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Alzheimer's Disease Epidemiology: Modifiable Risk Factors and Prevention

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ABSTRACT

Alzheimer's disease is a significant risk indicator that is age-based & refers to an array of human ailments & pathogenesis, solely neurodegenerative conditions. By 2050, the frequency of instances of Alzheimer's is projected to triple, making AD a significant threat to public health. This illness is signified by a gradual degradation of neurons, diminished motor or cognitive functions, & aberrant protein aggregates. AD can be treated with a variety of methods. A delayed assessment of AD, which might impact the outcomes of treatment, is a significant obstacle. AD pathology normally coincides along with further neurodegenerative and vascular diseases, specifically in the aging brain. With the goal to provide the proper treatment, assistance & tailored therapies, rapid assessment becomes crucial. When the alterations are relatively insignificant, it might be helpful to diagnose AD at an early stage (prognosis). Presently, there are an array of possible biomarkers for AD assessment & diagnosis. Early diagnosis of AD by means of biomarkers could assists researchers to achieve innovative approaches & therapies for preventing or postpone dementia. A few frequently used methods for AD screening include magnetic resonance imaging and positron emission tomography scans, which look at the brain's structure and function. One way to identify the progression of AD is to evaluate AD-associated proteins in biological fluids such blood, urine, saliva, and cerebrospinal fluid. The review discusses new biomarkers for AD. A table that outlines the differences between distinct biomarkers based on their applications, upsides, & downsides is also provided. At the moment, emphasis is placed on recent advancements in AD detection

Keywords: *Neurodegeneration, Alzheimer's, Oxidative stress, biomarkers, prognosis, diagnosis.*

1. INTRODUCTION

1.1 Neurons:

The nervous system's functioning units are called neurones. The cell body, dendrites, and axon are its three constituent elements. The axon and dendrites may be referred to as nerve fibres [1].

1.2 Anatomy of a neuron:

Among the numerous different forms of neurons, the cell body (soma) is the most variable, followed by the dendrites, axons, and connected axon terminals. (Figure 1).

a. Cell body- This structure is responsible for producing nearly all neuronal proteins and membranes and is characterized by the presence of a nucleus.

b. Dendrites- Neurons' extensions that receive impulses and send them to the cell body (soma) are called dendrites.

c. Axon (nerve fiber)- Axons are the postponements of neurons that carry messages from the cell body to neighboring neurons or other nerve cells.

d. Axon terminal (end-plate)- The term "axon terminal" describes the part of axons that connects to other nerve cells synaptically. It initiates the impulse transmission mechanism between nerve cells [2]

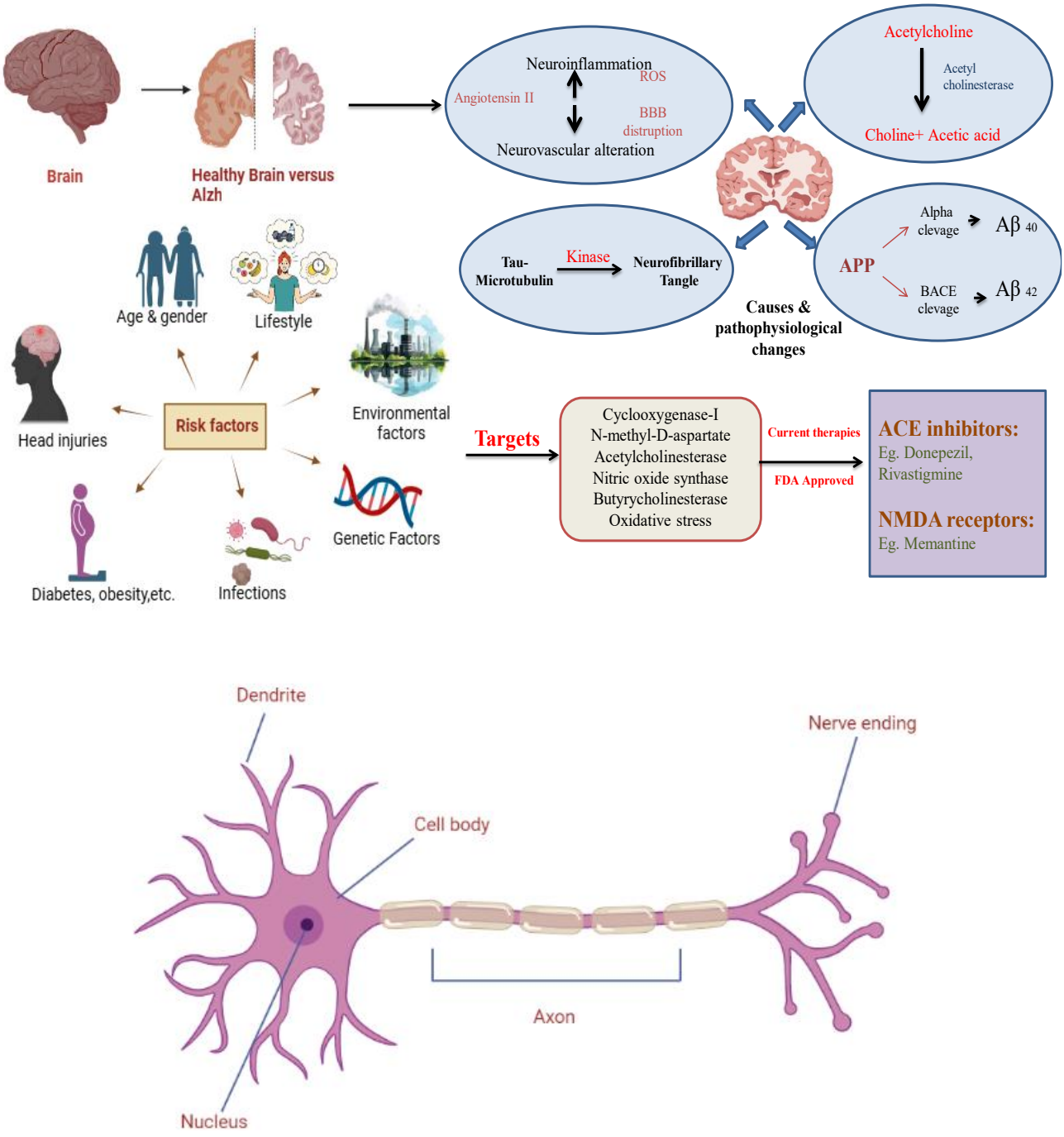

Figure 1: Structure of Neuron

2. NEURODEGENERATIVE DISEASES:

The term "neurodegeneration" is frequently used and is thought to have a clear definition. The origin of the word lies in the combination of "neuro-," a prefix denoting nerve cells (neurons), and "degeneration," a term used to describe the decline or loss of normal structure and function in bodily tissues or organs [3]. Neurodegeneration is fundamentally defined as the progressive deterioration of neural tissue, either in structure or function. This decline may result from a reduction in neuronal or glial cell populations, may primarily affect the central (CNS) or peripheral (PNS) nervous system, and often involves the death of these neural cells [4]. The most common neurodegenerative diseases are Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD). Neurodegenerative disorders are characterized by a progressive decline in motor and/or cognitive function and are caused by the selective degeneration and death of neurons in the central nervous system [5].

