Universidade de Lisboa

Faculdade de Farmácia

New advances in treatment of Alzheimer's disease

Helena Maci Cammarata

Monografia orientada pela Professora Doutora Cristina Luzia Dias de Mello Sampayo, Categoria Professora Auxiliar.

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Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

A doença de Alzheimer (DA) é uma doença neurodegenerativa progressiva caracterizada por declínio cognitivo, perda de memória e alterações comportamentais. Apesar da extensa pesquisa, atualmente não há cura para a DA e a patogénese exata permanece desconhecida. Esta tese fornece uma revisão abrangente dos avanços recentes na compreensão e tratamento da DA, explorando os mecanismos moleculares subjacentes à DA, incluindo a formação de placas beta-amiloides, hiper fosforilação da proteína tau, neuroinflamação e o papel de fatores genéticos, como o alelo ε4 da APOE. Adicionalmente, são discutidas as mais recentes abordagens terapêuticas, abrangendo tratamentos farmacológicos recorrendo tanto a inibidores da acetilcolinesterase e antagonistas dos recetores NMDA, como a novas terapias, incluindo anticorpos monoclonais como o Aducanumab. Estratégias não farmacológicas, como intervenções dietéticas com ácidos gordos ómega-3, ómega- 6 e flavonoides, bem como o uso potencial de psicadélicos para aumentar a neuroplasticidade, também são temas abordados nesta monografia. Ao longo da tese destacam-se pesquisas emergentes sobre o papel dos microRNAs e RNAs circulares na patogénese da doença de Alzheimer, apresentando novos potenciais tratamentos para intervenções personalizadas ao utente. Esta monografia sublinha a complexidade da Doença de Alzheimer e evidenciada a necessidade de abordagens de tratamento multifacetadas para gerir e potencialmente mitigar a progressão desta doença debilitante.

Palavras-chave: Doença de Alzheimer (DA), neurodegeneração, beta-amiloide (Aβ), hiperfosforilação de tau, neuroinflamação, APOE ε4, inibidores da acetilcolinesterase, antagonistas do recetor NMDA, Aducanumab, ácidos gordos ómega-3, flavonoides, psicadélicos, microRNAs (miRNAs), circular RNAs (circRNAs), neuroplasticidade.

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioural changes. Despite extensive research, there is currently no cure for AD, and the exact pathogenesis remains elusive. This thesis provides a comprehensive review of recent advances in the understanding and treatment of AD. It explores the molecular mechanisms underlying AD, including amyloid-beta plaque formation, tau hyperphosphorylation, neuroinflammation, and the role of genetic factors such as the APOE ε4 allele. Additionally, the thesis discusses the latest therapeutic approaches, encompassing both pharmacological treatments, such as acetylcholinesterase inhibitors and NMDA receptor antagonists, and novel therapies including monoclonal antibodies like Aducanumab. Non-pharmacological strategies, such as dietary interventions with omega-3 fatty acids and flavonoids, as well as the potential use of psychedelics to enhance neuroplasticity, are also examined. Emerging research on the role of microRNAs and circular RNAs in AD pathogenesis is highlighted, presenting new avenues for targeted interventions. This thesis underscores the complexity of AD and emphasizes the need for multi-faceted treatment approaches to manage and potentially mitigate the progression of this debilitating disease.

Keywords: Alzheimer's Disease (AD), neurodegeneration, amyloid-beta (Aβ), tau hyperphosphorylation, neuroinflammation, APOE ε4, acetylcholinesterase inhibitors, NMDA receptor antagonists, aducanumab, omega-3, omega-6, fatty acids, flavonoids, psychedelics, microRNAs (miRNAs), circular RNAs (circRNAs), neuroplasticity.

Abreviations

5-HT2A - 5-Hydroxytryptamine 2A receptor

AD - Alzheimer’s Disease

Aβ - Amyloid-beta

AICD - APP intracellular domain

APOE - Apolipoprotein E

APP - Amyloid precursor protein

BDNF - Brain-derived neurotrophic factor

CAA - Cerebral amyloid angiopathy

CNS - Central nervous system

CSF - Cerebrospinal fluid

DMT - Dimethyltryptamine

EOAD - Early-onset Alzheimer’s Disease

FDG-PET - 18F-fluorodeoxyglucose positron emission tomography

FDA - Food and Drug Administration

IEGs - Immediate early genes

KIBRA - Kidney/Brain protein

LOAD - Late-onset Alzheimer’s Disease

LSD: Lysergic acid diethylamide

MAP: Microtubule-associated protein

MCI: Mild cognitive impairment

MT: Microtubule

NMDA - N-methyl-D-aspartate

NFTs - Neurofibrillary tangles

NIA-AA - National Institute on Aging and Alzheimer's Association

PET - Positron emission tomography

PFC - Prefrontal cortex

PS1 - Presenilin 1

PS2 - Presenilin 2

P-tau181 - Phosphorylated tau 181

RNA - Ribonucleic acid

ROS - Reactive oxygen species

VaD - Vascular dementia

WHO - World Health Organization

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1 Introduction

1.1. Alzheimer’s Disease: From Prevalence to Risk Factors

Alzheimer's disease (AD) is a progressive neurological illness that primarily affects the older population worldwide resulting in deficits in memory and deterioration in cognitive function. As the most common form of dementia globally, the number of individuals with dementia is predicted, by the World Health Organization (WHO), to increase from 55 million in 2019 to 139 million in 2050 as our society ages. Additionally, it is estimated that the expenses related to dementia will more than triple, reaching $2.8 trillion by 2030 from US $1.3 trillion annually in 2019. (1).

AD, first recognized in 1906, has various possible causes, but researchers still don't fully understand what might be behind its origin. Even after more than a hundred years, science hasn’t been able to find a cure for the disease (2), but several efforts around symptom management and regression treatments have been developed over the last twenty-five years.

The risk of AD increases after the age of 65, with individuals over 85 years currently having up to a 30% chance of developing the disease. Given that aging is the primary risk factor for neurodegenerative conditions among other factors, the prevalence of AD increases alongside the evolving human longevity (3,4).

The disease can have two main presentable forms: late-onset AD (LOAD), occurring after 65 years of age, and early-onset AD (EOAD), usually between 30 and 65 years. Genetically, AD can be hereditary (familiar) or sporadic, with no familial history detailed (5,6) Early-onset AD is rare, representing fewer than 1% of patients with AD. Commonly, these patients inherit mutations in genes such as Amyloid-Beta Percussor Protein (APP), presenilin 1 (PS1), or presenilin 2 (PS2), which are involved in abnormal Aβ peptide production. Additionally, the APOE ε4 gene is the most important genetic risk factor for more common AD forms, coding the apoE4 lipid carrier protein (6). The presence of this gene is responsible for more than 99% of the Sporadic AD patients (7).

Over the years and through recent studies, various risk factors associated with the development of AD have been identified. Primary non-genetic risk factors include low education, severe head injury, cerebrovascular disease, diabetes, and obesity. However, it remains uncertain whether avoiding or minimizing these factors can effectively lower

the risk of developing AD. Additionally, other potential risks, such as exposure to pesticides, metals, and industrial surfactants, have yet to be fully accessed (6,8).

Furthermore, it has been thoroughly established that AD is more prevalent in women than in men. Upon examining sex-related variances in neuronal anatomy and function, researchers confirmed that gender may indeed be a significant risk factor in the variability of AD, with certain female-related risk factors contributing to this disparity. Indeed, there is evidence linking pregnancy, specifically hypertensive pregnancy disorders, menopause, depression, which tends to be more prevalent in women as well, and hormone therapy to AD. Recognizing these important distinctions could lead to breakthroughs in more personalized treatments for the future (9,10).

1.1 Objective

The primary objective of this thesis is to provide a comprehensive review of recent advances in the treatment of Alzheimer's disease (AD). This includes an exploration of the molecular mechanisms underlying AD, such as amyloid-beta plaque formation, tau hyperphosphorylation, and neuroinflammation. Additionally, the thesis aims to evaluate both established pharmacological treatments, like acetylcholinesterase inhibitors and NMDA receptor antagonists, and novel therapeutic approaches, such as monoclonal antibodies (e.g., Aducanumab), dietary interventions with omega-3 fatty acids and flavonoids, and the potential use of psychedelics to enhance neuroplasticity. Emerging research on the role of microRNAs and circular RNAs in AD pathogenesis will also be discussed, presenting new avenues for targeted interventions. This thesis underscores the complexity of AD and emphasizes the need for multi-faceted treatment approaches to manage and potentially mitigate the progression of this debilitating disease.

2 Methods

This monograph was written using a variety of sources, including Science Direct, PubMed, and Google Scholar. Preference was given to the most recent papers from 2016 onward in order to make the search for scientific articles easier. A few keywords were chosen, including Alzheimer’s Disease, dementia, neurodegeneration, β-amyloid, tau protein, therapy, Flavonoids, Omega-3, Omega-6 and Psychedelics, MiRNA. The research was conducted from January 2024 to June 2024.

Aside from the above-mentioned sources, data was also gathered from papers and webpages supplied by health organizations, including the Food and Drug Administration (FDA), Alzheimer's Disease International (ADI), European Alzheimer's Organisation, and National Institute on Aging - Alzheimer's Association (NIA-AA). To create consistent, well-founded work with current knowledge, all of this was necessary.

3 An overview of Alzheimer's Disease: Mechanism of Alzheimer’s Disease and Clinical Manifestations.

3.1 Alzheimer's disease-related brain lesions

An adult's healthy brain has billions of neurons linked by trillions of synapses. Fast signal transmission is made possible by these synapses, which support memory, cognition, emotions, and other cognitive processes.

AD is defined at the molecular level by neurodegeneration and synaptic dysfunction, neuroinflammation, and vascular dysfunction. The final cognitive deterioration observed in AD patients is believed to be caused by a confluence of increased inflammation and neuronal death resulting from extracellular accumulation of amyloid plaques (Aß) formed by clumped beta-amyloid proteins and of neurofibrillary tangles (NFTs) formed by aggregated tau proteins inside the neurons (4,11), the two of the main neuropathological indicators of AD. (12)

Additional pathological changes affect the neurovascular unit, comprised of neurons, blood vessels, and supporting cells such as pericytes. Accumulation of amyloid-beta (Aβ) along blood vessel walls, a condition known as cerebral amyloid angiopathy (CAA), and neurovascular inflammation reduces Aβ clearance, weakens cerebral blood flow, and promotes cognitive dysfunction (13). Autopsies of AD patients and diagnostic imaging technologies reveal a shrunken hippocampus and cortex, which is explained by a drop in pericyte number and density in these brain areas critical for memory and complex cognitive functions (13).

