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A Review on Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain and it is the main cause of dementia, which is characterized by a decline in thinking and independence in personal daily activities. This is caused by the mainly in the rare case by the B Amyloid and Tau protein. There are by increasing the folding of the B Amyloid and Tau protein to the cells of the brain then the level of the acetocholinetrase enzyme level increases and that causes acetocholine level decreases that result Alzheimer's disease occur. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease. There are various treatment are available to treat Alzheimer's disease. This review discusses currently available drugs and future theories for the development of new therapies for AD, such as disease-modifying therapeutics (DMT), chaperones, and natural compounds.

Keywords: Alzheimer's disease, neurodegeneration, B- amyloid peptide, tau protein, risk factors, acetocholine,acetocholinetrase.

1) Introduction

Alzheimer's disease first characterized by Alois Alzheimer in 1907, is a gradually progressive dementia affecting both cognition and behaviour. This disease profoundly affects the family as well as the patient.Alzheimer's disease is a progressive brain disorder. The disease gradually progress and destroys the patient's memory, lacking the ability to learn, communicate, carry out daily activities and to make judgment. The only cure for Alzheimer's disease is to give support and care to improve the quality of life of the person. Once the disease is diagnosed, the care should be give right from the diagnosis to the end of life..[1]Alzheimer's disease (AD) is a chronic neurodegenerative disease with well-defined pathophysiological mechanisms, mostly affecting medial temporal lobe and associative neocortical structures. Neurotic plaques and neurofibrillary tangles represent the pathological hallmarks of AD, and are respectively related to the accumulation of the amyloid-beta peptide (Aβ) in brain tissues, and to cytoskeletal changes that arise from the hyper phosphorylation of microtubule-associated Tau protein in neurons. According to the amyloid hypothesis of AD, the overproduction of Aβ is a consequence of the disruption of homeostatic processes that regulate the proteolysis cleavage of the amyloid precursor protein (APP). Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia.(2).It is the most common cause of the dementia syndrome, probably the fourth most common cause of death in the United States and is likely to become more common as the population ages.[3] Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease (AD) or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumours, and others.[4,5] Memory loss is the key symptom of Alzheimer's disease. Early signs include difficulty remembering recent events or conversations. But memory gets worse and other symptoms develop as the disease progresses. Everyone has memory lapses at times, but the memory loss associated with Alzheimer's disease persists and gets worse. Over time, memory loss affects the ability to function at work or at home. Everyone has memory lapses at times, but the memory loss associated with Alzheimer's disease persists and gets worse. Over time, memory loss affects the ability to function at work or at home.[6]

Figure no 1: Alzheimer's Disease

At present, there is no cure for Alzheimer's disease, although there are available treatments that just improve the symptoms.Onaverage.the life expectancy following diagnosis is approximately seven years. Fewer than three percent of individuals live more than fourteen years after diagnosis.[7]

2) Pathophysiology:

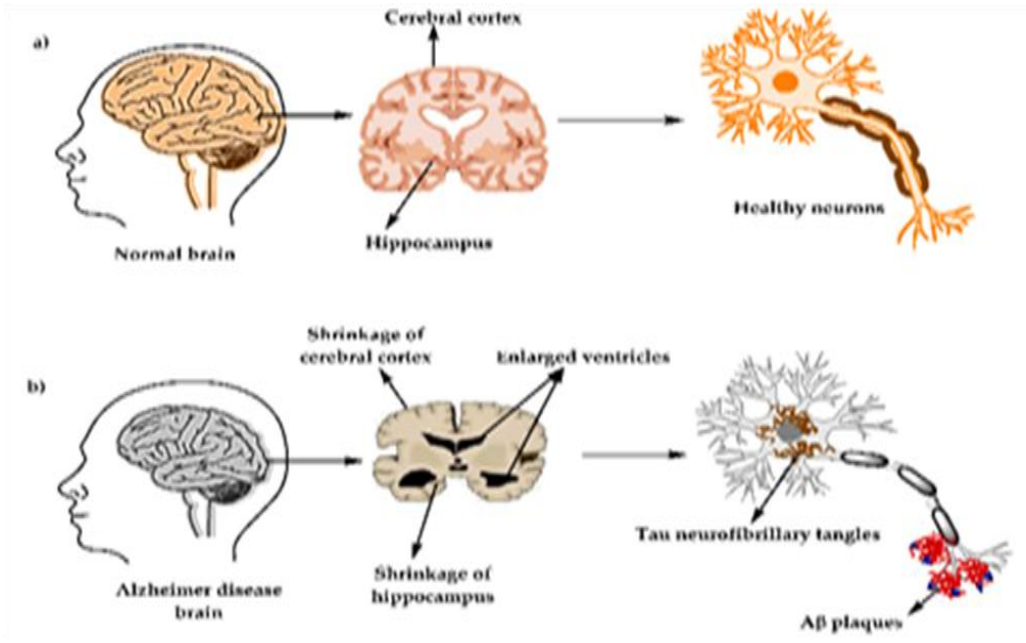


Figure 2:The physiological structure of the brain and neuron in {A} healthy brain and {B} Alzheimer disease

NORMAL BRAIN AND ALZEIMER BRAIN

It characterized by marked atrophy of the cerebral cortex and loss of cortical and sub cortical neurons. The pathological hall marks of Alzheimer's disease are senile plaques which are spherical accumulation of the protein beta amyloidal accompanied by degenerating neuronal processes and neurofibrillary tangles composed of paired helical filaments and other proteins. Although small numbers of senile plaques and neurofibrillary tangles can be observed in intellectually normal individuals, they are far more abundant in Alzheimer's disease and the abundance of tangles is roughly proportional to the severity of cognitive impairment. In advanced Alzheimer's disease senile plaques and neurofibrillary tangles are numerous. They are most abundant in the hippocampus and associative regions of the cortex, whereas areas such as visual and motor cortices are relatively spared. This corresponds to the chemical features of marked impairment of memory and abstract reasoning with preservation of vision and movement. The factors underlying the selective vulnerability of particular cortical neurons to the pathological effects of Alzheimer's disease are not known. Other abnormal chemical changes associated with this disease include nerve cell degeneration in certain areas of brain and defect in the supply of blood to the brain. [8,9]

3) NEUROCHEMISTRY

Analysis of neurotransmitter content in the cerebral cortex shows a reduction of many transmitter substances that parallels neuronal loss, there is a striking and disproportionate loss of acetyl choline. The anatomical basis of cholinergic deficit is the Direct atrophy and degeneration of sub cortical cholinergic neurons, particularly those in the basal fore -brain that provide cholinergic innervations to the whole cerebral cortex. The selective deficiency of acetyl choline in Alzheimer's disease as well as the observation that central cholinergic antagonists such as atropine can induce a confessional state that bears some resemblance to the dementia of Alzheimer's disease has given rise to the Cholinergic hypothesis which proposes that a deficiency of acetyl choline is critical in the genesis of the symptoms of Alzheimer's disease. It is important to note that the deficit in Alzheimer's disease is far more complex involving multiple neurotransmitter systems including serotonin, glutamate and neuropeptides and that in Alzheimer's disease there is destruction of not only cholinergic neurons but also the cortical and hippocampus targets that receive cholinergic input.[10]