Factors associated with neurodegenerative diseases (Figure 2) [6]-

- Abnormal protein dynamics with protein accumulation and breakdown.
- Development of reactive oxygen species (ROS) and oxidative stress.
- Excessive contact with metal and insecticides

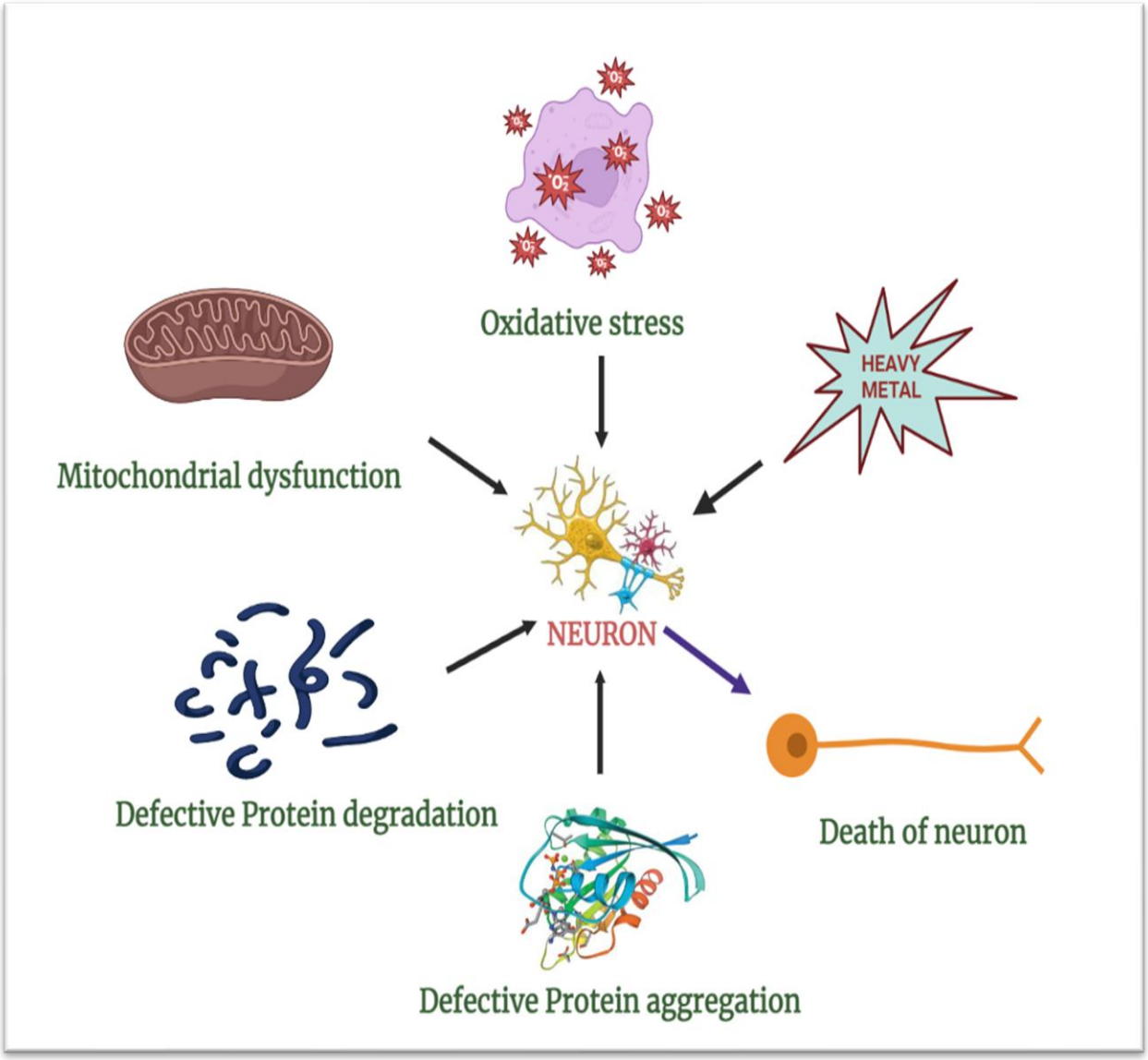

Figure 2: Neurodegenerative disease risk factors

2.1 Abnormal protein dynamics:

The complicated process of amyloid fibrillation involves the formation of several intermediates, such as liquid-like droplets of liquid, oligomers, protofibrils, and amyloid fibrils. Amyloid monomers are kept in a solvable and non-toxic condition in a healthy brain. But these monomers can reassemble into different mediates in a damaged brain, which can result in amyloid fibrils and, eventually, amyloid plaques. Drops that resemble liquid are thought to be crucial steps in the aggregation process because they enable the quick formation of amyloid fibrils. Additionally, gel like or glass like condensates might encourage the production of stable oligomers and protofibrils, which may contribute to amyloid fibrillation. Developing knowledge about how these intermediates contribute to amyloid fibrillation could assist to design treatment plans for neurological disorders linked to amyloid plaques (Figure 3) [7.8].

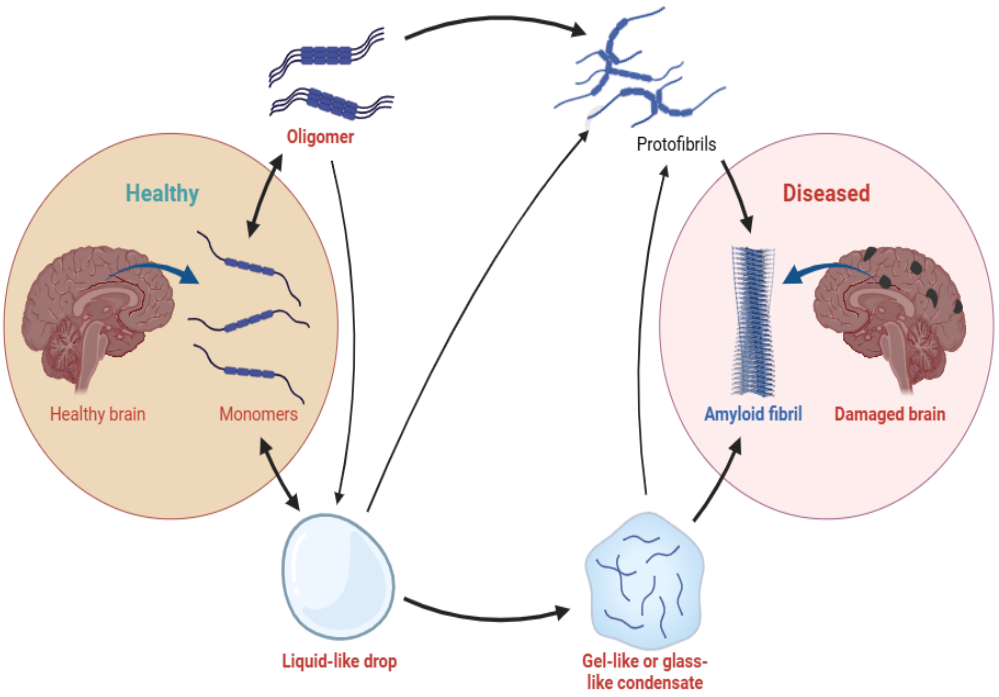

Figure 3: Abnormal protein dynamics with protein aggregation and breakdown

2.2 Oxidative Stress:

All biological organisms form cells typically yield reactive oxygen species (ROS) as a consequence of internal homeostasis systems and regular physiological processes. Under physiological settings, a number of processes, including immunological response, inflammation, synaptic plasticity, learning and memory are linked to low to direct connections of ROS. The working of cellular components like mitochondria may be directly impacted by the hazardous environment created by an excess of ROS, leading to a wide range of illnesses and ailments [9,10].

In order to counteract the effects of oxidants, the human body has a variety of antioxidant agents. These include the scaffolds of enzymes such as glutathione (GSH) and superoxide dismutase (SOD) [11]. The disruption of this balance, whether from the overrun of reactive oxygen species or the depletion of antioxidant compounds, may affect in oxidative impairment, which ultimately leads to the general impairment of cellular functions [12]. Numerous pathophysiological diseases, such as mitochondrial malfunction and other cellular abnormalities, exhibit this effect. Because of its high oxygen consumption, low antioxidant agent barriers and high polyunsaturated fat content the central nervous system and particularly the brain is helpless in contrast to oxidative stress and damage (Figure 4) [13-15].

