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Alzheimer's Disease: A Clinical and Basic Science Review:

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❖ Abstract :—

Dementia, which is characterised by a decline in thinking and independence in daily tasks, is mostly brought on by Alzheimer's disease (AD), a sickness that results in the degradation of brain cells. The disease AD is seen as multifaceted, and two basic hypotheses were Cholinergic and amyloid hypotheses have been put out as potential causes of AD. additionally, a number of risk elements ageing, genetics, head trauma, vascular disease, infections, and environmental factors.The disease is influenced by various factors. There are just two kinds of medications that have been licenced to treat AD, includes cholinesterase enzyme inhibitors and N-methyl d-aspartate antagonists (NMDA),They do neither treat or prevent AD; rather, they are primarily beneficial in managing its symptoms.

❖ Key words:-

chaperons, heat shock proteins, -amyloid peptide, tau protein, risk factors, and disease modifying therapies for Alzheimer's disease.

❖ INTRODUCTION

The world's population is ageing quickly, and dementia cases are predicted to rise as a result.climb to 65 million within the year from 35 million today 2030. 5 million people, or 1 in 9, live only in the United States.Those over 65 who have Alzheimer's live with it.dementia's most common cause is illness (AD). For according to the Centers for Disease Control, comparison & Prevention (estimates from 2009–2012), roughly 3 million Asthma affects older people in the United States, 20 million people have arthritis, 10 million have diabetes, and Hypertension affects 25 million people. primary care doctors and experts will come across elderly people who have increased occurrence of dementia during their careers. It is crucial for all-around doctors to have a thorough understanding of dementia since it has major ramifications for patients, their families, and our society. This review article's objective is to offer a succinct explanation of AD and the associated idea of only little cognitive impairment (MCI). The article highlights aspects of AD and MCI from the clinical and biological perspectives which medical students should be knowledgeable of. In the article also discusses developments in the utilisation of biomarkers for the

detection of AD and continuing efforts to create innovative treatment

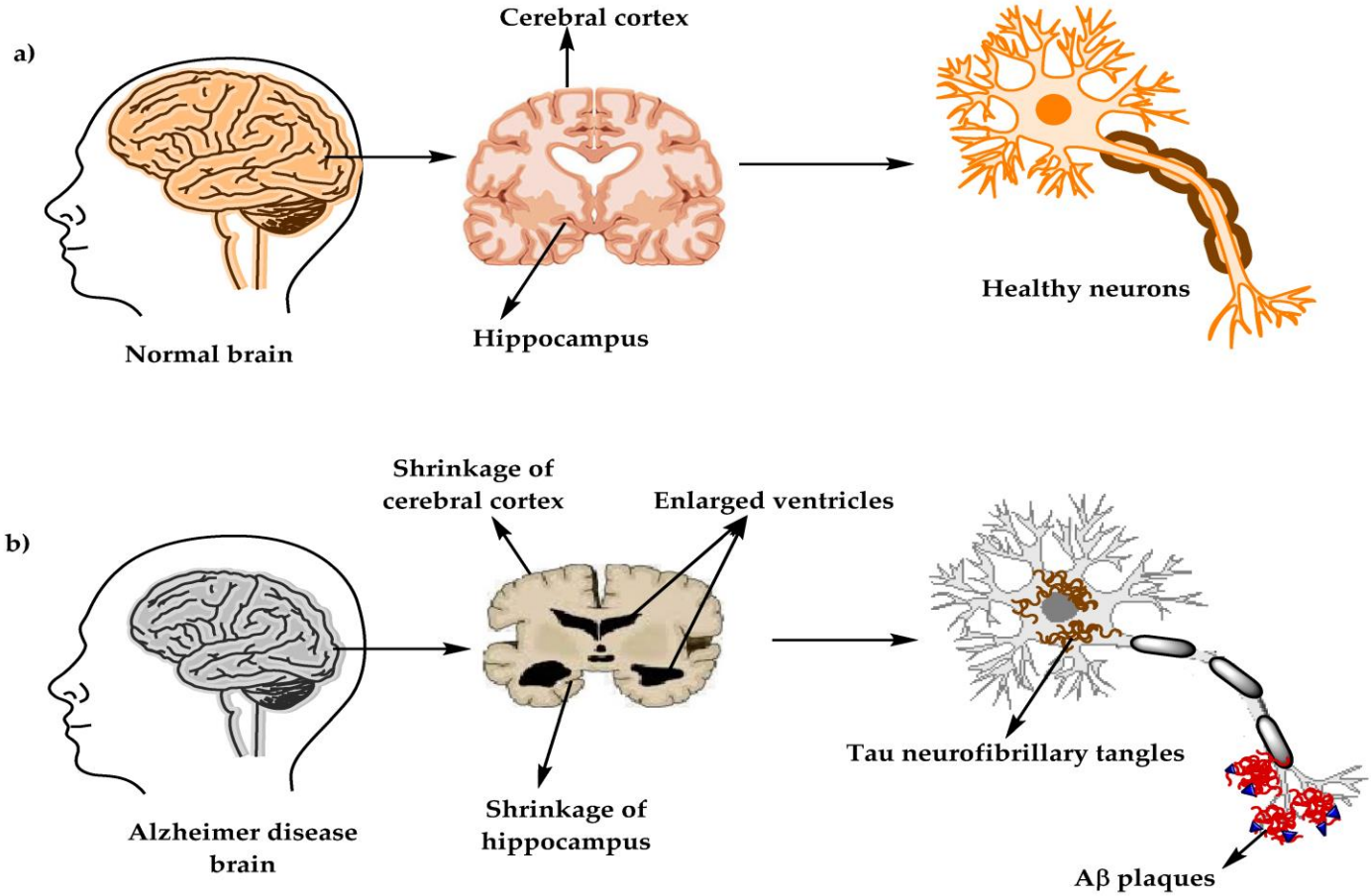

Figure 1. The physiological structure of the brain and neurons in

(a) healthy brain

(b) Alzheimer's disease (AD) brain

here are currently about 50 million AD sufferers globally, and it is predicted that this number will double every five years to reach 152 million by 2050. Individuals are affected by AD load,With annual costs of US$1 trillion anticipated for the entire world, their families, and the economy. At this time, Alzheimer's disease cannot be cured, although there are therapies that can only make the symptoms better.the signs [6,7]. This review's objective is to provide a concise explanation of AD diagnosis, pathophysiology, and cause, existing therapies, and to draw attention to the recently developed substances that could targeting a number of pathogenic pathways, such as A, can help prevent or cure AD. as well as tau aggregation and misfolding, swelling, oxidative harm, among other things

2 Alzheimer's Disease Diagnostic Criteria

A patient who is suspected of having AD should undergo a number of tests, including a neurological exam, MRI of the neurons, blood testing for vitamin B12, and other diagnostics in addition to the patient's medical and family histories [8]. According to certain research, vitamin (vit.) B12 insufficiency has long been known to be linked to neurologic issues and an increased risk of AD. Elevated homocysteine levels are a unique indicator of vitamin B12 deficiency and can lead to brain damage through oxidative stress, increased calcium influx, and apoptosis. Measurement of serum vitamin B12 levels together with tests for serum homocysteine levels and full blood counts can be used to diagnose vitamin B12 insufficiency [9,10].

