Pharmacological Modulation of Oxidative Stress, Neuroinflammation, and Synaptic Dysfunction for Precision Neuroprotection in Neurodegenerative Disorders: A Narrative Review

Muskan Tomar, Sangeeta Dwivedi and Gajanand Darwhekar

ABSTRACT

Neurodegenerative diseases such as Alzheimer's and Parkinson's remain major global challenges, characterized by progressive neuronal loss and cognitive decline in the aging population. Among their core pathogenic mechanisms, oxidative stress, neuroinflammation, and synaptic dysfunction play pivotal and interconnected roles. Pharmacological modulation of these pathways offers potential avenues for neuroprotection and therapeutic intervention. Antioxidant defence mechanisms, particularly the *Nrf2*/*HO-1* signaling axis, are essential in maintaining redox homeostasis and cellular integrity. Likewise, regulation of neuroinflammatory cascades involving *NF-κB* and pro-inflammatory cytokines may prevent sustained neuronal injury. Restoration of synaptic function through neurotrophic factors such as *BDNF* and modulation of dopaminergic neurotransmission further contributes to neuronal resilience. This narrative review summarizes current advances in understanding these mechanisms and explores both natural compounds and synthetic small molecules demonstrating preclinical or early translational potential. Despite challenges related to dosing, target specificity, and long-term safety, emerging multi-targeted pharmacological strategies hold significant promise for precision neuroprotection and improved brain health in neurodegenerative disorders. This narrative review follows the SANRA framework to ensure methodological transparency.

Keywords: BDNF, HO-1 signaling, Multifunctional antioxidant flavonoids, NLRP3 inflammasome inhibition, Nrf2, Precision multitarget neuroprotection, TrKB agonists

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Introduction

Ageing populations and a lack of effective treatments have led to an increase in the worldwide health burden of neurodegenerative diseases (NDs), including Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS).[1,2] Progressive loss of neurons, misfolding and aggregation of proteins, mitochondrial malfunction, and eventually cognitive or motor deterioration are the hallmarks of these illnesses. But the illness progresses due to a combination of glia-driven inflammation, synaptic integrity, and subtle disruptions in redox balance long before there is overt neuronal death.[3] Oxidative stress is a key factor in these early pathogenic alterations. Because of its high metabolic demand, abundance of metal ions, polyunsaturated lipids, and comparatively limited antioxidant reserves, the brain is particularly susceptible to reactive oxygen species (ROS). Lipid peroxidation, protein oxidation, DNA damage, and mitochondrial degradation are caused by an imbalance between ROS formation and antioxidant defenses.[4] These events then intensify ROS production in a vicious cycle. Another important factor in neurodegeneration is neuroinflammation, which is mostly caused by astrocytes and microglia. Proinflammatory cytokines, chemokines, and reactive nitrogen/oxygen species are released by activated glial cells in response to neuronal injury, protein aggregation, or damage-associated molecular patterns (DAMPs).[5] This reaction becomes maladaptive and persistent in many NDs, leading to further oxidative stress, synapse loss, and neuronal dysfunction. Importantly, synaptic dysfunction—which includes diminished plasticity, poor neurotransmission, and loss of synaptic proteins—often occurs prior to neuronal death and is more strongly associated with cognitive or motor disability. This implies that maintaining synaptic integrity may be a window of opportunity for neuroprotective treatment.[6] Mono therapeutic methods that target only one of these three axes—oxidative stress, neuroinflammation, and synaptic dysfunction—frequently fail to stop the course of the disease because of their interaction. Precision neuroprotection holds promise in terms of adjusting treatment plans to a patient's predominant pathophysiological signature (oxidative burden, inflammatory dominance, and synaptic vulnerability, for instance) and implementing combinatorial or sequential interventions that are matched to the disease stage and biomarker profiles.[7] The objective of this study is to develop precise neuroprotective paradigms in neurodegenerative diseases by discussing pharmaceutical approaches to influence oxidative stress, glia inflammation, and synaptic repair. Recent developments in redox modulators, anti-inflammatory drugs, and synaptic stabilizers are reviewed, along with how they may be incorporated into multi-tiered treatment plans.[8] These interconnected mechanisms contributing to neuronal death are schematically illustrated in Figure 1.

Overview of Neurodegenerative Disorders

Though clinically diverse, neurodegenerative disorders (NDs)—which include amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and related dementias—have common cellular and molecular characteristics, such as the progressive loss of particular neuronal populations, the buildup of misfolded proteins, mitochondrial dysfunction, excitotoxicity, oxidative stress, chronic neuroinflammation, and synaptic failure, all of which contribute to cognitive and motor decline.[9] Mechanistically, lipid, protein, and

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DNA oxidation is caused by excessive reactive oxygen species (ROS) production and compromised antioxidant defenses, which exacerbate mitochondrial dysfunction and encourage neuronal death. At the same time, persistent activation of microglia and astrocytes maintains a maladaptive inflammatory milieu that intensifies synaptic dysfunction and neurodegeneration. These interconnected circuits produce feed-forward cycles that turn susceptibility associated with aging into progressive illness.[10] Synaptic dysfunction is increasingly seen as an early and therapeutically tractable step in many NDs because of the significant effects on brain function, including early synaptic impairment (loss of synaptic proteins and plasticity), disrupted neurotransmission, and circuit disconnection that occur long before overt cell loss.[11]

Importance of Precision Neuroprotection

Targeting a single downstream mechanism rarely stops the multifactorial cascade, and neurodegenerative diseases are molecularly and temporally heterogeneous, which is one reason why traditional "one-size-fits-all" neuroprotective strategies (such as broad antioxidant supplements or single-target anti-inflammatory agents) have typically failed to produce robust clinical benefit. By identifying the predominant pathogenic mechanisms in a particular patient (e.g., immune-driven inflammation, protein Pathy-driven synaptic vulnerability, or mitochondria-dominated oxidative stress), customizing interventions to those mechanisms (e.g., combining immune modulators, targeted antioxidants, synaptic stabilizers, metabolic/mitochondrial therapies, or gene/biologic approaches), and implementing them at the appropriate disease stage to maintain synaptic function and neuronal resilience, precision neuroprotection seeks to both.[12] In order to transform mechanistic insights (oxidative stress, neuroinflammation, and synaptic dysfunction) into customized treatment plans that slow or stop progression rather than just treating symptoms, precision approaches make use of biomarkers (fluid, imaging, genetic and functional measures), molecular stratification, and combination therapies. Clinical translation necessitates thorough patient stratification and stage-appropriate combination therapy trials, but early preclinical and translational research suggests that interventions that concurrently alter redox balance, neuroimmune signaling, and synaptic health hold the greatest promise for long-lasting benefit.[13]
Figure 1 Pathophysiology Overview.

Methodology (Narrative Review Approach)

This work was conducted as a narrative review following the principles of the SANRA (Scale for the Assessment of Narrative Review Articles) framework to ensure transparency and quality. Relevant literature was identified through comprehensive searches in PubMed, Scopus, ScienceDirect, and Google Scholar databases for the period January 2010 to September 2025. The search combined keywords such as "oxidative stress," "neuroinflammation," "synaptic dysfunction," "neurodegenerative diseases," "*Nrf2*," "*NF-κB*," "*BDNF*," and "precision neuroprotection."[14] Inclusion criteria were:

(i) peer-reviewed original research articles, systematic reviews, and meta-analyses addressing pharmacological or molecular modulation of oxidative stress, inflammation, or synaptic signaling in neurodegenerative disorders (AD, PD, ALS, HD);
(ii) studies in English;
(iii) both preclinical (in vitro, animal) and clinical investigations

Exclusion criteria included non-peer-reviewed sources, editorials, or unrelated conditions (e.g., peripheral inflammation, non-neural oxidative models).

Evidence strength was qualitatively assessed based on study design (preclinical vs. clinical), reproducibility, biomarker validation, and translational potential. Data were organized thematically into oxidative,

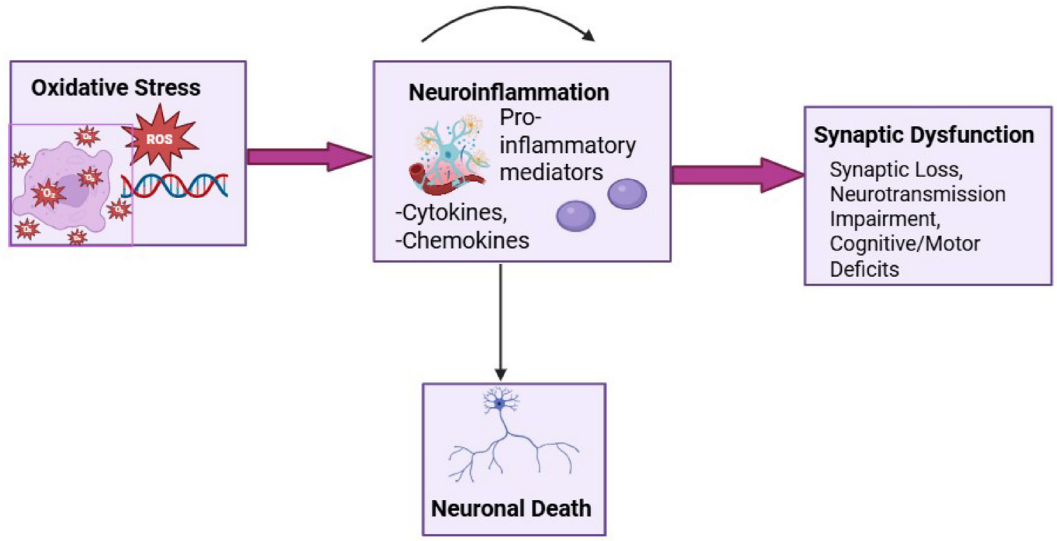

Fig 1 | Pathophysiology overview (Oxidative stress → Neuroinflammation → Synaptic dysfunction →Neuronal death)
Source: Created by authors using Bio Render for illustrative purposes.

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inflammatory, and synaptic domains to support the narrative synthesis.

References were verified and cross-checked for accuracy and relevance. No meta-analytic statistical synthesis was performed.

Methodological Transparency and Search Strategy

To ensure methodological transparency and reproducibility, the following full search strategy was applied.

Databases and Search Strings

- PubMed: ("oxidative stress" OR "redox") AND ("neuroinflammation" OR "microglia") AND ("synaptic dysfunction" OR "*BDNF*") AND ("neurodegenerative diseases").
- Scopus: TITLE-ABS-KEY ("neuroprotection" AND ("*Nrf2*" OR "*NF-κB*" OR "*BDNF*")) AND PUBYEAR > 2009.
- ScienceDirect: ("oxidative stress" AND "neuroinflammation" AND "synaptic plasticity") FILTER: 2010–2025.
- *Google Scholar:* "precision neuroprotection" + "pharmacological modulation" + "neurodegeneration."

Search Period and Final Date

January 2010 – 25 September 2025.

Record Counts and Screening

Initial records retrieved = 512 (PubMed 180, Scopus 140, ScienceDirect 120, Google Scholar 72). After duplicate removal and title/abstract screening, 174 articles underwent full-text review; 112 met all inclusion criteria and were incorporated into the final synthesis.

Simplified PRISMA-style summary of the literature search and selection process. Is presented in Figure 2. The review identified 512 records across PubMed, Scopus, ScienceDirect, and Google Scholar. After removing duplicates and applying inclusion/exclusion criteria, 112 studies were included in the final narrative synthesis following the SANRA framework.

Mechanisms of Neurodegeneration

Progressive neuronal death brought on by oxidative stress, neuroinflammation, and synaptic dysfunction is the hallmark of neurodegeneration, a complex process. Neuronal loss, cognitive decline, and functional disability are the final results of these systems' self-reinforcing cycle.[15]

Oxidative Stress: ROS and Mitochondrial Dysfunction

A common feature of almost all neurodegenerative disorders is oxidative stress. When cellular antioxidant defenses are overpowered by excessive synthesis of reactive oxygen species (ROS) and reactive nitrogen species (RNS), lipid peroxidation, protein carbonylation, and mitochondrial DNA (mtDNA) damage ensue.[16] ROS mostly originates from and is targeted by mitochondria. Excessive superoxide production is a result of decreased electron transport chain (ETC) function, especially at complexes I and III, in conditions like Parkinson's and Alzheimer's. Additionally, damaged mitochondria cause apoptosis by activating caspase and releasing cytochrome c. Malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), glutathione (GSH), superoxide dismutase (SOD), and catalase