3.2 Clinical Manifestations of Alzheimer’s Disease

In the early phases of the disease, the brain retains the ability to adapt to the damage, allowing individuals to carry on with their regular lives. As the disease progress, tangles and plaques develop in various parts of the brain alongside the areas responsible for cognitive function. Subsequently, nerve cell damage becomes so extensive that patients exhibit explicit cognitive decline, including behavioural symptoms like sadness and personality irregularities as well as cognitive symptoms like

memory loss and confusion about time and location (14,15). There are at present three stages of Alzheimer's disease that are currently recognized among all of the scientific community: preclinical AD, Mild Cognitive Impairment (MCI), and Dementia. The disease's symptoms and signs differ depending on the stage and are strongly associated with the harm inflicted on the neuronal cells, as shown in Table 1. (14,15).

Another stage of the disease is being characterized when individuals exhibiting symptoms that do not yet meet the criteria for dementia are often in the prodromal stage of Alzheimer's disease. This stage involves cognitive changes that are noticeable but not severe enough to interfere significantly with daily functioning. These early symptoms include mild memory loss, challenges in complex task performance, slight language difficulties, and subtle personality changes. The prodromal stage can last for several years and is characterized by the accumulation of amyloid-beta plaques and tau tangles in the brain, detectable through biomarkers and imaging studies (16).

Individuals in the stage of Preclinical AD, which remains under research, have quantifiable alterations in the blood, brain, and cerebrospinal fluid which relate to the preliminary biomarkers of Alzheimer's disease, but may not yet exhibit symptoms like memory loss.

Individuals with AD-associated MCI manifest cognitive decline and exhibit biomarkers of an AD's-related brain alteration, nevertheless, this decline does not severely interfere with daily functioning.

When AD reaches its severe stage, a person's capacity to express verbally is significantly reduced, and they may need 24-hour care. People get confined in bed as a result of injury to brain regions related to movement. Eating and drinking become challenging when there is damage to the brain regions responsible for swallowing. As a result, food particles have a chance to lodge in the lungs and create lung infections. Aspiration pneumonia is the name of the specific infection, which is a significant factor in the death of several Alzheimer's patients. (13)

Almost everyone diagnosed with AD experiences neuropsychiatric symptoms (NPS) at some stage of the disease, even though AD is typically classified as a cognitive disorder. While verbal and physical agitation are also common in all stages of MCI, depression and apathy are the most recognized NPS symptoms. Delusions, hallucinations, and violence increase in frequency as the disease worsens, but the most frequent NPS across all stages of AD is apathy. (14,15,17)

Table 1. Disease Progression Symptoms and Signs

	Preclinical AD	MCI	Dementia
Brain Alterations	Aβ and p-tau accumulation	CAA and drop in pericyte number	Shrunken Cortex and Hippocampus
Cognitive/ Behavioural Signs and Symptoms	Retrograde Amnesia	Anterograde Amnesia	In need of around the clock care
	Reduced power of judgment	Prosopagnosia	Hallucinations
	Forgetfulness	Depression	Seizures and Infections (pneumonia)
	Difficulties in carrying out daily tasks	Apathy	Aphasia
	Disorientation	Violent Behaviour	Death

3.3 Pathophysiology of Alzheimer's Disease

As discussed previously, AD is characterized by progressive biochemical, neurophysiological, neuroanatomical, and cognitive dysfunctions. The key pathological indicators are the excessive accumulation of Aβ plaques, the formation of neurofibrillary tangles, and neuronal death (18). Despite the genetic susceptibility, increased evidence has linked gliosis, inflammation, imbalances in the production and elimination of reactive oxygen species (ROS), mitochondrial dysfunction, and excessive metal ion build-up to the pathogenesis of Alzheimer's disease (19,20). The next subchapters concentrate on the most important pathological mechanisms associated with the disease, which are listed in order of science validation.

3.3.1 The amyloid cascade model

The amyloid cascade model highlights the vital function of Aβ, the main product of Amyloid Percussor Protein (APP) cleavage, in the aetiology of Alzheimer's disease. Aβ aggregates in neurotoxic amyloid plaques, leading to neuronal dysfunction and death (21,22). APP, found within both the somatodendritic and axonal compartments of neuronal cells, is a single-pass type I membrane protein featuring a transmembrane domain with a large extracellular domain and a short cytoplasmic tail (23).

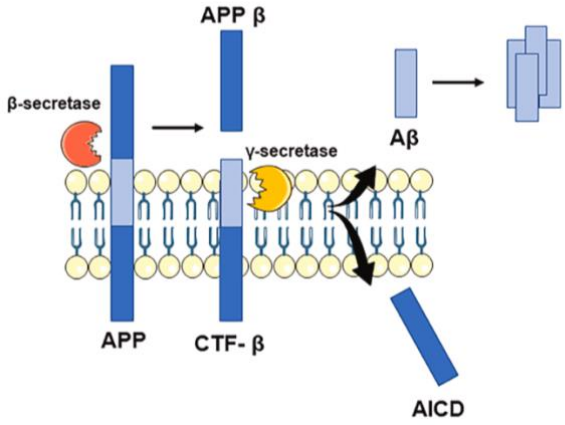


Figure 1. Amyloidogenic Pathway: Results in the formation of amyloid-beta (Aβ) plaques, characteristic of Alzheimer´s Disease.

The cleavage of APP within its extracellular domain can proceed via two different pathways: nonamyloidogenic and amyloidogenic. Initially, α- and β-secretases cleave APP in the extracellular domain, resulting in soluble ectodomains and membrane-tethered C-terminal fragments. In both processes, γ-secretase cleaves the membrane-tethered C-terminal segments, resulting in identical cytosolic polypeptides termed APP intracellular domains (AICDs). This dissertation will focus solely on the amyloidogenic route, also known as the pathogenic pathway. APP is cleaved by β-secretase to provide the C-terminal fragment β and the soluble ectodomain APPβ. Following that, the C-terminal segment β is repeatedly split by γ-secretase, producing Aβ peptides. (Fig.1) Through their self-aggregation into protofibrils and fibrils, these peptides induce neurotoxicity by modifying membrane permeability, oxidative stress, mitochondrial malfunction, inflammation, synaptic dysfunction, and excitotoxicity. In addition, Aβ impedes cell signalling by interfering with receptors and membrane proteins (21,23,24).

Although Aβ subtypes differ in their biochemical characteristics and posttranslational alterations, affect the speed of fibril aggregation (25,26). Aβ peptides have an intrinsic tendency to aggregate into oligomers, protofibrils, or full amyloid fibrils that ultimately deposit in plaques. The primary components of amyloid plaques are Aβ40 and Aβ42. In pathological circumstances, the Aβ42-to-Aβ40 ratio shifts in favour of a greater percentage of Aβ42, leading to the formation of plaques more rapidly (26).

The amyloid cascade theory is supported by the discovery that two genes, presenilin 1 (PSEN1) and presenilin 2 (PSEN2), constituted both an essential part of the enzyme γ-secretase, which is involved in the processing of APP, which indicates a strong link to familial Alzheimer's Disease (22)

3.3.2 Tau Hyperphosphorylation

Phosphoprotein Tau is one of the members of the microtubule-associated protein (MAP) family and is primarily present in axons, with lesser amounts also identified in glial cells and somatodendritic compartments. The MAPT gene on chromosome 17 encodes the protein tau, which is hydrophilic overall and has large naturally unfolded sections that are concentrated in the axons of growing and mature neurons. (27)This protein plays a role in the regulation of axon outgrowth and axonal transport by preserving the stability of axonal microtubules (MTs) in the brain (28)

Another major pathogenic hallmark of Alzheimer's disease is the development of neurofibrillary tangles (NFTs). Phosphorylated tau (pTau) accounts for nearly all the NFTs present in an AD patient (29) According to the literature, tau binds itself to microtubules in the brain to provide stability and facilitate axonal transmission. In the tau hypothesis for AD, it is reported that tau is hyperphosphorylated, ultimately resulting in its dissociation from microtubules and subsequent aggregation into the paired helical filaments found in both dystrophic neuritic cells and NFTs (28,30,31). Memory loss, neurodegeneration, and the onset of dementia are linked to this build-up of pTau, which is toxic for the health cells of the brain (29)

3.3.3 The role that inflammation serves in Alzheimer's Disease

The third vital element of the neuropathology of AD includes neuroinflammation. The resident immune cells of the central nervous system, known as microglia, activate when a threat becomes apparent (22).

The prevailing theory nowadays states that early in AD, Aβ plaques activate microglia, which subsequently phagocytoses Aβ (18). After a certain period, still unknown, microglia expand and lose their capacity to regulate Aβ as this component keeps on increasing in the brain. Through the release of proinflammatory cytokines (i.e., IL-1, TNF-α, and IL-6), the continuous activation of microglia sustains neuroinflammation, exacerbating neuronal damage and contributing to amyloid deposition. (30) Additionally, reactive astrocytes seem to have an important role in the engulfing of neuritic plaques in the brain. (22) Astrocytes protect synapses and neurons from damage and respond when they are damaged. It is yet unclear whether their activation in response to amyloid deposition is neurotoxic or serves a protective function, such as restricting the dimension of amyloid plaques. Reactive astrocytes, in any event, induce the transition of diffuse plaques into neuritic plaques by producing the proinflammatory cytokines IL-1 and TNF-α, β- and γ-secretase are upregulated by proinflammatory cytokines, resulting in an ongoing pattern wherein the amount of Aβ and cytokines both rises (22,32,33). It is cytokines, particularly IL-6, that induce tau hyperphosphorylation (32). Through this pathological hypothesis, microglia, and astrocytes both encourage neuroinflammation and are linked to tau and amyloid disease previously described (22).

3.3.4 Ferroptosis and Pyroptosis

Cell death can occur in two primary ways: ordered (controlled, program-like) and nonordered (necrosis). Apoptosis, autophagy, pyroptosis, ferroptosis, and other kinds of controlled cell death are among the more than twenty that have been discovered and investigated so far.

Pyroptosis has been implicated in various neurological disorders, including Parkinson’s disease, amyotrophic lateral sclerosis, and Huntington’s disease. In AD, there is growing evidence suggesting that dysfunctional pyroptosis contributes to the neuropathological lesions associated with the disease. Specifically, pyroptosis is involved in Aβ protein deposition and the hyperphosphorylation of tau, two hallmark features of AD pathology. The morphological characteristics of pyroptosis distinguish it from other forms of cell death. Pyroptotic cells display DNA fragmentation, chromatin condensation, and membrane rupture, leading to the release of inflammatory cytokines and cellular contents. Gasdermin, a family of pore-forming proteins, play a central role in executing pyroptosis by forming membrane pores.