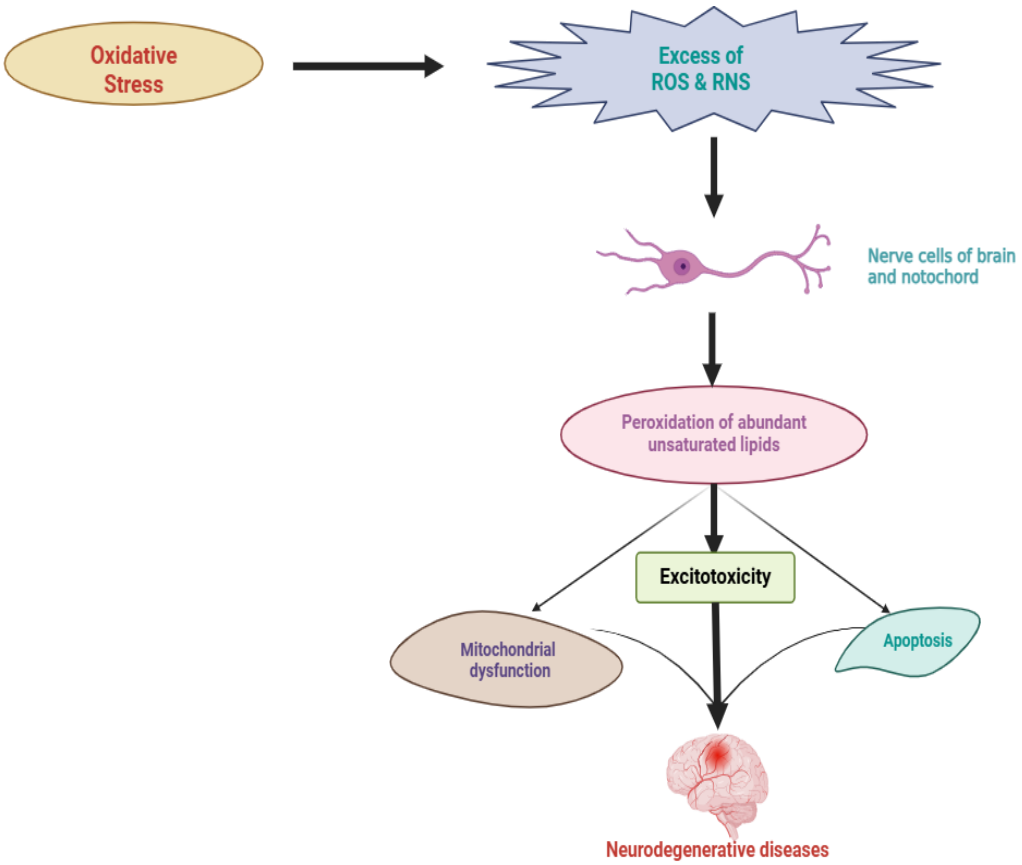

Figure 4: Production of reactive oxygen species (ROS) and oxidative stress

2.3 Excessive contact with metals and insecticides:

The progression of AD may be diminished down or accelerated by environmental risk factors. Prolonged contact to a number of heavy metals such as aluminum, arsenic, cadmium, lead and mercury, air contaminants, certain pesticides and metal containing nanoparticles constitute some of the well-known risk factors from the environmen been linked to AD. Neuronal cell death has been noted as a result of these heavy metals' willingness to elevate tau phosphorylation and amyloid β (Aβ) peptide which may contribute to the emergence that have of amyloid/senile plaques and neurofibrillary tangles [15]. Additionally it has remained reported that exposure to heavy metals, herbicides, and air particle contributes to genetic variation and AD susceptibility via genetic pathways. In order to gain additional insight into the association between AD and environmental risk factors as well as their mechanisms of action on brain functions (Figure 5) [17].

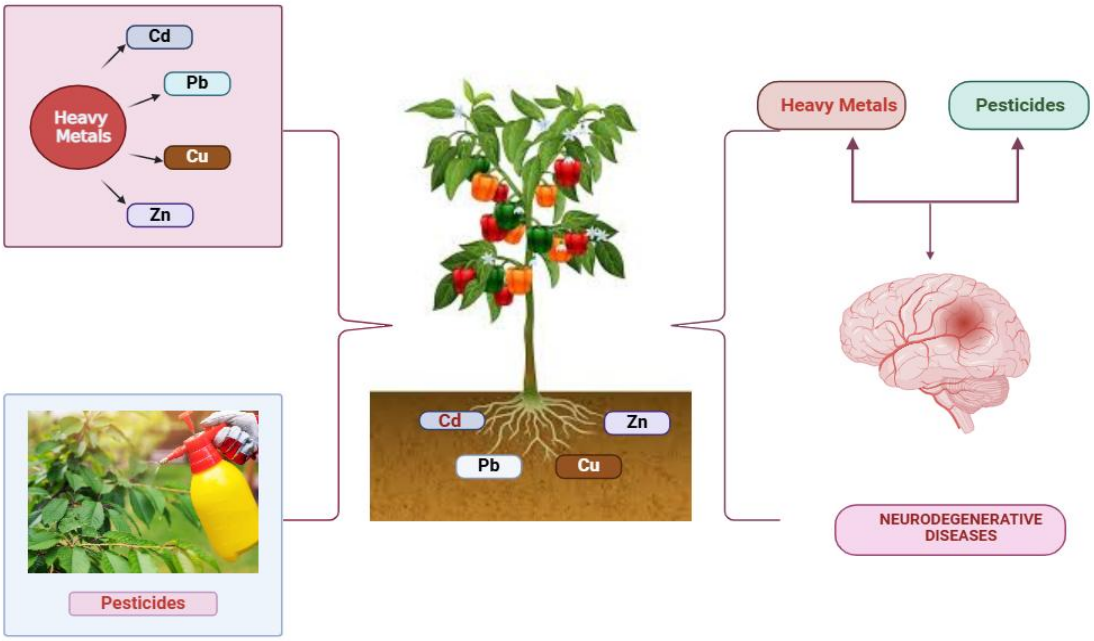

Figure 5: Excessive contact with metals and insecticides

2.4 Classification principles for diseases [18]

Based on the following criteria, neurodegenerative disorders are categorized as -

1. Clinical signs based on anatomical region exhibiting neuronal dysfunction.

2. Intracellular proteins that build up in glial or neuronal cells or in extracellular regions and display a variety of biochemical changes.

As a result, patterns of anatomical, cellular, and molecular susceptibility can be identified in neurodegenerative diseases.

3. ALZHEIMER

The most frequent neurological condition linked to ageing is Alzheimer disease (AD), which is also the most common cause of dementia. Due to genetic and environmental factors acting as risk or causative moderators, Alzheimer disease is a diverse disorder with a complex aetiology [19-21]. The most noticeable clinical symptom of Alzheimer's disease, is loss of memory and confusion, associated with neuronal degeneration in the hippocampal area. The progression of the disease is linked to neuropathological alterations such as the death of neurons, intracellular deposition of hyperphosphorylated tau (also known as "tangles"), and extracellular deposits of amyloid plaques [22,23].