In order to develop a clinical diagnostic's criteria for Alzheimer's disease, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) organised a study group (NINCDS-ADRDA) in 1984. Aphasia (language impairment), apraxia (a motor skills deficit), and agnosia are further symptoms of likely Alzheimer's disease, which can be identified by dementia that is validated by neuropsychological tests, gradual memory loss, and decreased everyday activities (a loss of perception).All of these symptoms may appear between the ages of 40 and 90, provided there are no systemic or brain diseases present; (2) Alzheimer's disease may be suspected in the absence of neurologic or psychiatric disorders and in the presence of another condition such as a systemic or brain disorder, though these conditions are not the main cause of dementia; and (3) Alzheimer's disease has been definitively diagnosed following histopathologic confirmation obtained from a biopsy or autopsy [11,12].

The NINCDS-ADRDA criteria were modified in 2011 by The National Institute on Aging—Association Alzheimer's for increased specificity and sensitivity in the diagnosis of Alzheimer's disease. Along with clinical biomarkers, the newly recommended criteria now include probable and possible AD dementia for use in clinical contexts as well as probable or possible AD dementia with pathophysiological evidence for research reasons. There are two types of biomarkers for Alzheimer's disease: (a) markers of brain amyloid, such as PET scans and cerebrospinal fluid (CSF), and (b) markers of neuronal injury, such as cerebrospinal fluid tau, fluorodeoxyglucose (FDG) scans to measure metabolic activity and magnetic resonance imaging (MRI) to measure atrophy [13–15].

3 Alzheimer's Disease's Neuropathology

1) Positive lesions (due to accumulation), which are characterised by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of AD patients, are one of two types of neuropathological changes in AD that provide evidence about disease progression and symptoms. In addition, there are two negative lesions (caused by losses) that are distinguished by significant atrophy brought on by neural, neuropil, and synaptic loss. In addition, other variables such neuroinflammation, oxidative stress, and damage to cholinergic neurons might result in neurodegeneration [16–18].

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3.1. Senile Plaques (SP)

The senile plaques, also known as neuritic, diffuse, dense-cored, classic, and compact type plaques, are extracellular deposits of beta-amyloid protein (A). The transmembrane amyloid precursor protein (APP) is used as a starting point for the production of A deposits by proteolytic cleavage enzymes such -secretase and -secretase [19–21]. These enzymes break down APP into a number of amino acid fragments, resulting in the final forms A40 and A42, which are amino acids 43, 45, 46, 48, 49, and 51.Large, soluble amyloid fibrils that can build up to create amyloid plaques and soluble oligomers that can spread throughout the brain are two different forms of A monomers. A is crucial for neurotoxicity and neurological function, therefore the buildup of thicker plaques in the cerebral cortex, amygdala, and hippocampus can impair cognition as well as stimulate astrocytes and microglia and harm axons, dendrites, and synapses. [21–23]

3.2. Neurofibrillary Tangles (NFTs)

The aberrant tau protein filaments known as NFT can sometimes form paired helical filaments (PHF) and accumulate in neuralperikaryal cytoplasm, axons, and dendrites. This results in a loss of cytoskeletal microtubules and proteins related with tubulin.In the brains of AD patients, hyperphosphorylated tau protein makes up the majority of NFTs, and its evolution can be interpreted in terms of the NFTs' morphological stages, which include: (1) the pre-tangle phase, one type of NFT, in which phosphorylated tau proteins accumulate in the somatodendritic compartment without the formation of PHF; (2) mature NFTs, which are characterised by tau protein filament aggregation and the displacement of the nucleus toNFTs)

3.3. Synaptic Loss

Memory impairment is typically seen in the early stages of AD and is caused by synaptic loss in the neocortex and limbic system. Defects in axonal transport, mitochondrial damage, oxidative stress, and other processes that can contribute in minor amounts, such as the buildup of A and tau at the synaptic sites, are some of the causes for synaptic loss. Pre-synaptic terminal loss, axonal degeneration, and loss of dendritic spines are the results of these processes over time [26]. Visinin-like protein-1 (VILIP-1) and synaptotagmin-1 are examples of synaptic proteins that act as biomarkers for the detection of synapses loss and severity [27,28]. Neurogranin is a postsynaptic neuronal protein.

4. The Stages of Alzheimer's Diseases

The pre-clinical or pre-symptomatic stage, which can extend for years or more, is one of the clinical stages of Alzheimer's disease. With no functional impairment in everyday activities and no clinical signs or symptoms of AD, this stage is characterised by modest memory loss and early degenerative alterations in the cortex and hippocampus [1,29,30]. (2) The moderate or early stage of AD, during which patients begin to experience a number of symptoms, including difficulty with everyday activities due to problems with attention and memory, loss of sense of location and time, changes in mood, and the emergence of depression [30,31]. (3) Moderate AD stage, where the illness has progressed to parts of the cerebral cortex and is causing memory loss that is worsened by difficulties identifying loved ones, lack of impulse control, and difficulty with reading, writing, and speaking [30]. (4) Severe AD or late-stage, which involves the disease spreading to the entire cortex area with a significant accumulation of neuritic plaques and neurofibrillary tangles, causing a progressive functional and cognitive impairment where patients cannot recognise their family at all and may become bedridden with difficulties in swallowing and urinating, ultimately leading to the patient's death as a result of these complications [1,32].

5. Causes and Risk Factors of Alzheimer's Disease

(Figure 2) illustrates the various risk factors for AD, which include advancing age, hereditary variables, brain traumas, vascular illnesses, infections, and environmental factors (heavy metals, trace metals, and others). The root cause of pathogenic modifications in It is still uncertain what causes Alzheimer's disease (A, NFTs, and synaptic loss). Several theories were put forth.a factor in AD, but two of them are thought to be the primary culprits: Some people think that a disability Changes in cholinergic function are a significant AD risk factor, while others contend that changes in amyloid The primary starting component is the generation and processing of -proteins. However, there isn't one at the moment.prevailing theory for describing the pathogenesis of AD [33, 34].