The molecular mechanisms underlying pyroptosis involve the activation of inflammasomes, multiprotein complexes that sense cellular stress and initiate inflammatory responses. In AD, the NLRP3 inflammasome is highly activated in microglia, astrocytes, and neurons, leading to the release of proinflammatory cytokines and neuronal damage. The association between pyroptosis and AD pathology extends to both Aβ and tau pathology. Aβ activates the NLRP3 inflammasome, leading to pyroptosis and neuroinflammation. Similarly, hyperphosphorylated tau induces pyroptosis in neurons, exacerbating neuroinflammatory processes.(34)

Ferroptosis, an iron-dependent, nonapoptotic form of regulated cell death, has emerged as a significant factor in the pathogenesis of AD, potentially contributing to neuronal death. The relationship between iron accumulation and neurodegeneration in AD has led to a closer examination of ferroptosis and its regulatory mechanisms. In AD, the brain tissue exhibits pathological changes consistent with ferroptosis, highlighting the potential involvement of this cell death mechanism in the disease process. Iron overload, a characteristic feature of AD, can initiate ferroptosis by oxidizing lipids (polyunsaturated fatty acids), leading to the propagation of lipid peroxidation and subsequent cell death. While the cytoplasmic free iron concentration is normally regulated, elevated iron levels in AD brains increase the likelihood of lipid peroxidation and ferroptosis.

The enzyme glutathione peroxidase 4 (GPx4) plays a crucial role in preventing ferroptosis by converting toxic lipid hydroperoxides into non-toxic lipid alcohols, using glutathione as a cofactor. However, in conditions of GSH depletion or GPx4 inhibition, such as those observed in AD, the protective mechanism against lipid peroxidation is compromised, promoting ferroptosis. It may involve direct interactions of cytoplasmic iron with membrane lipids, triggering lipid radical chain reactions and pore formation. (35)

3.3.5 **Gut Microbiome Disruption**

The brain-gut metabolic axis promotes reciprocal communication between the brain and the gastrointestinal tract. Numerous investigations have demonstrated a favourable association between AD and gut flora disturbance. Whenever the gut microbiota is disturbed, the body produces excess secondary cytotoxic bile acid, predominantly deoxycholic acid, which may penetrate the brain through the BBB and

promote neurodegeneration, insulin resistance, inflammation, apoptosis, and consequently the formation of reactive oxygen species. (36–38)

The synthesis, absorption, and transport of serotonin and GABA in the brain are all influenced by gut microorganisms. Specific bacterial species, as discussed in the following subchapter also have an impact on the production of amyloid plaque, which activates the inflammatory cascade and enhances the likelihood of AD. (39)

Nitric oxide (NO) is released when glutamate activates NMDA receptors. It is the main neurotransmitter of the enteric, noradrenergic, and noncholinergic neurological systems. Nitrite and nitrate are converted to NO by gut microorganisms such as *Lactobacilli* and Bifidobacterium. A change in any of these gut microorganisms' activity combined with an increase in nitrate consumption can result in an excess of NO being produced, which can induce neurodegenerative diseases, neuroinflammatory, and axonal damage.(40)

Consequently, a compromised gut microbiota is one of the contributing factors that encourage the advancement of AD.(36,38–40)

3.3.6 **Infectious Disease Hypothesis**

It is currently believed worldwide that microorganisms have a role in the development of senile plaques, a theory known as the "infectious etiology for AD". AD may be linked to a broad spectrum of pathogens, including viruses, bacteria, fungi, and protozoa. It has been suggested that Aβ plaques may possess antibacterial qualities, creating another possible mechanism for AD. (41)

Spirochetes, Borrelia burgdorferi, Chlamydia pneumonia, Treponema pallidum, and Helicobacter pylori are some of the that may be responsible for the production of many inflammatory molecules - cytokines such as IL-1β, IL-6, IL-18, TNF-α, IFN-γ, chemokines, and reactive oxygen species (ROS). (41,42)

Herpes Simplex Virus-1 (HSV-1), *Varicella zoster* virus, *Cytomegalovirus*, and Hepatitis C Virus have been reported to be a significant risk factor when present in AD patients who are carriers of apolipoprotein E-e4 (APOE-e4). The HSV-1 and APOE-e4 combination results in the accumulation of Aβ and AD-like tau, which in turn are the primary components of the characteristic NFTs and amyloid plaques of AD brains. (41)

Over the past thirty years, there have been several hypotheses on the potential infectious etiology of AD, particularly LOAD. This highlights the critical role that persistent infections with bacteria, viruses, and fungi play as the inflammatory pathways that cause AD. Numerous studies indicate that specific infections may play a significant role in AD (41).

2.3.7. Genetic Mutation of APOE: "ApoE Cascade Hypothesis

Synapse development and tissue healing in the central nervous system are significantly influenced by ApoE-mediated cholesterol and lipid transport. Through its role in the production of lipoprotein particles, peripheral ApoE contributes to the redistribution and metabolism of lipids, including phospholipids, cholesterol, cholesteryl esters, and triglycerides, to maintain lipid homeostasis (12).

The ε2 (APOE2), ε3 (APOE3), and ε4 (APOE4) alleles are the three prevalent APOE alleles in humans, and they carry different illness risks for the disease (12). The protein isoforms, apoE2, apoE3, and apoE4, are distinguished by the amino acids they contain at positions 112 and 158. The ε2 allele has cysteine at both positions, ε3 has cysteine at position 112 and arginine at position 158, and ε4 has arginine at both positions (43). While APOE2 almost entirely reduces the risk of AD and increases lifespan, APOE4 is a strong genetic risk factor for AD in a gene dose-dependent way, increasing risk by up to 15 times (12).

One of the main ways that ApoE increases the risk of developing AD appears to be through its interaction with abnormal Aβ deposition (44). Apart from initiating the development of Aβ plaques, ApoE also plays a role in the elimination of Aβ through many pathways, including receptor-mediated clearance and proteolytic destruction. It has been demonstrated that the absorption of Aβ/ApoE complexes by the LRP1 receptor in neurons mediates Aβ clearance (12,45). This absorption pathway is compromised in APOE4 carriers because of the decreased stability of the complex between apoE4 and Aβ (12). Receptor binding changes and ApoE's competition for Aβ receptor binding sites exacerbate this clearance impairment, leading to a significant reduction in receptor-mediated clearance when apoE4 is present (12,46).

One of the main indicators of AD pathology, in addition to Aβ plaque development, is the existence of NFTs made of hyperphosphorylated tau aggregates.

Once Aβ oligomers are present, apoE4 has been demonstrated to enhance tau phosphorylation in comparison to apoE2 and apoE3 (12,47,48).

Even though the scientific community has gained an extensive amount of knowledge on how ApoE contributes to AD, much more study is still required to validate the "ApoE Cascade Hypothesis" (48).

3.4 Diagnosis of Alzheimer's Disease

Cerebrospinal fluid (CSF) protein analysis and positron emission tomography (PET) of marker molecules are currently the main methods used to diagnose AD (49). Both methods show comparable accuracy and imply that the best test for the diagnosis relies on patient/provider preference, cost, and facility accessibility (50). As a result several biomarkers have been studied to face up to the challenging task of diagnosing AD before severe symptoms manifest. A biomarker is a piece of information that is considered while assessing pathological and normal biological activities, as well as the pharmacological effects of any medication. A biomarker can be employed in the case of AD to evaluate elderly patients' general health and disease state (51).

Dementia detection relies heavily on CSF markers of tau and amyloid, which reflect the underlying neuropathology of AD. In AD patients, CSF Aβ42 levels drop, most likely as a result of peptide deposition in plaques. But compared to Aβ42 alone, the ratio of Aβ42/Aβ40 revealed to be a more trustworthy biomarker. Although increased total tau is quite sensitive in identifying AD, it is also raised in frontotemporal dementia and vascular dementia (VaD). On the other hand, compared to total tau, increased phosphorylated tau, a significant constituent of NFTs, provides more specificity (37,52).

One promising biomarker for confirming and predicting Alzheimer's disease diagnosis is phosphorylated tau 181 (P-tau181). P-tau181 is a specific form of the tau protein that has undergone phosphorylation at the threonine 181 residue (53). This biomarker is found in the brain and is secreted into the cerebrospinal fluid (CSF), eventually crossing the BBB to be detectable in the bloodstream (54).

Particularly in the early stages of AD, combinations of these CSF markers have been used to improve diagnostic potential. People who have both high tau and low Aβ42 levels and MCI are much more likely to acquire AD. Even with these developments, CSF biomarkers could not offer the best discriminatory power for differential diagnosis

on their own. As a result, modern methods for presymptomatic assessment combine the findings of neuroimaging with CSF biomarker results (37,52).

Neuroimaging plays an important role in the diagnosis of AD. By monitoring brain metabolic rates of glucose metabolism (CMRglc), a proxy marker for neuronal activity, functional imaging methods like 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) are now able to identify loss of neuronal function in asymptomatic patients (52).

Another interesting biomarker for AD that has recently been studied more accurately is Kidney/Brain Protein (KIBRA). The KIBRA protein is found across the brain, however it is mostly concentrated in the hippocampus. It functions in memory-related processes through its interactions with several postsynaptic proteins, including dendrin and synaptopodin. In AD, Tracy et al. (2016) found atypical acetylation of K274 and K281 on tau, which exacerbated memory loss and interfered with synaptic plasticity by lowering postsynaptic KIBRA protein (37).

Ocular biomarkers are proving to be an important tool for the early detection and diagnosis of Alzheimer's disease. Several biomarkers within the eye reflect the neuropathological changes occurring in the brain of AD patients, providing a non-invasive means of early diagnosis.(55)

One of the most significant biomarkers is the presence of Aβ plaques in the retina. These plaques, which are also found in the brains of AD patients, can be detected using retinal imaging techniques such as optical coherence tomography (OCT). The accumulation of Aβ in the retina mirrors the cerebral amyloid pathology, making it a valuable early indicator of AD. Studies have highlighted the utility of OCT in visualizing these plaques, which can help in diagnosing AD at a preclinical stage (56).

Another important biomarker is the change in retinal vascular structure and blood flow. Retinal imaging, particularly OCT angiography (OCTA), can detect reductions in retinal blood flow and alterations in vessel density in AD patients. These vascular changes in the retina are believed to reflect similar cerebrovascular alterations associated with AD, thereby serving as an early diagnostic tool (57).

