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CONCEPTUAL REVIEW ON ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease. It is characterized by progressive cognitive deterioration together with declining activities of daily living and behavioral changes. It is the most common type of pre-senile and senile dementia. According to the world health organization (WHO), 5% of men and 6% of women of above of 60 years are affected with Alzheimer's type dementia. Numerous herbs have been shown to improve brain function and may have a role to play in AD treatment. AD is considered as a multifactorial disease: two main hypotheses were proposed as a cause for AD, cholinergic and amyloid hypothesis. Additional, severe risk factors such as increasing age, genetic factors, plays a role in the disease. Currently available treatments i.e., acetylcholinesterase inhibitors (Rivastigmine, Galantamine, Donepezil) and N-methyl d-aspartate receptor antagonist (Memantine) contribute minimal impact on the disease and target late aspect of the disease. These drugs decelerate the progression of the disease, provide symptomatic relief but fail to achieve definite cure. Some dietary sources like omega-3 fatty acid, vitamin-E and vitamin-B and folate are used for the treatment of AD. The earliest symptoms can include problems with language, mood swings, loss of motivation, not managing self-care and behavioral issues. As a person's condition declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to the death.

KEYWORDS: Alzheimer's Disease-(AD), beta-amyloid, tau protein, cholinergic.

INTRODUCTION

The most prevalent form of dementia, Alzheimer's disease (AD), named after the German psychiatric Alois Alzheimer, is characterized by neuritis plaques and neurofibrillary tangles (Figure-1) as a result of amyloid-beta (Aβ) buildup in the brain's most affected region, the

medical temporal lobe and neocortical structures.[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. Alzheimer's disease (AD) and other brain disorders, infections, abnormalities in the pulmonary and circulatory systems that reduce the amount of oxygen reaching the brain, nutritional deficiencies, vitamin B12 deficiencies, tumors, and other conditions can all contribute to the progressive loss of cognitive abilities.[2]

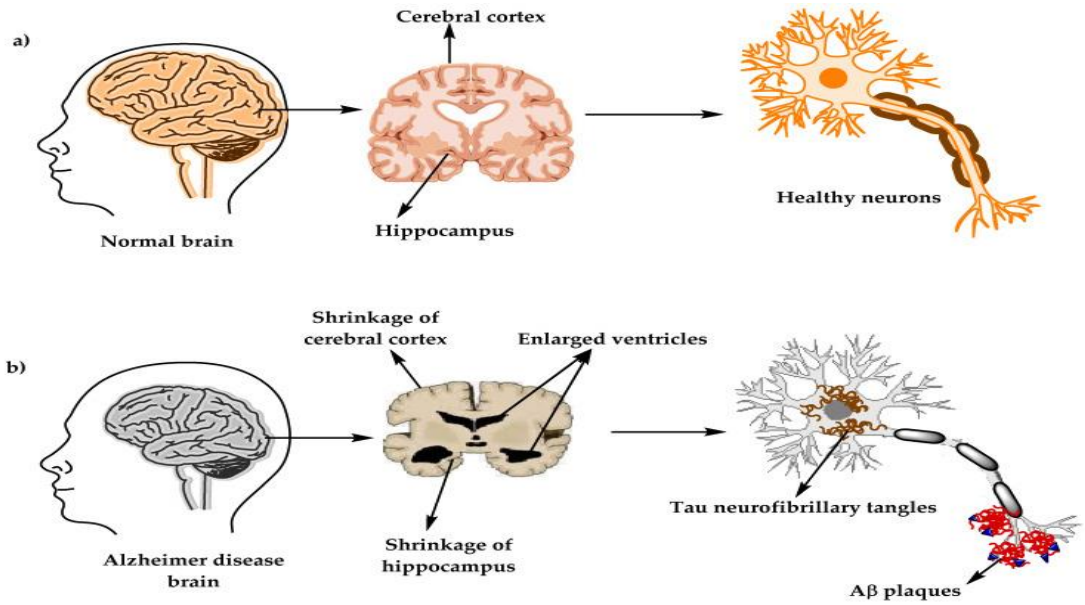

Figure 1: The structure of the brain and neurons in (a) healthy brain (b) Alzheimer's disease (AD) brain.