3.1 History

The neurodegenerative illness Alzhimer is characterised clinically by gradual cognitive decline, memory loss, emotional instability, aphasia, linguistic difficulties, and the inability to carry out routine daily activities. Currently, it is typically divided into two groups [24]:

1. Early onset AD (EOAD)
2. Late onset AD (LOAD)

3.2 Pathogenesis of alzhimer disease: Hypothesis

3.2.1 Cholinergic hypothesis:

It is the earliest theory based on cholinergic dysfunction . A cholinergic neurotransmitter that is involved in memory and learning is acetylcholine (ACh). It came to light that acetylcholinesterase deficiency may result in a reduction in cholinergic function linked to cognitive impairment. In comparison to normal brain, the cerebral cortex and all added parts of the brain from Alzhimer patients have decreased activity of choline acetyl transferase and acetylcholinesterase (Figure 6) [25].

3.2.2 Tau hypothesis:

An odd increase in the quantity of hyperphosphorylated tau proteins in the cytoplasm has been observed under pathogenic conditions. The cytoplasm of AD brains also contains an abundance of tau protein that has been excessively hyperphosphorylated. A pathological disturbance in the structural and regulatory activities of the cytoskeleton results from the loss of normal tau function [26]. These factors have an effect on the preservation of proper morphology, axonal transport, synaptic dysfunction, and neurodegeneration—all typical biological processes of neurons. The several pathogenic mechanisms contribute to tau aggregation formation, tau misfolding, and hyperphosphorylation. Even after extensive research, it is still unknown how excessive hyperphosphorylation of tau protein influences pathological and physiological conditions [27].

3.2.3 Amyloid Cascade Hypothesis:

The growth of amyloid beta (Aβ), which develops due to an imbalance between the biosynthesis or evacuation of Aβ peptides, is one of the principal pathogenic characteristics of AD. A neurodegenerative cascade is started when this imbalance causes the peptide to progressively accumulate and aggregate in the brain [28]. The enzymes α-secretase, β-secretase, and γ-secretase break down the precursor protein of amyloid (APP) into soluble small peptides known as amyloid beta (Aβ). The imbalance between the production and clearance of amyloid beta (Aβ) results in a variety of damaging oligomeric forms, such as protofibrils, fibrils, and plaques, depending on the degree of oligomerization. The exact cause of amyloid beta (Aβ) generation is still unknown, but its stability, concentration, and advancement all play important roles [29,30].

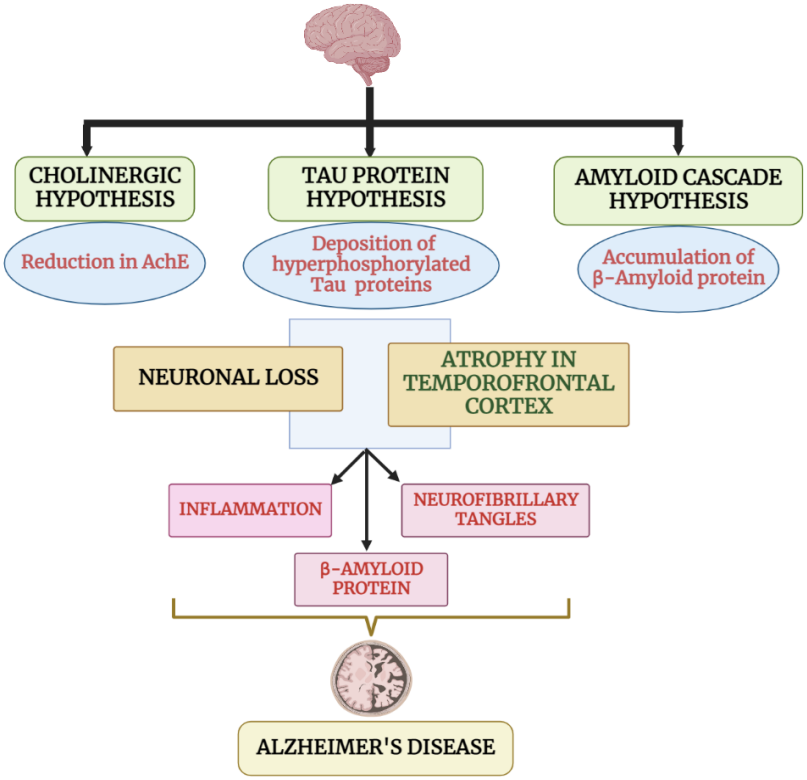

Figure 6: Pathogenesis of alzhimer disease

3.3 Pathophysiology of AD:

Alzheimer's disease (AD) predominantly affects individuals over the age of 65 and occurs more frequently in women than in men. Growing evidence indicates that AD is closely linked to neuroinflammation and heightened immune system activity. For example, inflammatory responses often trigger the activation of microglia and astrocytes, which in turn can lead to an increased production of β-amyloid protein [31]. Three key proteins have been implicated in familial cases of Alzheimer's disease: amyloid precursor protein (APP), which undergoes sequential cleavage by β- and γ-secretases to generate amyloid-β (Aβ) peptides, and presenilin-1 (PS1) and presenilin-2 (PS2), each of which serves as a critical component of the γ-secretase complex [32].

4. BIOMARKERS:

Biomarkers are measurable physiological, biochemical, or anatomical indicators that reflect specific pathological changes occurring in a disease and can be assessed in vivo. In the context of Alzheimer's disease (AD), biomarkers are commonly

classified based on the method of analysis into two main categories: biochemical biomarkers derived from cerebrospinal fluid (CSF) and imaging-based biomarkers. Table 1 summarizes the key biomarkers employed in the diagnosis and prognosis of AD [33].

Some of the most highly studied AD biomarkers are as follows:

4.1 Cerebrospinal Fluid Biomarker:

CSF analysis is a clinically useful and well-established method for analyzing the underlying causes of AD. It is affordable and more readily available than PET, requires no radioactive exposure, and uses fewer resources. A spinal tap, also called a lumbar puncture, is necessary for CSF analysis, even though it is usually a safe technique [34,35].

In recent years, cerebrospinal fluid (CSF) biomarkers have become integral to standard diagnostic procedures for Alzheimer's disease. Reflecting key pathological processes—namely, $A\beta_{42}$ aggregation and tau hyperphosphorylation—the concentrations of beta-amyloid peptide (Aβ), total tau (t-tau), and phosphorylated tau (p-tau) in CSF are regarded as specific biomarkers for Alzheimer's disease. These biomarkers play a crucial role in supporting the clinical diagnosis of probable Alzheimer's disease [36].

The FDA and European Medicines Agency (EMA) have validated and agreed a variety of CSF measurements during the past 20 years for the monitoring of tau and amyloid pathology in AD antemortem. In the previous decades, Aβ42, P-tau181 (tau hyperphosphorylated at threonine 181), and T-tau (total tau) were the CSF statistics of interest. More recently, it has been demonstrated that In multiple instances, tau biomarker tests (such as Lumipulse G P-tau181) have been legalized with SoTs indicative of amyloid pathology (amyloid PET), even though we regard amyloid and tau pathology biomarker findings as indications of amyloid and tau status, respectively [37].

Zetterberg and Blennow recently reviewed the topic of determining a concentration of CSF biomarkers via a variety of methodologies, which include chemiluminescence enzyme immunoassay (CLEIA), enzyme-linked immunosorbent assay (ELISA), immunoassay with electrochemiluminescence detection (ECL, commonly referred to as ECLIA), and single molecule array (Simoa) [38].