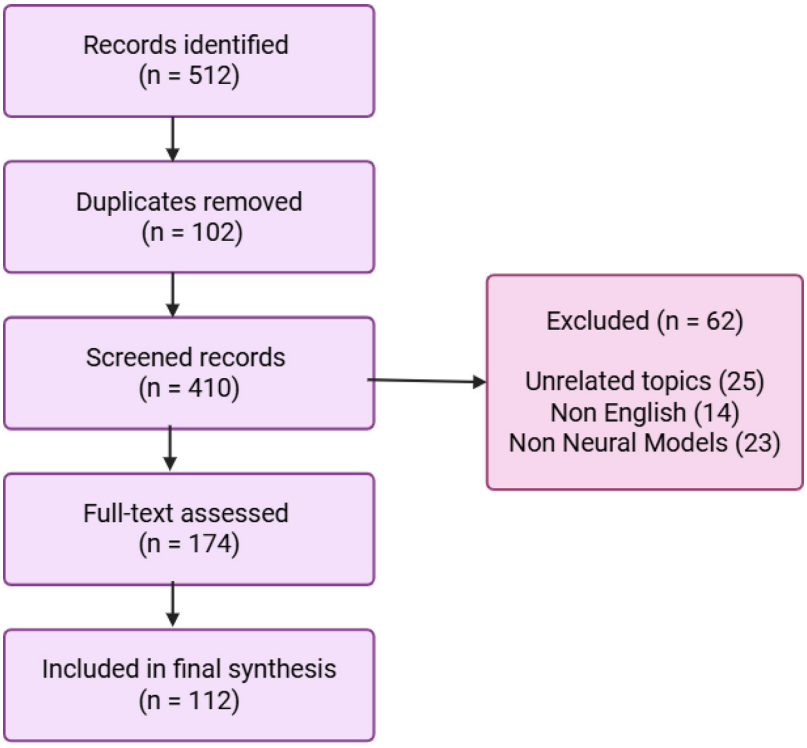

Fig 2 | PRISMA-style summary of literature screening and inclusion

Table 1 | Key oxidative stress markers & their role in neurodegeneration

Compound/Class	Primary Mechanism/Target	Evidence Tier	Approval/Regulatory Status	Key Safety/Outcome (Refs.)
Reactive Oxygen Species (ROS)	Excess ROS causes lipid, protein, and DNA damage, which accelerates the development of neurodegenerative disorders and causes cell death.	Animal & in vitro studies	Increased cell death, impaired synaptic function	N/A
Mitochondrial Dysfunction	Neuronal cell death pathways are triggered, ATP synthesis is decreased, and ROS generation is increased when mitochondrial respiration is impaired.[18,19]	Animal & human studies	Neurodegeneration progression, energy deficit	N/A
Lipid Peroxidation (MDA, 4-HNE)	Peroxidized lipids increase neurotoxicity by interfering with signaling and the integrity of neuronal membranes.[20]	Animal models	Increased neurotoxicity, synaptic impairment	N/A
Protein Oxidation (Carbonyls)	Proteins undergo oxidative alteration, which changes their structure and function and compromises neuronal survival and synaptic transmission.	In vitro & animal studies	Synaptic dysfunction, cell death	N/A
DNA Oxidation (8-OHdG)	Oxidized DNA bases contribute to neuronal death by causing mutations, genomic instability, and compromised repair processes.	Animal & human studies	Neuronal apoptosis, impaired repair	N/A
Antioxidant Enzymes (SOD, CAT, GPx)	Decreased antioxidant defences increases the burden of oxidative stress by impairing the capacity to neutralize ROS.	Animal & human studies	Exacerbated ROS-induced damage	N/A

Regulatory status is based on FDA/EMA classification as of 2025; "research-only" indicates compounds without clinical approval for neurodegenerative use

(CAT) are important oxidative indicators; changes in their levels are correlated with the advancement of illness and neural susceptibility.[17] The key oxidative stress markers and their mechanistic roles in neurodegeneration are summarized in Table 1.

Neuroinflammation: *NF-κB*, Cytokines, and Inflammasomes

In neurodegenerative diseases, neuroinflammation actively contributes to neuronal damage rather than being a passive observer. The two main innate immune effectors in the central nervous system (CNS) are astrocytes and microglia. These glial cells become persistently engaged in illness or stress, phagocytose synapses, generate proinflammatory mediators (cytokines, chemokines, reactive oxygen/nitrogen species), and increase neuronal susceptibility.[21,22]

Microglia and astrocytes exhibit abnormal and persistent *NF-κB* activation in neurodegenerative diseases. For instance, Alzheimer's disease (AD) brains have increased *NF-κB* activation, which is linked to amyloid pathology and cognitive loss.

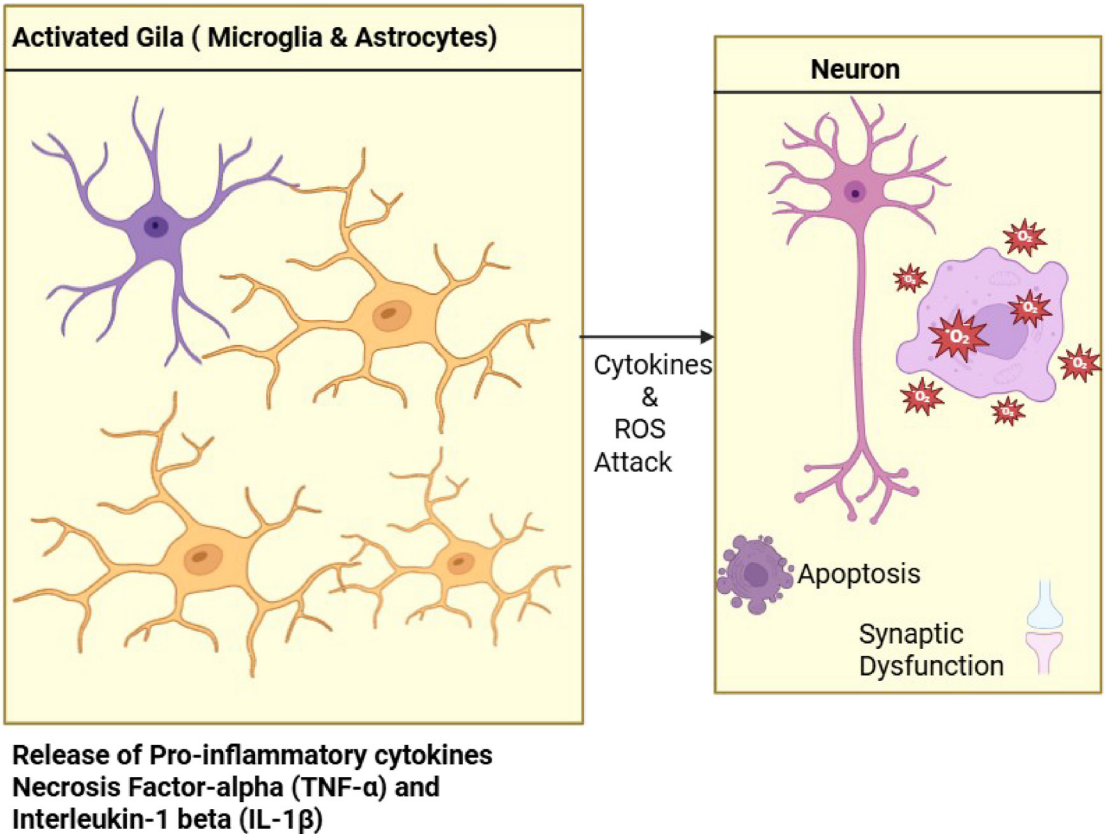

Fig 3 | Inflammatory signaling pathways in neurons and glia
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Cytokines, Cell–Cell Crosstalk, and Glia Activation

Following *NF-κB* activation, astrocytes and microglia release a series of cytokines and chemokines. Typical mediators consist of:

- TNF-α is an essential mediator that may activate cell death or survival pathways by acting on TNFR1/TNFR2 on neurons or glia. The advancement of Alzheimer's disease is linked to elevated TNF levels.[24]
- IL-1β and IL-6 are interleukins that can act locally on neurons or glia, either stimulating the JAK/STAT and MAPK pathways or encouraging more autocrine *NF-κB* activation.
- IL-18 can intensify inflammation and is frequently produced by inflammasome activation.[25]

Amplification loops are produced by glia-glia and glia-neuron interaction. For example, downregulation of EAAT transporters can cause reactive astrocytes (A1 phenotype) to lose their glutamate uptake ability, which can result in extracellular glutamate buildup and neuronal excitotoxicity. Simultaneously, microglia-derived cytokines can prime astrocytes to a neurotoxic state.[26]

Inflammasomes (especially NLRP3) and Pyroptotic Signalling

Inflammasome complexes, particularly NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3), play a significant role in neuroinflammation in addition to *NF-κB*. Usually, activation is done in two steps:

- Priming (Signal 1): Pro-IL-1β, pro-IL-18, and NLRP3 are transcriptionally upregulated upon *NF-κB* activation.[27]
- Activation (Signal 2): the NLRP3 inflammasome complex (NLRP3, ASC, and pro-caspase-1) is assembled in response to subsequent stimuli, such as mitochondrial ROS, mt DNA release, ionic fluxes, and lysosomal damage. In some situations, gasdermin D-mediated pyroptosis (a lytic inflammatory cell death) is triggered by the activation of caspase-1, which transforms pro-IL-1β and pro-IL-18 into mature, secretory versions.

Amyloid-β and tau aggregates can operate as NLRP3 activation signals in Alzheimer's disease models, connecting protein Pathy to pathogenesis generated by the inflammasome as illustrated in Figure 3.

Synaptic Dysfunction: *BDNF*, Dopamine, and Glutamate Imbalance

One of the first victims of many neurodegenerative diseases is synaptic integrity. Clinical signs like cognitive decline or motor deficiencies may be caused by synapse loss and dysfunction even before overt neuronal death.[28]

**BDNF* / pro*BDNF* Imbalance and Signalling Deficits*

Memory consolidation, synaptic plasticity (LTP), dendritic spine preservation, and neuronal survival all depend on brain-derived neurotrophic factor (*BDNF*). Pro-*BDNF*, the initial form of *BDNF*, is cleaved to produce the mature form (m*BDNF*). The relative balance between pro*BDNF* and m*BDNF* is important because m*BDNF* binds TrkB receptors to drive pro-survival and plasticity-promoting pathways (PI3K/Akt, MAPK/ERK, PLCγ), whereas pro*BDNF* preferentially binds p75^NTR and can trigger apoptotic or synaptic pruning signals.

Numerous disturbances have been documented in Alzheimer's disease and other neurodegenerative conditions: Reduced ability to convert pro*BDNF* to m*BDNF*, which causes pro*BDNF* to accumulate. Suppression of TrkB receptor signaling or expression. Decreased PI3K/Akt and ERK downstream activation, which results in lower synaptic resilience and increased susceptibility to excitotoxic stress.

According to a recent analysis, Alzheimer's disease is linked to improper cleavage of pro*BDNF*, which weakens synapses. Researchers are looking at *BDNF*-mimetic compounds or TrkB agonists to restore synaptic connections in AD. Furthermore, NF-α1 (neurotrophic factor α1) was demonstrated in gene therapy research to improve *BDNF*/TrkB signaling, supporting synaptic resilience in Alzheimer's models.

Glutamate Excitotoxicity and Receptor Dysregulation

The primary excitatory neurotransmitter in the brain, glutamate, mediates rapid synaptic transmission through NMDA and AMPA receptors.[29]

Overactivation of NMDA receptors due to excessive glutamate release or impaired reuptake (particularly by astrocytes) causes neuronal death and synaptic damage through excessive Ca2+ influx, mitochondrial overload, ROS generation, and activation of calcium-dependent proteases, phosphatases, and endonucleases (excitotoxicity).

Astrocytic dysfunction frequently lowers the expression and activity of glutamate transporters (such as EAAT1/GLAST and EAAT2/GLT–1) in neurodegeneration, which hinders the removal of glutamate from synaptic clefts and exacerbates excitotoxic stress.

Neuronal vulnerability is caused by changes in receptor desensitization, synaptic vs. extra synaptic NMDA receptor balance, and receptor subunit composition, according to a recent 2025 review on glutamatergic dysfunction in Parkinson's disease. Additionally, amyloid-β oligomers in Alzheimer's disease can disrupt glutamate transport dynamics in the synaptic cleft, further impairing synaptic transmission.

Dopaminergic Signaling and Synaptic Modulation

Dopamine deficit contributes to synaptic dysfunction in conditions such as Parkinson's disease (PD). Dopamine controls synaptic plasticity (e.g., long-term potentiation/depression) and affects glutamatergic synapses, particularly in striatal circuits.[30] Maladaptive synaptic remodeling, an imbalance between excitation and inhibition, and poor motor circuitry are all consequences of dopaminergic tone loss. Moreover, synaptic

degradation may be made worse by decreased neurotrophic support in Parkinson's disease (PD), such as decreased *BDNF* in nigrostriatal pathways. The function of *BDNF* in the pathogenesis of Parkinson's disease was reviewed in 2025. It was shown that low *BDNF* levels are associated with poor synapse maintenance in dopaminergic circuits.

Integrated Signaling Disruption and Downstream Effects

Dopamine loss, glutamate excitotoxicity, and *BDNF* deficiency all work together to cause:
Degradation of the proteins that support postsynaptic density (e.g. PSD-95, loss of synaptophysin)

Retraction or pruning of the dendritic spine affected the dynamics of long-term depression (LTD) and LTP, disturbed calcium homeostasis, mitochondrial stress, and ultimately synaptic loss[31]

For example, glutamate receptors and *BDNF* interact: during LTP induction stages, glutamate receptor activation can stimulate *BDNF* release, which in turn affects glutamatergic synapses through feedback signaling (PLCγ/IP3, MAPK/ERK, PI3K/Akt). The spatiotemporal communication between glutamate-activated cascades and *BDNF*-activated cascades maintains synaptic strengthening, according to a review of *BDNF*-glutamate interaction in LTP.

All things considered, trophic signaling loss (*BDNF*), neurotransmitter imbalance (glutamate, dopamine), receptor dysregulation, and cascade mitochondrial/oxidative damage are all components of synaptic dysfunction in neurodegeneration, as depicted in Figure 4.

Pharmacological Targets for Neuroprotection

Mechanistic targeting of the pathogenic triad—oxidative stress, neuroinflammation, and synaptic dysfunction—is necessary for effective neuroprotection. The primary pharmacological targets in each domain, typical chemical classes (including small molecules and biologics/gene approaches), and a selection of preclinical data demonstrating their neuroprotective potential are outlined below. While these findings demonstrate strong preclinical neuroprotective potential, their clinical efficacy remains under investigation and requires cautious interpretation.

