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Alzheimer's Disease in the Age of Precision Medicine: Advances in Pathophysiology, Clinical Management and Therapeutic Strategies

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ABSTRACT

Aim of the study: The aim of this study is to provide a comprehensive review of recent advancements in Alzheimer's disease (AD), focusing on its complex pathophysiology, diagnostic methods, and emerging therapeutic strategies.

Materials and methods: A detailed analysis of recent literature was conducted, reviewing major pathophysiological mechanisms including amyloid-beta accumulation, tau pathology, mitochondrial dysfunction, and chronic neuroinflammation. Diagnostic methods were evaluated, emphasizing biomarker-based approaches and the integration of artificial intelligence (AI) for improved precision in early detection.

Main results: The analysis revealed that currently approved therapies, such as cholinesterase inhibitors and NMDA receptor antagonists, provide only symptomatic relief without significantly slowing disease progression. New therapeutic approaches targeting multiple pathways, including monoclonal antibodies against amyloid and tau, mitochondrial modulators, anti-inflammatory drugs, and gene therapy, show potential but face clinical validation challenges. AI-based technologies have significantly enhanced diagnostic accuracy, allowing personalized patient management and better disease staging.

Conclusions: The future management of Alzheimer's disease will likely require a multimodal strategy integrating advanced diagnostic tools, personalized therapies, and targeted interventions addressing diverse disease mechanisms. Overcoming current research

limitations and healthcare accessibility issues will be critical to translating these innovations into effective clinical practice.

Keywords: Alzheimer's disease, amyloid, tau, mitochondrial function, neuroinflammation, biomarkers, monoclonal antibodies, neuroprotection, AI, personalized medicine

1. INTRODUCTION

1.1. DEFINITION AND EPIDEMIOLOGY OF ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, accounting for 60–80% of all dementia cases (Safiri i wsp. 2024). It is characterized by gradual cognitive decline, including memory loss, impaired judgment, and personality changes, ultimately leading to complete dependence on caregivers.

The disease primarily affects older adults, with age being the strongest risk factor. However, genetic predisposition—especially the APOE ε4 allele—and lifestyle factors, such as diet, physical activity, and cardiovascular health, also play significant roles (Rostagno 2022).

Epidemiological data indicate that over 50 million people worldwide suffer from AD, with projections suggesting this number will rise to 152 million by 2050 (Safiri i wsp. 2024). The incidence of AD doubles approximately every five years after age 65. Women are at a higher risk than men, possibly due to hormonal factors (estrogen decline post-menopause) and genetic susceptibility (Lei i wsp. 2021). The growing prevalence of AD places an immense burden on healthcare systems, with global costs exceeding $1 trillion annually (Scheltens i wsp. 2021).

1.2. PATHOGENESIS OF ALZHEIMER'S DISEASE – KEY MECHANISMS

Alzheimer's disease pathogenesis is a highly complex process that involves multiple interacting mechanisms. While the amyloid cascade hypothesis has historically been the dominant framework for understanding the disease, recent research highlights the role of tau pathology, mitochondrial dysfunction, metal ion dysregulation, and chronic neuroinflammation as equally important contributors to disease progression (Rostagno 2022) (Safiri i wsp. 2024). These mechanisms act synergistically, leading to widespread neuronal damage and cognitive decline.

A key hallmark of Alzheimer's disease is the abnormal aggregation of beta-amyloid peptides, which are derived from the amyloid precursor protein through abnormal cleavage. These

peptides accumulate in the extracellular space, forming senile plaques that trigger oxidative stress, synaptic dysfunction, and neurotoxic signaling cascades (Rostagno 2022). The disruption of neuronal homeostasis caused by amyloid plaques accelerates neurodegeneration and leads to cognitive impairment. An imbalance between beta-amyloid production and clearance has been identified as a major pathological feature of Alzheimer's disease, with positron emission tomography imaging studies revealing that amyloid-beta accumulation begins decades before clinical symptoms emerge (Jack i wsp. 2018). This finding has reinforced the importance of early intervention strategies targeting amyloid pathology. However, recent studies challenge the notion that amyloid-beta is the sole driver of Alzheimer's disease and suggest that a more multifactorial approach is necessary for understanding and treating the disease (Lei i wsp. 2021).

Beyond amyloid-beta accumulation, tau pathology plays a crucial role in Alzheimer's disease progression. Tau protein, which normally stabilizes microtubules in neurons, becomes hyperphosphorylated in the disease state, leading to the formation of neurofibrillary tangles (Breijyeh i Karaman 2020). These tangles disrupt axonal transport, impair neuronal function, and contribute to synaptic failure and widespread neuronal loss. Unlike amyloid pathology, tau aggregation correlates more closely with cognitive decline and follows a well-defined progression, spreading from the entorhinal cortex to the neocortex as the disease advances (Jack i wsp. 2018). This strong association with disease progression has led to an increased focus on tau-targeting therapies as a promising avenue for intervention (Safiri i wsp. 2024).

Mitochondrial dysfunction represents another major factor in Alzheimer's disease pathogenesis. Mitochondria, responsible for generating cellular energy in the form of adenosine triphosphate, show early signs of dysfunction in Alzheimer's disease. Amyloid-beta and tau proteins contribute to oxidative stress, impair ATP production, and disrupt mitochondrial homeostasis, ultimately leading to synaptic failure and neuronal apoptosis (Lei i wsp. 2021). These disruptions further exacerbate neurodegeneration, highlighting the need for mitochondrial-targeted therapeutic strategies (Safiri i wsp. 2024).

In addition to these pathological mechanisms, chronic neuroinflammation has been identified as a key driver of disease progression. Microglia, the brain's resident immune cells, initially play a protective role by attempting to clear amyloid-beta deposits. However, in Alzheimer's disease, prolonged activation of microglia results in excessive release of pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-alpha. This sustained

inflammatory response creates a toxic environment that accelerates neuronal damage and synaptic dysfunction. Instead of effectively clearing amyloid deposits, chronically activated microglia contribute to neurodegeneration by amplifying inflammatory signaling pathways, further fueling the progression of the disease.

Together, these interconnected pathological mechanisms underscore the complexity of Alzheimer's disease and reinforce the need for multi-targeted therapeutic approaches that address amyloid aggregation, tau pathology, mitochondrial dysfunction, and neuroinflammation simultaneously. Emerging research continues to explore novel strategies that integrate these diverse aspects of the disease to develop more effective treatment options.

1.3. WHY IS EFFECTIVE AD THERAPY DIFFICULT TO DEVELOP?

Despite extensive research, there is currently no cure for Alzheimer's disease, and several factors contribute to the challenges associated with developing effective treatments. One of the primary obstacles is the heterogeneous pathophysiology of the disease, which involves multiple interconnected mechanisms and necessitates multi-targeted therapeutic approaches (Jack i wsp. 2018). Additionally, late diagnosis remains a significant barrier, as Alzheimer's pathology begins decades before clinical symptoms emerge, making early intervention difficult (Safiri i wsp. 2024).

The failure of amyloid-targeting therapies further complicates treatment development. Most anti-amyloid monoclonal antibodies, such as aducanumab, have not demonstrated meaningful clinical benefits in trials, suggesting that amyloid clearance alone is insufficient to halt disease progression (Jack i wsp. 2018). Another major challenge is the blood-brain barrier, which prevents many potential drugs from effectively reaching the brain, thereby limiting their therapeutic efficacy (Breijyeh i Karaman 2020).