5.1. Alzheimer's Disease Hypotheses

5.1.1. Cholinergic Hypothesis

The enzyme choline acetyltransferase (ChAT), which is responsible for the production of acetylcholine, was implicated in the 1970s in neocortical and presynaptic cholinergic abnormalities (ACh). ACh plays a crucial part in cognitive function, hence a cholinergic hypothesis of AD was put up because of this. The ChAT enzyme produces ACh in the cytoplasm of cholinergic neurons from choline and acetyl-coenzyme A, and the vesicular acetylcholine transporter (VAChT) transports it to the synaptic vesicles (Figure 3). Memory, attention, sensory information, learning, and other crucial activities are only a few of the physiological processes in which ACh plays a role in the brain. Memory loss and cognitive function changes brought on the degeneration of the cholinergic neurons have been linked to AD. B-amyloid is thought to interfere with cholinergic neurotransmission, reduce choline absorption, and cause the release of ACh. The neurotoxicity of A oligomers and interactions between AChE and A peptide have been linked to cholinergic synaptic loss and the development of amyloid fibrils, according to studies. The reduction of nicotinic and muscarinic (M2) Ach receptors, which are found on presynaptic cholinergic terminals, as well as the deficit in excitatory amino acid (EAA) neurotransmission, where glutamate concentration and D-aspartate uptake are significantly reduced in many cortical areas in AD brains, are additional factors that contribute to the progression

of AD. Additionally, cholinergic receptor antagonists like scopolamine, which was shown to cause amnesia, are used. Utilizing substances that activate acetylcholine formation [35-37] will reverse this effect.

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Figure 2 : The risk factors for Alzheimer's disease

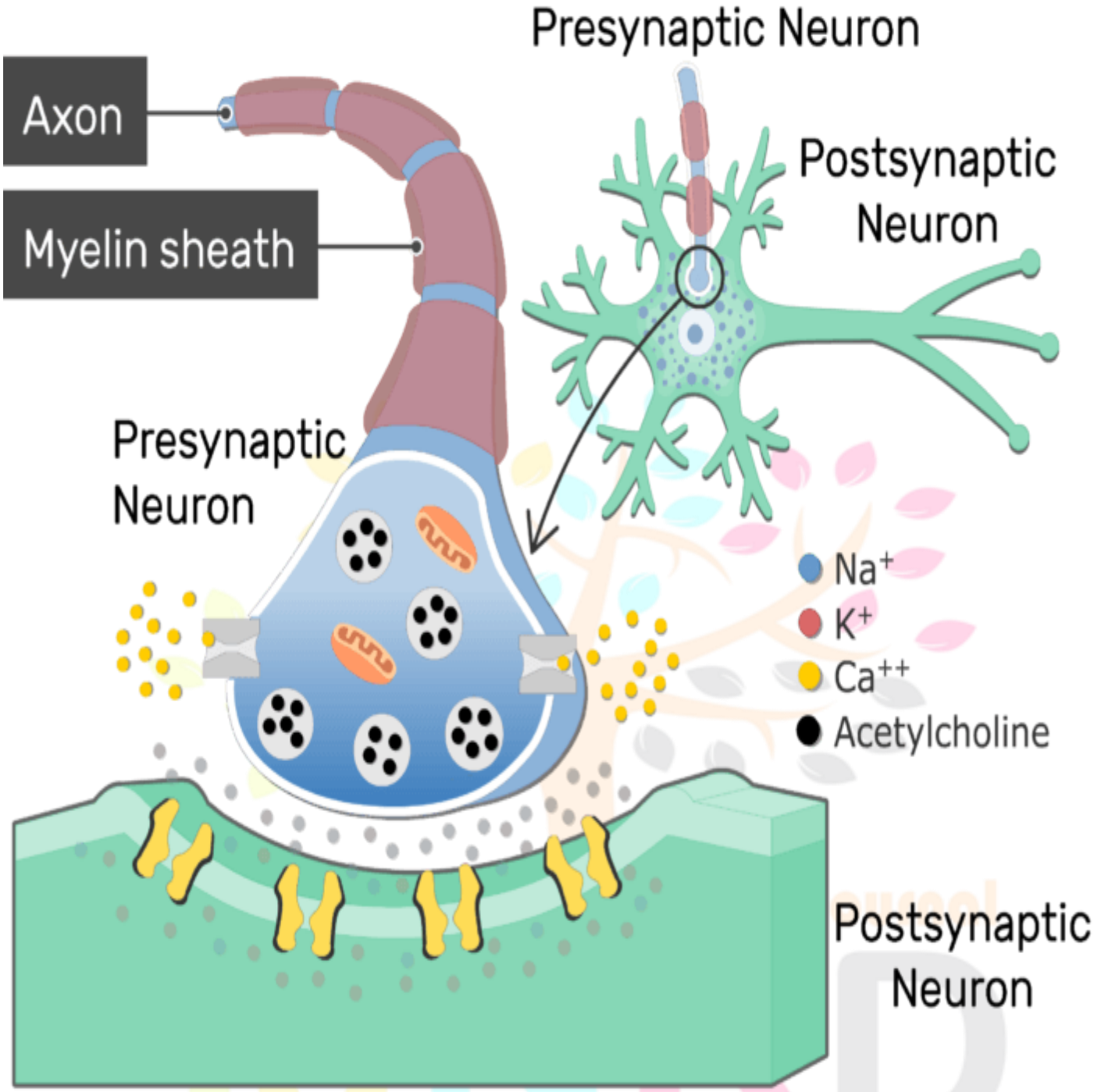


Figure 3: The pathway for thr synthesis and transportation of Acetylcholine between Presynaptic and postsynaptic nerve terminal

The three concepts that make up the cholinergic hypothesis are reduced presynaptic cholinergic markers in the cerebral cortex, severe neurodegeneration of the nucleus basalis of Meynert (NBM), the source of cortical cholinergic innervation, and the role of cholinergic antagonists in memory decline compared to agonists.

