CHAPTER N0.

11

Targeting redox imbalance and inflammatory cascades in the pathogenesis of neurodegeneration

IFRAHA ABBAS[1*], MARYAM KHAN SHERWANI[2], SANIA ALI[3], ARISHA MOAZZAM[3], VASMA ZAHID[3], FAIZAN RAMZAN[4], UMAR IKRAAM[5], AMNA MANZAR[1]

[1]Department of Pharmaceutical Sciences, Riphah International University, Faisalabad, Pakistan
[2]Yusra Institute of Pharmaceutical Sciences, Rawalpindi, Pakistan
[3]Institute of Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan
[4]Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan
[5]Faculty of Pharmacy, The University of Lahore., Pakistan
*Correspondence: ifraha.abbas@riphahfsd.edu.pk

ABSTRACT: Neurodegeneration is characterized as a pathological condition that primarily affects neurons. Neurodegenerative diseases are a broad category of neurological disorders that affect particular subsets of neurons in particular parts central nervous system and have a variety of clinical and pathological features. Oxidative stress and chronic neuroinflammation have a common convergent pathogenic axis in neurodegenerative diseases. The appearance of excessive reactive oxygen (ROS) and nitrogen species (NOS) production, dysfunction of the antioxidant defense mechanisms, and dysfunction of mitochondria facilitate the proliferation of oxidative injury to neuronal lipids, proteins, and nucleic acids. Simultaneously, prolonged stimulation of microglia and astrocytes results in the liberation of pro-inflammatory cytokines, chemokines, and nitric oxide that further increase redox imbalance and neuronal susceptibility. Targeting of these pathways has proven to be an effective treatment option. The possible benefits of antioxidants, anti-inflammatory agents, mitochondrial protectants, and natural phytochemicals include the minimization of oxidative damage, redox balance restoration, and inflammatory signal regulation. This chapter highlights the mechanistic interaction between oxidative stress and neuroinflammation and the new preclinical and clinical interventions aimed for redox homeostasis restoration and to treat neurodegenerative diseases.
Keywords: Neurodegeneration, Oxidative stress, Pro-inflammatory cytokines, Astrocytes

INTRODUCTION

The human brain is a complex organ that represents a hub of diversity, growth, structure, and function. It governed multiple molecular processes. It is made up of billions of cells called neurons that regulate how well our bodies work. Everything we do, including thinking, moving, and talking, is made possible by the stimulation and transmission of impulses by neurons (Sultana et al., 2024). As a result, even minor misunderstandings among cells in a certain region might cause interference with other brain-controlled functions, resulting in a serious brain disorder. Progressive loss of brain function brought on by a buildup of toxic proteins that manifest as clinical syndromes is a neurodegenerative illness (Behl et al., 2021). The words "Neuro," which means brain, and "Degenerative," which implies dying or disintegrating, combine to make the phrase "Neurodegenerative." Therefore, it is important to take brain disorders seriously because they might cause widespread issues that eventually lead to shrinkage and neuronal death. Insufficient communication between brain cells can have disastrous consequences, impacting a person's speech, memory, movement, and many other abilities (Milanifard and Ramezan, 2025). Neurodegeneration is a condition marked by an increase in neuronal loss and dysfunction. The buildup of proteins in neurons, abnormal environmental conditions, aging, and mitochondrial abnormalities are the causes of neurodegeneration. Protein deposition is the most frequent pathology associated with ND (Sajid et al., 2023).

Human functioning is diminished in neurodegenerative diseases (NDs), a category of neurological conditions linked to a progressive loss of nerve cells in the brain or nervous system (Begley et al., 2025). NDs encompass conditions such multiple sclerosis (MS), Parkinson's disease (PD), dementia, and Alzheimer's disease (AD). AD and PD are the most prevalent forms of ND; between 1990 and 2015, the prevalence of Parkinson's disease doubled worldwide, making it the ND with the greatest rate of growth. Growing health and financial burdens are consequently linked to the rising incidence and prevalence of NDs; in the United States, Parkinson's disease cost $51.9 billion in 2017, multiple sclerosis cost $85.4 billion in 2019, and dementia cost $1.3 trillion worldwide in 2019 (Wimo et al., 2023; Bebo et al., 2022; Yang et al., 2020).

Globally, as the population grows, the prevalence of neurodegenerative disorders is rising across all racial and geographic groups, genders, and geographic locations (Twiss et al., 2025). The development of novel drugs with efficient therapy approaches has become essential to combat these diseases because they are extremely complex and challenging to treat. By examining the highlighted sophisticated neural pathways, simulated models have been developed that have established as adjuvant resources for the development of novel

How to Cite: Abbas I, Mk Sherwani, S Ali, A Moazzam, V Zahid, F Ramzan, U Ikraam, A Manzar, 2025. Targeting redox imbalance and inflammatory cascades in the pathogenesis of neurodegeneration. In: Advances in Pharmacology and Integrative Therapeutics (Aslam B, W Majeed, A Iftikhar, S Javed, I Abbas, Eds). FahumSci, Lahore, Pakistan, pp: 68-74. ISBN: 978-627-7745-13-4. https://doi.org/10.61748/APIT.2025/11

therapeutic drugs (Jiang et al., 2025). In addition to offering more understanding of the pathophysiology of neurological disorders, the gathering of biomarkers or therapeutic targets can aid in the development of novel drugs (Das et al., 2024).