In addition to these biological constraints, individual variability plays a crucial role in treatment outcomes. Genetic factors, such as the presence of the APOE ε4 allele, as well as lifestyle influences, significantly impact disease progression and the response to treatment (Safiri i wsp. 2024). Given these challenges, research is increasingly shifting towards alternative therapeutic strategies, including tau-targeting drugs, neuroprotective agents, and anti-inflammatory therapies. In parallel, lifestyle interventions aimed at reducing risk factors are being explored as complementary approaches to disease management (Scheltens i wsp. 2021).

2. CURRENTLY APPROVED THERAPIES FOR ALZHEIMER'S DISEASE

AD remains an incurable neurodegenerative disorder. Modern medicine uses pharmacological treatments to provide symptomatic relief and slow functional decline. Currently, we work with two major drug classes for AD management:

- Cholinesterase inhibitors (ChEIs)
- N-methyl-D-aspartate (NMDA) receptor antagonists

These drugs address neurotransmitter imbalances, but do not stop neurodegeneration (Breijyeh i Karaman 2020).

2.1. Overview of Available Medications

Pharmacological treatment primarily enhances cholinergic neurotransmission and modulates glutamate activity, compensating for neuronal dysfunction but not preventing Aβ or tau pathology (Safiri i wsp. 2024).

2.1.1.CHOLINESTERASE INHIBITORS (DONEPEZIL, RIVASTIGMINE, GALANTAMINE)

ChEIs increase acetylcholine (ACh) availability by inhibiting acetylcholinesterase. These drugs can be used to delay symptoms progression in mild-to-moderate AD (Breijyeh i Karaman 2020).

Donepezil is approved for all AD stages, improves cognition and function, but benefits do decline over time. Rivastigmine also inhibits butyrylcholinesterase, available in patch form to reduce GI side effects. Galantamine modulates nicotinic receptors, enhancing cholinergic function uniquely.

ChEIs are most effective in early stages of disease, with limited benefits in advanced AD (Safiri i wsp. 2024).

2.1.2. NMDA RECEPTOR ANTAGONIST (MEMANTINE)

Memantine blocks excessive glutamate activity, reducing excitotoxicity and neuronal death. It is approved for moderate-to-severe AD, often combined with ChEIs for better symptom control (Breijyeh i Karaman 2020).

2.2. FUTURE DIRECTIONS IN AD TREATMENT

- Disease-modifying therapies (DMTs) – Monoclonal antibodies targeting Aβ (lecanemab, donanemab) (Jack i wsp. 2018).
- Tau-targeting drugs – Novel treatments for preventing NFT formation (Lei i wsp. 2021).
- Gene therapy & regenerative medicine – Stem cell-based interventions and genetic risk modulation (Safiri i wsp. 2024).

A holistic approach combining pharmacological and lifestyle interventions remains key to managing AD effectively (Safiri i wsp. 2024).

3.1. DRUGS TARGETING BETA-AMYLOID

Alzheimer's disease (AD) has long been associated with the accumulation of amyloid-beta (Aβ) plaques, leading to neuronal dysfunction and cognitive decline. The amyloid cascade hypothesis, first proposed in the 1990s, suggests that the overproduction or insufficient clearance of Aβ triggers a cascade of events that result in neurodegeneration(Rahman i wsp. 2023). This hypothesis has driven the development of therapies targeting Aβ, particularly monoclonal antibodies that aim to remove amyloid plaques and strategies designed to reduce Aβ production(Söderberg i wsp. 2023).

3.1.1. ADUCANUMAB AND OTHER MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAbs) targeting Aβ are among the most extensively studied disease-modifying treatments for AD. These antibodies are designed to bind aggregated Aβ and facilitate its clearance via the immune system, particularly through microglial phagocytosis(Hitt i wsp. 2023).

Aducanumab was developed by Biogen and Eisai. It is a human monoclonal antibody that selectively binds aggregated forms of Aβ. In 2021, the FDA granted accelerated approval for aducanumab based on its ability to reduce amyloid plaques, despite ongoing controversy regarding its clinical efficacy(Rahman i wsp. 2023).

- Mechanism of action: Aducanumab targets soluble and insoluble Aβ aggregates, promoting their clearance by activating microglia(Söderberg i wsp. 2023).
- Clinical trial results: Initial trials (EMERGE and ENGAGE) showed conflicting results. While EMERGE demonstrated a modest cognitive benefit, ENGAGE failed to confirm this effect(Malhis i wsp. 2021)】.

- Controversy: The approval was based on amyloid plaque reduction rather than direct cognitive improvement, leading to criticism from the scientific community and limited insurance coverage (Rahman i wsp. 2023).

Several other anti-Aβ monoclonal antibodies are in development or have undergone clinical trials:

- Lecanemab: Demonstrated a statistically significant slowing of cognitive decline in phase 3 CLARITY-AD trials, leading to FDA approval in 2023(Swanson i wsp.2021).
- Donanemab: Targets Aβ protofibrils, aiming to prevent plaque formation. It has shown promising but limited cognitive benefits(Hitt i wsp. 2023).
- Gantenerumab: Initially developed by Roche, this antibody failed to meet primary endpoints in late-stage trials, questioning its therapeutic potential(Malhis i wsp. 2021)】

Despite these advances, monoclonal antibody treatments do not reverse AD but may slow its progression, especially if administered at an early stage(Aggidis i wsp. 2024).

3.1.2. STRATEGIES TO REDUCE AMYLOID PRODUCTION

Beyond clearing existing plaques, another approach to Alzheimer's disease therapy focuses on reducing the production of amyloid-beta at its source. Amyloid-beta is generated through the sequential cleavage of amyloid precursor protein by beta-secretase (BACE1) and gamma-secretase, making these enzymes potential therapeutic targets (Aggidis i wsp. 2024). Initially, BACE1 inhibitors were developed to block amyloid-beta formation; however, clinical trials revealed that these drugs led to cognitive worsening and off-target effects, ultimately resulting in their failure (Malhis i wsp. 2021). Similarly, gamma-secretase inhibitors showed promise but were found to have unacceptable toxicity profiles, likely due to their interference with Notch signaling, a critical pathway in cell differentiation (Hitt i wsp. 2023).

Given the challenges associated with direct enzyme inhibition, newer strategies have shifted toward modulating amyloid precursor protein processing to promote non-amyloidogenic pathways. This approach focuses on enhancing alpha-secretase activity, which prevents amyloid-beta formation by favoring an alternative cleavage process (Malhis i wsp. 2021). Certain natural compounds, such as quercetin and resveratrol, are currently being investigated for their potential to stimulate non-amyloidogenic amyloid precursor protein processing (Khan i wsp. 2019).

Another emerging target in Alzheimer's disease therapy is apolipoprotein E, particularly the ε4 allele, which is a major genetic risk factor for the disease and plays a key role in amyloid-beta aggregation and clearance (Aggidis i wsp. 2024). Recent research suggests that modulating lipid metabolism could help reduce amyloid-beta deposition, providing a novel avenue for therapeutic intervention (Hitt i wsp. 2023).

3.2. DRUGS TARGETING TAU PROTEIN

While amyloid-beta (Aβ) accumulation has been a central focus in Alzheimer's disease (AD) research, growing evidence suggests that tau pathology plays an equally critical role in neurodegeneration. Tau protein is responsible for stabilizing microtubules, but in AD, it becomes hyperphosphorylated, leading to the formation of neurofibrillary tangles (NFTs) that disrupt neuronal function and contribute to cell death (Hitt i wsp. 2023) (Malhis i wsp. 2021). Unlike Aβ, tau pathology correlates more strongly with cognitive decline, making it a compelling therapeutic target (Aggidis i wsp. 2024).

