

Overview of Alzheimer Disease and it's Treatment

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ABSTRACT

Dementia, which is branded by a decline in thoughtful 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 cholinergic and amyloid hypotheses were put up as two key causes of AD, which is thought to be a complex disease. Numerous mechanisms, including cholinergic dysfunction, amyloid/tau toxicity, and oxidative stress/mitochondrial dysfunction, are thought to contribute to the pathogenesis of Alzheimer's disease. The condition is influenced by a number of risk factors, including advancing age, hereditary variables, head injuries, vascular problems, infections, and environmental factors. Due to its multiple positive effects and lack of negative side effects, herbal medications have gained widespread attention. For the treatment of several neurological illnesses, Lavandula angustifolia, Ginkgo biloba, and Melissa officinalis, have all been used extensively.

Keywords:- *Alzheimer's disease, neurodegeneration, beta-amyloid peptide, risk factors, disease treatment, herbal drugs.*

INTRODUCTION

The most prevalent form of dementia, Alzheimer's disease (AD), is characterized by neuritic plaques And neurofibrillary tangles as a result of amyloid-beta peptide (A) buildup in the brain's most affected Region, the medial temporal lobe and neocortical structures . AD is named after the German Psychiatric Alois Alzheimer and is classified as a slowly progressing neurodegenerative disease.[1] When Alois Alzheimer examined the brain of his first patient, who experienced memory loss and a Change in personality before passing away, he found the presence of amyloid plaques and a significant Loss of neurons. He defined the illness as a terrible disease of the cerebral cortex. In his psychiatric Handbook's eighth edition, Emil Kraepelin for the first time referred to this illness as Alzheimer's Disease [2-3] Symptoms of the late-onset variety typically begin to

show in the majority of patients in their mid-60s. Rarely, early-onset Alzheimer's strikes between the ages of 30 and 60. For older persons, Alzheimer's Disease is the most prevalent cause of dementia. German neuropathologist Alois Alzheimer originally described the condition in 1906. It was Acknowledged as the most prevalent type of dementia in older people by the early 21st century. In 2016, It was anticipated that 47.5 million individuals globally had dementia; by 2030, that number was Projected to rise to 75.6 million.[3].Alzheimer's disease (AD) and other brain disorders, infections, abnormalities in the pulmonary and Circulatory systems that reduce the amount of oxygen delivered to the brain, nutritional deficiencies, Vitamin B12 deficiencies, tumors, and other conditions can all contribute to the progressive loss of Cognitive abilities ⁴.There 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. AD burden has an impact on people, their families, And the economy, with annual expenditures estimated to be \$1 trillion globally.⁵

TYPES AND CLASSIFICATION OF ALZHEIMER'S DISEASE

Classification Based on the Severity –

Based on the intensity of the typical Alzheimer's symptoms, it can be classified into the Following subtypes:

1.Mild Alzheimer's

This includes the early stages of cognitive impairment that make it difficult to remember daily Chores including at-work tasks, bill-paying, and other things. The patients at this stage manage To remain functional with a fair amount of effort because these symptoms are not extremely Serious. They take longer to do an activity that they used to complete more quickly, and this Behavior develops into a pattern.

2.Moderate Alzheimer's

The symptoms of mild Alzheimer's are more severe due to a large amount of neuronal damage. As their memory loss increases and their bewilderment worsens, they rely more and more on Others. Despite being physically fit, some people are incapable of doing simple tasks because Their delusions interfere with their ability to integrate sensory information.

3.Severe Alzheimer's

The brain cells begin to degenerate as the plaques and tangles expand. Brain tissue shrinks as A result of this. Patients with this illness are frequently immobile and have very limited Communication skills.

Classification Based on the Inflammatory Response –

Based on the inflammatory response, there are three subtypes of Alzheimer's disease.

1.Inflammatory

This subtype displays high serum albumin to globulin ratio and high levels of C-reactive Protein in response to inflammation in addition to the behavioral and cognitive symptoms.

