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Alzheimer's Disease: Causes and Treatment

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➢ Abstract:-

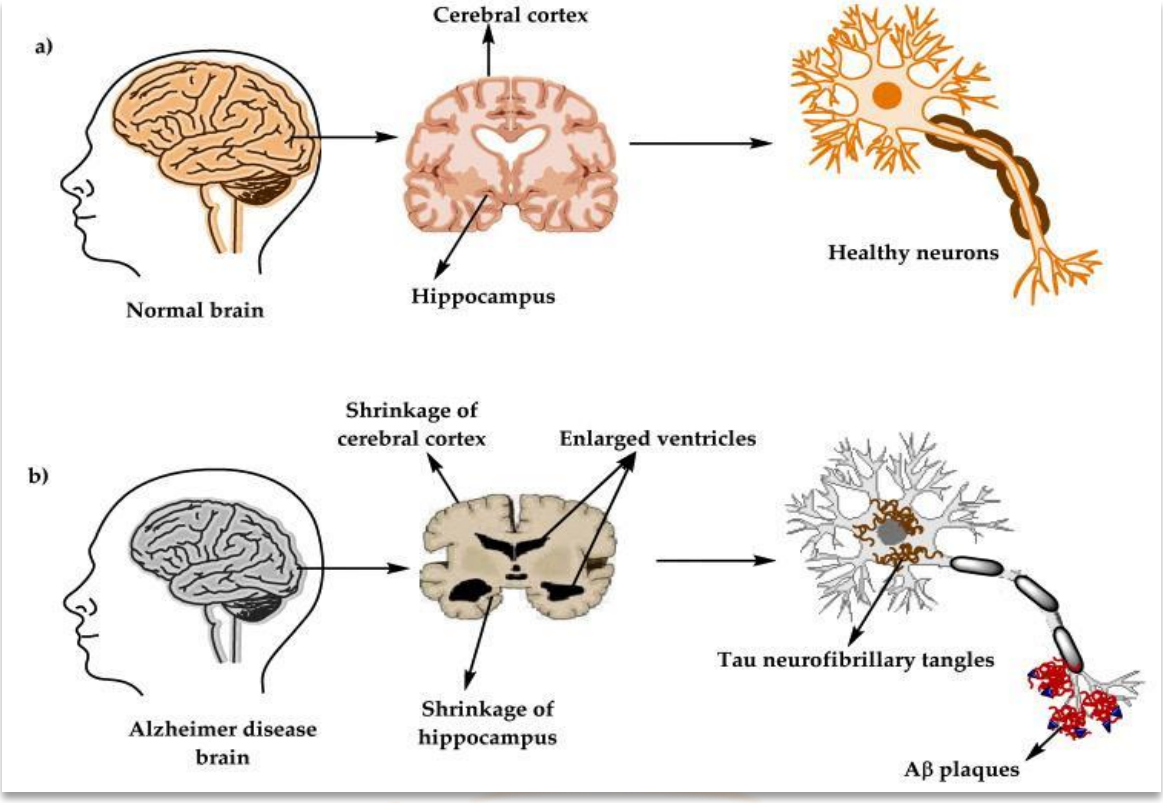
Alzheimer's disease (AD) is a disorder that causes degeneration of brain cells and is the leading cause of dementia characterized by reduced thinking ability and independence in daily personal activities. Alzheimer's disease is considered to be a multifactorial disease. Two main hypotheses have been proposed for the cause of Alzheimer's disease: cholinergic and amyloid. In addition, several risk factors such as advanced age, genetic factors, head trauma, vascular disease, infections, and environmental factors play a role in the disease. Currently, there are only two classes of drugs approved to treat AD, including cholinesterase enzyme inhibitors and N-methyl d-aspartate (NMDA) antagonists, which are only effective in treating the symptoms of AD but do not cure or prevent the disease. Currently, this study focuses on the understanding of AD pathology by aiming for several mechanisms, such as TAU proteins, β-amyloids, inflammatory reactions, cholin operation and free radical damage. We are trying to develop successful treatments. The presentation of the announcement in this review is currently discussing useful drugs and future theories on the development of new AD treatments, such as diseases (DMT), chaperon, and treatments for modifying natural compounds.

Keywords :-Alzheimer's disease, neurodegeneration, β-amyloid peptide, tau protein, risk factors, disease-modifying therapy, chap.erones, heat shock proteins

introduction:-

Alzheimer's disease (AD) (named in accordance with Psychiatric Alzheimer's disease in Germany) is the most common type of dementia, featuring nerve oxygen boards, nerve fibat plate, and nerve yarn -shaped peptides (Fig. 1). It can be slowly defined as a progressive neurodetative disease (Fig. 1) 1) Neurodes plate, neural boards, neurona plate, neuron nerve fibers, and nerve nerve plate and neural wire peptides. Following the fibat plate and peptide (FIG. 1) (FIG. 1) (FIG. 1) Following the peptide anamiloid system (FIG. 1) (FIG. 1), the peptide -after the result of the beading, the result of the nerve fuel bun peptide. (Fig. 1) -Beeholes (Fig. 1) (Aβ) Accumulated in the most affected areas of the brain, the inner side lobe and the new cortex structure [1]. Alzheimer's disease Alzheimer's

disease, while investigating the first patient's brain who suffered from amnesia and changes in personality before he died, noticed the existence of amyloid plaque and great loss of neuron, and as a severe disease in the cortex. I explained. Emil Kraepelin first named this disease Alzheimer's disease in his 8th edition of the textbook of psychiatry [2,3]. The progressive loss of cognitive function can be caused by a brain disorder such as Alzheimer's disease (AD) or by other factors such as toxicities, infections, abnormalities of the pulmonary and circulatory systems leading to decreased oxygen supply to the brain, nutritional deficiencies, vitamin B12 deficiency, tumors and others [4,5].



At present, there are around 50 million AD patients worldwide and this number is projected to double every 5 years and will increase to reach 152 million by 2050. AD burden affects individuals, their families, and the economy, with estimated global costs of US$1 trillion annually. There is currently no cure for Alzheimer's disease, but there are treatments that simply improve symptoms [6, 7]. The aim of this review is to briefly discuss the diagnosis, pathology, causes and current treatments of Alzheimer's disease, and to highlight the recent development of compounds that can prevent or treat Alzheimer's disease by targeting several pathogenic mechanisms such as Aβ and tau aggregation, misfolding, inflammation and oxidative damage.

Alzheimer's Disease Diagnostic Criteria:-

A patient suspected to have AD should undergo several tests, including neurological examination, magnetic resonance imaging (MRI) for neurons, laboratory examinations such as vitamin B12, and other tests besides the medical and family history of the patients [8]. Vitamin (vit) B12 deficiency has been long known for its association with neurologic problems and increasing risks of AD, according to some studies. A special marker of vit.B12 deficiency is elevated homocysteine levels, which can cause brain damage by oxidative stress, increasing calcium influx and apoptosis. Diagnosis of vitamin B12 deficiency can be made by measuring serum vitamin B12 levels. Test B12 levels and complete blood count and serum homocysteine levels [9,10].