4.2 Amyloid-beta (Aβ) as biomarker:

A protein fragment designated as Aβ builds up in the brain of individuals who have Alzheimers disease. Alzhimer disease is characterized by plaques, which developed as a result of Aβ deposition. A valuable screening for the analysis of Alzheimer's disease is the detection of Aβ in cerebrospinal fluid (CSF). According to research, Alzheimer's disease is indicated by low levels of Aβ42 and high contents of Aβ40 in the CSF [39]. As the key constituent of the amyloid plaques that characterize AD, it is currently believed that decreased CSF Aβ42 concentrations are the consequence of its sequestration and agglomeration in brain amyloid plaques. The quantities of Aβ42 are a form and the ratio of Aβ42 and Aβ40 isoforms are foremost widely renowned CSF amyloid manifestations [40].

4.3 Tau protein as biomarker:

Tau is a protein found in central nervous system neuron that stabilizes microtubules. Tau tangles arise in the brain as an outcome of dysfunctional tau protein in Alzheimer disease. One of the primary pathological features associated with Alzheimer's disease includes these tangles. Consequently, tau protein has been recognized as a potentially infectious biomarker. Tau biomarkers have become the subject of multiple research investigations focusing towards the identification and prognosis of Alzheimer's disease. According to one such study, it is attainable to distinguish between people with Alzheimer's disease and healthy controls by recognizing the amounts of phosphorylated tau (p-tau) in the cerebrospinal fluid (CSF). Likewise, an additional investigation demonstrated that determining blood levels of p-tau and total tau (t-tau) can also reliably identify Alzheimer's disease [41,42].

4.4 Neuroimaging Biomarkers:

Patients with Alzheimer's disease may have structural and functional changes in their brains that can be recognized using neuroimaging techniques like positron emission tomography (PET) and magnetic resonance imaging (MRI). For instance, PET imaging with amyloid-specific radiotracers can be utilized for detecting the presence of amyloid plaques. Early detection of AD can be achieved by the use of neuroimaging, a non-invasive biomarker [43].

4.5 Magnetic resonance imaging (MRI):

4.5.1 FUNCTIONAL MRI

Brain function can also be measured by MRI. Blood flow and oxygen levels can be determined by functional magnetic resonance imaging (FMRI) which calculates brain activity at rest or during mental, auditory, or motor activities. A blood-oxygenation-level dependent (BOLD) signal, which is obtained through variations in local blood flow and oxygenation, is the primary outcome assessed in FMRI investigation. The BOLD signal is a useful indicator of brain activation because activity-related brain metabolism is very closely linked to regional blood flow and oxygenation (i.e., blood flow increases to hold the regional oxygen level in the blood high during brain stimulation accompanied by increases in metabolic demand).

But the BOLD signal may change as the consequence of altered neuronal metabolism and blood flow coupling carried on by brain damage and/or inadequate perfusion [44].

4.5.2 Structural MRI

The early identification of structural MRI abnormalities during the asymptomatic phase indicates that they may be able to predict future dementia prior symptoms emerge. The first obvious symptoms of early AD that can be detected on a structural MRI are a drop in the width of the cerebral cortex in AD vulnerable regions and atrophy in middle temporal lobe, especially throughout the hippocampus. MTL atrophy can also be utilized as an indicator in the finding of probable AD, as evidenced by the strong correlation between the existence of MTL degenerative pathologies at autopsy and the degree of MTL atrophy as determined by MRI scans [45,46].

4.6 POSITRON EMISSION TOMOGRAPHY:

One of the most advanced and clinically utilized imaging biomarkers for Alzheimer's disease is positron emission tomography (PET) with ligands that target amyloid-beta (Aβ). This technique enables the in vivo visualization of both the distribution and density of Aβ plaques (amyloid PET) as well as neurofibrillary tangle (NFT) pathology (tau PET) in the brain. To date, three Aβ-specific radiotracers—florbetapir, florbetaben, and flutemetamol—have been approved for clinical use by the European Medicines Agency and the U.S. Food and Drug Administration. These tracers exhibit high diagnostic accuracy for detecting cortical amyloid deposition, a finding corroborated by postmortem pathological studies in elderly patients who underwent scanning shortly before death [47].

Despite their sensitivity, the clinical value of amyloid PET imaging lies more in its ability to exclude Alzheimer's disease than to definitively confirm it. While cerebral amyloidosis is a necessary feature of Alzheimer's pathology, it is not sufficient on its own for diagnosis. As such, amyloid PET has a high negative predictive value: a negative scan in a cognitively impaired individual strongly suggests that Alzheimer's disease is unlikely. However, its positive predictive value is more limited, given that up to 35% of cognitively normal individuals over the age of 60 may exhibit amyloid positivity.

Among the available tracers, Pittsburgh compound B (PIB) is a well-characterized Aβ ligand used in PIB-PET imaging to quantify both the global amyloid load and its spatial distribution in the brain. PIB-PET provides a valuable window into early Alzheimer's pathogenesis by capturing Aβ deposition—an upstream event that likely initiates the cascade leading to downstream neurodegeneration, which is more directly associated with cognitive decline [48].

4.7 Fluro-D-glucose PET (FDG-PET):

The evaluation of regional cerebral glucose metabolism using positron emission tomography (PET) with 2-deoxy-2-[18F]fluoro-D-glucose (FDG) as a tracer in the resting state is a well-established functional imaging technique for assessing brain activity. In Alzheimer's disease (AD), FDG-PET serves as a critical tool for detecting neurodegenerative changes, including amyloidosis and synaptic dysfunction. These pathological features are often accompanied by elevated levels of tau or phosphorylated tau in the cerebrospinal fluid, as well as structural changes such as cortical thinning and hippocampal atrophy. A characteristic biomarker of AD-related synaptic impairment is a reduction in FDG uptake, typically presenting as a temporoparietal pattern of hypometabolism [49,50].

Table 1: Biomarkers of Alzhimer's disease

Biomarkers	Application	Advantages	Disadvantages
FDG-PET	A biomarker based on topography to distinguish between atypical & typical AD. Clinical deficits in various kinds of AD are recognized by regional hypometabolism variations. Marker of the brain's synaptic activity, functioning of neurons, & neuronal metabolism.	A multiple diagnosis is provided. Has the ability to recognize hypometabolism in non-AD dementia manifestations that include frontotemporal dementia & Lewy bodies.	Access is limited & comparatively expensive It is not widely implemented & are unable to precisely determine the two primary pathological features that cause AD, tau & Aβ [51,52].
Amyloid PET	Imaging-to-autopsy investigations showcased exceptional accuracy with an extremely widely studied biomarker for amyloid plaque	A biomarker for prompt identification that might spot isolated Aβ deposits which could develop	It is typically employed in clinical trials & has limitations related to pinpointing fibrillar or insoluble Aβ plaques

	recognition (specificity: 100%; sensitivity: 92%).	prior to the general neocortical response turns unhealthy.	within the brain; it fails to detect any additional kinds of Aβ peptides [53].
Tau PET markers	Identify neurofibrillary tangles with greater efficiency than fluid biomarkers.	In individuals with intact cognitive abilities, it acts as a more reliable indicator of declining cognitive function comparing to amyloid PET [54].	
Synaptic vesicle glycoprotein 2A (SV2A) PET	The potential neuronal density biomarker towards tracking the progression of AD.	contribute to assessing the prognosis as well as staging of disorders.	Less frequently utilized in clinical studies and practically insignificant for multiple diagnosis [55].
Single-structure MRI markers	signifies volume decrease & grey matter atrophy, indicating signs of neurodegeneration.	An easy way to identify AD in the initial stages, when diagnosis might be extremely challenging.	The detection of atypical Alzheimer's disease is hindered by several limitations, including low molecular specificity, difficulty in accurately identifying amyloid-beta plaques and neurofibrillary tangles (NFTs), and a limited ability to fully recognize and interpret their pathological impact on the brain [56].
Serial registered structural MRI	A highly effective technique for assessing diminished brain function & tracking the course of AD by simultaneously taking numerous images (brain MRI).	lowers variability compared to a single structural MRI	Since it has its minimal molecular specificity, AD has no ability to recognize the impact of NFTs or amyloid beta plaque affecting the brain [57].
Diffusion tensor imaging MRI	Anisotropic migration is employed for assessing white matter or axonal degradation.	Early recognition of AD	Diffusion tensor imaging (DTI) is highly sensitive to patient motion, with even slight movements potentially leading to image misregistration and compromised data quality. To achieve reliable results, the technique requires a minimum of seven tensor orientations to be accurately fitted. As a result, DTI demands considerable time,