Antioxidant Modulation — *Nrf2* / *HO-1* and Glutathione Pathways

Rationale and Key Nodes

A master regulator of cellular antioxidant defenses, the transcription factor *Nrf2* (nuclear factor erythroid 2–related factor 2) translocate to the nucleus upon release from Keap1 and triggers the expression of genes encoding heme oxygenase-1 (*HO-1*), NAD(P)Quinone oxidoreductase 1 (NAD(P)H quinone oxidoreductase 1 (*NQO1*)1), glutathione synthesis enzymes (GCLC/GCLM), and other phase II detoxifying enzymes. As a result, *Nrf2* is a desirable node for neuroprotection as it increases cellular antioxidant capacity, maintains mitochondrial function, and lowers inflammasome activation. Preclinical evidence for *Nrf2* activation in models of AD, PD, ALS, and other NDs is compiled in a number of recent studies.[32]

Neuronal and astrocytic redox equilibrium depend on glutathione (GSH) production and recycling (GCL,

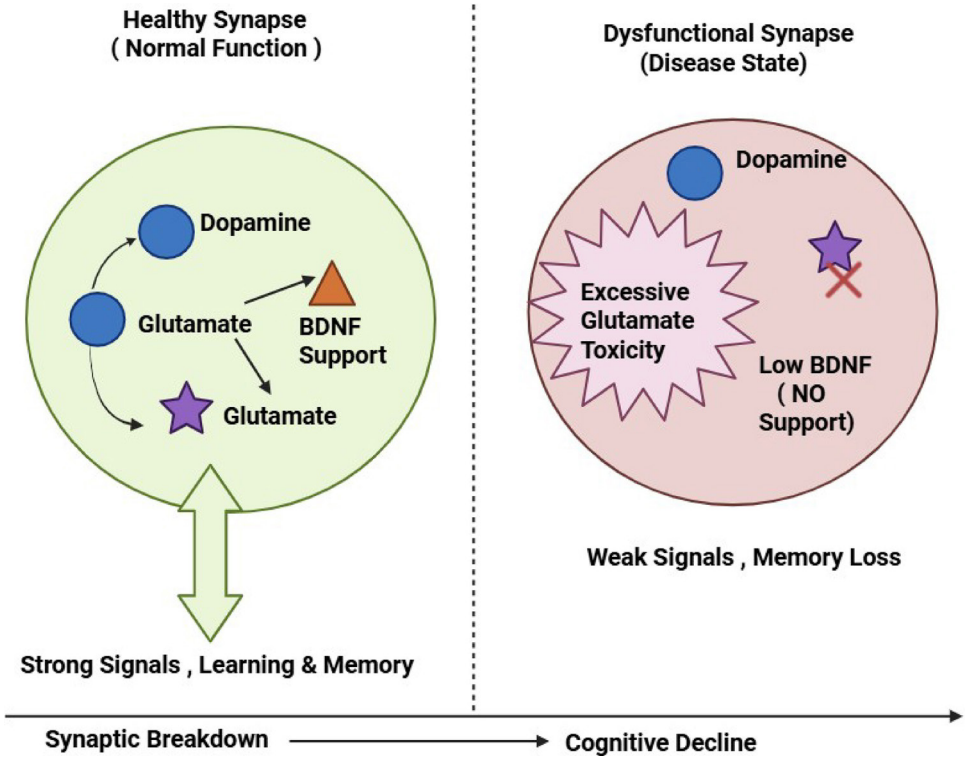

Fig 4 | Synaptic signaling and plasticity impairment
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glutathione reductase, and cystine/glutamate antiporter xCT). In both hereditary and toxic models, neuronal GSH depletion significantly increases the risk of neurodegeneration. In preclinical trials, restoring redox equilibrium and reducing disease can be achieved by targeting GSH production or providing precursors (N-acetylcysteine; cysteine donors).[33]

Evidence and Examples

Dimethyl fumarate (DMF), an electrophilic *Nrf2* activator that was licensed for multiple sclerosis, is frequently mentioned as a clinically proven *Nrf2* activator that can be used for CNS illnesses since it exhibits neuroprotective and anti-inflammatory benefits in a number of preclinical neurodegenerative models.[34]

In animal models of Parkinson's disease and Alzheimer's disease, omaveloxolone, bardoxolone-like triterpenoids, sulforaphane, carvacrol, and other phytochemicals or semisynthetic compounds have shown *Nrf2*/*HO-1* activation with a decrease in oxidative indicators and better behavioral results. However, off-target electrophilicity and pharmacokinetics provide translational difficulties.

In some animals, neuronal susceptibility is restored by GSH precursors (N-acetylcysteine, N-acetylcysteine amide) and methods to increase astrocytic GSH (by *Nrf2* or metabolic supports). The function of astrocytic *Nrf2* in sustaining basal GSH synthesis has been highlighted by recent research.

Clinical/translational note: In the majority of NDs, *Nrf2* activation is a promise but unproven disease-modifying therapy; toxicity and dosage windows continue to be significant limitations that necessitate careful patient/stage selection.[35]All compound names and regulatory classifications were verified from clinicaltrials.gov and FDA/EMA databases (accessed September 2025).

Anti-Inflammatory agents — *NF-κB* Inhibitors and Cytokine Modulators

Rationale and Key Nodes

Inflammatory amplification loops that harm synapses and neurons can be broken by altering maladaptive glia activation. There are two general approaches: (A) inhibit the upstream transcriptional programs that control the production of inflammatory genes (*NF-κB*/IKK pathway, for example), and (B) either directly neutralize effector cytokines or block their receptors (TNF-α, IL-1β, IL-6). Furthermore, inhibiting caspase-1 activity or inflammasome assembly (NLRP3) is a method that is being investigated more and more to reduce IL-1β/IL-18-induced neurotoxicity.[36]

Evidence and Examples

NF-κB pathway inhibitors: proteasome modulators that stop IκB degradation, small-molecule IKK inhibitors, and more recent oligonucleotide/nanOligomer® strategies that downregulate *NF-κB* components all show improved pathology and decreased cytokine production in animal models (e.g., nanOligomer®s targeting *NF-κB*/NLRP3 improved cognition in mice). On the other hand, systemic *NF-κB* suppression affects the physiological functions of neuronal *NF-κB* and runs the risk of immunosuppression.

In peripheral inflammatory illnesses, cytokine blockers, such as monoclonal antibodies and receptor antagonists (such as anti-TNF medicines, IL-1 receptor antagonist anakinra, and anti-IL-6R), have a solid track record. Clinical translation is mixed because of concerns about systemic immunomodulation and blood–brain barrier (BBB) penetration, however preclinical CNS investigations demonstrate benefit in specific animals.[37] There is research being done on comparative delivery methods (intrathecal, brain-targeted gene therapy, or BBB-penetrant biologics). In AD models where tau or amyloid drives inflammasome activation, NLRP3 inflammasome inhibitors (small compounds, biologics) have restored synaptic and cognitive endpoints and decreased IL-1β maturation.

Clinical/Translational Note: In order to optimize therapeutic index and prevent blunting of favorable immunological responses, biomarker-guided patient selection is necessary for anti-cytokine therapy (e.g., increased CSF cytokines, PET microglia activation). All compound names and regulatory classifications were verified from clinicaltrials.gov and FDA/EMA databases (accessed September 2025).

Synaptic Function Modulators — *BDNF* Enhancers and Dopamine Modulators

Rationale and Key Nodes

Clinical function depends on the preservation or restoration of synaptic signaling. Altering neurotransmitter systems (e.g., dopamine) to rectify circuit malfunction and lessen maladaptive plasticity that speeds up degeneration, and (A) boosting trophic support (*BDNF*/TrkB signaling) to stabilize synapses and encourage plasticity, are two feasible strategies.[38]

*TrkB and *BDNF* TrkB and *BDNF* Methods*

Poor brain dispersion and a brief half-life have hampered the use of direct *BDNF* administration. Therefore, preclinical research is actively focused on TrkB agonists (small compounds such as 7,8-dihydroxyflavone, LM22A-4, and tailored TrkB agonist antibodies or peptidomimetics), gene therapy to boost *BDNF* production, and small drugs that improve endogenous *BDNF* release. In a number of AD and stroke models, TrkB activation restores synaptic markers, spine density, and TrkB and *BDNF* methods.

Dopaminergic Tactics

Dopamine replacement therapy and MAO-B inhibition continue to be the cornerstones of symptom alleviation in models of Parkinson's disease.[39] In preclinical research, a number of dopaminergic drugs (such as rasagiline and selegiline) have neuroprotective properties that might be connected to antiapoptotic signaling and mitochondrial stability. To stop maladaptive synaptic alterations, new approaches include neurotrophic support of nigrostriatal neurons, dopamine-producing cell/gene treatments, and circuit-level Dopaminergic tactics.[40]

Table 2 | Summary of key pharmacological targets with mechanism, compound examples, and preclinical evidence

Compound/Class	Primary Mechanism/Target	Evidence Tier	Approval/Regulatory Status	Key Safety/Outcome (Refs.)
Nrf2 / HO-1 Pathway (Antioxidant Défense)	Activates antioxidant response elements (ARE); maintains redox equilibrium; cross-suppresses NF-κB; and upregulates HO-1, NQO1, GCLC, SOD, and CAT.	Mixed (Preclinical + Human)	Mouse models: CDDO-Im protects against ischemic brain injury; Mangifera activates Nrf2/HO-1 (Preclinical; triterpenoid derivative)	Neuroprotection, reduced oxidative damage
Glutathione (GSH) Pathway [43]	Reduces mitochondrial damage, neutralizes ROS, and increases glutathione production and recycling.[44]	Ebselen, glutathione esters, L-cysteine donors, and N-acetylcysteine (NAC)	Animal & in vitro	Improved mitochondrial function, decreased oxidative stress
NF-κB Signalling Inhibition	Attenuates neuroinflammation by blocking NF-κB nuclear translocation, which lowers TNF-α, IL-1β, IL-6, iNOS, and COX-2.	Mixed (Preclinical + Human)	AD models	Reduced neuroinflammation, hippocampal neuron protection
Cytokine Modulators (TNF-α, IL-1, IL-6)	Pro-inflammatory cytokine neutralization or receptor inhibition lowers neuronal death and microglia overactivation.[46]	Human (Off-label, AD)	Human pilot & animal studies	Cognitive improvement (Etanercept), reduced neuronal death (FDA approved (Rheumatoid arthritis); trialed off-label in AD)
NLRP3 Inflammasome Inhibition	Inhibits caspase-1 activation by blocking NLRP3, which lowers IL-1β and IL-18-mediated neurotoxicity.	Preclinical	AD animal models	Prevents amyloid-induced neuroinflammation
BDNF / TrkB Pathway (Neurotrophic Support)	Increases BDNF-TrkB signaling, which in turn encourages dendritic development, synaptic plasticity, LTP, and neurogenesis.	LM22A-4, Fingolimod, SSRIs (indirect BDNF enhancers), 7,8-Dihydroxyflavone (TrkB agonist), and exercise mimetics[48]	AD mice	Restores memory deficits, neurotrophic support
Dopamine Modulation (PD focus)	Protects the nigrostriatal pathway, lowers oxidative metabolism, and increases dopamine availability.	Ropinirole, Pramipexole, Rasagiline, Selegiline, and L-DOPA[49]	Animal & clinical PD	Neuroprotection, motor symptom relief
Glutamate / Excitotoxicity Modulation	Decreases Ca2+ excess and neuronal death by blocking NMDA overactivation.	Human (FDA approved, Epilepsy)	AD animal & clinical	Improves cognition, slows AD progression
Mitochondrial Protection	Maintains mitochondrial activity, enhances ATP generation, and blocks the permeability transition pore (mPTP).[51]	MitoQ, Creatine, Coenzyme Q10, and SS-31 peptide	PD animal models	Slows neurodegeneration
α-Synuclein Aggregation Inhibition	Stops α-synuclein from misfolding or aggregating in Parkinson's disease	Mixed (Preclinical + Human)	PD mice[52]	Reduces α-synuclein accumulation, neuronal death
Amyloid-β Targeting (AD focus)	decreases synaptic damage, avoids oligomer toxicity, and removes Aβ plaques.	Mixed (Preclinical + Human)	Animal & clinical	Improves cognition, synaptic protection
Tau Modulation[54]	Stops tau from being hyperphosphorylated and clumping together.	Derivatives of lithium, tideglusib, and methylene blue	AD models	Reduces neurofibrillary tangles
Microbiota-Gut-Brain Axis Modulation[55]	Restores the equilibrium of the gut microbiota, which lowers peripheral and central nervous system inflammation.	Probiotics, Short-chain fatty acids, Resveratrol	MCI & AD patients	Cognitive improvement, reduced inflammation

Regulatory status is based on FDA/EMA classification as of 2025; "research-only" indicates compounds without clinical approval for neurodegenerative use

NMDA receptor modulators (e.g., memantine in AD to minimize excitotoxicity), ampakines (positive AMPA receptor modulators), and synaptic scaffolding protein modulators are also being studied to restore LTP/LTD equilibrium. In animal models, combined strategies that increase *BDNF*/TrkB signaling and decrease oxidative/inflammatory stress seem to work well.[41] These core pharmacological targets, representative compounds, and supporting preclinical evidence are summarized in Table 2.