2.Non-Inflammatory

Inflammatory biomarkers are not enhanced in this form of Alzheimer's. However, this Problem Syndrome is typically accompanied by other metabolic problems.

3.Cortical

An overall zinc deficit in the brain's various brain areas leads to a cortical subtype. Even though This subtype is not accompanied by an inflammatory reaction, it nonetheless results in defects In normal brain function that eventually produce Alzheimer's disease.

Classification Based on the Onset or Trigger Type –

1.Early-Onset Alzheimer's

Early-onset Alzheimer's is the name of the subtype of the illness that affects those younger Than 65. Only 5 out of 100 Alzheimer's sufferers have this problem. The patients typically Experience the alterations in their late 40s or early 50s. It is thought that specific Characteristics of this illness result from a Chromosome 14 abnormality.

2.Late-Onset Alzheimer's

The majority of Alzheimer's cases have a late onset and affect adults over 65. The precise Genetic cause has not yet been found. However, a number of risk factors have been Identified by researchers, and more work is being done.

Familial Alzheimer's disease (FAD) is another subtype of the illness. One case out of 100 is Highly uncommon for this illness. Only when the precise genotypic pattern of the illness is Characterized by the family members and exact risk can be anticipated can a person be Diagnosed with FAD.Cognitive, bodily, and social capacities can all be negatively impacted by Alzheimer's disease. To stop or halt the

disease's progression, early recognition of the condition is essential.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Hippocampus, amygdala, entorhinal cortex, cortical association areas of the frontal, Temporal, and parietal cortices, as well as subcortical nuclei like the serotonergic dorsal Raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus, may all exhibit Neuronal loss or pathology. Much more so than the quantity of amyloid plaques, the size and Location of tangle development correlates closely with the severity of dementia.⁶

In the neuropathology of Alzheimer's disease, there is a loss of Neurons and atrophy in the temporofrontal cortex, which results in inflammation and the Deposition of amyloid plaques, an abnormal cluster of protein fragments, and tangled Bundles of fibers.

1. Hyperphosphorylated tau protein and amyloid β hypothesis:

The development of senile plaques (SP), which are brought on by the buildup of amyloid Beta (A), is one of the primary pathogenic characteristics of AD. The precursor protein of Amyloid (APP) is broken into soluble tiny peptides called A by the action of the enzymes Alpha-secretase, beta-secretase, and gamma-secretase. Depending on the degree of Oligomerization, the imbalance between - amyloid (A) synthesis and clearance results in Protofibrils, fibrils, and plaques, three different forms of hazardous oligomers. Although the Exact cause of A's production is yet unknown, its sequence, concentration, and Circumstances of stability all play significant roles.⁹ Numerous variables, including cholinergic Dysfunction, amyloid/tau toxicity, and oxidative stress/mitochondrial dysfunctions, are Implicated in the etiology of Alzheimer's disease⁷.

A. Oxidative stress hypothesis:

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in a variety Of healthy and unhealthy human processes. They play a dual role because both have Advantageous effects on cellular signaling pathways and toxic processes that can harm Cellular structures (such as DNA, lipid, and protein membranes). The brain is especially Susceptible to oxidative stress due to its high oxygen consumption, which uses 20% more Oxygen than other mitochondrial respiratory tissues.

Less glutathione in Neurons is one of the reasons of oxidative stress, as it can combine with ROS to induce the Lipid peroxidation reaction and molecular apoptosis.⁸

B. Metal ion hypothesis:

Metal dyshomeostasis has a role in the development and pathophysiology of illnesses, Including as cancer and neurodegenerative disorders. A number of these compounds are employed in clinical studies. Ionosphere and metal chelators are well known modulators of Transition metal homeostasis. Other medications besides metal-binding ones can also target the homeostasis of transition .