RISK FACTOR

Age: The single greatest risk factor for developing Alzheim-er's disease is age, one of the non-modi. able risk factors. Most cases of Alzheimer's disease are seen in older adults, ages 65 years or above. Between the ages of 65 and 74, approximately 5 percent of people have Alzheimer's disease. For those over 85, the risk increases to 50 percent.[2] Various studies show that aging can impair the body's self-repair mechanisms, including in the brain. And, many of the cardiovascular risk factors increase with age, such as high blood pressure, heart disease, and high cholesterol.

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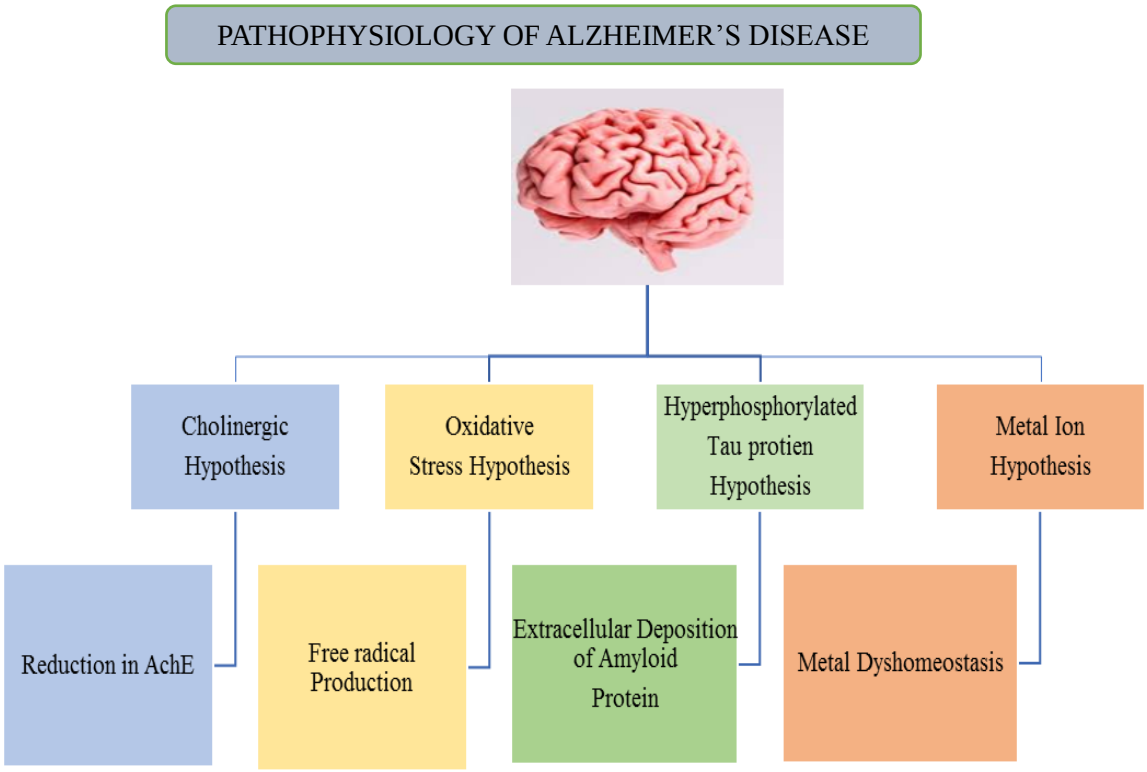
Coexisting Health Problems: Having heart disease, high blood pressure or high cholesterol can increase the risk of developing Alzheimer's disease to a greater extent. This is caused by damage to blood vessels in the brain, resulting in less blood flow and possible drastic brain tissue death. Type 2 diabetes may also increase the risk for Alzheimer's disease. Inefficiency of insulin to convert blood sugar to energy may cause higher levels of sugar in the brain, causing severe harm to the entire body. Symptoms such as forgetfulness and confusion are mild during the early stages of the disease as is observed in almost every case, but they gradually worsen as the disease progresses and damage to the brain becomes more severe and prominent. Some people with AD also have severe depression and don't know how to cope with a loss of cognitive and basic functions.[3]

