



REVIEW

Neuroinflammation and Oxidative Stress: Their Pathophysiological Roles in Amyotrophic Lateral Sclerosis and Alzheimer's Disease

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ABSTRACT: Neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD) are driven by complex, multifactorial mechanisms in which oxidative stress (OS) and neuroinflammation (NI) play central, mutually reinforcing roles. Their interaction is mediated through key signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), nuclear factor erythroid 2-related factor 2-Kelch-like ECH-associated protein 1 (Nrf2-Keap1), and the mitogen-activated protein kinase (MAPK) pathway, as well as mitochondrial dysfunction, microglial activation, and dysregulated redox homeostasis. Increasing attention has been directed toward understanding how Food and Drug Administration (FDA)-approved neuroprotective agents influence these interconnected processes. Drugs such as riluzole, edaravone, memantine, and acetylcholinesterase inhibitors exhibit diverse effects on glutamate excitotoxicity, free radical production, inflammatory cytokine release, and microglial reactivity, yet their modest clinical efficacy highlights the limitations of single-target approaches. This review synthesizes current evidence on the mechanistic relationship between OS and NI in ALS and AD and evaluates how existing therapeutics modulate these pathways, emphasizing the need for multitarget strategies to achieve meaningful disease-modifying outcomes.

KEYWORDS: Amyotrophic lateral sclerosis; Alzheimer's disease; neuroinflammation; oxidative stress; FDA-approved drugs

1 Introduction

Neurodegenerative diseases represent a series of progressive and often irreversible conditions that lead to devastating neuronal loss. The hallmark clinical symptoms of these diseases, including Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD), manifest as a gradual decline in essential motor and cognitive functions, significantly impairing the quality of life over time. The mechanisms driving these complex diseases are multifaceted and involve multiple contributing factors [1,2]. While genetic predisposition, proteostatic disorders, and environmental influences have long been recognized, emerging research underscores the critical roles of neuroinflammation (NI) and oxidative stress (OS). These two factors are now understood to be pivotal in triggering and perpetuating the progression of neurodegenerative diseases, amplifying the urgency for targeted interventions and innovative therapeutic strategies [3-5]. Both experimental and clinical research results indicate that the interaction between OS and NI causes permanent damage to nerve cells and plays a decisive role in disease progression [4,6].

The treatment of neurodegenerative diseases is not only symptomatic but also targets neuroprotective agents that address underlying processes, such as OS and NI [2]. Evaluating the efficacy of FDA-approved drugs for neurodegenerative diseases in processes such as NI and OS is a focal point of translational neuroscience research today [7–9]. This review aims to elucidate the mechanistic interplay between oxidative stress and neuroinflammation in the pathogenesis of ALS and AD, and to evaluate how FDA-approved therapeutics modulate these interconnected pathways. The paper contributes to the field by integrating mitochondrial biology, redox signaling, inflammasome activation, and glial immunometabolism into a unified framework that explains how oxidative and inflammatory processes co-evolve during neurodegeneration. The novelty of this work lies in its comprehensive synthesis of matrix-derived Reactive Oxygen Species (ROS) dynamics and disease-specific mitochondrial vulnerabilities in ALS and AD, offering a mechanistic rationale for repurposing existing therapeutics and guiding the development of future combination strategies that simultaneously target oxidative stress and neuroinflammation.

2 Literature Search

A narrative review was conducted to examine the interplay between oxidative stress and neuroinflammation in the pathophysiological mechanisms underlying ALS and AD, and to evaluate the effects of FDA-approved medications on these processes. Literature searches were performed using Google Scholar, PubMed, and Web of Science. The search strategy combined the following keywords: “Alzheimer’s disease”, “Amyotrophic Lateral Sclerosis”, “neuroinflammation”, “oxidative stress”, and “FDA-approved drugs.” Articles published between 1994 and 2025 were considered. Studies focusing on diseases other than ALS and AD were excluded from the review.

3 The Cellular Basis of Neuroinflammation

According to Berríos-Cárcamo et al. (2020), the brain, an organ with highly specialized immune surveillance, is largely protected from peripheral immune cells and circulating signals by the blood–brain barrier (BBB) [10]. Despite this relative isolation, the central nervous system (CNS) can mount an inflammatory response to local pathogens or tissue injury. This response is primarily mediated by astrocytes, the key regulators of neuronal and metabolic homeostasis, and microglia, the resident immune cells of the brain. In the CNS, oligodendrocytes, microglia, and/or astrocytes release proinflammatory mediators (cytokines, chemokines, etc.), which initiate and prolong the neuroinflammatory response [3,11].

However, the brain can mount its own inflammatory response to local pathogens or tissue injury through the activation of astrocytes, the primary regulators of neuronal, metabolic, and synaptic homeostasis, and microglia, the resident immune cells of the CNS. Both cell types produce cytokines and express pattern recognition receptors, including Toll-like receptors (TLRs), which enable them to monitor the microenvironment and initiate appropriate inflammatory signaling. Astrocytes play a central role in shaping the neuroinflammatory response. Upon exposure to danger-associated or pathogen-associated signals, astrocytes undergo reactive astrogliosis, characterized by hypertrophy, upregulation of glial fibrillary acidic protein (GFAP), and transcriptional reprogramming. Activated astrocytes release pro-inflammatory mediators such as Interleukin-1 beta (IL-1 β), Tumor necrosis factor-alpha (TNF- α), and IL-6, modulate chemokine gradients that recruit or influence microglial activity, and regulate extracellular glutamate levels through altered expression of glutamate transporters (e.g., EAAT1/EAAT2), thereby contributing to excitotoxic stress [12,13]. They also influence oxidative stress by altering antioxidant defenses, including glutathione metabolism, and by producing nitric oxide and other reactive species under sustained inflammatory conditions. Through these mechanisms, astrocytes amplify or sustain neuroinflammation and

propagate neuronal dysfunction. In response to pro-inflammatory stimuli, microglia undergo phenotypic and transcriptional changes, leading to the upregulation of oxidant-generating enzymes such as NADPH oxidase (NOX) and inducible nitric oxide synthase (iNOS). These enzymes drive the production of ROS and reactive nitrogen species (RNS), further intensifying oxidative stress within the neural milieu [14].

Microglial cells normally secrete neurotrophic factors to maintain tissue homeostasis. Still, when overstimulated, they switch to a proinflammatory phenotype, increasing the release of various cytokines [TNF- α , IL-1 β , IL-6, etc.] (Fig. 1) [3,15,16]. The resulting proinflammatory environment triggers the activation of the apoptotic pathway in neurons, primarily through Ca²⁺ imbalance and mitochondrial membrane damage. Long-term microglial activation causes glial cells to enter a state called “priming”, leading to excessive responses even to mild stimuli. This pattern is frequently observed in patients with AD and ALS [17,18]. The proinflammatory environment created by microglial activation also triggers OS by increasing ROS production. For this very reason, NI is considered not only a defense response but also a cyclical mechanism that perpetuates neuronal toxicity [19,20].

