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Review Paper

Pharmacological Innovations in Alzheimer's Disease: Recent Progress and Future Perspectives

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ABSTRACT

Alzheimer's disease is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide, posing a significant global health challenge due to its increasing prevalence in the aging population. The disease is characterized by progressive cognitive decline, memory impairment, and irreversible neuronal loss resulting from multiple interconnected pathological mechanisms. Although the precise etiology remains incompletely understood, substantial evidence indicates that AD is a multifactorial disorder involving amyloid-β deposition, tau protein hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, synaptic impairment, excitotoxicity, cholinergic deficits, blood–brain barrier disruption, insulin resistance, gut–brain axis dysregulation, and abnormalities in metal ion homeostasis. These mechanisms interact to promote neuronal degeneration, brain atrophy, and progressive cognitive impairment. Current pharmacological therapies primarily provide symptomatic relief by enhancing cholinergic neurotransmission or regulating glutamatergic signaling, while recently developed disease-modifying therapies target amyloid pathology. Ongoing research focuses on identifying novel therapeutic targets that simultaneously address multiple pathological pathways to slow disease progression and improve clinical outcomes. This review summarizes the major pathophysiological mechanisms involved in Alzheimer's disease and discusses their implications for the development of innovative pharmacological strategies and future therapeutic interventions

INTRODUCTION

Alzheimer's disease is a chronic, progressive, and irreversible neurodegenerative disorder that

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primarily affects older adults and is the leading cause of dementia worldwide.[1] Alzheimer's disease was first described in 1906 by the German psychiatrist and neuropathologist Dr. Alois Alzheimer, who reported the case of a 51-year-old woman, Auguste Deter, presenting with progressive memory loss, confusion, behavioral changes, and language impairment. Postmortem examination of her brain revealed characteristic pathological features, including extracellular amyloid plaques and intracellular neurofibrillary tangles, which remain the defining histopathological hallmarks of the disease today.[1] The pathogenesis of Alzheimer's disease is highly complex and multifactorial. Although the exact cause remains incompletely understood, extensive research has identified several interconnected pathological mechanisms contributing to disease progression. These include the accumulation of extracellular amyloid-beta (Aβ) peptides, hyperphosphorylation of tau protein leading to neurofibrillary tangles, chronic neuroinflammation mediated by activated microglia and astrocytes, oxidative stress, mitochondrial dysfunction, synaptic loss, impaired glucose metabolism, vascular abnormalities, and neuronal apoptosis. [1] Dementia is a clinical syndrome characterized by a decline in memory, cognitive abilities, language, reasoning, and daily functioning severe enough to interfere with an individual's independence. According to recent global estimates, more than 55 million people are living with dementia, and Alzheimer's disease accounts for approximately 60–70% of all dementia cases. With increasing life expectancy and population aging, the prevalence of Alzheimer's disease is expected to rise dramatically, potentially exceeding 130 million cases by 2050**,** making it one of the most significant public health challenges of the 21st century. The disease not only affects patients but also imposes substantial emotional, social, and economic burdens on families, caregivers, and healthcare systems.[2] These pathological processes ultimately result in progressive degeneration of neurons, particularly in the hippocampus and cerebral cortex, regions responsible for memory formation, learning, and higher cognitive functions. The multifactorial nature of Alzheimer's disease explains why therapeutic strategies targeting a single pathological pathway have frequently failed to produce substantial clinical benefits.[3]