PATHOPHYSIOLOGY



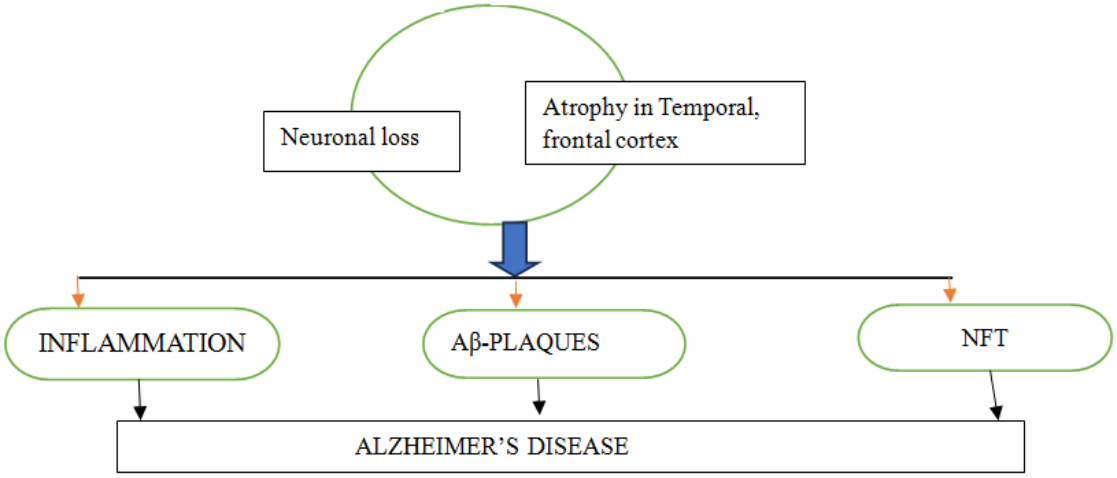


Figure 2: Pathophysiology of Alzheimer's disease.

Hyperphosphorylated tau protein and amyloid β hypothesis

Senile plaques (SP), which are brought on by the buildup of amyloid beta (A), are one of the keys of α-secretase, β-secretase, and γ-secretase, is normally converted into soluble tiny peptides called Aβ. Depending on the degree of oligomerization, the imbalance between β-amyloid (Aβ) generation and clearance results in protofibrils, fibrils, and plaques, which are three different types of hazardous oligomers. Although the exact cause of Aβ's production is yet unknown, the order, concentration, and stability conditions are crucial elements. A multitude of mechanisms, including cholinergic dysfunction, amyloid/tau toxicity, and oxidative stress/mitochondrial dysfunctions, are thought to contribute to the pathogenesis of Alzheimer's disease.[4]

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. The brain's fundamental functional unit, the neuron, is made up largely of polyunsaturated fatty acids. 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.[5]

Metal ion hypothesis

Metal 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.[6] Other medications besides metal-binding ones can also target the homeostasis of transition metals.10 the balance of redox transition metals, primarily copper (Cu), iron (Fe), and other trace metals, is changing, according to current findings. In AD, their brain levels are observed to be elevated. Other neurological diseases also involve copper, manganese, aluminum, and zinc.[7]

Cholinergic hypothesis

With mild to moderate AD, cholinergic receptor binding is decreased in particular brain areas, which is associated with neuropsychiatric symptoms. Lower receptor binding may result in reduced processing speed in older, healthy persons. Cholinergic receptor binding in vivo may give a possible biological therapy target and may link to other significant brain alterations linked to aging and AD. Clinical decline is associated with an extensive loss of cholinergic neurons produced in the medial forebrain nuclei and a corresponding decline in acetylcholine-mediated neurotransmission. 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.[5]