Pharmacological Agents: Natural and Synthetic

The field of neuroprotective pharmacology includes highly selective synthetic small compounds, biologics, and pleiotropic natural polyphenols and flavonoids. Antioxidant, anti-inflammatory, and synaptic trophic signaling are just a few of the numerous nodes that natural chemicals frequently work on. This can be helpful for multifactorial disorders, but it can also make dose/PK and target validation more difficult. Because of their improved target selectivity and more lucid mechanism of action, synthetic drugs frequently make biomarker-guided clinical development possible. A summary of representative natural and synthetic medicines, their primary targets, and current preclinical data demonstrating their potential for precision neuroprotection is provided below.[56]

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Natural Compounds (Flavonoids, Polyphenols)

The neuroprotective qualities of natural polyphenols and flavonoids, including as quercetin, curcumin, resveratrol, epigallocatechin gallate [EGCG], and kaempferol, have been well investigated.[57,58] Their main mechanisms of action include metal chelation, inhibition of *NF-κB* signaling, suppression of NLRP3/inflammasome activation, indirect activation of antioxidant transcriptional programs (*Nrf2*/antioxidant response element (ARE)), direct scavenging of ROS, and modulation of synaptic plasticity (e.g., upregulation of *BDNF*). Consistent neuroprotection is highlighted by recent thorough reviews and primary studies (2023–2025) in a variety of models (amyloid/tau-driven AD models, MPTP/6-OHDA PD models, and ischemia/reperfusion), frequently demonstrating decreases in oxidative markers and cytokines as well as preservation of synaptic proteins and behavior.

Important nstances

In AD models, quercetin decreases neuroinflammation, inhibits MAPK/*NF-κB* pathways, promotes *Nrf2* signaling, and maintains cognitive function.

Curcumin: Anti-inflammatory, anti-amyloid, and in certain animals, increases *BDNF* expression; nevertheless, its low bioavailability hinders practical translation; several attempts have been made to improve CNS delivery by Nano formulations.[59]

Green tea's EGCG and resveratrol have been shown to have synaptic protective, anti-inflammatory, and antioxidant properties in a variety of animals. Resveratrol also affects sirtuins and mitochondrial biogenesis.

Translational Notes: Although the multitarget characteristics of natural substances make them appealing for combination or adjunctive usage, effective translation necessitates strict PK/PD and target engagement data, regulated dosage, and enhanced CNS administration (nano-formulations, prodrugs).

Synthetic Small Molecules (Selective Pathway Modulators)

Synthetic agents provide higher specificity and often clearer clinical pathways. Notable classes with recent preclinical/clinical traction include:

Nrf2 activators, such as omaveloxolone (Skyclarys®) (licensed for Friedreich ataxia) and dimethyl fumarate (DMF, Tecfidera®), increase mitochondrial activity, lower inflammatory signals, and boost cellular antioxidant defenses. DMF improves cognition and reduces neuroinflammation in preclinical AD/PD models; the clinical approval of omaveloxolone highlights the translational viability of *Nrf2* activation, although evidence of disease-specific effectiveness is still pending.[60,61]

MCC950, a research tool/sulfonylurea scaffold, is one example of an inflammasome inhibitor (NLRP3 inhibitor) that has demonstrated strong preclinical benefits in lowering IL-1β/IL-18 and preserving synaptic and cognitive endpoints in AD/PD models. Safety and clinical lead optimization is still continuing.[62]

In preclinical investigations, *NF-κB*/IKK pathway modulators—small compounds and comparative oligonucleotide methods (nanOligomer®s)—can improve disease by lowering glia cytokine production and inflammasome priming. However, systemic *NF-κB*

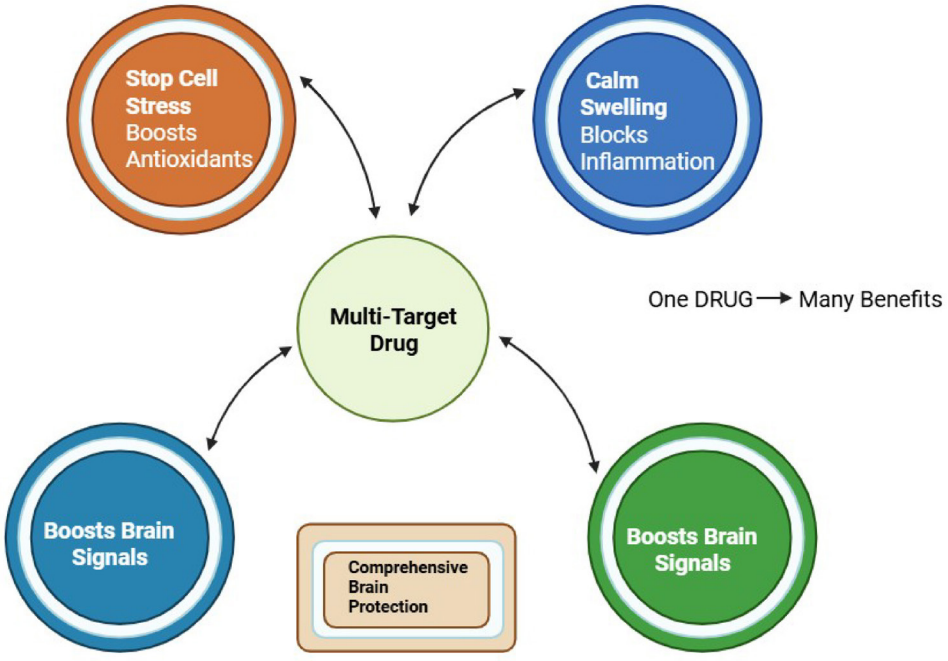

Fig 5 | Multi-target drug action on oxidative stress, inflammation, and synaptic pathways
Source: Created by authors using Bio Render for illustrative purposes.
(Depicts the necessity of a multi-target pharmacological strategy in neuroprotection, where a single agent or combination acts simultaneously on the three core pathologies. This approach interrupts the degenerative cycle by boosting antioxidants, suppressing neuroinflammation, and restoring synaptic function. It illustrates a multi-target neuroprotective approach integrating antioxidant, anti-inflammatory, and synaptic pathways).

Table 3 | Comparative efficacy of pharmacological agents in preclinical studies[64–68]

Compound/Class	Primary Mechanism/Target	Evidence Tier	Approval/Regulatory Status	Key Safety/Outcome (Refs.)
Curcumin (Natural polyphenol) (Nutraceutical/Research use only)	antioxidant and anti-inflammatory; decreases Aβ/tau aggregation, inhibits NF-κB, and reports Nrf2 activation	Mixed (Preclinical + Human)	Improved memory & motor scores; reduced neuroinflammation; decreased Aβ/tau pathology; enhanced synaptic markers.	Generally safe in rodents
EGCG (Epigallocatechin-3-gallate) (Natural catechin) (Research-grade; in Phase II trials for AD)	Anti-inflammatory, ROS scavenger, and proteostasis and mitochondrial function modulator	Mixed (Preclinical + Human)	Improved mitochondrial function & cognition; decreased oxidative markers; reduced microglia activation	Low toxicity in preclinical models
Sulforaphane (Natural isothiocyanate)	Activates Nrf2 → HO-1/NQO1; anti-inflammatory and antioxidant	"Aβ models ..., 6-OHDA PD mice"	Preserved dopaminergic neurons; reduced ROS & lipid peroxidation; improved motor & cognitive function	N/A
7,8-Dihydroxyflavone (DHF) (Natural/semisynthetic TrkB agonist)	TrkB agonist → BDNF-like signaling; improvement of synaptic plasticity and protection	Neuronal cultures, various transgenic models, and APP/PS1 AD mice	Restored synaptic density; improved LTP; rescued memory deficits	N/A
N-acetylcysteine (NAC) (Natural derivative/small molecule)	GSH precursor: restores glutathione; anti-inflammatory and antioxidant	Rodent models of Aβ, PD, ischemia, and toxin; variations of NACA (amide)	Enhanced cognition & synaptic markers; restored brain GSH; reduced oxidative stress	Minimal toxicity
MitoQ (Synthetic mitochondria-targeted antioxidant)	protects mitochondrial function by targeting ubiquinone conjugate, or mitochondrial ROS.	PD, ischemia, and TBI in rodent models	Reduced mitochondrial ROS; decreased lesion size; improved motor & cognitive recovery	N/A
SS-31/Elamipretide (Synthetic mitochondria-targeting peptide)	preserves ATP synthesis, lowers mitochondrial ROS, and stabilizes IMM.	TBI models, ischemia models, and APP transgenic AD mice	Enhanced cognition & synaptic function; improved mitochondrial bioenergetics	N/A
MCC950 (Small-molecule NLRP3 inhibitor) (Research-only (NLRP3 inhibitor))	decreases the activation of microglia inflammasomes and inhibits the NLRP3 inflammasome via inhibiting caspase-1 and IL-1β/IL-18.	Preclinical	Improved cognition; decreased neuroinflammation & neuropathology	N/A
Anle138b (Synthetic aggregation inhibitor) (Preclinical (Research only))	prevents α-synuclein and other amyloidogenic proteins from forming oligomers.	Preclinical	Increased motor performance; preserved dopaminergic neurons; reduced α-syn aggregation	N/A
CDDO-Im (Synthetic triterpenoid; Nrf2 activator) (Preclinical; triterpenoid derivative)	Strong Nrf2 inducer → increases HO-1, anti-inflammatory, and antioxidant enzymes	Ex vivo models of oxidative stress and inflammation in rodents	Strong Nrf2 activation; decreased oxidative damage & inflammation	N/A
Memantine (Synthetic NMDA antagonist)	lowers excitotoxicity by blocking extra synaptic NMDA receptors; this may indirectly increase BDNF.	Neuronal cultures, ischemia, AD, and TBI models in rodents	Improved behavior; reduced Aβ-induced damage; decreased infarct size	Mild neurotoxicity in high doses
Coenzyme Q10/related (endogenous antioxidant; supplement)	antioxidant and mitochondrial electron carrier that lowers ROS and promotes ATP	Models of Parkinson's disease, toxins, and mitochondrial dysfunction	Delayed dopaminergic degradation; improved motor outcomes	Generally safe
Memantine derivatives/novel NMDA modulators (synthetic)	NMDA modulation with an enhanced profile or an additional NO-donor (e.g., MN-08)	Experimental models for glaucoma, stroke, and neurodegeneration	Improved neuroprotection vs memantine	N/A
Probiotics/microbiota modulators (Natural/nutraceutical approach)	changes the gut-brain axis, which lowers systemic inflammation and modifies microglia priming.	Antibiotic, germ-free, and rodent models of AD/MCI	Improved cognition; decreased neuroinflammation via SCFA & immune modulation	N/A

Regulatory status is based on FDA/EMA classification as of 2025; "research-only" indicates compounds without clinical approval for neurodegenerative use

suppression necessitates brain-selective administration or temporary modulation and carries the risk of immunosuppression.[63]

Synaptic modulators and neurotransmitter modulators: rasagiline/selegiline (MAO-B inhibitors) give symptomatic dopamine support and exhibit preclinical neuroprotective signals; memantine (NMDA partial antagonist) decreases excitotoxicity (clinical usage in AD for symptomatic benefit). Advanced preclinical testing is underway for small-molecule synaptic enhancers and comparative TrkB agonists (7,8-DHF analogy, peptidomimetics).

Translational notes: stage-specific therapies are made easier by synthetic compounds that enable customized PK/brain exposure and biomarker formation (target engagement) (e.g., *Nrf2* activation in oxidative-dominant patients; NLRP3 inhibition in inflammasome-high patients). Practical issues still include safety, blood–brain barrier (BBB) penetration, and effects on targets' physiological functions, while the integrated multi-target action of these agents on oxidative stress, inflammation, and synaptic pathways is summarized in Figure 5.

Depicts the necessity of a multi-target pharmacological strategy in neuroprotection, where a single agent

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or combination acts simultaneously on the three core pathologies. This approach interrupts the degenerative cycle by boosting antioxidants, suppressing neuroinflammation, and restoring synaptic function. A comparative overview of the preclinical efficacy of these pharmacological agents is presented in Table 3. It illustrates a multi-target neuroprotective approach integrating antioxidant, anti-inflammatory, and synaptic pathways.

Preclinical and Translational Evidence

Preclinical Understanding the molecular mechanisms of oxidative stress, neuroinflammation, and synaptic dysfunction in neurodegenerative illnesses is greatly aided by in vitro models. To mimic neuronal oxidative damage, human neuroblastoma SH-SY5Y, PC12, and primary cortical neurons are frequently used. Research has demonstrated that antioxidants including quercetin, resveratrol, and curcumin efficiently reduce the production of reactive oxygen species (ROS) and maintain mitochondrial function in these cell line. Furthermore, anti-inflammatory drugs like luteolin and berberine inhibit the production of cytokines (TNF-α, IL-6) and *NF-κB* activation in LPS-stimulated microglial cells, confirming their function in neuroimmune regulation. Improvements in synaptic vesicle recycling efficiency and neural connection have been demonstrated by synaptic modulators such dopamine receptor agonists and *BDNF* mimetics.[69,70]

Animal Models

Preclinical research on transgenic mice, zebrafish, and rats has yielded a wealth of information on the neuroprotective effectiveness of pharmaceuticals. To assess dopaminergic neuron loss and motor dysfunction, for example, 6-hydroxydopamine (6-OHDA) and MPTP-induced Parkinson's models are frequently employed. By upregulating *Nrf2*/*HO-1* and suppressing pro-inflammatory mediators, natural antioxidants including baicalein and epigallocatechin gallate (EGCG) decreased nigral degeneration and enhanced motor coordination.[71–73] Treatment with quercetin nanoparticles improved memory function and decreased amyloid β-plaque formation in App, Psen1 transgenic Alzheimer's mice. This was linked to decreased oxidative indicators (MDA, NO) and increased synaptic proteins. Additionally, as compared to free substances, polyphenolic nanocarriers have demonstrated better brain penetration and bioavailability, which results in increased antioxidant and anti-inflammatory effects.