Clinically, Alzheimer's disease progresses gradually through several stages, beginning with a preclinical phase during which pathological changes accumulate years before symptoms become apparent. This is followed by mild cognitive impairment **,** characterized by measurable memory deficits without significant impairment in daily activities. As the disease advances, patients develop mild, moderate, and eventually severe dementia, with progressive deterioration in memory, executive function, language, orientation, judgment, and behavior. In the advanced stages, individuals lose the ability to perform basic activities of daily living, become bedridden, and require continuous care. Non-cognitive manifestations such as depression, anxiety, agitation, hallucinations, sleep disturbances, and psychosis further complicate disease management and significantly reduce quality of life.[4] The etiology of Alzheimer's disease involves a combination of genetic, environmental, and lifestyle factors. Age remains the strongest risk factor, with incidence increasing exponentially after 65 years of age. Genetic mutations in the amyloid precursor protein (APP)**,** presenilin-1 (PSEN1)**,** and presenilin-2 (PSEN2) genes are responsible for rare cases of early-onset familial Alzheimer's disease, whereas the apolipoprotein E ε4 (APOE ε4) allele is the most important genetic risk factor for the more common late-onset form. Other contributing factors include

cardiovascular diseases, diabetes mellitus, hypertension, obesity, hypercholesterolemia, traumatic brain injury, physical inactivity, smoking, and low educational attainment. These findings have strengthened the concept that Alzheimer's disease results from complex interactions between genetic susceptibility and modifiable environmental influences.[5] For more than three decades, pharmacological management of Alzheimer's disease focused primarily on symptomatic treatment. The currently approved conventional medications include acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine), which enhance cholinergic neurotransmission by inhibiting acetylcholine breakdown, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, which reduces glutamate-mediated excitotoxicity. While these agents provide modest improvements in cognition and daily functioning, they do not prevent neuronal degeneration or significantly alter disease progression. Consequently, the need for disease-modifying therapies capable of targeting the underlying pathological mechanisms has become a major focus of pharmaceutical research.[6]

Over the past decade, significant advances in molecular biology, neuroimaging, biomarker development, immunotherapy, and precision medicine have transformed the therapeutic landscape of Alzheimer's disease. The approval of anti-amyloid monoclonal antibodies, including lecanemab and donanemab in selected patient populations, represents the first generation of therapies designed to slow disease progression by reducing amyloid plaque burden. Although these therapies provide only modest clinical benefits and require careful patient selection because of risks such as amyloid-related imaging abnormalities (ARIA), they represent a major milestone in Alzheimer's disease treatment.[7] Simultaneously, research efforts have expanded beyond the traditional amyloid hypothesis to include therapies targeting tau protein aggregation, neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic protection, autophagy, insulin signaling, and the gut–brain axis. Novel pharmacological strategies involving gene therapy, RNA-based therapeutics, stem cell therapy, nanotechnology-based drug delivery, artificial intelligence-assisted drug discovery, and pharmacogenomics-guided precision medicine are opening new avenues for personalized treatment. Advances in blood- and cerebrospinal fluid-based biomarkers have also enabled earlier diagnosis, better disease monitoring, and more accurate selection of patients for targeted therapies.[8]