IMPACT OF OXIDATIVE STRESS ON NEURODEGENERATION

Oxidative stress is caused by a reduction in the antioxidant system's response and an increase in ROS production, which includes non-radical species like hydrogen peroxide, and free radicals like superoxide anion (O^{2-}) and hydroxyl radical (OH) (Ansari et al., 2025). A frequent feature of many different types of brain illnesses, from neurological to vascular, oxidative stress occurs when the amount of intracellular ROS surpasses the defense mechanisms (Houldsworth, 2024). The body's ability to counteract their harmful effects through antioxidants. This imbalance can damage cellular macromolecules, contributing to a variety of diseases, particularly neurodegenerative disorders. These diseases often involve the selective loss of certain neurons and are associated with abnormal accumulations of cytoskeletal proteins forming inclusions within nerve and glial cells (Juan et al., 2021). Oxidative stress in neurodegenerative disorders has been linked to neuronal malfunction and cell death. A self-sustaining process that intensifies oxidative damage and speeds up the progress of disease result from elevated ROS levels. In addition to interfering with vital cellular functions including differentiation, apoptosis, and inflammation, excessive ROS also damages DNA, which leads to genomic instability (Bej et al., 2024).

Both mitochondrial DNA mutations and oxidative stress play a key role in the aging process, which is the most significant risk factor for neurodegenerative conditions. In fact, mitochondrial dysfunction is believed to occur early in disease development and may directly contribute to the progression of these disorders (Kowalska et al., 2020). The brain is especially susceptible to oxidative damage due to its high oxygen consumption and large amounts of lipids that are prone to peroxidation. Thus, oxidative stress is considered a central factor in the shared mechanisms underlying various neurodegenerative diseases (Hajam et al., 2022).

MAJOR PATHWAYS OF OXIDATIVE STRESS INVOLVED IN NEURODEGENERATION

Mitochondrial Dysfunction Pathway

Mitochondria are a major source of energy in the cells and are the main producers of ROS during oxidative phosphorylation. Mitochondrial dysfunction leads to pathological alterations. It induces an imbalance between oxidant and antioxidant (Xu et al., 2025). Defects in the mitochondrial electron transport chain led to leakage of electrons and (Fig. 1) formation of superoxide radicals. This damages mitochondrial DNA, impairs ATP synthesis, and triggers apoptosis (Tabbasum et al., 2020).

NADPH Oxidase (NOX) Pathway

Mitochondria and NADPH oxidase are primary sources for the exhibition of ROS. The NOX family plays a significant role in the regulation of oxidative stress signaling, gene modifications, and the preparation of various physiological conditions. The elevation of NOX activity and superoxide in astrocytes plays a vital role in the progression of Alzheimer's and Parkinson's disease (Fiadeiro et al., 2024).

Metal-Catalyzed Oxidative Reactions

Excessive accumulation of metals such as iron and copper can catalyze Fenton reactions, producing highly reactive hydroxyl radicals. These radicals damage neuronal membranes and DNA. Increased metal ion buildup encourages

