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Alzheimer's Disease (AD) is A Progressive Neurodegenerative Disorder

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Abstract: *Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioral impairment caused by amyloid beta (Aβ) plaques, tau neurofibrillary tangles, oxidative stress, neuroinflammation, and mitochondrial dysfunction. Despite extensive research, current FDA-approved drugs—acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine—only provide symptomatic relief without halting disease progression. Recent advances focus on multi-target approaches and disease-modifying strategies, including anti-amyloid and anti-tau therapies, mitochondrial antioxidants, autophagy enhancers, and anti-inflammatory agents. Novel drug targets such as BACE1, TREM2, SIRT1, and metal-chelating compounds are under investigation, while computational drug repositioning offers efficient identification of new candidates. Current and emerging therapies highlight the importance of early intervention and combination strategies aimed at restoring neuronal function, reducing pathology, and developing effective, disease-modifying treatments for Alzheimer's disease.*

Keywords: •Alzheimer's Disease •Amyloid Beta (Aβ) •Tau Protein •Neuroinflammation • Multi-Target Drug Therapy

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative disease and is the most common form of dementia among the elderly population. It's characterized not just by memory loss, but also by a host of other cognitive and behavioral symptoms that increasingly impair a person's ability to perform daily activities, such as disorientation, confusion, agitation, and depression. The major pathological hallmarks of AD in the brain are the presence of extracellular amyloid plaques and intraneuronal neurofibrillary tangles (NFTs). While significant advances have identified amyloid plaques as a potential factor, the precise sequence of events leading to neuronal loss and dementia is still being investigated. AD is a complex disorder, often associated with age, and while a small percentage of early-onset cases are linked to mutations in genes like *APP*, *PS1*, and *PS2*, the vast majority of late-onset cases do not show these specific mutations, suggesting a heterogeneous etiology involving various genetic and environmental factors. Current research is focusing on better understanding the underlying mechanisms of AD, as well as developing new diagnostic and therapeutic strategies based on key hypotheses like the amyloid, tangle, and cholinergic theories.[1] Alzheimer's disease (AD) is the most common cause of dementia, characterized as a progressive neurodegenerative disorder leading to loss of memory and cognitive functions due to the gradual death of neurons. The defining molecular features of the disease are the accelerated accumulation of extracellular amyloid (beta) plaques around neurons and intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein. The formation ofA beta plaque, primarily the 42-residue long beta 42, is linked to the amyloidogenic pathway where the amyloid precursor protein (APP) is cleaved by beta-secretase and then gamma$-secretase, replacing the normal, harmless alpha-secretase pathway. A beta plaques and oligomers are neurotoxic, disrupting synaptic communication and contributing to neuronal dysfunction. AD is generally classified as early-onset/familial AD (FAD), caused by dominant mutations in genes like

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APP, *presenilin-1*, or *presenilin-2*, and the more common sporadic AD (SAD), where risk factors include aging, the presence of the Apo-epsilon 4 allele (Apolipoprotein E4), and vascular diseases. The progression of AD is typically broken down into preclinical, mild cognitive impairment, and dementia stages. Given the growing global prevalence of AD, a major focus of therapeutic research is the identification and development of effective ligands against key targets, often utilizing computer-aided drug design techniques like molecular docking.[2] Alzheimer's disease (AD) is an escalating global epidemic and the most frequent cause of dementia, for which there is currently no cure or treatment to halt its progression. The disease is primarily characterized by the main neuropathological features of amyloid A beta plaques and neurofibrillary tangles (NFTs) of the aggregated protein tau, which lead to neuronal death and loss of cognitive functions. However, AD involves a wider range of functional alterations, including issues with energy metabolism, inflammation, and synaptic activity. Given the failure of many clinical trials focused solely on A beta and tau, the scientific community is now exploring diverse and novel targets that aim to improve brain physiology, which may result in effective preventive or modifying strategies for AD. This comprehensive review highlights emerging therapeutic avenues, proposing that AD should be tackled using combination therapies that go beyond A betaand tau to include targets related to insulin and cholesterol metabolism, vascular function, synaptic plasticity, epigenetics, the neurovascular junction/blood-brain barrier (BBB), and the gut microbiota. The goal is to promote research into diverse targets and encourage a multi-faceted approach as a future strategy for this complex disease.