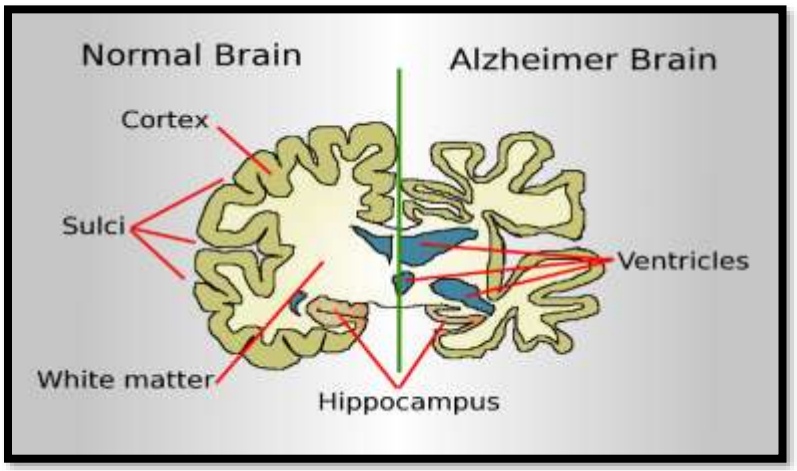

Fig No. 1. Alzheimer Brain and Normal Brain Difference

Despite these remarkable developments, Alzheimer's disease remains incurable, and many investigational therapies continue to face challenges related to efficacy, safety, blood–brain barrier penetration, treatment cost, and long-term clinical outcomes. Nevertheless, growing understanding of disease biology has shifted the focus from symptomatic management toward disease modification and prevention. The future of Alzheimer's disease pharmacotherapy is likely to involve multimodal therapeutic approaches that simultaneously target multiple pathological pathways while incorporating personalized medicine based on genetic, molecular, and biomarker profiles.[9] This review aims to provide a comprehensive overview of recent pharmacological advances in Alzheimer's disease, with emphasis on emerging therapeutic targets, disease-modifying agents, ongoing clinical trials, novel drug delivery systems, precision medicine approaches, and future perspectives that may reshape the management of this devastating neurodegenerative disorder.

Table No. 1. Overview of Animal Models Used in Preclinical Alzheimer's Disease Studies[10–17]

Animal Model	Species	Method/Genetic Modification	Key Pathological Features	Application	Reference
APP Transgenic Mouse	Mouse	Overexpression of human APP gene with familial AD mutations	Amyloid-β plaque formation, memory impairment	Evaluation of anti-amyloid drugs, disease mechanisms	[18]
APP/PS1 Double Transgenic Mouse	Mouse	Human APP + Presenilin-1 (PSEN1) mutations	Early amyloid plaque deposition, cognitive deficits	Drug screening, biomarker studies	[19]
5xFAD Mouse	Mouse	Five familial AD mutations (APP and PSEN1)	Rapid amyloid accumulation, gliosis, neuronal loss	Preclinical testing of disease-modifying therapies	[20]
3xTg-AD Mouse	Mouse	APP, PSEN1, and Tau mutations	Amyloid plaques, neurofibrillary tangles, cognitive decline	Studies of combined amyloid and tau pathology	[21]
Tau Transgenic Mouse (P301S/P301L)	Mouse	Mutant human tau gene	Tau aggregation, neurofibrillary tangles	Evaluation of anti-tau therapies	[22]
Tg2576 Mouse	Mouse	Swedish mutation in APP gene	Progressive amyloid plaque formation	Early-stage drug discovery	[23]
Knock-in APP Mouse	Mouse	Humanized APP mutations without overexpression	Physiological amyloid production	Better mimicry of human disease	[24]

SAMP8 Mouse	Mouse	Naturally accelerated aging strain	Age-related cognitive impairment, oxidative stress	Aging and neuroprotection studies	[25]
Intracerebroventricular Streptozotocin (ICV-STZ) Rat	Rat	Intracerebroventricular injection of streptozotocin	Insulin resistance, oxidative stress, cognitive dysfunction	Sporadic AD research	[26,27]
Scopolamine-Induced Model	Mouse/ Rat	Administration of scopolamine	Temporary memory impairment due to cholinergic blockade	Screening of memory-enhancing drugs	[28,29]
$AlCl_3$ (Aluminum Chloride) Model	Rat/ Mouse	Chronic aluminum chloride administration	Oxidative stress, memory deficits, neuronal damage	Neuroprotective and antioxidant studies	[30,31]
Aβ Peptide Injection Model	Rat/ Mouse	Intracerebral injection of amyloid-β peptides	Local amyloid toxicity, neuroinflammation, cognitive impairment	Testing anti-amyloid compounds	[32,33]
D-Galactose-Induced Aging Model	Mouse/ Rat	Chronic D-galactose administration	Oxidative stress, aging-like changes, cognitive deficits	Anti-aging and antioxidant drug studies	[34,35]
Non-Human Primate Model	Monkey	Naturally aged or experimentally induced	Amyloid deposition, cognitive decline	Translational pharmacology	[36,37]
Zebrafish AD Model	Zebrafish	Genetic manipulation or chemical induction	Amyloid deposition, neurodegeneration	High-throughput drug screening	[38,39]
Drosophila AD Model	Fruit Fly	Expression of human APP or tau genes	Neurodegeneration, locomotor deficits	Genetic studies, rapid screening	[40,41]
Caenorhabditis elegans (C. elegans)	Nematode	Human Aβ or tau expression	Protein aggregation, paralysis	Molecular mechanisms, high-throughput screening	[42,43]