5.1.2. Amyloid Hypothesis

The amyloid hypothesis was developed after it was realised for many years that aberrant -sheet deposition in the central nervous system strongly correlated with dementia. However, it was discovered that with ageing, amyloid plaques (AP) also accumulate in healthy, normal brains, raising the question of whether or not AP deposition is the cause of the start

of AD. Alternative theories for the non-inherited form of AD (NIAD) have thus been put forth in recent years, but at this time, the amyloid hypothesis is still the most widely accepted pathological mechanism for inherited AD. According to the amyloid hypothesis, ageing or pathological conditions impair - and -secretase's ability to break down A, which results in the accumulation of A peptides (A40 and A42).Increasing the A42/A40 ratio causes the development of A amyloid fibrils, which causes neurotoxicity and the induction of tau pathology, ultimately ending in the death and degeneration of neuronal cells. A catabolism and anabolism were discovered to be affected by AD risk factors and mutations of multiple genes, including APP, PSEN1, and PSEN2, which quickly lead to a buildup of A and a rapid onset of neurodegeneration [39–41].

5.2. Alzheimer's Disease Risk Factors

5.2.1. Aging

Aging is the main risk factor for AD. Rarely do younger people develop this condition, and the majority of AD cases begin to manifest beyond the age of 65 [42]. The process of ageing is intricate and irreversible; it affects many organs and cell systems, resulting in a decline in brain size and weight, the loss of synapses, and the swelling of some ventricles along with SP deposition and NFT. Additionally, as people age, a number of illnesses include glucose hypometabolism, dyshomoeostasis of cholesterol, mitochondrial dysfunction, depression, and cognitive decline may manifest. It is challenging to tell the cases from early AD apart because these changes also occur with normal ageing [43,44].According to the age at which symptoms appear, AD can be divided into two categories: early-onset AD (EOAD), a rare form with only 1-6% of cases, and familial AD, which affects people between the ages of 30 and 65 and is characterised by the presence of multiple affected family members in different generations. The second kind, known as late-onset AD (LOAD), is more prevalent when it manifests after the age of 65. People who have a family history of AD or families with a late-onset disease may develop either type [45].

5.2.2. Genetics

Over the years, genetic factors have been uncovered, and it has been determined that they significantly contribute to the onset of AD. Most cases of EOAD are inherited in an autosomal dominant pattern, and mutations in the dominant genes Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2), and apolipoprotein E (ApoE) are linked to AD [46,47]. Genetic factors were responsible for 70% of the cases of AD.

Herein, we discuss the strong genetic risk factors in AD

- Amyloid Precursor Protein (APP)

  The APP gene on chromosome 21 codes for a type I transmembrane protein that is cleaved by the enzymes -, -, and -secretase to release A and other proteins. The APP gene has been identified to contain thirty mutations, of which twenty-five are linked to AD and result in an accumulation of A with increased levels. One protective mutation, A673T, however, guards against AD by reducing the secretion of A, A-40, and A-42 [48, 49]. All mutations that affect the secretase cleavage site, such as the KM670/671NL mutation in mouse models, have been associated with an increase in amyloid plaques in the cortex and hippocampus but no NFTs.NFT

- Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2)

  The autosomal dominant genes for EOAD, PSEN1 and PSEN2, are situated on chromosomes 14 and 1, respectively. PSEN-2 and PSEN-1 are homologous, sharing 67% of their amino acid sequences, but differ in their hydrophilic region and N-terminus. While there are more than 200 mutations in the PSEN1 gene, the PSEN2 gene has a rarer variant with less than 40 mutations [53,54]. PSEN1 is a core protein that plays a crucial part in the synthesis of A from APP by activating the -secretase complex. PSEN1 plays a crucial role in preserving memory and neurons, as shown by PSEN1 knockout studies that resulted in synaptic dysfunction and memory impairment in mice [51].Simple PSEN1 mutations include a single amino acid substitution, whereas severe changes can occur when two amino acids are substituted [55]. By lowering the levels of A-40, mutations in the PSEN1 gene increase the ratio of A-42 to A-40.

According to the findings of the Sun et al. study, C410Y or L435F mutations in PSEN1 knock-in mice caused a greater reduction in A40, which led to an increase in the A42/A40 ratio [56].

- Apolipoprotein E (ApoE)

ApoE protein is a glycoprotein that is highly expressed in the liver, brain, and some microglia. It functions as a receptor-mediated endocytosis ligand for cholesterol-containing lipoprotein particles, which are necessary for the production of myelin and healthy brain function. Due to single-nucleotide polymorphisms (SNPs) that alter the coding sequence, the ApoE gene on chromosome 19 has three isoforms, ApoE2, ApoE3, and ApoE4. When compared to ApoE2 and ApoE3 alleles, which are linked to a lower risk and a protective impact, respectively, EOAD and LOAD, the ApoE4 allele is a significant risk factor [58]. Cerebral amyloid angiopathy (CAA), which is recognised as a hallmark for AD, is caused by ApoE4 and plays a significant role in the deposition of A as a senile plaque [59]. Additionally, it has been demonstrated that ApoE4 contributes to the development of AD by causing vascular injury in the brain [60].

- ATP Binding Cassette Transporter A1 (ABCA1)

Like apolipoproteins-AI (ApoAI) and ApoE, the ATP-binding cassette transporter A1 (ABCA1) is a member of a large family of ABC transporters that controls cholesterol efflux in the bloodstream. In addition, ABCA1 plays a role in atherosclerosis and cardiovascular diseases by maintaining the stability of ApoE lipidation and acting as a mediator for the production of high-density lipoprotein (HDL). Studies using the AD mouse model demonstrated that a lack of ABCA1 promotes amyloid plaques and prevents ApoE lipidation [61]. Tangier disease, which is caused by a mutation in ABCA1 in humans, is characterised by low plasma levels of high-density lipoprotein (HDL) and ApoAI, an accumulation of cholesterol in tissues, and the pathogenesis of AD [62].

- Gene (CLU) and Bridging Integrator 1 (BIN1)

Clusterin (CLU) and Bridging Integrator 1 (BIN1) genes are unique risk factors for LOAD, in contrast to PSEN1, PSEN2, and APP mutations that cause familial or EOAD. The chromosome 8 gene known as the CLU is upregulated in the cortex and hippocampus of AD brains as well as in AD cerebrospinal fluid (CSF) and plasma, making the CLU a promising biomarker for AD.The CLU gene was discovered in 2009 using genome-wide association studies (GWAS). The CLU may act in a neurotoxic or neuroprotective manner depending on how it interacts with A and influences its clearance. Whether the CLU role is neuroprotective or neurotoxic is determined by the A ratio values [63].

