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Unravelling Alzheimer's Disease: Exploring the complexity of a neurological disorder

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ABSTRACT:

Alzheimer's disease (AD) is a neurodegenerative disorder and main cause for dementia and characterized mainly by memory deficits. Causes and risk factors of AD includes increasing age, head injuries, genetic factors, environmental factors, vascular diseases, infections, etc. There is no proper cure for Alzheimer's disease, only symptomatic treatments are available Cholinesterase enzyme Inhibitors and N-methyl d-aspartate (NMDA) antagonists are two classes of approved drugs to treat AD. Medicinal plants are traditionally used in the treatment of Alzheimer's disease. This paper focuses on the types of Alzheimer, diagnosis, neuropathology, stages, causes, risk factors and treatment of Alzheimer's disease. There is a special focus on various classes of treatments, future theories for the development of new therapies for AD like disease-modifying therapeutics (DMT) and natural extracts.

Keywords: Alzheimer's disease, neurodegenerative disorder, natural extracts, Cholinesterase enzyme Inhibitors and N-methyl d-aspartate (NMDA) antagonists.

INTRODUCTION:

As per WHO Dementia is defined as a syndrome usually of chronic or progressive in nature which results to deterioration in cognitive function. It majorly affects memory, thinking, calculation, orientation, learning capacity, comprehension, language, and judgment. It does not affect consciousness. The cognitive function impairment is commonly accompanied, and occasionally preceded, with changes in mood, behavior, emotional control or motivation.[1]

Alzheimer's disease is defined as a progressive neurologic disorder which causes the brain to shrink and brain cells to die. Most common cause for Dementia is Alzheimer's disease. It is characterized by continuous decline in thinking, social skill and behavior which affects a person's ability to function independently.

Alzheimer's disease is named after Doctor Alois Alzheimer who in 1906 noticed changes in the woman's brain tissue suffering from unusual mental illness. Her symptoms were memory loss, unpredictable behaviour and language problems. He examined her brain after her death and found several abnormal clumps (now known as amyloid plaques) and several tangled bundles of fibers (now known as neurofibrillary, or tau, tangles).

These amyloid plaques and neurofibrillary tangles of the brain are still considered to be the few main features of Alzheimer's disease. Other feature includes loss of connections between nerve cells (neurons) which affect neurons in transmitting messages within the different parts of the brain, and also from the brain to organs and muscles.[2]

Alzheimer's disease accounts about 60-80% of total dementia cases.

As per the estimation of AAIC (Alzheimer's Association International Conference) 2021 held in Denver, every year 100 in every 1 million individuals get dementia with early onset (below the age of 65). This leads to globally 350,000 new cases of early onset dementia every year.

During the time period 1999 to 2019, U.S. mortality rate due to Alzheimer's in the overall population has significantly increased from 160 to 300 deaths per million population, which means there is 88% increase in mortality rate due to Alzheimer's.

In US, rural areas of East South-Central region had the highest mortality rate due to Alzheimer's, which was 2740 per million in the age group more than 65.

As per the findings of Nichols and team dementia is expected to increase from 57.4 (50.4 to 65.1) million cases across the globe in 2019 to 152.8 (130.8 to 175.6) million cases by 2050. The highest increases are expected in North Africa, Eastern sub-Saharan Africa, North Africa and the Middle East. The analysis also suggested that population growth and aging will be the major factors behind the increase in cases, although increase in cases could largely be attributed to population growth and aging and the relative importance of these two factors is varied by world regions.

They estimated an increase of 6.8 million dementia cases between 2019 and 2050 across the globe due to the changes in these risk factors. Few researchers have also concluded that expected changes in literacy level will lead to a decline in dementia cases by 6.2 million individuals globally between 2019 and 2050. These two opposing trends almost balance each other.

In India overall prevalence rate of 0.84% (95% CI, 0.61 to 1.13) for all dementias with a CDR score of at least 0.5 in the population aged 55 years and older, and for the population aged more than 65 years, the prevalence rate is of 1.36% (95% CI, 0.96 to 1.88). The overall prevalence rate for AD was 0.62% (95% CI, 0.43 to 0.88) in the population aged 55+ and 1.07% (95% CI, 0.72 to 1.53) in the population aged more than 65.[3]

ALZHEIMER'S DISEASE

It is a progressive disease which destroys memory and various other important mental functions. In Alzheimer's disease the Brain cell connections along with the cells themselves get degenerated and die, this eventually destroys memory and other important mental functions.