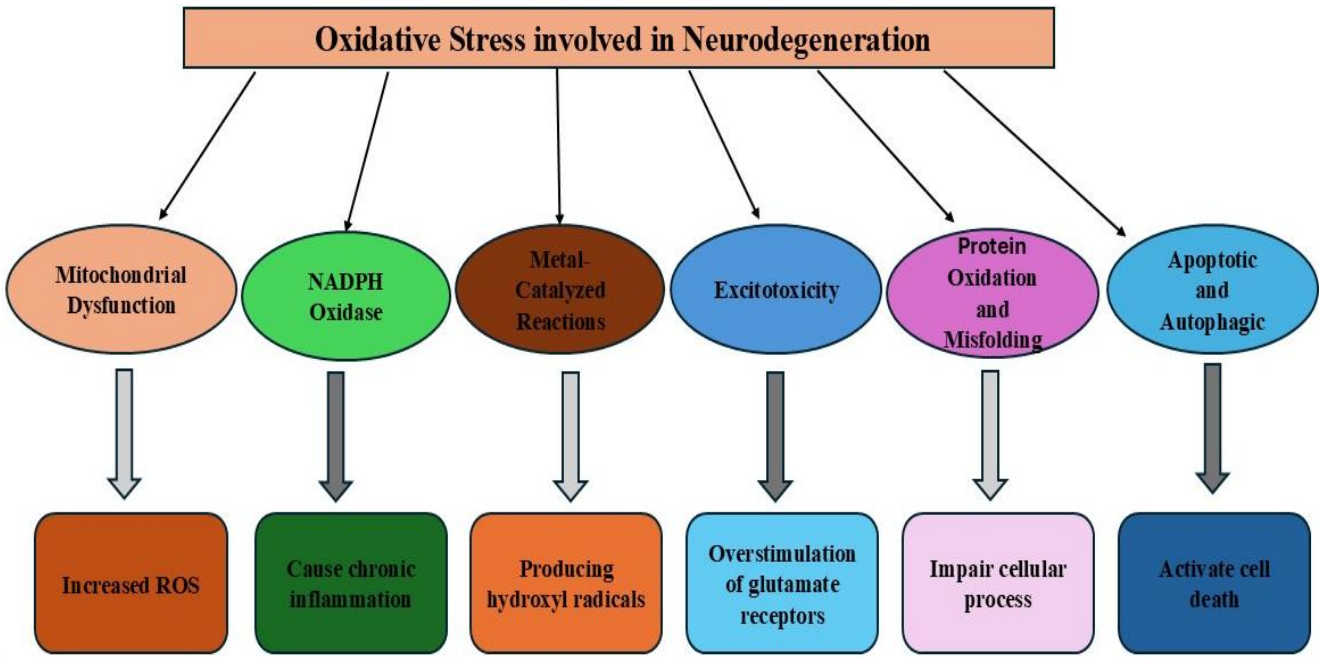

Fig. 1. Oxidative stress pathways involved in neurodegeneration

the conformational transformation of Aβ peptides into aggregates, which impairs brain function and sets off AD (Tan et al., 2025).

Impaired Antioxidant Defense Pathway

Oxidative stress in the central nervous system damages the brain by increasing the production of reactive nitrogen species such as peroxynitrite and nitric oxide, leading to detrimental effects of brain (Perluigi et al., 2024). Under normal conditions, antioxidants like glutathione (GSH), superoxide dismutase (SOD), and catalase neutralize ROS. In neurodegenerative states, depletion of these antioxidants increases oxidative damage (Olufunmilayo et al., 2023).

Excitotoxicity Pathway

Overstimulation of glutamate receptors (especially NMDA receptors) leads to excessive calcium influx in neurons. This activates nitric oxide synthase (NOS) and brings forth reactive nitrogen species (RNS) such as peroxynitrite, resulting in oxidative neuronal injury (Ma et al., 2023).

Protein Oxidation and Misfolding Pathway

ROS can modify amino acids and promote misfolding of neuronal proteins such as α-synuclein, tau, and amyloid-β. These aggregated proteins impair proteasomal degradation and autophagy, leading to neuronal death (Abramov et al., 2020).

Apoptotic and Autophagic Pathways

Oxidative stress activates cell death signaling cascades involving p53, JNK, and caspases. Mitochondrial damage leads to the release of cytochrome C and activation of apoptosis. In parallel, excessive ROS disrupts normal autophagy, leading to the accumulation of damaged organelles (Gupta et al., 2021).

EFFECT OF OXIDATIVE STRESS ON ALZHEIMER'S DISEASE

There is a strong indication that the tissue of AD patients' brains is susceptible to OS throughout the progression of the disease. Since OS results from an imbalance between the body's antioxidant defenses and the production of ROS, both factors are considered to have a key role in cognitive decline and neurodegeneration. The indication of OS in AD is demonstrated through elevated levels of oxidized proteins, lipid peroxidation products, advanced glycation end products and formation of toxic species, such as alcohols, aldehydes, free carbonyls, cholesterol and ketone, and oxidative damage to nuclear and mitochondrial DNA (Perluigi et al., 2024).

Protein Oxidation

In the context of Alzheimer's disease (AD), excessive protein carbonylation plays a critical pathogenic role. Oxidatively modified proteins tend to lose their structural integrity and functional activity, making them prone to misfolding and aggregation. These dysfunctional proteins accumulate as insoluble deposits, contributing to hallmark AD features such as amyloid plaques and neurofibrillary tangles. Moreover, impaired proteasomal degradation in AD amplifies this accumulation, creating a vicious cycle of oxidative stress and protein aggregation that accelerates neuronal dysfunction and cognitive decline (Sultana and Butterfield, 2024).

Lipid Oxidation in Alzheimer's Disease

Amyloid beta (Aβ) in Alzheimer's disease causes oxidative damage to brain cell membranes. This damage leads to lipid peroxidation, which produces toxic molecules like HNE (4-hydroxy-2,3-nonenal) (Anwar, 2022).

EFFECT OF OXIDATIVE STRESS IN PARKINSON'S DISEASE

Oxidative stress has great importance in the degeneration of dopaminergic neurons in Parkinson's disease (PD). Cellular components in the PD substantia nigra developed for oxidative damage. There are many processes for the generation of ROS which recognize metabolism of dopamine, mitochondrial dysfunction, iron, neuroinflammatory cells, calcium and aging. OS is involved in the degradation of dopaminergic neurons in PD (Chakrabarti and Bisaglia, 2023). Cell death may result from biological events that interfere with the normal maintenance of neuron redox potential. PD has been linked to both oxidative and nitrative damage. PD reduces dopamine releasing neuron in the substantia nigra, which is a reactive chemical that, by auto-oxidation, produces reactive oxygen species in this area of the brain, resulting in OS (Houldsworth, 2024).

PD is largely composed of oxidative stress and mitochondrial dysfunction. Because antioxidant genes like SOD2, catalase, and glutathione peroxidase are less active and expressed as we age, we are less able to sustain antioxidant mechanisms against OS (Anik et al., 2022). Dopamine is an unstable chemical that produces quinones and reactive species by auto-oxidation. Dopamine quinones alter the activity of the superoxide dismutase enzyme, which has consequences for PD. PD results from the loss of dopamine-expressing brain cells within the substantia nigra (Chang and Chen, 2020).