Early Clinical Trials

The results of recent clinical trials investigating anti-inflammatory and antioxidant pharmacotherapies have been encouraging yet inconsistent. For instance, in individuals with early-stage Parkinson's and Alzheimer's disease, supplements of N-acetylcysteine (NAC) and Coenzyme Q10 have shown some improvement in cognitive and motor abilities. Furthermore, due to improved blood–brain barrier penetration, resveratrol and curcumin Nano formulations have entered Phase II studies for Alzheimer's disease, showing safety, tolerability, and a little improvement in cognitive function. Another study demonstrated enhanced hippocampus volume and synaptic activity on MRI, highlighting *BDNF*-enhancing peptides as a possible supplementary treatment for moderate cognitive impairment. Overall, translation from preclinical success to consistent human benefit remains limited, underscoring the need for stage-specific and biomarker-guided clinical validation, as outlined in Figure 6. Translational pipeline from bench to clinic.[74–76] The major translational challenges and potential strategies for neuroprotective drug development are summarized in Table 4.

Critical Appraisal and Translational Considerations

We critically weighed the positive, neutral, and negative findings across preclinical and early clinical studies to contextualize translational potential. While multiple agents show convergent neuroprotective signals in animals, effect sizes and endpoints vary across models, indicating heterogeneity in mechanisms, dosing, and outcome measures.[77]

- Coenzyme Q10 and related mitochondrial supplements show robust preclinical signals but mixed or negative findings in late clinical settings of Parkinson's disease; species/model differences and subtherapeutic CNS exposure likely contribute.

Table 4 | The major translational challenges and potential strategies for neuroprotective drug development

Compound/Class	Primary Mechanism / Target	Evidence Tier	Approval / Regulatory Status	Key Safety / Outcome (Refs.)	NCT ID	Outcomes Summary Regulatory Status
Nrf2 Activators	Dimethyl Fumarate (FDA approved (Multiple Sclerosis))	II	Alzheimer's Disease	Safety, CSF Nrf2 markers	NCT04213322	Safe; biomarker increase
Polyphenolic Nano formulations	Curcumin Nano, Resveratrol (Nutraceutical / Research use only)	Mixed (Preclinical + Human)	Mild Cognitive Impairment	Cognitive change (ADAS-Cog)	NCT04137968	Minor cognitive gain
Cytokine Modulators	Etanercept (anti-TNF) (FDA approved (Rheumatoid arthritis); trialed off-label in AD)	Human (Off-label, AD)	Alzheimer's Disease	Cognitive score (ADAS-Cog)	NCT01068353	Mixed efficacy
NLRP3 Inhibitors	MCC950 (Research) (Research-only (NLRP3 inhibitor))	Preclinical	AD/PD models	IL-1β suppression	-	Strong preclinical signal
BDNF/TrkB Enhancers	7,8-DHF analogues (Research-only; TrkB agonist (preclinical)	Preclinical	Parkinson's Disease	Safety, PK	NCT05620304	Safe; dose-response noted

Regulatory status is based on FDA/EMA classification as of 2025; "research-only" indicates compounds without clinical approval for neurodegenerative use.

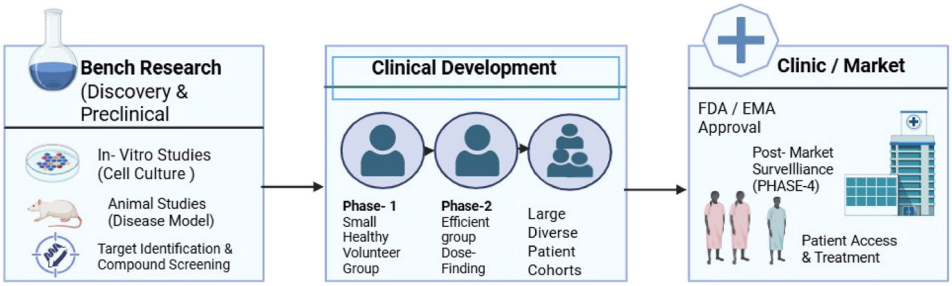

Fig 6 | Translational pipeline from bench to clinic
Source: Created by authors using Bio Render for illustrative purposes.
(Illustrates the structured, multi-stage process required to transform a potential neuroprotective compound into an approved clinical drug. It highlights the progression from Basic Research (at the "bench," involving in vitro and in vivo animal models to prove efficacy and safety) through the three rigorous phases of Clinical Trials (in humans). The diagram highlights key translational checkpoints from preclinical research through Phase III trials leading to potential clinical application.)

- Curcumin and other polyphenols demonstrate multi-target benefits preclinically but face bioavailability and target-engagement challenges; human data remain heterogeneous despite nano formulation progress.
- Memantine provides symptomatic benefit in AD with consistent preclinical neuroprotection against excitotoxicity, yet disease-modifying effects are limited clinically.[78]
- Cytokine-targeted strategies (e.g., anti-TNF) report pilot cognitive signals in small human studies but lack consistent efficacy across larger, controlled trials, partly due to blood–brain barrier (BBB) penetration, timing, and safety constraints.
- LRP3 inhibitors (e.g., MCC950) yield strong target-directed effects in rodent AD/PD models, but human safety and pharmacology remain to be established.

Translational Failure Modes

- Model-to-human gaps: toxin or transgenic models capture only subcircuits of human disease; endpoints (rotarod, Morri's water maze) may not track clinical decline.
- PK/PD and delivery: inadequate brain exposure (blood–brain barrier (BBB) limits), rapid metabolism, or transient target engagement undermine efficacy signals.[79]
- Timing and heterogeneity: interventions applied early in animals are often tested late in humans; patient subtypes differ in dominant pathology (oxidative vs inflammatory vs synaptic).

Safety and PK/PD Uncertainties to Address Preclinically/Early-Clinically

- *Nrf2* activators (e.g., DMF, triterpenoids): off-target electrophilicity, immunomodulation, and dose window definition require careful monitoring; confirm CNS target engagement via *HO-1*/NAD(P)H quinone oxidoreductase 1 (*NQO1*)1 induction.
- NLRP3 blockade: infection risk, immune reactivity, and hepatic safety profiling are essential alongside IL-1β/IL-18 pharmacodynamics.[80]
- Dopaminergic modulators: long-term dyskinesia risk (L-DOPA) and MAO-B inhibitor interactions warrant PK/DDI characterization.
- Polyphenols: quantify brain exposure (LC–MS/MS), stability, and metabolite activity; avoid assuming antioxidant effects without target engagement.

Biomarker-based Patient Stratification (Concrete Examples)

- To reduce heterogeneity and enrich for responders, we propose aligning interventions with mechanistic biomarker profiles:
- Oxidative-dominant phenotype: elevated CSF/Plasma F2-isoprostanes, MDA/4-HNE adducts, low GSH or GSH/GSSG ratio; imaging or MRS lactate signatures → consider *Nrf2*/GSH-pathway support (e.g., DMF, NAC) with confirmation of *HO-1*/NAD(P)H quinone oxidoreductase 1 (*NQO1*)1 induction.[81]
- Inflammasome-high phenotype: increased CSF IL-1β/IL-18, ASC specks, high peripheral inflammasome transcript signatures; TSPO-PET microglial activation → evaluate NLRP3 inhibitors or cytokine modulators with PD readouts on IL-1β/IL-18.
- Excitotoxic/synaptic phenotype: elevated MR spectroscopy Glx, reduced synaptic markers (CSF neurogranin, SNAP-25), EEG-based LTP-like plasticity deficits → NMDA modulation (memantine/next-gen) ± *BDNF*/TrkB augmentation.[82]
- Dopaminergic degeneration phenotype (PD): DAT-SPECT deficits, CSF/seeded α-synuclein assays, low *BDNF* in nigrostriatal circuits → dopaminergic support with adjunct trophic or mitochondrial protectants.

These distinctions between preclinical and clinical findings were emphasized to maintain proportionality and avoid overstating therapeutic efficacy.

Challenges and Future Directions

Numerous translational and mechanistic issues still need to be addressed, despite tremendous advancements in the identification of pharmacological modulators for neuroprotection.

Dose Optimization, Specificity, and Safety

The therapeutic effectiveness of both synthetic and natural neuroprotective agents is frequently constrained by their pharmacokinetic characteristics. The effective concentration at the neuronal target locations

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is decreased by limited bioavailability, fast metabolism, and poor blood–brain barrier (BBB) permeability. In vitro, curcumin and quercetin, for instance, have potent neuroprotective effects; nevertheless, because to inadequate absorption and systemic clearance, clinical trials have not consistently shown positive results. Safety profiles are still difficult to determine since long-term *NF-κB* suppression may affect normal wimmunological function, while chronic stimulation of antioxidant pathways (such as *Nrf2*) might disrupt redox homeostasis. To increase CNS bioavailability and reduce systemic toxicity, target-specific delivery methods and dosage optimization are therefore being explored. Examples of these include polymeric nanoparticles, liposomes, and intranasal formulations.[83]

Table 5 | Current challenges vs possible solutions in pharmacological neuroprotection

Compound/Class	Primary Mechanism/Target	Evidence Tier	Approval/Regulatory Status
Dose Optimization & Pharmacokinetics[85]	Despite encouraging preclinical outcomes, subtherapeutic brain exposure or systemic toxicity resulted in ineffectiveness.	Employ preclinical-to-clinic bridging techniques such as PK/PD modeling, brain-penetrant prodrugs, nanoparticle/targeted delivery, and therapeutic drug monitoring.	For instance, employ prodrugs or Nano formulations to increase the bioavailability of polyphenols; employ PET ligand research and micro dialysis to expose the brain.
Blood–Brain Barrier (BBB) Permeability[86]	Many substances are unable to achieve adequate CNS concentrations.	Use targeted ultrasound (temporary BBB opening), cell-penetrating peptides, receptor-mediated transcytosis, and BBB-penetrating vectors.	For targeted entrance, conjugate medications to transferrin receptor ligands, employ liposomes or PEGylated nanoparticles, or employ ultrasound-assisted administration.
Specificity & Off-Target Effects	Safety is limited by off-target toxicity, immunological activation, or metabolic limitations.	Allosteric modulators, conditional/prodrug activation, reduced systemic exposure by local administration, and structure-based design for selectivity	To lessen peripheral exposure, create biased agonists or brain-selective prodrugs, or administer them locally or intranasally.
Safety & Long-Term Tolerability	Long-term safety is necessary for chronic neurodegenerative therapy; studies are stopped by unanticipated side effects.[87]	Immune profiles, multi-species long-term research, early chronic-dose toxicity testing, and pharmacovigilance strategies	Track autoimmunity, neuroinflammation indicators, and a gradual increase in early human biomarker investigations.
Target Validation & Disease Heterogeneity	Patient heterogeneity and complex disease pathways can cause single-target medicines to fail.	Employ precision/umbrella trial designs, stratify patients based on biomarkers, and verify targets using systems biology and multi-omics.	For instance, NLRP3 activation and amyloid/tau status are biomarker-based inclusions that improve the likelihood of finding benefit in subgroups.[88]
Poor Reproducibility & Model Limitations	Preclinical signals that are too hopeful but do not replicate in people	Make use of blinded/randomized animal experiments, standardized, stringent preclinical procedures, and multi-model validation (in vitro, organoids, several species).	For translational significance, employ human iPSC-derived neurons and organoids, preregister animal experiments, and follow ARRIVE standards.[89]
Timing of Intervention (Disease Stage)	The window of efficacy is frequently unclear, and late intervention may be futile.	Create long-term biomarker research to determine treatment windows and conduct prodromal or early-stage testing.	Utilize fluid/PET biomarkers and longitudinal cohorts to determine the best times for interventions (e.g., preclinical AD).[90]
Combination Therapy Complexity	Risk of drug-drug interactions, regulatory requirements, and trial design intricacy	Adaptive trial designs, sequential dosage, comprehensive DDI investigations, and rational polytherapy based on complementary processes[87]	For instance, employ adaptive trial platforms, conduct PK/PD interaction studies first, and combine Nrf2 activator with NLRP3 inhibitor.
Biomarker Limitations (Sensitivity/Specificity)	Predicting clinical benefit and measuring target engagement are challenging tasks.	Create and validate functional, fluid, and imaging biomarkers for target engagement and downstream effects.	Make use of PET tracers, electrophysiological biomarkers, CSF/plasma phospho-tau, neurofilament light (NFL), and digital endpoints.[91,92]
Manufacturing & Scale-Up of Complex Agents (Biologics, Nanoparticles)[93]	Regulatory obstacles, cost, and repeatability for complex modalities	Strong characterisation and release tests; scalable formulation science; early interaction with GMP facilities	Implement GLP/GMP pipelines and quality-by-design (QbD); schedule CMC early in the translation process.
Regulatory & Ethical Hurdles for Novel Delivery Methods	If the safety profile or mechanism is unclear, there may be delays or rejection.	Risk mitigation strategies, a strong nonclinical safety package, and early regulatory contact (pre-IND/scientific advice)	Incorporate device concerns for focused ultrasound or intranasal devices into FDA/EMA scientific advice meetings.[94]
Clinical Trial Design Challenges (Endpoints, Duration)	Extensive trials with insensitive endpoints result in significant failure risk and hefty costs.n[95]	Employ decentralized evaluations, enrichment techniques, adaptive and platform trials, and sensitive surrogate biomarkers.	To cut down on sample size and length, use digital cognitive tests, composite endpoints, and biomarker-guided enrichment.
Cost & Accessibility of New Therapies[93]	Population impact and uptake are limited by high prices.	Think about tiered pricing, repurposing authorized medications, cost-effective manufacturing, and public-private collaborations.	Negotiate access programs, seek generic channels when feasible, and repurpose medicines (such as NAC and dimethyl fumarate analogs). (FDA approved (Multiple Sclerosis))
Immunogenicity (Biologics / Repeated Dosing)	Immune adverse effects or neutralizing antibodies decrease effectiveness.	Immuno-monitoring, intermittent dosage, tolerance induction techniques, and humanized biologics	Create less immunogenic scaffolds and include ADA monitoring into mitigation strategies and trials.
Translational Gaps Between Animal Models and Humans	Variations among species in pathology, immunological response, and metabolism	Refine models using humanized models, neural systems produced from iPSCs, and back-translation from human biomarker data.	Combine iterative model refinement utilizing clinical data, human ex vivo testing, and animal experiments.