Alzheimer's disease is characterized mainly by neuritic plaques and neurofibrillary tangles due to accumulation of amyloid-beta peptide's (Aβ) along most affected areas of the brain, the medial temporal lobe and in neocortical structures.

TYPES OF ALZHEIMER'S DISEASE:

There are two types of Alzheimer

- Early onset Alzheimer
- Late onset Alzheimer

Early onset Alzheimer:

In this type of Alzheimer signs appear in a person between the age of 30 and 60. It is usually caused by gene changes which is passed on genetically from parents to child. They are very rare type of Alzheimer and patient with Down syndrome has greater risk.

Late onset Alzheimer:
In this type of Alzheimer signs appear in persons mid-60s. It is usually involving a gene like APOE ε4. They are the most prevailing type of Alzheimer's.

Causes and risk factors of AD

AD is basically considered to be a multifactorial disease as it is associated with several risk factors like

- Increasing age
- Vascular diseases
- Genetic factor
- Head injuries,
- Infections, and
- Environmental factors (like trace metals, heavy metals, and others).

- Aβ precursor protein
- Presenilins
- Down syndrome
- Inflammation
- Cerebral, cardiovascular disease and diabetes

The development of AD is influenced by both hereditary and environmental risk factors. Age is the main risk element. At age 65, the likelihood of getting AD is around 3%, but by age 85, it has increased to almost 30%. Although the prevalence of AD among people under the age of 65 is less known, estimations indicate that this age group represents about 3% of all AD cases. Age-specific incidence appears to be declining in a number of nations even while overall numbers are rising due to the ageing population.

In contrast to sporadic AD, familial AD exhibits Mendelian (often dominant) inheritance. As a result of mutations in the genes APP, PSEN1 or PSEN2, almost all instances of EOAD are familial, whereas the vast majority of cases of LOAD are sporadic. More than 20 risk loci have since been identified by genome wide association studies (GWAS) and sequencing, however many sporadic instances lack a clear genetic aetiology.[4-9]

Aβ precursor protein[10-15]

The first gene identified as having autosomal dominant mutations causing AD is the A precursor protein (APP). The discovery of A by John Hardy and colleagues in 1991 as the precursor of the aggregated peptide in amyloid plaques gave rise to the "amyloid hypothesis," which holds that the hazardous build-up of A triggers a chain of events that results in neuronal death and illness. Over 50 APP mutations are already recognised, and they account for 10% of family cases. The majority of these mutations cluster around the cleavage sites for and -secretase. Well-studied ones include the London (V717I), Swedish (KM670/671NL), Indiana (V717F), and Artic (E693G) variants. According to research, several of these mutations boost A production or the A 42:40 ratio, which causes more amyloid to accumulate.

Presenilins[16-21]

The catalytic subunits of -secretase, an enzyme complex involved in the processing of APP, are encoded by the presenilins PSEN1 and PSEN2, respectively. PSEN1 variations, the most well-known Mendelian genetic aetiology of autosomal dominant AD and thought to be responsible for between 30 and 50 percent of family EOAD cases, are

caused by presenilin mutations. Research indicates that PSEN1 and PSEN2 mutations increase A production similarly to APP mutations, but oddly likely to confer loss of function, raising questions about how this fits the amyloid theory.

Other genetic risk factors[22-26]

TREM2, CLU, SORL1, APOE, BIN1, and PICALM are other genes with recognised mutations linked to an increased risk of Alzheimer's disease. The most prevalent genetic risk factor for AD is the E4 allele of the fat-metabolizing protein APOE, which has an allele frequency of around 13.7%. The risk is tripled when this allele is heterozygous. TREM2R47H (triggering receptor expressed on myeloid cells 2) has a similar impact size although being more uncommon. TREM2 is a receptor that is found on various immune cell types, and this relationship suggests that inflammation plays a part in the aetiology of AD.

Down syndrome[27-30]

Up to 80% of people with Down syndrome (DS) experience dementia by the age of 65. Even at a young age of 40, amyloid and tau pathology are already present, like in other cases of EOAD. The APP gene is placed on chromosome 21, which is trisomy, and having three copies of this gene is enough to raise A levels. The triplication of additional genes on chromosome 21 may also contribute to the higher chance of acquiring the disease.