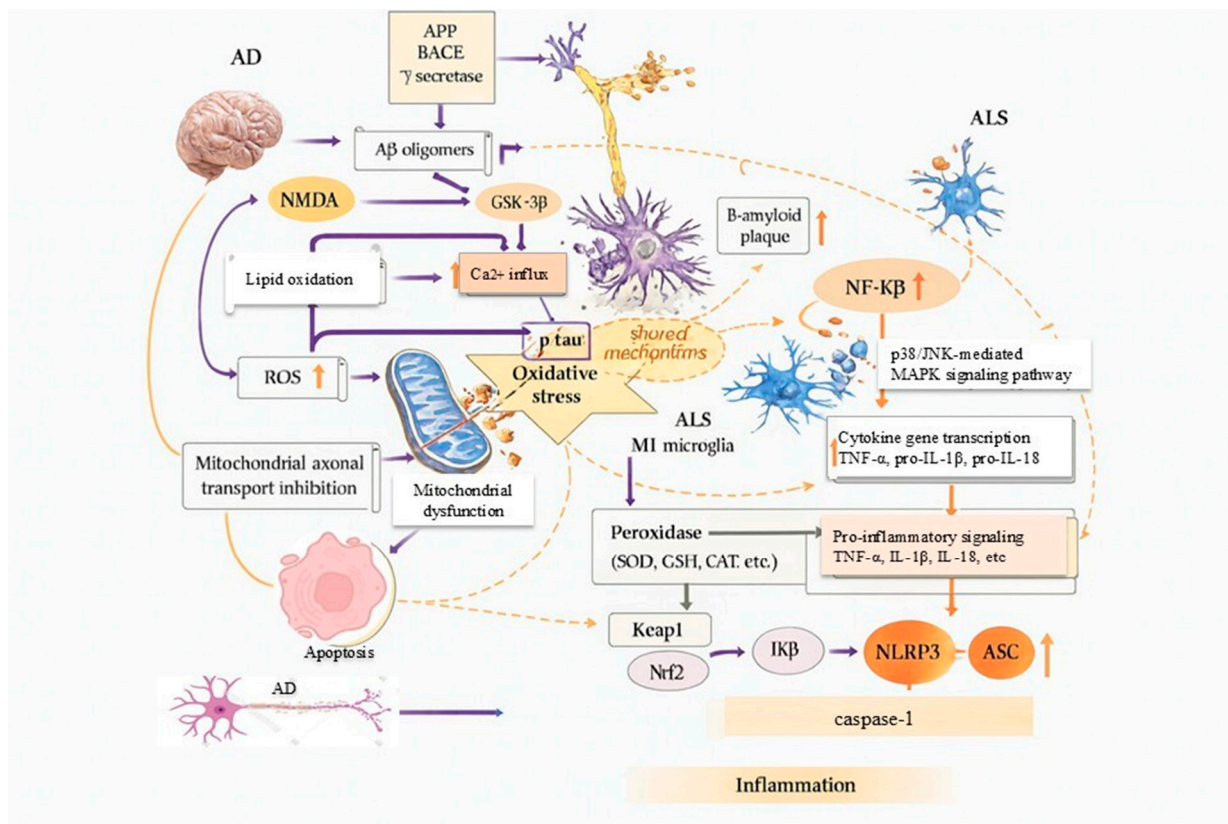


Figure 1: Common and disease-specific pathophysiological mechanisms in Alzheimer’s disease (AD) and Amyotrophic Lateral Sclerosis (ALS). This figure is adapted from Iliyasa et al. (2023) [21]. This figure summarizes the key molecular and cellular pathways involved in the pathogenesis of AD and ALS, as well as the common pathophysiological intersections among them. In AD, A β oligomers formed by β -secretase (BACE) and γ -secretase-mediated proteolytic processing of amyloid precursor protein (APP) trigger neuronal dysfunction via N-methyl-D-aspartate (NMDA) receptor activation and glycogen synthase kinase-3 beta (GSK-3 β) signaling pathways. GSK-3 β activation initiates two parallel and independent pathological processes: excitotoxicity, characterized by increased Ca²⁺ influx, and hyperphosphorylation of tau proteins (p-tau). p-tau accumulation disrupts microtubule dynamics and inhibits

mitochondrial axonal transport, weakening neuronal integrity and indirectly contributing to cellular death. A β -mediated lipid oxidation and increased production of reactive oxygen species (ROS) lead to mitochondrial dysfunction and oxidative stress. Oxidative stress potentiates inflammatory responses and microglial activation as a central pathogenic axis shared in AD and ALS. In the context of ALS, activation of microglia in the M1 phenotype results in increased p38/JNK-mediated MAPK signaling and nuclear factor kappa B (NF- κ B) activity, stimulating transcription of pro-inflammatory cytokine genes (TNF- α , pro-IL-1 β , pro-IL-18). This process, driven by the activation of the NLRP3 inflammasome complex (NLRP3, ASC, and caspase-1), sustains chronic neuroinflammation. Antioxidant defense mechanisms are regulated via the Keap1–Nrf2 axis, which controls superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and related peroxidase systems. Disruption of these protective mechanisms contributes to increased oxidative stress and inflammatory signaling. Overall, the diagram illustrates the mutually reinforcing pathological cycles of oxidative stress, mitochondrial dysfunction, and inflammation in AD and ALS, accelerating disease progression. The yellow upward arrow represented an increase. APP, Amyloid precursor protein; A β , Beta-amyloid; BACE, β -secretase; ROS, Reactive oxygen species; NMDA, N-methyl-D-aspartate; GSK-3 β , Glycogen synthase kinase 3 beta; p-tau, Phosphorylated tau; ALS, Amyotrophic lateral sclerosis; TNF- α , Tumor necrosis factor- α ; IL-18, Interleukin-18; IL-1 β , Interleukin-1 β ; GSH, Glutathione; NF- κ B, Nuclear factor kappa B; SOD, Superoxide Dismutase; CAT, Catalase; NLRP3, NLR family pyrin domain containing-3; ASC, apoptotic speck-like protein containing a caspase recruitment domain; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; Keap 1, Kelch-like ECH-associated protein 1; Ca²⁺, Calcium.