4) ROLE OF THE B AMYLOID IN THE ALZHEIMER'S DISEASE

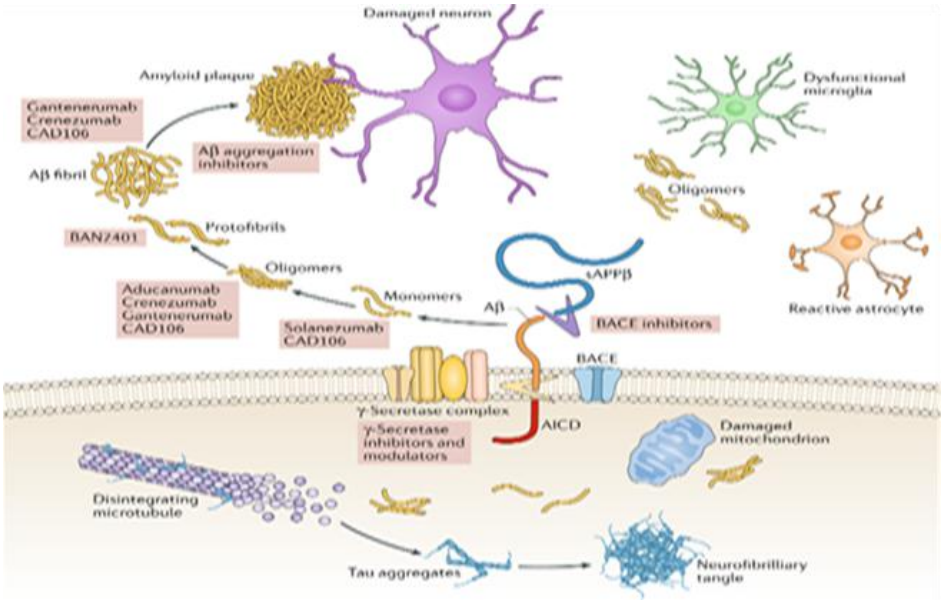


Figure no- 3 B Amyloid in Alzheimer's disease

The presence of aggregates of beta amyloidal is a constant feature of Alzheimer's disease. Beta amyloidal was isolated from affected brains and found to be a short polypeptide of 42 to 43 amino acids. This information leads to the cloning of amyloidal precursor protein [APP] a much larger protein of more than 700 amino acids which is widely expressed by neurons throughout the brain in normal individuals as well as in those with Alzheimer's disease. It is possible for abnormalities in amyloidal precursor protein or its processing to cause Alzheimer's disease. Alzheimer's disease has been identified as aproteinmisfolding disease (proteopathy). caused by accumulation of abnormally folded amyloidal beta and amyloidal tau proteins in gives rise to fibrils of beta-amyloidal, which form clumps that deposit outside neurons in dense formations known as senile plaques.[11]

5) EPIDERMINOLOGY

The global prevalence of dementia has been estimated to be as high as 24 million, and is predicted to double every 20 years until at least 2040. As the population worldwide continues to age, the number of individuals at risk will also increase, particularly among the very old. Alzheimer disease is the leading cause of dementia beginning with impaired memory. [12]

6) ETIOLOGY

The exact etiology of the Alzheimer's disease is not know. Scientists regard to abnormal microscopic structures called plaques and trangles as Alzheimer's disease hall marks. Amyloids plaque are clumps of protein that accumulate out side the brains nerve cells.Trangles are twisted strands of another protein that form inside cells. There are severe risk factors involved in the Alziimer's disease. They are :[13]

A} Age -The greatest known risk factor is increasing age and most individuals with the illness 65 and older. After age 85 the risk reaches nearly 50%.[14]

B} Genetic- Genetic factors were discovered over the years and were found to play a major role in the development of AD. 70% of the AD cases were related to genetic factors: most cases of EOAD are inherited in an autosomal dominant pattern and mutations in the dominant genes such as *Amyloid precursor protein (APP)*, Presenilin-1 (PSEN-1), *Presenilin-2 (PSEN-2)*, and apolipoprotein E (ApoE) are associated with AD [15,16]

C} Enviromental factors - A number of environmental factors have been associated with increased risk of Alzheimer's disease including stroke, alcohol abuse, small head circumference, repeated or severe head trauma, and lower levels of education. In particular, traumatic head injury in combination with the apo E4 genotype has been associated with an increased risk of Alzheimer's disease.[17]