Inflammation[31-34]

Cerebral hypoperfusion and inflammation are two of the most frequent environmental and genetic risk factors that contribute to sporadic AD. Cognitive impairment has been linked to both short-term and long-term inflammation brought on by trauma, sepsis, and infection. Dementia risk is linked to traumatic brain injury and even bone fractures in the elderly. Interleukin 6 (IL-6) and other inflammatory indicators are associated with increased risk of Alzheimer's disease and vascular dementia. In the brain, where plaques and tangles frequently form, AD patients frequently have elevated levels of certain inflammatory markers as well as active microglia and astrocytes. Additionally, a quicker deterioration in cognitive function is linked to higher levels of these markers.

Cerebral, cardiovascular disease and diabetes[35-40]

Vascular disease and dementia are closely related. AD risk is enhanced by both cerebrovascular disease like ischemia and cardiovascular disease such high blood pressure and heart attacks. Dementia risk factors include metabolic and lifestyle risk factors for vascular disease development, such as poor diet, obesity, high cholesterol, and sedentary lifestyle. Low-quality food and excessive cholesterol can affect oxygen levels and cause systemic and cerebral metabolic abnormalities. Additionally, the risk of dementia is almost doubled in people with type 2 diabetes.

Other environmental risk factors[41-43]

The list of environmental and metabolic risk factors presented here is not meant to be exhaustive, especially given that epidemiology in populations with various genetic make-up and lifestyles frequently results in the absence of clear evidence for key pathways. Exposure to heavy metals, stress, and pollution are other risk factors that have been linked. It can be challenging to identify how the existence of these risk factors impacts the brain because many of them share some traits with one another.

ALZHEIMER DISEASE DIAGNOSIS:

A patient with symptoms of AD must undergo several tests which includes

- neurological examination,
- MRI (Magnetic Resonance Imaging) for neurons,

- Laboratory examinations of vitamin B12 deficiency and
- Other tests besides the medical and family history of the patients.[44]

Deficiency of Vitamin (vit.) B12 also signifies to an extent the presence of neurologic problems and increasing risks of AD. Elevated homocysteine level is a special marker of vit. B12 deficiency which may lead to brain damage by increasing calcium influx, oxidative stress and apoptosis. [45,46]

In 1984, a clinical diagnostic criterion for Alzheimer's disease was set up by the work group NINCDS-ADRDA which was formed in coordination the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA).

Criteria given NINCDS-ADRDA includes:

1. **Probable Alzheimer's disease**: It can be diagnosed by dementia which is confirmed with progressive memory loss, neuropsychological tests, impaired daily-life activity, and with other symptoms like apraxia (a motor skills disorder), aphasia (impairment of a language), and agnosia (a loss of perception). These symptoms can start from the age of 40–90, with the absence of any other systemic or brain diseases,

2. **Possible Alzheimer's disease**: It can be applied when there is absence of neurologic and psychiatric disorders but there is the presence of another illness like systemic or brain disorder, which are not the primary cause of dementia, and

3. **Definite Alzheimer's disease:** It is confirmed using histopathological confirmation which can be obtained either from a biopsy or by autopsy [47,48]

Later on in 2011, the 1984 NINCDS-ADRDA criteria were updated by The National Institute on Aging—Alzheimer's Association.

Proposed new criteria included probable and possible AD dementia. It included biomarkers for diagnosis.

Alzheimer's disease biomarkers have two categories

a. Markers of brain amyloid detected using Positron Emission Tomography (PET) and in Cerebro Spinal Fluid (CSF), and

b. Markers of neuronal injury such as Cerebro Spinal Fluid tau, Fluoro Deoxy Glucose (FDG) to detect metabolic activity, and Atrophy measurement using Magnetic Resonance Imaging (MRI).[49,50]

NEUROPATHOLOGY OF ALZHEIMER'S DISEASE:

Neuropathological changes in AD that provides evidence about disease progress and symptoms are