			advanced technical expertise, and substantial computational resources for proper acquisition and analysis [58].
Resting-state functional MRI	To assess the functional fluctuations in neural connectivity that are assumed to take place previous to structural changes in the brain, as well as foraging at the brain's fundamental networks while it is at rest. The neuron's synaptic activity is monitored via Blood Oxygen Level Dependent (BOLD) Indicators.	Superior spatial resolution & noninvasiveness as compared to various other imaging methods.	It is currently unclear how distinct variations in neurological activity occur in both awake & resting phases [59].
Task-related functional MRI	Analyse BOLD indications whereas patients accomplish cognitive activities.	Task-related MRI may recognize early neurological impairment associated with AD & monitor immediate rehabilitation action, identical to resting stage MRI.	Patients with substantial disabilities can't accomplish cognitive activities [60].
T2-weighted or susceptibility-weighted imaging (SWI) or MRI	Early identification of microhemorrhages associated with amyloid plaque angiopathy in Alzheimer disease patients.	a fresh & more precise method for emphasizing the apparent association of Alzheimers disease & cerebral amyloid angiopathy & microhemorrhages	Although not yet utilized in the majority of clinical trials it might become increasingly essential to address imaging abnormalities linked to amyloid [60,61].
CSF Amyloid and tau protein biomarkers	Identification of AD through the measurement of tau proteins in CSF, which include total tau & p-tau. P-tau is a more precise indicator of Alzheimer's disease.	identify metabolic changes associated with AD, even in the initial as well as asymptomatic stages of the illness's evolution, and have even exhibited an ability to predict cognitive decline.	extremely expensive & requires extremely specialized facilities & personnel that are acquainted with this technique [62].
CSF tau	Identification of AD through the measurement of tau proteins in CSF, which include total tau & p-tau. P-tau is a more precise indicator of Alzheimer's disease.	An additional approach for precisely diagnosing AD besides PET scanning. Both atypical	Highly expensive & demands highly sophisticated facilities & personnel who have undergone training in this approach [63].

		phenotypic & non-AD cognitive impairment can have higher levels of this neuronal degeneration biomarker.	
CSF Amyloid	The Alzheimer's brain gets impacted by plaques that appear when atypically high levels of CSF amyloid protein accumulate & hinder the activity of cells.	deliver a quantitative evaluation of the cumulative impact of biomarkers.	Until the whole neocortical signal grows problematic, Aβ-PET may recognize Aβ depositions in specific locations. Expensive & lacks comprehension [64].
CSF neurofilament light chain (NfL)	Cognitive impairments as well as an intriguing biomarker of a neurological condition.	An extremely reliable system that could be employed as a neurodegenerative biomarker as a substitute for total tau.	utilized as generic biomarkers rather than specific biomarkers of a particular neurodegenerative disorder [65].
CSF- Chitinase 3 like 1 protein (CHI3L1/YKL-40)	A robust biomarker that can help distinguish Alzheimer's disease from other types of dementia and facilitate early detection during the initial stages of its pathophysiology.	An intriguing preclinical biomarker for AD predictions	more concerned regarding the staging & prognosis of diseases rather than differential diagnosis [66].
CSF-Glial fibrillary acidic protein (GFAP)	A biomarker for AD along with other neurodegenerative conditions, such as dementia of the frontal lobe and Lewy body dementia, is determined employing astrocytes.	ascertain the disease's current status & anticipate its future progress.	Neurodegenerative biomarker although non-specific [67].
CSF synaptic & postsynaptic (neurogranin) biomarkers	AD has been linked to elevated levels of presynaptic proteins such as Growth-associated protein-43 (GAP-43), Synaptosomal-Associated protein-25 (SNAP-25), synaptotagmin-1 and postsynaptic protein Neurogranin.	It is feasible to precisely differentiate symptomatic AD from other dementias.	engaged in ailments staging & predictions as opposed to making a differential diagnosis [68].
Plasma amyloid, tau & other protein biomarkers	may suggest an appearance of amyloid modifications, damaged neurons, or a neurological disorder in the brain.	PET-positive findings & their associated CSF concentrations have correlations with blood stream levels of p-tau & Aβ peptides.	It does not constitute an appropriate test for recognizing AD or any additional kind of dementia on its own. but used when coupled with additional diagnostic methods [69].

Blood Apolipoprotein E (Apoe ε 4) gene biomarker	A potential genetic biomarker for the detection of AD & amyloid etiology	An important hereditary risk indicator for AD that arises subsequently.	It is not an appropriate tool for diagnosing AD or any other sort of dementia on its own. But integrated with various additional diagnostic techniques [70].
Retinal imaging	Brain neurodegeneration, brain damage to blood vessels, or other disease-related actions may be associated to variations in the eye.	Retinal imaging might serve as a cost-effective, non-invasive, along with accurate assessment technique.	Not employed in healthcare facilities [71].
Saliva biomarkers	For determining the level of tau & amyloid proteins in saliva	A simple but non-intrusive approach	not applied in a therapeutic context [72].
Urine biomarkers	Finding AD-related proteins in urine	Non-intrusive, simple, along with affordable approach	Unreliable in addition rarely utilized [73].

5. DISEASE-MODIFYING THERAPY FOR AD:

5.1 Alcohol

Numerous epidemiological studies have raised concerns about the impact of alcohol consumption on cognitive function. Despite its negative effects, excessive alcohol intake has been scientifically linked to dementia. A French study revealed that older adults who regularly consume alcohol are at a higher risk of developing Alzheimer's disease (AD) compared to other age groups. Conversely, research from the Rotterdam Study suggested that moderate alcohol consumption may have a protective effect on cognitive health [74,75]. Additionally, a Mendelian randomization study uncovered a significant association between alcohol use and earlier onset of AD, implying that even moderate alcohol intake could potentially be detrimental to brain health. The protective effects of alcohol are often attributed to its antioxidant properties [76-78].

5.2 Education and Early-Life Experience:

The likelihood of developing AD is significantly more for those who have insufficient education than for those who receive adequate education. An AD person's educational attainment won't change, but a higher level of education may reduce the likelihood of developing the illness [79]. The quantity of formal education received is proven to be a significant factor that affects resilience. It is unclear if broadly enlightening achievement serves as a stand-in for other inherited or natural effects. As an instance, a sign of ensuing intellectual impedance is phonetic ability throughout the second decade of life. ***Whalley et al.*** discovered that youngsters who eventually had AD beyond the age of 65 had lower-than-normal cognitive ability ratings. In a similar vein, Seo *et al.* and Cho *et al*. observed that patients with early-stage AD who were more educated had faster progressive atrophy of the cortex than those who were less educated [80,81]. The cognitive reserve hypothesis demonstrates a possible link amongst higher education and accelerated disease evolution. It illustrates that early symptoms of AD may be less apparent in more educated people, hindering diagnosis until neurodegeneration gets more progressed [82]. In support of this hypothesis, Amieva *et al.* stumbled that, although global cognition did not deteriorate until seven years prior to sustaining a dementia diagnosis, more highly educated people showed mild indications of cognitive impairment 15 to 16 years prior. In distinction, subjects with lower levels of education experienced a single period of cognitive decline that lasted roughly seven years [83]. These results suggest that the factors that contribute to these illnesses are typically established early in life and may therefore affect an individual's ability to perform educational tasks. As a result, those who prospered from these traits in their early years are less likely to acquire an illness later in life [84,85].