1] Air Pollution - The air pollution is characterized by modifying the nature of the atmosphere through the introduction of chemical, physical, or biological pollutants. It is associated with respiratory and cardiovascular diseases and recently, its association with AD was documented. Six air pollutants have been defined by National Ambient Air Quality Standards (NAAQSs) in the USA as a threat to human health, including ozone (O_3), nitrogen oxides (NO_x), carbon monoxide (CO), particulate matter (PM), sulfur dioxide (SO_2), and lead.[18]

2] Metal- Aluminum is used significantly in the industries such as processed foods, cosmetics, medical preparations, medicines, and others. In the body, aluminum is bound to plasma transferrin and to citrate molecules that can mediate the transfer of aluminum to the brain. Studies demonstrated that Al accumulates in the cortex, hippocampus, and cerebellum areas, where it interacts with proteins and causes misfolding, aggregation, and phosphorylation of highly phosphorylated proteins like tau protein, characteristic of AD .[19]

D} Medical factors –

1] Cardiovascular disease - CVDs are recognized as an important risk factor for AD, such as the stroke that is associated with increased risk of dementia due to a neural tissue loss, which enhances degenerative effect and influences amyloid and tau pathology.Heart failure affected the pumping of the heart that result the blood supply to the body and brain decreases hence leads to the neural damage. Several factors are affected relating the cardiovascular disease causes Alzheimer'sdisease.[20]

2] Obesity and diabetes- Obesity is a term used for too much body fat in individuals due to consuming more calories than they burn and can be calculated by using the body mass index(BMI). Increasing the body fat is associated with a decreased brain blood supply which promotes brain ischemia, memory loss, and vascular dementia. The obesity, unhealthy diet, and other factors can cause impaired glucose tolerance (IGT) or diabetes, which is characterized by hyperglycaemia that affects peripheral tissues and blood vessels. Chronic hyperglycaemia can induce cognitive impairment as a result of increasing amyloid-beta accumulation, oxidative stress, mitochondrial dysfunction, and neuroinflammation. [21,22]

7) STAGES OF COGNITIVE DECLINE IN ALZHEIMER'S DISEASE

STAGE 1- NORMAL

No subjective or objective change in intellectual functioning.[1]

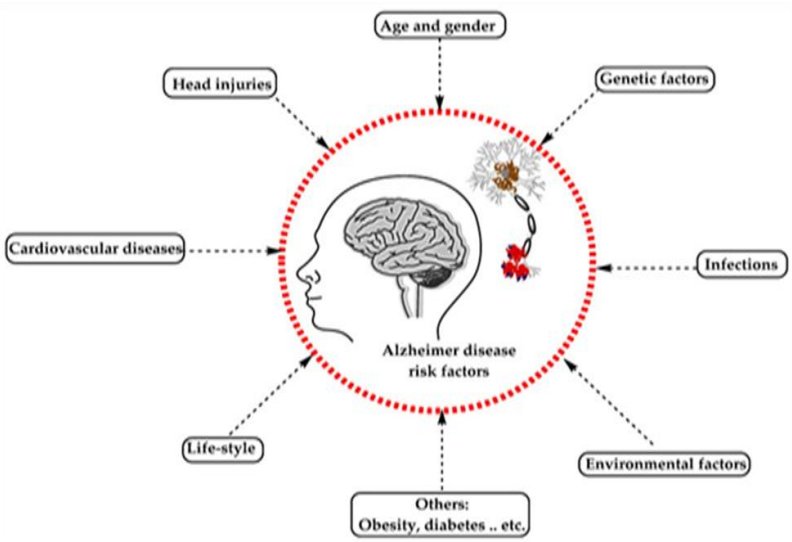


Figure no.4 Risk factors of Alzheimer's disease.