- **Positive lesions** (caused due to accumulation), It is indicated with the accumulation of neurofibrillary tangles, dystrophic neuritis, amyloid plaques, neuropil threads, and other deposits found in the brains of AD patients.
- **Negative lesions** (caused due to losses) are indicated by large atrophy caused by neuropil, neural and synaptic loss. There are other factors which involves neurodegeneration such as neuroinflammation, oxidative stress, and injury of cholinergic neurons.[51,52]

Neuropathology of AD includes

a. **Senile Plaques (SP):** These are mainly the extracellular deposits containing beta-amyloid protein (Aβ) in different morphological forms like dense-cored, neuritic, diffuse or compact and classic type. Biosynthesis

of Aβ deposits are due to proteolytic cleavage enzymes like β-secretase and γ-secretase from transmembrane amyloid precursor protein (APP) [19–21]. Proteolytic cleavage enzymes cleave APP into several amino acid fragments like 43, 45, 46, 48, 49, and 51 amino acids. It finally forms into Aβ40 and Aβ42. There are several other types of Aβ monomers among which some includes large and insoluble amyloid fibrils. These fibrils accumulate to form amyloid plaques and soluble oligomers which can easily spread throughout the brain. Aβ causes neurotoxicity and loss of neural function, thus accumulation of plaques in denser amount in the region of cerebral cortex, hippocampus and amygdala may lead to stimulation of microglia and astrocytes, can also damage to axons, dendrites, and progressive loss of synapses along with the cognitive impairments.[53,54]

b. **Neurofibrillary Tangles (NFTs)**: These are abnormal filaments made of hyperphosphorylated tau protein which gets twisted around each other forming a paired helical filament (PHF), accumulate at various sites like neural perikaryal cytoplasm, axons, and dendrites, resulting in loss of cytoskeletal microtubules and tubulin-associated proteins. These hyperphosphorylated tau protein are responsible for NFTs in the brains of AD patients,

Stages of NFT formation includes

1. **Pre-tangle phase**: The phosphorylated tau proteins get accumulated in the somato dendritic compartment.

2. **Mature NFTs stage:** In this stage filament aggregation of tau protein occurs with the displacement of nucleus to other part of soma, and

3. **The extracellular tangles, or the ghost NFTs stage**: Neuronal loss occurs in this stage due to large amounts of filamentous tau protein and has partial resistance to proteolysis [55,56].

c. **Synaptic Loss:** This is due to Synaptic damage at neocortex and limbic system resulting into memory impairment and commonly observed in the early stages of AD. Mechanism of Synaptic loss is due to defects in mitochondrial damage, axonal transport, oxidative stress, and to some extent accumulation of Aβ and tau protien at synaptic sites are also responsible. Synaptic loss leads to loss of pre-synaptic terminals, dendritic spines, and axonal dystrophy. Synapses loss, and its severity is detected using synaptic proteins which serve as biomarkers.[57]

d. Mitochondrial dysfunction and oxidative stress[58-62]

Mitochondrial function is one of the many mechanisms that AD compromises. In AD, it has been noted that there are changes in mitochondrial morphology, number, and transport, as well as decreased cytochrome oxidase activity, deficiencies in metabolic proteins, altered mitochondrial membrane potential, and an increase in oxidative stress. Because of their high metabolic needs, neurons are heavily dependent on mitochondria, which build up at synapses. Oxidative stress can result from a combination of low antioxidant levels and the high levels of ROS generation that occur at synapses. Additionally, the brain contains significant concentrations of cholesterols, which are extremely susceptible to oxidative damage. As a result, the brain is prone to oxidative damage due to its high energy requirements and high lipid concentration. The mitochondrial cascade hypothesis contends that genetic and environmental variables affect the rate of mitochondrial decline, which in turn dictates the rate of ageing and subsequently AD, rather than ageing driving amyloid pathology as in the case of the amyloid hypothesis. In terms of EOAD, APP or Aβ causes mitochondrial deficiencies, which accelerates ageing and predisposes some individuals to AD. This has been proposed as a potential EOAD and LOAD pathogenesis connection. Thy-1-APP mice exhibit decreased ATP synthesis and mitochondrial membrane potential as well as increased ROS generation, which is consistent with this theory. Similar to human transgenic APP mice, transgenic APP mice have a rise in A in synaptic mitochondria, which causes malfunction and oxidative stress prior to plaque deposition.

e. Insulin[63-65]