5.3 Mental & Leisure Activity:

Engaging in both physical and mental activities in later life has been consistently linked to a reduced risk of Alzheimer's disease (AD). Individuals who maintain complex activity routines such as continuous intellectual engagement, an active lifestyle, and regular physical exercise are significantly less likely to develop the disease. The Canadian Study of Health &

Aging highlighted that consistent physical activity, in particular, yields the most substantial positive effects in lowering AD risk [86].

5.4 Smoking:

A significant number of research investigations have indicated that smokers are two to four times more likely to develop AD. People without an APO-ε4 allele also exhibit this. The vascular disease associated with smoking might provide sign for the role of smoking in the development of neurological dysfunction, but more recent research also links the neurotoxins—such as distinct metals or polycyclic aromatic hydrocarbons—found in tobacco plant and cigarette smoke to an increased risk of AD [87,88]. A fresh research investigation explored passive smoking as a risk factor for AD in 2037 women from the China Health and Pensions longitudinal cohort who were between the ages of 55 and 64 and had never been exposed to cigarettes. In the subsequent follow-up, they discovered that the memory score decreased by 0.01 points for every extra year of indirectly smoke exposure [89,90]. Lastly, research indicates that abandoning smoking may help prevent dementia instances since those who scaled back on their smoking required a lower risk of acquiring dementia than those who erupted [91,92]. It is speculated in these investigations that smoking intensivists the danger of dementia by confounding the brain arteries. In an additional study, transgenic mice feeding nicotine and sucrose outlined an 80% reduction in Aβ 1-42 peptide levels. It was discovered that the mice given nicotine had a significant decrease in the prefrontal intractable peptides Aβ 1–40 and Aβ 1–42. Conversely, abandoning smoking could have certain benefits [93,94].

5.5 Depression:

Alzheimer's disease can emerge following a prolonged period of depression. A study by Devanand *et al.* (1996) established a correlation between a depressive mood and an increased likelihood of developing dementia among elderly patients. As a result, depression may serve as a predictor or early indicator of Alzheimer's disease [95].

5.6 Traumatic Head Injury:

According to reports, the risk of Alzheimer's disease is significantly increased by severe head injuries. A variety of studies, involving both humans and rodents, have provided substantial evidence supporting this connection [96].

5.7 Hyperlipidemia:

High blood lipid (fat) levels, or hyperlipidemia, are typically linked to cardiovascular disease or stroke as possible precursors to AD. Inflammation, oxidative stress and the development of amyloid plaque are some of the possible mechanisms that hyperlipidemia is recognized as having a role in the pathophysiology of Alzheimer disease. A hallmark of Alzheimer disease, amyloid-beta plaques may develop in the brain in consequence of elevated cholesterol levels, notably low-density lipoprotein (LDL). Oxidative stress and free radicals' production are two consequences of high lipid levels, specifically cholesterol, which are capable of damaging neurons and expedite dementia. It may be possible to establish the correlation between hyperlipidemia and Alzheimer's disease most precisely in middle life, years before dementia manifests. Perhaps hyperlipidemia is solely linked to heart disease and stroke is still up for dispute [97].

5.8 Anti-inflammatory Agents:

The prevalence of Alzheimer disease shown to be more modest amongst those who took anti-inflammatory drugs. Anti-inflammatory drugs are thought to have an overwhelming positive interaction with Aβ1-42 that offers individuals this protective effect against AD. Furthermore, it appears that certain mitigating medicines alter gamma secretase which is essential for the biosynthesis of Aβ peptides, without significantly altering other APP pathways [98,99].

5.9 Diabetes Mellitus:

Diabetes, comprising both juvenile type I and adult-onset type 2, is linked to an elevated risk of AD and recognized an inevitable risk factor for the disease. Multiple features of AD and diabetes mellitus are identical, including an increased risk after age 65, substantial effects on quality of life, and an accompanying spike in expenditures on healthcare. Research showcases that individuals who have acquired diabetes, particularly those who have inadequate control of their glucose levels are more likely to develop AD and other types of dementia [100]. Insulin resistance, a hallmark of diabetes, may influence brain function by compromising neuronal glucose metabolism. Neurodegeneration, a defining feature of Alzheimer's, can arise from this. Despite this, several connections between Aβ and DM have already been tracked down. The Aβ receptor that exists in neurons, microglia, and endothelial cells is called the receptor for innovative glycation end-products (RAGE). Through the blood-brain barrier, RAGE facilitates the circulation of Aβ from the plasma entering the brain's interstitial fluid (ISF). Brain Aβ levels and the accumulation of amyloid plaque are reduced by plasma insulin growth factor I (IGF-I). Evidence stipulates a link between insulin resistance and amyloid-beta formation, however research on the subject is currently under way [101,102].

6. THERAPEUTIC APPROACH

6.1 Anti-Amyloid Therapy

Anti-amyloid antibodies have been at the forefront of extensive research in Alzheimer's disease (AD). These antibodies can

effectively reduce amyloid plaques in the brain in a dose- and time-dependent manner, which has been linked to a slowdown in cognitive decline. Amyloid plaques consist of Aβ peptides that accumulate in the extracellular space. Aβ is produced from amyloid precursor protein (APP), a transmembrane protein, through cleavage by β-secretase and γ-secretase, resulting in the formation of pathological Aβ. The buildup of Aβ leads to neurotoxicity, contributing significantly to the progression of AD. Consequently, reducing Aβ accumulation has become a central therapeutic aim in AD treatment. Anti-amyloid strategies include three primary approaches: secretase inhibitors, Aβ aggregation inhibitors, and Aβ immunotherapy [103]. Aducanumab, Donanemab, and Lecanemab are a couple of the notorious anti-amyloid antibodies. They each target a distinct stage of Aβ: Donanemab tackles Aβ plaques, Lecanemab exclusively binds to Aβ protofibrils, and Aducanumab concentrates on Aβ42 oligomers. Aducanumab's two phase-3 clinical investigations, EMERGE and ENGAGE, accomplished differing results. The ENGAGE trial failed to achieve the primary endpoint, while the EMERGE trial perpetrated. On an assumption of the drug's artificial gestation endpoint—a decrease in Aβ plaques in brain PET scans within the two trials—the FDA nevertheless granted abstain authorization. Furthermore, in order to officially approve the medicine, the FDA asked for a conclusive trial to demonstrate its effectiveness [104,105]. After its first accelerated clearance, lecanemab was recently granted full FDA approval. In patients with early AD, lecanemab diminished amyloid load and cognitive deterioration over an 18-month period when when compared with a placebo in a phase-3 experiment called CLARITY-AD. The reliability and efficacy of lecanemab during different stages of AD, such as preliminary preclinical stages, and foremost inherited AD, are also being investigated by the ongoing investigations (NCT03887455, NCT04468659, and NCT05269394) [106]. A recent phase-3 randomized clinical trial (TRAILBLAZER-ALZ2) concluded that donanemab substantially shortened the progression of the disease among individuals with early-symptomatic AD.

6.2 Tau-targeted therapy

Clinical trials are currently being conducted on tau-targeted interventions, which include anti-hyperphosphorylation medicines and drugs that target microtubule integrity and agglomeration. Despite the fact that valproic acid and lithium may both diminish tau phosphorylation, their effects in controlled, randomized investigations were not favorable [107]. More recently, after 50 weeks of therapy, those with minor and moderate Alzheimer's disease showed modest improvements in cognitive functioning in a phase II clinical investigation of the tau aggregation inhibitor Methylene blue. This promising result prompted further research into LMTX, a methylene blue derivative [108-110]. But when associated to the placebo group, the subsequent two phase-3 trials failed to demonstrate any discernible cognitive improvement.