Neurofibrillary tangles (NFTs) in the retina, composed of hyperphosphorylated tau protein, are another critical biomarker. NFTs are a hallmark of AD pathology and can be detected through advanced imaging technologies and molecular probes.

Detecting these tangles in the retina provides a non-invasive method to monitor disease progression and the effectiveness of therapeutic interventions (56).

In addition to these, other potential ocular biomarkers include changes in the retinal nerve fibber layer (RNFL) thickness and ganglion cell layer (GCL) integrity. Thinning of the RNFL and degeneration of GCLs have been observed in AD patients, which can be quantified using OCT. These structural changes in the retina may correlate with the degree of neurodegeneration in the brain (58).

In summary, the most important ocular biomarkers for Alzheimer's disease include amyloid-beta plaques, retinal vascular changes, neurofibrillary tangles, and structural changes in the retinal nerve fibber and ganglion cell layers. These biomarkers, detectable through non-invasive retinal imaging techniques, hold significant promise for early diagnosis and monitoring of Alzheimer's disease. Improving the disease's early identification in the preclinical stage is the focus of current difficulties and an important challenge for new treatment and studies (55).

4 Current Treatment Approaches

Despite the increased understanding of the molecular, biochemical, and cellular mechanisms involved, the true causes and reasons for the rapid progression of AD remain not fully understood. This poses challenges for developing effective disease-modifying drugs.(18)Although several therapeutic approaches have been investigated in clinical trials over the course of several decades, the majority of medications that are now on the market are symptomatic as opposed to curative (59,60) Studies have indicated that modifiable risk factors may account for over 30% of AD cases worldwide. These variables offer intriguing and promising targets for preventative treatments aimed at lowering the likelihood of AD-related cognitive decline and perhaps non-verbal dementia (ND) in general. (61–63) The central nervous system's protective barriers make it difficult to efficiently target and transport molecules of interest to the brain during AD therapies. One challenge that must be addressed when targeting the brain is the BBB. Although BBB shields the central nervous system (CNS) from pathogens, chemicals, and potential neurotoxins, it also restricts the availability of many therapeutic medication molecules in the CNS (64).

There are now four authorized small molecule medications on the market: galantamine, rivastigmine, memantine, donepezil and the monoclonal antibody Aducanumab. Those small molecule medications fall into two families: anticholinesterase inhibitors and anti-glutaminergic. The oral or transdermal routes are used to administer these medicines (65,66).

This chapter will evaluate the current pharmacological and non-pharmacological treatment approaches and their main limitations.

2.1 Pharmacology Treatments Available

2.1.1. Acetylcholinesterase inhibitors' effectiveness in Alzheimer’s.

A key contributor to the impaired mental function observed in AD and adult-onset dementia diseases is cholinergic neurotransmission. Acetylcholine plays an important role in cognitive functions such as learning and memory. A major treatment target for AD is the enzyme cholinesterase (ChE) (67).

The primary cause of AD is the decrease in the production of acetylcholine (ACh). Hence, blocking the biological activity of acetylcholinesterase (AChE) is one possible

therapeutic approach to raising cholinergic levels in the brain (68). Acetylcholinesterase inhibitors (AChEIs): these enzymes, which metabolize Ach into an inactive form, include galantamine, rivastigmine, and donepezil. By increasing neurotransmitters, they prevent Ach from decreasing and improve cognitive function. Given the comparable efficacy of these treatment alternatives, the decision should be made with the patient's tolerance and budget in mind. While rivastigmine and donepezil are approved for severe cases of Alzheimer's disease, they are advised for mild to moderate cases only (69). The most frequent side effects linked to this pharmacological class include cramping in the muscles, weariness, and gastrointestinal side effects. Given these side effects, it is expected that one-third of patients are unable to tolerate AChEIs. As a result, these medications should be started at the lowest possible dosage and, if an increase is required, it should be carried out gradually (52).

2.1.2 N-methyl-D-aspartate receptor antagonist effectiveness in Alzheimer's

Since memantine is a low-affinity, non-competitive N-methyl-D-aspartate receptor antagonist (NMDA), its exact mode of action is unknown, although it is thought to reduce the excitatory neurotoxicity of glutamate (70).

Although the process of learning and memory is mostly dependent on synaptic transmission and plasticity, NMDA-type glutamate receptors (NMDARs) have lately been linked to AD due to their excessive activation. An aberrant Ca^{2+} level and glutamate overstimulation caused by excessive NMDAR activation leads to excitotoxicity, synaptic malfunction, neuronal cell death, and a reduction in cognitive abilities. Thus, by non-competitively inhibiting the NMDA receptor, memantine may aid in slowing the rate of synapse loss in AD. Memantine may also lessen Aβ toxicity and tau protein phosphorylation (71).

Once a patient develops severe illness and is intolerant to AChEIs, Memantine is recommended for intermediate disease. In comparison to AChEIs, it is generally well tolerated and has fewer side effects. On the other hand, patients could feel lightheaded, drowsy, hypertensive, and dizzy. Memantine and donepezil combined treatment may be helpful for those with intermediate Alzheimer's disease (52,72).

2.1.3 Aducanumab as a treatment for Alzheimer's

The only medications available to physicians until June 2021 were three AChE inhibitor- and NMDA-antagonist- receptor medications. The human immunoglobulin

G1 monoclonal antibody Aducanumab is a recombinant that targets insoluble fibrils and soluble amyloid beta (73).

Aducanumab belongs to an emerging class of monoclonal anti-Aβ antibodies that target Aβ aggregates selectively. So, aducanumab's remarkable selectivity for Aβ aggregates—including soluble oligomers and insoluble fibrils—represents a significant improvement over earlier anti-Aβ antibodies. Thirty studies showed that aducanumab's binding stimulates microglial phagocytosis, which in turn facilitates the removal of Aβ aggregates. Aducanumab's affinity and binding stoichiometry to Aβ aggregates make it the sole antibody that, aside from clearance, inhibits the Aβ aggregation process by preventing secondary nucleation, or the creation of oligomers on the fibril surface (74).

Sadly, aducanumab has a one-sided action and does not affect the cholinergic pathway, which is also very significant, or other pro-neurodegenerative elements like oxidative stress (73).

Although the theory-based medication aducanumab has demonstrated good efficacy, the newly developed therapy is insufficient to reverse neurodegeneration and is only available to a restricted number of patients due to its high cost. The eligibility criteria for patients include:

- Diagnosis Stage: Aducanumab is indicated for patients with mild cognitive impairment (MCI) due to Alzheimer's disease or those in the mild dementia stage, reflecting the population studied in clinical trials.
- Amyloid PET Scan: Patients must undergo an amyloid PET scan to confirm amyloid plaques in the brain, which Aducanumab targets.
- MRI Screening: Regular MRI scans are necessary before and during treatment to monitor for amyloid-related imaging abnormalities (ARIA), such as brain swelling and microhaemorrhage’s.
- APOE ε4 Genetic Testing: Testing for the APOE ε4 gene is recommended, as carriers may have a higher risk of ARIA. This helps tailor the treatment plan and monitor for side effects.
- Health and Age Considerations: Generally prescribed to patients under 85 years old, Aducanumab requires that patients be in good health without significant comorbid conditions (75,76).

2.2 Non-Pharmacological Treatments

Non-pharmacological treatments (NPTs) have the potential to be crucial in both primary and secondary dementia prevention. These can be useful in managing clinical symptoms. NPTs offer several advantages, including that they are typically well tolerated, have few negative side effects, and may be used in combination with pharmaceutical therapies and other NPTs both concurrently and repeatedly without causing significant problems. NPTs can also be used for various clinical phases of the illness, such as dementia, moderate cognitive impairment (MCI), and even individuals without cognitive impairment who are at risk of developing dementia (77,78).

Methods such as Cognitive stimulation therapy (CST), Cognitive rehabilitation (CR), and Cognitive training (CT) are important in creating new neurological pathways in the brain and delaying the continuous progression of the disease (78).

Additionally, a healthy diet is critical for the brain given that it plays a role in biological processes that lower inflammation and oxidative stress, support vascular health, enhance neuronal cell signalling, as well as improve the function of neuronal cells. Through the consumption of certain supplements in combination with food, nutritional therapies seek to alter the dietary intake of macronutrients (proteins, fats, and carbohydrates) and/or micronutrients (vitamins and minerals) (78–80). The results are encouraging despite the lack of information regarding the impact of dietary interventions on cognitive outcomes and the substantial methodological obstacles. Studies have demonstrated the positive effects of B vitamin supplementation on memory function in individuals with memory cognitive impairment (MCI) who have elevated homocysteine levels. Additionally, cognitive performance and memory are improved by supplements of flavonols, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), (78,80) a topic that will be discussed later in this dissertation.

Other non-pharmacological treatments, such as exercise training and sleep therapies, have been taken into consideration while treating AD patients. These treatments have been shown to improve the patient's quality of life (78).

5 New advances in the treatment of Alzheimer's Disease

The rising incidence of AD patients, as well as the increasing worldwide health problem the illness poses, demand the need for medication to prevent, postpone initial onset, decrease the progression, and improve the symptoms of AD (81).

Figure 2. 2024 Alzheimer's drug development Pipeline. This diagram illustrates the diverse range of therapeutic agents currently in development for Alzheimer's Disease, categorized by their mechanisms of action, clinical trial phases, and subject characteristics. **Mechanisms of Action (color-coded):** Amyloid (red) APP, Lipids and Lipoprotein Receptors (light blue), Epigenetic Regulators (purple), Growth Factors and Hormones (light pink), Immunomodulatory (yellow), Metabolism/Bioenergetics (orange), Neurogenesis (light green), Neurotransmitter Receptors (pink), Oxidative Stress (brown), Proteostasis/Proteinopathy (green), Synaptic Plasticity/Neuroprotection (blue), Tau (teal), Vasculature (dark purple), Other (grey); **Clinical Trial Phases:** Phase 1 (outermost circle), Phase 2 (middle circle) and Phase 3 (innermost circle); **Therapeutic Categories:** Disease-Modifying Biologic (upper half), Disease-Modifying Small Molecule (right section), Neuropsychiatric Symptom Tx (bottom half), Cognitive Enhancer (left section), **Subject Characteristics (shape-coded):** Healthy Volunteers (circle), Preclinical (triangle), Prodromal/Prodromal-Mild (inverted triangle)**,** Mild-Moderate Dementia (square)**,** Severe Dementia (diamond).

