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A REVIEW ON OXIDATIVE STRESS, NEUROINFLAMMATION, AND SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia, contributing to nearly two-thirds of global cases and posing a major healthcare challenge. With over 55 million people currently affected, prevalence is expected to reach 139 million by 2050, accompanied by escalating social and economic burdens. Clinically, AD progresses gradually from subtle memory deficits to profound cognitive impairment, behavioral disturbances, complete dependency, and eventual death. Its neuropathological hallmarks include amyloid-β (Aβ) accumulation, tau hyperphosphorylation leading to neurofibrillary tangles, and extensive synaptic and neuronal loss. These features interact with secondary processes such as oxidative stress, chronic neuroinflammation, and mitochondrial dysfunction, which together accelerate neurodegeneration. Oxidative stress, driven by excessive reactive oxygen species (ROS) and mitochondrial failure, damages proteins, lipids, and DNA. Persistent activation of microglia and astrocytes promotes the release of pro-inflammatory cytokines, impairing amyloid clearance and amplifying neuronal injury. Synaptic dysfunction—the strongest correlate of cognitive decline—arises from Aβ- and tau-mediated toxicity, neurotransmitter imbalance, and excitotoxic signaling. Current treatments, including cholinesterase inhibitors and NMDA receptor antagonists, provide only symptomatic relief, while disease-modifying therapies against amyloid and tau show limited success. Promising approaches under investigation include antioxidant therapies, anti-inflammatory agents, synaptic repair strategies, and multi-target interventions addressing AD's multifactorial pathology. Future progress will rely on sensitive biomarkers for early detection, precision medicine tailored to genetic and molecular risk factors, and improved translational models that better reflect human disease. A deeper mechanistic understanding of how oxidative stress, inflammation, and synaptic failure converge is vital for developing effective and transformative therapies for AD.

KEYWORDS: Alzheimer's disease, Amyloid-β, Cognitive decline, Neuronal death, Oxidative stress.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia, accounting for nearly two-thirds of all cases worldwide. It is a progressive neurodegenerative disorder that affects memory, cognition, and behavior, ultimately leading to complete loss of independence. With the aging of the global population, AD has become one of the most pressing public health challenges of the modern era. Current estimates indicate that more than 55 million people worldwide live with dementia, with AD representing the majority of these cases. Projections suggest this number will rise sharply to 78 million by 2030 and 139 million by 2050, driven largely by increases in life expectancy and the growing proportion of elderly individuals in both developed and developing nations. The prevalence of AD increases steeply with age, doubling approximately every five years after the age of 65, with the greatest burden occurring in people above 75 years. Notably, women are disproportionately affected, which is attributed not only to their longer lifespan but also to possible sex-specific biological and hormonal factors.[1]

Beyond its health impact, the global burden of AD extends to profound social and economic consequences. The cost of dementia care exceeded US $1.3 trillion in 2019, and this figure is expected to almost double by 2030. These costs include direct medical expenses, social care, and the informal care provided by family members, which often goes uncompensated yet contributes significantly to the overall burden. The strain is especially severe in low- and middle-income countries where awareness, diagnostic capacity, and healthcare resources remain limited. In addition to economic implications, AD places heavy emotional and psychological demands on patients, caregivers, and healthcare systems, further emphasizing the urgent need for effective interventions.[2]

The clinical course of AD is gradual and progressive, typically beginning with subtle cognitive changes. Early manifestations are characterized by mild forgetfulness, difficulty recalling recent events, or challenges in performing complex tasks. As the disease advances to the moderate stage, symptoms become more pronounced, with worsening memory loss, disorientation, impaired judgment, language difficulties, and behavioral disturbances such as irritability, agitation, or depression. In severe stages, patients lose the ability to communicate, recognize loved ones, or carry out basic activities of daily living.[3] Motor dysfunction and complete dependency on caregivers eventually follow, with death typically occurring 8–12 years after diagnosis, though disease progression can vary considerably. Neuropathologically, AD is defined by extracellular amyloid-β (Aβ) plaque deposition, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, and widespread neuronal death, particularly within the hippocampus and cerebral cortex, regions critical for memory and cognition.[4]