3.2.1. ANTI-TAU ANTIBODIES

One of the leading strategies for tau-targeting therapies involves monoclonal antibodies designed to clear pathological tau or prevent its spread. These antibodies work by binding to abnormal tau forms, facilitating microglial clearance or preventing cell-to-cell propagation (Suzuki i wsp. 2024) (Hitt i wsp. 2023).

- Gosuranemab (Biogen): Designed to target extracellular tau, this antibody failed to show cognitive benefits in phase 2 trials, leading to its discontinuation (Hitt i wsp. 2023).
- Tilavonemab (AbbVie): Initially promising, but also failed to meet its primary endpoint in clinical trials (Aggidis i wsp. 2024).
- Semorinemab (Genentech/Roche): Despite showing some reduction in tau pathology, its cognitive benefits were minimal, raising questions about whether extracellular tau clearance alone is sufficient (Suzuki i wsp. 2024).
- Zagotenemab (Lilly): Targeted aggregated tau but was ultimately ineffective in slowing disease progression, reinforcing the need for better tau-directed approaches (Malhis i wsp. 2021).

While anti-amyloid monoclonal antibodies have reached clinical use, anti-tau antibodies have largely failed in trials, suggesting that either tau pathology is a downstream effect of other pathological processes or that alternative mechanisms must be targeted (Hitt i wsp. 2023).

3.2.2. TAU AGGREGATION INHIBITORS

Another approach to tau therapy focuses on preventing the aggregation of hyperphosphorylated tau, thereby stopping the formation of NFTs (Aggidis i wsp. 2024) (Malhis i wsp. 2021).

Key Tau Aggregation Inhibitors:

- Methylthioninium chloride (Rember®) and LMTM (TauRx Therapeutics):
    - Initially, methylene blue derivatives showed potential in disrupting tau fibrils. However, clinical trials failed to demonstrate clear cognitive improvements, likely due to bioavailability issues (Aggidis i wsp. 2024).
- Anle138b:
    - A small molecule capable of penetrating the blood-brain barrier, Anle138b has shown promising effects in preclinical models, reducing tau aggregation and neurotoxicity (Malhis i wsp. 2021).

Challenges and Future Directions:

- The exact mechanism of tau propagation remains unclear, making it difficult to design effective inhibitors (Hitt i wsp. 2023).
- Tau pathology might be secondary to other pathological events, meaning that targeting it directly may be insufficient (Suzuki i wsp. 2024).
- Combination therapies, integrating anti-tau and anti-amyloid approaches, may be necessary for meaningful clinical benefits (Malhis i wsp. 2021).

3.3. NEUROPROTECTIVE THERAPIES

As current pharmacological strategies targeting amyloid-beta (Aβ) and tau have yielded limited clinical success, an alternative approach focuses on neuroprotection. This strategy aims to support neuronal function, enhance synaptic plasticity, and prevent further neurodegeneration in Alzheimer's disease (AD) (Yelanchezian i wsp. 2022) (Khan i wsp. 2019) (Zheng i wsp. 2022).

Neuroprotection involves stimulating neuronal resilience, promoting synaptic repair, and counteracting oxidative stress and inflammation (Wang i wsp. 2022). Several classes of neuroprotective compounds are being investigated, including drugs that enhance neuroplasticity, synaptic function, and metabolism.

3.3.1. DRUGS AFFECTING NEUROPLASTICITY

Neuroplasticity, defined as the brain's ability to reorganize and form new neural connections, plays a crucial role in cognitive resilience (Yelanchezian i wsp. 2022). In Alzheimer's disease, synaptic dysfunction occurs before neuronal loss, making interventions that enhance neuroplasticity a promising therapeutic strategy (Wang i wsp. 2022). Among the potential neuroprotective agents, caffeine has been extensively studied for its cognitive benefits, particularly in mitigating age-related cognitive decline. It acts by blocking adenosine receptors, which enhances neurotransmission and reduces neuroinflammation (Yelanchezian i wsp. 2022). Epidemiological studies suggest that caffeine consumption is associated with a lower risk of developing Alzheimer's disease. Furthermore, caffeine has been shown to modulate tau phosphorylation, potentially preventing the formation of neurofibrillary tangles (Yelanchezian i wsp. 2022). It also increases brain-derived neurotrophic factor levels, which supports synaptic plasticity and cognitive function (Wang i wsp. 2022). Although caffeine is widely available and easily accessible, its long-term efficacy in preventing Alzheimer's disease remains under investigation.

Another promising avenue of research involves flavonoid-based therapies, particularly quercetin, which has been proposed as a natural neuroprotective compound due to its antioxidant and anti-inflammatory properties (Khan i wsp. 2019). Quercetin has been shown to enhance synaptic plasticity by modulating the MAPK and PI3K signaling pathways, both of which are disrupted in Alzheimer's disease (Khan i wsp. 2019). Additionally, it plays a role in reducing oxidative stress and neuroinflammation, contributing to overall brain health (Wang i wsp. 2022). However, despite its potential, challenges such as limited bioavailability and difficulty in crossing the blood-brain barrier remain obstacles in the widespread clinical application of flavonoid-based therapies (Khan i wsp. 2019).

3.3.2. STIMULATING SYNAPTIC FUNCTION

Synaptic dysfunction is a hallmark of AD, leading to impaired neuronal communication and cognitive deficits (Wang i wsp. 2022). Strategies aimed at preserving synaptic health may offer disease-modifying benefits. Originally developed as an antidiabetic drug, metformin has recently emerged as a potential neuroprotective agent (Zheng i wsp. 2022).

- Mechanism of action: Metformin activates AMPK (AMP-activated protein kinase), which plays a role in reducing neuroinflammation and promoting synaptic function (Zheng i wsp. 2022).

- Clinical evidence: A Mendelian randomization study found that metformin use is associated with a lower risk of developing AD, likely due to its effects on mitochondrial function (Xu i wsp. 2021) (Zheng i wsp. 2022).
- Potential challenges: While metformin is widely used in diabetes, its direct role in AD remains under investigation, with concerns regarding individual variability in response (Xu i wsp. 2021).

3.4. ANTI-INFLAMMATORY AND METABOLIC APPROACHES

Chronic neuroinflammation is increasingly recognized as a major contributor to Alzheimer's disease (AD) progression. The activation of microglia, the brain's resident immune cells, leads to the release of pro-inflammatory cytokines, which exacerbate neuronal damage (Xue i Du 2021) (Wang i wsp. 2022). Additionally, metabolic dysregulation, including insulin resistance and mitochondrial dysfunction, has been linked to both Aβ and tau pathology (Zheng i wsp. 2022) (Xu i wsp. 2021).

Targeting these pathways through anti-inflammatory drugs and metabolic modulators offers potential new directions in AD treatment.

3.4.1. NSAIDS AND MICROGLIAL INHIBITORS

Microglia play a crucial role in Alzheimer's disease pathology by clearing amyloid-beta plaques; however, in the disease state, they become dysfunctional and shift into a pro-inflammatory state. This transition leads to the release of cytokines such as TNF-α and IL-1β, exacerbating neurodegeneration (Xue i Du 2021) (Wang i wsp. 2022). Given their role in disease progression, therapies aimed at modulating microglial activation have gained significant attention in recent years.