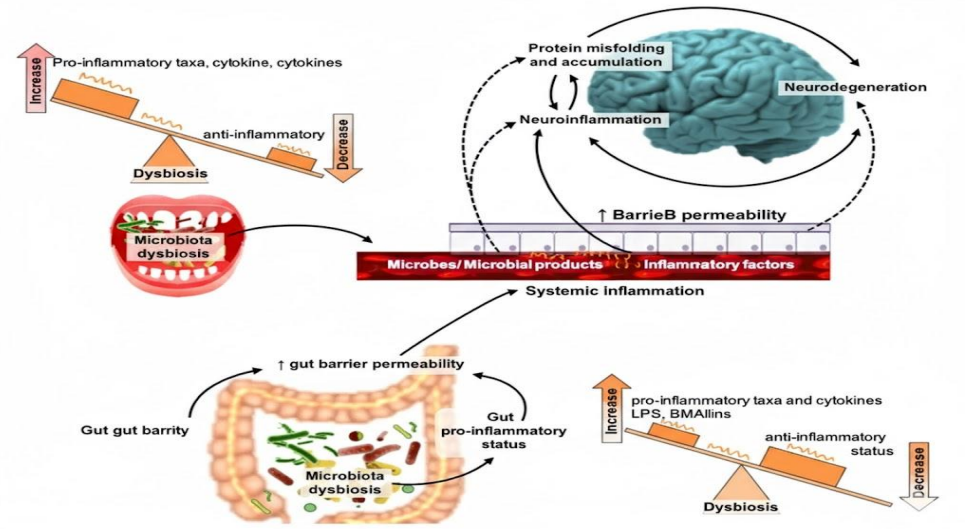

Fig. 1 Possible pathophysiologic role of microbiota in Alzheimer's disease. BBB, blood–brain barrier; BMAA, b-N methylamino-L-alanine; HSV-1, herpes simplex virus type 1; LPS, lipopolysaccharide. From: Marazion et al.

The metallobiology of Alzheimer's disease (AD) is a critical area of research, proposing that the interaction of metal ions with Amyloidis a key driver of pathology. The "metal hypothesis" of AD is based on the significant increase in concentrations of Iron Fe Zinc (Zn, Copper (Cu), and Aluminum observed within senile plaques, where they can reach high millimolar concentrations. This metal accumulation accelerates A beta aggregation, enhances A beta-mediated oxidative damage by acting as catalysts for Reactive Oxygen Species ROS) production, and may even drive the aggregation of hyperphosphorylated tau into neurofibrillary tangles (NFTs). The abnormal processing of the Amyloid Precursor Protein APP is the initiating event, and its regulation is directly linked to metal homeostasis, such as the Fe-responsive element IRE in the APP transcript. Given this critical role, disrupting these aberrant metal-peptide interactions via metal chelation therapy has emerged as a promising and rational therapeutic strategy to halt AD progression by reducing beta toxicity, dissolving plaques, and restoring normal metal ion balance in the brain.[4]

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Current drug development for Alzheimer's disease (AD)

Current drug development for Alzheimer's disease (AD) is based on two primary, though often overlapping, hypotheses: the Cholinergic Hypothesis and the Misfolded and Aggregated Protein Hypothesis. The Cholinergic Hypothesis is the most established theory, focusing on the severe loss of cholinergic function contributing to cognitive symptoms. The symptomatic drugs currently available work primarily by this mechanism: Acetylcholinesterase (AChE inhibitors like donepezil, rivastigmine, and galantamine increase the deficient levels of acetylcholine. Additionally, the NMDA type glutamate receptor antagonist memantine is used to manage excitotoxicity. In contrast, the Misfolded and Aggregated Protein Hypothesis is based on the disease's pathological hallmarks: beta-amyloid plaques and neurofibrillary tangles. The text A beta$ Cascade Hypothesis posits that the formation of insulin A beta peptides and subsequent plaques is the initiating event. This led to a focus on inhibiting the enzyme beta-secretase BACE1, which performs the rate-limiting step in A beta generation; however, many BACE1 inhibitors have failed in trials due to side effects, although compounds like Elenbecestat and CN -520$ remain in the clinical pipeline. Both traditional symptomatic treatment and disease-modifying efforts are increasingly incorporating the Multi-Target-Directed Ligands MTDL approach to address the multiple pathological mechanisms simultaneously.[5]