I. Pathophysiology of Alzheimer's Disease:

a. Neuronal Loss and Neurodegeneration

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by widespread neuronal loss and structural abnormalities in several regions of the brain. The earliest and most significant pathological changes occur in the hippocampus, entorhinal cortex, and amygdala, which are responsible for learning, memory formation, and emotional regulation. As the disease progresses, neurodegeneration extends to the association cortices of the frontal, temporal, and parietal lobes, leading to progressive impairment of cognitive functions, language, executive abilities, and behavior. Subcortical

structures, including the locus coeruleus, dorsal raphe nucleus, and basal nucleus of Meynert, are also affected, resulting in disturbances of noradrenergic, serotonergic, and cholinergic neurotransmission.[44] One of the characteristic pathological features of AD is the formation of neurofibrillary tangles composed of abnormal tau protein. These tangles develop in a predictable sequence, beginning in the transentorhinal cortex, followed by the entorhinal cortex, the CA1 region of the hippocampus, and eventually spreading to the association cortices. The extent and distribution of neurofibrillary tangles closely correlate with the severity of cognitive impairment and dementia, making tau pathology one of the strongest indicators of disease progression. Progressive neuronal degeneration is accompanied by marked cortical atrophy, particularly within the temporofrontal regions. This neuronal damage triggers chronic neuroinflammatory responses characterized by activation of microglial cells, infiltration of immune cells such as monocytes and macrophages, and the accumulation of extracellular amyloid-β plaques. Together, neuronal loss, synaptic degeneration, inflammation, and protein aggregation contribute to the irreversible cognitive decline observed in Alzheimer's disease.[45]

b. Amyloid-β Hypothesis

The amyloid-β (Aβ) hypothesis is one of the most extensively studied mechanisms underlying Alzheimer's disease. According to this hypothesis, abnormal accumulation of amyloid-β peptides initiates a cascade of pathological events that ultimately result in neuronal dysfunction and cognitive impairment. Amyloid-β peptides are generated from the amyloid precursor protein through sequential enzymatic cleavage by β-secretase (BACE1) and γ-secretase. Under physiological conditions, APP can also be cleaved by α-secretase, which prevents the formation of amyloid-β and produces non-toxic peptide fragments. In Alzheimer's disease, increased amyloidogenic processing favors the production of amyloid-β peptides, particularly Aβ42, which has a strong tendency to aggregate. An imbalance between amyloid-β production and its clearance leads to the accumulation of soluble oligomers that subsequently form protofibrils, fibrils, and extracellular amyloid plaques. Among these forms, soluble oligomers are considered the most neurotoxic because they interfere with synaptic communication, impair neuronal signaling, and trigger inflammatory responses. Amyloid-β deposition activates microglia and astrocytes, resulting in the release of inflammatory cytokines, reactive oxygen species, and neurotoxic mediators. The resulting chronic inflammation promotes oxidative stress, mitochondrial dysfunction, synaptic loss, and ultimately neuronal death. Amyloid accumulation also accelerates tau protein hyperphosphorylation, further amplifying neurodegeneration. Although the amyloid hypothesis remains central to Alzheimer's disease research, increasing evidence suggests that amyloid deposition alone cannot fully explain disease progression. Instead, it interacts with multiple pathological mechanisms, including tau pathology, neuroinflammation, oxidative stress, and vascular dysfunction, to produce the clinical manifestations of Alzheimer's disease.[46,47]