4 Molecular Dynamics of Oxidative Stress

OS and NI are driven by tightly coupled molecular events within neural tissue, with mitochondria serving as the principal source of ROS. Electron leakage from Complexes I–III of the electron transport chain generates superoxide, but Complex I is the dominant source of ROS within the mitochondrial matrix, where oxidative damage is particularly harmful. Matrix-directed ROS formation arises through two mechanistically distinct processes. During forward electron transfer (FET), electrons flow from NADH to ubiquinone; a fraction of them prematurely reduce oxygen at the FMN site, generating superoxide directly in the matrix. Under metabolic stress, ischemia-reperfusion, or impaired downstream electron flow, reverse electron transfer (RET) occurs, in which electrons move backward from ubiquinol to Complex I. RET is one of the most potent physiological triggers of ROS production, generating orders of magnitude more superoxide than FET due to the combination of a highly reduced ubiquinone pool and an elevated mitochondrial membrane potential [22]. The matrix environment—rich in NADH, flavin adenine mononucleotide (FMNH₂), iron–sulfur clusters, and tightly packed respiratory complexes—further favors one-electron oxygen reduction. Because ROS are produced adjacent to mitochondrial DNA, cardiolipin-rich inner membranes, and TCA cycle enzymes, matrix ROS inflict disproportionate structural and metabolic damage [23].

Accumulation of ROS and RNS disrupts redox homeostasis, initiating lipid peroxidation, DNA breaks, and protein oxidation [24]. These oxidative insults activate redox-sensitive inflammatory pathways, particularly NF- κ B, which induces IL-1 β , Cyclooxygenase-2 (COX-2), TNF- α , and iNOS, thereby amplifying microglial and astrocytic activation. Activated glia further increase ROS production through NOX enzymes and nitric oxide pathways, reinforcing mitochondrial dysfunction [25,26]. In contrast, the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway coordinates antioxidant defense by upregulating heme oxygenase-1, glutathione peroxidase, and other detoxifying enzymes; however, chronic inflammation and aging diminish Nrf2 activity, shifting the balance toward sustained NF- κ B activation. This reciprocal suppression of antioxidant defenses and reinforcement of inflammatory signaling establishes

a self-perpetuating cycle in which oxidative stress and neuroinflammation mutually intensify, driving progressive neuronal vulnerability [27,28].

5 The Bidirectional Microglia–Mitochondria Interaction

It has been reported that dysregulation of inflammatory responses triggered by mitochondrial components or products contributes to numerous human diseases, ranging from those driven by excessive inflammation to those arising from inefficient inflammatory reactions [29]. In recent years, it has been shown that mitochondrial function is not limited to energy production but also plays an active role in regulating the immune response [25,26]. During microglial activation, elevated levels of mitochondria-derived reactive oxygen species (mtROS) serve as key triggers for the assembly of NLRP3 inflammasome complexes, leading to caspase-1 activation and the subsequent release of IL-1 β and IL-18, which amplify the inflammatory response. Multiple signaling pathways link mitochondrial dysfunction to innate immune activation. One major pathway involves the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS), which is activated when damaged mitochondria release oxidized mitochondrial DNA (mtDNA) into the cytosol. Activated cGAS produces cyclic GMP-AMP (cGAMP), which binds to and activates the adaptor protein interferon response cGAMP interactor 1 (STING1), initiating type I interferon signaling and promoting a pro-inflammatory transcriptional program. In parallel, both mtROS and cytosolic mtDNA directly stimulate inflammasome activation, particularly NLR family pyrin domain containing 3 (NLRP3), by promoting thiol oxidation, mitochondrial membrane destabilization, and the release of mitochondrial danger-associated molecular patterns. Together, these pathways illustrate how mitochondrial dysfunction serves as a central molecular hub, integrating mtROS, mtDNA leakage, and innate immune signaling to drive sustained neuroinflammation [30–32].

Mitochondrial ROS activate inflammasome complexes (NLRP3), leading to the release of IL-1 β and IL-18. Conversely, inflammation can further exacerbate mitochondrial dysfunction, creating a bidirectional cycle between oxidative stress and innate immune activation. Pro-inflammatory cytokines such as TNF- α , IL-1 β , and interferon gamma (IFN- γ) impair electron transport chain activity, reduce mitochondrial membrane potential, and increase mitochondrial permeability transition, all of which promote additional mitochondrial ROS production. Activated microglia and astrocytes release nitric oxide and RNS that inhibit Complex I and Complex IV, leading to electron leakage and further mitochondrial damage. Inflammatory signaling also disrupts mitochondrial dynamics by promoting excessive fission, inhibiting fusion, and impairing mitophagy, resulting in the accumulation of dysfunctional mitochondria that release even more ROS and mitochondrial DNA into the cytosol. Thus, inflammation not only arises from mitochondrial dysfunction but also feeds back to intensify it, reinforcing a self-perpetuating cycle of mitochondrial impairment, oxidative stress, and neuroinflammation [33,34]. TNF- α and IL-6 have been reported to reduce mitochondrial membrane potential and limit ATP production. Due to this bidirectional interaction, OS and inflammation are characterized as a “vicious cycle” that continuously feeds each other [35]. In both ALS and AD, mitochondrial dysfunction and the resulting release of mitochondrial danger signals act as central drivers of innate immune activation. In AD, amyloid- β (A β) aggregates impair Complex I activity and destabilize mitochondrial membranes, promoting excessive mitochondrial ROS (mtROS) production and leakage of oxidized mtDNA into the cytosol. Cytosolic mtDNA activates the cGAS–STING pathway, triggering type I interferon signaling and amplifying microglial inflammatory responses. A β also directly enhances STING activation, further reinforcing this pro-inflammatory cascade. In ALS, mutant superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP-43), and Fused in Sarcoma (FUS) proteins accumulate on the outer mitochondrial membrane and within the matrix, disrupting electron transport, increasing mtROS generation, and promoting mtDNA release.

These mitochondrial disturbances activate both the NLRP3 inflammasome and the cGAS–STING axis, leading to caspase-1 activation and the maturation of IL-1 β and IL-18. Thus, in both diseases, pathological protein aggregates converge on a shared mechanism—mtROS-driven mitochondrial damage and mtDNA leakage—that fuels chronic neuroinflammation through NLRP3 and cGAS–STING signaling [30,36].

6 Signaling Pathways of Neuroinflammation and Oxidative Stress

The interaction between NI and OS in pathophysiological processes largely depends on the activation of specific signaling pathways. These pathways encompass a broad network ranging from the regulation of intracellular stress responses to the synthesis of inflammatory mediators [6]. The Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B), Nrf2, Kelch-like ECH-associated protein 1 (Keap1), Mitogen-Activated Protein Kinase (MAPK), and inflammasome signaling pathways are recognized as the primary molecular mediators of neuronal damage in neurodegenerative diseases (Fig. 1) [37–39].