As of the index date of January 1, 2024, there were a total of 164 Phase 1, 2, or 3 clinical trials evaluating 127 distinct therapies for AD. Phase 3 clinical trials included 32 substances, Phase 2 trials included 81 substances, and Phase 1 trials included 25 molecules (note that some compounds are involved in several trials; Figure 2.

Among the therapeutic agents studied, Disease-Modifying Therapies (DMTs) constituted the majority, comprising 96 agents, which accounted for 76% of the total number of drugs in these trials. Within the DMT category, there were 43 biologics and 53 small molecules.

The main targets of the treatment medicines differed, indicating the complex character of AD from a mechanistic approach. Among the most important mechanistic targets were amyloid, tau, inflammation, synaptic plasticity/neuroprotection, metabolism and bioenergetics, oxidative stress, and proteostasis/proteinopathy. Furthermore, 28 treatments (including medications intended to improve cognitive function and reduce neuropsychiatric symptoms) specifically targeted neurotransmitters (82).

The objective of this chapter is to present a thorough summary of these recent developments, covering a wide range of treatment modalities such as biologics, small molecule drugs, and novel non-pharmacological approaches. Through careful evaluation of the effectiveness, safety, and prospective effects of these innovative medicines, seeking to highlight the promising directions that might influence Alzheimer's disease care in the future, with the ultimate goal of enhancing patient outcomes and quality of life.

5.1 The Impact of Omega family fatty acids and Flavonoids as Promising Neuroprotectants.

Dietary treatments have shown promise in the field of preventive medicine as a way of lowering the risk of a number of illnesses, including neurodegenerative disorders like AD. Polyunsaturated fatty acids as omega-3 and omega-6 fatty acids and flavonoids are two of the many dietary components that are being studied for their possible neuroprotective properties.

Docosahexaenoic acid and eicosapentaenoic acid are two examples of the omega-3 long-chain polyunsaturated fatty acids that are essential to the body's cellular membranes. They are crucial in regulating the viscosity in cell membranes and reducing

inflammation. Particularly in the brain and retina, where it supports neuronal structure and function, DHA stands out as an essential component of cell membranes. Studies have demonstrated the importance of DHA in maintaining cognitive function by connecting decreased blood levels of the fatty acid with cognitive decline in older adults (83,84). While DHA is essential for cognitive processes, such as learning and memory, because of its anti-apoptotic and anti-nociceptive properties, which affect nigrostriatal activity and synaptic plasticity, EPA largely contributes to cell signalling. DHA can counteract brain shrinkage and cognitive decline by reducing neuronal loss and enhancing learning and memory (85).

Moreover, EPA and DHA function as precursors for powerful lipid mediators that are essential for immune system control and inflammation resolution. By being incorporated into cell membranes, they produce bioactive metabolites that aid in the prevention and treatment of a number of illnesses. It is impossible to ignore the negative effects of inadequate dietary intake, especially high consumption of trans and saturated fats (SFAs), on cognitive performance. Elevated intake of trans isomers and SFAs has been associated with elevated risk factors for a number of illnesses, including neurological conditions. On the other hand, those who eat a diet high in monounsaturated (MUFA) and polyunsaturated fatty acids (PUFAs), particularly those in the omega-3 family, have a lower risk of developing dementia. The potential of MUFAs and PUFAs to prevent cognitive decline is highlighted by their antioxidant characteristics, as well as their capacity to enhance insulin sensitivity and glucose metabolism (83,86,87).

Additionally, Flavonoids, pigments found in plants, boast a wide array of pharmacological properties, serving as antioxidants, antivirals, anti-inflammatory agents, anticarcinogens, antibacterial, neurotrophic, neuroprotectants, and immunological stimulants (88). These substances show promise in reducing the risk of neurodegenerative illnesses due to having neuroprotective, anti-inflammatory, and antioxidant properties. Flavonoids have been shown in studies to modulate neuronal signalling cascades, have positive effects on the central and peripheral nervous systems, and perhaps prevent AD and age-related cognitive decline (84).

The Mediterranean diet, which is well-known for having a lot of fibre, omega-3 fatty acids, antioxidants, and flavonoids, is an example of a dietary pattern linked to a lower risk of AD and other neurological illnesses. Consuming foods high in flavonoids

and omega-3 fatty acids, such as nuts, seeds, fatty fish, fruits, and vegetables, may help people avoid cognitive decline and maintain the good health of their brains (86).

5.1.1 Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA)

Lipids are a diverse category of compounds with hydrophobicity as a common characteristic. Lipids can have simple, short hydrocarbon chains or more intricate chains, such as phospholipids, sterols, triacylglycerols, and sphingolipids. Their length, saturation level, and hydroxylation are used to identify their physicochemical characteristics. Lipids have a role in the control of transcription factor expression as well as a number of metabolic activities, including the synthesis of fatty acids, oxidation, sensitivity to insulin, and the nervous system's function. There are several classifications of fatty acids, such as cis, trans, polyunsaturated, monounsaturated, and saturated fats. Overall, fatty acids are important constituents of all lipid forms. These combined with cholesterol produce the lipid bilayer that surrounds cells and organelles. Membranous proteins' activity and mobility, as well as the fluidity and permeability of membranes, are all influenced by the varying fatty acid content of individual cells. (89)About half of the lipids in the brain are phospholipids, less than 40% are glycolipids, and 10% are cholesterol. There are also cholesterol esters, trace amounts of triglycerides, and long-chain fatty acids (90).

Fatty acids classified as polyunsaturated fatty acids (PUFAs) have two or more double bonds in their hydrocarbon chain. The beginning double bond's location in relation to the final omega methyl group can be used to categorise PUFAs. The existence of a double bond three or six atoms away from the omega terminal carbon, respectively, is what distinguishes omega-3 or omega-6 PUFAs.

The human body can create only a certain amount of linoleic acid (LA) and α-linoleic acid (ALA), which are precursor molecules for the synthesis of all other types of PUFAs and so are referred to as vital fatty acids. As a result, additional nutrients are required to satisfy needs. It has been clearly shown that essential fatty acid deficit might potentially lead to dermatitis, renal hypertension, mitochondrial activity abnormalities, cardiovascular illnesses, type 2 diabetes, poor brain development, arthritis, depression, and lowered body resistance to infection (89).

Omega-3 fatty acids include ALA, EPA, and DHA and omega-6 fatty acids include LA and arachidonic acid (AA). The human body can metabolise them even if it is

unable to synthesise them due to a lack of omega-3-desaturase, one of the conversion enzymes (89). ALA of the omega-3 family and LA of the omega-6 family are two examples of PUFAs that are crucial to human brain health. PUFAs must be obtained from food since humans are unable to synthesise them. Soybean, sunflower, corn, safflower oils are among the vegetable oils that contain LA. Walnuts, linseed, rapeseed, soybean oils and Olive oil are foods rich in ALA (91). ALA is the starting point of the omega-3 PUFA series, and further β-oxidation, elongation, and desaturation processes provide the additional omega-3 PUFAs (91). The synthesis of arachidonic acid (AA) requires lignoceric acid as a precursor, while the production of longer chain omega fatty acids, such as EPA and DHA, need ALA as a substrate (83).

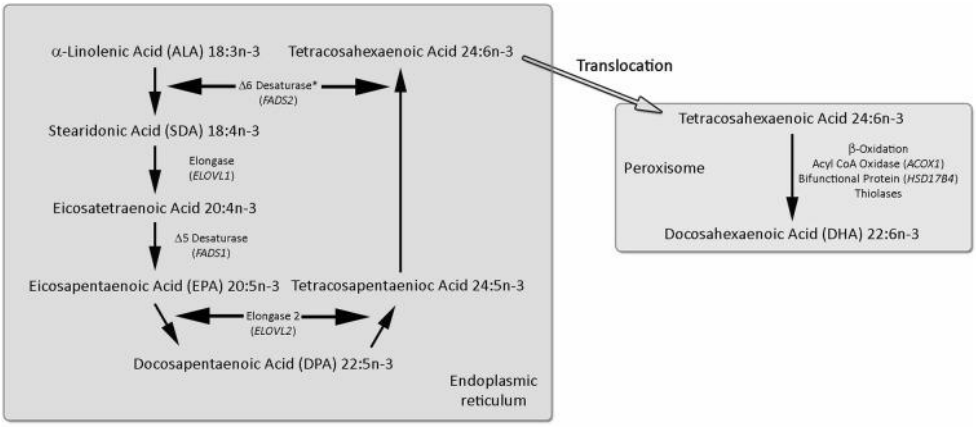


Figure 3. Pathway of Omega-3 Fatty Acid Biosynthesis: This diagram illustrates the biosynthesis pathway of omega-3 fatty acids, detailing the conversion steps from α-Linolenic Acid (ALA) to Docosahexaenoic Acid (DHA).

Studies indicate that the consumption of certain fatty acids, such as EPA, DHA and LA through diet may impact brain function by changing the composition of fatty acids in cerebral membranes. Although supplementation has the potential to be beneficial, the method used may differ based on age and PUFA consumption levels. Research indicates that meals high in EPA and DHA may improve the proportion of these fats in inflammatory cell membranes while lowering the amounts of AA (92). Increases in omega-3 PUFA levels in CSF can be achieved by oral supplementation; however, carrier particles are necessary for effective translocation across the BBB. DHA especially needs brain-specific carriers for transportation, such as 1-lyso and 2-docosahexaenoyl-glycerophosphocholine (LysoPC-DHA). Improved carriers like

AceDoPC, which has demonstrated neuroprotective qualities and accelerates the transfer of DHA to the brain, are being explored by scientists (93).

Research into the use of omega-3 fatty acids in AD has been extensive. However, a randomized controlled trial conducted by Lin et al. (2022) found that omega-3 fatty acids did not improve cognitive and functional decline or depressive symptoms in AD patients. Interestingly, they did observe an improvement in spoken language ability. This suggests that omega-3 fatty acids might need to interact with other micronutrients to have a beneficial effect.

Jernerén et al. (2019) proposed that adequate levels of B vitamins are necessary for omega-3 fatty acids to impact cognition effectively. Additionally, carotenoids and vitamin E may also contribute to improving memory and mood. Notably, this effect appears to be more significant in milder-to-moderate stages of the disease (94).

The absence of a sufficient supply of cholesterol to neurons can compromise synaptic plasticity and nerve signal transmission, leading to tau pathology and neurodegeneration. Conversely, an increase in cholesterol levels has been linked to the generation of Aβ and has been detected in the early stages of AD patients. Therefore, contradictory data regarding the cholesterol concentration and its impact on AD may be explained by differences in disease stages (90).