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) formed a working group to develop clinical diagnostic criteria for Alzheimer's disease (NINCDS-ADRDA). The criteria include (1) suspected Alzheimer's disease, diagnosed by symptoms such as dementia confirmed by neuropsychological testing, progressive memory loss, impairment in activities of daily living, aphasia (language impairment), apraxia (motor skill impairment), and agnosia (perception loss). All of these symptoms can develop between the ages of 40 and 90 in the absence of systemic or brain disease; (2) suspected Alzheimer's disease is met in the absence of neurological or psychiatric disease and the presence of another disease, such as a systemic or brain disorder, but which is not the primary cause of dementia; and (3) definite Alzheimer's disease, confirmed by histopathological confirmation obtained from biopsy or autopsy [11,12]. In 2011, the National Institute on Aging-Alzheimer's Disease Association updated the 1984 NINCDS-ADRDA criteria with several modifications to increase specificity and sensitivity in diagnosing Alzheimer's disease. In addition to clinical biomarkers, the newly proposed criteria include possible and probable AD dementia for use in clinical practice and possible or probable AD dementia with pathophysiological evidence for research purposes. There are two categories of Alzheimer's disease biomarkers: (a) brain amyloid markers such as positron emission tomography (PET) and cerebrospinal fluid (CSF) for metabolic activity and (b) magnetic resonance imaging (MRI) to measure neuronal damage markers such as tau protein and fluorodeoxyglucose (FDG) for atrophy [13 , 14 , 15].

- **Alzheimer's Disease's Neuropathology:-**

There are two types of neuropathological changes in AD that indicate disease progression and its symptoms: (1) positive lesions (due to accumulation), which are characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropils and other deposits. They have been found in the brains of Alzheimer's disease patients, and (2) negative lesions (due to loss), which are characterized by extensive atrophy due to loss of neurons, neuropils and synapses. In addition, other factors, such as neuroinflammation, oxidative stress, and damage to cholinergic neurons, can also lead to neurodegeneration [16 , 17 , 18].

3.1.Senile Plaques (SP):-

Senile plaques are extracellular deposits of amyloid beta (Aβ) protein with various morphologies, including senile, diffuse, dense-core, or classical compact plaques. Proteolytic cleavage enzymes, such as β-secretase and γ-secretase, are involved in the biogenesis of Aβ deposits from the transmembrane amyloid precursor protein (APP) [19, 20, 21]. These enzymes break down the application into some fragments of amino acids: 43, 45, 46, 48, 49, 51 amino acids reach the final form of Aβ40 and Aβ42. There are several types of monomers, such as the formation of the amyloid plate and the formation of soluble oligomers that can spread throughout the brain, such as large and insoluble amyloid fibrilles. Since Aβ plays an important role in neurotoxicity and neuronal function, the accumulation of dense plaques in the hippocampus, amygdala, and cerebral cortex can lead to astroglial and microglial stimulation, axonal damage, dendritic and synaptic loss, in addition to cognitive impairment [21 , 22 , 23].

3.2.Neurofibrillary Tangles (NFTs):-

NFT are anomalous threads of the Tau hyperforilized protein, which at some stages can be twisted around each other, forming a steam spiral thread (PHF) and accumulated in the cytoplasm of Neuralperikaryal, axons and dendritis, which cause the loss of cytoskeleton microdrubes and trumpeter proteins, which cause the loss of cytocracy microderflies and tubular proteins, as well as tubular proteins and proteins caused by tube and proteins caused by tubes and processed tubes and trumpeters with a field of hyperforidated Tau protein is the main component of patients with AD, and its evolution can reflect the morphological stages of NFTS, which include : (1) The preliminary tightening phase, one type of NFT, where the phosphorized Tau proteins accumulate into a somatododendritis compartment without the formation of PHF, (2) mature NFT, which are characterized by aggregation of the thread of the core of the nucleus to the periphery of the catfish, and (3) extracellular tangle or extracurricular cups or The stage of ghostly NFT, this is the result of the loss of neurons from a large amount of tau filamentary protein with partial resistance to proteolysis [24,25].

3.3.Synaptic Loss:-

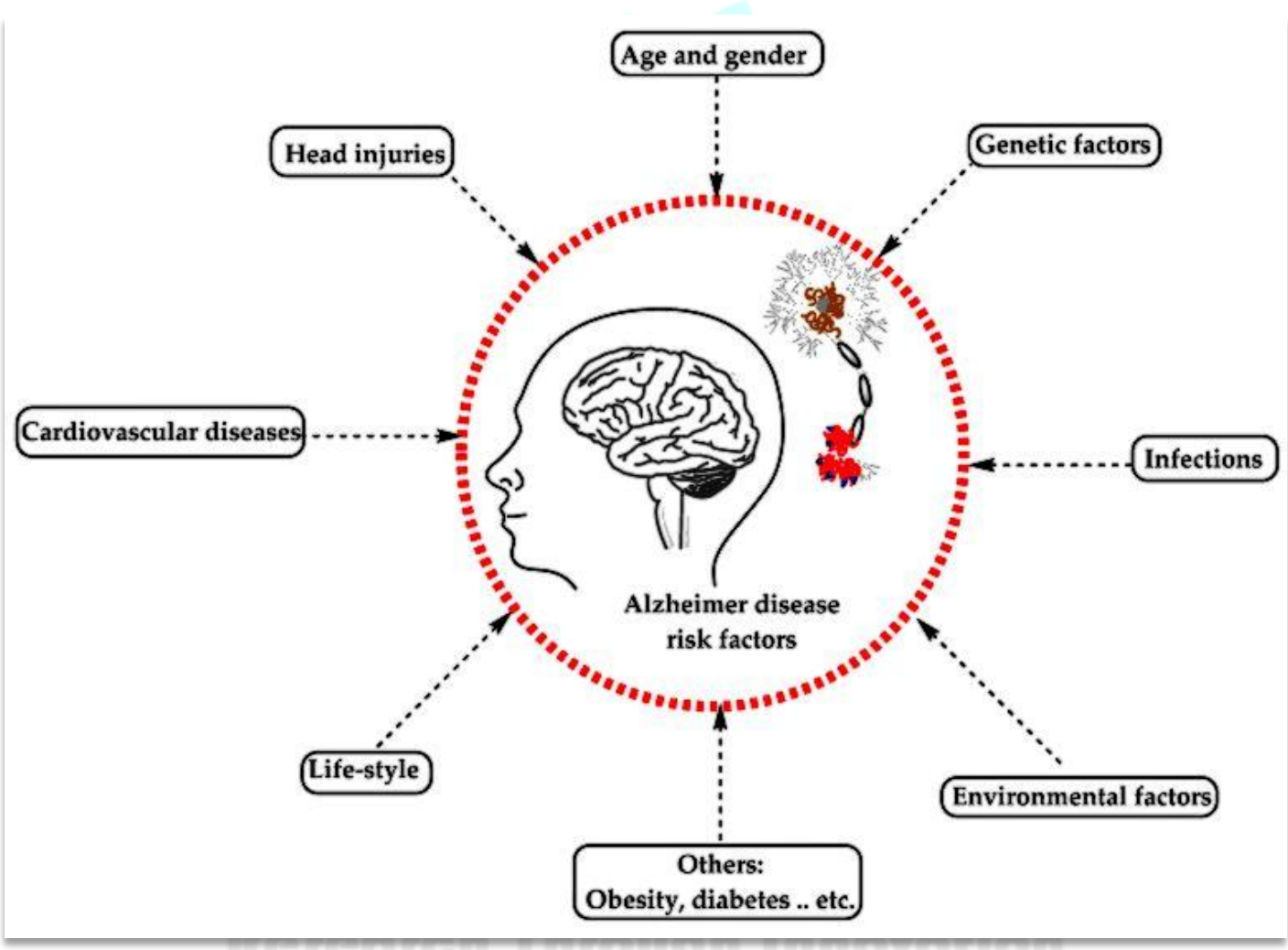
Synaptic damage to the neocortex and limbic system leads to memory impairment and is commonly observed in the early stages of Alzheimer's disease. Mechanisms of synapse loss include defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that may contribute to minor portions such as the accumulation of Aβ and tau at synaptic sites. These processes ultimately lead to the loss of dendritic spines, presynaptic terminals, and axonal degeneration (26).Synaptic proteins such as neurogranin, neuronal postsynaptic protein, visinin-like protein-1 (VILIP-1), and synaptotagmin-1 serve as biomarkers to detect synapse loss and severity [27,28].