STAGES OF ALZHEIMER'S DISEASE

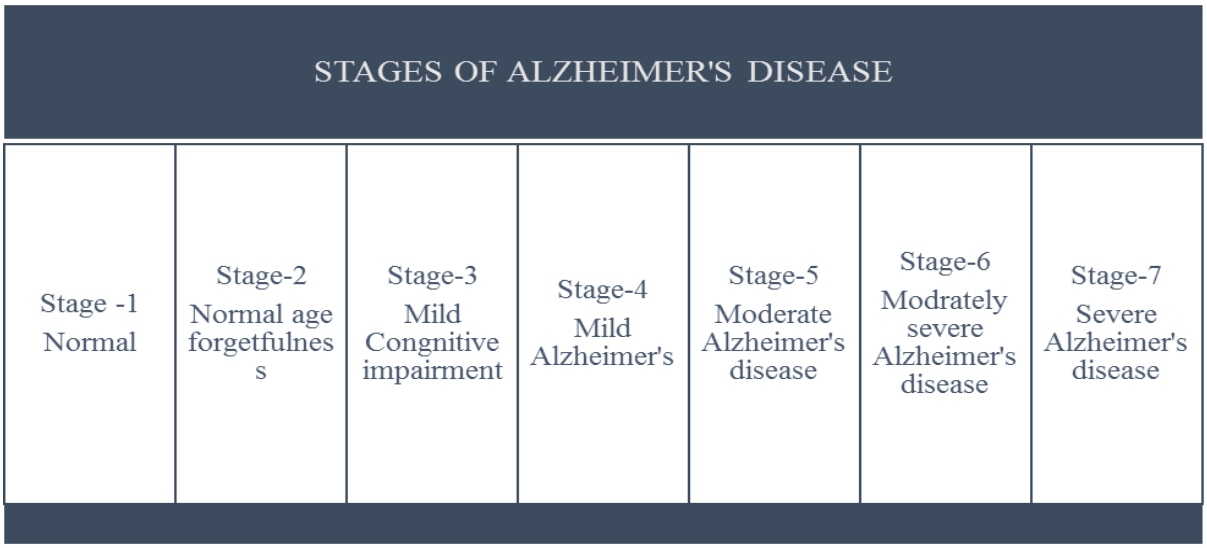


Figure 3: Different stages of Alzheimer's disease.[8]

EPIDEMIOLOGY

By the middle of the century, there will be 152 million dementia sufferers globally, with the highest growth anticipated in low and medium-income nations. AD became the fifth-largest cause of death in American old people. Notably, caregivers would experience more mental stresses and negative emotional influences. Therefore, the social and family burden of caring for AD population will be huge and unsustainable. According to data and numbers from 2023 about Alzheimer's disease, there may be 5.8 million to 13.8 million AD patients in America by 2050, a significant increase. In recent years, community-dwelling studies conducted in China and Japan have clearly shown an increase in the prevalence of AD.

In particular, age-specific global prevalence in women was 1.17 times greater than in men, and the age-standardized death rate of women was also higher than that of males, indicating that the longer lifetime was not the only factor contributing to the domination of women.[9]

CLINICAL PRESENTATION OF ALZHEIMER'S DISEASE

General

- The patient may have vague memory complaints initially or the patient's significant other may report that the patient is "forgetful". Behavioral disturbances may be present in moderate stages. Loss of daily function is common in advanced stages.

Symptoms

Cognitive

- Memory loss (poor recall and losing items)
- Aphasia (circumlocution and anomia)
- Apraxia
- Agnosia
- Disorientation (impaired perception of time and unable to recognize familiar people)

Noncognitive

- Depression, psychotic symptom (hallucinations and delusions)

Functional

- Inability to care for self (dressing, bathing, eating).[10]

Diagnosis of Alzheimer's disease

In the past, Alzheimer's disease was only definitively identified after death when a microscope examination of the brain revealed plaques and tangles. Alzheimer's disease during

a person's lifetime can now be diagnosed with greater accuracy by medical professionals and researchers. Plaques and tangles can be found using biomarkers. Tests that assess amyloid and tau proteins in the fluid component of blood and cerebral spinal fluid are examples of biomarker tests, as are specific kinds of PET scans.

Physical and neurological exam

A physical examination will be carried out by a medical practitioner. Testing may be part of a neurological examination.