- Evolutionarily Conserved Signaling Intermediate in Toll pathway (ECSIT)

Protein oxidation is increased by a substantial A buildup in AD brains, which highlights the crucial function of mitochondria in A cytotoxicity and AD pathogenesis. On chromosome 19, the ECIST gene, an evolutionary conserved signalling intermediate in the Toll pathway, is linked to an elevated risk of AD. The adaptation protein, which is also a cytoplasmic and signalling protein and is in charge of maintaining the mitochondrial respiratory complex, is encoded by ECSIT. Additionally, nuclear factor (NF)-B, interferon regulatory factors (IRFs), and activating protein-1 are all activated by the adaptor protein. Additionally, it participates in the coupling of the homeostatic bone morphogenetic pathway (BMP), immunological toll-like receptor (TLR), and transforming growth factor-beta (TGF-b) pathways [66,67].

- Estrogen Receptor Gene (ESR)

Both men and women can get AD, however women account for over two-thirds of AD cases. According to numerous research, women with AD suffer from worse mental decline than males. In addition, some genetic variations, like as the ApoE4 allele, greatly raise the risk of AD in women relative to men. Because oestrogen controls a number of processes in the brain, including neurotransmission, neural development, survival, protection from oxidative stress, reduction of A-peptide levels, and attenuation of tau hyperphosphorylation, other studies have shown that AD risk in women is related to the loss of ovarian hormones during menopause. Estrogen receptors (ERs) mediate the action of oestrogen (intracellular, transmembrane, and membrane-bound ERs)The two main subtypes of these receptors are

known as ER and Er, and they are both encoded by separate genes on chromosomes 6 and 14, respectively. ER receptors are located in the hippocampus and cortex, whereas ER receptors are found in the hypothalamus and amygdala. SNPs in the ER and ER genes may modify exogenous oestrogen in older women and have an impact on cognitive ageing. Examples of SNPs discovered in ER include PvuII (rs9340799) and Xbal (rs223493), which are linked to AD and cognitive decline. Additionally, several SNPs in ER have been shown to put women at risk for AD [69–72].

- Other Gene

The vitamin D receptor (VDR) gene polymorphism, which affects the affinity of vitamin D to its receptor and may cause neurodegenerative diseases and neuronal damage, is another gene polymorphism linked to an increased risk of AD [73]. Additionally, epigenetic elements such as DNA methylation, histone modifications, and chromatin modifications have been shown to play a role in AD [33,74].

5.2.3. Environmental Factors

Not all cases of AD can be accounted for by ageing and genetic risk factors. Air pollution, nutrition, metals, infections, and many other environmental risk factors can cause oxidative stress and inflammation, which raises the likelihood of developing AD. In this article, we discuss the most significant environmental elements and how they relate to AD [75,76].

- Air Pollution

By introducing chemical, physical, or biological contaminants into the atmosphere, air pollution alters the composition of the atmosphere. It has lately been shown to be linked to AD as well as respiratory and cardiovascular illnesses. National Ambient Air Quality Standards (NAAQSs) in the USA have identified six air pollutants—ozone (O3), nitrogen oxides (NOx), carbon monoxide (CO), particulate matter (PM), sulphur dioxide (SO2), and lead—as threats to human health. Studies on animals and cellular models have demonstrated that exposure to high amounts of air pollution can cause damage to the frontal cortex region as well as the olfactory mucosa and bulb, similar to what is seen in AD.

- Diet

There have been more investigations on the connection between nutrition and AD in recent years. In contrast to saturated fatty acids and high calorie intake, certain dietary supplements, including antioxidants, vitamins, polyphenols, and fish, were reported to reduce the incidence of AD [79]. As a result of the non-enzymatic glycation of free amino groups in proteins, lipids, and nucleic acids, food processing results in the degradation of heat-sensitive micronutrients (such as vitamin C and folates), significant water loss, and the formation of toxic secondary products (advanced glycation end products, or AGEs). The capacity of AGEs to cause oxidative stress and inflammation by altering the structure and function of body proteins and cell surface receptors is referred to as their toxic effect.

- Metals

Metals are present in both natural and biological systems and can be classified as either bio-metals (such as copper, zinc, and iron), which have a physiological purpose in living organisms, or toxicological metals (such as aluminium and lead), which have no biological function. Aluminum is widely employed in a variety of businesses, including those that produce processed foods, cosmetics, pharmaceuticals, and medical supplies. Aluminum is bonded to citrate molecules and plasma transferrin in the body, which can facilitate the transfer of aluminium to the brain. Al interacts with proteins and promotes misfolding, aggregation, and phosphorylation of highly phosphorylated proteins like tau protein, which is indicative of AD, in the cortex, hippocampus, and cerebellar regions of the brain, according to studies [83]. Lead can quickly cross the blood-brain barrier (BBB), where it can alter neural differentiation and synaptogenesis and cause severe damage.Lead competes with bio-metals like calcium for the binding site.According to studies, acute lead exposure increased -secretase expression and A buildup and was linked to AD. A water-soluble metal known as cadmium can cross the BBB and induce neurological conditions like AD. Results have shown that cadmium ions have a role in tau self-aggregation and A plaque aggregation in the AD brain. Metals are one of the risk factors for the development of AD, according to the evidence gathered on them [84].

- Infections

Chronic infections of the central nervous system (CNS) are regarded as risk factors for AD because they can result in the formation of A plaques and NFT. Dr. Itzhaki's research revealed that patients who carried the ApoE-4 allele had herpes simplex virus (HSV-1) DNA, explaining the elevated risk for AD. HSV-1 can multiply in the brain, which can activate the inflammatory response and increase A deposition. These effects can cause damage to neurons and the slow onset of AD. However, the findings of Miklossy and Balin's study have demonstrated the significance of persistent bacterial infections in AD.For instance, neurofibrillary tangle-like lesions were created by the syphilitic dementia brought on by spirochete bacteria (Treponema pallidum), which build up in the cerebral cortex and induce fatal neurodegenerative illnesses. Additionally, the Chlamydia pneumonia bacterium raises the chance of developing AD and can cause late-onset AD by activating astrocytes and cytotoxic microglia, interfering with calcium regulation, and causing apoptosis [85–87]

5.2.4. Medical Factors

Alzheimer's disease development is influenced by a number of risk factors. Older people with AD typically have medical conditions like cardiovascular disease (CVD), obesity, diabetes, and others, to add to the list. These ailments are all linked to an elevated risk of AD [88,89].