The Stages of Alzheimer’s Disease:-

The clinical phases of Alzheimer’s disease can be divided into (1) the preclinical or presymptomatic stage, which may last several years or more. This stage is characterized by mild memory loss and early pathological changes in the cortex and hippocampus, without functional impairment in daily activities and without clinical signs and symptoms of Alzheimer’s disease [1,29,30]. (2) Mild or early stage Alzheimer’s disease. Patients begin to show a variety of symptoms, including problems with daily life, such as decreased concentration and memory, disorientation to place and time, mood changes, and the onset of depression. [31]. (3) Moderate stage Alzheimer’s disease. The disease spreads to areas of the cerebral cortex, causing difficulty recognizing family and friends, increasing memory loss, loss of impulse control, and difficulty reading, writing, and speaking. [30] (4) Severe or advanced Alzheimer’s disease, in which senile plaques and neurofibrillary tangles accumulate significantly and spread throughout the cerebral cortex, causing progressive functional and cognitive impairment, leading to the patient being completely unable to recognize their family members and developing Alzheimer’s disease, difficulty swallowing and urinating, becoming bedridden, and ultimately leading to the death of the patient from these complications [1,32].

Causes and Risk Factors of Alzheimer's Disease:-

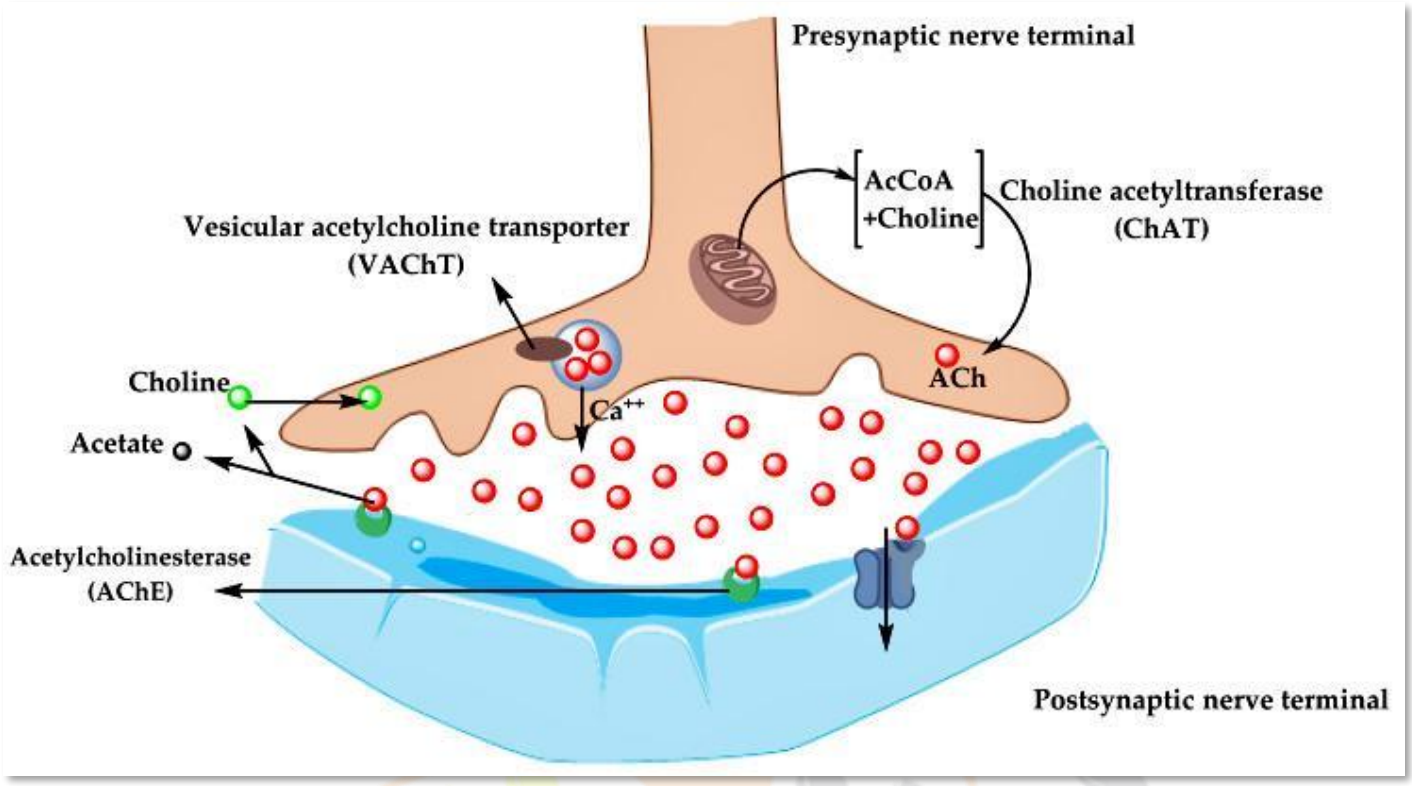
Alzheimer's disease is considered to be a multifactorial disease associated with several risk factors, such as age, genetic factors, head trauma, vascular diseases, infections, and environmental factors (heavy metals, trace metals, etc.) (Figure 2). The underlying causes of the pathological changes of Alzheimer's disease (Aβ, NFTs, synapse loss) are still unknown. Several hypotheses have been proposed as the cause of Alzheimer's disease, but two are considered to be the main ones. Some consider impaired cholinergic function to be a significant risk factor for Alzheimer's disease, while others suggest that alterations in the production and conversion of amyloid-β protein are the main initiating factors. However, there is currently no generally accepted theory explaining the pathogenesis of AD [33,34].



- ## Alzheimer's Disease Hypotheses:-

In the 1970s, it was reported that the new cortex and the colin of choline before synaptic were related to the acetylcoliner zecoline enzyme (CAT), which caused the synthesis of acetylcholine (Ach). According to the essential role of Ach in cognitive function, AD choline activity hypothesis is proposed. Ach is synthesized in the cytoplasm of cholinergic neurons from choline and acetyl-coenzyme A by the enzyme ChAT and transported into synaptic vesicles by the vesicular acetylcholine transporter (VAChT) (Figure 3). In the brain, Ach is involved in several physiological

processes such as memory, attention, sensory information, learning, and other important functions. Degeneration of cholinergic neurons has been shown to occur in Alzheimer's disease, leading to cognitive changes and memory loss. Amyloid-β is thought to affect cholinergic neurotransmission, causing a decrease in choline uptake and Ach release. Studies have shown that the loss of cholinergic synapses and the formation of amyloid fibrils are associated with the neurotoxicity of Aβ



oligomers and the interaction between AChE and Aβ peptides. Other factors also contribute to the progression of Alzheimer's disease, such as the reduction of nicotinic and muscarinic (M2) ACh receptors located on presynaptic cholinergic terminals and deficits in excitatory amino acid (EAA) neurotransmission, where glutamate concentrations and D-aspartate uptake are significantly reduced in many cortical regions of the brain in Alzheimer's disease. This is in addition to the use of cholinergic receptor antagonists such as scopolamine, which causes amnesia. This effect can be reversed by using compounds that activate acetylcholine production [35, 36, 37].

As a result, the cholinergic hypothesis is based on three concepts: a reduction in presynaptic cholinergic markers in the cerebral cortex, severe neurodegeneration of the basal nucleus of Meynert (BNM) in the basal forebrain, a source of cortical cholinergic innervation, and the role of cholinergic antagonists in reducing memory performance compared to agonists with the opposite effect [38].