c. Tau Protein Hyperphosphorylation

Tau is a microtubule-associated protein that plays an essential role in maintaining neuronal structure and facilitating intracellular transport. Under normal physiological conditions, tau stabilizes microtubules within neuronal axons and supports efficient transport of nutrients, neurotransmitters, and cellular organelles. In Alzheimer's disease, tau undergoes excessive hyperphosphorylation, causing it to detach from microtubules and lose its stabilizing function. The abnormal tau proteins

aggregate into paired helical filaments that accumulate as intracellular neurofibrillary tangles. These tangles disrupt axonal transport, impair synaptic function, and eventually lead to neuronal degeneration. Unlike amyloid plaques, the distribution and severity of tau pathology correlate strongly with cognitive decline, hippocampal atrophy, and disease severity. Tau pathology progressively spreads from one brain region to another through interconnected neuronal networks, contributing to the continuous worsening of clinical symptoms. Because of its close association with disease progression, hyperphosphorylated tau has become an important therapeutic target, with ongoing research focusing on tau aggregation inhibitors, anti-tau antibodies, kinase inhibitors, and tau-directed vaccines.[48,49]

d. Oxidative Stress Hypothesis

Oxidative stress is considered a major contributor to neuronal damage in Alzheimer's disease. It occurs when the production of reactive oxygen species and reactive nitrogen species exceeds the antioxidant defense capacity of the brain. Although ROS and RNS participate in normal cellular signaling, excessive production causes oxidative damage to proteins, lipids, nucleic acids, and cellular membranes. The brain is particularly vulnerable to oxidative stress because it consumes large amounts of oxygen, contains abundant polyunsaturated fatty acids that are highly susceptible to lipid peroxidation, and possesses relatively limited antioxidant defenses. Neurons are especially sensitive to oxidative injury due to their high metabolic activity and relatively low concentrations of endogenous antioxidants such as glutathione. Oxidative stress promotes mitochondrial dysfunction, DNA damage, protein oxidation, calcium dysregulation, and activation of apoptotic pathways, all of which contribute to progressive neuronal death. Furthermore, oxidative stress enhances amyloid-β production and tau hyperphosphorylation, creating a self-perpetuating cycle that accelerates disease progression. Consequently, antioxidant-based therapeutic strategies continue to be explored as potential interventions for Alzheimer's disease.[50–52]

e. Metal Ion Hypothesis

Disturbances in metal ion homeostasis have emerged as another important mechanism involved in Alzheimer's disease. Essential transition metals such as copper (Cu), iron (Fe), and zinc (Zn) play critical roles in neuronal function, enzyme activity, neurotransmission, and antioxidant defense. However, abnormal accumulation or redistribution of these metals can promote neurodegeneration. Excessive concentrations of copper and iron catalyze the formation of reactive oxygen species through redox reactions, thereby increasing oxidative stress and neuronal injury. These metals also facilitate aggregation of amyloid-β peptides and promote the formation of amyloid plaques. In addition to copper and iron, altered levels of manganese and aluminum have also been associated with neurodegenerative processes, although their precise roles remain under investigation. These findings have led to increasing interest in metal-chelating agents, ionophores, and metal-modulating compounds as potential therapeutic approaches aimed at restoring metal homeostasis and reducing neurotoxicity.[50,53]

f. Cholinergic Hypothesis

The cholinergic hypothesis is one of the earliest and most influential theories proposed to explain the cognitive decline associated with Alzheimer's disease. It suggests that degeneration of cholinergic neurons within the basal forebrain, particularly the basal nucleus of Meynert, leads to

a marked reduction in the neurotransmitter acetylcholine, which is essential for learning, memory, attention, and cognition. Progressive loss of cholinergic neurons results in impaired cholinergic neurotransmission and reduced activation of cholinergic receptors throughout the cerebral cortex and hippocampus. This neurotransmitter deficiency contributes significantly to memory impairment and cognitive dysfunction observed in patients with Alzheimer's disease. The cholinergic hypothesis forms the basis for currently approved symptomatic treatments, including acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine. These drugs inhibit the breakdown of acetylcholine, thereby increasing its concentration within synaptic clefts and temporarily improving cognitive function. However, because they do not prevent neuronal degeneration or modify disease progression, their therapeutic benefits remain limited. Recent studies indicate that genetic factors, including the apolipoprotein E (APOE) genotype, may influence both disease susceptibility and treatment response. Current evidence suggests that cholinergic dysfunction represents only one component of the complex pathological network underlying Alzheimer's disease and interacts with amyloid accumulation, tau pathology, oxidative stress, and neuroinflammation.[54,55]