- Cardiovascular Disease (CVDs)

CVDs are acknowledged as a significant risk factor for AD. For example, a stroke is linked to a higher risk of dementia due to the loss of neural tissue, which accelerates the degenerative process and affects amyloid and tau pathology. Additionally, embolisms brought on by atrial fibrillation result in strokes and a decline in memory and cognitive abilities. In addition, heart failure impairs the heart's ability to pump blood, which reduces the amount of blood reaching the body and the brain, causing hypoxia and neurological damage.According to the coronary heart disease theory, AD risk is enhanced by atherosclerosis, peripheral artery disease, hypoperfusion, and emboli. Chronic cases of hypertension may result in cerebral edoema and thickening of the vessel walls, which reduce cerebral blood flow and narrow the lumen. These changes all contribute to the risk of AD and CVD. By concentrating on how the CVD affects AD, one can find a way to prevent and postpone the disease [89,90]. The CVD is a modifiable risk factor.

- Obesity and Diabetes

The body mass index can be used to calculate an individual's level of obesity, which is defined as having too much body fat due to ingesting more calories than they burn (BMI). Having more body fat is linked to having less blood flow to the brain, which encourages brain ischemia, memory loss, and vascular dementia. Obesity, a poor diet, and other factors can lead to diabetes, which is defined by hyperglycemia that damages peripheral tissues and blood vessels, or impaired glucose tolerance (IGT). As a result of growing amyloid-beta accumulation, oxidative stress, mitochondrial dysfunction, and neuroinflammation, chronic hyperglycemia can cause cognitive impairment. Increased pro-inflammatory cytokine release from adipose tissue, which in turn activates macrophages and lymphocytes and eventually causes both local and systemic inflammation, is a hallmark of obesity.. This inflammation encourages hyperinsulinemia, insulin resistance, and ultimately hyperglycemia. Obesity is a recognised risk factor for type 2 diabetes, CVDs, and cancer, all of which have been linked to dementia and AD. Microglia proliferate more due to brain inflammation, which also affects neurogenesis and reduces synaptic plasticity. Insulin receptor substrate 1 (IRS-1) can be impacted by microglia, and this can prevent intracellular insulin signalling, which is crucial for the health of the nervous system. Therefore, a change in insulin action may cause the buildup of A and decrease the AD-related tau protein breakdown [91–94].

6. Treatment

Around 24 million people are said to have Alzheimer's disease worldwide as of right now, and by 2050, experts predict that number will have quadrupled. Even though AD is a public health concern, only two kinds of medications are currently approved to treat AD: N-methyl-d-aspartate antagonists and cholinesterase enzyme inhibitors (naturally occurring, synthetic, and hybrid versions) (NMDA).Ca2+ influx results in overactivation of the NMDAR glutamate receptor, which is then brought back to normal. Even though these two classes have a therapeutic impact, they only work to treat AD's symptoms; they cannot reverse or stop the illness [98,99]. Only a few clinical trials on AD were unfortunately conducted in the past ten years, and they were a huge failure. To modify the pathogenesis of AD and provide effective

treatments, a number of mechanisms, including aberrant tau protein metabolism, -amyloid, inflammatory response, cholinergic and free radical damage, have been postulated [30,100].On the other hand, the majority of risk factors for AD that are changeable, including cardiovascular disease or lifestyle choices, can be avoided without the help of a doctor. The activation of brain vascularization, plasticity, neurogenesis, and inflammation reduction by reducing A production—all of which lead to an improvement in cognitive performance in older people—have been shown in studies to improve brain health and minimise AD. Additionally, the Mediterranean diet (MD), intellectual exercise, and higher education may all slow the deterioration of AD and memory loss and improve cognitive abilities. According to a number of studies, a multi-domain intervention involving lifestyle changes (diet, exercise, and cognitive training), the reduction of AD symptoms, and the management of cardiovascular risk factors can improve or maintain cognitive function and reduce the risk of developing AD in older people [101].

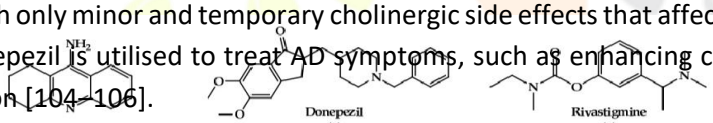
6.1. Symptomatic Treatment of AD

6.1.1. Cholinesterase Inhibitors

The cholinergic theory holds that AD results from a decrease in acetylcholine (ACh) production. One of the therapeutic approaches that improves cognitive and neural cell performance is increasing cholinergic levels by inhibiting acetylcholinesterase (AChE). Acetylcholine breakdown in synapses is prevented by AChEIs, leading to continuous ACh buildup and cholinergic receptor activation. Tacrine (tetrahydroaminoacridine) (1, Figure 4) was the first cholinesterase inhibitor drug for the treatment of AD that the FDA (Food and Drug Administration) had approved. It works by increasing ACh in muscarinic neurons, but it was taken off the market right away due to a high incidence of side effects like hepatotoxicity and a lack of benefits, which were seen in several trials.

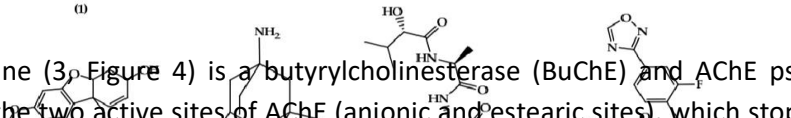
- Donepezil

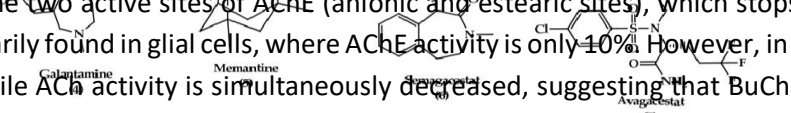
The most effective medication for treating AD is donepezil (2, Figure 4), an indanonebenzylpiperidine derivative and a member of the second generation of AChEIs. A larger concentration of ACh is present at the synapses as a result of donepezil's reversible binding to acetylcholinesterase and inhibition of acetylcholine hydrolysis. The medication is well-tolerated, with only minor and temporary cholinergic side effects that affect the neurological and gastrointestinal systems. Notably, donepezil is utilised to treat AD symptoms, such as enhancing cognition and behaviour, without affecting the AD progression [104–106].

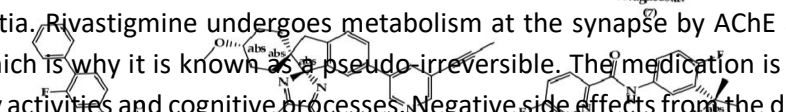


- Rivastigmine

Rivastigmine (3, Figure 4) is a butyrylcholinesterase (BuChE) and AChE pseudo-irreversible inhibitor. It works by attaching to the two active sites of AChE (anionic and estearic sites), which stops ACh metabolism. In the healthy brain, BuChE is primarily found in glial cells, where AChE activity is only 10%. However, in the AD brain, BuChE activity is increased to 40–90% while ACh activity is simultaneously decreased, suggesting that BuChE activity may be a sign of moderate to severe dementia. Rivastigmine undergoes metabolism at the synapse by AChE and BuChE and dissociates more slowly than AChE, which is why it is known as a pseudo-irreversible. The medication is used in cases of mild to moderate AD.It enhances daily activities and cognitive processes. Negative side effects from the drug's oral administration include nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss.