5.1.2.Amyloid Hypothesis:-

For decades, abnormal deposition of β-sheets in the central nervous system was thought to be strongly correlated with dementia, giving rise to the concept of the amyloid hypothesis. However, amyloid plaques (AP) have been found to deposit in normal, healthy brains with age, raising the question of whether AP deposition is responsible for the development of Alzheimer's disease. Therefore, in recent years, alternative hypotheses have been proposed for non-inherited AD (NIAD), but currently the amyloid hypothesis remains the most accepted pathological mechanism for inherited AD (IAD). The amyloid hypothesis proposes that the degradation of Aβ derived from APP by β- and γ-secretase is reduced with age or in pathological conditions, leading to the accumulation

of Aβ peptides (Aβ40 and Aβ42). An increase in the Aβ42/Aβ40 ratio leads to the formation of Aβ amyloid fibrils, inducing neurotoxicity and tau pathology, and consequently neuronal death and neurodegeneration. Mutations in several genes, including Alzheimer's disease risk factors and APP, PSEN1, and PSEN2, have been shown to affect Aβ catabolism and anabolism, leading to the rapid progression of Aβ accumulation and neurodegeneration (39 , 40 , 41).

5.2.Alzheimer’s Disease Risk Factors:-

5.2.1Aging:-

The most important risk factor in MA is aging. This disease rarely occurs in young people. In most cases, there is a start starting 65 years later. Aging is a complex and irreversible process occurring in multiple organs and cellular systems, and is accompanied by loss of brain volume and weight, loss of synapses, and regional ventricular enlargement, along with the deposition of SPs and NFTs. Furthermore, several conditions can occur during aging, including glucose hypometabolism, cholesterol dyshomeostasis, mitochondrial dysfunction, depression, and cognitive decline. These changes also appear during normal aging, making it difficult to distinguish early AD cases [43,44].Alzheimer's disease can be classified based on the age of onset into early-onset Alzheimer's disease (EOAD), a rare form that accounts for approximately 1-6% of cases, mostly familial Alzheimer's disease, characterized by the presence of "one in more than one" cases in a generation with Alzheimer's disease, ranging in age from 30 to 60 or 65 years. The second type, late-onset AD (LOAD), is more common in people over the age of 65. Both types can occur in individuals with a family history of Alzheimer’s disease or in family members with late onset of the disease.[45]

5.2.2.Genetics:-

Genetic factors have been discovered over the years and play a key role in the development of Alzheimer's disease. 70% of Alzheimer's disease cases are associated with genetic factors. Most cases of EOAD are inherited in an autosomal dominant pattern and are inherited with mutations in dominant genes such as amyloid precursor protein (APP), presenilin-1 (PSEN-1), presenilin-1. 2 (PSEN-2) and apolipoprotein E (ApoE) are associated with Alzheimer's disease [46, 47].

Here we discuss important genetic risk factors for Alzheimer's disease.

Amyloid Precursor Protein (APP):-

APP is a type I transmembrane protein that is cleaved by α-, β-, and γ-secretases to release Aβ and other proteins, and is encoded by the APP gene on chromosome 21. Thirty mutations have been found in the APP gene, 20 of which are associated with Alzheimer's disease and cause increased accumulation of Aβ. On the other hand, there exists one protective mutation, A673T, that protects against AD by reducing the secretion of Aβ, Aβ40, and Aβ42 [48, 49]. All mutations surround the secretase cleavage site. For example, the KM670/671NL mutation in mouse models showed increased amyloid plaque levels in the hippocampus and cortex without NFTs. Mutations A673V, D678H, D678N, E682K, and K687N showed cortical atrophy, whereas E682K showed hippocampal

atrophy. Neuropathological reports on the A673V mutation have demonstrated the presence of NFTs and Aβ, microglial and astrocytic activation, and neuronal loss compared to the remaining mentioned mutations, with neuropathological reports showing no changes in intracellular Aβ [48, 50]. Other mutations such as T714I, V715A, V715M, V717I, V717L, L723P, K724N, and I716V affect the γ-secretase cleavage site and cause an increase in the Aβ42/Aβ40 ratio, while mutations E693G, E693K, D694N, and A692G affect the α-secretase cleavage site and cause polymorphic aggregation that may disrupt the bilayer integrity. Furthermore, the E693δ mutation is a deletion mutation that promotes the formation of synaptic toxic Aβ [51 , 52].

- ## Apolipoprotein E (ApoE)

ApoE protein is abundantly produced in the liver and brain astrocytes as well as in some microglia and acts as a ligand for receptor-mediated endocytosis of lipoprotein particles such as cholesterol, crucial for myelin synthesis and proper brain function. On chromosome 19, the ApoE gene has three variants - ApoE2, ApoE3, and ApoE4 - as a result of single-nucleotide polymorphisms (SNPs) that alter the coding sequence. The ApoEε4 allele poses a higher risk for both EOAD and LOAD in comparison to ApoEε2 and ApoEε3 alleles which offer lower risk and protective effects, respectively [58]. ApoEε4 has a significant impact on Aβ accumulation as a senile plaque and leads to cerebral amyloid angiopathy (CAA), which is recognized as a hallmark of AD [59]. ApoEε4 was also found to be related to brain vascular damage, leading to the development of Alzheimer's disease [60].

- ## ATP Binding Cassette Transporter A1 (ABCA1)

ABCA1, a member of the ATP-binding cassette transporter family, plays a role in controlling the movement of cholesterol out of circulation, similar to ApoAI, and into the brain, similar to ApoE. Moreover, ABCA1 plays a crucial role in both the stability of ApoE lipidation and the production of high-density lipoprotein (HDL), influencing its impact on atherosclerosis and cardiovascular conditions. Research on AD mice model found that ABCA1 deficiency enhances amyloid plaques and disrupts lipidation of ApoE [61]. A mutation in ABCA1 in humans leads to Tangier disease, marked by reduced levels of high-density lipoprotein (HDL) and ApoAI in the bloodstream, buildup of cholesterol in tissues, and Alzheimer's disease development [62].

- ## Clusterin Gene (CLU) and Bridging Integrator 1 (*BIN1*)

Unlike PSEN1, PSEN2, and APP mutations that cause familial or EOAD, clusterin (CLU) and Bridging Integrator 1 (BIN1) genes are newly identified risk factors for LOAD. In 2009, the CLU gene on chromosome 8 was pinpointed by Genome-Wide Association Studies as being upregulated in the cortex and hippocampus of AD brains, as well as in AD cerebrospinal fluid (CSF) and plasma, making

it a potential biomarker for AD. The CLU can have a protective function through interactions with Aβ, facilitating its removal, or a harmful function by impeding Aβ clearance. The ratios of Aβ are used to determine if CLU's role is protecting or harming the brain.

BIN1 is a protein known as a Bin-Amphiphysin-Rvs (BAR) adaptor, playing a role in creating membrane curvature and various functions related to endocytosis within cells. BIN1 comes in various forms: certain ones are located in the brain and interact with proteins like clathrin, synaptojanin, and amphiphysin 1, while others are involved in controlling synaptic vesicle endocytosis. Recently, BIN1 was identified as the second most crucial risk factor for LOAD following ApoE, where it is involved in Aβ production and acts as a modulator for tau and NFT pathology [64,65].