The AD brain exhibits insulin resistance and a reduction in insulin receptors. Insulin resistance in the brain also results from advanced diabetes. Since cells significantly rely on the metabolism of glucose to produce energy, this can result

in energy shortages that could cause oxidative stress. Additionally, it has been established that insulin participates in neurotransmission and has neuroprotective properties in the presence of insults like ischemia. Additionally, it has been noted that both wild-type and Tg2576 mice (an APP transgenic model) have elevated levels of -secretase in response to insulin and metabolic inhibitors. This also led to an increase in A levels in Tg2576 mouse models. However, as other sources claim that insulin has a protective role, it is likely that there is a specific.

f. Hypoglycemia and vascular dysfunction[66-69]

The association between diabetes and AD may also be brought on by changes in metabolic proteins, changes in glucose receptors and transporters, or even hypoglycemia brought on by overmedication. In both the healthy ageing brain and the AD brain, glucose metabolism declines. Additionally, it has been noted that the expression of the glucose transporter at the blood-brain barrier (BBB) is declining in old wild-type mice, AD patients, and animal models of the disease. In addition, both in vitro and in vivo studies have demonstrated that insulin-induced hypoglycemia kills neurons. In addition to increasing oxidative stress, hypoglycemia has also been associated to raising tau levels.

Although it is currently unknown whether it is hypoglycemia, hypoxia, a change in another blood component, or a combination of these that increases a person's risk of disease, hypoglycemia may also be the link between cardiovascular, cerebral-vascular, and dementia. Finally, AD patients and animal models have demonstrated aberrant angiogenesis and abnormalities of the vasculature, including changes in blood flow.

g. Inflammation[70-73]

A more recent area of focus in the realm of AD is inflammation. As was previously said, dementia is more common in people with inflammation, and patients with dementia who have greater levels of inflammatory markers tend to decline more quickly. Inflammation has been linked to both in vivo and in vitro cognitive impairment, neuronal injury, and synaptic loss in studies using animal models. Although inflammation and microglia activation are known to have a neuroprotective effect in short-term situations, over time they may cause neurotoxicity and an increase in Aβ burden. The activation of microglia by Aβ is considered to draw them to plaques and promote phagocytosis. Potentially, the microglial response to Aβ is protective, but after prolonged activation, the microglia start to behave negatively, creating a destructive feedback loop. In a similar vein, it has been demonstrated that immune cells can impact the formation of ROS and that elevated ROS levels can raise inflammatory markers, illustrating the intricate relationship between oxidative stress, inflammation, and Aβ.

h. Ubiquitin-proteasome system[74-75]

Overproduction and misfolded proteins are degraded by the ubiquitin-proteasome system (UPS). In synapse function, where there is a high turnover of proteins, it is particularly crucial. In an enzymatic process, proteins that need to be broken down are marked with polyubiquitin chains that the proteasome then recognises and breaks down. Plaques and tangles have been demonstrated to potentially hinder the proteasome's ability to function because both are monomeric proteins, which the proteasome is not thought to break down. This might result in a hazardous accumulation of extra and improperly folded proteins in the brain, specifically synapses.

i. Autophagy lysosome pathway[76-77]

Another theory for the pathophysiology of AD involves autophagy and lysosomal dysfunction. Tau is removed through autophagy, which also contributes to the production and removal of A. Trafficking through the endo-lysosomal route is a component of APP amyloidogenic processing. BIN1, SORL1, and PICALM are three AD-associated genes that are involved in endosomal recycling, and research suggests that each of these genes may directly influence the processing of APP endosomes.

j. Cholinergic hypothesis[78-79]

One of the earliest hypotheses on how AD manifests was the cholinergic theory. This resulted from abnormally high amounts of acetylcholine in AD brain tissue. The transcription and activity of the enzyme choline acetyltransferase (ChAT) is decreased in the surviving neurons. Cholinergic neurons of the basal forebrain are one of the first brain

regions to be damaged by AD. A link between acetylcholinesterase (AChE) and A accumulation has also been demonstrated by studies. Linking cholinergic with other AD diseases has been challenging as the AD science has advanced. In fact, the greatest number of pyramidal neurons—mostly glutamatergic neurons—are destroyed in areas with plaques and tangles.