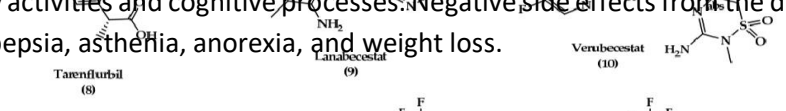


Figure 4. The chemical structures of approved drugs for symptomatic treatment of AD (tacrine1, donepezil 2, rivastigmine 3, galantamine 4, and memantine 5) and disease-modifying compounds thatentered clinical trials (semagacestat 6, avagacestat 7, tarenflurbil 8, lanabecestat 9, verubecestat 10,atabecestat 11, umibecestat 12, methylene blue 13, tideglusib 14, and saracatinibin 15).

- Galantamine (GAL)

The most effective medication for treating AD is AChEIs. A larger concentration of ACh is present at the synapses as a result of donepezil's reversible binding to acetylcholinesterase and inhibition of acetylcholine hydrolysis. The medication is well-tolerated, with only minor and temporary cholinergic side effects that affect the neurological and gastrointestinal systems. Notably, donepezil is utilised to treat AD symptoms, such as enhancing cognition and behaviour, without affecting the AD progression. [104–106] Figure 4 shows the chemical compositions of medications authorised to treat the symptoms of AD (tacrine1, donepezil 2, rivastigmine 3, galantamine 4, and memantine 5) as well as disease-modifying substances that have entered clinical studies (semagacestat 6, avagacestat 7, tarenflurbil 8, lanabecestat 9, verubecestat 10,atabecestat 11, umibecestat 12, methylene blue 13, tideglusib 14, and saracatinibin 15). Galaxtine (GAL) For mild to severe AD cases, galantamine (4, Figure 4) is regarded as the usual first-line treatment. AChE is competitively inhibited by the selective tertiary isoquinoline alkaloid GAL, which also has the ability to bind allosterically to the -subunit of nicotinic acetylcholine receptors and activate them. Similar to other AChE inhibitors, GAL has good efficacy and tolerability and can improve behavioural symptoms, everyday activities, and cognitive performance.

6.1.2. N-methyl d-aspartate (NMDA) Antagonists

It is thought that NMDAR plays a starring role in the pathophysiology of AD. Ca2+ influx brought on by NMDAR stimulation promotes signal transduction, which in turn causes gene transcription necessary for the development of a long-term potentiation (LTP), which is crucial for synaptic neurotransmission, plasticity, and memory formation. The principal excitatory amino acid in the CNS, glutamate, is overstimulated by excessive NMDAR activation, which results in excitotoxicity, synaptic malfunction, neuronal cell death, and a loss in cognitive abilities.Numerous NMDAR uncompetitive antagonists have been created and tested in clinical settings, however most of them were ineffective and had undesirable side effects. In addition, other NMDAR uncompetitive antagonist compounds are being developed, such as RL-208(3,4,8,9-tetramethyltetracyclo [4.4.0.03,9.04,8]dec-1-yl)methylamine hydrochloride), a polycyclic amine compound that may have a promising therapeutic effect in age-related cognitive issues and AD [115-117]. Memantine (5, Figure 4) is the only drug in this category that has been approved to treat moderate

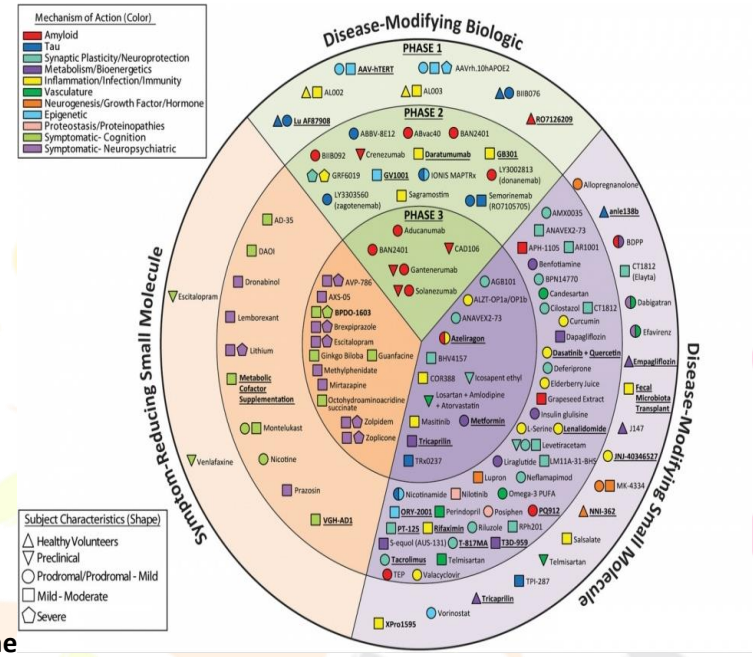
- Memantine

Memantine (5, Figure 4) is a low-affinity uncompetitive antagonist of the NMDAR, a subtype of glutamate receptor, which stops the glutaminergic system from being overexcited and causing neurotoxicity in AD cases. Memantine is used alone or in combination with AChEI to treat mild to severe AD. Due to memantine's low affinity, which is displaced quickly from NMDAR by high glutamate concentrations, the medication is safe and well-tolerated and blocks the excitatory receptor without interfering with normal synaptic communication, preventing a chronic blockage. The latter is linked to serious adverse effects, particularly those that affect memory and learning [99,118].

6.2. Promising Future Therapies

6.2.1. Disease-Modifying Therapeutics (DMT)

DMTs, or disease-modifying therapies, slow the course of AD by addressing a number of pathophysiological pathways. This contrasts with symptomatic therapy, which focuses on enhancing cognitive abilities and reducing signs of illness like depression or delusions without altering or affecting the condition. Orally administered DMTs, such as immunotherapies or small compounds, are being developed to halt the progression of AD or prevent it altogether. A number of DMTs have been created and are currently undergoing clinical trials, including AN-1792, a synthetic A-peptide (human A1-42 peptide of 42 amino acids with the immune adjuvant QS-21) and the first active immunotherapy for AD, which entered phase II clinical trials but was abandoned due to a side effect that caused meningoencephalitis in 6% of the patients.