EFFECT OF OXIDATIVE STRESS IN HUNTINGTON'S DISEASE (HD)

Dementia, gradual cognitive decline, and motor dysfunction are the hallmarks of Huntington's disease (HD), an NDD. The aberrant expansion of CAG triplets, which encode the amino acid glutamine and are found in the initial exon of the huntingtin gene (HTT), is the etiology of HD. While mutant HTT enzyme toxicity (mHTT) is the primary cause of HD, other variables and processes related to neuronal destruction may also play a role. Incorrect protein folding, aberrant degradation of proteins, accumulation of proteins, excitotoxicity, and OS are a few of these variables (Tang et al., 2020).

OS can be utilized as a biomarker of the course of the disease, prognosis, and responsiveness to treatment, as it has a major impact on the progression of HD. The imbalance of oxidative species in HD happens preceding the start of symptoms, indicating that ROS are important aspects of

neurodegeneration (Kunwar and Singh, 2025). The existence of mHTT deposits brought on by elevated ROS levels may be the source of oxidative injury in these patients. Oxidative damage-induced DNA repair may cause the mutant HTT gene's CAG repeats to expand and become unstable, which would encourage aggregation and cause neuronal death (Deshmukh et al., 2021).

Numerous biomolecules have been proposed as possible OS biomarkers. First, OS promotes damage to lipids (MDA, HNE, as well as thiobarbituric acid reactive compounds), proteins (3-NT), and DNA (8OHdG). Additionally, concentrations of antioxidant enzymes are rising and oxidant concentration is decreasing. The mitochondrial failure leads to overproduction of ROS, oxidative damage, and neuronal death, which is thought to be a major problem in the pathophysiology of HD. The most prevalent excitatory neurotransmitter in the central nervous system, glutamate, is also made more excitotoxic by OS (Sienes Bailo et al., 2022).

EFFECT OF OXIDATIVE STRESS IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis is characterized by the gradual loss of both lower and higher motor neurons in the brain stem, cerebral cortex, and spinal cord. Because of the aberrant energy metabolism it induces, OS brought on by the generation and buildup of ROS is an underlying cause of ALS (Hemerkova and Valis, 2021). It is associated with ageing, environmental conditions, or glutamate-mediated excitotoxicity, which leads to an overabundance of free radicals. There are a few known mechanisms that contribute to OS and motor neuron injury. 10% of disease cases are caused by a mutation in the SOD1 gene, while the remaining 90% are random. The most significant neural antioxidant enzyme, SOD, is encoded by this gene. In a dismutation reaction, SOD triggers the scavenging of superoxide radicals, increasing ROS and oxidative damage. In the blood, urine, CSF, as well as tissue of ALS patients, several OS biomarkers have been found in proteins (carbonylated proteins, 3-NT), lipid peroxidation products, and DNA and RNA oxidation products (8OHdG) (Cunha-Oliveira et al., 2020).

These results show that OS, as well as ROS, are important factors in brain injury. Mitochondrial dysfunction is also brought on by a mutation in the SOD1 gene. This is crucial to illnesses linked to aberrant calcium retention capacity, ROS generation, and impaired oxidative phosphorylation, all of which may encourage OS (Smith et al., 2019).

MECHANISMS INVOLVED IN THE PROGRESSION OF NEUROINFLAMMATION

Microglia Activation

Microglia can initiate signaling pathways that result in the generation of ROS and RNS. Microglia become persistently engaged in neuroinflammatory situations like neurodegenerative disorders, releasing both anti-inflammatory cytokines like interleukin-10 during recovery and pro-inflammatory cytokines such as tumor necrosis-α and IL-6. They use chemoattractants to attract more microglia and migrate to damaged locations (Kotwica-Mojzych et al., 2021).

Astrocytes Activation

The most prevalent type of glial cell, that is, astrocytes, supports the structure and metabolism of neurons. In addition to developing reactive and altering mechanisms like calcium signaling and neurotransmitter absorption, activated astrocytes can release inflammatory and reactive oxygen species of oxygen. Their intricate role in brain function is highlighted by their interactions with microglia through a variety of released mediators (Schober et al., 2022).

Mitochondrial Dysfunction

Additionally, misfolded alpha-synuclein that penetrates the mitochondria and inhibits Complex 1 is extremely sensitive to mitochondria. This results in an energy crisis and an increase in oxidative product levels. Such ROS may be involved in the start of inflammation (Giorgi et al., 2018).

Blood-Brain Barrier Dysfunction

By passing across the blood-brain barrier and communicating through endothelial cells or peripheral organs, pro-inflammatory cytokines and immunological mediators might encourage a pro-inflammatory milieu in the central nervous system. Studies on animals have demonstrated that peripheral inflammation increases BBB permeability and activates glial cells, which enhance neuroinflammatory pathways (Slevin et al., 2020).