THE STAGES OF ALZHEIMER'S DISEASE:

Clinical phase of AD can be classified into

1. **Pre-clinical or the pre-symptomatic stage:**

- Last for several years or more
- Early pathological changes in both cortex and hippocampus
- Mild memory loss
- No functional impairment in the daily activities
- Absence of clinical signs and symptoms of AD [80,81]

2. The mild/ Early stage of AD:

- Several symptoms start to appear
- Loss of concentration and memory
- Disorientation of place and time
- Change in the mood, with development of depression [82,83]

3. Moderate AD stage

- Disease spreads in the areas of cerebral cortex
- Increased memory loss and finds difficult to recognize family and friends
- There is Loss of impulse control
- Difficulty in reading, writing, and speaking.

4. Severe AD or late-stage

- Entire cortex area gets affected
- Neuritic plaques and neurofibrillary tangles are severely accumulated
- Functional and cognitive impairment is progressive
- Forgets their family, bedridden with vital difficulties like difficulty in swallowing and urination
- Leading to the patient's death due to these complications [84].

CAUSES AND RISK FACTORS OF ALZHEIMER'S DISEASE AD[85]

AD is a multifactorial disease and associated with several risk factors as shown in Figure 1

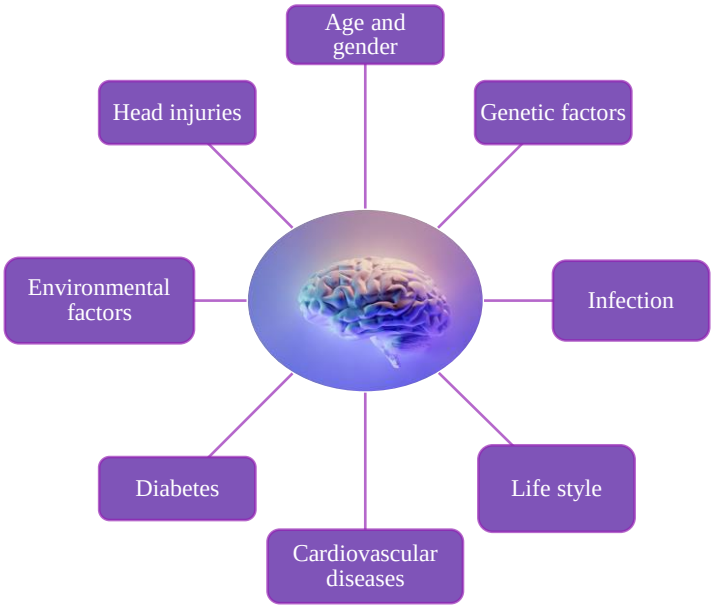

Figure 1: Alzheimer's Disease Risk Factors

Alzheimer 's disease Risk Factors

Aging: It is the most common and important risk factor in AD as younger individuals rarely prone to AD and generally starts after the age of 65 years.[86] Aging is an irreversible process which occurs at multiple organs and cell systems. This causes reduction in both brain volume and weight along with the loss of synapses, and ventricles' enlargement.

Based on age AD can be divided into

Early-onset AD (EOAD):

Rare and occurs in 1–6% of cases, occurs in the age range of 30–60. They can be genetic or may be due to infection or Head injury.

Late-onset AD (LOAD):

Common and occurs in the individuals above 65 years. Occurs mainly in the individual with positive family history of AD[87].

Genetics: 70% of total AD is due to Genetic factors. Most of the EOAD are inherited either in autosomal dominant pattern or by mutations in the dominant genes like Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2), and apolipoprotein E (ApoE) are associated with AD [88,89].

Environmental Factors: It includes, air pollution, metals, infection, diet, oxidative stress and inflammation. These factors increases the risk of developing AD.[90-91]

- Air Pollution The air pollution is basically characterized with modified nature of the atmosphere by introduction of chemical, physical, or biological pollutants. National Ambient Air Quality Standards (NAAQSs), USA has listed six pollutants as a threat to human health which includes ozone (O3), carbon monoxide (CO), nitrogen oxides (NOx), particulate matter (PM), lead and sulfur dioxide (SO2). Animal Studies has shown that exposure to those air pollution at high level causes damage tool factory mucosa and bulb, along with frontal cortex region, which is observed cases of AD.