In conclusion, the role of nutrition in AD remains an area of active research and interest. While the profile of dietary lipids, particularly omega-3 fatty acids, has been proposed as a potential risk factor in AD pathogenesis, the evidence regarding their efficacy in slowing cognitive decline is uncertain. Studies have shown that adequate levels of omega-3 polyunsaturated fatty acids, especially EPA and DHA, are associated with slower rates of cognitive decline and reduced risk of AD. However, conflicting results, indicate that the significant efficacy of omega-3 fatty acids in AD treatment is still unknown. While nutritional interventions show promise as non-pharmacological tools for AD treatment, more studies with robust methodological quality are needed to draw definitive conclusions. Addressing knowledge gaps and conducting other studies that concern the association between nutrition and AD are recommended to develop more effective strategies for managing and treating AD (85,90,94).

5.1.2 Flavonoids: Potential Therapeutic Agents

On a chemical level, flavonoids are composed of two benzene rings, designated A and B, connected by a third pyranosic ring, C. The structural properties of the B ring and the extent of hydroxylation and glycosylation of the third ring differentiate the various subclasses of flavonoids (95).

Flavonoids are abundant in the kingdom of plants and have a variety of chemical structures with many substituents. This gives them unique properties that are advantageous for the well-being of the organism and have the potential to be therapeutic agents. But not all flavonoids are biologically effective; only those with particular attributes can be used for certain purposes. The antioxidant activity of flavonoids, for example, is closely linked to the quantity of hydroxyl groups on the B ring. More free hydroxyl groups often translate into stronger scavenging activities, but where these groups are located in the flavonoid structure is significant. As these hydroxyl groups provide hydrogen atoms and electrons to radical species, reducing their reactivity, they aid in the repair of damage caused by ROS and reactive nitrogen species (RNS). As a result, this method produces a flavonoid radical that is comparatively stable, which helps to reduce oxidative stress that is caused by free radicals (95,96). Experimental findings show that flavonoids have unique chelating activities against transition metals, primarily iron and copper ions, in addition to their direct impact on free radicals. Flavonoids' capacity to fend off oxidative stress is further strengthened by their chelating action. The biological activity of flavonoids is thought to be primarily mediated by their chelating activity, as metallocomplexes impact several biochemical attributes as lipophilicity, membrane transport, and interaction with biomolecules (95).

Considering that flavonoids can travel across the BBB, it is possible that these substances will directly impact the brain. The bioactivity of flavonoids against neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington's, and other neurological illnesses has been shown in several research. Finding natural alternative treatments for AD has been suggested to be essential to maintaining brain function given these chemicals are frequently simple to extract and have well-established safety profiles and pharmacokinetics (97).

At clinically low quantities, flavonoids such as Epicatechin-3-gallate, Baicalein, Naringerin, Quercetin, Myricetin, among others, have been proven to scavenge free radicals, prevent β-amyloid and Tau aggregation, and sequester metal ions (95).

- Epigallocatechin gallate: Green tea contains a polyphenol called epigallocatechin gallate (EGCG), which has a number of neuroprotective benefits for AD patients. According to in vivo data, EGCG boosted α-secretase activity and lowered β- and γ-secretase activities, which in turn reduced Aβ levels and improved memory. In addition, EGCG prevented Aβ oligomerization in vivo and aggregation in vitro. Moreover, it promoted the clearance of phosphorylated tau in vivo and suppressed tau aggregation in vitro. Also, in vivo studies have revealed that EGCG possesses anti-inflammatory and antioxidant properties (97).

- Baicalein: Natural flavonoids called baicalein are found in the roots of *Scutellaria baicalensis Georgi*. Baicalein may lessen oxidative stress by preventing the generation of ROS, according to in vitro research. Also, it disintegrates Aβ fibrils and inhibits Aβ fibrillation and oligomerization, according to in vitro data. Baicalein has been shown to decrease β-secretase and boost α-secretase activities, which in turn reduces the formation of Aβ (97).

- Quercetin: A naturally occurring polyphenolic component found in fruits, vegetables, and plants. Quercetin lowered oxidative stress and improved memory and cognitive deficits in an AD model, according to *in vivo* research (98). Furthermore, data obtained *ex vivo* revealed that quercetin lowers the amounts of Aβ in the brains of AD model mice by preventing Aβ aggregation, inhibiting the creation of Aβ fibrils, and destabilising Aβ fibrils (99–101). Furthermore, this substance was shown to be an inhibitor of taupathy and β-secretase *in vivo* investigations (97).

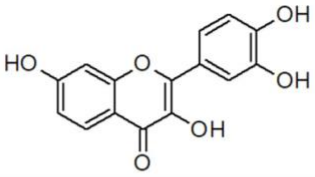
- Myricetin: A flavonoid called myricetin is taken from a variety of fruits, vegetables, and plants. In vitro demonstrations shown that myricetin's ability to inhibit β-secretase and enhance α-secretase activity reduces Aβ aggregation and the ensuing fibrillation (102,103). Furthermore, myricetin inhibited the structural alterations on Aβ *in vitro*, resulting in a decrease in Aβ levels (104). Furthermore, *in vitro* disintegration of Aβ fibrils was noted. Consequently, an

in vivo investigation demonstrated that myricetin exacerbated the memory and learning deficits in a model of AD rats (97,103).

- Naringenin: It is the primary flavanone component in the *Rutaceae* family *citrus junos Siebold ex Tanaka* (95) Naringenin decreased the amounts of phosphorylated tau and inhibited the activity of β-secretase (105). Additionally, data demonstrated the compound's anti-inflammatory and antioxidant properties, which enhanced the motor coordination, memory, and learning of AD rats (106). Natural naringenin may be found in tomatoes and citrus fruits (95,97).

5.1.2.1 Senolytic Drug: Fisetin

Fisetin, a flavonoid compound with the chemical name 3,7,3′,4′-tetrahydroxyflavone or 7,3′,4′-flavon-3-ol, is gathering attention for its multifaceted pharmacological properties. This polyhydroxy flavonoid has gained recognition for its antioxidant, anti-inflammatory, anti-cancer, and neuroprotective effects. Moreover, Fisetin finds its use in the management of vascular dementia. Naturally occurring in various fruits and vegetables such as apples, onions, strawberries, grapes, and cucumbers, Fisetin offers a promising role for therapeutic intervention in numerous neurological conditions (88).



Name	Fisetin
Chemical name	2-(3,4 dihydroxyphenyl)-3,7-dihydroxychromen-4-one)
Molecular formula	$C_{15}H_{10}O_6$
Molecular weight (g/mol)	286.2363
Appearance	Yellow powder
Melting point (°C)	330
Boiling point (°C)	599.4 at 760 mmHg
Flash point	233
LogP	3.2
Solubility	Low aqueous solubility (10.45 µg/mL), moderately soluble in ethanol (5 mg/mL), highly soluble in DMF and DMSO (30 mg/mL)

Figure 4. Chemical structure and Properties of Fisetin - This image presents the structural formula and key chemical properties of Fisetin, a flavonoid compound.

Preclinical studies have demonstrated its efficacy in combating neurological complications associated with other conditions like Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, vascular dementia, schizophrenia, stroke, depression, diabetic neuropathy, and traumatic brain injury. Acting as both an antioxidant and an anti-inflammatory agent, Fisetin exhibits promising neuroprotective effects by mitigating inflammation, senescent cell accumulation, and oxidative stress, particularly in aging brains (88).

One of the notable mechanisms underlying Fisetin’s neuroprotective effects is its ability to regulate mitochondrial activity. By restoring mitochondrial function, enhancing metabolic processes, and scavenging ROS, Fisetin helps alleviate oxidative stress-induced cellular damage, thereby preserving neuronal health. Furthermore, it has been shown to modulate key neurotrophic factor-induced signalling pathways, which play crucial roles in neuronal survival and function (88,97).

Moreover, Fisetin demonstrates the capacity to prevent lipid peroxidation and increase levels of the antiapoptotic factor Bcl2, thereby protecting against neuronal death induced by oxidative stress. Notably, Fisetin has been observed to safeguard neuronal cells against glutamate toxicity and hypoglycaemia-induced neuronal death, highlighting its potential as a therapeutic agent for various neurological disorders (88).

In addition to its neuroprotective effects, Fisetin possesses senolytic properties, making it a promising candidate for targeting senescent cells implicated in age-related diseases. Senescent cells (SC) are cells that have ceased to divide and proliferate due to various stressors such as DNA damage, oxidative stress, or telomere shortening. While senescence is initially a protective mechanism to prevent the proliferation of damaged cells, SC can accumulate with age and contribute to tissue dysfunction and inflammation. These cells are characterized by a unique senescence-associated secretory phenotype (SASP), wherein they secrete pro-inflammatory cytokines, growth factors, and proteases that can disrupt tissue homeostasis and promote chronic inflammation. SC play a significant role in aging-related diseases and age-associated decline in tissue function. Fisetin has shown to selectively eliminate senescent cells, thereby alleviating age-related pathologies and improving overall health span. This senolytic action further enhances Fisetin's therapeutic potential in aging-related neurodegenerative diseases (88,107).

5.2 The role of miRNAs in Alzheimer's Disease

MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules approximately 18–22 nucleotides in length, playing crucial roles in post-transcriptional gene regulation. They achieve this by binding to complementary sequences within the 3' untranslated regions (3′-UTRs) of target messenger RNAs (mRNAs), thereby regulating their expression either by inhibiting translation or by inducing mRNA degradation. The dysregulation of miRNAs has been implicated in various human diseases, including AD, cancer, heart disease, hypertension, arthritis, diabetes, and obesity. The unique characteristics of miRNAs, including their ability to target multiple mRNAs and their responsiveness to environmental stressors, make them attractive candidates for therapeutic intervention. MiRNA-based therapeutics offer the potential to modulate complex molecular networks dysregulated in disease states, providing a promising avenue for the development of novel treatment strategies. In recent years, the significance of miRNAs in the pathogenesis of AD and other neurodegenerative disorders has garnered increasing attention. Studies have revealed alterations in miRNA expression profiles in AD brains, suggesting their involvement in disease progression. Additionally, miRNAs have been implicated in regulating key processes such as neuroinflammation, synaptic function, and the accumulation of pathological proteins like Aβ and tau, hallmark features of AD pathology (108–110).