Regulatory status is based on FDA/EMA classification as of 2025; "research-only" indicates compounds without clinical approval for neurodegenerative use

Table 6 | Phenotype-guided strategy linking biomarkers to agents, trials, PD/PK and safety [96–100]

Compound/Class	Primary Mechanism / Target	Evidence Tier	Approval / Regulatory Status	Key Safety / Outcome (Refs.)	Evidence Summary
Oxidative-Dominant	↑ F2-isoprostanes, ↓ GSH/GSSG, MRS lactate	Human (Phase III, FDA approved)	HO-1/NQO1 induction, CSF: plasma ratio	LFTs, CBC, infection monitoring	CoQ10 mixed results, DMF in MS, exploratory (FDA approved (Multiple Sclerosis))
Inflammasome-High	↑ IL-1β/IL-18, TSPO-PET activation	Preclinical	IL-1β suppression, CSF › IC50	CRP, infection/ reactivation	Anti-TNF mixed, MCC950 strong preclinical (Research-only (NLRP3 inhibitor))
Excitotoxic/Synaptic	↑ MRS Glx, ↓neurogranin/ SNAP-25	NMDA/AMPA modulators, TrkB/BDNF enhancers	TMS-EEG plasticity, EC50 target modulation	Seizure threshold, LFTs	Memantine symptomatic, TrkB early-phase
Dopaminergic	DAT-SPECT deficit, α-syn biomarkers	MAO-B inhibitors, dopamine agonists, GDNF	DAT-SPECT stability, brain exposure	Dyskinesia, BP/ ECG, hepatic/renal	Symptomatic benefit; GDNF mixed trials

Regulatory status is based on FDA/EMA classification as of 2025; "research-only" indicates compounds without clinical approval for neurodegenerative use.

Potential for Combination Therapies

A viable strategy for precision neuroprotection is combination treatment, given the complex pathophysiology of neurodegenerative diseases. For example, by concurrently addressing oxidative, inflammatory, and apoptotic pathways, the co-administration of antioxidants and anti-inflammatory drugs (such as resveratrol + melatonin or N-acetylcysteine + minocycline) has demonstrated additive neuroprotection. Additionally, by simultaneously modifying ROS, cytokines, and synaptic proteins, multi-target nanomedicines and phytopharmaceutical combinations have shown synergistic benefits in preclinical models.[84] Personalized neurotherapy may undergo a revolution thanks to precision-based combination design informed by biomarkers (such as oxidative indicators and inflammatory cytokine profiles) Current challenges vs possible solutions in pharmacological neuroprotection are summarized in Table 5.

Operational Precision Framework for Neuroprotection

Rationale. Patients with neurodegeneration present heterogeneous, partly overlapping biology. We operationalize four pragmatic phenotypes—oxidative-dominant, inflammasome-high, excitotoxic/synaptic, dopaminergic—and map each to candidate agent classes, enrichment biomarkers, signal-finding trial designs, pharmacodynamic (PD) target-engagement readouts, pharmacokinetic (PK) exposure targets, and safety monitoring. Importantly, we integrate negative/neutral human data where applicable to calibrate expectations and this operational precision framework is summarized in Table 6.

Table 7 | Minimal phenotype-wise biomarker panels (clinic-ready)

Phenotype	Minimal Core Panel (4–5 tests)	Optional Add-ons
Oxidative-dominant	Plasma/CSF F2-isoprostanes (LC–MS/MS); GSH/GSSG (HPLC); 4-HNE adducts (LC–MS/MS); ^1H-MRS lactate	8-OHdG, mitochondrial copy-number
Inflammasome-high	CSF IL-1β/IL-18 (multiplex); ASC specks; TSPO-PET	Caspase-1 activity, IL-18BP
Excitotoxic/synaptic	^1H-MRS Glx; CSF neurogranin; CSF SNAP-25; TMS-EEG LTP index	Resting-state EEG connectivity
Dopaminergic	DAT-SPECT; RT-QuIC α-syn; NfL; BDNF	DaT quantitative MRI (if available)

Biomarker Thresholds & Example Assays (Operational Cut-offs)

(A) Oxidative-dominant Phenotype

- Primary biomarkers: CSF/plasma F2-isoprostanes, 4-HNE adducts, MDA, GSH/GSSG ratio, brain MRS lactate.
- Assays/platforms:
  - F2-isoprostanes, 4-HNE: LC–MS/MS (preferred) or ELISA (confirmatory LC–MS/MS).
  - GSH/GSSG: HPLC or LC–MS/MS (hemolysis-controlled sampling).

Table 8 | PD/PK target-engagement readouts (what proves "it's hitting the target")

Compound/Class	Primary Mechanism / Target	Evidence Tier	Approval / Regulatory Status
Nrf2 activators (DMF, Omaveloxolone)	PBMC/CSF HO-1 & NQO1 mRNA/protein ↑ ~1.5–2× from baseline; ↓ oxidative markers (F2-isoprostanes, 4-HNE)	CSF: plasma ratio stable; trough above preclinical EC50-informed target	LFTs, CBC, infection screen
NLRP3 / anti-cytokine (MCC950/Anakinra/ Etanercept)	IL-1β/IL-18 ↓ ≥30–50%; ↓ ASC/caspase-1 activity; TSPO-PET signal trend ↓	Preclinical	CRP, CBC, infection/ reactivation
NMDA/AMPA modulators (Memantine/ Perampanel)	MRS Glx ↓ toward norm; TMS-EEG LTP index ↑; CSF neurogranin ↓	Human (FDA approved, Epilepsy)	CNS AEs, seizure threshold, LFTs
BDNF/TrkB enhancers (7,8-DHF analogues, SSRIs indirect)	pTrkB/BDNF-responsive gene set ↑ in PBMC; EEG plasticity ↑; synaptic marker trend	Preclinical	Mood/sleep, ECG (if needed)
Dopaminergic (MAO-B inhibitors/agonists)	DAT-SPECT decline stabilization; UPDRS slope flattening	Label-guided Cmin/Cmax with DDI check	BP/ECG, dyskinesia, hepatic/renal

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- MRS: single-voxel ^1H-MRS (Glx, lactate).
- Operational thresholds (illustrative):
  - F2-isoprostanes ≥1.5× URL or >75th percentile vs controls;
  - GSH/GSSG ≤0.7× lab median;
  - MRS lactate detectable/elevated above site reference.

(B) Inflammasome-high phenotype

- Primary biomarkers: CSF IL-1β/IL-18, ASC specks, peripheral inflammasome transcript signature, TSPO-PET binding.
- Assays/platforms: Luminex/mesoscale multiplex for cytokines; flow/cell-free ASC; TSPO-PET (e.g., ^18F-DPA-714) with genotype correction (rs6971).
- Operational thresholds:
  - CSF IL-1β/IL-18 ≥1.5× URL;
  - TSPO-PET standardized uptake ratio (SUVR) > site-specific z-score +1.

(C) Excitotoxic/synaptic phenotype

- Primary biomarkers: MRS Glx, CSF neurogranin/SNAP-25, EEG/TMS-EEG LTP-like plasticity metrics.
- Assays/platforms: ^1H-MRS, Simoa/ELISA (neurogranin, SNAP-25), paired-pulse/TMS-EEG protocols.
- Operational thresholds:
  - Glx z-score ≥+1 vs site norms;
  - Neurogranin ≥1.5× URL or rising trend;
  - LTP-like plasticity index below lab lower limit.

(D) Dopaminergic phenotype (PD-dominant)

- Primary biomarkers: DAT-SPECT deficit (striatal binding ratio), CSF/seeded α-syn RT-QuIC, *BDNF* (nigrostriatal), ± NfL.
- Assays/platforms: [^123I]-FP-CIT SPECT; RT-QuIC; Simoa (NfL).
- Operational thresholds:
  - DAT-SBR ≤−2 SD vs age-norm;
  - RT-QuIC positive;
  - NfL elevated above age-adjusted URL.

Minimal phenotype-wise biomarker panels (clinic-ready)

Minimal phenotype-wise biomarker panels (clinic-ready) are summarized in Table 7.

PD/PK target-engagement readouts (what proves "it's hitting the target")

PD/PK target-engagement readouts (what proves "it's hitting the target") are summarized in Table 8.

Brief case vignette (how to apply at bedside)

Case: 64-yo woman, amnestic MCI with fatigue.
Baseline biomarkers: Plasma F2-isoprostanes 1.8× URL, GSH/GSSG low (0.6× ref), ^1H-MRS lactate detectable; CSF cytokines normal; MRS Glx mildly ↑; DAT-SPECT normal.
Phenotype call: Oxidative-dominant (no strong inflammation or dopaminergic signal).
Plan: Start *Nrf2*-pathway support (e.g., DMF or omaveloxolone per risk–benefit) + NAC adjunct; lifestyle oxidative load counseling.
PD targets (12–16 weeks): PBMC *HO-1*/*NQO1* ↑~1.5–2×; F2-isoprostanes ↓≥30%; GSH/GSSG ↑ toward lab median; MRS lactate ↓.
PK: Maintain exposure in therapeutic window; CSF: plasma ratio stable if sampled.
Safety: LFTs, CBC, infection screen at baseline, 1, 3, 6 months; dose adjust if AEs.
Outcome anchor: Cognitive battery composite z-score and patient-reported fatigue at baseline vs 4 months.

Limitations

This is a narrative review, potential selection bias and heterogeneity in study design were considered during evidence interpretation.

Conclusion

The multifaceted etiology of neurodegenerative illnesses, which include oxidative stress, neuroinflammation, and synaptic dysfunction, makes them one of the most complicated medical problems of our generation. In preclinical and early translational research, pharmacological approaches that target these mechanisms—through antioxidants (*Nrf2*/*HO-1*), anti-inflammatory modulators (*NF-κB*, cytokines), and synaptic enhancers (*BDNF*, dopamine pathways)—have shown great promise. Advances in tailored pharmacology, biomarker analysis, and nanotechnology are revolutionizing neuroprotection and opening the door to precision neuroprotective treatment. For conditions including Alzheimer's, Parkinson's, and Huntington's, better results can be achieved by the integration of multi-target medicines, optimum dose, and patient-specific therapy procedures. However, overcoming present obstacles is necessary to achieve clinical translation, especially those pertaining to drug administration, long-term safety, and repeatability in human models. Most data summarized here are derived from preclinical and early-phase trials; therefore, conclusions should be interpreted as exploratory rather than confirmatory. For effective and secure neuroprotection, future studies must concentrate on AI-driven medication development, genetic profiling for patient selection, and intelligent nanocarrier-based delivery methods.