- ## Evolutionarily Conserved Signaling Intermediate in Toll pathway (ECSIT)

An important buildup of Aβ in AD brains leads to heightened protein oxidation, highlighting the crucial involvement of mitochondria in Aβ-induced cell damage and the development of AD. The gene ECSIT, which is a signaling intermediate in the Toll pathway and is evolutionarily conserved, can be found on chromosome 19 and is linked to an elevated likelihood of developing AD. ECSIT codes for the adaptive protein that acts as a cytoplasmic and signaling protein and plays a role in supporting the stability of the mitochondrial respiratory complex. Furthermore, the adaptor protein plays a role in activating nuclear factor (NF)-κB, interferon regulatory factors (IRFs), and activating protein-1. Additionally, it plays a role in connecting the immune toll-like receptor (TLR), homeostatic bone morphogenetic pathway (BMP), and transforming growth factor-beta (TGF-b) pathways [66,67].

ECSIT engages with mitochondrial proteins like Lon protease homolog (LONP1) and glutaryl-CoA dehydrogenase (GCDH), which play roles in intra-mitochondrial proteolysis and redox signaling, before interacting with AD seed nitric oxide synthase (NOS3). Furthermore, research has demonstrated specific connections between ECSIT and the Alzheimer's disease genes ApoE, PSEN-1, and PSEN-2. These interactions confirm ECSIT's role as a molecular connection in oxidative stress, inflammation, and mitochondrial dysfunction in AD [66,68]

- ## Estrogen Receptor Gene (ESR)

Alzheimer's disease impacts both genders, but the majority of cases (approximately 66%) are found in women. Numerous studies indicate that women with Alzheimer's disease suffer greater cognitive decline compared to men. Furthermore, at the genetic level, certain gene variations, such as the ApoE4 allele, substantially elevate the risk of developing AD in women as opposed to men. Additional research has shown that women's risk of developing Alzheimer's disease is linked to the decline of ovarian hormones following menopause. This is because estrogen plays a role in various brain functions including neurotransmission, neural development, protection against oxidative stress, lowering Aβ peptide levels, and reducing tau hyperphosphorylation. Estrogen's effects are carried out by estrogen receptors (ERs) found inside cells, on cell surfaces, and within cell membranes. The two primary subcategories of these receptors are ERα and ERβ, which are formed by two separate genes and are situated on chromosome 6 and 14, respectively. ERα receptor is located in the hypothalamus and amygdala, while ERβ receptors can be found in the hippocampus and cortex. Variations in individual nucleotides in ERβ and ERα genes could impact how exogenous estrogen

impacts cognitive aging in elderly women. SNPs such as PvuII (rs9340799) and XbaI (rs223493) have been discovered in ERα and are linked to Alzheimer's disease and cognitive decline. Moreover, various SNPs in ERβ have been demonstrated to elevate the likelihood of Alzheimer's disease in women.

- Other Genes

Additional genetic variations linked to an elevated risk of AD consist of polymorphisms in the vitamin D receptor (VDR) gene. These variations impact the binding ability of vitamin D to its receptor and could lead to neurodegenerative disorders and neural harm. Additionally, DNA methylation, histone, and chromatin modifications have been shown to play a role in AD.

5.2.3. Environmental Factors

Not all cases of AD can be accounted for by aging and genetic risk factors. Environmental factors such as air pollution, diet, metals, infections, and others can cause oxidative stress and inflammation, raising the likelihood of developing Alzheimer's disease. Here, we present the key environmental factors and their connections to AD [75,76].

- Air pollution

Air pollution is defined as altering the atmosphere by adding chemical, physical, or biological pollutants. Its link to respiratory and cardiovascular illnesses is well-known, and more recently, its connection to Alzheimer's Disease was confirmed. The National Ambient Air Quality Standards (NAAQSs) in the USA have identified six air pollutants that pose a risk to human health: ozone (O3), nitrogen oxides (NOx), carbon monoxide (CO), particulate matter (PM), sulfur dioxide (SO2), and lead. Research conducted on animals and cellular models indicate that high levels of air pollution can cause damage to the olfactory mucosa, bulb, and frontal cortex region, resembling the effects seen in Alzheimer's disease. A connection exists between oxidative stress, neuroinflammation, and neurodegeneration in individuals exposed to air pollutants, with hyper-phosphorylated tau and Aβ plaques found in the frontal cortex. Air pollution is linked to heightened production, buildup, and hindered cognitive abilities related to Aβ42 [77,78].

- Diet

Recently, there has been a rise in the amount of research focusing on the impact of nutrition on AD. Various dietary supplements like antioxidants, vitamins, polyphenols, and fish have been shown to lower the risk of AD, while saturated fatty acids and high-calorie intake were linked to an increased risk of AD [79]. Food processing leads to the breakdown of heat-sensitive micronutrients like vitamin C and folates, loss of significant amounts of water, and creation of harmful secondary products (AGEs) through non-enzymatic glycation of free amino groups in proteins, lipids, and nucleic acids. The harmful impact of AGEs is known for causing oxidative stress and inflammation by altering the structure and function of cell surface receptors and body proteins. Various researches have shown a correlation between higher AGEs levels in the blood and the development of cognitive decline and the advancement of Alzheimer's disease. The RAGE receptor, found in various parts of the body such as microglia and astrocytes, has been discovered to be highly expressed in the brains of Alzheimer's disease patients, where it functions as both a transporter and a cell surface receptor for Aβ. Malnutrition poses another potential threat for AD. A lack of essential nutrients like folate, vitamin

B12, and vitamin D can lead to a decline in cognitive abilities, along with the added challenge of eating and swallowing issues in Alzheimer's disease patients, increasing the likelihood of malnutrition.

- ## Metals

Metals exist in both nature and biological systems and can be categorized as bio-metals with a biological role in living organisms (such as copper, zinc, and iron) and toxicological metals lacking biological function (like aluminum and lead) [82]. Aluminum is commonly utilized in various industries like processed foods, cosmetics, medical preparations, medications, and more. Aluminum in the body attaches to plasma transferrin and citrate molecules, which help transport aluminum to the brain. Research has shown that aluminum builds up in the cortex, hippocampus, and cerebellum regions, where it interacts with proteins and leads to misfolding, grouping, and phosphorylation of highly phosphorylated proteins such as tau, which is a hallmark of Alzheimer's disease. Lead can quickly pass through the blood-brain barrier (BBB) and interfere with the binding site of bio-metals such as calcium, impacting neural development and causing significant harm. Research found that a sudden exposure to lead was linked to Alzheimer's disease and resulted in an elevation of β-secretase levels and the buildup of Aβ. Cadmium is a metal that can cause cancer, dissolves in water, and is able to pass through the blood-brain barrier, leading to neurological disorders such as Alzheimer's disease. The findings indicate that Cadmium ions play a role in the clustering of Aβ plaques and the self-clustering of tau in the brain affected by AD. The data collected on metals suggests they play a role in the onset of Alzheimer's disease, as one of the risk factors.

- ## Infection

Long-term infections in the central nervous system (CNS) can lead to a buildup of Aβ plaques and NFT, making them a risk factor for Alzheimer's disease (AD). Research conducted by Dr. Itzhaki revealed that individuals who carry the ApoE-ε4 allele are at a higher risk for developing Alzheimer's disease due to the presence of herpes simplex virus (HSV-1) DNA in their system. Replication of HSV-1 in the brain can lead to activation of the inflammatory response and an increase in Aβ deposition, causing neuronal damage and gradual progression of AD. Contrastingly, Miklossy and Balin's research findings have demonstrated the impact of persistent bacterial infections in AD. As an illustration, syphilitic dementia induced by spirochete bacteria (Treponema pallidum), which gather in the cerebral cortex, resulted in lesions resembling neurofibrillary tangles, resulting in severe neurodegenerative conditions. In addition, Chlamydia pneumonia bacteria may cause late-onset Alzheimer's disease by stimulating astrocytes and cytotoxic microglia, interfering with calcium regulation and apoptosis, leading to cognitive decline, and raising the likelihood of developing AD [85,86,87].