Despite extensive research, the exact etiology of AD remains incompletely understood. The classical amyloid cascade and tau hypotheses explain much of the observed pathology, but growing evidence highlights the importance of additional mechanisms. Oxidative stress, resulting from mitochondrial dysfunction and excess production of reactive oxygen species, has been strongly implicated in neuronal damage.[5] Likewise, neuroinflammation, mediated by microglial and astrocytic activation, contributes to a chronic inflammatory state that accelerates disease progression. Synaptic dysfunction, driven by Aβ oligomers and tau pathology, disrupts neurotransmission and underlies the cognitive decline that defines AD. These processes are interlinked, forming a vicious cycle that amplifies neuronal injury and loss.

Currently approved therapies, such as cholinesterase inhibitors and NMDA receptor antagonists, offer only symptomatic relief without halting or reversing disease progression. More recently, disease-modifying approaches

targeting amyloid and tau have been developed, but their clinical efficacy remains under debate. Thus, a comprehensive mechanistic understanding of AD—spanning oxidative stress, neuroinflammation, synaptic failure, and their interactions—is critical for identifying novel therapeutic targets and developing more effective treatments.[6]

Alzheimer's disease represents a growing global health crisis with profound clinical, social, and economic implications. Its insidious clinical progression devastates patients and caregivers alike, while its multifactorial pathogenesis poses significant challenges for therapeutic development. A deeper exploration of the mechanistic underpinnings of AD is therefore essential for advancing early detection, prevention, and intervention strategies that can meaningfully alter the course of this devastating disorder.[7]

2. Pathological Hallmarks of Alzheimer's Disease

Alzheimer's disease (AD) is defined by a set of characteristic neuropathological changes that underlie its clinical manifestations. The most widely recognized hallmarks are amyloid-β (Aβ) aggregation, tau hyperphosphorylation with neurofibrillary tangle (NFT) formation, and synaptic loss accompanied by neuronal death. Together, these processes interact to drive neurodegeneration and progressive cognitive decline.[8]

2. 1. Amyloid-β (Aβ) Aggregation

The amyloid cascade hypothesis posits that abnormal deposition of Aβ peptides initiates AD pathology. Aβ is derived from the amyloid precursor protein (APP), which is cleaved sequentially by β-secretase (BACE1) and γ-secretase. This produces peptides of various lengths, among which Aβ42 is the most aggregation-prone.[9]

In AD, reduced clearance and excessive production of Aβ promote the formation of soluble oligomers, fibrils, and eventually extracellular amyloid plaques. Soluble Aβ oligomers are considered the most toxic species, as they disrupt synaptic transmission, impair long-term potentiation, and promote oxidative stress and mitochondrial dysfunction. Amyloid plaques accumulate particularly in the hippocampus, amygdala, and neocortex, regions critical for memory and cognition. Although amyloid burden alone does not fully explain disease severity, it sets off a cascade of downstream events, including tau pathology, synaptic failure, and chronic neuroinflammation. Advances such as amyloid-PET imaging have enabled visualization of Aβ deposition in vivo, improving early diagnosis and patient stratification in research and clinical practice.[10]

2. 2. Tau Hyperphosphorylation and Neurofibrillary Tangles (NFTs)

Another central hallmark of AD involves pathological changes in tau protein, a microtubule-associated protein essential for maintaining cytoskeletal stability and axonal transport. Under normal conditions, tau is regulated by phosphorylation; however, in AD, it becomes hyperphosphorylated, loses its affinity for microtubules, and aggregates into paired helical filaments (PHFs), which subsequently assemble into intraneuronal NFTs.[11]

These tangles disrupt neuronal architecture and axonal transport, impairing communication between neurons. Importantly, the distribution of NFTs correlates more strongly with cognitive decline than amyloid burden. Braak staging describes the stereotypical progression of tau pathology, beginning in the transentorhinal cortex, spreading to the hippocampus, and ultimately invading widespread cortical regions. Recent evidence suggests that tau pathology may spread in a "prion-like" manner, where misfolded tau seeds propagate to neighboring neurons, amplifying

neurodegeneration. Beyond structural disruption, tau abnormalities contribute to excitotoxicity, mitochondrial impairment, and synaptic failure, further compounding cognitive deficits.[12]