In AD, their Brain levels are observed to be elevated. Other neurological diseases also involve copper, manganese, aluminum, and zinc.⁹

C. Cholinergic hypothesis:

Acetyl-cholinesterase inhibitors (AChEIs) and the impact of apo-lipo-protein E (APOE) Genotype in Alzheimer's disease patients. The AChEI drugs are the cornerstone of AD Treatment, and the most significant risk factor for AD is the APOE genotype. The "Cholinergic Hypothesis" of AD, which dates from 1976, is used to analyze the lack of significant effects of APOE by recognizing that cholinergic neurons are not the primary target of AD

and might Offer a possible molecular target for treatment.¹⁰

For more than 20 years, donepezil and other drugs that tend to normalize acetylcholine transmitter level have been the cornerstone of symptomatic therapy for AD.

Neuropsychiatric symptoms are linked to decreased cholinergic receptor binding in particular brain regions in mild to moderate AD. Lower receptor restricting may Bring about decreased handling speed in more established, solid people.

ALZHEIMER'S DISEASE NEUROPATHOLOGY

Positive sores (because of collection), which are described by the aggregation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil strings, and other deposits found in the brains of AD patients, are one of two types of neuropathological changes in AD that provide evidence about the disease's progression and symptoms.

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). Biosynthesis of A deposits from transmembrane amyloid precursor protein (APP) is carried out by proteolytic cleavage enzymes such – beta-secretase and gamma-secretase [11-13]. 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. Since A is Crucial for neurotoxicity and neural function, the buildup of denser plaques in the cerebral cortex, amygdala, and hippocampus may stimulate astrocytes and microglia, damage axons and dendrites, and eliminate synapses in addition to impairing cognitive function [14-16].

NFTs, or neurofibrillary tangles

The abnormal 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 associated 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 characterized by tau protein filament aggregation and the displacement of the nucleus toor the ghost NFTs stage, which develops as a result of neuronal death brought on by high levels of filamentous tau protein that exhibit Partial proteolysis resistance [17-18]

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 [PH] [19]. Visinin-like protein-1 (VILIP-1) and synaptotagmin-1 are examples of synaptic proteins that act as biomarkers for the identification of synapses loss and severity[20]. Neurogranin is a postsynaptic neuronal protein.

THE STAGES OF ALZHEIMER' DISEASE

1.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 characterized by modest memory loss and early degenerative alterations in the cortex and hippocampus [21]

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

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

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 recognize 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 [22-24]

CAUSES AND RISK FACTOR OF ALZHEIMER'S DISEASE

An increasing age, hereditary variables, head injuries, vascular illnesses, infections, and environmental factors (heavy metals, trace metals, and others) have all been identified as risk factors for AD. It is currently unclear what causes the pathological alterations in Alzheimer's disease (A, NFTs, and synaptic loss). The main causes of AD are thought to be two of the many hypotheses that have been put forth: some contend that cholinergic

dysfunction is a significant risk factor for AD, while others contend that changes in the production and processing of amyloid - protein are the primary initiating factors. Alzheimer's Disease Hypotheses

A.Cholinergic Hypothesis :

The enzyme choline acetyltransferase (ChAT), which is in charge of acetylcholine (Ach) Synthesis, has been linked to neocortical and presynaptic cholinergic deficiencies. 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 . Ach plays a key role in the brain's physiological processes Related to memory, attention, sensory perception, learning, and other crucial processes.

b. Amyloid Hypothesis:

The amyloid hypothesis was developed after it was realized for many years that aberrant –Sheet deposition in the central nervous system strongly correlated with dementia. However, it was discovered that with aging, amyloid plaques (AP) also accumulate in healthy, normal brains, raising the question of whether or not AP deposition is the cause of AD development. Alternative hypotheses for the non-inherited type of AD (NIAD) have therefore been put out in recent years, but the amyloid hypothesis continues to be the most widely recognized pathogenic mechanism for hereditary AD (IAD).

