergic signaling that exacerbates neuroinflammation, OS and A β toxicity. By reducing neuroinflammation and ROS levels and protecting against A β -induced synaptic dysfunction, Carvedilol holds promise in slowing AD progression and promoting neuronal survival through its neuroprotective effects on oxidative and inflammatory pathways [200,201]. Carvedilol is currently in phase IV clinical trials with 29 participants enrolled. This study, designed as a randomized, triple-blind, and parallel assignment, has shown that Carvedilol inhibits apoptosis, reduces ROS levels, and mitigates A β toxicity. Carvedilol promotes neuronal growth and survival by regulating Interleukin-1 beta (IL-1 β) expression. Furthermore, it activates the Nrf2/ARE pathway, as shown in Figure 4, increasing the levels of heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase-1 (NQO-1) in HT22 cells, thereby alleviating OS [202,203].

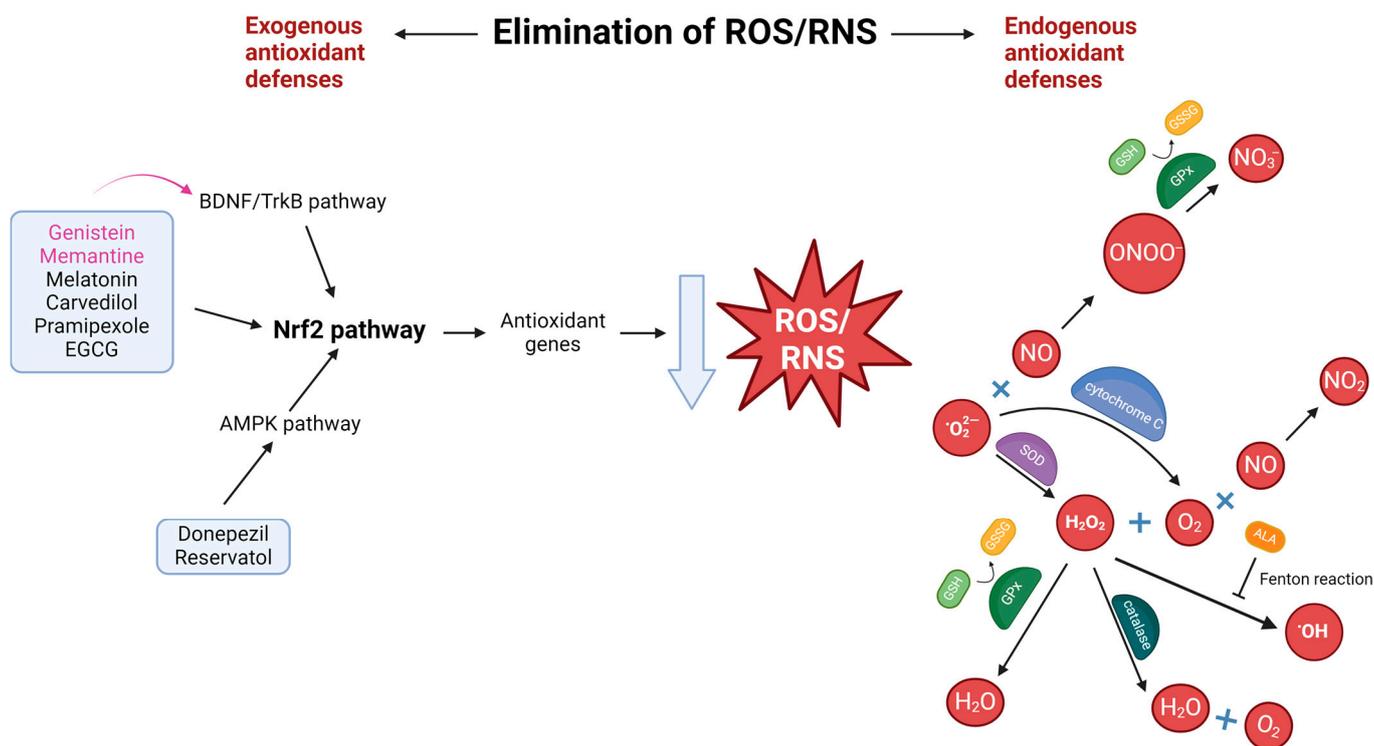


Figure 4. Summary of the primary exogenous and endogenous antioxidant defenses for ROS/RNS elimination.