One of the proposed therapeutic strategies involves the use of non-steroidal anti-inflammatory drugs. Epidemiological studies indicate that chronic NSAID use is associated with a lower risk of developing Alzheimer's disease, potentially due to their ability to reduce neuroinflammation (Hampel i wsp. 2020) (Wang i wsp. 2022). However, clinical trials have produced inconsistent results. While ibuprofen and naproxen demonstrated some protective effects in preclinical models, large-scale trials failed to show significant cognitive benefits in Alzheimer's patients (Hampel i wsp. 2020). Similarly, selective COX-2 inhibitors, such as celecoxib, were initially considered to offer neuroprotection but ultimately did not yield meaningful clinical improvements (Hampel i wsp. 2020). Furthermore, concerns about the long-term use of NSAIDs include an increased risk of gastrointestinal bleeding and

cardiovascular events, which limit their widespread application in Alzheimer's patients (Hampel i wsp. 2020).

Due to the limited success of broad anti-inflammatory treatments such as NSAIDs, recent research has shifted toward targeted microglial modulators. One promising approach involves the use of TREM2 agonists, as the TREM2 receptor regulates microglial phagocytosis, and its activation has been shown to enhance amyloid-beta clearance (Xue i Du 2021). Another strategy involves CSF1R inhibitors, which modulate microglial proliferation, preventing chronic inflammatory activation while preserving normal immune function (Wang i wsp. 2022). Additionally, minocycline, a broad-spectrum antibiotic, has demonstrated potential in reducing microglial activation and tau phosphorylation, though further studies are required to confirm its efficacy (Xue i Du 2021).

3.4.2. METFORMIN AND OTHER METABOLIC MODULATORS

AD is sometimes referred to as "Type 3 diabetes", given the strong link between insulin resistance and cognitive decline (Zheng i wsp. 2022) (Xu i wsp. 2021). Insulin plays a crucial role in neuronal energy metabolism, and impaired insulin signaling contributes to synaptic failure and neuroinflammation (Xu i wsp. 2021).

Metformin, an AMPK activator widely used for Type 2 diabetes, has shown neuroprotective properties in preclinical and observational studies:

- Enhances mitochondrial function, reducing oxidative stress and neurotoxicity (Zheng i wsp. 2022).
- Reduces tau phosphorylation, potentially slowing disease progression (Xu i wsp. 2021).
- Improves insulin sensitivity, counteracting metabolic dysfunction in the AD brain (Xu i wsp. 2021).

However, clinical trials remain inconclusive, and further research is needed to determine optimal dosage and patient selection criteria (Zheng i wsp. 2022).

Other Metabolic Modulators:

- Resveratrol: A polyphenol found in grapes, resveratrol activates SIRT1, a pathway associated with longevity and neuroprotection (Xu i wsp. 2021).
- Ketogenic Diet: Enhancing ketone metabolism may provide alternative energy sources for AD patients, as glucose metabolism is impaired in the disease (Wang i wsp. 2022).

3.5. NOVEL DRUG DELIVERY STRATEGIES

The development of disease-modifying therapies for Alzheimer's disease (AD) faces significant challenges, particularly in drug delivery. The blood-brain barrier (BBB), a highly selective membrane that protects the brain from toxins, also limits the effective transport of therapeutic agents into the central nervous system (Sudhakar i Richardson 2019). Traditional small-molecule drugs and biologics such as monoclonal antibodies and enzyme inhibitors often fail to reach therapeutic concentrations in the brain, necessitating innovative drug delivery strategies (Sudhakar i Richardson 2019).

New approaches, including nanotechnology-based drug carriers and gene therapy, offer potential solutions to improve drug penetration and targeted delivery to affected brain regions (Sudhakar i Richardson 2019).

3.5.1. NANOTECHNOLOGY AND LIPID-BASED CARRIERS

Most AD drugs suffer from low bioavailability, limited ability to cross the BBB, and off-target effects that increase the risk of toxicity (Sudhakar i Richardson 2019). Nanotechnology-based carriers provide a more efficient way to deliver therapeutics by enhancing stability, solubility, and brain penetration (Sudhakar i Richardson 2019).

Types of Nanoparticle Drug Carriers

1. Lipid-Based Nanocarriers:
    - Liposomes and solid lipid nanoparticles (SLNs) can encapsulate both hydrophilic and lipophilic drugs, improving their stability and targeted release (Sudhakar i Richardson 2019).
    - Lipid-based carriers enhance drug uptake via receptor-mediated endocytosis, bypassing traditional BBB limitations (Sudhakar i Richardson 2019).
2. Polymeric Nanoparticles:
    - Polymers such as PLGA (poly(lactic-co-glycolic acid)) allow for sustained drug release, reducing the need for frequent dosing (Sudhakar i Richardson 2019).
    - These systems have been used to transport anti-tau and anti-amyloid agents directly into neuronal cells (Sudhakar i Richardson 2019).
3. Metallic and Magnetic Nanoparticles:
    - Gold and iron oxide nanoparticles have been explored for targeted drug delivery and imaging, offering potential dual therapeutic and diagnostic applications (Sudhakar i Richardson 2019).

Although nanotechnology-based therapies show promising preclinical results, challenges such as long-term toxicity, immune responses, and large-scale manufacturing remain obstacles to clinical application (Sudhakar i Richardson 2019).

3.5.2. GENE THERAPY FOR ALZHEIMER'S DISEASE

Gene therapy represents a paradigm shift in neurodegenerative disease treatment, offering long-term therapeutic effects by modifying gene expression at the molecular level (Sudhakar i Richardson 2019). In AD, gene therapy aims to:

- Correct dysfunctional pathways associated with Aβ and tau pathology.
- Deliver neuroprotective factors to enhance neuronal survival.
- Modify immune responses to reduce chronic neuroinflammation (Sudhakar i Richardson 2019).

Viral vectors, particularly adeno-associated viruses (AAVs) and lentiviruses, are commonly used for gene delivery in neurodegenerative diseases (Sudhakar i Richardson 2019).

- AAV-Based Gene Therapy:
    - AAV vectors have been used to deliver genes encoding neurotrophic factors such as BDNF (brain-derived neurotrophic factor), which supports neuronal survival (Sudhakar i Richardson 2019).
    - AAVs are considered safe, but their small genetic payload limits their application in AD (Sudhakar i Richardson 2019).
- Lentiviral Gene Therapy:
    - Lentiviruses can carry larger genetic payloads and integrate into the host genome for long-term expression (Sudhakar i Richardson 2019).
    - However, concerns remain regarding insertional mutagenesis and potential tumorigenicity (Sudhakar i Richardson 2019).

Several experimental gene therapies are being explored for AD:

1. Enhancing Amyloid Clearance:
    - Gene therapies delivering enzymes that degrade Aβ, such as NEP (neprilysin), have shown promise in animal models (Sudhakar i Richardson 2019).
2. Tau Suppression Strategies:
    - Antisense oligonucleotides (ASOs) and siRNA therapies aim to reduce tau expression, preventing NFT formation (Sudhakar i Richardson 2019).
3. Neurotrophic Factor Delivery:

- NGF (nerve growth factor) and BDNF gene therapy have been proposed to enhance neuronal resilience and counteract synaptic loss (Sudhakar i Richardson 2019).

While gene therapy is a highly promising approach, challenges such as immune responses, precise targeting, and ethical concerns remain barriers to widespread clinical application (Sudhakar i Richardson 2019).

4.1. DIET AND GUT MICROBIOME IN ALZHEIMER'S DISEASE

Growing evidence suggests that dietary interventions and gut microbiome modulation play a crucial role in Alzheimer's disease (AD) prevention and management. The gut-brain axis, a bidirectional communication system between the gastrointestinal tract and the central nervous system, has been implicated in neuroinflammation, amyloid-beta accumulation, and cognitive function (Stefaniak i wsp. 2022) patterns, the Mediterranean diet (MD) and the ketogenic diet (KD), have gained significant attention for their potential neuroprotective effects.