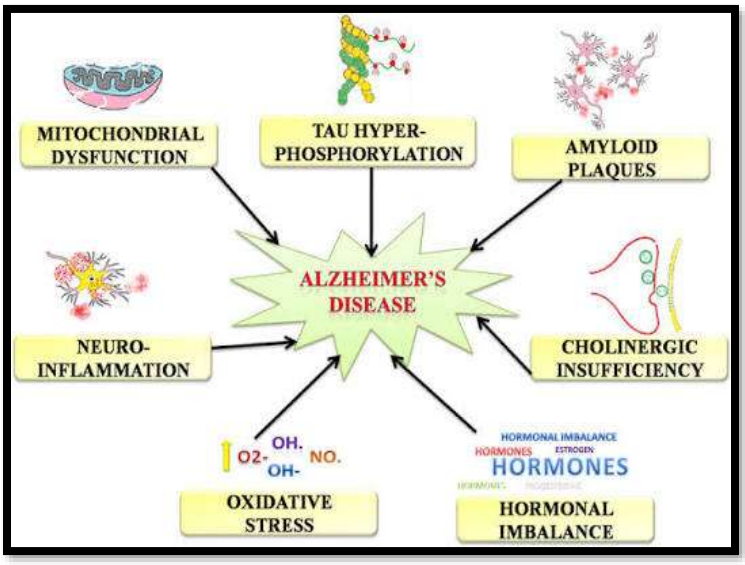

Fig No. 2.

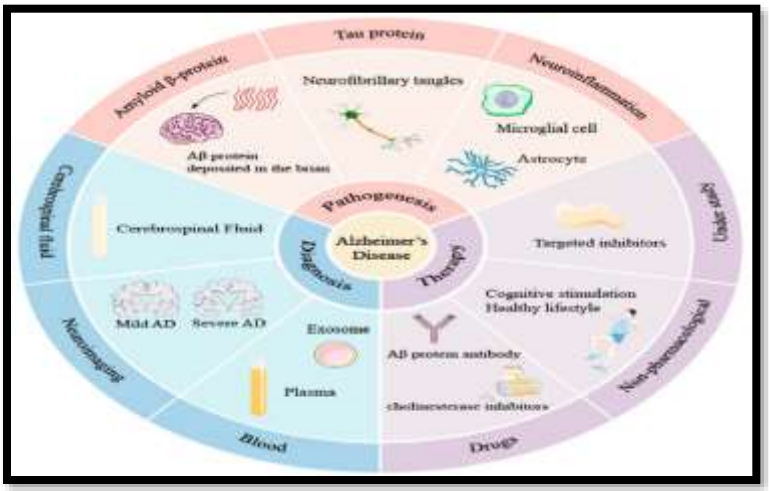

Fig No. 3.