- Reflexes.
- Strength and muscle tone.
- Being able to stand up from a chair and move around the room.
- Senses of hearing and sight.
- Coordination.
- Balance.[11]

Lab test

Blood testing might help rule out further potential reasons of forgetfulness and confusion, such as a thyroid condition or inadequate vitamin levels. Beta-amyloid and tau protein levels can also be determined by blood testing, however access to these procedures may be restricted.[12]

Brain imaging

- (MRI) Magnetic resonance imaging: A powerful magnetic field and radio waves are used in MRI to provide sharp images of the brain. MRI scans not only rule out other illnesses, but they may also reveal shrinkage of particular brain regions linked to Alzheimer's disease. In general, an MRI is preferred to a CT scan when assessing dementia.
- CT, or computer tomography: You can get cross-sectional images of your brain using the specialist X-ray technique known as a CT scan. Usually, it's used to rule out brain traumas, strokes.
- Using positron emission tomography (PET), the disease process can be visualized. In order to see a specific aspect of the brain during a PET scan, a low-level radioactive tracer is injected into the blood. Examples of PET imaging include.
- Areas of the brain that poorly metabolize nutrition can be seen using fluorodeoxyglucose (FDG) PET imaging examinations. It may be possible to discriminate various dementias by looking for patterns in the regions with poor metabolism.

- The number of amyloid deposits in the brain can be quantified via PET imaging with amyloid. This test may be utilized if a person exhibits unusually early or late onset dementia symptoms. It is primarily used in research.
- In research settings, tau PET imaging is frequently utilized to quantify the tangles in the brain.[12]

TREATMENTS

MANAGEMENT OF AD USING HERBS

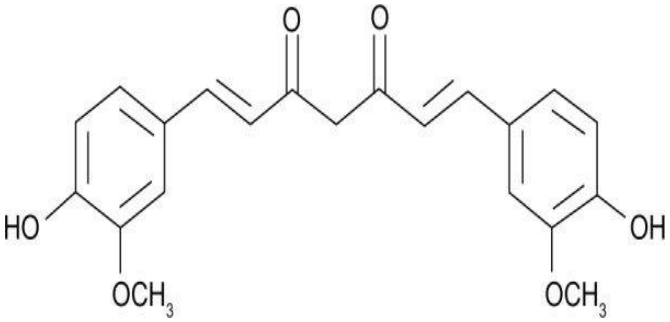
Due to the naturally occurring phytochemicals, several herbs have the capacity to enhance brain processes. By combating oxidative stress, which is scientifically connected to one of the accelerators of Alzheimer's disease, these plants rich in antioxidants (flavonoids, beta-carotene, vitamin C, and vitamin E) might help lessen the pathogenesis of neurodegenerative symptoms. Traditional medicine has been practiced all across the world since the beginning of humanity. These herbal remedies, as well as medicinal plants, have been used for the treatment for disorders like Alzheimer's disease, dementia, amnesia, and others Ancient Chinese, Indian, and Egyptian culture are where herbal remedies first appeared. There is a resurgence of scientific interest in the use of medicinal plants to treat AD because of the major impact on the use of herbs, medicinal plants, and their biologically active compounds to treat disease and enhance of herbs, medicinal plants, and their biologically active compound to treat disease and enhance health without noticeable side effects.

Ginkgo biloba, Centella asiatica, Withania somnifera, Tinospora cordifolia, Lepidummeyenii, Curcuma longa, Glycyrrhiza glabra, Magnolia officinalis, Convolvulus pluricaulis, and other medicinal plants have all been studied and reported to be used in the treatment of AD.[13]

❖ Curcuma Longa(curcumin)

Zingiberaceae is the family that includes curcuma longa. Due to its anti-amyloidogenic, antioxidant, and anti-inflammatory properties, it is used to treat Alzheimer's patients. Studies on rats show that Curcuma longa plant extracts may be able to prevent the growth of fibrils and A aggregation. The outcomes of the investigation also revealed a decrease in oxidative stress and an enhancement of cognitive abilities. This might be as a result of the extract's capacity to inhibit COX (cyclooxygenase)-2 and NF-kB-induced Inducible Nitric Oxide Synthase (iNOS) in activated B cells (NF-kB).[13]

Curcuma longa

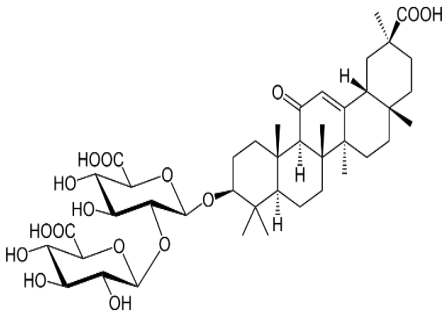


Curcumin

❖ **Glycyrrhiza glabra** (Glycyrrhizic acid)