Zooming out: from target proteins to target organelles

The amyloid hypothesis has long guided Alzheimer's disease (AD) research, focusing on reducing amyloid beta (Aβ) production derived from amyloid precursor protein (APP). APP is sequentially cleaved by β-secretase (BACE1) and γ-secretase, with BACE1 acting as the rate-limiting enzyme in Aβ formation and therefore a major drug target. Structural studies of BACE1 enabled design of inhibitors, initially peptide but later replaced by smaller, more membrane-permeable molecules such as GRL-8234 and CTS-21166. However, many inhibitors failed due to poor efficacy in cellular assays, partly because they did not account for BACE1's primary localization and activity in acidic organelles like endosomes and the trans-Golgi network. To address this, researchers developed a membrane-anchored transition-state inhibitor linked to a sterol moiety to enhance endosomal targeting and inhibitory efficiency. In parallel, mitochondrial dysfunction has emerged as another crucial factor in AD pathogenesis, characterized by impaired respiratory chain enzymes (complexes I, III, and IV), increased mitochondrial autophagy, and direct toxicity from soluble Aβ oligomers. Aβ accumulation in mitochondria disrupts the electron transport chain, elevates reactive oxygen species (ROS) levels, and contributes to synaptic damage, creating a vicious cycle that promotes further Aβ production. Since mitochondria are a major source and target of oxidative stress, mitochondria-specific antioxidant strategies have been proposed. Among these, MitoQ—a coenzyme Q10 derivative conjugated to a lipophilic cation triphenylphosphonium—selectively accumulates in mitochondria via the membrane potential. Once inside, it converts to its active reduced form ($MitoQH_2$), neutralizing free radicals directly at their source. MitoQ, currently in Phase II clinical trials, shows promise as a potent therapeutic candidate for mitigating mitochondrial oxidative damage in neurodegenerative diseases such as AD. [6]

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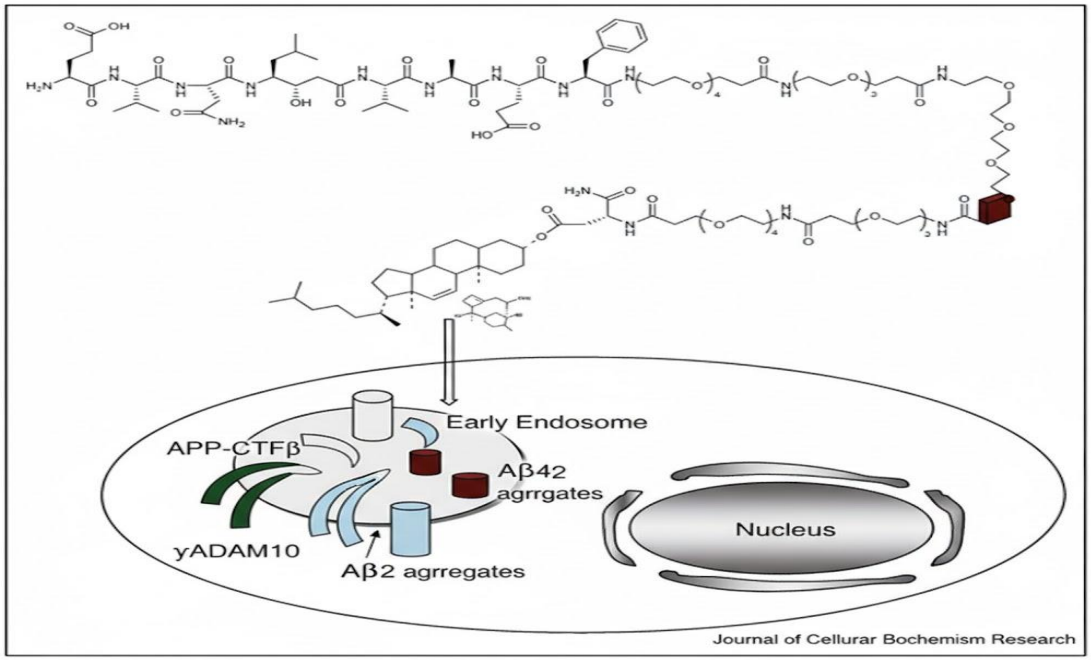