DISCUSSION

Alzheimer's disease is increasingly recognized as a multifactorial neurodegenerative disorder in which several pathological mechanisms operate simultaneously rather than independently. Earlier research primarily focused on the amyloid cascade hypothesis, suggesting that amyloid-β deposition was the initiating event responsible for disease progression. Although amyloid accumulation remains a central hallmark of Alzheimer's disease and has led to the development of disease-modifying therapies such as monoclonal antibodies, clinical studies have demonstrated that reducing amyloid burden alone does not completely halt cognitive decline. This has shifted scientific attention toward understanding the complex interactions among multiple pathological processes. Tau protein hyperphosphorylation has emerged as a critical determinant of disease severity because neurofibrillary tangle formation closely correlates with neuronal loss, hippocampal atrophy, and cognitive impairment. Increasing evidence indicates that abnormal tau aggregation disrupts neuronal transport, impairs synaptic communication, and accelerates neurodegeneration. Consequently, tau-targeted therapies, including monoclonal antibodies, aggregation inhibitors, and vaccines, are being actively investigated as potential disease-modifying interventions. Neuroinflammation also plays a pivotal role in Alzheimer's disease progression. Chronic activation of microglia and astrocytes results in sustained production of inflammatory cytokines, chemokines, and reactive oxygen species, thereby amplifying neuronal injury. Rather than serving only as a consequence of amyloid deposition, inflammation is now considered an active contributor to disease progression, making immune-modulating therapies promising therapeutic candidates. Oxidative stress and mitochondrial dysfunction further contribute to neuronal degeneration by impairing cellular energy metabolism, increasing free radical production, damaging DNA, proteins, and lipids, and triggering apoptotic pathways. These mechanisms create a vicious cycle that enhances amyloid production, tau phosphorylation, and inflammatory responses. Similarly, disturbances in metal ion homeostasis involving copper, iron, and zinc have been implicated in amyloid aggregation and oxidative damage, suggesting that restoration of metal balance may offer additional therapeutic benefits. The cholinergic hypothesis continues to explain many of the cognitive manifestations of Alzheimer's disease and remains the basis for currently approved symptomatic therapies. However, the limited efficacy of acetylcholinesterase inhibitors highlights the need for treatments capable of modifying the underlying disease process rather than merely improving neurotransmission. Additional mechanisms such as glutamatergic excitotoxicity, blood–brain barrier dysfunction, insulin resistance, and gut microbiota dysregulation have broadened the understanding of Alzheimer's disease and opened new avenues for therapeutic intervention. Recent advances in molecular biology, biomarker discovery, pharmacogenomics, artificial intelligence, and nanotechnology have accelerated the identification of novel therapeutic targets and personalized treatment approaches. Future management of Alzheimer's disease will likely depend on combination therapies that simultaneously target amyloid pathology, tau aggregation, neuroinflammation, oxidative stress, mitochondrial dysfunction, and metabolic abnormalities. Such multimodal approaches may provide greater clinical benefit than therapies directed at a single pathological pathway.

CONCLUSION

Alzheimer's disease is a complex and progressive neurodegenerative disorder resulting from the interaction of multiple pathological mechanisms, including amyloid-β accumulation, tau protein hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, cholinergic deficits, excitotoxicity, blood–brain barrier disruption, insulin resistance, and alterations in the gut–brain axis. These interconnected processes collectively contribute to synaptic dysfunction, neuronal loss, cerebral atrophy, and progressive cognitive decline. Although conventional pharmacological therapies provide symptomatic improvement by enhancing cholinergic neurotransmission or regulating glutamatergic activity, they do not effectively prevent disease progression. Recent advances in disease-modifying therapies, particularly anti-amyloid monoclonal antibodies, represent important milestones in Alzheimer's disease treatment; however, their clinical benefits remain modest and are associated with certain limitations. A growing understanding of the molecular mechanisms underlying Alzheimer's disease has shifted research toward the development of therapies targeting multiple pathological pathways simultaneously. Emerging strategies involving anti-tau agents, anti-inflammatory drugs, antioxidants, mitochondrial protectants, gene therapy, RNA-based therapeutics, nanotechnology-mediated drug delivery, and precision medicine offer promising opportunities for improving treatment outcomes. Future research should focus on early diagnosis through sensitive biomarkers, personalized therapeutic approaches based on genetic and molecular profiling, and combination therapies capable of addressing the multifactorial nature of the disease. Continued advances in neuroscience, pharmacology, and biotechnology are expected to facilitate the development of safer and more effective interventions that may delay disease progression, preserve cognitive function, and improve the quality of life of patients affected by Alzheimer's disease.

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