Table 2. Overview of miRNAs Associated with Alzheimer's Disease (AD) - This table provides a comprehensive overview of the miRNAs associated with various aspects of Alzheimer's Disease pathology, including amyloid-beta (Aβ) accumulation, tau pathology, and neuroinflammation, along with their target mRNAs. (110)

AD Phenotype	miRNA	Target mRNA
Aβ	miR-16, miR-17, miR-20a, miR-101, miR-106a	APP
	miR-106b, miR-147, miR-153, miR-520c	
	miR-15a, miR-15b, miR-29a, miR-29b, miR-29c	BACE1
	miR-103, miR-107, miR-298, miR-328, miR-195	
	miR-485	
Tau	miR-128	BAG2
	miR-9	SIRT1
	miR-922, miR-181b	UCHL1
	miR-124	Caveolin-1
	miR-132	ITPKB

	miR-34a	Tau
	miR-26b	Rb1
Neuroinflammation	miR-7, miR-223	NLRP3
	miR-9	NLRP1
	miR-22	GSDMD
	let-7 family	TLR4, IL-6
	miR-485	AKT3

5.2.1 miRNAs modulation of Aβ

As discussed previously, the amyloid hypothesis, posits that Aβ accumulation, resulting from the processing of APP, plays a central role in the pathogenesis of AD. Aβ, primarily the Aβ-42 isoform, is generated through sequential cleavage of APP by β-secretase and γ-secretase, leading to the formation of neurotoxic Aβ plaques, which are implicated in disrupting neuronal homeostasis and inducing synaptic dysfunction (18).

Emerging evidence suggests that miRNAs play crucial roles in modulating key players in the amyloidogenic pathways. Various miRNAs, including miR-20a, miR-106a, miR-106b, miR-17-5p, miR-16, miR-101, miR-147, miR-153, and miR-520c, have been identified to directly regulate APP expression by targeting its 3′-UTR. Notably, suppression of miR-106b and miR-101 in AD brains correlates with increased APP expression and Aβ production. Additionally, certain AD-associated genetic variations influence the regulatory activity of miR-147 and miR-20a on APP.

Furthermore, disruption of the regulation of miRNAs has been linked to aberrant levels of β-secretase cleaving enzyme 1 (BACE1), a key enzyme involved in Aβ production. Several miRNAs, such as miR-107, miR-298, miR-328, miR-15a, miR-15b, miR-195, miR-103, and miR-485, target the 3′-UTR of BACE1 and are found to be lowered in AD patients. Notably, reduced levels of miR-29a and miR-29b correlate with elevated BACE1 levels, suggesting miR-29's role as an endogenous regulator of BACE1. Moreover, miRNAs influence AD pathology beyond amyloidogenesis. Decreased levels of monocyte lysosomal hydrolases, including cathepsin B, D, and S, contribute to Aβ accumulation. Recent studies indicate that the enhancement of miR-128 leads to suppression of these lysosomal enzymes. Inhibition of miR-128 in monocytes from AD patients restores lysosomal enzyme expression and enhances Aβ

degradation capacity, suggesting a role for miRNAs in modulating Aβ clearance via enzymatic regulation (110).

5.2.2 miRNAs modulating Neuroinflammation

As referenced earlier, the accumulation of proteins associated with AD pathology triggers immune responses via receptors on microglia and astrocytes, leading to the release of inflammatory mediators. While a short-term inflammatory response aids in removing the causative agent and facilitating recovery, persistent inflammation results in irreversible tissue damage. In AD patients, continuous inflammatory responses contribute to neuronal loss, exacerbating disease progression (18,21,32).

Research indicates activation of the NLRP3-inflammasome in microglia in AD, upregulating inflammasome-forming factors like NLRP3, caspase-1, and ASC. This activation leads to heightened secretion of pro-inflammatory cytokines, including interleukin (IL)-1 beta and IL-18, ultimately inducing neuronal death (110).

Studies demonstrate that miR-7 inhibits NLRP3-inflammasome activity in microglia, with anti-miR-7 conversely activating the inflammasome. In mouse models, miR-7 reduces the inflammatory response (111). Similarly, other studies found that miR-9 overexpression suppresses NLRP1-inflammasome activation by regulating NLRP1 expression, subsequently reducing IL-1β and IL-18 levels (112).

In the context of neuroinflammation, inflammasome activation leads to pyroptotic cell death and the secretion of proinflammatory cytokines. miR-22 targets Gasdermin D (GSDMD), a key player in pyroptosis. Reduced miR-22 expression in AD patients correlates with increased inflammation. Overexpressing miR-22 in an APP/PS1 mouse model enhances memory and behaviours while suppressing proinflammatory cytokine expression by inhibiting GSDMD, thereby preventing pyroptotic cell death. These findings suggest that miRNAs wield significant influence over neuroinflammation regulation, offering a potential avenue for AD treatment (110).

5.2.3 miRNAs modulating Tau

As stated before, Tau, a microtubule-associated protein originating from the alternative splicing of the MAPT gene, is primarily situated in neuronal axons, governing microtubule integrity, cytoplasmic transport, synaptic structure, and

neuronal signalling. In AD, hyperphosphorylation of tau disrupts microtubule architecture, impairs tubulin polymerization, and prompts the formation of insoluble aggregates within neurons, culminating in synaptic loss and cellular dysfunction. (28,31).

miRNAs play an important role in tau protein homeostasis regulation. For instance, miR-128a modulates chaperone protein BAG2 expression, crucial for tau degradation and aggregation. Additionally, miR-124, miR-132, and miR-9 influence endogenous tau accumulation, while miR-34a and miR-26b suppress tau expression and affect NFT formation. The upregulation of miR-9 coincides with decreased Sirtuin 1 (SIRT1) expression, implicating miRNAs in maintaining microtubule and synaptic integrity through tau regulation.

Tau phosphorylation is essential in AD progression. Suppression of miR-101 enhances phosphorylated tau levels, while miR-922-mediated reduction of Ubiquitin Carboxyl-terminal Hydrolase Isozyme L1 (UCHL1) expression mitigates phosphorylated tau levels. Conversely, elevated miR-138 levels in AD models promote tau phosphorylation via the retinoic acid receptor alpha/GSK-3β pathway. On the other hand, miR-326 diminuition reduces tau phosphorylation. These findings underscore the intricate involvement of miRNAs in managing tau phosphorylation. In conclusion, miRNAs represent promising therapeutic targets for moderating tau-related pathological characterists (110).

5.2.4 Circular RNA in Alzheimer's disease

Circular RNAs (circRNAs) are a type of RNA molecule characterized by a continuous loop structure, distinct from the linear structure of conventional messenger RNA (mRNA). They are widely expressed across various mammalian cells and can exhibit tissue-specific patterns. Unlike linear mRNA, which is generated through conventional splicing of exons in a linear way, circRNAs are formed through a process called back-splicing. During back-splicing, a splice donor site is joined to an upstream splice acceptor site or another upstream exon, resulting in the formation of a circular transcript. This circularization process can be facilitated by RNA-binding proteins (RBPs) and various splicing factors such as QK1, ADAR, ESRP1, and FUS. The

cerebellum has the highest concentration of circRNAs, followed by the prefrontal cortex and hippocampus (113,114).

One prominent mechanism by which circRNAs contribute to AD pathology is through their interaction with disease-associated miRNA. For example, ciRS-7 has been extensively studied due to its dense binding sites for miR-7. CiRS-7 acts as a miRNA antagonist (also referenced scientifically as “sponge”), regulating the expression of miR-7 target genes implicated in AD, such as ubiquitin-protein ligase A (UBE2A).(114–116) Additionally, circRNA-138 (circHDAC9) has been implicated in regulating Aβ metabolism by modulating miR-138 expression, leading to alterations in APP processing and Aβ accumulation (114,116). Moreover, circRNA-mediated dysregulation of tau protein phosphorylation. CircRNA circPCCA, for example, competitively binds to miR-138-5p, thereby modulating glycogen synthase kinase-3β activation and tau phosphorylation (114,116,117).

Further insights into circRNA dysregulation in AD have been gained through analysis of CSF and tissue samples from AD patients. Differential expression of numerous circRNAs has been observed, with some enriched in pathways associated with AD pathology. For example, circLPAR1, circAXL, and circGPHN were upregulated, while circPCCA, circHAUS4, circKIF18B, and circTTC39C were downregulated in AD patients (114). Moreover, emerging evidence suggests that circRNAs may exert regulatory functions beyond miRNA antagonizing, including acting as templates for translation, serving as delivery vehicles, or assembling RBP factories (118).

In summary, circRNAs represent a promising avenue for understanding the molecular mechanisms underlying AD pathology (114,116).

5.3 Psychedelics as a Treatment for Alzheimer's Disease Dementia

The term "psychedelic" was introduced by psychiatrist Humphry Osmond in 1956 to describe a class of compounds that induce profound changes in consciousness. Derived from Greek roots meaning "mind-manifesting," the term reflects the compounds' ability to alter perception and cognition. In recent years, there has been growing interest in exploring alternative treatments for AD, including the potential use of psychedelics (119,120). This chapter aims to examine the potential of psychedelics

as a treatment for AD dementia, exploring their mechanisms of action and their effects on neuroplasticity, neuroinflammation, and neural cell regeneration. Observations of cognitive enhancements from micro-dosing, combined with recent advances in psychedelic research, particularly with regard to compounds such as psilocybin, lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), point to the potential therapeutic applications of these drugs in a range of neurological and psychiatric conditions (121).

Psychedelics are a class of hallucinogenic drugs that produce mind-altering and reality-distorting effects, such as hallucinations, which can trigger delusions, emotional swings, and feelings of detachment. Hallucinogens are generally divided into two main categories: dissociative drugs (like dextromethorphan, ketamine, and Phencyclidine (PCP)) and classic serotonergic and dopaminergic hallucinogens, which interact with serotonin and dopamine receptors. Classic serotonergic and dopaminergic hallucinogens include lysergamides (like LSD and ergotamine), phenethylamines (such as 3,4-methylenedioxy-N-methamphetamine (MDMA), mescaline, and related compounds), and tryptamines (like DMT, psilocin, and psilocybin) (122).

5.3.1 Mechanism of action of Psylocibin, LSD and DMT

5.3.1.1 Psylocibin

Naturally present in certain mushrooms, psilocybin is quickly transformed into its active metabolite, psilocin, when consumed. With a strong affinity for the 5-HT2A receptor, psilocin predominantly functions as a partial agonist at serotonin (5-HT) receptors. Perception, emotion, and cognitive function are all affected when these prefrontal brain receptors are activated. Increased cortical activity and connectivity as a result of psilocin interaction with 5-HT2A receptors is thought to underpin its therapeutic effects in a variety of psychiatric disorders, including depression and anxiety, which are common symptoms of late-onset Alzheimer's disease and as the disease progresses (121,123).