2. 3. Synaptic Loss and Neuronal Death

Synaptic degeneration and neuronal death represent the final common pathway of AD pathology and are the strongest correlates of cognitive decline. Both Aβ oligomers and hyperphosphorylated tau contribute to synaptic dysfunction by impairing neurotransmitter release, altering receptor function, and disrupting synaptic plasticity mechanisms such as long-term potentiation.[13]

Cellular events such as mitochondrial failure, calcium imbalance, oxidative stress, and excitotoxicity further accelerate synaptic injury and neuronal death. Specific neuronal populations are particularly vulnerable, including cholinergic neurons in the basal forebrain, noradrenergic neurons in the locus coeruleus, and serotonergic neurons in the raphe nuclei. Their loss contributes not only to memory deficits but also to the behavioral and neuropsychiatric symptoms of AD.[14]

Extensive neuronal death occurs in the hippocampus and cortical regions, explaining the profound memory impairment and cognitive dysfunction characteristic of advanced stages of AD.[15]

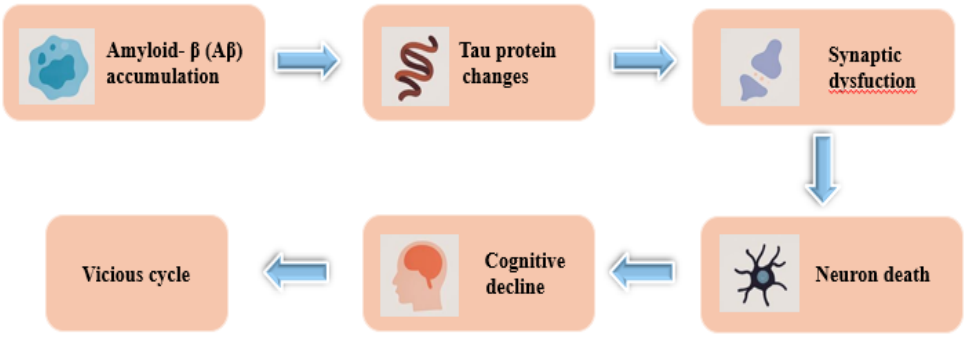

Fig. No. 1: Pathological Cascade of Alzheimer's Disease.

3. Oxidative Stress in Alzheimer's Disease

Oxidative stress is one of the key contributors to the development and progression of Alzheimer's disease (AD). It occurs when harmful molecules called reactive oxygen species (ROS) are produced in excess and the body's natural defense systems cannot neutralize them effectively. The brain is especially sensitive to oxidative stress because it uses a lot of oxygen, contains high levels of fatty acids, and has relatively weaker antioxidant defenses compared to other organs.[16]

3. 1. Sources of Reactive Oxygen Species (ROS) in the Brain

ROS in the brain mainly come from mitochondria, the cell's powerhouses, during energy production. Other enzymes, such as NADPH oxidase and xanthine oxidase, also generate ROS. In AD, abnormal amyloid-β (Aβ) plaques and tau tangles increase ROS production by activating immune cells in the brain. Heavy metals like iron and copper can further speed up free radical formation, worsening the oxidative load.[17]

3. 2. Mitochondrial Dysfunction and Energy Problems

Mitochondria are both a major source and target of oxidative damage. When they are impaired, they release more ROS, which further damages their function, leading to less energy (ATP) for neurons. This energy shortage affects brain signaling and the survival of nerve cells. Aβ can accumulate inside mitochondria and interfere with key enzymes, worsening energy failure and increasing oxidative stress.[18]

3. 3. Damage to Proteins, Lipids, and DNA

ROS attack important cell components. Proteins can lose their normal shape and function, leading to toxic clumps. Lipid peroxidation damages cell membranes, disrupting nerve communication. ROS also attack DNA in both the nucleus and mitochondria, causing mutations and faulty gene expression, which speed up neuron loss in AD.[19]

3. 4. Antioxidant Defense Systems

The body has natural antioxidants to fight ROS, including enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as non-enzymatic molecules like vitamin E, vitamin C, and glutathione. In AD, these defenses are often weakened, so the brain cannot cope with the oxidative damage effectively.[20]