- Diet: There are several dietary supplements which helps in decreasing AD like antioxidants, polyphenols, vitamins, and fish. Whereas food containing saturated fatty acids and high-calorie tends to increase the risk of AD.[92]Deficiency in nutrients like Vitamin B12, vitamin D and folate can decrease cognitive function in the patient with AD.

- **Metals**: Metals are naturally present in our biological systems which is divided into bio-metals and toxicological metals.

    - Biometals generally have a physiological function.eg. copper, zinc, and iron.

    - Toxicological metals do not possess any biological function e.g., aluminum and lead[31]. Aluminum is generally used in industries with processed foods, medical preparations, cosmetics, medicines, and others.

  Aluminum: Aluminum in the body bounds to plasma transferrin and to citrate molecules mediating the transfer of aluminum into the brain. As demonstrated in study aluminum gets accumulated in the cortex, cerebellum areas, and hippocampus, where Aluminum interacts with proteins and causes aggregation, misfolding, and phosphorylation in highly phosphorylated proteins such as tau protein, which is the characteristic of AD.[93]

  Lead: It competes with calcium in the binding site and crosses the blood–brain barrier (BBB) rapidly, causing severe damage. Acute exposure to lead leads to increase in β-secretase expression and Aβ accumulation resulting in AD.

  Cadmium: It is carcinogenic and water-soluble metal which cross the BBB and causes aggregation of Aβ plaques and self-aggregation of tau in AD brain.

  Cardiovascular Disease (CVDs): It is an important risk factor for AD. Conditions like stroke cause degenerative effect and influences amyloid and tau pathology.

  Hypertension: Thickening of blood vessel walls and narrowing in the lumen is the characteristic of hypertension. Hypertension results in reduced cerebral blood flow, cerebral edema which are the risk factors for AD and CVD.

  Obesity and Diabetes: Increase in body fat decreases brain blood supply resulting into brain ischemia, Chronic hyperglycemia increases amyloid-beta accumulation, oxidative stress, neuroinflammation and mitochondrial dysfunction which induces cognitive impairment.

TREATMENT:

Currently there are around 24 million cases of AD worldwide and it is estimated to increase 4 times by 2050. We have two classes of approved drug to treat AD, They are inhibitors to cholinesterase enzyme and antagonists to N-methyl d-aspartate (NMDA).

Symptomatic Treatment of AD

1. **Cholinesterase Inhibitors:[94-105]**

   As per the cholinergic hypothesis, Alzheimer is characterized by the reduction in the biosynthesis of acetylcholine (ACh). Symptoms of AD can be treated by increasing cholinergic levels via inhibiting acetylcholinesterase (AChE).

AChEIs(acetylcholinesterase inhibitors) inhibits acetylcholine degradation at synapses, Tacrine (tetrahydroaminoacridine) a cholinesterase inhibitor drug was the first drug approved by FDA (Food and Drug Administration)for the treatment of AD. It acts by increasing ACh in muscarinic neurons. It was immediately out of market as it had high incidence of side effects such as hepatotoxicity and dearth of benefits. After which several other AChEIs were introduced, like donepezil, rivastigmine and galantamine and are currently in use for the symptomatic treatment of AD.

Symptomatic Treatment of AD

Drug	Mechanism of action
Cholinesterase inhibitor	
Tacrine (tetrahydroaminoacridine)	Inhibits cholinesterase and increases Ach in Muscarinic neurons
Donepezil (indanonebenzylpiperidine derivative)	Binds to acetylcholinesterasereversibly, inhibiting Ach hydrolysis, thus increases concentration of ACh at the synapses.
Rivastigmine	Pseudo irreversible inhibitor of AChE and butyrylcholinesterase, prevents ACh metabolism.
Galantamine (tertiary isoquinoline alkaloid)	Fist line of drug, it has dual mechanism of action. They acts as a competitive inhibitor of AChEand alsobinds allosterically to the α-subunit of nicotinicacetylcholine
N-methyl d-aspartate (NMDA) Antagonists	
Memantine	Uncompetitive antagonist of NMDA

Table no 1: Symptomatic Treatment of AD

Promising Future Therapies[106-111]

Drugs in Phase 3 trial

Drug	Mechanism Of Action
Disease-Modifying Therapeutics (DMT)	
Aducanumab	Monoclonal antibody—targets β-amyloid and removes it.
Gantenerumab	Monoclonal antibody—binds and removes β-amyloid.
CAD106b	Amyloid vaccine—stimulates production of antibodiesagainst β-amyloid.
BAN2401	Monoclonal antibody—reduces protofibrillar β-amyloid.