5.3.1.2 Lysergic Acid Diethylamide (LSD)

One synthetic substance with strong hallucinogenic effects is LSD. Numerous receptors are bound by LSD, including: dopamine D1 and D2, α-adrenergic receptors, 5-HT1A, 5-HT2A/C, and others. Its strong affinity for 5-HT2A receptors is especially interesting since its hallucinogenic effects depend on this interaction. LSD's distinct

psychopharmacological profile, which includes effects on mood and cognition that can last up to 12 hours, is also influenced by its action on dopamine receptors (121,124).

5.3.1.3 N,N-Dimethyltryptamine (DMT)

N,N-Dimethyltryptamine is a powerful psychedelic found in several plants and animals. DMT is unique among psychedelics for its rapid onset and short duration of action. It primarily acts as an agonist at the 5-HT2A receptor but also affects other serotonin receptor subtypes such as 5-HT1A and 5-HT2C. In its traditional form, Ayahuasca, DMT is combined with monoamine oxidase inhibitors (MAOIs) to prevent its rapid degradation, allowing it to be orally active. The acute effects of DMT, which include intense visual and auditory hallucinations, typically last for about 15-30 minutes when smoked or injected, and up to several hours when ingested as Ayahuasca (121,125).

5.3.1.4 5-Methoxy-N,N-dimethyltryptamine (5-MeO-DMT)

5-MeO-DMT is a potent, naturally occurring psychedelic compound found in various plant species and it primarily acts as a serotonin receptor agonist. It has a high affinity for 5-HT1A receptors, which distinguishes it from other psychedelics that mainly target 5-HT2A receptors. This binding profile is thought to be responsible for its unique effects (126). Recent research has indicated that 5-MeO-DMT may have therapeutic potential, particularly in the treatment of mood disorders such as depression and anxiety. Preliminary studies suggest that it can induce neuroplasticity and neurogenesis, contributing to its antidepressant effects (127).

Table 3: Pharmacological Profile of Selected Psychedelics - This table provides a detailed comparison of the receptors, pharmacokinetics, and dosage information for the psychedelic compounds Psilocybin, lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT) and 5-MeO-DMT.

Psychedelic	Receptors	Pharmacokinetics	Dosage Information
Psilocybin	5-HT1A/B/D/E, 5-HT2A (high affinity), 5-HT2B, 5-HT5, 5-HT6, 5-HT7	Linear pharmacokinetics over 0.3–0.6 mg/kg oral dose range. Degraded into active metabolite psilocin.	Typical oral dose: 0.3–0.6 mg/kg. Effects start 10–40 min post-ingestion.

LSD	5-HT1A/D, 5-HT2A/B/C, 5-HT6, dopamine D1 and D2, α-adrenergic receptors	Dose-proportional pharmacokinetics. Maximum plasma concentration at 1.5 h after ingestion.	Typical dose: 75–150 μg orally. Effects last 6–12 h.
DMT	5-HT1A/D, 5-HT2A, 5-HT6	Effects arise within minutes when inhaled or injected.	
5-MeO-DMT	5-HT1A, 5-HT2A/B/C	N/A (typically not ingested orally without MAOIs)	

5.3.2 The importance of Neuroplasticity in AD

Neuroplasticity, or brain plasticity, refers to the brain's ability to adapt and reorganize itself by forming new neural connections throughout life. This process is crucial for learning, memory, and recovery from brain injuries, and it plays a significant role in countering neurodegenerative diseases like AD (128) Research on traditional psychedelics including LSD, psilocybin, and ayahuasca that contains DMT has risen in recent years. These drugs have demonstrated promise in the treatment of mental health conditions such as addiction, anxiety, and depression, symptoms that are present in late on-set AD and that worsen with the progression of the disease. The potential of psychedelics to promote neuroplasticity quickly and persistently—the neural system's ability to reorganize itself in response to experiences and environmental changes—is thought to be the source of the long-lasting therapeutic advantages seen in patients (129). So, this information poses the question: how can psychedelics be relevant in Alzheimer's Disease?

Several mechanisms are thought to be involved in how psychedelics increase neuroplasticity: they stimulate dendritogenesis (dendrite growth), synaptogenesis (synapse formation), neurogenesis (new neuron generation), and upregulate the expression of genes linked to plasticity, such as immediate early genes (IEGs) and brain-derived neurotrophic factor (BDNF) (119). These results have been confirmed by research conducted on animals, which demonstrates that psychedelics can promote dendritic and synaptic development as well as the expression of genes linked to synaptic

plasticity (122). Less is known about how psychedelics affect neurogenesis; some seem to increase it while others have no impact or perhaps slightly decrease it. Psychedelics have had varying effects on peripheral BDNF levels in human studies. After using LSD and ayahuasca, some research shows elevated BDNF levels; other investigations reveal no discernible alterations (128,129).

The primary mechanism by which psychedelics improve neuroplasticity is through the stimulation of the 5-HT2A receptor, which is also responsible for mediating many of their subjective effects. When this receptor is activated, extracellular glutamate levels rise and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are stimulated. This starts a feedback loop that involves the mammalian target of Rapamycin (mTOR), BDNF pathways and promotes dendritic development. Furthermore, sigma-1 and 5-HT1A receptors may be the route via which DMT and 5-MeO-DMT trigger their effects, respectively. Psychedelics primarily improve neuroplasticity in areas of the brain like the neocortex that have large quantities of 5-HT2A receptors. (130) Increased dendritic development and overexpression of genes associated to plasticity in cortical neurons have been seen in animal studies. Psychedelics quickly enhance presynaptic density and upregulate genes linked to neuroplasticity in the prefrontal cortex (PFC). The hippocampus has less consistent effects, which may be attributed to a larger density of 5-HT1A receptors in that region (119,121,128). Further study is necessary, however some data points to the possibility that psychedelics may also improve neuroplasticity in subcortical areas including the thalamus, locus ceruleus, and claustrum (122,128).

Psychedelic drugs like LSD, psilocybin, and DMT have been studied for their potential to enhance neuroplasticity. Research in rats has shown that doses of LSD ranging from 0.2 mg/kg to 1 mg/kg promote neuroplasticity-related changes in gene expression, with some genes peaking at lower doses (130). In human studies, sub-hallucinogenic doses of LSD (between 5 and 20 µg) have demonstrated significant short-term enhancements in plasma BDNF. However, higher doses (25 µg to 200 µg) showed significant effects on BDNF only at the highest dose (200 µg), and some studies did not find significant changes even at this dose. This suggests that sub-hallucinogenic doses may still enhance neuroplasticity without causing significant hallucinations (131–133).

For psilocybin, a dose of 4 mg/kg is required to induce neuroplasticity-related changes in rats, with the effect increasing in a dose-dependent manner. In humans, the typical therapeutic dose ranges from 0.3 to 0.6 mg/kg, which also falls within the hallucinogenic range. This overlap indicates that distinguishing between neuroplastic and hallucinogenic effects might be challenging (130).

DMT has shown that a sub-hallucinogenic dose of 1 mg/kg can increase functional plasticity in rat cortical slices (134). In humans, DMT typically induces hallucinogenic effects at common doses due to its rapid onset and short duration. Less is known about sub-hallucinogenic doses in humans, but the rat studies suggest potential for neuroplasticity enhancement without significant hallucinations (130).

Hallucinogenic effects in humans are typically observed at higher doses. For instance, LSD induces hallucinations at doses starting from about 75 µg, with common doses ranging between 75-150 µg orally. This suggests that sub-hallucinogenic doses (below 75 µg) can enhance neuroplasticity without causing significant hallucinations (130,135).

The possibility of using sub-hallucinogenic doses to enhance neuroplasticity is promising for clinical applications. For example, sub-hallucinogenic doses of LSD (5-20 µg) have shown potential in enhancing neuroplasticity without significant hallucinogenic effects. Future research should focus on clearly defining the minimum and optimal doses for stimulating neuroplasticity across different psychedelics, while minimizing or avoiding hallucinogenic effects (130).

Leveraging the therapeutic potential of psychedelics requires an understanding of how they enhance neuroplasticity. To more accurately measure neuroplastic changes, future research should investigate protocols that go beyond peripheral indicators. Examples of such protocols include producing long-term potentiation (LTP)-like alterations or implementing PET scans with synaptic density markers in further studies Targeted therapy development for mental health illnesses and AD will benefit from research on the biochemical pathways and interactions between receptors (129).

6 Conclusion

This research has highlighted the multifaceted nature of AD, resulting in genetic, biochemical, and environmental factors contributing to its pathology. Based on the findings and discussions throughout this thesis, several critical insights into AD and its potential treatments have emerged.

The exploration of miRNAs and circRNAs has revealed their significant roles in regulating gene expression related to tau phosphorylation and Aβ metabolism. These small non-coding RNAs present promising therapeutic targets for moderating tau-related pathological characteristics and Aβ accumulation, thereby offering new avenues for therapeutic interventions in AD.

Furthermore, the potential of psychedelics in enhancing neuroplasticity and possibly improving symptoms of AD has been underscored. Psychedelics like LSD, ayahuasca, and DMT activate 5-HT2A receptors, leading to increased neurogenesis, synaptogenesis, and expression of genes linked to synaptic plasticity. These findings suggest a new approach to treatment, using the unique properties of psychedelics to promote neural repair and cognitive function improvement in AD patients.

The investigation into the role of nutrition, particularly the impact of omega-3 fatty acids and other dietary components, has highlighted their importance in brain health. Although results are still uncertain, few studies suggest that omega-3 PUFAs, in combination with other micronutrients, may slow cognitive decline and improve memory and mood, particularly in the early stages of AD. These insights call for further research into dietary interventions as a non-pharmacological strategy for managing AD and preventing AD in populations.

Pharmacological advancements, including the development of NMDA receptor antagonists and monoclonal antibodies like Aducanumab, mark significant strides in treatment options. While Aducanumab has shown promise in reducing amyloid plaques, its high cost and limited patient eligibility highlight the need for more accessible and comprehensive treatment solutions.

In conclusion, this thesis has provided a comprehensive overview of the complex etiology and pathophysiology of AD, alongside emerging therapeutic strategies. The integration of molecular research with innovative treatment approaches, including

RNA-based therapies, psychedelics, nutritional interventions, and advanced pharmacological treatments, represents a multi strategy approach to combat AD. Future research should focus on refining these approaches, ensuring their efficacy and accessibility to improve the quality of life for individuals affected by this debilitating disease and making it accessible worldwide.

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