4.1.1. MEDITERRANEAN AND KETOGENIC DIETS

The Mediterranean diet is characterized by a high intake of fruits, vegetables, whole grains, olive oil, and lean proteins such as fish and poultry. This diet is rich in polyphenols, antioxidants, and omega-3 fatty acids, which have been associated with reduced neuroinflammation and improved cognitive function (De Lima i wsp. 2025). One of the key benefits of this diet comes from its antioxidant and anti-inflammatory properties. Polyphenols derived from olive oil, berries, and red wine help reduce oxidative stress and inflammatory markers linked to Alzheimer's disease (Twarowski i Herbet 2023). Additionally, omega-3 fatty acids, particularly DHA and EPA from fish, contribute to the protection of neuronal membranes and the maintenance of synaptic integrity (Stefaniak i wsp. 2022). Another important aspect of the Mediterranean diet is its impact on gut microbiota. Studies indicate that it increases beneficial gut bacteria such as Bifidobacteria and Lactobacilli, which in turn contribute to reduced neuroinflammation and amyloid-beta clearance (Da Silva 2024). A higher dietary fiber intake promotes the production of short-chain fatty acids, which exert neuroprotective effects and further support brain health (Twarowski i Herbet 2023). Longitudinal studies have shown that adherence to the Mediterranean diet is associated with a thirty percent lower risk of cognitive decline in older adults (Stefaniak i wsp. 2022). Moreover, meta-analyses suggest that individuals following this diet experience slower brain atrophy rates and better cognitive outcomes (De Lima i wsp. 2025).

The ketogenic diet is a high-fat, low-carbohydrate dietary approach that induces ketosis, shifting the brain’s primary energy source from glucose to ketone bodies. This metabolic switch may be beneficial for Alzheimer's disease patients, as impaired glucose metabolism is a hallmark of the disease (Valverde-Guillén i wsp. 2024). Neuroprotective mechanisms of the ketogenic diet include increased mitochondrial efficiency, which helps reduce oxidative stress and neurodegeneration (Valverde-Guillén i wsp. 2024). Additionally, ketones have anti-inflammatory properties and may lower microglial activation, thereby reducing neuroinflammation (Twarowski i Herbet 2023). The diet has also been linked to enhanced synaptic plasticity and increased production of brain-derived neurotrophic factor, which supports neuronal survival (Weller i Budson 2018). Some studies suggest that a ketogenic diet may reduce amyloid-beta accumulation and decrease tau hyperphosphorylation, potentially slowing the progression of Alzheimer's disease (Yeganeh Markid i wsp. 2025). However, while the diet shows promise in animal and small-scale human studies, long-term adherence remains challenging, and potential cardiovascular risks must be considered (Stefaniak i wsp. 2022).

4.1.2. PROBIOTICS AND THEIR IMPACT ON COGNITIVE FUNCTION

The gut microbiome plays a vital role in modulating neuroinneurotransmitter production, and immune responses, all of which are relevant to AD (Da Silva 2024) .

- Gut Dysbiosis in AD:
    - Studies show that AD patients exhibit altered gut microbiota composition, with higher pro-inflammatory bactereduced beneficial bacteria such as Bifidobacteria (Twarowski i Herbet 2023) .
    - Increased intestinal permeability ("leaky gut") may facilitate neuroinflammation and amyloid-beta aggregation (Stefaniak i wsp. 2022) .
- Probiotics:
    - Lactobacillus and Bifidobacterium strains have been shown to reduce neuroinflammation, improve synaptic plasticity, aognitive performance (Da Silva 2024) .
    - Probiotics modulate neurotransmitter levels, increasing serotonin and GABA, which support cognitive function and mood regulation (Weller i Budson 2018) .
- Clinical Triotic Supplementation:

- A 12-week randomized controlled trial in AD patients demonstrated improved Mini-Mental State Examination (MMSE) scores following probiotic supplementation (Twarowski i Herbet 2023) .
- Other studies highlight reductions in neuroinflammatory markers and better gut microbiota balance in AD patients receiving probiotics (Stefaniak i wsp. 2022) .

4.2. PHYSICAL ACTIVITY AND BRAIN REHABILITATION IN ALZHEIMER'S DISEASE

Physical activity has emerged as a crucial non-pharmacological intervention for Alzheimer's disease (AD), with strong evidence suggesting that regular exercise can enhance neuroplasticity, promote neurogenesis, and delay cognitive decline (Weller i Budson 2018) (Da Silva 2024) . Additionally, cognitive training and structured rehabilitation programs are increasingly recognized as potential strategies to preserve cognitive function in AD patients (Twarowski i Herbet 2023) (Yeganeh Markid i wsp. 2025) .

4.2.1. AEROBIC EXERCISE AND NEUROGENESIS

Aerobic exercise has been linked to increased hippocampal volume, improved cerebral blood flow, and enhanced synaptic plasticity in aging populations and AD patients (Weller i Budson 2018) . Regular physical activity is associated with:

- Increased Brain-Derived Neurotrophic Factor (BDNF):
  - BDNF supports neuronal survival, synaptic remodeling, and neurogenesis, particularly in the hippocampus (Da Silva 2024) .
  - Studies show that BDNF levels are significantly lower in AD patients, and exercise-induced increases may counteract neurodegeneration (Weller i Budson 2018) .
- Reduction in Neuroinflammation:
  - Exercise modulates the activity of microglia, reducing chronic neuroinflammation and oxidative stress (Twarowski i Herbet 2023) .
  - Lower levels of inflammatory cytokines (IL-6, TNF-α) have been observed in physically active AD patients (Twarowski i Herbet 2023) .
- Enhanced Mitochondrial Function:
  - Physical activity stimulates mitochondrial biogenesis, leading to better energy metabolism and reduced oxidative damage (Valverde-Guillén i wsp. 2024) .

Evidence supporting the role of exercise in Alzheimer's disease (AD) management continues to grow. A 12-month randomized controlled trial demonstrated that moderate-intensity

aerobic exercise led to an increase in hippocampal volume and improved memory scores in patients with early-stage AD (Weller i Budson 2018). Additionally, meta-analyses indicate that regular physical activity is associated with a 30–40% reduction in dementia risk, with the most significant benefits observed in individuals engaging in vigorous exercise (Da Silva 2024). Even low-intensity activities, such as walking and yoga, have shown positive effects by improving executive function and reducing depressive symptoms in AD patients (Twarowski i Herbet 2023).

4.2.2. COGNITIVE TRAINING AND INTERVENTIONS

Cognitive training consists of structured exercises aimed at improving memory, attention, executive function, and problem-solving skills (Yeganeh Markid i wsp. 2025). Unlike passive activities, targeted cognitive training is designed to stimulate neuroplasticity and potentially delay cognitive decline (Weller i Budson 2018). One of the most extensively studied approaches is computerized cognitive training (CCT), which utilizes interactive software to engage various cognitive domains. Programs such as BrainHQ and CogniFit have been investigated in AD patients, demonstrating modest improvements in processing speed and working memory (Yeganeh Markid i wsp. 2025). A six-month trial of CCT reported increased functional connectivity in the default mode network (DMN), a key brain region affected by AD (Weller i Budson 2018).

Another effective approach is memory strategy training, which includes methods such as spaced retrieval, mnemonic devices, and associative learning to enhance information retention in AD patients (Yeganeh Markid i wsp. 2025). Research indicates that structured memory training programs can lead to improved daily functioning and greater independence in individuals with mild AD (Twarowski i Herbet 2023).