5.2.4. Medical Factors

Various factors increase the risk of developing Alzheimer's disease. In addition, elderly individuals with Alzheimer's disease often have health issues like cardiovascular disease (CVD), obesity, and diabetes among others. All these circumstances are linked to a higher chance of developing AD [88,89].

- ## Cardiovascular system

Cardiovascular diseases are known to be a significant risk factor for Alzheimer's disease, with conditions like stroke increasing the likelihood of dementia by causing neural tissue loss, which can

worsen degenerative effects and impact amyloid and tau pathology. Atrial fibrillation can also result in embolisms, leading to strokes and a decline in memory and cognitive abilities. In addition, heart failure impacts the heart's ability to pump effectively, leading to inadequate blood flow throughout the body and reduced blood supply to the brain, resulting in hypoxia and damage to the nerves. The hypothesis of coronary heart disease suggests that atherosclerosis, peripheral artery disease, hypo-perfusion, and emboli are all connected to a higher risk of AD. Increased blood pressure leads to thickening of the walls of blood vessels and narrowing of the lumen, resulting in decreased cerebral blood flow. Long-term cases can also lead to cerebral edema, increasing the risk of Alzheimer's disease and cardiovascular disease. Focusing on the connection between CVD and AD can provide a way to prevent and delay the disease, as CVD is a risk factor that can be changed.

- Obesity and diabetes

Obesity is the result of an excess accumulation of body fat caused by a caloric intake exceeding the amount of calories burned, and can be determined using the body mass index (BMI). Elevating body fat levels is linked with reduced blood flow to the brain, leading to conditions such as brain ischemia, memory problems, and vascular dementia. Factors such as obesity, poor diet, and others can lead to impaired glucose tolerance (IGT) or diabetes, which is identified by high blood sugar impacting peripheral tissues and blood vessels. Persistent high blood sugar levels can lead to cognitive decline by causing the buildup of amyloid-beta, oxidative stress, dysfunctional mitochondria, and neuroinflammation. Obesity is defined by the rising production of pro-inflammatory cytokines from fat cells, which activate macrophages and lymphocytes, causing both local and systemic inflammation. This inflammation causes insulin resistance and hyperinsulinemia leading to hyperglycemia as a result. Obesity is a recognized factor that increases the risk of developing type 2 diabetes, CVDs, and cancer, all known as risk factors for dementia and AD. Increased microglia due to brain inflammation leads to reduced synaptic plasticity and impaired neurogenesis. Microglia have the ability to influence insulin receptor substrate 1 (IRS-1) and inhibit internal insulin signaling, which plays a crucial role in neural wellness. As a result, changes in insulin function may lead to the buildup of Aβ and hinder the breakdown of tau protein linked to AD [91,92,93,94].

6. Treatment

At present, there are approximately 24 million cases of Alzheimer's disease globally, and by 2050, it is projected that the total number of individuals with dementia will quadruple. Despite being a public health concern, there are currently only two approved drug classes for treating AD: cholinesterase enzyme inhibitors (natural, synthetic, and hybrid analogues) and N-methyl D-aspartate antagonists. Various AD-related physiological mechanisms damage cells that produce Ach, leading to decreased cholinergic transmission across the brain. Acetylcholinesterase inhibitors (AChEIs) fall into three categories - reversible, irreversible, and pseudo-reversible - and work by inhibiting cholinesterase enzymes (AChE and BChE) to prevent the breakdown of ACh, leading to higher ACh levels in the synaptic cleft [95,96,97]. However, excessive activation of NMDAR results in elevated levels of infused Ca2+, causing cell death and synaptic dysfunction. NMDAR antagonist stops excessive NMDAR glutamate receptor activation, reducing Ca2+ influx and returning it to its typical function. Although these two categories have a therapeutic impact, they only address the symptoms of AD and do not provide a cure or prevention for the disease [98,99]. Regrettably, just a handful of clinical trials for AD were initiated in the past ten years and they were largely unsuccessful. Multiple theories have been suggested to comprehend AD progression in order to alter its course and create effective therapies, such as disrupted tau protein processing, β-amyloid, immune system reaction, as well as cholinergic and oxidative stress injury [30,100]. However, the majority of modifiable risk factors for

AD, such as cardiovascular issues or lifestyle choices, can be avoided without the need for medical treatment. Research has indicated that engaging in physical activity can enhance brain health and decrease the risk of Alzheimer's disease by boosting brain vascularization, plasticity, neurogenesis, and reducing inflammation through decreased Aβ production, ultimately leading to improved cognitive function in older individuals. Additionally, the Mediterranean seas

6.1. Symptomatic Treatment of AD

6.1.1. Cholinesterase Inhibitors

According to the cholinergic hypothesis, AD is due to the reduction in acetylcholine (ACh) biosynthesis. Increasing cholinergic levels by inhibiting acetylcholinesterase (AChE) is considered one of the therapeutic strategies that increases cognitive and neural cell function. AChEIs are used to inhibit acetylcholine degradation in the synapses, which results in continuous accumulation of ACh and activation of cholinergic receptors. Tacrine (tetrahydroaminoacridine) (**1,** Figure 4) was the first FDA (Food and Drug Administration)-approved cholinesterase inhibitor drug for the treatment of AD, which acts by increasing ACh in muscarinic neurons, but it exited the market immediately after its introduction due to a high incidence of side effects like hepatotoxicity and a lack of benefits, which was observed in several trials. Later on, several AChEIs were introduced, such as donepezil (**2**, Figure 4), rivastigmine (**3**, Figure 4), and galantamine (**4**, Figure 4), and are currently in use for the symptomatic treatment of AD [34,97,102,103]. Another strategy that may help in the treatment of AD is increasing choline reuptake and as a result, increasing acetylcholine synthesis at the presynaptic terminals. This can be achieved by targeting choline transporter (CHT1) which is responsible for supplying choline for the synthesis of ACh. Developing drugs that are capable of increasing CHT1 at the plasma membrane may become the future therapy of AD [36].

- Donepezil

Donepezil, shown in Figure 4, is a derivative of indanonebenzylpiperidine and belongs to the second generation of AChEIs, being regarded as the top drug for treating AD. Donepezil attaches to acetylcholinesterase in a reversible manner and hinders the breakdown of acetylcholine, resulting in an increased level of ACh at the synapses. The medication is well-received with mild and temporary cholinergic side effects that are associated with the digestive and nervous systems. Donepezil is commonly utilized in the treatment of Alzheimer's disease to enhance cognitive function and behavior while not affecting the progression of the disease itself.

- Revastigmine

Rivastigmine (3, Figure 4) is a pseudo irreversible inhibitor of AChE and BuChE. It works by attaching to both active sites of AChE (anionic and estearic sites), thus blocking ACh metabolism. BuChE is predominantly located in glial cells with just 10% of AChE activity in the healthy brain. In Alzheimer's disease, BuChE activity rises to 40–90%, while ACh activity decreases. This indicates that BuChE activity could signal moderate to severe dementia. Rivastigmine breaks apart at a slower rate than AChE, making it known as a pseudo-irreversible substance, and it is metabolized by AChE and

BuChE at the synapse. The medication is prescribed for individuals with mild to moderate Alzheimer's disease. It enhances mental processes and everyday tasks. Taking the drug by mouth can lead to negative reactions like feeling sick, throwing up, indigestion, weakness, loss of appetite, and decrease in weight. Often, these side effects are the primary cause of discontinuing medication, but they can be alleviated over time, making the drug easier to tolerate. Rivastigmine can be administered via transdermal patches to provide a steady and controlled release of the medication through the skin, resulting in improved tolerance and caregiver contentment. Additionally, patches can provide a smaller amount of medication in comparison to tablets, leading to decreased side effects. The majority of individuals with AD experience memory loss and difficulties with swallowing, leading to challenges in consistently taking oral medications. Hence, transdermal patches are the most suitable technique for administering the medication to AD patients [107,108,109,110].