List of Abbreviations:

AD – Alzheimer's disease
ALS – Amyotrophic lateral sclerosis
ASC – Apoptosis-associated speck-like protein containing a CARD
Aβ – Amyloid-β
blood–brain barrier (BBB) – Blood–brain barrier
BDNF – Brain-derived neurotrophic factor
CAT – Catalase
COX-2 – Cyclooxygenase-2
CSF – Cerebrospinal fluid
DAMPs – Damage-associated molecular patterns
DAT – Dopamine transporter
DMF – Dimethyl fumarate
DOPAC – 3,4-Dihydroxyphenylacetic acid
EEG – Electroencephalography
ETC – Electron transport chain

F2-IsoPs – F2-Isoprostanes
GDNF – Glial cell line–derived neurotrophic factor
GPx – Glutathione peroxidase
GSH – Glutathione (reduced form)
GSSG – Glutathione (oxidized form)
HD – Huntington's disease
HO-1 – Heme oxygenase-1
IL – Interleukin
IKK – IκB kinase
iNOS – Inducible nitric oxide synthase
L-DOPA – Levodopa
LFTs – Liver function tests
LTP/LTD – Long-term potentiation / Long-term depression
MAO-B – Monoamine oxidase-B
MCC950 – NLRP3 inflammasome inhibitor compound
MDA – Malondialdehyde
MPTP – 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRS – Magnetic resonance spectroscopy
NAC – N-acetylcysteine
NAD(P)H – Nicotinamide adenine dinucleotide phosphate (reduced form)
NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3 – NOD-, LRR-, and pyrin domain-containing protein 3
NMDA – N-methyl-D-aspartate
NAD(P)H quinone oxidoreductase 1 (*NQO1*)1 – NAD(P)H quinone oxidoreductase 1
Nrf2 – Nuclear factor erythroid 2–related factor 2
PD – Parkinson's disease
PD/PK – Pharmacodynamic / Pharmacokinetic
PK/PD – Pharmacokinetic / Pharmacodynamic
RNS – Reactive nitrogen species
ROS – Reactive oxygen species
SCFA – Short-chain fatty acids
SOD – Superoxide dismutase
TBI – Traumatic brain injury
TLR – Toll-like receptor
TNF – Tumor necrosis factor
TrkB – Tropomyosin receptor kinase B
TSPO-PET – Translocator protein positron emission tomography

References

1 Wang S, Jiang Y, Yang A, Meng F, Zhang J. The expanding burden of neurodegenerative diseases: an unmet medical and social need. Aging and disease. 2024;16(5):2937. https://doi.org/10.14336/AD.2024.1071
2 Lamptey RN, Chaulagain B, Trivedi R, Gothwal A, Layek B, Singh J. A review of the common neurodegenerative disorders: current therapeutic approaches and the potential role of nanotherapeutics. International journal of molecular sciences. 2022;23(3):1851. https://doi.org/10.3390/ijms23031851
3 Huang S, Lu Y, Fang W, Huang Y, Li Q, Xu Z. Neurodegenerative diseases and neuroinflammation-induced apoptosis. Open Life Sciences. 2025;20(1):20221051. https://doi.org/10.1515/biol-2022-1051
4 Olufunmilayo EO, Gerke-Duncan MB, Holsinger RD. Oxidative stress and antioxidants in neurodegenerative disorders. Antioxidants. 2023;12(2):517. https://doi.org/10.3390/antiox12020517
5 Quinn PM, Ambrósio AF, Alves CH. Oxidative stress, neuroinflammation and neurodegeneration: the chicken, the egg and the dinosaur. Antioxidants. 2022;11(8):1554. https://doi.org/10.3390/antiox11081554
6 Dejanovic B, Sheng M, Hanson JE. Targeting synapse function and loss for treatment of neurodegenerative diseases. Nature Reviews Drug Discovery. 2024;23(1):23–42. https://doi.org/10.1038/s41573-023-00823-1
7 Strafella C, Caputo V, Galota MR, Zampatti S, Marella G, Mauriello S, Cascella R, Giardina E. Application of precision medicine in neurodegenerative diseases. Frontiers in neurology. 2018;9:701. https://doi.org/10.3389/fneur.2018.00701
8 Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vladâcenco O, Roza E, Costăchescu B, Grumezescu AM, Teleanu RI. An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. 2022;23(11):5938. https://doi.org/10.3390/ijms23115938
9 Peggion C, Calì T, Brini M. Mitochondria dysfunction and neuroinflammation in neurodegeneration: who comes first. Antioxidants. 2024;13(2):240. https://doi.org/10.3390/antiox13020240
10 Guo C, Sun L, Chen X, Zhang D. Oxidative stress, mitochondrial damage and neurodegenerative diseases. Neural regeneration research. 2013;8(21):2003–14. https://doi.org/10.3969/j.issn.1673-5374.2013.21.009
11 Taoufik E, Kouroupi G, Zygogianni O, Matsas R. Synaptic dysfunction in neurodegenerative and neurodevelopmental diseases: an overview of induced pluripotent stem-cell-based disease models. Open biology. 2018;8(9):180138. https://doi.org/10.1098/rsob.180138
12 Rossi SL, Subramanian P, Bovenkamp DE. The future is precision medicine-guided diagnoses, preventions and treatments for neurodegenerative diseases. Frontiers in Aging Neuroscience. 2023;15:1128619. https://doi.org/10.3389/fnagi.2023.1128619
13 Hampel H, Caraci F, Cuello AC, Caruso G, Nisticò R, Corbo M, Baldacci F, Toschi N, Garaci F, Chiesa PA, Verdooner SR. A path toward precision medicine for neuroinflammatory mechanisms in Alzheimer's disease. Frontiers in immunology. 2020;11:456. https://doi.org/10.3389/fimmu.2020.00456
14 Baethge C, Goldbeck-Wood S, Mertens S. SANRA—a scale for the quality assessment of narrative review articles. Research integrity and peer review. 2019;4(1):5. https://doi.org/10.1186/s41073-019-0064-8
15 Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K. Neuroinflammation in Alzheimer's disease. The Lancet Neurology. 2015;14(4):388–405. https://doi.org/10.1016/S1474-4422(15)70016-5
16 Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signaling agents. Nature reviews Molecular cell biology. 2020;21(7):363–83. https://doi.org/10.1038/s41580-020-0230-3
17 Angelova PR, Abramov AY. Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. FEBS letters. 2018;592(5):692–702. https://doi.org/10.1002/1873-3468.12964
18 Bustamante-Barrientos FA, Luque-Campos N, Araya MJ, Lara-Barba E, de Solminihac J, Pradenas C, Molina L, Herrera-Luna Y, Utreras-Mendoza Y, Elizondo-Vega R, Vega-Letter AM. Mitochondrial dysfunction in neurodegenerative disorders: Potential therapeutic application of mitochondrial transfer to central nervous system-residing cells. Journal of Translational Medicine. 2023;21(1):613. https://doi.org/10.1186/s12967-023-04493-w
19 Yang HM. Mitochondrial Dysfunction in Neurodegenerative Diseases. Cells. 2025;14(4):276. https://doi.org/10.3390/cells14040276
20 Bradley-Whitman MA, Lovell MA. Biomarkers of lipid peroxidation in Alzheimer disease (AD): an update. Archives of toxicology. 2015;89(7):1035–44. https://doi.org/10.1007/s00204-015-1517-6
21 Voet S, Srinivasan S, Lamkanfi M, van Loo G. Inflammasomes in neuroinflammatory and neurodegenerative diseases. EMBO molecular medicine. 2019;11(6):e10248. https://doi.org/10.15252/emmm.201810248
22 Yang D, Su J, Chen Y, Chen G. The NF-κB pathway: Key players in neurocognitive functions and related disorders. European Journal of Pharmacology. 2024;984:177038. https://doi.org/10.1016/j.ejphar.2024.177038

23 Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. Journal of neuroinflammation. 2022;19(1):206. https://doi.org/10.1186/s12974-022-02565-0
24 Plantone D, Pardini M, Righi D, Manco C, Colombo BM, De Stefano N. The role of TNF-α in Alzheimer's disease: a narrative review. Cells. 2023;13(1):54. https://doi.org/10.3390/cells13010054
25 Sarapultsev A, Gusev E, Komelkova M, Utepova I, Luo S, Hu D. JAK-STAT signaling in inflammation and stress-related diseases: implications for therapeutic interventions. Molecular biomedicine. 2023;4(1):40. https://doi.org/10.1186/s43556-023-00151-1
26 Pajarillo E, Rizor A, Lee J, Aschner M, Lee E. The role of astrocytic glutamate transporters GLT-1 and GLAST in neurological disorders: Potential targets for neurotherapeutics. Neuropharmacology. 2019;161:107559. https://doi.org/10.1016/j.neuropharm.2019.03.002
27 Liao Y, Kong Y, Chen H, Xia J, Zhao J, Zhou Y. Unraveling the priming phase of NLRP3 inflammasome activation: Molecular insights and clinical relevance. International Immunopharmacology. 2025;146:113821. https://doi.org/10.1016/j.intimp.2024.113821
28 Gasiorowska A, Wydrych M, Drapich P, Zadrozny M, Steczkowska M, Niewiadomski W, Niewiadomska G. The biology and pathobiology of glutamatergic, cholinergic, and dopaminergic signaling in the aging brain. Frontiers in aging neuroscience. 2021;13:654931. https://doi.org/10.3389/fnagi.2021.654931
29 Dong XX, Wang Y, Qin ZH. Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacologica Sinica. 2009;30(4):379–87. https://doi.org/10.1038/aps.2009.24
30 Bazzari AH, Parri HR. Neuromodulators and long-term synaptic plasticity in learning and memory: A steered-glutamatergic perspective. Brain sciences. 2019;9(11):300. https://doi.org/10.3390/brainsci9110300
31 Buchanan H, Mackay M, Palmer K, Tothová K, Katsur M, Platt B, Koss DJ. Synaptic loss, ER stress and neuro-inflammation emerge late in the lateral temporal cortex and associate with progressive tau pathology in Alzheimer's disease. Molecular Neurobiology. 2020;57(8):3258–72. https://doi.org/10.1007/s12035-020-01950-1
32 Bellezza I, Giambanco I, Minelli A, Donato R. Nrf2-Keap1 signaling in oxidative and reductive stress. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2018;1865(5):721–33. https://doi.org/10.1016/j.bbamcr.2018.02.010
33 Bains JS, Shaw CA. Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death. Brain research reviews. 1997;25(3):335–58. https://doi.org/10.1016/S0165-0173(97)00045-3
34 Linker RA, Lee DH, Ryan S, van Dam AM, Conrad R, Bista P, Zeng W, Hronowsky X, Buko A, Chollate S, Ellrichmann G. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain. 2011;134(3):678–92.https://doi.org/10.1093/brain/awq386
35 Dinkova-Kostova AT, Kazantsev AG. Activation of Nrf2 signaling as a common treatment of neurodegenerative diseases. Neurodegenerative Disease Management. 2017;7(2):97–100. https://doi.org/10.2217/nmt-2017-0011
36 Heneka MT, McManus RM, Latz E. Inflammasome signaling in brain function and neurodegenerative disease. Nature Reviews Neuroscience. 2018;19(10):610–21. https://doi.org/10.1038/s41583-018-0055-7
37 Maher PA, Schubert DR. Metabolic links between diabetes and Alzheimer's disease. Expert review of neurotherapeutics. 2009;9(5):617–30. https://doi.org/10.1586/ern.09.18
38 Sulzer D, Surmeier DJ. Neuronal vulnerability, pathogenesis, and Parkinson's disease. Movement Disorders. 2013;28(1):41–50. https://doi.org/10.1002/mds.25095
39 Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE. Parkinson disease. Nature reviews Disease primers. 2017;3(1):1–21. https://doi.org/10.1038/nrdp.2017.13
40 Liu TC, Sheu JJ, Lin HC, Jensen DA. Increased risk of parkinsonism following chronic periodontitis: A retrospective cohort study. Movement Disorders. 2013;28(9):1307–8. https://doi.org/10.1002/mds.25359
41 Barde YA. The physiopathology of brain-derived neurotrophic factor. Physiological Reviews. 2025. https://doi.org/10.1152/physrev.00038.2024
42 Leeson HC, Aguado J, Gómez-Inclán C, Chaggar HK, Fard AT, Hunter Z, Lavin MF, Mackay-Sim A, Wolvetang EJ. Ataxia Telangiectasia patient-derived neuronal and brain organoid models reveal mitochondrial dysfunction and oxidative stress. Neurobiology of disease. 2024;199:106562. https://doi.org/10.1016/j.nbd.2024.106562
43 Carnicero-Senabre D, Barata MA, Almeida CG, Cuadrado A, Rojo AI. Therapeutic targeting of NRF2 in Alzheimer's disease: S II_2. Free Radical Biology and Medicine. 2024;218:3. https://doi.org/10.1016/j.freeradbiomed.2024.04.017
44 Balakrishnan R, Garcia PA, Veluthakal R, Huss JM, Hoolachan JM, Thurmond DC. Toward ameliorating insulin resistance: targeting a comparative PAK1 signaling pathway required for skeletal muscle mitochondrial function. Antioxidants. 2023;12(9):1658.
45 Pensabene KM, LaMorte J, Allender AE, Wehr J, Kaur P, Savage M, Eggler AL. Acute oxidative stress can paradoxically suppress human NRF2 protein synthesis by inhibiting global protein translation. Antioxidants. 2023;12(9):1735. https://doi.org/10.3390/antiox12091735
46 Herrera ML, Champarini LG, Basmadjian OM, Bellini MJ, Hereñú CB. IGF-1 gene therapy prevents spatial memory deficits and modulates dopaminergic neurodegeneration and inflammation in a parkinsonism model. Brain, Behavior, and Immunity. 2024;119:851–66. https://doi.org/10.1016/j.bbi.2024.05.013
47 Dempsey C, Araiz AR, Bryson KJ, Finucane O, Larkin C, Mills EL, Robertson AA, Cooper MA, O'neill L, Lynch MA. Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice. Brain, behavior, and immunity. 2017;61:306–16. https://doi.org/10.1016/j.bbi.2016.12.014
48 Hashimoto K, Chaki S. Ketamine and its metabolites: Potential as comparative treatments for depression. Neuropharmacology. 2023.
49 Rose EP, Osterberg VR, Gorbunova V, Unni VK. Alpha-synuclein modulates the repair of genomic DNA double-strand breaks in a DNA-PKcs-regulated manner. Neurobiology of disease. 2024;201:106675.https://doi.org/10.1016/j.nbd.2024.106675
50 Nuzum ND, Szymlek-Gay EA, Loke S, Dawson SL, Teo WP, Hendy AM, Loughman A, Macpherson H. Differences in the gut microbiome across typical ageing and in Parkinson's disease. Neuropharmacology. 2023;235:109566. https://doi.org/10.1016/j.neuropharm.2023.109566
51 Heppner DE, Ogboo BC, Patel KB, Reis J, Massari M, Marchese S, Mattevi A. Design and characterization of NOX-targeting compounds for improved understanding of covalent inhibitors: ECR_1. Free Radical Biology and Medicine. 2024;218:5. https://doi.org/10.1016/j.freeradbiomed.2024.04.025
52 Massari CM, Dues DJ, Bergsma A, Sipple K, Frye M, Williams ET, Moore DJ. Neuropathology in an α-synuclein preformed fibril mouse model occurs independent of the Parkinson's disease-linked lysosomal ATP13A2 protein. Neurobiology of Disease. 2024;202:106701. https://doi.org/10.1016/j.nbd.2024.106701
53 Tariot PN, Riviere ME, Salloway S, Burns JM, Snaedal JG, Borowsky B, Reversibility of cognitive worsening observed with BACE inhibitor umibecestat in the Alzheimer's Prevention Initiative (API) Generation Studies. Alzheimer's & Dementia. 2024;20(11):7745–61. https://doi.org/10.1002/alz.14237
54 Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. Nature Reviews Neurology. 2018;14(7):399–415. https://doi.org/10.1038/s41582-018-0013-z
55 Kowalski K, Mulak A. Brain-gut-microbiota axis in Alzheimer's disease. Journal of neurogastroenterology and motility. 2019;25(1):48. https://doi.org/10.5056/jnm18087
56 Rehman MU, Wali AF, Ahmad A, Shakeel S, Rasool S, Ali R, Rashid SM, Madkhali H, Ganaie MA, Khan R. Neuroprotective strategies for neurological disorders by natural products: an update. Current neuropharmacology. 2019;17(3):247–67. https://doi.org/10.2174/1570159X16666180911124605
57 Kalu A, Ray SK. Epigallocatechin-3-Gallate, Quercetin, and Kaempferol for Treatment of Parkinson's Disease Through Prevention of Gut Dysbiosis and Attenuation of Multiple Molecular Mechanisms of Pathogenesis. Brain Sciences. 2025;15(2):144. https://doi.org/10.3390/brainsci15020144
58 Tkaczenko H, Buyun L, Kołodziejska R, Kamiński P, Kurhaluk N. Neuroactive Phytochemicals as Multi-Target Modulators of Mental Health and Cognitive Function: An Integrative Review. International Journal of Molecular Sciences. 2025;26(18):8907. https://doi.org/10.3390/ijms26188907