3. 5. Evidence from Research and Clinical Studies

Studies in animals and humans show that oxidative stress is strongly linked with AD. Patients with AD often have higher levels of oxidative damage markers (like lipid peroxidation products and oxidized DNA) and lower levels of antioxidants in blood, brain tissue, and cerebrospinal fluid. Although antioxidant treatments have shown benefits in experimental models, clinical trials in patients have given mixed results, suggesting that oxidative stress is only one part of the complex picture of AD.[21]

4. Neuroinflammation in Alzheimer's Disease

Neuroinflammation is now widely regarded as a hallmark of Alzheimer's disease (AD) pathogenesis. While initially considered a secondary phenomenon triggered by amyloid deposition, accumulating evidence suggests that inflammatory processes play a central and active role in disease progression. Neuroinflammation represents a double-edged sword: early activation of glial cells aids in clearance of amyloid-β (Aβ) and cellular debris, but persistent and uncontrolled activation promotes neuronal damage, synaptic dysfunction, and cognitive decline.[22]

4. 1. Microglial activation and astrocytic responses

Microglia, the innate immune cells of the brain, are the first line of defense against abnormal protein aggregates such as Aβ. In the early stages of AD, microglia attempt to phagocytose and degrade Aβ deposits. However, chronic exposure to oligomeric and fibrillar Aβ drives them into a sustained pro-inflammatory state. Activated microglia release cytokines (e.g., TNF-α, IL-1β), chemokines, and reactive oxygen/nitrogen species (ROS/RNS), creating a neurotoxic environment that damages surrounding neurons.

Astrocytes, which normally support neuronal function by maintaining homeostasis, recycling neurotransmitters, and supplying metabolic substrates, also undergo profound changes during AD. Reactive astrocytes exhibit hypertrophy, increased GFAP expression, and altered signaling patterns. Instead of exerting neuroprotective effects, they secrete inflammatory mediators, contribute to glutamate excitotoxicity, and lose their ability to provide trophic support to neurons. This dual microglial–astrocytic dysfunction establishes a sustained inflammatory state within the brain.[23]

4. 2. Cytokines, chemokines, and inflammatory mediators

The inflammatory milieu in AD brains includes elevated levels of TNF-α, IL-1β, IL-6, MCP-1, and complement cascade proteins. Activation of inflammasomes, particularly NLRP3, amplifies cytokine release and contributes to synaptic pruning and neuronal apoptosis. Chronic production of these mediators disrupts neuronal signaling, impairs plasticity, and further compromises blood–brain barrier (BBB) integrity.[24]

4. 3. Interaction between neuroinflammation and amyloid pathology

Neuroinflammation and Aβ pathology are intricately linked in a self-reinforcing loop. Aβ oligomers activate microglia and astrocytes, leading to cytokine release and oxidative stress. In turn, these inflammatory responses impair Aβ clearance, accelerate its aggregation, and promote plaque formation. Genetic studies underscore this relationship: mutations in immune-related genes such as TREM2, CD33, and CR1 significantly influence AD risk by altering microglial phagocytic function and inflammatory signaling.[25]

4. 5. Chronic inflammation and neuronal degeneration

Although transient immune activation can be protective, sustained neuroinflammation leads to progressive neurodegeneration. Chronic activation of glial cells damages synapses, weakens BBB function, and fosters a toxic environment that accelerates tau hyperphosphorylation and neuronal death. This long-term inflammatory state is now recognized as a key driver of disease progression, making it a major therapeutic target in AD research.[26]

5. Synaptic Dysfunction in Alzheimer’s Disease

Synaptic loss is the most reliable correlate of cognitive decline in Alzheimer’s disease and precedes widespread neuronal death. Both Aβ and tau pathology converge at synapses, causing structural and functional deficits that undermine memory and learning.[27]

5. 1. Synaptic plasticity impairment (LTP and LTD alterations)

Synaptic plasticity, particularly long-term potentiation (LTP) and long-term depression (LTD), underpins learning and memory. In AD, soluble Aβ oligomers disrupt this balance by blocking LTP while enhancing LTD. This imbalance weakens synaptic connections, leading to early impairments in memory encoding and recall.[28]