Aβ has served as the target of the majority of pharmacological development aimed at aggregation inhibition. The following illustrates the prevailing stage of clinical development for TAGIs, since they are preceded by valuable antecedents. Methylene blue84 and it's demethylated derivatives such azure A, are at the vanguard of TAGIs that have effectively proficient from preclinical research to clinical trials [111].

6.3 Complement-targeted therapy

Complement could restrict AD pathogenesis by modulating Aβ clear, even though it is typically recognized as a detrimental component to AD. Clinical trials have demonstrated that eculizumab, a monoclonal antibody, is well tolerated and has few side effects. It is agreed for use in patients with paroxysmal nocturnal hemoglobinuria and hinders the fragmentation of C5 to C5a and C5b molecules. Eculizumab treatment may stop AD patients' an excess of production of activated complement and restore normal the baseline levels. Memory impairment, decline in memory, and alterations in behavior are all indicators of Alzheimer's disease, a degenerative and irreversible brain ailment. It is believed that around 6 million Americans are influenced by Alzheimer's disease. Alzheimer's has no FDA-approved treatment, although there are treatments that may help control manifestations and reduce the progression of the disease [112].

6.4 Cholinesterase Inhibitors

Acetylcholine levels in the brain are raised by medications referred to as cholinesterase inhibitors. An essential neurotransmitter for memory and cognition is acetylcholine. By inhibiting the enzyme responsible for breaking down acetylcholine, cholinesterase inhibitors boost the amount of this neurotransmitter in the brain. Galantamine, Rivastigmine and Donepezil are certain examples of cholinesterase inhibitors [113].

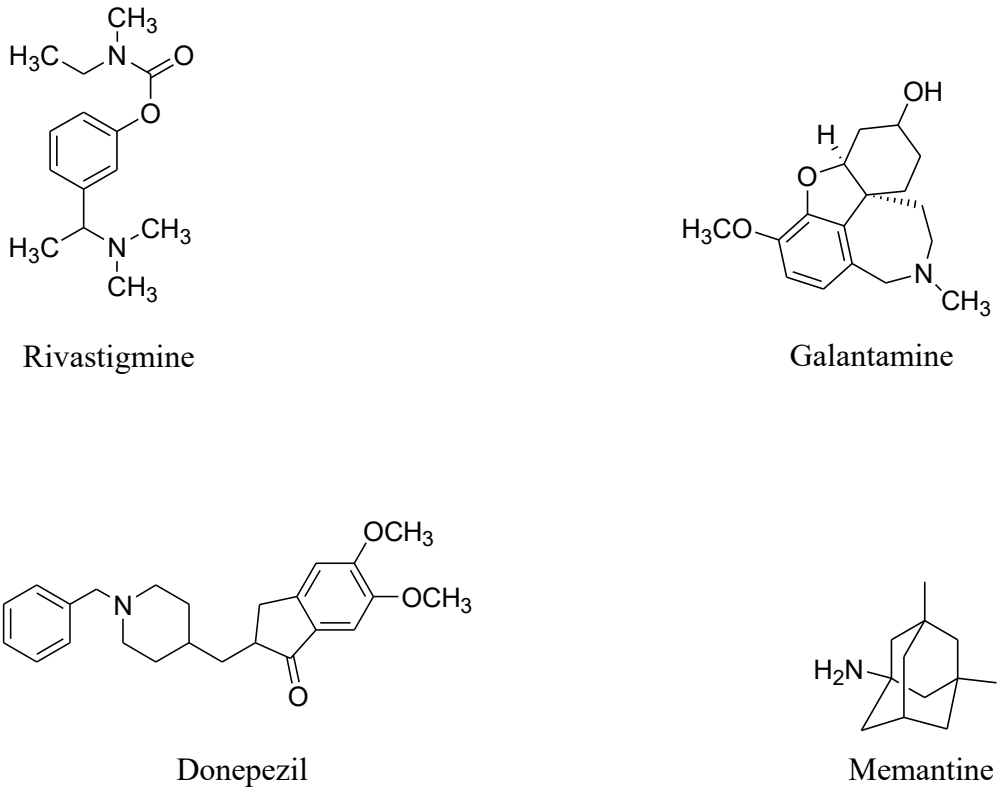

Figure 7: Chemical structure of cholinesterase inhibitors rivastigmine, galantamine, donepezil & N-methyl-D-aspartate (NMDA) antagonist memantine.

6.5 Memantine

Glutamate is a neurotransmitter responsible for learning and retention, and memantine operates by modulating its activity. Alzheimer's disease with severity ranging from moderate to fatal is treated via it. Memantine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor that distresses by restricting glutamate from interacting abnormally in the brain. Namenda and Ebixa are memantine examples [114].

6.6 Lifestyle Changes

A nutritious diet, routine physical activity, and interactions with others are all examples of lifestyle modifications that can help minimize Alzheimer's disease symptoms. Exercise been demonstrated to mitigate the risk of dementia along with improving cognitive function. An omega-3 fatty acid-rich, fruit-and vegetable-rich diet may also aid forestall cognitive deterioration. Alzheimer's disease risk can be diminished through social engagement, which includes taking part in social events and preserving social ties [115].

6.7 Cognitive Stimulation Therapy

A therapeutic approach called cognitive stimulation therapy incorporates scheduled tasks to help individuals suffering from Alzheimer's disease comprehend effectively. Activities like crossword puzzles, mental gymnastics, and nostalgia sessions are all part of the therapy. It has been demonstrated that cognitive stimulation therapy enhances mood, standard of life, and cognitive function among individuals with Alzheimer's disease [116].

6.8 Musical Rehabilitation

Individuals suffering from Alzheimer's disease, musical rehabilitation is alternative therapies tactics that involves engaging or listening to music to boost cognitive and emotional abilities. In patient with Alzheimer's disease, musical rehabilitation has demonstrated to enhance quality of life, alleviate anxiety, and strengthen cognitive performance [117].

7. CONCLUSION

An assortment of safeguarding & predictive variables for AD have been found in numerous longitudinal research investigations. Additionally, some of these variables may be able to be effectively addressed to avoid the development of AD or prolong its onset; corrective measures can also assist in slowing down the progression of the disease. New advances in biomarkers have led to some fascinating findings. The onset & progression of AD can be conveniently analyzed,

alterations linked to the chaos can be seen in healthy individuals and efficiency of intriguing medications and other potential treatment can be assessed. Since oxidative stress appears to be associated with adverse consequences on an array of pathways, additional investigation regarding this topic is recommended. Early AD diagnosis is even more significant considering clinical trials tend to concentrate on individuals suffering from the initial stages of AD (moderate cognitive impairment from AD or early AD dementia). New diagnostic, prognostic, & therapeutic possibilities have emerged as the consequence of the recognition of Aβ & tau pathologies and the subsequent finding of CSF and neuroimaging biomarkers, which has enhanced the diagnosis of AD. There should be more public initiatives aimed at popularizing education and encouraging social or cognitive activity. Maintaining everyday behaviors that are nutritious & properly dealing with pre-existing conditions might prevent AD. Preventing AD also depends significantly on environmental protection, particularly with regard to air contaminants. Additional studies should, if at all feasible, concentrate on people who are at high risk of AD or who are in the prodromal stage of the disease, as these are the people who are most likely to benefit from everyday preventions and neuroprotective measures

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