Additionally, dual-task training, which combines cognitive and physical exercises, has gained attention as a promising intervention. Activities such as walking while performing arithmetic tasks have been shown to enhance executive function and gait stability, ultimately reducing fall risk in AD patients (Weller i Budson 2018).

4.3. BRAIN STIMULATION THERAPIES IN ALZHEIMER'S DISEASE

Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), are gaining attention as potential therapeutic approaches for cognitive enhancement in Alzheimer's disease (AD). These methods modulate neuronal excitability, synaptic plasticity, and network connectivity, aiming to counteract neurodegenerative changes and improve cognitive functions (Su i wsp. 2025) .

4.3.1. TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Transcranial Magnetic Stimulation (TMS) operates through electromagnetic induction, delivering pulses of magnetic fields that penetrate the scalp and induce electrical activity in targeted brain regions (Su i wsp. 2025). The effects of TMS depend on the stimulation frequency, where high-frequency stimulation exceeding 5 Hz enhances cortical excitability and neuroplasticity, while low-frequency stimulation below 1 Hz reduces cortical hyperactivity, which may be beneficial in mitigating AD-related overactivity in specific brain areas (Su i wsp. 2025).

The primary brain region targeted by TMS in AD research is the **dorsolateral prefrontal cortex (DLPFC)**, which is involved in working memory, executive function, and attention. Most studies focus on stimulating this area to enhance cognitive performance. Additionally, emerging research suggests that stimulating the **parietal cortex and hippocampus** may improve spatial memory and cognitive flexibility, further expanding the potential applications of TMS in AD treatment (Su i wsp. 2025).

Clinical trials investigating TMS for AD have yielded promising results. A six-week study utilizing high-frequency TMS over the DLPFC demonstrated significant improvements in memory recall and attention in patients diagnosed with mild-to-moderate AD (Su i wsp. 2025). Long-term research indicates that repetitive TMS (rTMS) may slow cognitive decline, especially when combined with cognitive training, suggesting a potential synergistic effect between the two interventions (Su i wsp. 2025). However, the effectiveness of TMS varies depending on patient responsiveness, disease severity, and the specific stimulation protocol employed.

Despite its therapeutic potential, TMS presents several challenges and limitations. One of the primary issues is that its beneficial effects tend to diminish once stimulation sessions end, necessitating repeated applications to maintain cognitive improvements (Su i wsp. 2025). Additionally, individual variability plays a significant role in treatment outcomes, as responsiveness to TMS depends on factors such as brain atrophy levels and baseline neural connectivity. Accessibility is another concern, as TMS requires specialized equipment and trained professionals, limiting its widespread clinical implementation.

4.3.2. TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

TDCS involves applying a weak electrical current to the scalp, modulating neuronal activity by shifting membrane potentials (Su i wsp. 2025) . Unlike TMS, tDCS does not directly induce neuronal firing, but instead alters cortical excitability:

- Anodal tDCS (+ stimulation) enhances neuronal excitability.
- Cathodal tDCS (- stimulation) suppresses overactive brain regions.

Clinical Evidence on tDCS in AD

- Studies suggest that anodal tDCS over the DLPFC enhances working memory and learning capacity in mild-to-moderate AD patients (Su i wsp. 2025) .
- tDCS paired with cognitive training appears more effective than tDCS alone, reinforcing synaptic plasticity (Su i wsp. 2025) .
- A 4-week randomized trial found that daily tDCS sessions improved processing speed and executive function, though effects diminished after treatment cessation.

Advantages and challenges associated with this approach include several important factors. Among its advantages are that it is non-invasive, portable, and cost-effective when compared to Transcranial Magnetic Stimulation (TMS). Additionally, it can be self-administered at home, provided there is appropriate guidance. However, it also faces certain challenges, notably that the therapeutic effects tend to be modest and temporary, requiring repeated sessions to sustain benefits. Moreover, standardized treatment protocols are still lacking, complicating comparisons across different studies.

4.4.1. MUSIC THERAPY

Music therapy is a structured intervention that involves listening to, performing, or engaging with music to stimulate cognitive and emotional responses (Weller i Budson 2018). Research suggests that music can enhance memory recall, reduce anxiety, and improve communication in Alzheimer's disease patients, even in cases where verbal abilities have significantly declined (Twarowski i Herbet 2023).

One of the key effects of music on brain function in Alzheimer's disease is its ability to enhance memory and recognition. Musical memories often remain intact even when other forms of memory are severely impaired, providing a valuable tool for cognitive stimulation (Weller i Budson 2018). Functional MRI studies have shown that listening to familiar music activates the medial prefrontal cortex, a region that is relatively preserved in the early stages of Alzheimer's disease (Twarowski i Herbet 2023). In addition to cognitive benefits, music therapy has been linked to a reduction in neuropsychiatric symptoms such as agitation, depression, and anxiety, particularly in moderate-to-severe Alzheimer's patients (Weller i Budson 2018). A meta-analysis of randomized controlled trials further supports these findings, demonstrating that music therapy significantly reduces behavioral disturbances associated with Alzheimer's disease (Twarowski i Herbet 2023).

Beyond its cognitive and emotional benefits, music therapy also plays a role in stimulating social interaction. Group music sessions foster social bonding and communication, even among patients with limited verbal abilities, providing an alternative means of expression and engagement (Weller i Budson 2018). Clinical evidence supporting the efficacy of music therapy includes a six-month randomized trial in which Alzheimer's patients who received weekly music therapy sessions showed significant improvements in mood and cognitive function compared to control groups (Twarowski i Herbet 2023). Another study reported that daily personalized music sessions improved emotional well-being and reduced the need for sedative medications in nursing home residents with Alzheimer's disease (Weller i Budson 2018).

Despite these promising results, music therapy is not without challenges and limitations. Individual variability plays a significant role in treatment outcomes, as some patients respond more positively than others depending on their personal history and musical preferences (Weller i Budson 2018). Additionally, the lack of standardized protocols in music therapy makes it difficult to compare studies and optimize the duration and frequency of therapy sessions for maximum benefit (Twarowski i Herbet 2023). While these challenges remain, ongoing research continues to explore ways to refine and standardize music therapy as a complementary intervention for Alzheimer's disease.

4.4.2. LIGHT THERAPY

Light therapy involves controlled exposure to specific wavelengths of light to regulate circadian rhythms, improve sleep patterns, and reduce cognitive decline in AD (Weller i Budson 2018) . Many AD patients experience circadian disruptions, leading to sleep disturbances and worsening neuropsychiatric symptoms (Twarowski i Herbet 2023) .

Effects of Light Therapy on AD

- Regulation of Circadian Rhythms:
    - Bright light exposure in the morning improves melatonin regulation, enhancing sleep quality and daytime alertness (Weller i Budson 2018) .
- Cognitive and Mood Improvements:
    - Exposure to blue light (460–480 nm) has been shown to stimulate cognitive activity and reduce apathy in AD patients (Twarowski i Herbet 2023) .
    - Some studies suggest that photobiomodulation (PBM) therapy, using near-infrared light, may promote neuronal repair and mitochondrial function, potentially slowing neurodegeneration (Weller i Budson 2018) .

Clinical Evidence on Light Therapy

- A 4-week study found that AD patients who received morning bright light therapy exhibited fewer episodes of agitation and better nighttime sleep quality (Twarowski i Herbet 2023) .
- Another trial using blue light stimulation demonstrated improved attention and executive function in early AD patients (Weller i Budson 2018) .