AGB101	Low-dose levetiracetam—improves synaptic function and reducesamyloid-induced neuronal hyperactivity
TRx0237 (LMTX)	Tau protein aggregation inhibitor.
Azeliragon	RAGE (Receptor for Advanced Glycation End-products)antagonist—reduces inflammation and amyloid transport intothe brain
Masitinib	Tyrosine kinase inhibitor—modulates inflammatory mast cell andreduces amyloid protein and tau phosphorylation
ALZT-OP1 (cromolyn + ibuprofen)	Mast cell stabilizer and anti-inflammatory—promotes microglialclearance of amyloid

Table no 2: Mechanism of action of drug in phase 3 Clinical trial

Drugs in Phase 2 Clinical Trials

Drug	Mechanism of Action
Disease-Modifying Therapeutics (DMT)	
Crenezumab	Monoclonal antibody—targets β-amyloid and removes it.
BAN2401	Monoclonal antibody—removes amyoid protofibrils and reducesamyloid plaques
ABBV-8E12	Monoclonal antibody—prevents tau propagation
LY3002813 (donanemab)	Monoclonal antibody—removes amyloid by recognizing aggregatedpyroglutamate form of Aβ
BIIB092	Monoclonal antibody- acts by removing tau and reducing tau propagation
Lithium	Neurotransmitter receptors ion channel modulator—improvesneuropsychiatric symptoms
Riluzole	Glutamate receptor antagonist—reducesglutamate-mediated excitotoxicity

Table no 3: Mechanism of action of drug in phase 2 Clinical trial

Drug in Phase 1 Clinical trial

Drug	Mechanism of Action
Disease-Modifying Therapeutics (DMT)	
Lu AF87908	Monoclonal antibody—removes tau
anle138b	Aggregation inhibitor—reduces tau aggregation
RO7126209	Monoclonal antibody—removes amyloid

Table no 4: Mechanism of action of drug in phase 1 Clinical trial

Natural Extract[51,52]

There are many medicinal plants as per folklore claim to treat memory related disorders.

Natural extracts	Mechanism of action
Disease-Modifying Therapeutics (DMT)	
Schisantherin A, Ginsenoside Rh2, and Angelica sinensis extracts	Aβ formation inhibitors
Rhynchophylline (RIN), INM-176 (ethanolic extract ofAngelica gigas), HouttuyniacordataThunb.(Saururaceae) water extracts, Huperzine A, and ethylacetate extract from Diospyros kaki L.f	Inhibition of Aβ Neurotoxicityand reduce over-activation of microglial cells,neuroinflammation, oxidative stress, and disruptionof calcium homeostasis, which lead to neuron loss
TongmaiYizhi Decoction (TYD) (which includes six rawmaterials: safflower yellow (SY) fromCarthamustinctorius L., geniposide from the fruit of G.jasminoides J. Ellis, ginsenoside Rd from Panax ginsengC. A. Mey, crocin from Crocus sativus L., and quinones)	Inhibition of hyperphosphorylated tau protein andits aggregation
Shengmai (SM) formula, Uncarinic acid C,andTanshinone IIA (TIIA) extract	Reduction of Aβ accumulation
Withaniasomnifera	enhances dendrite and axon regeneration
Crocus sativus	effective similar to memantine

Table no 5: Natural extracts used in treatment of Alzheimer's disease.

Lacenemab, theracurmin and oligomennate are one among the potential modern therapeutic agents for AD[115-116]

CONCLUSION:

In this article we have tried explain the Alzheimer's disease, their stage, causes and risk factors and possible strategies used for the treatment of AD. We currently have two methods of symptomatic treatment of AD i.e. acetylcholinesterase inhibitors (donepezil , rivastigmine, galantamine), and N-methyl d-aspartate receptor antagonist (memantine).These drugs helps to decelerate the progression of AD and provides symptomatic relief. Till now there is no drug which can achieve a definite cure. In future we have a great scope of developing a cure AD using Natural products as there are various plants which has folklore claim to treat memory disorders.

CONFLICT OF INTEREST

This article does not contain any conflict of interest.

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