Figure 2 Zooming out: from target proteins to target organelles

Targets Symptomatic Targets

Currently, five medications are approved by the U.S. Food and Drug Administration for Alzheimer's disease (AD) treatment. These drugs provide symptomatic relief without significantly altering disease progression. The main therapeutic targets are neurotransmitter-based. Acetylcholinesterase inhibitors (AChEIs) prevent the breakdown of acetylcholine and are effective throughout AD progression, while memantine, an NMDA receptor antagonist, regulates glutamatergic activity and improves cognition in moderate-to-severe cases. Combined administration of these two classes may offer greater and longer-lasting benefits. Beyond these, several neurotransmitter systems present potential new targets. Nicotinic receptor agonists aim to stimulate the cholinergic system, as nicotinic receptors decline in AD, but clinical results so far have been inconclusive. The GABAergic system, which modulates inhibitory neurotransmission, has also drawn attention; however, trials of both GABAB antagonists and GABAA modulators such as etazolate yielded mixed or limited results, often due to side effects like anxiety or seizures. Another therapeutic avenue involves serotonergic modulation, as several serotonin receptor subtypes (5-HT1A, 5-HT4, 5-HT6) are linked to memory and decline in AD. Some selective agonists and antagonists show cognitive benefits in preclinical studies, with encouraging early clinical results for 5-HT6 antagonists. Histamine H3 receptor antagonists, which enhance levels of various neurotransmitters including acetylcholine and dopamine, are also promising since H3 receptor expression remains stable throughout AD progression, and ongoing trials are testing their efficacy. Additionally, phosphodiesterase inhibitors improve synaptic signaling by activating the CREB pathway and restoring long-term potentiation (LTP); some existing PDE inhibitors, including those used for erectile dysfunction, are being repurposed for AD due to their safety profile. Metabolic enhancement is another strategy, targeting the brain's early hypometabolic state in AD. Although glucose administration alone is ineffective, alternative energy sources like ketogenic substances have improved cognitive symptoms in controlled trials and received FDA approval as medical food. Insulin therapies, particularly intranasal insulin, have demonstrated cognitive improvements as well. Given insulin's role in amyloid degradation and the link between diabetes and AD risk, PPAR-γ agonists such as rosiglitazone were tested, but cardiovascular concerns and lack of efficacy limited their use. Overall, while these symptomatic approaches offer cognitive and functional benefits, they have yet to address the underlying neurodegenerative mechanisms of AD.[7]

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II. MULTIFACTORIAL ASPECTS OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system most prevalent in individuals over 65 years of age. It leads to gradual decline in memory, cognition, motor function, and daily living abilities. Although its exact cause remains unclear, AD is known to result from multiple interconnected biological mechanisms. A major feature is the overproduction and abnormal cleavage of amyloid precursor protein (APP) by β- and γ-secretases, generating amyloid beta (Aβ) fragments, particularly Aβ1-42, which aggregate into neurotoxic amyloid plaques. These plaques, together with hyperphosphorylation of tau proteins that form neurofibrillary tangles, disrupt neuronal structure, impair microtubule stability, and trigger neuronal death. Soluble Aβ oligomers also play a vital role in mitochondrial dysfunction, leading to excessive reactive oxygen species (ROS) production, impaired ATP synthesis, calcium dysregulation, and mitochondrial structural breakdown through the opening of the mitochondrial permeability transition pore (mPTP), ultimately inducing apoptosis. In addition, abnormal regulation of enzymes such as glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (CDK5), and protein phosphatase 2A (PP-2A) further contributes to tau pathology. Oxidative stress is another key aspect, resulting from ROS overproduction, mitochondrial failure, reduced antioxidant defense, and metal ion imbalance. Metals such as copper, zinc, and iron interact with Aβ to promote aggregation and hydrogen peroxide generation, intensifying oxidative damage. Cholesterol levels also influence Aβ production, as high cholesterol favors β-secretase activity and amyloidogenic APP processing, while lower levels favor α-secretase activation; thus, statins have shown potential benefit in modulating this pathway. Chronic neuroinflammation, driven primarily by activated microglia, leads to the release of cytokines and neurotoxins that accelerate neuronal degeneration. Given the multifactorial nature of AD involving amyloid toxicity, tau pathology, oxidative stress, metal dyshomeostasis, and neuroinflammation, single-target therapies have proven inadequate. This realization has led to the emergence of multi-target directed ligand strategies, which design molecules capable of simultaneously modulating multiple disease pathways. Through molecular hybridization, these compounds seek to achieve improved efficacy and broader therapeutic benefit, offering hope for more effective treatments and potentially a cure for Alzheimer's disease in the future.[8]

III. ALZHEIMER'S DISEASE: INVOLVEMENT OF SEVERAL GENES

Mutations and polymorphisms in several genes located on chromosomes 1, 10, 14, 19, and 21 are implicated in the development of Alzheimer's disease (AD). Research has identified point mutations in at least nine genes that contribute to or cause the disorder. Among them, mutations in three genes—amyloid precursor protein (APP) on chromosome 21, presenilin 1 (PS1) on chromosome 14, and presenilin 2 (PS2) on chromosome 1—are dominantly inherited and lead to familial AD (FAD) with nearly complete penetrance, typically manifesting in early-onset forms between the ages of 40 and 60. The apolipoprotein E (APOE) gene on chromosome 19 is a major risk factor for late-onset AD, with the ε4 allele significantly increasing the likelihood and lowering the age of onset compared to the ε3 allele. Additional genetic associations have been identified with several loci on chromosome 10, including those coding for the insulin-degrading enzyme (IDE) and αT-catenin, both implicated in Aβ metabolism and clearance. IDE, in particular, has been linked to plasma Aβ42 levels, suggesting its role in amyloid regulation. Other genes such as α-2 macroglobulin on chromosome 12, urokinase-type plasminogen activator (UPA) on chromosome 10, and the angiotensin-converting enzyme (ACE) on chromosome 17 have been associated with late-onset AD. Interestingly, ACE can degrade Aβ, inhibit its aggregation and fibril formation, and reduce its cytotoxicity, making it a significant modulator in AD pathology. αT-catenin is also emerging as a potential contributor to neurodegenerative mechanisms in late-onset AD. Genome-wide association and linkage studies have supported these findings, identifying multiple susceptibility loci, particularly on chromosome 10q. Despite these advances, the complexity of AD genetics and its increasing prevalence in aging populations indicate that additional, as yet unidentified, genetic and environmental risk factors likely play crucial roles in disease onset and progression.[9]