Protein Misfolding

Numerous neurodegenerative disorders are primarily caused by misfolded protein aggregation as well as deposition, which is due to the Tau protein and amlyoid-β in AD, and alpha-synuclein in PD. These misfolded proteins can be exported by neurons that are susceptible to their toxicity, which can activate microglia and disseminate toxicity to nearby neurons, like prion-like processes. This triggered toxicity and inflammation, which gradually impact different parts of the brain. Inflammation will change the activity of astrocytes, which are adjacent to the blood-brain-barrier and release glutamate, which is a stimulator of inflammation (Ward et al., 2022).

Peripheral Inflammatory Markers

By passing across the blood-brain barrier and communicating through endothelial cells and circumventricular organs, systemic proinflammatory cytokines and immunological and inflammatory mediators might encourage a proinflammatory milieu in the central nervous system. Research on animals has demonstrated that peripheral inflammation increases BBB permeability and activates glial cells to enhance neuroinflammatory pathways (Chang et al., 2019).

INFLAMMATION IN AD

The majority of age-related illnesses have an inflammatory etiology, such as AD. Inflammation has a distinct mechanism that can manifest in two ways in neurodegenerative disorders. Cytokines like tumor necrosis factor-α, Interleukin 6, and interleukin 1β influence and penetrate the blood-brain-barrier (BBB) in peripheral inflammation, causing the release of inflammatory mediators and becoming more cell-permeable, allowing leukocytes to reach the brain. These phenomena set off a series of events in the brain that result in astrocyte and microglial reactions that include additional generation of ROS, RNS, and proinflammatory mediators, among other things (Xie et al., 2022).

INFLAMMATION IN PD

The development of Parkinson's disease has been linked to inflammatory processes, according to growing biological data in recent years. It has been suggested that inflammation originates in the central nervous system (CNS) through the activation of microglia, which may be a key factor in the progression of inflammatory cascades linked to dopaminergic neuron death (Qin et al., 2023). Specifically, pro-inflammatory cytokines, including interleukin (IL) 6 as well as tumor necrosis factor-α (TNF-α), are produced when toxic microglia are activated, which eventually damages dopamine neurons. Moreover, mitochondrial stress can cause inflammation by releasing molecular patterns linked to damage. implying that the peripheral tissue may be involved in the inflammatory cascades' genesis (Bottigliengo et al., 2022).

INFLAMMATION IN HD

By triggering the release of inflammatory cytokines, including interleukin (IL)-6, mHTT appears to affect astrocyte and microglia activity in the central nervous system. The NF-kB signaling pathway can be favorably regulated by the mHTT, which causes the release of chemokines and cytokines associated with inflammation, like IL-6 as well as IL-8, respectively (Saba et al., 2022). As the disease progresses, HD patients' cytokine profiles show rises in TNF-α, IL-4, and IL-10. Reactive astrocytes and microglia have accumulated in the brains of HD patients, according to Positron Emission Tomography studies, and microglial activation is correlated with HD pathology. Inflammatory pathways can be triggered by neuronal death alone, creating a vicious cycle of inflammation and neurodegeneration that may worsen neuronal damage in HD (Valadao et al., 2020).

INFLAMMATION IN ALS

Prior research indicated that patients with ALS had elevated expression of inflammatory mediators. Many inflammatory cytokines and chemokines, such as granulocyte colony-stimulating factors, are elevated in the blood and CSF of ALS patients when compared to controls. Furthermore, correlations between variables of disease progression and cerebrospinal fluid concentrations of particular proinflammatory molecules, as well as interferon-γ, have been reported. Systemic inflammation may be a helpful biomarker linked to the disease's progression (Leone et al., 2022). There is a lot of variation in the cytokines examined between studies that aids in forecasting the course of the illness. In this work, a wide range of inflammatory mediators are diagnosed in degenerative neurological conditions and a group of recently diagnosed ALS patients (Olesen et al., 2020).

NEUROINFLAMMATION IN AD

Microglia, as well as astrocytes, are known to be the main mediators of inflammation in the central nervous system. Originating from basic hematopoietic progenitors, microglia are the brain's resident innate immune cells. Microglia move to injury locations, release a variety of inflammatory chemicals, and phagocytose aggregated proteins and debris by changing states in AD. It is becoming more and more evident that microglia contribute to neuron destruction, synaptic impairment, and the accumulation of neurotoxic substances in the initial phases of AD (Leng and Edison, 2021). As a component of the blood-brain barrier, astrocytes generate neurotransmitters and promote synaptogenesis as well as synaptic neurotransmission. Astrocytes may directly contribute to neuroinflammatory mechanisms associated with AD, according to research conducted in animal models. Additionally, astrocytes control the removal of tau and Aβ (Price et al., 2021)

NEUROINFLAMMATION IN HD

The underlying cause of HD is linked to neuroinflammatory processes, just like other neurodegenerative diseases. Studies using Positron Emission Tomography (PET) have revealed that HD patients have upregulated translocator protein (TSPO), which is expressed by activated microglia at much greater levels than in normal individuals. Additionally, elevated concentrations of the proinflammatory cytokines such as interleukin-6 (IL-6), IL-8, as well as tumor necrosis factor-α (TNF-α), as well as mRNA concentrations of IL-10, CCL2, and MMP-9 were found in the striatum of HD patients' CNS tissues after death. Cortical areas also exhibit increased expression of IL-8, IL-6, and IL-1β (Rocha et al., 2021). Astrocytes and microglia are the main producers of cytokines as well as inflammatory mediators in HD, which leads to neuroinflammation. Compared to premanifest carriers, manifest HD patients had significantly more activated microglia, suggesting that inflammation may have a role in the development of the disease and neurodegeneration. Models with HD have also shown signs of peripheral and cerebral inflammation (Saba et al., 2022).