6.1 NF- κ B Signaling Pathway

NF- κ B, a key transcription factor that regulates proinflammatory gene expression, is usually found in the cytoplasm in an inactive state, bound to its inhibitory protein I κ B [40]. Under OS conditions, ROS induce the phosphorylation and degradation of I κ B α , leading to the nuclear translocation of NF- κ B. As a result of this process, the expression of inflammatory genes such as IL-1 β , TNF- α , COX-2, and iNOS increases [4,6]. Chronic NF- κ B activation leads to the conversion of microglial cells to a proinflammatory phenotype and to deeper oxidative damage in surrounding tissues [41]. Post-mortem analyses in AD and PD patients indicate increased NF- κ B activity, which correlates positively with the severity of neurodegeneration [42,43].

6.2 Nrf2–Keap1 Signaling Pathway

The pathway that counterbalances NF- κ B is the main regulator of the antioxidant defense system. Under physiological conditions, Nrf2 is kept inactive by forming a complex with the Keap1 protein in the cytoplasm [44]. Under OS, oxidation of critical cysteine residues in Keap1 releases Nrf2, allowing it to translocate to the nucleus, where it binds to antioxidant response elements (ARE). This binding induces the expression of antioxidant enzymes, including heme oxygenase-1, SOD, and glutathione peroxidase [44]. Decreased Nrf2 activity in conditions such as aging or chronic NI leads to the accumulation of oxidative damage and the predominance of NF- κ B activity [45]. This dynamic is considered an important balancing mechanism that explains the progressive nature of neurodegenerative diseases.

6.3 MAPK Signaling Pathway

The MAPK family is a multi-step phosphorylation cascade that modulates cellular stress responses. Within this family, the c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38 MAPK subunits, in particular, play a critical role in neuronal cell death [46,47]. MAPK activation, triggered by ROS accumulation or inflammatory cytokines, both increases proapoptotic gene expression and contributes to the progression of the inflammatory process by enhancing NF- κ B signaling [48]. In ALS animal models, excessive activation of the MAPK cascade has been shown to accelerate neuronal loss, whereas inhibitors of p38 or JNK increase neuronal survival [49,50]. These findings suggest the pathway's potential as a therapeutic target.

6.4 Inflammasome Activation

Another mechanism that directly links OS and NI is the activation of the inflammasome complex. The NLRP3, in particular, is triggered by increased mitochondrial ROS. NLRP3 activation promotes caspase-1 maturation and consequently the release of potent proinflammatory cytokines (IL-1 β and IL-18) [51]. Chronic inflammasome activation deepens NI damage by driving a persistent proinflammatory phenotype in microglial cells. Elevated NLRP3 activation markers in brain tissue from AD patients support the importance of this pathway in disease progression [52].

6.5 The Integrative Effect of Signaling Networks and Their Relationship with Neuroprotective Agents

The four main signaling pathways interact with each other. While excessive NF- κ B activation initiates the inflammatory process, decreased Nrf2 activity weakens antioxidant defenses. The MAPK and inflammasome pathways, on the other hand, reinforce the process by acting at the intersection of these two systems. Therefore, a cyclical mechanism emerges in which NI and OS mutually trigger one another. The therapeutic effects of neuroprotective drugs are also primarily based on these molecular networks. For example, riluzole reduces ROS production by inhibiting glutamate release [53]. Edaravone supports Nrf2 activation by directly scavenging free radicals and reduces the level of 3-nitrotyrosine in CSF, a marker of oxidative damage [7,54]. The balancing effect of these agents on the NF- κ B and Nrf2 axes is considered an essential strategic approach in breaking the NI-OS cycle.

7 Cross-Mechanisms: Neuroinflammation–Oxidative Stress Interaction

Current data suggests another vicious cycle. OS not only triggers inflammation, but inflammation also increases ROS production [55]. In fact, OS and NI can be defined as two processes that mutually reinforce each other in neurodegenerative diseases. For example, microglia activated via NF- κ β increase superoxide production. The ROS generated in this process triggers cell death in neurons through lipid peroxidation and DNA damage. At the same time, this oxidative damage reactivates surrounding microglia, perpetuating the cycle. While ROS accumulation activates the NF- κ B pathway, increasing inflammation, inflammatory cytokines such as TNF- α and IL-6 accelerate mitochondrial ROS production [19]. This interaction creates a positive feedback loop that triggers neuronal death. This bidirectional interaction acts as a “silent accelerator” in the progression of neurodegenerative diseases. Therefore, when developing treatment strategies, it is necessary to target inflammatory signaling pathways in addition to suppressing oxidative stress, requiring a dual-pronged approach.

Neuroinflammation and oxidative stress exhibit distinct yet partially convergent profiles across disease stages in ALS and AD. In ALS, the early stages are characterized by subtle yet detectable increases in oxidative stress markers within motor neurons, accompanied by microglial priming and mild astrocytic activation, often preceding overt motor symptoms. As ALS progresses, this evolves into a more pronounced proinflammatory milieu, with sustained microglial activation, elevated proinflammatory cytokines, and amplification of mitochondrial ROS production, creating a self-reinforcing OS–NI loop that accelerates motor neuron degeneration [56]. In AD, mild stages are typically associated with regionally restricted microglial activation around amyloid plaques and moderate oxidative damage affecting synapses and dendrites, correlating with early cognitive decline. In moderate-to-severe AD, neuroinflammation becomes more diffuse and sustained, oxidative damage extends to lipids, proteins, and nucleic acids, and the failure of endogenous antioxidant and resolution pathways further entrenches the chronic OS–NI cycle, paralleling extensive neuronal and synaptic loss [57].

8 Clinical and Therapeutic Perspective

The growing evidence that NI and OS play a central role in the pathogenesis of neurodegenerative diseases has led to a reassessment of currently FDA-approved agents, not only for their symptomatic effects but also for their neuroprotective potential [3]. Agents such as riluzole, edaravone, memantine, and acetylcholinesterase (AChE) inhibitors (AChEIs) (donepezil, rivastigmine, galantamine) interfere with key processes at different levels, including glutamate excitotoxicity, free-radical production, microglial activation, and proinflammatory cytokine release [58–60]. Research on the repurposing of FDA-approved Alzheimer's drugs has shown that donepezil and memantine are the most effective at crossing the blood-brain barrier [61]. However, the generally modest clinical efficacy of these drugs highlights the limitations of single-target approaches and the need for multi-target strategies.