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Stages/ Onset of AD	Major Gene	Chromosome
Early (~40s and 50s)	PS1	14q24
Early (~50s)	PS2	1q31-42
Early (~50s)	APP	21q21
Late-onset	APOE (ε4 earlier than e3)	19q13
Late-onset	α-2 macroglobulin	12p13
Late-onset	IDE	10q24
Late-onset	UPA	10q24
Late-onset	ACE	17q23
Late onset	αT-catenin	10q21

Table 1. Selected Genes Implicated in Alzheimer's Disease.

Alzheimer's Drug Targets

Multiple molecular targets are currently being explored for Alzheimer's disease (AD) drug discovery, encompassing enzymes, receptors, transcription factors, and peptides involved in amyloid processing, neurotransmission, oxidative stress, and inflammation. β-secretase (BACE1), a type 1 transmembrane aspartic protease, plays a critical role in generating amyloid beta (Aβ) peptides from amyloid precursor protein (APP); its increased expression in AD brains makes it a major therapeutic target. Similarly, γ-secretase, a multi-subunit protease complex containing presenilin-1, contributes to Aβ formation, making it another focus of inhibition studies. Butyrylcholinesterase (BuChE), responsible for hydrolyzing choline esters, shows altered activity in AD and is linked to amyloid and neurofibrillary tangle formation. Calcium-permeable AMPA receptors (CP-AMPARs), involved in synaptic plasticity, are implicated in synaptic dysfunction, while calcitonin gene-regulated peptide (CGRP) enhances memory and learning processes. Phosphodiesterases (PDEs), particularly PDE2A, PDE5, and PDE9, regulate cAMP and cGMP signaling involved in memory formation. Muscarinic acetylcholine receptors (mAChRs), especially M1 and M2 subtypes, influence cholinergic signaling, tau phosphorylation, and synaptic responses. Dopamine D2 receptors, part of the GPCR family, play roles in cognition and motor control; their activation via levodopa reduces Aβ plaques in animal models. GABA receptors act as inhibitory neurotransmitters, with their decline correlating with AD-related neuronal loss. Nuclear factor E2-related factor 2 (Nrf2) regulates antioxidant and detoxifying genes, and its activation protects against Aβ toxicity. Metabotropic glutamate receptor 5 (mGluR5) is another potential target, as it mediates excitatory signaling and interacts with Aβ42 and prion proteins. Other crucial targets include N-myc downstream-regulated gene 2 (NDRG2), linked to brain aging; serotonin 5-HT6 receptors, which modulate cognition, neurogenesis, and neurotransmitter systems; and protein tyrosine phosphatase 1B (PTP1B), involved in neuroinflammation and synaptic regulation. Monoamine oxidase-B (MAO-B), associated with oxidative stress and reactive oxygen species generation, is upregulated in AD brains, while NAD(P)H quinone oxidoreductase 1 (NQO1) plays a key role in redox regulation and may provide protection against oxidative imbalance. Neurotrophic receptor tyrosine kinase 1 (NTRK1), encoding the TrkA receptor for nerve growth factor, is vital for neuronal survival but is downregulated in AD. APP itself, located on chromosome 21, is central to amyloidogenic and non-amyloidogenic processing pathways, forming the basis of the amyloid hypothesis. Peroxisome proliferator-activated receptor-γ (PPAR-γ) influences lipid metabolism, glucose regulation, and amyloid clearance, offering metabolic and neuroprotective benefits.M Chemokine receptor CCR5 modulates neuroinflammation through cytokine signaling, while nicotinic acetylcholine receptors (nAChRs) contribute to cognitive processes but undergo functional alteration in AD brains. Angiotensin II receptors, particularly AT1, mediate neuroinflammatory and neuroprotective mechanisms, with angiotensin receptor blockers (ARBs) showing