Due to the inclusion of coumarins, isoflavonoids, saponins, flavonoids, and stilbenoids, this plant from the Fabaceae family is employed in the treatment of Alzheimer's disease.[14] Together, these phytochemicals suppress the production of ROS, cytotoxicity, and GSH activity.[15] Additionally, glycyrrhiza inflata extract, a distinct species of glycyrrhiza, greatly reduced Aβ aggregation and radical-scavenging activities, according to a study by Tapia-Rojas. It reduced mitochondrial biogenesis and oxidative stress. This could be attributed to the actions of the plant extract's licochalcone A and liquiritigenin.[16]

Glycyrrhiza glabra



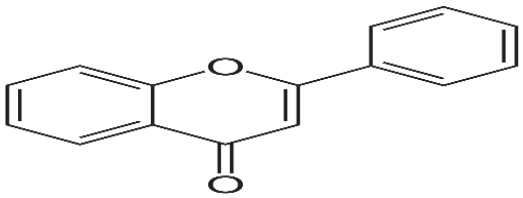
Glycyrrhizic acid

❖ **Pistacia vera** (Flavon)

In the Anacardiaceae family of cashews, there is a genus of flowering plants called Pistacia. Scientific research has confirmed that the Pistacia plant has important neuroprotective potentials like antioxidant activity, anti-Aβ aggregation, anti-neuroinflammatory characteristics, and AChE inhibitory activity as a result of its long use in traditional medicine. According to a scientific study, Pistacia vera extract helps prevent cognitive and motor damage brought on by cisplatin and vincristine. Its high flavonoid and phenolic content might be to blame for this behavior. Pistacia has demonstrated a range of promise in the treatment of AD. Different solvents were used for the extraction, and the hydroalcoholic pistachio nut extract greatly increased learning and memory, while the aqueous methanolic extract

suppressed AChE and the hexane solvent extract of the pistachio nuts and gum shown antioxidant activity.[16]

Pistacia vera

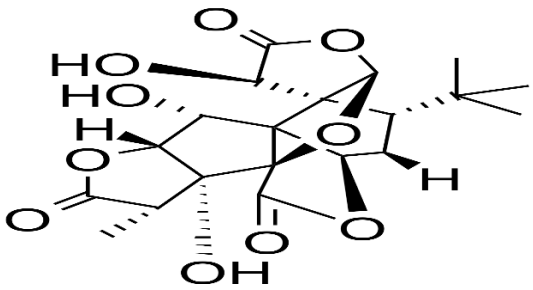


Flavon

❖ **Ginkgo biloba** (Ginkolides)

This plant's leaves are used to treat cognitive impairment in Alzheimer's sufferers.[11] It is a natural remedy. Terpene lactones (6%), and flavone glycosides (24%) are both present in the plant extracts. The terpene lactones include bilobalide, A, B, and C ginkgolides, while the flavone glycosides include quercetin, kaempferol, and isorhamnetin. Through the control of glutathione peroxidase, catalase, and SOD activity, this plant extract prevents A-induced neurotoxicity by preventing neuronal apoptosis, ROS accumulation, glucose uptake, mitochondrial dysfunction, and activation of ERK and c-JUN N-terminal kinase (JNK) pathways.[16]

Ginkgo biloba



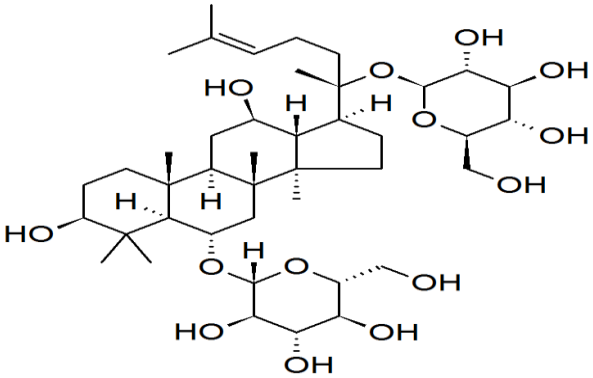
Ginkolides

❖ **Ginseng** (Ginsenoside)