8.1 Riluzole: Excitotoxicity, Oxidative Stress, and Microglial Activation

Riluzole is a benzothiazole derivative that primarily reduces glutamatergic neurotransmission, blocks voltage-gated Na⁺ channels, and exerts a multimodal mechanism of action with neuroprotective/antioxidant properties [62,63]. Clinical data show that it provides a limited but meaningful extension of life span [64,65]. Beyond this, recent experimental studies have demonstrated that riluzole can not only reduce presynaptic glutamate release but also modulate OS and inflammatory markers [66,67]. However, several studies have reported that riluzole attenuates oxidative damage caused by ALS pathogenesis in neuronal cells [62]. Riluzole also has antioxidant properties in other disease models. Studies using riluzole-treated AD rat models have shown that riluzole exerts neuroprotective effects in AD by decreasing AChE activity and OS markers [68]. Riluzole treatment in ALS patients has been reported to increase survival and improve motor function [65]. In human or animal-derived neuronal and glial cell models, riluzole has been shown to reduce ROS production, strengthen antioxidant defenses, and suppress microglial activation and proinflammatory cytokine release [69]. These data suggest that riluzole's modest effect observed in the clinic may be partially related to the partial disruption of the NI-OS cycle. Results from preclinical studies evaluating its impact on AD indicate that riluzole treatment reduces glutamate excitotoxicity, microglial and astrocyte activation, ROS, and OS, while increasing synaptic plasticity and improving learning and memory [70,71]. However, most of these mechanistic findings are at the preclinical level and need to be validated in prospective, biomarker-based clinical studies. Therefore, riluzole can be considered one of the "first-generation neuroprotective agents" that target both glutamate excitotoxicity and the inflammatory response from the current perspective.

8.2 Edaravone: Free Radical Scavenging Effect and Nrf2 Modulation

Edaravone is a molecule developed as a classic free-radical scavenger that directly neutralizes hydroxyl radicals and other ROS and is primarily approved for acute ischemic stroke. It has subsequently been introduced for use in ALS. Both clinical and experimental data show that edaravone reduces lipid peroxidation, limits oxidative damage to DNA and proteins, and thereby increases neuronal survival [72]. The literature indicates that edaravone's effects are not limited to direct radical scavenging; it can also activate the Nrf2 pathway and NF-κB-mediated inflammation [73,74]. This dual effect positions edaravone as a "bridge" agent in the NI-OS-inflammation axis [75]. However, its effect on survival in ALS patients remains relatively limited, and response heterogeneity is notable. Due to its potential impact on OS and neurodegeneration, edaravone has been reported to reduce Aβ accumulation, tau phosphorylation, and mitochondrial dysfunction processes in preclinical studies on AD [76]. Edaravone treatment has been reported to reduce microglia activation, inhibit the NF-κB/MAPK pathway, and improve cognitive

performance [77,78]. Although no completed clinical studies have evaluated edaravone treatment in AD patients, the Alzheimer Study Using Oral Edaravone (ASURE) aims to evaluate the safety of oral edaravone in AD patients, its effects on OS biomarkers, and its early cognitive/functional effects [79].

8.3 Memantine: NMDA Antagonism, Anti-Inflammatory Effects, and Potential New Indications

Memantine is a voltage- and usage-dependent N-methyl-D-aspartate (NMDA) receptor antagonist used in moderate-to-severe AD that limits excitotoxicity without completely suppressing physiological glutamatergic transmission [80,81]. Recent reviews suggest that memantine may have regulatory effects not only at the synaptic level but also on microglial activity and proinflammatory signaling pathways [80]. In experimental models, memantine has been reported to reduce microglial activation, TNF- α and IL-1 β levels, and NF- κ B activity in the NI response induced by lipopolysaccharide (LPS) or trauma; it also contributes to antioxidant defense by increasing SOD and total thiol levels [82,83]. The clinical data set is expanding with studies investigating the potential benefits of memantine in some neurological conditions other than AD (vascular dementia, traumatic brain injury, other neuroinflammatory conditions), but the level of evidence for these indications remains limited [84–86]. Memantine has been suggested to be effective in ALS because it can reduce glutamate toxicity in SOD1 (G93A) mice by antagonizing NMDA receptors [87,88]. The literature generally reports that patients tolerate memantine well. However, data from large-scale randomized controlled trials specifically targeting “dementia-related motor-cognitive processes” in these disease groups are not yet sufficient. This situation makes memantine a repurposable candidate for an anti-excitotoxic and anti-inflammatory agent.

8.4 Acetylcholinesterase Inhibitors: From Symptomatic Treatment to a Multitarget Approach

AChEIs, primarily donepezil, rivastigmine, and galantamine, have traditionally been used to improve symptoms in AD [89,90]. However, in recent years, there has been increasing evidence that these agents can suppress microglial activation via the cholinergic anti-inflammatory pathway, reduce OS markers, and partially preserve mitochondrial function [4,91]. Microglial activation has been linked to increased AChE, and AChEIs may suppress this process [91]. Another study specifically reported that donepezil treatment suppressed inflammasome (NLRP3) activation in microglial cells following LPS and A β stimulation [92]. It has been shown that galantamine and donepezil can promote neuronal survival through effects on nicotinic receptor modulation, sigma-1 receptor interactions, and antioxidant defense, independent of AChE inhibition [93–95]. It was traditionally accepted that AChEIs were drugs that only improved symptoms (memory, attention, daily life) by increasing acetylcholine, that they did not stop the disease, but only alleviated the symptoms. Studies show that AChEIs not only increase acetylcholine but also reduce microglial activation, suppress NF- κ B and Nrf2 pathways, reduce OS, support mitochondrial function, and increase neurotrophic factors (especially galantamine) [91]. Therefore, AChEIs are now also considered multi-target drugs with neuroprotective potential that affect multiple pathological targets. These findings suggest that AChEIs can be reframed as components of multi-target neuroprotective strategies rather than “single-target symptomatic agents.” However, the disease-modifying effects of AChEIs at the clinical level remain unclear.

8.5 Combination Therapies and Multi-Targeted Approaches

The progression of NI and OS through intertwined networks limits the clinical efficacy of drugs developed based on the single-molecule–single-target logic. Consequently, several major trends have emerged over the past decade. Pharmacological combinations involving multiple drugs include the riluzole

+ edaravone combination in ALS treatment, which simultaneously targets excitotoxicity and OS [96]; the use of memantine with AChEIs [97]; Treatment and prevention strategies involving antioxidants or phytochemical agents (*Origanum* species, resveratrol, curcumin, etc.) [98,99] have shown synergistic effects at the preclinical level. However, randomized, controlled clinical trials remain insufficient.

The polypharmacology approach, in which a single drug affects multiple receptors or mechanisms via the development of multi-targeted, directed ligands (MTDLs), offers a promising treatment strategy that simultaneously modulates multiple interconnected pathways in AD pathology [100]. Polypharmacology is also trending in ALS treatment, as it is an effective way to address a multifactorial etiology involving excitotoxicity, mitochondrial dysfunction, OS, and microglial activation. Multi-target molecules, in which a single molecule is deliberately designed to affect multiple targets, particularly those derived from donepezil and memantine, aim to combine antioxidant, anti-inflammatory, and anti-amyloid properties within a single structure, in addition to AChE inhibition [101]. Recent reviews have reported that these hybrid molecules may offer a stronger neuroprotective profile by suppressing OS and microglial activity [102].