Alzheimer's drug development pipeline

6.2.2. Chaperones

Hazardous protein aggregations originate from toxic protein misfolding brought on by mutations or environmental factors, and their buildup leads to neurodegenerative diseases like AD. Cells naturally create protein quality control (PQC) systems that prevent protein misfolding before it has a chance to cause harm. This equilibrium changes as we age, and the misfolded shapes overwhelm the PQC system. This, in turn, activates the unfolded protein response (UPR), which inhibits protein synthesis and boosts the production of chaperones. Human cells typically contain proteins that enable other proteins to function and reach their intended locations within the cell. "Chaperones" is the term for these proteins. Protein folding and increasing the effectiveness of the PQC system are both aided by chaperones. As a result, it is viewed as a prospective candidate for the treatment of neurodegenerative illnesses. It can be divided into three categories: **(1) pharmacological chaperones**, which are low molecular weight substances (enzymes, receptor-ligands, or selective binding molecules) that cause refolding of proteins, stabilise their structure, and restore their function; **(2) molecular chaperones**, which are proteins that aid other nonnative proteins in their folding or unfolding; and **(3) chemical chaperones,** also low molecular weight substances. These two groups' members lack a distinct mode of action and necessitate substantial concentrations to perform their curative effects [129].

- Heat Shock Proteins (Hsps)

Most neurodegenerative illnesses are brought on by protein misfolding and aggregation, which kill cells. Heat shock proteins (such as Hsp40, Hsp60, Hsp70, Hsp90, Hsp100, and Hsp110) are an example of internal molecular chaperones, while clustering and alpha-macroglobulin are examples of extracellular molecular chaperones. HSPs are crucial for the folding of proteins and shield cells from damaging stress-related events.

1. Hsp60

Hsp60 is crucial for the folding of proteins in mitochondria. Its function in AD is unclear; some think the protein protects, while others think it harms since activated microglia can overexpress it, increasing pro-inflammatory factors including toll-like receptor 4 (TLR-4), which stimulates neuronal cell death. Therefore, a promising approach to preventing neurodegenerative disorders is to reduce Hsp60 expression and activated microglia.

2. Hsp70

According to research, Hsp70 interacts to A 42 and inhibits self-aggregation. Mart n-Pea et al. investigated the cytosolic and extracellular forms of Hsp70 in Drosophila flies AD models and assessed their protective function against memory impairment brought on by A42 aggregation.The investigations on animals demonstrated that Hsp70 serves two distinct purposes: protecting against A-42 neurotoxicity and synaptic loss both intracellularly and extracellularly. It not only inhibits tau production by binding to tau and its hyperphosphorylated form, but also reduces aggregation and encourages tau attachment to microtubules. Hsp70 works by energising microglia, an enzyme that breaks down insulin, and tumour growth factor 1, which breaks down -amyloids and guards against memory loss. [132,133]

3. Hsp90

Another form of HSP called Hsp90 controls the phosphorylation and dephosphorylation of tau.Because tau kinases are reduced when Hsp90 is inhibited, there is a decrease in the phosphorylation of tau, which is assumed to be the cause of tau pathogenesis when it is overactivated. Hsp90 inhibitors are now used to treat cancer, but they are also thought to be a viable treatment for AD.

- Vacuolar sorting protein 35 (VPS35)

Cellular protein homeostasis is disturbed by protein buildup in neurons and glial cells. Proteins are transported by the endosomal-lysosomal pathway for recycling and breakdown. Numerous disorders, including Alzheimer's disease, can develop as a result of any systemic problem. Sorting nexin (SNX1, 2, 5, 6) and vacuolar sorting proteins (VPS26, 29, 35) make up the complex of regulator proteins known as retromer, which is in charge of moving trans-Golgi network receives endosome-bound cargo molecules . Downregulation of VPS35 due to retromer malfunction can enhance A formation, result in cognitive deficits, and cause synaptic disruption, all of which have been observed in AD patients [140,141].

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According to studies, protein misfolding and aggregation are linked to the buildup of gangliosides in neurodegenerative disorders. In AD brains, abnormal concentrations of mono-sialoganglioside (GM1, GM2, and GM3) have been seen. A peptide complexes with gangliosides (ganglioside-bound A (GA) peptide) are formed in mutant forms of A, such as the Dutch mutant APPE693Q, which exhibit pro-aggregation properties of GM2 and GM3. This accelerates the aggregation and accumulation of A peptides.

6.2.3. Natural Extract

Natural substances have long been employed as therapeutic agents for a number of degenerative conditions, and current research has revealed that they also have a neuroprotective impact. Natural substances have been shown to offer therapeutic potential for AD in both in vitro and in vivo tests, allowing some of them to move into the clinical trial stages. The first natural substance included in clinical trials for AD was nicotine. Subsequently, other substances, such as vitamins C, E, and D, attracted more interest due to their protective effects against neuroinflammation and oxidative damage.

7. Conclusions

The National Institute on Aging—Association Alzheimer's modified the 1984 NINCDS-ADRDA criteria for improved specificity, sensitivity, and early identification of patients at risk of developing AD because Alzheimer's disease is now regarded as a global health concern. For a more precise diagnosis of AD, a number of criteria have been put forth, including clinical biomarkers, body fluids, and imaging tests. Despite this, the prognosis for AD has not changed, and treatment is still symptomatic. Memory and alertness are enhanced by cholinesterase enzyme inhibitors like galantamine, donepezil, and rivastigmine and NMDA antagonists like memantine, but progression is unaffected. Numerous studies have demonstrated that altering lifestyle practises, such as diet and exercise, can enhance brain health and lessen AD without requiring medical attention. This is why it is recommended as a first-line intervention for all AD patients. Recently, research has shifted its attention to pathogenic aspects of AD like A and p-tau. Future treatments that target the A pathway may be able to slow the progression of AD. Several drugs, including AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil, have entered clinical trials but have not been successful in showing efficacy in the final stages of the trials. The efficacy of additional DMTs, including those that target the A- and tau-pathologies and include aducanumab, gantenerumab, crenezumab, tideglusib, lithium, and others, is still being studied.

In conclusion, early administration of AD medication and patient monitoring for disease development via biomarker diagnostics are essential for its success. The development of AD pathology might be slowed in the future by treatments that specifically target tau pathology and by using combination medicines. To treat AD sufferers as well as those who are at risk for getting the condition, it is urgently necessary to develop a potent, discerning, and efficient medicine.

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