STAGE 2-FORGETFULLNESS

Complaints of loosing things or forgetting names of acquaintances.Does not interfere with job or social functioning. Generally a component of normal ageing.[1]

STAGE 3-EARLY CONFUSION

Cognitive decline causes interference with work and social functioning. Anomia, difficulty in remembering right word in conversation, and recall difficulties are present and noticed by family members. Memory loss may cause anxiety for patient.[1]

STAGE 4-LATE CONFUSION (EARLY ALZHEIMER'S DISEASE)

Patient can no longer manage finance or home making activities. Difficulty in remembering recent events.Begins to withdraw from difficult task and to give up hobbies.May deny memory loss.[23,24]

STAGES 5-EARLY DEMENTIA (MODERATE ALZHEIMER'S DISEASE)

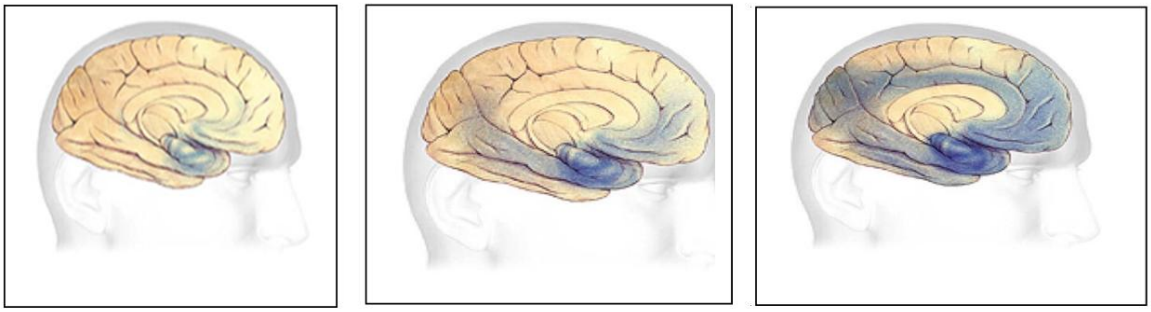
Patient can no longer survive without assistance. Frequently disoriented with regard to time (date, year, season). Difficulty in selecting clothing Recall for recent events is severely unpaired: may forget some details of past life (for eg. school attended or occupation) Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tear full. Loses ability to drive safely.[24,25]

STAGE 6-MIDDLE DEMENTIA (MODERATELY SEVERE ALZHEIMER'S DISEASE)

Patients need assistance with activities of daily living (eg, bathing, dressing, and toileting Patients experience difficulty in interpreting their surroundings, may forget names of family and care givers.[25]

STAGE 7- LATE DEMENTIA - Patient loses ability to speak(may only grunt or screum), walk and feed self- Incontinent of urine and feces. Consciousness reduced to struper or coma. [26]

8)



Diagnostic of Alzheimer's disease

The National Institute on Aging and the Alzheimer's Association charged a workgroup with the task of revising the 1984 criteria for Alzheimer's disease (AD) dementia. The workgroup sought to ensure that the revised criteria would be flexible enough to be used by both general healthcare providers without access to neuropsychological testing, advanced imaging, and cerebrospinal fluid measures, and specialized investigators involved in research or in clinical trial studies who would have these tools available. We present criteria for all-cause dementia and for AD dementia. We retained the general framework of probable AD dementia from the 1984 criteria. On the basis of the past 27 years of experience, we made several changes in the clinical criteria for the diagnosis. A physician should be consulted about concerns with memory, thinking skills and changes in behavior. It is also important for a physician to determine the cause of memory loss or other symptoms. Some dementia like symptoms can be reversed if they are caused by treatable conditions, such as depression, drug interaction, excess use of alcohol or certain vitamin deficiencies. It can be diagnosed by performing mini-mental status exam which will helps in confirming defects in cognition.[27]

- Other diagnostic methods include

1. Electro encephalogram
2. CT Scanning
3. MRI Scanning
4. Positron emission Tomography. [28]

9) Treatment

- RECENT THERAPEUTIC APPROACHES FOR MANAGEMENT OF ALZHEIMER'S DISEASE

Mainly five distinct approaches are there;