Current studies focus on small molecules, antibodies, and cell-based therapies aimed at reprogramming the microglial phenotype from an M1-like proinflammatory profile to an M2-like neuroprotective profile [16]. Targeting microglia and immunomodulatory approaches also aim to control microglia numbers through depletion and subsequent repopulation. Modulation of microglia is a new and promising area in AD and ALS. It is hoped that microglial modulation, when combined with strategies targeting OS and inflammation, may provide meaningful neuroprotection. Currently, there is no FDA-approved drug developed explicitly as a microglia modulator for neurodegenerative diseases. Existing FDA-approved medicines for neurodegenerative diseases were initially approved based on different mechanisms of action. Still, research indicates that some drugs may have secondary effects on microglia or are being actively investigated for this potential. The preclinical and clinical evidence, as well as the translational status, of pharmacological and immunomodulatory agents targeting microglial and neuroinflammatory pathways in AD and ALS are evaluated in Table 1.

Table 1: Pharmacological and immunomodulatory agents targeting microglial and neuroinflammatory pathways in Alzheimer’s disease and amyotrophic lateral sclerosis: clinical evidence and translational status.

Therapy/Agent	Disease	Target Mechanism(s)	Pathway	Clinical Evidence Level	Clinical Efficacy Summary (Inline-Referenced)	Model/ Population	Dose, Treatment Duration, Recovery Rate	Classification According to Clinical Maturity Level
Riluzole	ALS	Glutamate release inhibition	Excitotoxicity attenuation	Approved (ALS)	provides modest but reproducible survival and progression benefits in ALS and remains standard of care [64,103].	ALS patients	50 mg orally twice daily; chronic use	Approved/Clinically established treatments
Edaravone	ALS	Free-radical scavenging	Oxidative stress reduction	Moderate clinical evidence	Meta-analyses show statistically significant but clinically modest slowing of functional decline in selected ALS patients, while real-world studies do not support consistent long-term disease modification [13,104,105].	ALS patients	60 mg i.v; 6 cycles over 24 weeks	
Donepezil	AD (mild-severe)	AChE inhibition	Cholinergic signaling	Moderate-quality evidence	provides modest but statistically significant symptomatic benefits across AD stages, maintained only during active treatment, without disease modification [106,107].	AD patients	5–10 mg/day (23 mg ER explored); 12–50 weeks	
Memantine	AD (moderate-severe)	NMDA receptor antagonism	Glutamatergic signaling	High-certainty evidence	shows small symptomatic benefits in moderate-to-severe AD, but no benefit in mild AD or ALS, and no sustained post-treatment efficacy [108–110].	AD patients; ALS patients	20 mg/day; ~6–7 months (up to 40 weeks) optimal; recovery unclear	

Table 1: Cont.

Therapy/Agent	Disease	Target Mechanism(s)	Pathway	Clinical Evidence Level	Clinical Efficacy Summary (Inline-Referenced)	Model/ Population	Dose, Treatment Duration, Recovery Rate	Classification According to Clinical Maturity Level
Masitinib	AD (mild to moderate)	c-Kit and Lyn inhibition	NF- κ B/NLRP3 modulation	Phase III	demonstrated modest cognitive improvement in mild-to-moderate AD in Phase III trials; disease-modifying effects remain unconfirmed [111].	AD patients	4.5 mg/kg/day; 24 weeks	
Usnoflast (ZYIL1)	ALS	NLRP3 inhibition	Inflammasome signaling	Phase II	Phase II data showed acceptable safety, with non-significant trends toward a slower decline in ALSFRS-R, supporting further study [112].	ALS patients	25–75 mg orally BID for 12 weeks	
Low-dose IL-2(Aldesleukin)	AD	Treg expansion	IL-2/Treg immunoregulation	Phase 2a	The Phase 2a study demonstrated safety, Treg expansion, and exploratory biomarker changes, but did not demonstrate definitive efficacy [113].	AD patients	10 ⁶ IU/day SC in cycles; recovery not established	Late phase/advanced clinical development
Foralumab	Early AD	Intranasal anti-CD3	T-cell immunomodulation	Phase II (ongoing)	Preclinical studies showed reduced neuroinflammation; a Phase II trial is ongoing, with no efficacy readout yet [114–116].	Rodents; early AD patients	50–100 μ g intranasal cycles; efficacy pending	
AL002	AD	TREM2 agonism	TREM2–DAP12 signaling	Preclinical, Phase I–II	Preclinical efficacy and Phase I target engagement were observed, but Phase II failed to meet the primary endpoint in early AD [117–120].	Mice; humans	15–60 mg/kg i.v.; no clinical benefit demonstrated	
Baricitinib	AD	JAK1/JAK2 inhibition	JAK-STAT signaling	Exploratory trial	An exploratory AD trial demonstrated CSF penetration and biomarker modulation without a clinical efficacy assessment [121,122]	AD patients	2–4 mg/day for 24 weeks; efficacy not established	Early phase/target validation studies

Table 1: Cont.

Therapy/Agent	Disease	Target Mechanism(s)	Pathway	Clinical Evidence Level	Clinical Efficacy Summary (Inline-Referenced)	Model/ Population	Dose, Treatment Duration, Recovery Rate	Classification According to Clinical Maturity Level
MCC950	AD preclinical	NLRP3 inhibition	Inflammasome signaling	Preclinical	MCC950 reduced inflammasome activation and improved pathology in AD mouse models [123].	Rodent models	~10 mg/kg i.p.; preclinical only	Preclinical/translational candidates
Fingolimod	AD preclinical	S1P modulation	Immune trafficking reduction	Preclinical	Fingolimod reduced amyloid pathology and improved behavior in AD mouse models [124,125].	AD mouse models	0.03–1 mg/kg/day; preclinical	
Dimethyl fumarate (Tecfidera)	AD preclinical	NRF2 activation	NRF2/ARE pathway	Preclinical	Evidence for AD remains preclinical despite strong efficacy in MS [126,127].	MS patients; AD models	240 mg BID (MS); no AD dosing	
Omaveloxolone	AD preclinical	NRF2 activation	NRF2/ARE signaling	Preclinical	Omaveloxolone improved pathology and cognition in AD mouse models only [128].	APP/PS1 mice	Preclinical regimens only	
Anakinra	NI	IL-1 receptor antagonism	IL-1 blockade	Phase II (ICH)	Clinical benefit shown in ICH but no evidence for AD efficacy [129].	ICH patients	100 mg/s.a short course	
Rilonacept	IL-1 axis	IL-1 cytokine trap	IL-1 sequestration	Approved auto-inflammatory syndrome (non-AD)	No clinical evidence supports efficacy in AD [130].	Humans	320 mg loading then 160 mg weekly; no AD efficacy	Mechanistic comparators (non-AD efficacy)
Canakinumab	IL-1 β axis	Anti-IL-1 β mAb	IL-1 β blockade	Approved auto-inflammatory syndrome (non-AD)	No evidence supports efficacy in AD or other neurodegenerative diseases [131].	Humans	150 mg SC every 8 weeks; no AD efficacy	