In a related effort, melatonin is undergoing phase III trials to treat AD by decreasing OS and amyloidogenesis. Melatonin scavenges ROS and activates the Nrf2/HO-1 pathway, elevating antioxidant levels such as catalase, superoxide dismutase, and GPx [204–206]. As a pineal hormone, melatonin inhibits β and γ secretase enzymes while increasing α secretase activity, thus reducing amyloidogenesis. It is highly efficient in neuroprotection during early-stage AD. Similarly, Pramipexole is in phase II trials with an open-label, single-group assignment design involving 20 participants. Preclinical studies in APP^{swE}/PS1^{dE9} mice models have shown that Pramipexole, a dopamine agonist, exhibits neuroprotective effects by scavenging free radicals and mitigating OS in mitochondria. It activates the Nrf2/HO-1 pathway, increases IL-10 generation, and improves cognitive functions. Additionally, Pramipexole activates the CREB pathway, reducing over-expressed RCAN1 levels [23,207–209].

Moreover, Resveratrol is in phase II trials to evaluate its effectiveness in preventing AD progression. This randomized, single-centered study with quadruple masking and parallel

group assignment includes 119 participants. Preclinical studies in Tg19959 and APP/PS1 transgenic mice models have shown that Resveratrol reduces tau pathology by activating AMPK and reducing OS. It also inhibits the Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT) pathway and stimulates PP2A activation, promoting tau dephosphorylation and neuronal survival [210–212]. In addition, Etanercept is in phase I clinical trials with an open-label, crossover assignment model involving 12 participants. Studies in AD mouse models have demonstrated that Etanercept decreases TNF- α levels in the brain, reducing ROS production via NADPH oxidase and improving cognitive function. As an anti-TNF- α drug, Etanercept reduces OS, evidenced by decreased MDA levels and increased antioxidant levels such as SOD and GPx [213–217].

Epigallocatechin-gallate (EGCG) is under evaluation in phase III trials for its benefits in early-stage AD. With 200 participants, this randomized, double-blind, crossover assignment study has shown that EGCG, which contains hydroxyl groups, neutralizes free radicals, modulates pro-apoptotic proteins Bax and Bad, and regulates mitochondrial permeability. It also activates the Nrf2/ARE pathway, alleviating OS and providing neuroprotection [218,219].

Genistein is under evaluation in a phase II trial with a randomized, parallel assignment and quadruple masking study design that involves 27 participants. Experiments on streptozotocin-induced rat models have shown that Genistein induces autophagy and promotes A β clearance. It hinders kinases such as cyclic Adenosine Monophosphate (cAMP)-dependent protein kinase, protein kinase C, and phosphorylase kinase. Genistein also promotes neuronal survival by attenuating OS via the Phosphoinositide 3-Kinase/Protein Kinase B (Akt)/Nuclear Factor Erythroid 2-Related Factor 2/Kelch-like ECH-Associated Protein 1 (PI3K/Akt/Nrf2/Keap1) pathway and activates the cAMP/CREB-BDNF-TrkB signaling pathway, enhancing cAMP levels and CREB and TrkB phosphorylation [220–222].

Figure 4 illustrates how exogenous and endogenous antioxidant defenses work together to eliminate ROS/RNS, highlighting the Nrf2 pathway's activation and its role in OS regulation.

9. Conclusions and Future Directions

OS plays an essential role in the pathophysiology and progression of AD. ROS and RNS contribute to neuronal toxicity through lipid peroxidation, protein oxidation, and DNA damage. Mitochondrial dysfunction aggravates ROS production, disrupting cellular metabolism and accelerating neurodegeneration. Moreover, OS interacts with key pathological hallmarks of AD, including A β aggregation, tau hyperphosphorylation, and synaptic dysfunction, creating a self-perpetuating cycle of neuronal injury. Despite growing evidence showing the linking of OS to AD, antioxidant-based therapeutic strategies have resulted in inconsistent clinical outcomes, showing the complexity of the disease. While significant progress has been made in understanding OS-driven neurodegeneration, numerous challenges hinder the clinical translation of OS-targeting therapies. One of the significant limitations is the inconsistent efficacy of antioxidants in clinical trials, which can be attributed to poor bioavailability, inadequate BBB permeability, and interindividual variability in OS profiles. Moreover, conventional antioxidant administration often results in systemic distribution rather than targeted neuroprotection. Advances in nanotechnology, particularly nanoparticle-based and liposomal delivery systems, may enhance brain-specific antioxidant delivery and improve therapeutic outcomes. The heterogeneity of AD pathogenesis further complicates OS-targeted interventions, as genetic, environmental, and lifestyle factors contribute to disease variability. A shift toward personalized medicine, rather than a one-size-fits-all antioxidant approach, is critical for improving treatment efficacy.