1. Cholinergic hypothesis.

2. Hormone replacement approaches.

3. Anti-inflammatory approaches.

4. Neurotropic approaches.

5. An approach to inhibit formation of amyloid and neurofibrillary tangles.

1) Cholinergic hypothesis- According to the cholinergic hypothesis, memory impairment in patients with senile dementia of Alzheimer's disease results from a deficit cholinergic function. It was found in the postmortem analysis of Alzheimer's disease affected brains that the loss of cholinergic servations of the hippocampus and cerebral cortex couples with the loss of cholinergic neurons in the basal fore brain. Therefore treatment for memory loss in Alzheimer's disease has mainly been focused on cholinergic hypothesis.

Three different approaches of enhancing cholinergic function include;

a) Increase the acetylcholine levels using acetyl cholinesterase inhibitors.

b) Administration of acetylcholine precursors or acetylcholine releasing agents.

c) Inhibition of acetyl choline degradation and directly stimulating cholinergic receptors using cholinomimetics.

A]Acetyl cholinesterase inhibitors- Acetylcholine (ACh) is an important excitatory neurotransmitter involved in learning, memory and other higher behaviours. The level of ACh can be affected by the central cholinergic nervous system through regulating the synthesis and release of Ach [30]. Basic forebrain cholinergic neurons (BFCNs) are of significance in learning, memory, and cognitive function.Threre are amino Amyphyoid and Tau protein plaque are covered to the neuron that causes acetocholinestrase level increases hence acetocholin level decrease then neuronal damage causes the Alzheimer's disease. [31]The enhancement of the central cholinergic function has been regarded as one of the most promising approaches for the treatment of Alzheimer's disease by means of acetyl cholinesterase inhibitors. Recent studies have shown that acetyl cholinesterase inhibitors interact with both peripheral and active site of enzyme. In addition to acetyl cholinesterase inhibition, it also act as potential inhibitor for formation of beta amyloid. Many research groups have reported over the last decade on compounds that inhibit acetylcholinesterase as approaches to treat Alzheimer's disease. Increasing cholinergic levels by inhibiting acetylcholinesterase (AChE) is considered one of the therapeutic strategies that increases cognitive and neural cell function. AChEIs are used to inhibit acetylcholine degradation in the synapses, which results in continuous accumulation of ACh and activation of cholinergic receptors. Tacrine [Tetra hydro amino acridine] was found to be a first FDA[Food DrugAdminstration] approved potent acetylcholinesterase inhibitor for the treatment of the AD. which acts by increasing ACh in muscarinic neurons, but it exited the market immediately after its introduction due to a high incidence of side effects like hepatotoxicity and a lack of benefits, which was observed in several trials. Later on, several AChEIs were introduced, such as donepezil , rivastigmine , and galantamine and are currently in use for the symptomatic treatment of AD.[32,33,34,35]

B] CHOLINERGIC AGENTS- The cholinomimetic effect of these compounds is based on increase in the amount of Acetyl choline precursor. Compounds that have such a cognition stimulating mechanism include exogenous choline, lecithin and phosphatide choline Ghatilin and acetyl-1-carnitine (ALCAR) have been reported for the treatment of Alzheimer's disease from this class.[37]

2) HORMONE REPLACEMENT APPROACHES

Estrogen replacement therapy in post-menopausal women resulted in a 40-50% reduction in the risk of developing Alzheimer's disease. 17 beta estradiol protects neurons against oxidative damage induced by beta amyloid as well as other oxidants such as hydrogen peroxide and glutamate. Animal studies have shown that the administration of estrogentoestrogen deficient laboratory animal restores the number of neural synapsis causing beta amyloid to be more soluble. [38]