NEUROINFLAMMATION IN PD

Parkinson's disease (PD) neurons were found to have active microglial infiltrations in the early 1980s, underscoring the part neuroinflammation plays in the pathophysiology of PD. Studies reveal elevated proinflammatory cytokines such as TNF-α, IL-1β, as well as IL-6, which are released by activated microglia linked to injured neurons (Ishijima and Nakajima, 2021). Studies using neuroimaging have verified persistent neuroinflammation associated with microglial activation. By dysregulating the TLR2 and TLR4 signaling pathways and increasing the production of TNF-α and IL-1β, the accumulation of misfolded α-synuclein aggravates

Parkinson's disease. When aggregated, α-synuclein interacts with microglial receptors, and neuroinflammatory pathways are activated. Research shows that while regulatory T cells offer protection, T helper cell subsets that are impacted by α-synuclein immune responses contribute to dopaminergic neurodegeneration (Liu et al., 2022).

NEUROINFLAMMATION IN ALS

Motor neuron degeneration is a hallmark of ALS, which is a deadly neurodegenerative disease of the CNS. MN degeneration in ALS is caused by several mechanisms, including oxidative damage, intracellular protein aggregate formation, axonal transport system damage, mitochondrial dysfunction, impaired RNA metabolism and DNA damage recovery, along with excess activation of glutamate receptors resulting in neurotoxicity (Fig. 2). Furthermore, there is mounting evidence that neuroinflammation plays a role in the damage of motor neurons (Mead et al., 2023). Microglia, astroglia, as well as infiltrating immune cells are the mediators of inflammation in the CNS (Adetuyi et al., 2021). The idea of non-cell autonomous elements triggering ALS disease was first proposed by the inclusion of non-neuronal cells in the pathophysiology of the disease. It was remarkably found that anti-inflammatory T regulatory (Treg) cells were reduced in the blood levels of ALS patients, and in better correspondence with dysfunction of the immune system marked by the activation of microglial cells in the spinal cord of patients with increased biomarkers of neuro-inflammation in the CSF of patients, along with pro-inflammatory gene of blood monocytes (Gille et al., 2019).

CONCLUSION

In the majority of NDs, oxidative stress and inflammation are the basis of the pathological cascade. The vicious cycle they form as a result of their close interaction continues to destroy neurons and speed up the disease progression. To stop this cycle, a jointly acting treatment option including redox imbalance and inflammatory signaling is essential. A better understanding of the underlying cellular and molecular processes of inflammation and oxidative stress in neurodegeneration will be necessary to effectively target inflammatory signals to treat neurodegenerative diseases. There are more opportunities to change the disease progression with the help of natural compounds, lifestyle interventions, and new targeted drugs. In general, the study of oxidative stress and neuroinflammation is a strong and promising avenue in the development of effective therapies that can prevent the neurodegeneration process.

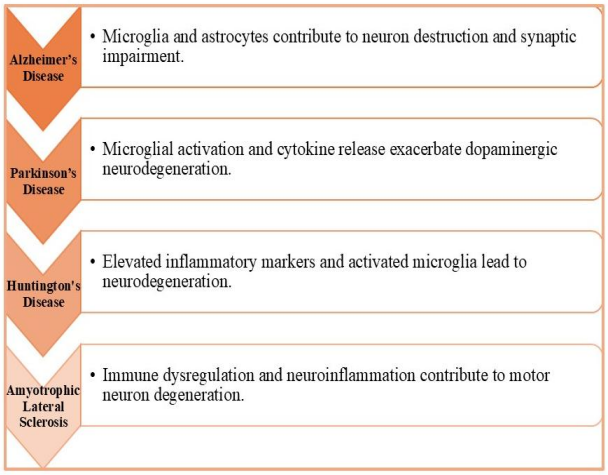

Fig. 2: Neuroinflammation in neurodegenerative diseases

REFERENCES

Abramov AY, PE Potapova, VV Dremin et al., 2020. Interaction of oxidative stress and misfolded proteins in the mechanism of neurodegeneration. Life 10:101.

Adetuyi BO, PEY Toloyai, ET Ojugbeli et al., 2021. Neurorestorative roles of microgliosis and astrogliosis in neuroinflammation and neurodegeneration. Scicom Journal of Medical and Applied Medical Sciences 1:1-5.

Anik MI, N Mahmud, MI Masud et al., 2022. Role of reactive oxygen species in aging and age-related diseases: a review. ACS Applied Bio Materials 5:4028-54.

Ansari WA, K Srivastava, M Nasibullah et al., 2025. Reactive oxygen species (ROS): sources, generation, disease pathophysiology, and antioxidants. Discover Chemistry 2:191.