- Galantamine

Galantamine (Figure 4, 4) is commonly prescribed as the initial treatment for mild to moderate cases of Alzheimer's disease. GAL is an isoquinoline alkaloid that selectively acts as a competitive inhibitor of AChE and can also bind to the α-subunit of nicotinic acetylcholine receptors to activate them in a dual mechanism of action. GAL can enhance behavioral symptoms, daily life activities, and cognitive performance effectively and with good tolerability, like other AChE inhibitors. Various methods for enhancing drug delivery to the brain were created, including attaching GAL to ceria-containing hydroxyapatite particles by Wahba et al. for targeted drug delivery to specific areas in the brain. Misra et al. utilized solid-lipid nanoparticles while Fornaguera et al. employed nano-emulsification techniques to transport GAL hydrobromide. The findings of these studies showed a potential approach for the secure transportation of the medication. Hanafy et al. created nasal GAL hydrobromide/chitosan complex nanoparticles that demonstrated effective pharmacological results, whereas Woo et al. employed a patch system to deliver a controlled release dosage of the drug.

6.1.2. *N*-methyl D-aspartate (NMDA) Antagonists

NMDAR is thought to play a primary role in the pathophysiology of AD. Stimulation of NMDAR leads to an influx of Ca2+ that triggers signal transduction and, in turn, initiates gene transcription crucial for the creation of long-term potentiation (LTP), necessary for synaptic neurotransmission, plasticity, and memory establishment. Excessive NMDAR activation leads to increased Ca2+ signaling and heightened glutamate stimulation, the main excitatory amino acid in the central nervous system, causing excitotoxicity, synaptic malfunction, neuronal demise, and cognitive decline. Many NMDAR uncompetitive antagonists were created and tested in clinical trials, but the majority of them were unsuccessful due to their low effectiveness and side effects. Memantine (5, Figure 4) is the sole authorized medication in this class for addressing moderate to severe AD; furthermore, there are ongoing developments of other NMDAR uncompetitive antagonist compounds like RL-208 (3,4,8,9-tetramethyltetracyclo [4.4.0.03,9.04,8]dec-1-yl)methylamine hydrochloride), a polycyclic amine compound that could offer a potential therapeutic benefit for age-related cognitive issues and AD [115,116,117].

- Mamantine

Memantine (5, Figure 4) is a weak-binding inhibitor that competes with NMDAR, a specific type of glutamate receptor. It helps to block excessive glutaminergic system activation linked to neurotoxicity in Alzheimer's disease. Memantine is prescribed for managing moderate to severe Alzheimer's Disease either by itself or along with AChEI. The medication is deemed secure and easily endured,

as it inhibits the excitatory receptor without disrupting regular synaptic communication thanks to memantine's weak attachment. It gets quickly replaced by high levels of glutamate on the NMDAR, preventing extended obstruction. The second option is linked to significant side effects, particularly affecting learning and memory [99,118].

6.2. Promising Future Therapies

6.2.1. Disease-Modifying Therapeutics (DMT)

The advancement of Alzheimer's disease through the targeting of various pathophysiological mechanisms. This differs from symptomatic therapy by focusing on enhancing cognitive functions and reducing symptoms like depression or delusions without changing the disease. DMTs, whether they are immunotherapies or small molecules, are given through the mouth and are in the process of being created to stop AD or slow down its advancement. Numerous DMTs have been created and went through clinical trials, like AN-1792, a man-made Aβ peptide (human Aβ1–42 peptide of 42-amino acids with the immune adjuvant QS-21) which was the initial active immunotherapy for AD. It reached phase II trials but was stopped because 6% of patients experienced meningoencephalitis as a side effect. Additional medications were created but did not succeed during the clinical tests, such as the anti-Aβ antibody (solanezumab and bapineuzumab), γ-Secretase inhibitors (semagacestat 6, avagacestat 7, and tarenflurbil 8) (Figure 4) and β-secretase inhibitors (BACE) (Lanabecestat 9, verubecestat 10, and atabecestat 11) (Figure 4). Several reasons account for the failures of DMTs, including late initiation of therapy, targeting the wrong main issue, administering incorrect drug doses, and a lack of understanding of AD's pathophysiology. Numerous immunotherapies listed in Table 1 have been created over many years, such as CAD106 and CNP520. CAD106 is an Aβ immunotherapy that generates Aβ antibodies in animals by using multiple copies of Aβ1–6 peptide linked to Qβ coat protein, while CNP520 is a small molecule that blocks BACE-1 to prevent Aβ formation and is depicted in Figure 4. CNP520 was discovered to decrease Aβ plaque accumulation and Aβ concentrations in the brain and CSF in rats, dogs, and healthy adults aged ≥ 60 years, and remains in the process of clinical testing. Moreover, aducanumab, gantenerumab, and crenezumab are all monoclonal antibodies specific to human Aβ that have a strong affinity for aggregated forms.

Besides the anti-amyloid drugs, tau aggregation blockers are also a potential disease-modifying therapy. Tau serves as a biomarker for neurofibrillary tangles in Alzheimer's disease and plays a role in regulating microtubule stability, signaling pathways, and axonal transport. Changing the shape of tau leads to harmful clumping. Hence, inhibiting tau aggregation is a promising strategy in drug research to slow down the advancement of AD. Research in mice has demonstrated that tau oligomers lead to harm to mitochondria, interference with neural communication, decreased synaptic connections, and memory decline. Small molecules, such as disease-modifying therapeutics (DMT), can be utilized to block the first stage of tau aggregation and consequently lower its buildup. Methylene blue, depicted as number 13 in Figure 4, is a blue dye that has been tested in phase II clinical trials for treating mild to moderate AD, showing potential in inhibiting tau aggregation. After the drug was given, the urine turned blue, showing a lack of effectiveness in binding, leading to strong criticism of the study. Alternative methods propose that blocking certain kinases, like glycogen synthase kinase 3 (GSK3β), can prevent tau hyperphosphorylation and prevent tau deposition. Entities like tideglusib (14, or NP-031112 (NP-12), Figure 4), a thiazolidinedione-derived compound, lithium, pyrazolopyridines, pyrazolopyrazines, sodium valproate, and others are examples. Saracatinib (AZD0530) is also another protein kinase inhibitor (15, Figure 4) that works by blocking tyrosine kinase. It has demonstrated positive outcomes in enhancing memory in transgenic mice and is presently undergoing phase II trials [125,126,127]. Davidowitz and colleagues used the hatu mouse model of tauopathy to investigate how effective a primary small molecule is in halting tau

build-up. The research findings showed a notable decrease in tau levels and its phosphorylated form levels, suggesting the potential to block the entire tau aggregation pathway by utilizing a refined lead compound [128].

6.2.2. Chaperones

Mutations or environmental factors lead to protein misfolding, which results in toxic aggregations causing neurodegenerative disorders such as AD. Cells naturally create protein quality control (PQC) systems to prevent protein misfolding from causing harm. As individuals grow older, the equilibrium is disrupted and the faulty structures start to outnumber the PQC system, triggering the unfolded protein response (UPR) that halts protein creation and boosts chaperone manufacturing. In humans, cells usually contain proteins that help other proteins function properly and reach their intended location within the cell. These proteins are referred to as "chaperones". Chaperones play a role in protein folding and enhancing the efficiency of the PQC system. Hence, it is regarded as a potential option for addressing neurodegenerative disorders. It can be categorized into three groups: (1) molecular chaperones, such as heat shock proteins (Hsps) that aid in the folding and unfolding of proteins, acting as neuroprotective agents when overexpressed, (2) pharmacological chaperones that are small molecules inducing protein refolding and restoring function, and (3) chemical chaperones, including osmolytes and hydrophobic compounds, which are low molecular weight substances. Both groups' members do not operate via a particular mechanism and require high concentrations to produce their therapeutic results [129].