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potential therapeutic value. Non-amyloid-beta component precursor (NACP), a presynaptic protein related to α-synuclein, promotes amyloid formation. Stress-activated c-Jun N-terminal kinases (JNKs), especially JNK-3, induce tau phosphorylation and oxidative stress, while DJ-1 (PARK7) serves as a neuroprotective antioxidant and chaperone protein, making it another promising target. Finally, triggering receptor expressed on myeloid cells 2 (TREM2), located on microglia and macrophages, regulates immune responses around amyloid plaques, with genetic variants strongly linked to AD risk. Collectively, these diverse targets reflect the multifactorial nature of AD and offer multiple avenues for the development of next-generation therapeutics that address both the symptoms and underlying pathology of the disease.[10]

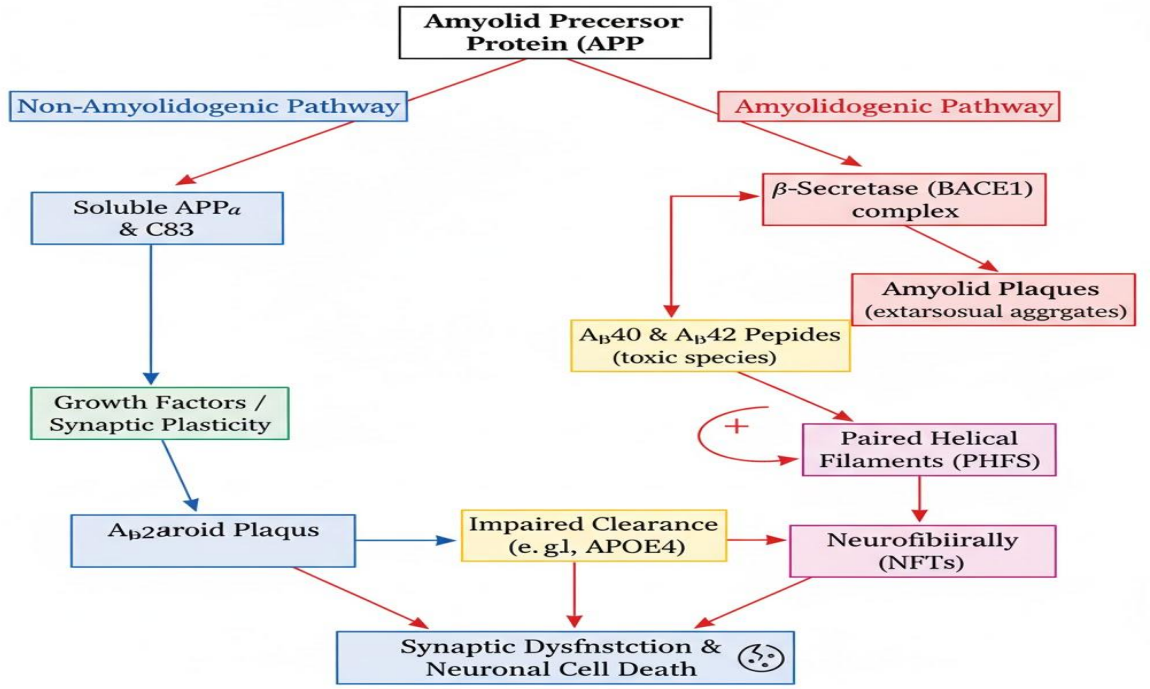

Figure 3: Hypothetical model of AD pathophysiology (Pathophysiological pathway and Amyloidgenic pathway)

Novel Targets and Investigational Drugs for Disease Modification

Inflammation plays a critical role in the onset and progression of Alzheimer's disease (AD). The process involves activation of microglial cells, release of pro- and anti-inflammatory cytokines, and interaction with other immune cells in the brain and periphery. Recent advancements have revealed inflammation as a major therapeutic target in AD, following amyloid- and neurotransmitter-based strategies. Numerous drugs aimed at modulating neuroinflammation are in clinical development. Among Phase 3 candidates, masitinib, a tyrosine kinase inhibitor targeting c-kit, regulates mast cell–derived inflammatory mediators and has shown improvement in spatial learning and synaptic markers in preclinical models. NE3107, which inhibits the NF-κB/ERK pathway, reduces production of inflammatory cytokines, oxidative stress, amyloid beta (Aβ), and tau phosphorylation while improving insulin sensitivity. Semaglutide, a glucagon-like peptide-1 agonist, primarily used for diabetes, exhibits anti-inflammatory benefits that are associated with reduced dementia risk. In Phase 2 trials, several immunomodulatory and anti-inflammatory agents are under investigation. AL002, a monoclonal antibody that agonizes the TREM2 receptor, promotes microglial activation and Aβ clearance. The Bacillus Calmette–Guérin (BCG) vaccine, known for its immunostimulatory effects, improved cognition and immune regulation in AD mouse models. Baricitinib, a Janus kinase (JAK) inhibitor, suppresses the JAK-STAT pathway, reducing proliferation of immune cells and neuroinflammation. Canakinumab, an anti-IL-1β