Anwar MM, 2022. Oxidative stress: A direct bridge to central nervous system homeostatic dysfunction and Alzheimer's disease. Cell Biochemistry and Function 40:17-27.

Bebo B, I Cintina, N LaRocca et al., 2022. The economic burden of multiple sclerosis in the United States: estimate of direct and indirect costs. Neurology 98:1810-17.

Begley E, J Thomas and C Senior, 2025. Behavioural analysis of factors influencing prescribing for neurodegenerative diseases: A rapid review. PLoS One 20:0322324.

Behl T, R Makkar, A Sehgal et al., 2021. Current trends in neurodegeneration: Cross talks between oxidative stress, cell death, and inflammation. International Journal of Molecular Sciences 22:7432.

Bej E, P Cesare, AR Volpe et al., 2024. Oxidative stress and neurodegeneration: insights and therapeutic strategies for Parkinson's disease. Neurology International 16:502-17.

Bottigliengo D, L Foco, P Seibler et al., 2022. A Mendelian randomization study investigating the causal role of inflammation on Parkinson's disease. Brain 145:3444-53.

Chakrabarti S and M Bisaglia, 2023. Oxidative stress and neuroinflammation in Parkinson's disease: the role of dopamine oxidation products. Antioxidants 12:955.

Chang EH, SS Chavan and VA Pavlov, 2019. Cholinergic control of inflammation, metabolic dysfunction, and cognitive impairment in obesity-associated disorders: mechanisms and novel therapeutic opportunities. Frontiers in Neuroscience 13:263.

Chang KH and CM Chen, 2020. The role of oxidative stress in Parkinson's disease. Antioxidants 9:597.

Cunha-Oliveira T, L Montezinho, C Mendes et al., 2020. Oxidative stress in amyotrophic lateral sclerosis: pathophysiology and opportunities for pharmacological intervention. Oxidative Medicine and Cellular Longevity 20:5021694.

Das J, U Bhui, S Chowdhary et al., 2025. Biomarkers Unveiling Neurodegeneration: Keys to Progression and Therapeutic Insights. Indian Journal of Pharmaceutical Education and Research 59:1-15.

Deshmukh AL, A Porro, M Mohiuddin et al., 2021. FAN1, a DNA repair nuclease, as a modifier of repeat expansion disorders. Journal of Huntington's Disease 10:95-122.

Fiadeiro MB, JC Diogo, AA Silva et al., 2024. NADPH oxidases in neurodegenerative disorders: mechanisms and therapeutic opportunities. Antioxidants and redox signaling, 41:522-41.

Gille B, M De Schaepdryver, L Dedeene et al., 2019. Inflammatory markers in cerebrospinal fluid: independent prognostic biomarkers in amyotrophic lateral sclerosis?. Journal of Neurology, Neurosurgery and Psychiatry 90:1338-46.

Giorgi C, S Marchi, IC Simoes et al., 2018. Mitochondria and reactive oxygen species in aging and age-related diseases. International review of cell and molecular biology 340:209344.

Gupta R, RK Ambasta and P Kumar, 2021. Autophagy and apoptosis cascade: which is more prominent in neuronal death?. Cellular and Molecular Life Sciences 78:8001-47.

Hajam YA, R Rani, SY Ganie et al., 2022. Oxidative stress in human pathology and aging: molecular mechanisms and perspectives. Cells 11:552.

Hemerkova P and M Valis, 2021. Role of oxidative stress in the pathogenesis of amyotrophic lateral sclerosis: Antioxidant metalloenzymes and therapeutic strategies. Biomolecules 11:437.

Houldsworth A, 2024. Role of oxidative stress in neurodegenerative disorders: a review of reactive oxygen species and prevention by antioxidants. Brain Communications 6:356.

Jiang Q, J Liu, S Huang et al., 2025. Antiageing strategy for neurodegenerative diseases: from mechanisms to clinical advances. Signal Transduction and Targeted Therapy 10:76.

Juan CA, JM Pérez de la Lastra, FJ Plou et al., 2021. The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. International Journal of Molecular Sciences 22:4642.

Kotwica-Mojzych K, B Jodłowska-Jędrych and M Mojzych, 2021. CD200: CD200R interactions and their importance in immunoregulation. International Journal of Molecular Sciences 22:1602.

Kowalska M, T Piekut, M Prendecki et al., 2020. Mitochondrial and nuclear DNA oxidative damage in physiological and pathological aging. DNA and Cell Biology 39:1410-1420.

Kunwar OK and S Singh, 2025. Neuroinflammation and neurodegeneration in Huntington's disease: Genetic hallmarks, role of metals and organophosphates. Neurogenetics 26:21.

Leng F and P Edison, 2021. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here?. Nature Reviews Neurology 17:157-72.

Leone MA, J Mandrioli, S Russo et al., 2022. Neutrophils-to-lymphocyte ratio is associated with progression and overall survival in amyotrophic lateral sclerosis. Biomedicines 10:354.

Liu TW, CM Chen and KH Chang, 2022. Biomarker of neuroinflammation in Parkinson's disease. International Journal of Molecular Sciences 23:4148.