5.1. AI IN ALZHEIMER'S DISEASE DIAGNOSIS

The rapid development of artificial intelligence (AI) and machine learning (ML) is transforming the field of Alzheimer's disease (AD) diagnosis, offering new possibilities for early detection, risk assessment, and disease progression monitoring. Traditional AD diagnosis relies on cognitive assessments and clinical observations, which are often subjective and prone to variability. However, AI-powered technologies are now being used to analyze neuroimaging data, biomarker profiles, and genetic information, enabling more accurate and objective detection of AD at its earliest stages (Rehan i wsp. 2025).

AI models can identify complex patterns in large datasets that might be imperceptible to human experts. These models are particularly valuable in predicting disease onset and progression, allowing for earlier interventions and improved patient management (Rehan i wsp. 2025) (Da Silva 2024).

5.1.1. AI IN NEUROIMAGING AND PATTERN RECOGNITION

Neuroimaging plays a crucial role in AD diagnosis, providing detailed structural and functional insights into the brain. Techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT) allow researchers to visualize hippocampal atrophy, amyloid-beta accumulation, and disruptions in brain connectivity. However, traditional neuroimaging analysis is time-consuming and subjective, often requiring expert interpretation that varies between clinicians (Rehan i wsp. 2025).

AI-based approaches, particularly deep learning models, have significantly improved the ability to detect and classify AD-related brain changes. Convolutional neural networks (CNNs), a subset of deep learning, are highly effective in analyzing MRI and PET images, achieving diagnostic accuracies exceeding 90% in some studies (Rehan i wsp. 2025).

Structural MRI scans provide valuable information about hippocampal and cortical atrophy, both of which are strong indicators of early-stage AD. AI models trained on large MRI datasets can detect subtle neurodegenerative changes years before clinical symptoms emerge, making them a powerful tool for preclinical AD diagnosis (Rehan i wsp. 2025).

Similarly, amyloid and tau PET imaging is used to measure the accumulation of pathological proteins in the brain. AI-assisted PET scan analysis enhances early amyloid and tau detection, increasing the reliability of biomarker-based diagnosis and allowing for more precise disease staging (Da Silva 2024).

Despite these advances, several challenges remain. Variability in imaging protocols, scanner types, and patient demographics can affect AI model performance. Additionally, most AI models are trained on single-center datasets, limiting their ability to generalize across different populations (Rehan i wsp. 2025). Furthermore, the computational complexity of AI-driven neuroimaging analysis requires substantial processing power, making it costly for widespread clinical use. Addressing these issues will be essential for integrating AI into real-world clinical practice.

5.1.2. MACHINE LEARNING FOR BIOMARKER-BASED AD DETECTION

In addition to neuroimaging, AI is being increasingly integrated with biomarker-based diagnostic tools, improving the detection of AD through non-invasive blood tests and cerebrospinal fluid (CSF) analysis. Biomarkers provide quantifiable measures of disease-related changes, and AI-powered algorithms are helping to analyze and interpret biomarker profiles more efficiently (Da Silva 2024).

One of the most promising applications of AI in biomarker research is its ability to analyze plasma and CSF levels of amyloid-beta (Aβ) and tau proteins. AI models trained on large datasets can predict which individuals are at risk for AD based on their Aβ42/Aβ40 ratio or p-Tau levels, even in pre-symptomatic stages (Da Silva 2024) (Rehan i wsp. 2025). The ability to detect AD biomarkers through blood tests rather than invasive lumbar punctures represents a major advancement in early diagnosis accessibility.

Additionally, AI is being used to assess neurofilament light chain (NfL) levels, a marker of neuronal damage. AI-based biomarker models can distinguish AD from other neurodegenerative disorders, improving differential diagnosis (Da Silva 2024) (Valverde-Guillén i wsp. 2024).

AI also plays a role in integrating genetic and epigenetic factors into AD risk assessment. Machine learning models incorporating APOE genotyping, polygenic risk scores, and DNA methylation patterns provide a more personalized approach to AD prediction, tailoring interventions based on an individual's genetic profile (Da Silva 2024).

The integration of multi-omics data, combining biomarkers, neuroimaging, and genetic risk factors, represents the next frontier in AI-assisted AD diagnosis. By analyzing multiple data

sources simultaneously, AI models can offer a more comprehensive understanding of disease mechanisms, paving the way for precision medicine approaches in AD management (Rehan i wsp. 2025).

5.2. Emerging Biomarkers for AD Diagnosis

The identification of reliable biomarkers has revolutionized the diagnosis and monitoring of Alzheimer's disease (AD), enabling earlier detection and more precise disease staging. Traditionally, AD was diagnosed based on clinical symptoms and neurocognitive assessments, often leading to late-stage detection when neurodegeneration was already advanced. However, advances in biomarker research now allow for objective and preclinical detection, offering new opportunities for personalized treatment strategies (Da Silva 2024).

Biomarkers for AD can be categorized into three main groups: fluid biomarkers (blood and cerebrospinal fluid - CSF), neuroimaging biomarkers, and genetic/epigenetic markers. These tools are being integrated with artificial intelligence (AI) and machine learning to improve diagnostic accuracy and facilitate large-scale screening efforts (Valverde-Guillén i wsp. 2024) (Da Silva 2024).

5.2.1. Blood and CSF Biomarkers

Among the most widely studied AD biomarkers are those related to amyloid and tau pathology, the two hallmarks of the disease. Changes in cerebrospinal fluid (CSF) levels of these proteins are detectable years before cognitive symptoms appear, making them valuable for early diagnosis.

A decline in CSF amyloid-beta (Aβ42) levels is indicative of abnormal amyloid accumulation in the brain, which is a defining feature of AD. This is particularly relevant when assessing the Aβ42/Aβ40 ratio, which improves diagnostic accuracy by reducing variability between individuals (Da Silva 2024). Recent technological advancements have made it possible to measure plasma amyloid levels, reducing the need for invasive lumbar punctures. AI-assisted models analyzing blood-based amyloid measurements have shown promising results in predicting amyloid positivity in PET scans, making this a viable screening tool for AD (Rehan i wsp. 2025).

Similarly, phosphorylated tau (p-Tau) has emerged as a highly specific biomarker for AD, with p-Tau181 and p-Tau217 showing strong correlations with neurofibrillary tangle pathology. These markers are detectable in both CSF and blood, and their levels increase as AD progresses (Da Silva 2024). The development of blood-based p-Tau assays is an important step toward making AD diagnosis more accessible and less invasive.

Apart from amyloid and tau, neurofilament light chain (NfL) has gained attention as a marker of neurodegeneration. NfL is a structural protein found in axons, and its release into CSF and blood is associated with neuronal damage. While NfL is not specific to AD, its elevated levels can indicate widespread neurodegeneration, making it a useful tool for differentiating AD from other neurodegenerative disorders (Da Silva 2024) (Valverde-Guillén i wsp. 2024).

Additionally, biomarkers of neuroinflammation and metabolic dysfunction are increasingly being explored. Markers such as YKL-40 and GFAP (glial fibrillary acidic protein) provide insights into astrocyte activation and neuroinflammatory processes, which are thought to play a major role in disease progression (Da Silva 2024). Another emerging approach involves the detection of mitochondrial dysfunction markers, as mitochondrial abnormalities contribute to oxidative stress and energy deficits in AD. Blood-based assays assessing mitochondrial metabolites are currently being investigated for their potential diagnostic value (Valverde-Guillén i wsp. 2024).

5.2.2. NEUROIMAGING-BASED BIOMARKERS

Beyond fluid biomarkers, neuroimaging techniques have become essential in diagnosing and monitoring AD progression, as they provide a direct visualization of pathological changes in the brain (Rehan i wsp. 2025).