- ### Heat Shock Proteins (Hsps)

Protein misfolding and aggregation are the main reasons for the majority of neurodegenerative diseases, resulting in cell demise. The molecular chaperone may exist inside the cell, like heat shock proteins (e.g. Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, and Hsp110), or outside the cell, like clustering and alpha-macroglobulin. HSPs are crucial in the process of protein folding and safeguard cells from damaging stress-related occurrences. There are two groups of Hsps: (a) traditional Hsps that have a molecular weight of 60 kD or higher and contain an ATP-binding site. This group comprises Hsp100, Hsp90, Hsp70, and Hsp60, along with smaller Hsps like αB-crystalline, Hsp27, Hsp20, HspB8, and HspB2/B3 that do not have an ATP-binding site, all weighing 40 kD or less. These proteins can aid other Hsps in their task of refolding. Dysfunction in these mechanisms may result in oxidative stress, malfunction in mitochondria, and various conditions leading to harm, neuron loss, and the advancement of neurodegenerative illnesses. Various heat shock proteins can inhibit the formation of clumps by misfolded proteins, such as amyloidogenic proteins (Aβ and tau), and facilitate their breakdown [130,131].

- ### Hsp60

Hsp60 has a crucial function in folding proteins in mitochondria. The protein's function in Alzheimer's disease is uncertain; some argue it may offer protection while others believe it could be detrimental, as it may be excessively produced by activated microglia, leading to the rise of pro-inflammatory

factors like toll-like receptor 4 (TLR-4) that trigger neuronal cell death. Thus, blocking activated microglia and Hsp60 production may be an effective approach to prevent neurodegenerative disorders. Compounds like mizoribine (an immunosuppressant) and pyrazolopyrimidine EC3016 (both shown in Figure 5) are examples of inhibitors of Hsp60. Both substances function by inhibiting protein folding through blocking ATPase activity of Hsp60. In contrast, avrainvillamide and epolactaene, both metabolites (18 and 19, Figure 5), function by attaching to the cysteine residues of Hsp60 and blocking its ability to fold proteins. Nevertheless, the involvement of Hsp60 in AD is a topic of debate and further studies are necessary in order to comprehend its function [130].

- ## Hsp70

Research has indicated that Hsp70 interacts with Aβ42 and inhibits its self-aggregation. Martín-Peña et al. examined the protective function of cytosolic and extracellular isoforms of Hsp70 in Drosophila flies AD models against memory decline caused by Aβ42 aggregation. Animal research demonstrated that Hsp70 serves a double purpose, both inside and outside cells, safeguarding against Aβ42-induced neurotoxicity and loss of synapses. It not only binds to tau and its hyper-phosphorylated form to inhibit its formation, but also reduces aggregation and enhances tau binding to microtubules. Hsp70 works by stimulating microglia, insulin-degrading enzyme, and tumor growth factor-β1 to break down β-amyloids and protect against memory deficits [132,133]. Certain research in Alzheimer's disease brain tissue showed increased levels of Hsp70 and a connection to activated glia and stressed neurons. Additionally, it was discovered that Hsp70 is linked to extracellular accumulations in Alzheimer's disease. Drug treatments focusing on Hsp70, primarily involving anticancer medications that block Hsp70 ATP-binding site, are being looked at as potential options for treating AD because of their effectiveness in lowering tau levels in lab settings both in vitro and ex vivo. MKT-077(1-ethyl-2-((Z)-((E)-3-ethyl-5-(3-methylbenzo [d]thiazol-2(3H)-ylidene)-4-oxothiazolidin-2-ylidene)methyl)pyridin-1-ium chloride) (20, Figure 5) is a rhodacyanine compound with anticancer properties that binds to mortalin, a mitochondrial Hsp70 site, and functions as an anti-proliferative agent. However, its usage was discontinued due to its toxic side effects and limited ability to penetrate the blood-brain barrier. In contrast, YM-01 (21, Figure 5), a stronger MKT-077 derivative, was created by substituting the ethyl group on the pyridinium nitrogen of MKT-077 with a methyl group. JG-98 (22, Figure 5) is another derivative of MKT-077 that exhibits a 60-fold greater affinity for Hsp70 compared to YM-01 [130,134,135,136].

- ## Vacuolar sorting protein 35 (VPS35)

The build-up of proteins in neurons and glial cells disrupts the balance of cellular protein levels. The endosomal-lysosomal system transports proteins for recycling and degradation. A malfunction in the system could result in various illnesses, including Alzheimer's disease. Retromer is made up of sorting nexin (SNX1, 2, 5, 6) and vacuolar sorting proteins (VPS 26, 29, 35) and functions in moving cargo molecules from the endosome to the trans-Golgi network. Dysfunction of retromer leads to decreased levels of VPS35, promoting Aβ production, leading to cognitive decline and synaptic dysfunction observed in individuals with Alzheimer's disease [140,141]. An experiment was done on 3xTg mice brains to investigate how VPS35 overexpression impacts memory function. The research

indicated that elevated levels of VPS35 were linked to decreased levels of Aβ peptide and tau pathology, along with improvements in synaptic dysfunction and a decrease in neuroinflammation. Hence, VPS35 holds significant potential as a therapeutic target for treating Alzheimer's disease. R55, a small molecule known as thiophene-2,5-diylbis(methylene) dicarbamimidothioatedihydrochloride (27, Figure 5), a derivative of thiophenethiourea, has the potential to improve retromer stability and function. This can be achieved by boosting retromer proteins, relocating AOO from the endosome, and decreasing pathological processing of APP. It could be a beneficial treatment option for neurodegenerative conditions [143].

7. Conclusion:

Alzheimer's disease is now seen as a global health issue, so the National Institute on Aging—Alzheimer's Association has revised the 1984 NINCDS-ADRDA criteria to improve specificity, sensitivity, and early detection of individuals who may develop AD. Various criteria have been suggested to improve the accuracy of diagnosing AD, such as clinical biomarkers, bodily fluid analysis, and imaging tests. However, AD treatment still focuses on managing symptoms rather than changing the disease's outcome. Galantamine, donepezil, rivastigmine, and memantine enhance memory and alertness by blocking cholinesterase enzyme and NMDA receptors, although they do not stop advancement. Multiple research studies have demonstrated that changing lifestyle habits such as diet and exercise can enhance brain health, decrease the progression of AD without the need for medical treatment, and is seen as the primary approach for all AD patients. Lately, the research is directed towards addressing the abnormal characteristics of AD like Aβ and p-tau. Upcoming treatments like disease-modifying therapy can change the course of AD by focusing on the Aβ pathway, with various medications like AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil have gone through clinical trials without showing effectiveness in the last stages. Additional DMTs are currently being studied, including aducanumab, gantenerumab, crenezumab, tideglusib, lithium, and more, which aim at Aβ and tau pathologies. Alternative compounds known as chaperones, such as heat shock proteins and vacuolar sorting protein 35 (VPS35), help other proteins function correctly and reach their intended location within the cell, making them a potential therapy for neurodegenerative disorders. In addition, the natural plant-based ingredients in traditional Chinese medicine have demonstrated significant promise in treating Alzheimer's disease by affecting various pathways in the body. To sum up, the effectiveness of treating AD hinges on beginning treatment promptly and closely monitoring patients for disease advancement through biomarkers.

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