A promising research area for future investigation is the development of precision antioxidant therapies that selectively target ROS sources while preserving essential redox signaling. Mitochondria-targeted antioxidants offer a potential strategy to mitigate oxidative damage while maintaining metabolic integrity. Additionally, multi-target therapeutic approaches combining antioxidants with neuroprotective agents, anti-inflammatory compounds, and amyloid-targeting strategies may enhance overall treatment efficacy. Early detection remains crucial for successful intervention, necessitating the identification of reliable redox-based biomarkers for AD diagnosis. Peripheral markers such as oxidized glutathione (GSSG), HNE, and F2-isoprostanes may facilitate early disease progression detection and monitoring. Another emerging area of interest is the gut–brain axis in OS regulation. Alterations in gut microbiota composition have been implicated in neuroinflammation and oxidative imbalance, suggesting that probiotic-based and microbiota-targeted interventions may offer novel avenues for modulating OS and mitigating AD pathology.

Longitudinal cohort studies will be essential to establish causal relationships between OS and AD progression. Given that oxidative damage accumulates over decades before clinical symptoms emerge, long-term follow-up studies are necessary to validate therapeutic interventions and optimize the timing of interventions. Addressing these challenges will be critical to advancing OS-targeted therapies and developing more effective AD prevention and treatment strategies.

Author Contributions: All authors contributed to this manuscript's conceptualization, writing, editing, and reviewing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full Term
3-NT	3-nitrotyrosine
4-HNE	4-hydroxynonenal
53BP1	P53-binding protein 1
8-OHG	7,8-dihydro-8-oxoguanine
8-OHdG	8-hydroxy-deoxyguanosine
ABAD	A β -binding alcohol dehydrogenase
AD	Alzheimer's disease
AMP	Adenosine Monophosphate
APP	Amyloid precursor protein
ASK-1	Apoptosis Signal-regulating Kinase 1
ATP	Adenosine triphosphate
Akt	Akt kinase
A β	Amyloid- β
BBB	Blood–brain barrier
BER	Base excision repair
Bax	Bcl-2-associated X protein
Ca $_2^+$	Calcium ions
DPL1	Dihydrosphingosine phosphate lyase

DSB	Double-strand break
sSBs	Single-strand breaks
EGCG	Epigallocatechin gallate
EPR	Electron paramagnetic resonance
ERK1/2	Extracellular signal-regulated kinase 1/2
ETC	Electron transport chain
F2-IsoPs	F2-isoprostanes
FDA	Food and Drug Administration
Fe ²⁺	Ferrous ions
GLAST	Glutamate aspartate transporter
GLT-1	Glutamate transporter 1
GRX-1	Glutaredoxin-1
GS	Glutamine synthetase
GSK3-β	Glycogen synthase kinase 3β
GSSG	Glutathione
HO-1	Heme oxygenase-1
HSP60	Heat shock protein 60
H ₂ O ₂	Hydrogen peroxide
IL-1β	Interleukin-1 beta
Keap1	Kelch-like ECH-Associated Protein 1
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase
MnSOD	Mitochondrial superoxide dismutase
NADPH	Nicotinamide adenine dinucleotide phosphate
NFTs	Neurofibrillary tangles
NFκ-β	Nuclear Factor kappa B
NMDAR	N-methyl-D-aspartate receptors
NOS	Nitric oxide synthase
NO•	Nitric oxide
NQO-1	NAD(P)H quinone oxidoreductase-1
Nrf2	Nuclear factor erythroid 2-related factor 2
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
ONOO ⁻	Peroxynitrite
OS	Oxidative stress
NS	Nitrosative stress
PCAD	Preclinical Alzheimer's disease
PCs	Protein carbonyls
PI3K	Phosphoinositide 3-kinase
PI3K/AKT	Phosphoinositide 3-kinase/protein kinase b
PI3K	Phosphoinositide 3-Kinase
PP2A	Protein phosphatase 2A
PS-1	Presenilin-1
Pin1	Peptidyl-prolyl cis-trans isomerase 1
QH2	Ubiquinol
RIRR	ROS-induced ROS release
ROS	Reactive oxygen species
ROS/RNS	Reactive oxygen/nitrogen species
SOD	Superoxide dismutase
SOD1	Copper-zinc SOD
SOD2	Mitochondrial SOD
SSBs	Single-strand breaks
TNF-α	Tumor Necrosis Factor-alpha
Trx-1	Thioredoxin-1

aMCI	Amnesic mild cognitive impairment
cAMP	Adenosine monophosphate
mPTP	Mitochondrial permeability transition pore
mtDNA	Mitochondrial DNA

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