ALZHEIMER'S DISEASE RISK FACTOR

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 -

44. The process of aging 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 can be challenging to tell the cases from early AD apart because these changes also happen with normal aging [25-26]

GENETICS OF ALZHEIMER DISEASE

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 [27-28]. Genetic factors were responsible for 70% of the cases of AD.

a. Amyloid Precursor Protein (APP)

The APP gene on chromosome 21 codes for a type I transmembrane protein that is cleaved by the enzymes alpha, beta, and gamma-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 safeguarding mutation, A673T, exists at the moment against AD by decreasing A β , A β 40, and A β 42 secretion [29-30].

b. 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 [31-32]

PSEN1 is a key protein that plays a crucial part in the synthesis of A from APP by activating the γ -secretase complex. PSEN1 plays a crucial role in preserving memory and neurons.

c Apolipoprotein E (ApoE)

ApoE protein is a glycoprotein that is abundantly expressed in the liver, brain, and certain microglia. It functions as a receptor-mediated endocytosis ligand for cholesterol-containing lipoprotein particles, which are necessary for the synthesis 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.

d. Other Genes

The vitamin D receptor (VDR) gene polymorphism, which changes the binding of vitamin D to its receptor and may cause neurodegenerative disorders and neuronal damage, is another gene polymorphism linked to an increased risk of AD³³. Additionally, epigenetic elements such as DNA methylation, histone modifications, and chromatin changes have been shown to have a role in AD[34-45]

ENVIRONMENTAL FACTORS

The chance of developing AD may be increased by environmental risk factors such as food, metals, infections, and air pollution, which may cause oxidative stress and inflammation.

a. 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 (NO_x), carbon monoxide (CO), particulate matter (PM), sulfur 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. There is a connection between oxidative stress, neuroinflammation, and neurodegeneration in people exposed to air pollution.

b. Diet

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. Due to 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. Numerous investigations have shown that a raised AGEs serum level is linked to cognitive deterioration and the development of AD. An additional risk factor for AD is malnutrition. In addition to the fact that AD patients experience issues with eating

and swallowing, which may raise the risk of malnutrition, deficiencies in minerals including folate, vitamin B12, and vitamin D may result in a decline in cognitive function [36].

c. 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 aluminum and lead), which have no biological function. Aluminum is bonded to citrate molecules and plasma transferrin in the body, which can facilitate the transfer of aluminum 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 [37].

MEDICAL FACTORS

Alzheimer's disease development is influenced by a number of risk factors. Older adults with AD typically have medical issues like cardiovascular disease (CVD), obesity, diabetes, and others, which is another addition to this list. These ailments are all linked to an elevated risk of AD [38,39].

A. Cardiovascular Disease

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 cerebral tissue, which accelerates the degenerative process and affects amyloid and tau pathology. 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

peripheral artery disease, atherosclerosis, hypoperfusion, and emboli. Chronic cases of hypertension may result in cerebral edema and thickening of the artery walls, which restrict cerebral blood flow and narrow the lumen. These changes all contribute to the risk of AD and CVD. A strategy to preventing and delaying the disease can be found by focusing on the CVD, which is a modifiable risk factor [40,41].

B. Obesity and Diabetes

Body mass index (BMI) 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. An increase in body fat is linked to a decline in the 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. 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. Therefore, a change in insulin action may cause A to accumulate while reducing the AD-related tau protein breakdown [42-45].

DIAGNOSIS

The diagnosis of Alzheimer's disease is made by exclusion because there are no other reliable diagnostic procedures than post-mortem. However, given that AD is the most common form of dementia, the exclusionary diagnostic criteria should be flexible. Early diagnosis is crucial since at this point, reversible disorders or co-

morbidities can be successfully treated with medication, delaying the need for hospitalization as long as possible [46]. A clear description of the overlap between aging and mild dementia is currently a top issue. Mild Cognitive Impairment (MCI) is the term used to describe this condition. The MCI is an objective abnormal memory loss for a subject's age and educational background. MCI requirements include:

- Memory problems that are confirmed by a family member.
- Normality of other cognitive functions, and
- Routine daily activities.
- Age-inappropriate abnormal memory.
- Lack of dementia

In the neuropsychological tests, there are episodic memory deficiencies, which become better with facilitation. Adults with MCI are more likely to progress to dementia (12% annually) than healthy adults, who experience dementia at a rate of 1-2% annually. According to these statistics, the majority of MCI patients will experience dementia 3 to 4 years after diagnosis [47].