Structural magnetic resonance imaging (sMRI) is widely used to assess hippocampal and cortical atrophy, which are characteristic features of AD. The hippocampus is one of the earliest structures to be affected in the disease, and progressive volume loss in this region correlates with cognitive decline. AI-powered MRI analysis allows for automated volumetric assessments, improving the detection of subtle atrophy patterns that may otherwise go unnoticed in conventional clinical evaluations (Graff-Radford i wsp. 2021).

Positron emission tomography (PET) provides functional imaging that enables the detection of amyloid and tau deposits in the brain. Amyloid PET imaging can confirm the presence of amyloid plaques, while tau PET imaging is increasingly used to assess tau burden and its relationship with disease severity (Rehan i wsp. 2025). These imaging modalities, when combined with AI algorithms, allow for precise disease staging and differentiation between AD and other forms of dementia (Da Silva 2024).

While neuroimaging biomarkers are highly valuable, their cost and limited availability present challenges for widespread implementation. However, advancements in machine learning models are improving the ability to extract meaningful insights from routine clinical scans,

making neuroimaging-based AD diagnostics more accessible in the future (Rehan i wsp. 2025).

5.3. The Future of AI and Biomarkers in AD Therapy

The integration of AI and biomarker-based approaches is shaping the future of Alzheimer's disease (AD) treatment, focusing on personalized medicine, drug discovery, and monitoring therapeutic efficacy. AI-driven analysis of biomarkers, neuroimaging, and genetic data allows for more precise treatment selection, increasing the likelihood of successful interventions (Rehan i wsp. 2025) (Da Silva 2024).

5.3.1. AI-Assisted Drug Discovery and Personalized Medicine

Traditional drug discovery for AD has been slow and costly, with many clinical trials failing due to poor target selection and ineffective compounds. AI models now accelerate this process by analyzing large-scale biological datasets, identifying promising drug candidates, and predicting their potential efficacy (Rehan i wsp. 2025).

Machine learning algorithms are particularly useful for:

- Screening drug libraries to identify compounds that interact with amyloid-beta and tau proteins.
- Predicting drug toxicity and optimizing dosing regimens to minimize side effects.
- Repurposing existing drugs, reducing the time required for clinical approval (Da Silva 2024).

AI-driven analysis is also revolutionizing personalized medicine in AD. By integrating biomarker levels, genetic risk factors, and neuroimaging data, AI can help predict which patients will respond best to specific treatments, avoiding unnecessary side effects (Rehan i wsp. 2025).

5.3.2. Biomarkers for Monitoring Treatment Efficacy

As disease-modifying therapies (DMTs) emerge, reliable biomarkers are essential to assess their real-world impact. AI-powered biomarker analysis allows clinicians to track individual treatment responses and make adjustments based on disease progression (Da Silva 2024).

Key biomarker-based monitoring strategies include:

- Tracking changes in plasma p-Tau and NfL levels to evaluate treatment effects on neurodegeneration.
- AI-assisted MRI analysis to measure hippocampal atrophy rates over time.

- Functional connectivity assessment using fMRI, providing insights into synaptic recovery (Rehan i wsp. 2025) (Valverde-Guillén i wsp. 2024).

The combination of biomarkers and AI models will play a critical role in the next generation of AD therapies, helping to refine precision treatment strategies and optimize long-term patient outcomes.

6. THE FUTURE OF AD TREATMENTS AND CHALLENGES

As research advances, the future of Alzheimer's disease (AD) treatment is shifting toward multi-targeted approaches, combining pharmacological and non-pharmacological interventions. While anti-amyloid and anti-tau therapies continue to be developed, emerging strategies focus on neuroprotection, metabolic modulation, gene therapy, and lifestyle interventions. Despite progress, significant challenges remain, including high clinical trial failure rates, disease complexity, and treatment accessibility (Da Silva 2024) (Rehan i wsp. 2025).

Future AD treatments are likely to adopt combination therapies, addressing multiple disease pathways simultaneously. Targeting neuroinflammation and synaptic dysfunction alongside amyloid and tau clearance may offer better clinical outcomes. For example, research into anti-inflammatory agents, mitochondrial enhancers, and neurotrophic factors suggests that restoring brain homeostasis is essential for slowing disease progression (Valverde-Guillén i wsp. 2024). Additionally, gene therapy is gaining interest, particularly in targeting APOE ε4 and other genetic risk factors, although ethical and technical hurdles remain (Da Silva 2024).

Beyond pharmacological treatments, non-invasive interventions such as brain stimulation, exercise, and dietary modifications are proving to be valuable adjunct therapies. Studies indicate that transcranial magnetic stimulation (TMS) may enhance cognitive function, while ketogenic diets and metabolic therapies offer potential benefits by reducing neuroinflammation and oxidative stress. AI-driven precision medicine models are also playing a growing role in optimizing treatment selection, ensuring that therapies are tailored to individual patient profiles based on biomarkers, genetics, and neuroimaging data (Rehan i wsp. 2025).

Despite these innovations, several barriers must be overcome before these treatments can be widely implemented. One of the biggest challenges is early diagnosis, as many treatments are more effective in preclinical or mild AD stages but fail to reverse severe neurodegeneration. Additionally, the cost and availability of advanced treatments, such as monoclonal antibodies and biomarker-based diagnostics, pose challenges for large-scale clinical adoption.

Regulatory hurdles and variability in patient responses also complicate drug approval and treatment standardization (Da Silva 2024).

Ultimately, the future of AD treatment will likely involve a multimodal approach, integrating AI-driven diagnostics, biomarker-based monitoring, and personalized therapeutic strategies. While significant challenges remain, ongoing research and technological advancements continue to offer hope for more effective interventions, improving both quality of life and disease outcomes for AD patients (Rehan i wsp. 2025).

7. SUMMARY AND FUTURE PERSPECTIVES

Advancements in Alzheimer's disease (AD) research have led to significant progress in understanding the disease's pathophysiology, diagnosis, and treatment. This review has explored key aspects of AD, including its molecular mechanisms, currently approved therapies, emerging pharmacological and non-pharmacological interventions, the role of AI, and biomarker-driven approaches. While no cure currently exists, a combination of disease-modifying drugs, lifestyle interventions, and advanced diagnostic tools is shaping the future of AD care (Da Silva 2024) (Rehan i wsp. 2025).

One of the most critical findings from the literature is the complexity of AD pathogenesis, with multiple interacting factors contributing to neurodegeneration. Therapeutic strategies targeting amyloid-beta and tau have yielded mixed results, highlighting the need for broader treatment approaches that address neuroinflammation, mitochondrial dysfunction, and synaptic loss (Valverde-Guillén i wsp. 2024). Recent innovations in monoclonal antibodies, tau aggregation inhibitors, and metabolic therapies have shown potential but require further clinical validation (Da Silva 2024).

Non-pharmacological interventions, such as exercise, cognitive training, brain stimulation, and dietary modifications, are increasingly recognized as effective complementary treatments that may slow cognitive decline. AI-driven research has also contributed to earlier and more accurate AD diagnosis, improving biomarker analysis, neuroimaging interpretation, and personalized treatment strategies (Rehan i wsp. 2025).

Looking ahead, the future of AD treatment will likely involve a multimodal approach, integrating AI-assisted diagnostics, biomarker-based monitoring, and precision medicine. Advances in gene therapy, neuroprotective compounds, and combination therapies may offer new hope for slowing or even preventing AD progression. However, challenges related to treatment accessibility, high clinical trial failure rates, and healthcare system integration must be addressed (Da Silva 2024) (Rehan i wsp. 2025).

Overall, while significant obstacles remain, continued research and technological innovation provide optimism that more effective, personalized AD treatments will become available in the near future, improving both patient outcomes and quality of life.

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