Table 1: *Cont.*

Therapy/Agent	Disease	Target Mechanism(s)	Pathway	Clinical Evidence Level	Clinical Efficacy Summary (Inline-Referenced)	Model/ Population	Dose, Treatment Duration, Recovery Rate	Classification According to Clinical Maturity Level
Resveratrol	AD; ALS preclinical	SIRT1 activation	NF- κ B modulation	Phase II: preclinical	Phase II AD trial showed safety and biomarker modulation without cognitive benefit; ALS efficacy limited to preclinical models [132–134].	Humans; ALS models	50–2000 mg/day (AD); preclinical ALS dosing	Nutraceutical/low translation success
Curcumin	AD; ALS	Anti-inflammatory	NF- κ B inhibition	Phase II: preclinical	Clinical trials in AD and ALS failed to show a significant benefit despite promising preclinical data [135–137].	Humans; animal models	600 mg–4 g/day; 6–12 months; no recovery	

Note: AD, Alzheimer Diseases; NI, Neuroinflammation; ALS, Amyotrophic Lateral Sclerosis; AChE, Acetylcholinesterase; ICH, Intracerebral Hemorrhage; MS, Multiple Sclerosis; ER, Extended Release; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale—Revised; mAb, Monoclonal antibody; NF- κ B, Nuclear Factor kappa-light-chain-enhancer of activated B cells; IL-2, Interleukin-2; NLRP3, NLR family pyrin domain containing 3; Treg, Regulatory T cell; NMDA, N-methyl-D-aspartate; i.v, Intravenous; ER, Extended release; BID, Bis in die.

Candidates for microglia-targeted approaches include Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) targeting (AL002), IL-2 immunomodulation, masitinib (an oral tyrosine kinase inhibitor developed for cancer treatment), and CD3 modulation (foralumab) in AD (Table 1). TREM2 is a lipid receptor expressed on microglia and other tissue macrophages. It supports their survival and proliferation by transmitting activating signals into cells via the adaptor DAP12 [138]. When TREM2 is deficient, microglia cannot effectively cluster around A β , resulting in less compact plaques with longer, more branched amyloid fibrils. This increased plaque surface exposure directly correlates with more severe neuritic tau hyperphosphorylation and axonal dystrophy around amyloid deposits. The defective microglial response disrupts the formation of a neuroprotective barrier that normally regulates amyloid compaction and insulation, thereby exacerbating neuritic damage [139,140]. A study was planned to evaluate the efficacy of low-dose IL-2 in expanding regulatory T cells (Tregs) to modulate disease progression in AD patients, based on literature findings suggesting that Tregs may be a modifiable therapeutic target. Low-dose IL-2 treatment was reported to sustainably increase Treg numbers in AD biomarkers and clinical scales and improve A β 42 levels. TREM2-associated microglia clustering around plaques is thought to be necessary to control A β plaques and associated neuropathology. In the study, no overall reduction in A β or increase in microglia clustering around A β plaques was observed in mice treated with AL002c; however, it was reported to reduce A β plaque toxicity and alleviate neuritic dystrophy associated with AD-related neuronal dysfunction [118]. The anti-CD3 antibody has been demonstrated to elicit regulatory immune mechanisms in the periphery and reduce microglial activation in neurological diseases, including AD [141,142]. Dimethyl fumarate (Tecfidera), an approved MS treatment, can affect glial cells and reduce inflammation in MMS. Dimethyl Fumarate has been shown to exert its effects by modulating NF- κ B signaling through its Nrf2-activating properties and immunomodulatory activities [143,144]. Baricitinib, an FDA-approved JAK inhibitor for rheumatoid arthritis, is being evaluated in the literature for its potential effects on AD and ALS by inhibiting NI mediated through the Janus kinase/Signal transducer and activator of transcription 3 (JAK/STAT3) pathway. Treatment of AD rats with baricitinib has been shown to alleviate abnormal JAK2/STAT3 signaling pathway activation induced by ovariectomy/D-galactose, leading to significant reductions in p-JAK2 and p-STAT3 levels and activation of the AKT/PI3K/mTOR signaling, as well as reducing parameters of NI (e.g., NF- κ B, TNF- α , and IL-6) and OS (e.g., iNOS and MDA) [145,146].

The activation of the NLRP3 inflammasome, which is essential for the maturation and release of proinflammatory cytokines, can lead to lysosomal damage through the accumulation of A β and Tau. In a study focusing on NLRP3-mediated NI, the underlying mechanisms of MCC950-mediated attenuation of AD-like pathology were investigated. The NLRP3 inflammasome is reported to initiate inflammatory responses by activating caspase-1 and promoting the release of proinflammatory cytokines such as IL-1 β and IL-18. The study results indicate that MCC950 is an effective anti-inflammatory agent [111]. Masitinib is the strongest candidate for a microglia-targeted approach in ALS, but most strategies are currently at the preclinical level, and human clinical trials are limited. Masitinib is a tyrosine kinase inhibitor that targets mast cells and microglia cells. In a study in which masitinib was administered in addition to a cholinesterase inhibitor and/or memantine in patients with AD-related dementia, masitinib (4.5 mg/kg/day) was reported to improve overall cognitive function [147]. Fingolimod (Gilenya), a modulator of the sphingosine 1-phosphate receptor, is an FDA-approved drug for the treatment of multiple sclerosis. The literature indicates that fingolimod may suppress NI and convert microglia from a proinflammatory (M1) to an anti-inflammatory (M2) phenotype [148]. In a study in which fingolimod was administered intranasally to repolarize microglia and reduce A β expression, a ROS-responsive, carrier-free gene-delivery nanosystem (FTBR-NAC) was developed. Upon reaching the brain, FTBR responded to high ROS levels in the pathological

region, enabling Fingolimod release. This application was reported to improve cognitive function in AD-mice [148]. Another study reported that, when administered orally to APP/PS1 mice for 2 months, fingolimod reduced NI, enhanced cognitive function, and alleviated brain A β accumulation. Furthermore, the treatment was reported to alleviate AD-related pathologies, including tau hyperphosphorylation, NI, and neurodegeneration [125]. Additionally, Fingolimod was shown to exert a protective effect via its immunomodulatory action in an experimental ALS model [149]. Safety has also been established in a phase-2 clinical trial in ALS patients [150]. Using publicly available transcriptomic data and bioinformatics analyses, a study of drug repurposing identified distinct gene expression profiles in SOD1G93A microglia and SOD1G93A motor neurons. Belinostat, auranofin, COT-10b, BRD-K78930611, and AZD-80552 were reported as candidates for ALS treatment, mimicking the protective state of microglia and reversing the toxic state of motor neurons. Researchers predict that establishing a link between the M2 state of microglia and drug repositioning could provide a new perspective on ALS pathophysiology [151].