Several assessments, including the Cohen-Mansfield Agitation Inventory, Neuropsychiatric Inventory, Brief Psychological Rating Scale, Behaviour Rating Scale for Dementia, ADAS, and non-cognitive subscale, assess psychiatric symptoms.

Brain computed axial tomography (CAT) provides information on brain malignancies, hydrocephalus, vascular damage, ventricular enlargement, and cortical and subcortical atrophy. If the patient's personality permits it, nuclear magnetic resonance is a convenient test to request since it allows us to see damage to the white matter, particularly in vascular dementia and one of the subtypes of AD. Leucoaraiosis, or the hyperintensity of white substances, can be a malignant condition or a natural part of

aging. Compared to CAT, the cortical-subcortical damage can be better understood. We can identify changes in the neural metabolism using functional investigations like Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET).

The following proteins can be dosed in CSF, plasma, and/or urine: Apolipoprotein E-4, the amyloid precursor protein (APP), the beta-amyloid protein, the alfa-1 antitrypsin, the Tau protein hyperphosphorylated, the neural thread protein (AD7C-NPT), and melanotransferrin (protein P 97).

Differential diagnoses are made between the aging process as a whole, various forms of dementia (including vascular, mixed, Lewy, frontal, hydrocephalic, normotensive, alcoholic, infected, toxic, metabolic, and neurological diseases), the amnesic syndrome, delirium, and depression.

TREATMENT

Symptomatic Treatment of AD

- **Cholinesterase Inhibitors**

The decline in acetylcholine (ACh) biosynthesis, according to the cholinergic hypothesis, is what causes AD. One of the therapy methods that improves neuronal cell and cognitive function is thought to be increasing cholinergic levels by suppressing acetylcholinesterase (AChE). Acetylcholine breakdown in synapses is prevented by AChEIs, leading to continuous ACh buildup and cholinergic receptor activation.

Tacrine (tetrahydroaminoacridine) 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. Later, a number of AChEIs were

developed, including donepezil, rivastigmine, and galantamine, and are now utilized to treat the symptoms of AD [48-51].

Increasing choline reuptake and, as a result, the production of acetylcholine at presynaptic terminals, may be another method for treating AD. This can be done by concentrating on the choline transporter (CHT1), which provides choline for the creation of ACh. Future AD treatments may involve creating medications that can raise CHT1 at the plasma membrane [52].

A. Donepezil

The most effective medication for treating AD is donepezil, an indanonebenzylpiperidine derivative and a member of the second generation of AChEIs. A larger concentration of acetylcholine (ACh) is present at 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. It should be highlighted that donepezil treats AD symptoms including bettering cognition and behavior without affecting how AD progresses [53,54].

B. Rivastigmine

Rivastigmine is a butyrylcholinesterase (BuChE) and AChE pseudo-irreversible inhibitor. It works by attaching to the two active sites of AChE (anionic and esteric sites), which stops ACh metabolism. In the healthy brain, BuChE is mostly located in glial cells, where AChE activity is only 10%. However, in the AD brain, BuChE activity is elevated to 40–90% while ACh activity is simultaneously decreased, suggesting that BuChE activity may be a sign of mild to severe dementia.

The medication is used in cases of mild to moderate AD. It enhances daily activity

and cognitive processes. Negative side effects from the drug's oral administration include nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss.