59 Feng Y, Yu X, Han J. Quercetin Regulates the Polarization of Microglia through the NRF2/Heme oxygenase-1 (HO-1) Pathway and Mitigates Alzheimer's Disease. Actas Españolas de Psiquiatría. 2024;52(6):786. https://doi.org/10.62641/aep.v52i6.1713

60 Lynch DR, Perlman S, Schadt K. Omaveloxolone for the treatment of Friedreich ataxia: clinical trial results and practical considerations. Expert Review of Neurotherapeutics. 2024;24(3):251–8. https://doi.org/10.1080/14737175.2024.2310617

61 Lynch DR, Chin MP, Boesch S, Delatycki MB, Giunti P, Goldsberry A, Efficacy of omaveloxolone in Friedreich's ataxia: delayed–start analysis of the MOXIe extension. Movement disorders. 2023;38(2):313–20. https://doi.org/10.1002/mds.29286

62 Zahid A, Li B, Kombe AJ, Jin T, Tao J. Pharmacological inhibitors of the NLRP3 inflammasome. Frontiers in immunology. 2019;10:2538. https://doi.org/10.3389/fimmu.2019.02538

63 Sun E, Motolani A, Campos L, Lu T. The pivotal role of NF-κB in the pathogenesis and therapeutics of Alzheimer's disease. International journal of molecular sciences. 2022;23(16):8972. https://doi.org/10.3390/ijms23168972

64 Grabarczyk M, Justyńska W, Czpakowska J, Smolińska E, Bielenin A, Glabinski A, Szpakowski P. Role of plant phytochemicals: Resveratrol, curcumin, luteolin and quercetin in demyelination, neurodegeneration, and epilepsy. Antioxidants. 2024;13(11):1364. https://doi.org/10.3390/antiox13111364

65 Ege D. Action mechanisms of curcumin in Alzheimer's disease and its brain targeted delivery. Materials. 2021;14(12):3332. https://doi.org/10.3390/ma14123332

66 Jang SW, Liu X, Yepes M, Shepherd KR, Miller GW, Liu Y, Wilson WD, Xiao G, Blanchi B, Sun YE, Ye K. A selective TrkB agonist with potent neurotrophic activities by 7, 8-dihydroxyflavone. Proceedings of the National Academy of Sciences. 2010;107(6):2687–92. https://doi.org/10.1073/pnas.0913572107

67 Turdi S, Han X, Huff AF, Roe ND, Hu N, Gao F, Ren J. Retraction notice to "Cardiac-specific overexpression of catalase attenuates lipopolysaccharide-induced myocardial contractile dysfunction: Role of autophagy"[Free Radic. Biol. Med. 53/6 (2012) 1327–1338]. Free Radical Biology and Medicine. 2022;189:178. https://doi.org/10.1016/j.freeradbiomed.2022.07.011

68 Majkutewicz I. Dimethyl fumarate: A review of preclinical efficacy in models of neurodegenerative diseases. European Journal of Pharmacology. 2022;926:175025. https://doi.org/10.1016/j.ejphar.2022.175025

69 Yang Y, Tan X, Xu J, Wang T, Liang T, Xu X, Ma C, Xu Z, Wang W, Li H, Shen H. Luteolin alleviates neuroinflammation via downregulating the TLR4/TRAF6/NF-κB pathway after intracerebral hemorrhage. Biomedicine & Pharmacotherapy. 2020;126:110044. https://doi.org/10.1016/j.biopha.2020.110044

70 Zhu L, Bi W, Lu D, Zhang C, Shu X, Lu D. Luteolin inhibits SH-SY5Y cell apoptosis through suppression of the nuclear transcription factor-κB, mitogenactivated protein kinase and protein kinase B pathways in lipopolysaccharide-stimulated cocultured BV2 cells. Experimental and therapeutic medicine. 2014;7(5):1065–70. https://doi.org/10.3892/etm.2014.1564

71 Wang Y, Wei N, Li X. Preclinical evidence and possible mechanisms of baicalein for rats and mice with Parkinson's disease: A systematic review and meta-analysis. Frontiers in Aging Neuroscience. 2020;12:277. https://doi.org/10.3389/fnagi.2020.00277

72 Zhang W, Dong X, Huang R. Antiparkinsonian effects of polyphenols: a narrative review with a focus on the modulation of the gut-brain axis. Pharmacological Research. 2023;193:106787. https://doi.org/10.1016/j.phrs.2023.106787

73 Perdigão JM, Teixeira BJ, Baia-da-Silva DC, Nascimento PC, Lima RR, Rogez H. Analysis of phenolic compounds in Parkinson's disease: a bibliometric assessment of the 100 most cited papers. Frontiers in Aging Neuroscience. 2023;15:1149143.https://doi.org/10.3389/fnagi.2023.1149143

74 Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JA. Coenzyme Q10 and dementia: a systematic review. Antioxidants. 2023;12(2):533. https://doi.org/10.3390/antiox12020533

75 Shults CW, Beal MF, Song D, Fontaine D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. Experimental neurology. 2004;188(2):491–4. https://doi.org/10.1016/j.expneurol.2004.05.003

76 Liu L, He H, Du B, He Y. Nanoscale drug formulations for the treatment of Alzheimer's disease progression. RSC advances. 2025;15(6):4031–78. https://doi.org/10.1039/D4RA08128E

77 Wang Z, Wang C, Wei T, Mi Y, Zhou S, Liu X, Jia J, Li L, Zhao G, Tang Y. Impaired temporal coding associated with central auditory dysfunction and cognitive impairment in Alzheimer's disease. Science bulletin. 2024;69(24):3838–43. https://doi.org/10.1016/j.scib.2024.10.012

78 Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine. 2003;348(14):1333–41. https://doi.org/10.1056/NEJMoa013128

79 Rodriguez–Antona C, Savieo JL, Lauschke VM, Sangkuhl K, Drögemöller BI, Wang D, van Schaik RH, Gilep AA, Peter AP, Boone EC, Ramey BE. PharmVar Gene Focus: CYP3A5. Clinical Pharmacology & Therapeutics. 2022;112(6):1159–71. https://doi.org/10.1002/cpt.2563

80 Sharma B, Satija G, Madan A, Garg M, Alam MM, Shaquiquzzaman M, Khanna S, Tiwari P, Parvez S, Iqubal A, Haque SE. Role of NLRP3 inflammasome and its inhibitors as emerging therapeutic drug candidate for Alzheimer's disease: a review of mechanism of activation, regulation, and inhibition. Inflammation. 2023;46(1):56–87. https://doi.org/10.1007/s10753-022-01730-0

81 Fan Z, Yan Q, Song J, Wei J. Reactive human plasma glutathione peroxidase mutant with diselenide bond succeeds in tetramer formation. Antioxidants. 2022;11(6):1083. https://doi.org/10.3390/antiox11061083

82 Bittner S, Oh J, Havrdová EK, Tintoré M, Zipp F. The potential of serum neurofilament as biomarker for multiple sclerosis. Brain. 2021;144(10):2954–63. https://doi.org/10.1093/brain/awab241

83 Fan X, Jiang K, Geng F, Lu W, Wei G. Ocular therapies with biomacromolecules: From local injection to eyedrop and emerging noninvasive delivery strategies. Advanced drug delivery reviews. 2023;197:114864. https://doi.org/10.1016/j.addr.2023.114864

84 Li M, Cheng S, Fan J, Shang Z, Wan H. Many heads are better than one: A multiscale neural information feature fusion framework for spatial route selections decoding from multichannel neural recordings of pigeons. Brain Research Bulletin. 2022;184:1–2. https://doi.org/10.1016/j.brainresbull.2022.03.007

85 Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood–brain barrier: Structure, regulation and drug delivery. Signal transduction and targeted therapy. 2023;8(1):217. https://doi.org/10.1038/s41392-023-01481-w

86 Haqqani AS, Bélanger K, Stanimirovic DB. Receptor-mediated transcytosis for brain delivery of therapeutics: receptor classes and criteria. Frontiers in Drug Delivery. 2024;4:1360302. https://doi.org/10.3389/fddev.2024.1360302

87 Weemering dn, beelen a, kliest t, van leeuwen la, van den berg lh, van eijk rp. Trial participation in neurodegenerative diseases: barriers and facilitators: a systematic review and meta-analysis. Neurology. 2024;103(1):E209503. Https://doi.Org/10.1212/Wnl.0000000000209503

88 Lai R, Li B, Bishnoi R. P-tau217 as a Reliable Blood-Based Marker of Alzheimer's Disease. Biomedicines. 2024;12(8):1836. https://doi.org/10.3390/biomedicines12081836

89 Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M. The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. Journal of Cerebral Blood Flow & Metabolism. 2020;40(9):1769–77. https://doi.org/10.1177/0271678X20943823

90 Salvadó G, Janelidze S, Bali D, Dolado AO, Therriault J, Brum WS, Binette AP, Stomrud E, Mattsson-Carlgren N, Palmqvist S, Coomans EM. Plasma Phosphorylated Tau 217 to Identify Preclinical Alzheimer Disease. JAMA neurology. 2025. https://doi.org/10.1001/jamaneurol.2025.3217

91 Palmqvist S, Warmenhoven N, Anastasi F, Pilotto A, Janelidze S, Tideman P, Stomrud E, Mattsson-Carlgren N, Smith R, Ossenkoppele R, Tan K. Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform. Nature Medicine. 2025:1–8. https://doi.org/10.1038/s41591-025-03569-4

92 Götze K, Vrillon A, Dumurgier J, Indart S, Sanchez-Ortiz M, Slimi H, Raynaud-Simon A, Cognat E, Martinet M, Zetterberg H, Blennow K. Plasma neurofilament light chain as prognostic marker of cognitive decline in neurodegenerative diseases, a clinical setting study. Alzheimer's Research & Therapy. 2024;16(1):231. https://doi.org/10.1186/s13195-024-01572-3

93 Jiao Y, Yang L, Wang R, Song G, Fu J, Wang J, Gao N, Wang H. Drug Delivery Across the Blood–Brain Barrier: A New Strategy for the Treatment of Neurological Diseases. Pharmaceutics. 2024;16(12):1611. https://doi.org/10.3390/pharmaceutics16121611
94 Pagé G, Novell A, Larrat B. Imaging strategies to assess efficacy and safety of ultrasound-induced blood-brain barrier opening. npj Acoustics. 2025;1(1):20. https://doi.org/10.1038/s44384-025-00024-7
95 Weemering DN, Beelen A, Kliest T, van Leeuwen LA, van den Berg LH, van Eijk RP. Trial participation in neurodegenerative diseases: Barriers and facilitators: a systematic review and meta-analysis. Neurology. 2024;103(1):e209503. https://doi.org/10.1212/WNL.0000000000209503
96 Cummings J, Zhou Y, Grill JD, Brody DL, Mucke L. Translating preclinical neuroprotection into clinical success: lessons from Alzheimer's and Parkinson's disease trials. Nat Rev Drug Discov. 2024;23(5):355–377. https://doi.org/10.1038/s41573-023-00743-8
97 Zahid A, Li B, Kombe AJ, Jin T, Tao J. Pharmacological inhibitors of then NLRP3 inflammasome. Front Immunol. 2019;10:2538. https://doi.org/10.3389/fimmu.2019.02538
98 Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003;348(14):1333–1341. https://doi.org/10.1056/NEJMoa013128
99 Whone AL, Barker RA, Kelly C, Brooks DJ, Rodriguez-Oroz MC, et al. Randomized trial of intermittent intraputaminal glial cell line–derived neurotrophic factor in Parkinson's disease. Brain. 2019;142(2):512–525. https://doi.org/10.1093/brain/awy325
100 Linker RA, Gold R, Luhder F. Fumaric acid esters exert neuroprotective effects in models of neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain. 2011;134(3):678–692. https://doi.org/10.1093/brain/awq386