One of the herbs used to treat AD is ginseng (Panax ginseng/Araliaceae). It is a well-known herb that is used to improve memory and vitality in China, Japan, and Korea. Chinese ginseng, also known as ginseng, contains phytochemicals like ginsenosides (saponins), a derivative of the triterpenoid dammarane, and 20(S)-protopanaxadiol, which prevents amyloid-beta (Aβ) from aggregating, clears Aβ from neurons, boosts the secretion of neurotrophic factor, and alleviates mitochondrial dysfunction.[14] Ginsenosides, which are contained in ginseng, have substantial AChE inhibitory activities, which are an efficient

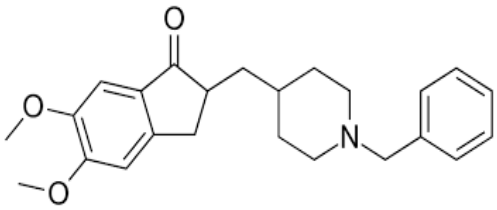
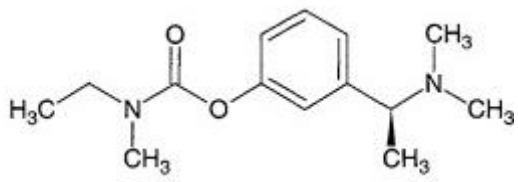
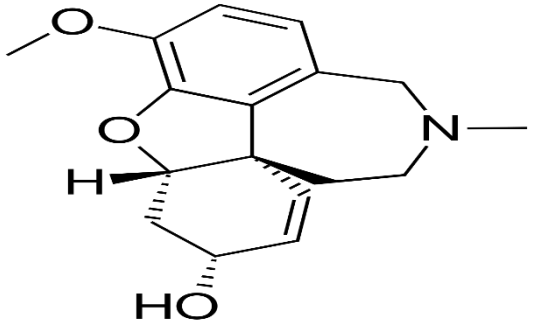
strategy for lowering the symptoms of AD. Gintonin modulates the G protein-coupled lysophosphatidic acid receptors, which affects the cholinergic system and neutrotrophic factors, reducing the level of plaque formation. Gintonin has been proven in decrease in a plaque deposition and the release of s AβPPα in the body.[17]

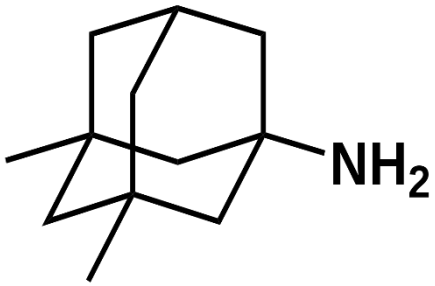
Ginseng



Ginsenoside

Table 1: Drugs Used For The Tratment Of Ad.

DRUGS	PHARMACOLOGICAL ACTIONS	ADVERSE EFFECTS	DOSE
1.Acetylcholinerase inhibitors **Donepezil** 	It acts by inhibiting the breakdown of a neurotransmitter called acetylcholine which is important for memory and cognitive function.[18]	-fatigue -muscle cramps -weight loss vomiting -loss of appetite.[19]	5-10mg daily in mild to moderate AD. 10-23mg daily in moderate to severe AD. [10]
Rivastigmine 	It inhibits the breakdown of acetylcholine help in improving cognitive function in AD.[18]	-Anxiety drowsiness -fatigue -asthenia Depression.[20]	3-6mg twice a day capsule or solution 9.5-13.3 mg per day transdermal patches.[10]
Galantamine 	It acts by inhibition of breakdown of acetylcholine and also by working as positive allosteric modulator of nicotinic acetylcholine receptor.[18]	-chest pain headache dizziness -fainting shakiness in legs, arm, hands.[21]	8-12mg twice a day Tablet, oral solution. 16-24 mg extended release of capsule to treat AD.[10]
2.NMDA receptor antagonist	It blocks the effect of	-bloating or	10mg twice

Memantine 	glutamate a neurotransmitter in the brain that leads to neuronal excitability and excessive stimulation in AD.[18]	swelling of the face, arm, hands, lower legs or feet. -blurred vision.[22]	daily. 26mg daily Extended-release capsule to treat AD.[10]