3) ANTI INFLAMMATORY APPROACHES -Prostaglandins are implicated in the pathology of the Alzheimer's disease. Recently, it has been reported that non-steroidalanti-inflammatory drugs alleviate inflammatory changes in the brain of patients with Alzheimer's disease. Although NSAIDS would not be expected to modify the abnormal metabolism of beta amyloid, they could reduce the response of microglia to the protein. The neural damage in Alzheimer's disease may be due to the inflammatory reaction with consequent free radical and protease release than to the presence of amyloid precursor protein. Thus inhibition of inflammation may delay or even about the loss of neurons consequent on amyloid deposition. In a recent report ibuprofen and naproxen have been found to reduce the severity of Alzheimer's disease.[39]

4] AGENTS THAT STIMULATE NEURO TROPHIC EFFECTS

Compounds namely propentofyline, citicoline, anapests and AIT-082 that have a neuroprotective and cognition-stimulating activity via stimulation of neurotropic function in central nervous system. The main effect of propentofyline is the inhibition of the adenosine re-uptake system. This results in the accumulation of adenosine in CNS and consequent activation of adenosine receptors. Citicoline is an endogenous intermediate in the biosynthesis of structural membrane phospholipids and brain acetylcholine. Citicoline may improve memory via its neurotropic effect. AIT-082 acts at the site of hemeoxygenase to generate carbon monoxide and by activation of guanylylcyclase induces a cascade of biochemical reaction through the second messenger system leading to the production of mRNA neurotrophins, it is currently in phase-III clinical trials.[40]

5] INHIBITION OF AMYLOID FORMATION AND NEUROFIBRILLARY TANGLES

The proteolysis of the membrane APP results in the generation of the beta amyloid peptide that is thought to be caused for the pathology and subsequent cognitive decline in Alzheimer's disease. The amyloid approaches postulate that agents that decrease amyloid protein level in vivo would have promising therapeutic benefit in Alzheimer's disease. Amino acid derivatives, amine and urea analogs and hydroxyl hexanamidederuivative have been shown to inhibit amyloid protein synthesis or its release. Apo lipoprotein E4 is found in both senile plaques and neurofibrillary tangles. Apo E4 interacts with and precipitates beta amyloid protein. The oxygen mediated complex formation was implicated. This suggest that anti-oxidant may have therapeutic potential in Alzheimer's disease.A major component of neurofibrillary tangles is tau, a family of microtubule associated protein which are important for the maintenance of the neuronal cytoskeleton. Neurofibrillary angle associated tau is excessively phosphorylated which may result from neural calcium neuroprotective properties that show promise as a treatment for Alzheimer's disease and ne degenerative disorders.[41]

- **Herbal medicines are used in the treatment of the Alzheimer's disease**

AD over the years has remained the most form of dementia, creating a global concern especially in elderly people .[42] The treatment of Alzheimer's disease is through regulation of neurotransmitters enzymes such as cholinesterase inhibitors or NMDA receptors through synthetic drugs which has not given perfect therapeutic solution.[43] Herbal medicine is currently in the front line as an alternative measure to ameliorating Alzheimer's neurological disorder. Some herbs have the ability to improve brain functions as a result of the naturally dawned phytochemicals. These plants with antioxidants

(flavonoids, beta-carotene, vitamin C, and vitamin E) can help reduce the pathophysiology of neurodegenerative symptoms through countering of oxidative stress that is scientifically linked to one of the accelerators of Alzheimer disorder.[44,45]