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antibody, targets a master regulatory cytokine linked to neuronal injury around Aβ plaques. Daratumumab, an anti-CD38 antibody, demonstrated reduced Aβ accumulation and improved memory in preclinical studies. Dasatinib combined with quercetin works as a senolytic therapy eliminating senescent cells and attenuating amyloid- and tau-related pathology. Other agents in Phase 2 include lenalidomide, which suppresses proinflammatory cytokines and upregulates IL-10; L-serine, a safe dietary amino acid that restores synaptic function and long-term potentiation; and montelukast, a leukotriene receptor antagonist that mitigates neuroinflammation and neuronal loss. Pepinemab, targeting semaphorin 4D (SEMA4D), inhibits glial activation and supports glial function. Proleukin, a recombinant interleukin-2 (IL-2), helps restore immune balance through activation of regulatory T cells. Rapamycin, an inhibitor of the mTOR pathway, reduces Aβ and phosphorylated tau levels via autophagy and insulin-degrading enzyme upregulation. Sargramostim, a recombinant GM-CSF, enhances microglial-mediated amyloid clearance and improves cognition. Senicapoc, a KCa3.1 channel inhibitor, reduces neuroinflammation by controlling microglial and macrophage activity. TB006, an anti-galectin-3 antibody, modulates TREM2 and toll-like receptor pathways to decrease amyloid pathology. Vaccination and antiviral strategies have also emerged as potential interventions. The Tdap vaccine, which protects against tetanus, diphtheria, and pertussis, shows epidemiological evidence for reducing dementia risk by approximately 42 percent. Valacyclovir, an antiviral agent effective against herpes simplex virus (HSV), is being assessed for its ability to mitigate inflammation-related neurodegeneration possibly triggered by viral infection. XPro1595, an inhibitor of soluble tumor necrosis factor (sTNF), has demonstrated reduction of inflammatory cytokines, restoration of synaptic function, and decreased amyloid load in preclinical models. Together, these anti-inflammatory and immunomodulatory approaches represent one of the most active and promising areas in AD drug development, aiming not only to suppress harmful inflammation but also to restore immune balance and enhance amyloid clearance.[11]

Alzheimer's disease drug screening, **network analysis**, and **transcriptome analysis**

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide, affecting around 6% of people aged 65 and older. Its prevalence is rapidly increasing due to population aging, with projections estimating over 100 million cases globally by 2050. AD not only causes severe cognitive and functional decline but also poses a major socioeconomic burden, with U.S. healthcare costs expected to reach one trillion dollars annually within three decades. Currently, FDA-approved drugs—cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the NMDA receptor antagonist memantine—only provide symptomatic relief by enhancing neurotransmission or regulating glutamate levels but do not halt disease progression. Antibody-based therapies targeting amyloid beta and tau proteins have also shown limited success due to adverse effects and lack of cognitive improvement. Given the 99% failure rate of clinical trials for new AD drugs, drug repositioning—repurposing existing approved drugs for new therapeutic uses—has emerged as a promising alternative. This strategy reduces cost, time, and safety risks compared to developing new compounds. In this study, researchers identified potential AD drug candidates through a systematic computational pipeline integrating genomic, proteomic, and pharmacological data. They collected AD-related genes from major databases (KEGG, OMIM, and Phagemid), resulting in 561 genes, and compiled 5595 drugs with known targets from Drug Bank. Using a human protein–protein interaction (PPI) network of over 493,000 interactions, the proximity between drugs and AD-related genes was calculated to identify drugs closely associated with AD pathways. Further, drug-induced gene expression profiles from the LINCS L1000 dataset were analyzed using Inverted Gene Set Enrichment Analysis (IGSEA), an approach that evaluates whether drug treatments can reverse AD-associated gene expression patterns. Drugs showing statistically significant reversal effects (FDR < 0.25) were identified as candidate therapeutics for AD. This network-based integrated approach highlights computational drug repositioning as an efficient and effective method to accelerate AD drug discovery.[12]

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Emerging Therapeutic Approaches for Alzheimer's Disease