DIETARY SUPPLEMENT

Omega-3 Fatty acid

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) are believed to have a positive impact on how well the brain functions. They may help or delay memory loss and the inability of people with dementia to do daily chores, according to certain theories. In this review, we looked at randomized controlled trials (clinical studies where participants are assigned at random to one of two or more treatment groups) comparing omega-3 PUFA supplementation or dietary augmentation with placebo (a sham treatment) in dementia patients with the most prevalent dementia subtypes.[23] There have long been claims that omega-3 fatty acids in fish oil, like docosahexaenoic acid and eicosapentaenoic acid, may be helpful for AD patients. Recently, there was a report on a sizable prospective, placebo-controlled trial of docosahexaenoic acid in AD patients. The majority of the results were disappointing, and while it could not be completely ruled out that certain population subsets benefited, the main study end points were unfavorable. Docosahexaenoic acid is not currently advised for the treatment of AD due to a lack of sufficient data.[24]

Vitamin-E

Vitamin E is a term that includes a group of eight compounds and belongs to the fat-soluble vitamins. In this group we can find α-, β-, γ-, and δ-tocopherols and tocotrienols, their main characteristic is their antioxidant potential. However, vitamin E also has neuroprotective, anti-inflammatory, and hypocholesterolemia properties driving to its importance for brain health.

Moreover, vitamin E is considered one of the most important antioxidants in the brain and especially the α-tocopherol form. This is due to the high levels found in the brain of its transporter α-TTP (α-tocopherol transfer protein) whose functions include the regulation and distribution of levels of vitamin E in different tissues. Its critical role in brain function is

underscored by the fact that human carriers of a mutation in the α-TTP gene develop progressive spinocerebellar ataxia, areflexia, loss of proprioception, and extremely low vitamin E levels.[25]

Vitamin-B and folate

Increased serum homocysteine levels and decreased vitamin B12 levels have been linked to a higher risk of AD, according to numerous studies.[26] The connection between AD and serum folate levels has not been as strong. However, it is generally recognized that folate and homocysteine metabolism are related. Due to their participation in neuronal metabolic pathways, the majority of the B complex vitamins have been proven to be either directly or indirectly related to neuronal health. The significance that the B vitamins play in energy metabolism through their function as methyl donors is one of their crucial roles. Specific neurological illnesses like Wernicke's/Korsakoff's (vitamin B1 deficiency), subacute combined degeneration (vitamin B12 deficiency), and pellagra (vitamin B6 deficiency) have been explicitly related to such vitamin deficiencies. In the context of cognitive decline or impairment, current treatment recommendations include routine laboratory measurement of these vitamin levels and replacement if found to be inadequate. Methyl cobalamin, methyl folate, and acetylcysteine are ingredients in a supplement called Cerefolin NAC that has been approved for addressing vitamin deficits linked to memory loss. Despite widespread media coverage and consumer appeal, there is little evidence for its use, and study is ongoing. The role of high dose B vitamin and folic acid supplementation in the prevention of AD has not yet been established in other clinical trials examining folic acid and vitamin B supplementation. These studies, despite universal correction of deficiencies and downstream homocysteine levels, failed to demonstrate convincing results in neurologic improvement.[26]

CONCLUSION

The National Institute on Aging—Alzheimer's Association modified the 1984 NINCDS-ADRDA criteria for improved specificity, sensitivity, and early identification of patients at risk of developing AD because Alzheimer's disease is now regarded as a global health concern. For a more precise diagnosis of AD, a number of criteria have been proposed, along with imaging tests. Memory and alertness are enhanced by cholinesterase enzyme inhibitors like galantamine, donepezil, and rivastigmine and NMDA antagonists like memantine, but

progression is unaffected. Numerous studies have demonstrated that altering lifestyle practices, including as food and exercise, can enhance brain function and lessen AD without requiring medical attention. This is why it is recommended as a first-line strategy for all AD patients. Numerous herbs like Curcuma longa, Glycyrrhiza glabra, Pistacia vera, Ginkgo biloba, Ginseng have been shown to improve brain function and may have a role to play in AD treatment. Various dietary supplements are used for the treating of AD like omega3 fatty acid, vitamin E, vitamin B and folate.

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