Ma T, Q Cheng, C Chen et al., 2020. Excessive activation of NMDA receptors in the pathogenesis of multiple peripheral organs via mitochondrial dysfunction, oxidative stress, and inflammation. SN Comprehensive Clinical Medicine 2:551-69.

Mead RJ, N Shan, HJ Reiser et al., 2023. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nature Reviews Drug Discovery 22:185-212.

Milanifard M and M Ramezani, 2025. Clinical and neurological problems and clinical tests in Alzheimer's patients specializing in Alzheimer's disease. Eurasian Journal of Chemical, Medicinal and Petroleum Research 4:152-63.

Olesen MN, A Wuolikainen, AC Nilsson et al., 2020. Inflammatory profiles relate to survival in subtypes of amyotrophic lateral sclerosis. Neurology: Neuroimmunology and Neuroinflammation 7:697.

Olufunmilayo EO, MB Gerke-Duncan and RD Holsinger, 2023. Oxidative stress and antioxidants in neurodegenerative disorders. Antioxidants 12:517.

Perluigi M, F Di Domenico and DA Butterfield, 2024. Oxidative damage in neurodegeneration: roles in the pathogenesis and progression of Alzheimer disease. Physiological Reviews 104:103-197.

Price BR, LA Johnson and CM Norris, 2021. Reactive astrocytes: The nexus of pathological and clinical hallmarks of Alzheimer's disease. Ageing Research Reviews 68:101335.

Qin J, Z Ma, X Chen et al., 2023. Microglia activation in central nervous system disorders: A review of recent mechanistic investigations and development efforts. Frontiers in Neurology 14:1103416.

Rocha NP, O Charron, LB Latham et al., 2021. Microglia activation in basal ganglia is a late event in Huntington disease pathophysiology. Neurology: Neuroimmunology and Neuroinflammation 8:984.

Saba J, FL Couselo, J Bruno et al., 2022. Neuroinflammation in Huntington's disease: a starring role for astrocyte and microglia. Current Neuropharmacology 20:1116-1143.

Sajid MR, I Abbas, NU Khan et al., 2023. Prominent medicinal plants for the treatment of neurodegenerative disorders. In: Complementary and Alternative Medicine: One Health Perspective: FahumSci, Lahore, Pakistan, pp: 124-130. ISBN: 978-627-7745-01-1.

Schober AL, LE Wicki-Stordeur, KK Murai et al., 2022. Foundations and implications of astrocyte heterogeneity during brain development and disease. Trends in Neurosciences 45:692-703.

Sienes Bailo P, E Llorente Martín, P Calmarza et al., 2022. The role of oxidative stress in neurodegenerative diseases and potential antioxidant therapies. Advances in Laboratory Medicine 3:342-50.

Slevin M, F García-Lara, B Capitanescu et al., 2020. Monomeric C-reactive protein aggravates secondary degeneration after intracerebral hemorrhagic stroke and may function as a sensor for systemic inflammation. Journal of Clinical Medicine 9:3053.

Smith EF, PJ Shaw and KJ De Vos 2019. The role of mitochondria in amyotrophic lateral sclerosis. Neuroscience Letters 710:132933.

Sultana OF, M Bandaru, MA Islam et al., 2024. Unraveling the complexity of human brain: Structure, function in healthy and disease states. Ageing Research Reviews 100:102414.

Sultana R and DA Butterfield, 2024. Protein oxidation in aging and Alzheimer's disease brain. Antioxidants 13:574.

Tabassum N, IS Kheya, S Asaduzzaman et al., 2020. A review on the possible leakage of electrons through the electron transport chain within mitochondria. Life Sciences 6:105-13.

Tan KT, Cheong KW, Wong LC et al., 2025. Metal in Medicine: Unlocking New Avenues for Neurodegenerative Disease Treatment. Frontiers in Chemical Biology, 4:1696058.

Tang Q, H Liu, XJ Shi et al., 2020. Blood Oxidative Stress Marker Aberrations in Patients with Huntington's Disease: A Meta-Analysis Study. Oxidative Medicine and Cellular Longevity 20:9187195.

Twiss E, C McPherson and DF Weaver, 2025. Global Diseases Deserve Global Solutions: Alzheimer's Disease. Neurology International 17:92.

Valadao PAC, KBS Santos, THF e Vieira et al., 2020. Inflammation in Huntington's disease: A few new twists on an old tale. Journal of Neuroimmunology 348:577380.

Ward RJ, DT Dexter and RR Crichton, 2022. Iron, neuroinflammation and neurodegeneration. International Journal of Molecular Sciences 23:7267.

Wimo A, K Seeher, R Cataldi et al., 2023. The worldwide costs of dementia in 2019. Alzheimer's and Dementia 19:2865-73.

Xie J, L Van Hoecke and RE Vandenbroucke, 2022. The impact of systemic inflammation on Alzheimer's disease pathology. Frontiers in Immunology 12:796867.

Xu X, Y Pang and X Fan, 2025. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. Signal Transduction and Targeted Therapy 10:190.

Yang W, JL Hamilton, C Kopil et al., 2020. Current and projected future economic burden of Parkinson's disease in the US. Nature Partner Journals Parkinson's Disease 6:15.