Novel treatment strategies for Alzheimer's disease (AD) focus on multi-target approaches addressing amyloid beta (Aβ) and tau pathology, oxidative stress, mitochondrial dysfunction, neuroinflammation, and synaptic failure. Current FDA-approved drugs—donepezil, galantamine, rivastigmine, tacrine, and memantine—only slow disease progression without reversing cognitive decline. Ongoing trials for monoclonal antibodies such as aducanumab, crenezumab, and gantenerumab aim to enhance Aβ clearance but face challenges due to limited efficacy and safety issues. Recent preclinical strategies explore new acetylcholinesterase inhibitors like 4-(1-benzylpiperidin-4-yl) thiosemicarbazone (BPT) analogues and Kojo tacrine, which show multitarget effects against oxidative stress, metal ion imbalance, and autophagy impairment. The compound A03 acts as a novel NMDA receptor antagonist that also enhances SIRT1 expression, potentially reducing tau pathology and oxidative damage. Endothelin B receptor agonist IRL-1620 improves Aβ clearance, blood flow, and neurogenesis. Mitochondrial-targeted drugs like DDQ restore mitochondrial integrity and synaptic activity by regulating fission-fusion dynamics and reducing Aβ-DRP1 interactions. Compounds targeting autophagy, such as lanthionine ketamine-ethyl ester (LKE), normalize CRMP2 phosphorylation and enhance protein clearance, while CDK5 inhibitors help regulate tau and CRMP2 hyperphosphorylation. These emerging therapies, combining neuroprotective, antioxidant, and anti-aggregative mechanisms, represent promising directions for developing effective and disease-modifying AD treatments.[13]

Clinical trials of new drugs for Alzheimer disease

Anti-amyloid therapy in Alzheimer's disease (AD) aims to reduce amyloid beta (Aβ) accumulation through β- and γ-secretase inhibition, immunotherapy, or enhanced Aβ degradation. However, many phase 3 trials, including those involving BACE inhibitors (verubecestat, atabecestat, lanabecestat) and antibodies like solanezumab and bapineuzumab, have failed due to inefficacy or worsened cognition. Aducanumab showed mixed results, with later analyses suggesting modest cognitive improvement and amyloid reduction in early-stage AD, leading to its conditional approval. Current trials focus on early or preclinical stages, as late intervention shows little benefit. Novel agents such as GV-971, which modulates gut microbiota and inhibits Aβ aggregation, and crenezumab and gantenerumab are under evaluation. Complementary strategies include anti-tau immunotherapies (TRx0237, AADvac1, zagotenemab), neuroprotective drugs targeting mitochondrial function and glutamate toxicity (troriluzole, Ginkgo biloba extract), and anti-inflammatory agents like pioglitazone and azeliragon. Cognitive enhancers (intepirdine, EVP-6124) and therapies for behavioral symptoms (AXS-05, aripiprazole, suvorexant) are being explored to improve quality of life. Overall, new research emphasizes early intervention, multi-target therapy, and disease-modifying approaches to slow AD progression rather than reverse established damage.[14]

Advanced AD Pharmacological Studies

Currently approved Alzheimer's disease (AD) drugs target either acetylcholinesterase (AChE) or the N-methyl-D-aspartate (NMDA) receptor. AChE inhibitors such as tacrine, donepezil, rivastigmine, and galantamine are used for mild to moderate AD, while memantine, an NMDA receptor antagonist, treats moderate to severe cases. These drugs work by enhancing cholinergic signaling or reducing glutamate-induced excitotoxicity. Donepezil selectively inhibits AChE, rivastigmine blocks AChE active sites linked to plaque formation, and galantamine also stimulates nicotinic receptors to increase acetylcholine release. Although they modestly slow cognitive decline, combination therapy with donepezil and memantine provides additional benefit. Common side effects include nausea, vomiting, and diarrhea, while tacrine was discontinued due to liver toxicity. Despite their limited efficacy, these drugs remain widely prescribed, with donepezil being the most affordable and frequently used treatment for AD.[15]

IV. CONCLUSION

Alzheimer's disease (AD) remains a major global health challenge with no curative treatment currently available. Its complex pathology, involving amyloid beta aggregation, tau neurofibrillary tangles, oxidative stress, mitochondrial

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dysfunction, metal ion imbalance, and neuroinflammation, highlights the need for multi-target therapeutic strategies. Existing drugs such as cholinesterase inhibitors and memantine provide only symptomatic relief without halting disease progression. Recent research has shifted toward disease-modifying approaches, including anti-amyloid and anti-tau immunotherapies, metabolic and mitochondrial protectants, and anti-inflammatory agents. Advances in computational drug repositioning and molecular hybridization are accelerating the discovery of promising candidates. Ultimately, early intervention, personalized multi-target treatments, and combination therapies offer the best potential to slow or prevent AD progression and improve patient outcomes.

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