5. 2. Aβ-induced synaptic toxicity

Aβ oligomers interfere with postsynaptic receptors such as NMDA and AMPA, altering calcium signaling and causing excitotoxicity. This overstimulation induces mitochondrial dysfunction, oxidative damage, and cytoskeletal disruption. Structural changes, including loss of dendritic spines, are prominent and closely correlated with cognitive impairment.[29]

5. 3. Role of tau pathology in synaptic failure

Hyperphosphorylated tau mislocalizes to dendritic spines, where it disrupts postsynaptic density proteins and signaling pathways. It also destabilizes microtubules, impairing axonal transport of synaptic vesicles and essential proteins. When combined with Aβ toxicity, tau pathology synergistically accelerates synaptic degeneration, amplifying neuronal vulnerability.[30]

5. 4. Neurotransmitter system disruption

In addition to structural synaptic loss, neurotransmitter systems are severely affected in AD. The cholinergic system, critical for attention and memory, undergoes marked degeneration, providing the rationale for current cholinesterase

inhibitor therapies. The glutamatergic system is disrupted through Aβ-mediated NMDA receptor overactivation, leading to excitotoxicity. Meanwhile, disturbances in serotonergic and noradrenergic systems contribute to mood disorders, agitation, and other neuropsychiatric symptoms observed in patients.[31]

6. Interconnection Between Oxidative Stress, Neuroinflammation, and Synaptic Dysfunction

Alzheimer's disease (AD) pathology is driven by the interplay of oxidative stress, chronic inflammation, and synaptic loss. These processes are not isolated but form a self-reinforcing cycle that accelerates neuronal degeneration and cognitive decline.[32]

6. 1. Vicious cycle of ROS, inflammation, and synaptic loss

Excessive generation of reactive oxygen species (ROS) results from mitochondrial dysfunction, amyloid-β (Aβ) accumulation, and tau pathology. Elevated ROS damages lipids, proteins, and DNA, impairing neuronal viability. Oxidative stress simultaneously activates microglia and astrocytes, leading to the release of pro-inflammatory cytokines. This inflammatory environment further amplifies oxidative damage while disrupting synaptic signaling. Progressive synaptic loss feeds back into the cycle, reducing neuronal resilience and exacerbating ROS production.[33]

6. 2. Cross-talk between microglia, mitochondria, and neurons

Mitochondrial impairment is a central event linking oxidative stress and inflammation. Dysfunctional mitochondria release ROS and danger-associated molecular patterns (DAMPs), which activate microglia and propagate neuroinflammation. Activated microglia, in turn, release inflammatory mediators that further damage neuronal mitochondria. This microglia–mitochondria–neuron cross-talk sustains a toxic loop, culminating in widespread synaptic dysfunction and neuronal death.[34]

6. 3. Contribution to cognitive decline

Together, oxidative damage, inflammatory signaling, and synaptic breakdown disrupt neural network connectivity in the hippocampus and cortex—regions critical for memory and executive function. This triad underlies the hallmark clinical features of AD, including progressive memory loss, impaired learning, and cognitive decline.[35]

7. Therapeutic Perspectives

Given the multifactorial nature of AD, therapeutic approaches must target oxidative stress, inflammation, and synaptic dysfunction simultaneously. Several strategies have been explored, ranging from natural compounds to multi-target drug designs.[36]

7. 1. Antioxidant-based therapies

Antioxidants aim to reduce ROS-mediated neuronal damage. Natural compounds such as curcumin, resveratrol, quercetin, and green tea polyphenols have shown neuroprotective effects in preclinical studies. Nutraceuticals enriched with vitamins C and E, coenzyme Q10, and omega-3 fatty acids have also been investigated for their ability to counteract oxidative stress. Additionally, pharmacological antioxidants are being evaluated to restore redox balance and protect mitochondria.[37]

7. 2. Anti-inflammatory interventions

Non-steroidal anti-inflammatory drugs (NSAIDs) have long been studied for their potential to modulate neuroinflammation. Although clinical results are mixed, experimental evidence supports their role in reducing

microglial activation. More specific approaches focus on microglial modulators (e.g., TREM2 agonists, colony-stimulating factor 1 receptor inhibitors) and inhibitors of inflammasome activation, aiming to curb harmful inflammation without compromising protective immune responses.[38]