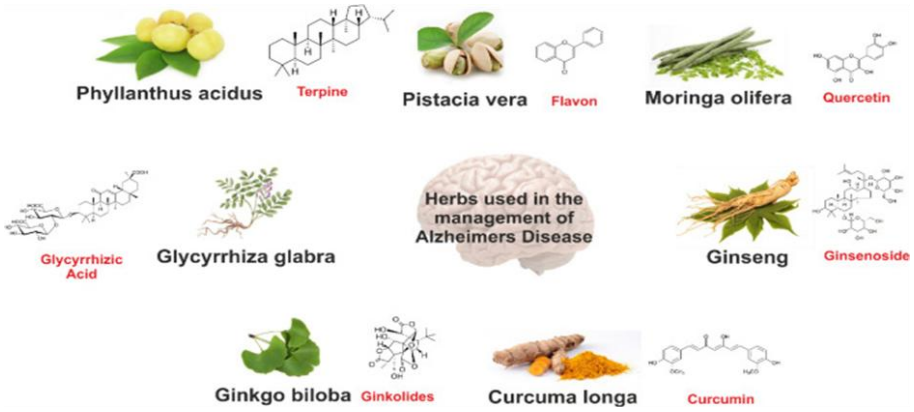


Figure No- 6 herbs used in the Alzheimer's disease

10) RESEARCH –

Vaccines used in the Alzheimer's disease

A] Anti-Beta-amyloid vaccines- Many, but not all, people with Alzheimer's disease will have a build-up of beta-amyloid plaques. It's not clear exactly how these plaques lead to dementia. Vaccines targeting beta-amyloid plaques seek to train your immune system to recognize and remove these plaques.[46]

B] Anti-Tau vaccines- Tau is a protein that typically helps keep your neurons (nerve cells) functioning properly, but if you have Alzheimer's disease, then tau can bunch up in long tubes called neurofibrillary tangles (NFTs). These tangles make it difficult for your neurons to work properly. Some vaccine candidates are designed to prevent the processes that allow NFTs to form.[47]

C] Immune-modulating vaccines-Immune-modulating vaccines can either block or activate different parts of your immune system to treat the underlying disease. One example would be a vaccine to reduce neuroinflammation, which is associated with Alzheimer's disease. [48]

11) NGO WORKS FOR ALZIMIER'S

1.American holistic health association (AHHA) Alzheimer's

2. Indian Herb may potentially cure Alzheimer's disease.

3. International NGO, statement for the world health organization (WHO) ministerial conference one dementia, 16-17 march 2015, Geneva

4. Silver Inning NGO, India caring for someone with Alzheimer's from Lisa W Smith.

5. Alzheimer's and related disorders society of India (ARDS) Mumbai-JJ Hospital.

6. Civics Alzheimer society NGO by Robbie Jin on Prezi.

7. Alzheimer's and Related disorders society of India Udaan.

8. NGO for Dementia.

9. Role of non-Governmental organization in mental health in India

12) AGENCY WORKS FOR ALZIMIER'S-

1. Agency for healthcare research Quality (AHRQ)

2. Alzheimer's Diseases Resource Agency of Alaska (ADRAA)

3. European medicines Agency.

4. National Institutes of Health it the lead Federal agency for Alzheimer's disease Research (NIA).

5. National Institute on aging.

6. ADEAR centre-Alzheimer's disease education and referral centre in 1990.

13]CONCLUSION

Alzheimer's disease is now considered a world health concern; as a consequence, the National Institute on Aging—Alzheimer's Association reclassified and updated the 1984 NINCDS-ADRDA criteria for higher specificity, sensitivity, and early identification of patients at risk of developing AD. Several criteria have been proposed for a more accurate diagnosis of AD, including clinical biomarkers, bodily fluids, and imaging studies. Despite that, the treatment of AD remains symptomatic, without alteration in the disease's prognosis. Inhibitors to cholinesterase enzyme such as galantamine, donepezil, and rivastigmine, and NMDA antagonists such as memantine, improve memory and alertness but do not prevent progression. Several studies have shown that modification in lifestyle habits like diet and exercise can improve brain health and reduce AD without medical intervention and is considered as a first-line intervention for all AD patients. Recently, the research is focusing on targeting the pathological features of AD such as Aβ and p-tau. Future therapies such as disease-modifying treatment can alter the progression of AD by targeting the Aβ pathway, and many drugs have entered the clinical trials, like AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil, but failed in demonstrating efficacy in the final clinical stages. Other DMTs are still under investigation, such as those targeting Aβ and tau pathologies, such as aducanumab, gantenerumab, crenezumab, tideglusib, lithium, and others.

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