Small-molecule therapies are promising; compounds such as metformin, rapamycin, and ketone bodies can modulate microglial metabolism [152]. Cell-based therapies involve pre-conditioned microglia and monocytes/macrophages that can migrate to damaged brain regions and release protective remodeling factors [153]. Evidence suggests these approaches are particularly important for stroke, AD, and Parkinson's diseases, with researchers highlighting their potential to reduce neuroinflammation and enhance neuroprotection [154]. However, most studies are preliminary, and translational research is still needed to establish definitive clinical protocols. The heterogeneity of microglial cells, variation in microglial phenotype with disease stage, and differences between humans and mice are the main limitations that have prevented clinical translation so far. To advance in this area, it is essential to identify disease-specific strategies, use biomarkers to guide treatment, and understand microglial heterogeneity.

8.5.1 Microglial Phenotypic Transformation (M1/M2) and Drug Intervention Targets

Although microglial activation is traditionally defined by M1 and M2 phenotypes, it is increasingly recognized that the microglial response in neurodegenerative diseases is dynamic, disease-stage-dependent, and highly heterogeneous [155]. In the context of AD and ALS, key regulatory factors that determine microglial phenotypic transformation include innate immune sensors (e.g., the NLRP3 inflammasome) [156], NF- κ B, phagocytosis, and disease-associated microglia (DAM) programs (TREM2-DAP12 signaling) [156–158], and redox balance [156]. Activation or suppression of these pathways is a critical factor determining whether microglial cells adopt a pro-inflammatory or more protective phenotype. Specifically, danger-related molecular signals, such as A β and tau accumulation, enhance the microglial inflammatory response, whereas TREM2-mediated signaling can support phagocytic capacity and cellular survival. Additionally, Nrf2 activation may exert an indirect regulatory effect on the microglia phenotype by weakening the vicious cycle between oxidative stress and inflammation [156,157]. These regulatory mechanisms offer specific therapeutic targets for microglia-targeted pharmacological interventions. TREM2 agonists aim to increase phagocytosis, NLRP3 inhibitors aim to suppress inflammasome activation, and agents targeting NF- κ B pathways aim to reduce pro-inflammatory cytokine production [156]. In addition, dimethyl fumarate, an immunomodulatory agent, is being evaluated as a potential therapeutic approach that may contribute to the indirect reprogramming of microglial activity and a more stable phenotypic profile [159,160].

8.5.2 Holistic Assessment and Translational Perspective

The findings discussed in this study reveal that microglial activation in neurodegenerative diseases cannot be explained solely by a binary M1/M2 phenotype distinction, but should be evaluated within a

dynamic, continuous spectrum that depends on disease stage, tissue microenvironment, and metabolic status. In pathologies such as AD, ALS, and Parkinson's disease, the microglia response is simultaneously shaped by numerous interconnected mechanisms, including innate immune sensors, inflammatory signaling, phagocytosis, and redox balance [161,162]. In this context, the NLRP3 inflammasome, NF- κ B, and MAPK pathways stand out as the main regulators of the pro-inflammatory microglial response [51,163], while TREM2-DAP12 signaling supports phagocytosis capacity and cellular survival through DAM programs [164,165]. In addition, the Nrf2-mediated antioxidant response plays an indirect but critical role in the microglial phenotype as a high-level regulatory axis that limits the interaction between oxidative stress and inflammation [166,167]. Microglia-targeted therapeutic strategies aim to interfere with different nodes of this multi-layered regulatory network. NLRP3 inhibitors [168], small-molecule inhibitors targeting the JAK/STAT and NF- κ B pathways [169], TREM2 agonists [170], and tyrosine kinase inhibitors [171] are among the prominent approaches for suppressing the inflammatory response and optimizing phagocytosis. However, pre-conditioned microglia or monocyte/macrophage-based cellular therapies with small molecules such as metformin and rapamycin targeting microglial metabolism offer a promising framework for phenotypic reprogramming [172,173]. However, much of the current data is based on preclinical studies, and the interspecies differences in human microglial biology pose significant limitations in translating these approaches into clinical practice. Therefore, future studies focusing on disease-stage-specific biomarkers, patient subgroup identification, and combinatorial treatment strategies are critical for the clinical success of microglia-targeted therapies.

8.6 Clinical Limitations and Future Trends

Although current FDA-approved agents demonstrate some regulatory effects on NI and OS, their disease-modifying effects are limited in most disease states and do not provide a radical treatment. The main reasons for this are the complex nature of neurodegenerative diseases, late diagnosis and consequently late treatment, the assumption of a 'one-size-fits-all' treatment approach for heterogeneous patient groups, the bioavailability of drugs, their affinity for the BBB, and the dynamic nature of the neuroinflammatory response (incomplete suppression can also be harmful). Therefore, the current trend is to focus on the following areas: New molecules that target the selective activation of Nrf2 while inhibiting NF- κ B (e.g., omaveloxolone [129,174,175], dimethyl fumarate [176], diroximel fumarate [177]; canakinumab, riloncept and anakinra, which are NLRP3 inflammasome inhibitors [178]; and microglia phenotype modulators; the personalised use of current agents based on biomarkers; and the rational combination of classical drugs with plant polyphenols and other antioxidants.

9 Conclusion

Inflammation and OS form a tightly interlinked pathological axis that drives neuronal vulnerability in ALS and AD. Mitochondrial dysfunction—particularly matrix-derived ROS production, mtDNA leakage, and activation of NLRP3 and cGAS–STING pathways—emerges as a central mechanism connecting these two processes. This review highlights the novelty of integrating these mitochondrial, redox, and innate immune pathways into a unified framework, offering a clearer understanding of how OS and NI co-evolve during neurodegeneration. Although current FDA-approved neuroprotective agents provide only partial modulation of these mechanisms, they reveal underrecognized effects on redox balance and inflammatory signaling that may guide rational drug repurposing. The most important insight of this work is the identification of shared molecular leverage points—such as mitochondrial ROS control, inflammasome inhibition, and restoration of antioxidant defenses—that could be targeted simultaneously to disrupt the OS–NI cycle. Together,

these findings support the development of multi-targeted and combination therapeutic strategies as the most promising route toward achieving genuine disease-modifying effects in ALS and AD. In this context, based on the modeling methods used, a strategy can be developed to evaluate the efficacy and reliability of combination therapies with Memantine or Donepezil, which have strong CNS penetration, together with antioxidant/anti-inflammatory drugs. Future research should prioritize standardized experimental models, longitudinal analyses, and high-resolution mitochondrial and immunometabolic profiling to more precisely map the OS–NI cycle and identify actionable molecular checkpoints.

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