7. 3. Synaptic restoration approaches

Therapies directed at synaptic health include cholinesterase inhibitors (donepezil, rivastigmine, galantamine), which provide symptomatic relief by enhancing cholinergic transmission. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) have been explored for their ability to promote synaptic resilience and regeneration. Novel drugs targeting glutamatergic transmission (e.g., NMDA receptor antagonists like memantine) and synaptic modulators are under development.[39]

7. 4. Multi-targeted therapeutic strategies

Since AD involves overlapping pathological cascades, single-target drugs often yield limited benefits. Multi-targeted strategies—including hybrid molecules, combinational therapies, and natural polyphenols with pleiotropic actions—are gaining attention. Such approaches simultaneously address oxidative stress, inflammation, and synaptic impairment, offering broader therapeutic potential.[40]

8. Future Directions and Challenges

Despite advances in understanding AD pathophysiology, major challenges remain in translating research into effective therapies.

8. 1. Biomarker development for early detection

Early diagnosis is critical for therapeutic success. Biomarkers in cerebrospinal fluid (Aβ, tau, neurofilament light chain), blood-based markers, and neuroimaging techniques (PET, MRI) are being refined to detect AD at preclinical stages. Reliable, minimally invasive biomarkers could enable timely interventions before irreversible neurodegeneration occurs.[41]

8. 2. Personalized and precision medicine approaches

Genetic variability, lifestyle factors, and comorbidities influence disease onset and progression. Precision medicine approaches aim to stratify patients based on genetic profiles (e.g., APOE genotype, TREM2 variants) and biomarker signatures, enabling personalized therapeutic regimens tailored to individual risk profiles.[42]

8. 3. Translational gaps between preclinical and clinical findings

Many therapies that show promise in animal models fail in clinical trials. This gap reflects the limitations of existing models, which often fail to fully capture the complexity of human AD. Bridging this gap requires the use of advanced human-derived systems, such as induced pluripotent stem cell (iPSC)-based neuronal cultures, organoids, and multi-omics approaches to validate therapeutic targets.[43]

CONCLUSION

Alzheimer’s disease (AD) is a multifaceted neurodegenerative disorder with profound clinical, social, and economic impacts. Its hallmark pathology—amyloid-β accumulation, tau hyperphosphorylation, synaptic loss, oxidative stress, and chronic neuroinflammation—forms an interconnected network that drives progressive neuronal damage and cognitive decline. Current treatments provide only limited symptomatic relief, and disease-modifying therapies

targeting amyloid or tau have shown modest efficacy, underscoring the need for broader therapeutic strategies. Future advances depend on early and accurate detection through reliable biomarkers, precision medicine approaches tailored to genetic and molecular profiles, and translational models that closely replicate human disease. Multi-targeted interventions that simultaneously address oxidative stress, inflammatory signaling, and synaptic dysfunction offer significant promise for more effective treatment. A comprehensive understanding of the interplay among these pathological mechanisms is crucial for identifying novel therapeutic targets. By integrating early diagnosis, personalized therapy, and multi-faceted treatment strategies, it may be possible to slow or alter the progression of AD, alleviating its burden on patients, caregivers, and healthcare systems globally.