These side effects are frequently the primary cause of quitting the medication, however they can subside over time, making the medication more tolerable. Transdermal patches can be used to administer rivastigmine for controlled and continuous skin absorption, improving tolerability and caregiver satisfaction. The majority of AD patients have difficulties swallowing and remembering things, which makes it difficult for them to take their oral medications on schedule. Transdermal patches are so the most suitable delivery route for the medication in AD patients [56-59]

C. Galantamine (GAL)

For mild to severe AD cases, galantamine 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 α -subunit of nicotinic acetylcholine receptors and activate them. Similar to other AChE inhibitors, GAL has good efficacy and tolerability and can reduce behavioral symptoms and improve daily activities, cognitive performance, and mood.

D. Memantine

Memantine is a low-affinity uncompetitive antagonist of the NMDAR, a subtype of glutamate receptor that stops the glutaminergic system from over-activating 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.

HERBAL MEDICINES TREATMENT OF AD

Since ancient times, herbal remedies and complementary medicines have been utilized to treat neurological diseases.

***Lavandula angustifolia* Mill**

The Lamiaceae family comprises the native aromatic plant known as lavender, *Lavandula angustifolia*, which produces throughout the Mediterranean region. Traditional treatments have used this plant's essential oil, aqueous extract, alcoholic extract, hydroalcoholic extract, and phenolic extract, among other extract types. While linalool and linalyl acetate are the two primary components of lavender essential oil, caffeic acid and luteolin are the two main components of the aqueous extract of lavender [60].

Researchers have focused on lavender as a candidate drug for the treatment of AD due to a number of characteristics of herbal medicines, including anti-inflammatory and anti-oxidant activities, inhibition of glutamate-induced neurotoxicity, prevention of A β polymerization, anti-oxidant properties, and an AChE inhibitory effect [61].

Ginkgo biloba

The giant ginkgo tree, often known as a ginkgo, has an angular crown and long, erratic branches. This well-known traditional Chinese medicine herb works in a variety of ways. It has been employed in folk medicine for countless years to treat a variety of illnesses. It has been demonstrated that *G. biloba* can improve learning and memory in AD by restoring normal ACh receptor function in the hippocampus and stimulating neurotransmitter activity [62]. *G. biloba*'s potent AChE inhibitory action was demonstrated by a study. The *G. biloba*

extract inhibits various A-induced processes, such as ROS formation and accumulation, mitochondrial dysfunction, and apoptosis, and protects brain cells from toxicity caused by A plaques. Additionally, free cholesterol circulation is inhibited by herbal medicine, and A production is interfered with [63].

Melissa Officinalis

Lemon balm, *Melissa officinalis*, is a member of the Lamiaceae family. During the summer, this plant produces tiny white flowers, and its leaves have a light lemon aroma. This herbal remedy is indicated to improve conduct and motivation in dementia sufferers. This plant is said to have anti-oxidant, anti-depressant, anxiolytic, and anti-inflammatory properties. Triterpenes, phenolic acids, and flavonoids are the key active ingredients in this herbal medication, and these are what give it its therapeutic properties [64].

CONCLUSION

The National Institute on Aging—Alzheimer's Association reclassified and revised the 1984 NINCDS-ADRDA criteria for improved specificity, sensitivity, and early identification of patients at risk of developing AD because the disease is now recognized as a global health concern. A number of criteria, including imaging scans, body fluids, and clinical biomarkers, have been put forth for a more precise diagnosis of AD. That being said, the prognosis for AD remains same, and treatment just addresses symptoms. While NMDA antagonists like memantine and cholinesterase enzyme inhibitors like galantamine, donepezil, and rivastigmine increase alertness and memory, they do not stop the disease's progression. A first-line strategy for all AD patients, lifestyle modifications including as diet and exercise have been shown in numerous studies to improve brain function and diminish AD without the

need for medicinal intervention. Lately, research has been concentrating on addressing the pathogenic characteristics of AD, namely A β and p-tau. Future treatments that target the A β pathway, such as disease-modifying medications, have the potential to slow down the progression of AD.

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