REFERENCE

1. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. The Lancet, 2021 Apr 24; 397(10284): 1577-90.
2. Scheltens P, Blennow K, Breteler MM, De Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. The Lancet, 2016 Jul 30; 388(10043): 505-17.
3. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. the Lancet, 2011 Mar 19; 377(9770): 1019-31.
4. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nature reviews disease primers, 2015 Oct 15; 1(1): 1-8.
5. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nature reviews disease primers, 2015 Oct 15; 1(1): 1-8.
6. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nature reviews disease primers, 2015 Oct 15; 1(1): 1-8.
7. Lopez JA, González HM, Léger GC. Alzheimer's disease. Handbook of clinical neurology, 2019 Jan 1; 167: 231-55.
8. Wang H, Yang J, Schneider JA, De Jager PL, Bennett DA, Zhang HY. Genome-wide interaction analysis of pathological hallmarks in Alzheimer's disease. Neurobiology of aging, 2020 Sep 1; 93: 61-8.
9. Finder VH, Glockshuber R. Amyloid-β aggregation. Neurodegenerative Diseases, 2007 Apr 13; 4(1): 13-27.
10. Bruggink KA, Müller M, Kuiperij HB, Verbeek MM. Methods for analysis of amyloid-β aggregates. Journal of Alzheimer’s Disease, 2012 Feb 20; 28(4): 735-58.
11. Brion JP, Anderton BH, Authelet M, Dayanandan R, Leroy K, Lovestone S, Octave JN, Pradier L, Touchet N, Tremp G. Neurofibrillary tangles and tau phosphorylation. InBiochemical Society Symposia, 2001 Feb 1; Vol. 67: 81-88 Portland Press Limited.
12. Metaxas A, Kempf SJ. Neurofibrillary tangles in Alzheimer's disease: elucidation of the molecular mechanism by immunohistochemistry and tau protein phospho-proteomics. Neural regeneration research, 2016 Oct 1; 11(10): 1579-81.
13. Bessis A, Béchade C, Bernard D, Roumier A. Microglial control of neuronal death and synaptic properties. Glia, 2007 Feb; 55(3): 233-8.
14. Fricker M, Tolkovsky AM, Borutaite V, Coleman M, Brown GC. Neuronal cell death. Physiological reviews, 2018 Apr 1; 98(2): 813-80.
15. Pettmann B, Henderson CE. Neuronal cell death. Neuron, 1998 Apr 1; 20(4): 633-47.
16. Smith MA, Rottkamp CA, Nunomura A, Raina AK, Perry G. Oxidative stress in Alzheimer’s disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 2000 Jul 26; 1502(1): 139-44.

17. Adam-Vizi V. Production of reactive oxygen species in brain mitochondria: contribution by electron transport chain and non–electron transport chain sources. Antioxidants & redox signaling, 2005 Sep 1; 7(9-10): 1140-9.
18. Zsurka G, Kunz WS. Mitochondrial dysfunction and seizures: the neuronal energy crisis. The Lancet Neurology, 2015 Sep 1; 14(9): 956-66.
19. Lyras L, Cairns NJ, Jenner A, Jenner P, Halliwell B. An assessment of oxidative damage to proteins, lipids, and DNA in brain from patients with Alzheimer's disease. Journal of neurochemistry, 1997 May; 68(5): 2061-9.
20. Dumanović J, Nepovimova E, Natić M, Kuča K, Jaćević V. The significance of reactive oxygen species and antioxidant defense system in plants: A concise overview. Frontiers in plant science, 2021 Jan 6; 11: 552969.
21. Naci H, Ioannidis JP. How good is “evidence” from clinical studies of drug effects and why might such evidence fail in the prediction of the clinical utility of drugs?. Annual review of pharmacology and toxicology, 2015 Jan 6; 55(1): 169-89.
22. 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 Apr 1; 14(4): 388-405.
23. Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer’s disease. Journal of neuroinflammation, 2022 Aug 17; 19(1): 206.
24. Doganyigit Z, Eroglu E, Akyuz E. Inflammatory mediators of cytokines and chemokines in sepsis: From bench to bedside. Human & experimental toxicology, 2022 Jan 21; 41: 09603271221078871.
25. Carnevale D, Mascio G, Ajmone-Cat MA, D'Andrea I, Cifelli G, Madonna M, Cocozza G, Frati A, Carullo P, Carnevale L, Alleva E. Role of neuroinflammation in hypertension-induced brain amyloid pathology. Neurobiology of aging, 2012 Jan 1; 33(1): 205-e19.
26. Perry VH. Contribution of systemic inflammation to chronic neurodegeneration. Acta neuropathologica, 2010 Sep; 120(3): 277-86.
27. Tönnies E, Trushina E. Oxidative stress, synaptic dysfunction, and Alzheimer’s disease. Journal of Alzheimer’s disease, 2017 Apr 19; 57(4): 1105-21.
28. Malenka RC. Synaptic plasticity in the hippocampus: LTP and LTD. Cell, 1994 Aug 26; 78(4): 535-8.
29. Tu S, Okamoto SI, Lipton SA, Xu H. Oligomeric Aβ-induced synaptic dysfunction in Alzheimer’s disease. Molecular neurodegeneration, 2014 Nov 14; 9(1): 48.
30. Wu M, Zhang M, Yin X, Chen K, Hu Z, Zhou Q, Cao X, Chen Z, Liu D. The role of pathological tau in synaptic dysfunction in Alzheimer’s diseases. Translational neurodegeneration , 2021 Nov 10; 10(1): 45.
31. Slikker Jr W, Xu ZA, Levin ED, Slotkin TA. Mode of action: disruption of brain cell replication, second messenger, and neurotransmitter systems during development leading to cognitive dysfunction—developmental neurotoxicity of nicotine. Critical reviews in toxicology, 2005 Jan 1; 35(8-9): 703-11.
32. Tönnies E, Trushina E. Oxidative stress, synaptic dysfunction, and Alzheimer’s disease. Journal of Alzheimer’s disease, 2017 Apr 19; 57(4): 1105-21.
33. Jurcău MC, Andronie-Cioara FL, Jurcău A, Marcu F, Ţiț DM, Pașcalău N, Nistor-Cseppentö DC. The link between oxidative stress, mitochondrial dysfunction and neuroinflammation in the pathophysiology of Alzheimer’s disease: therapeutic implications and future perspectives. Antioxidants, 2022 Oct 31; 11(11): 2167.
34. Parsons AL, Bucknor EM, Castroflorio E, Soares TR, Oliver PL, Rial D. The interconnected mechanisms of oxidative stress and neuroinflammation in epilepsy. Antioxidants, 2022 Jan 14; 11(1): 157.

35. Kamat PK, Kalani A, Rai S, Swarnkar S, Tota S, Nath C, Tyagi N. Mechanism of oxidative stress and synapse dysfunction in the pathogenesis of Alzheimer's disease: understanding the therapeutics strategies. Molecular neurobiology, 2016 Jan; 53(1): 648-61.
36. Kralisch S, Klein J, Bluher M, Paschke R, Stumvoll M, Fasshauer M. Therapeutic perspectives of adipocytokines. Expert opinion on pharmacotherapy, 2005 Jun 1; 6(6): 863-72.
37. Tschape JA, Hartmann T. Therapeutic perspectives in Alzheimer's disease. Recent Patents on CNS Drug Discovery (Discontinued), 2006 Jan 1; 1(1): 119-27.
38. Pardo-Moreno T, González-Acedo A, Rivas-Domínguez A, García-Morales V, García-Cozar FJ, Ramos-Rodríguez JJ, Melguizo-Rodríguez L. Therapeutic approach to Alzheimer's disease: current treatments and new perspectives. Pharmaceutics, 2022 May 24; 14(6): 1117.
39. Appelbaum LG, Shenasa MA, Stolz L, Daskalakis Z. Synaptic plasticity and mental health: methods, challenges and opportunities. Neuropsychopharmacology, 2023 Jan; 48(1): 113-20.
40. Fu RG, Sun Y, Sheng WB, Liao DF. Designing multi-targeted agents: An emerging anticancer drug discovery paradigm. European journal of medicinal chemistry, 2017 Aug 18; 136: 195-211.
41. Pepe MS, Etzioni R, Feng Z, Potter JD, Thompson ML, Thornquist M, Winget M, Yasui Y. Phases of biomarker development for early detection of cancer. Journal of the National Cancer Institute, 2001 Jul 18; 93(14): 1054-61.
42. Seymour CW, Gomez H, Chang CC, Clermont G, Kellum JA, Kennedy J, Yende S, Angus DC. Precision medicine for all? Challenges and opportunities for a precision medicine approach to critical illness. Critical Care, 2017 Oct 18; 21(1): 257.
43. Mahalmani V, Sinha S, Prakash A, Medhi B. Translational research: Bridging the gap between preclinical and clinical research. Indian journal of pharmacology, 2022 Nov 1; 54(6): 393-6.