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AN COMPREHENSIVE REVIEW ON ALZHEIMER: A NEURODEGENERATIVE DISORDER

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ABSTRACT

AD is a neurodegenerative disorder that affects a large number of individuals worldwide. It is the most common cause of dementia and the most frequent cause of cognitive impairment. AD is characterized by the presence of tau proteins in the brain, which are essential for the development and progression of the disease. This review focuses on the pathogenesis of AD and its pathophysiology, including the role of Tau proteins in AD. The importance of biosensors in the diagnosis and treatment of AD is highlighted. In this review, we will focus on the various biomarkers associated with AD diagnosis, as well as their application in the clinical diagnosis of AD. Biosensors utilising nanotechnology are being created to enable the precise and sensitive detection of Neurodegenerative Biomarkers, including Tau proteins, which could facilitate early identification and predicting disease progression.

KEYWORDS: Alzheimer disease (AD), Tau angle, Amyloid plaque, Dementia.

INTRODUCTION

Dementia is most commonly caused by AD, a degenerative neurological condition that accounts for 60 to 80 percent of dementia cases. It predominantly impacts memory, cognition and behaviour resulting in notable deficits in day to day functioning. Alzheimer`s often become apparent after the age of 65, while people as young as 30 might develop early onset cases of the disease.

There are multiple functional origins of AD.AD can coexist with other neurodegenerative disorders and cerebrovascular diseases particularly in older populations. The prodormal phase of AD which precedes the clinical manifestation of disease involve a significant acceleration in cognitive decline that can begin years before the onset of dementia.[1]

This phase can be identified through various methods, including functional magnetic resonance imaging which has shown potential in detecting morphological brain changes in individuals at risk. Globally, it is estimated that over 55 million individuals are affected by AD or dementia. According to recent estimate there were approximately 4.6 million cases of AD and related dementia among senior citizen aged 60 and older in India as of 2050. Over 4 million individuals in India are affected by various forms of dementia with alzheimers being the most prevalent type. The economic effects of AD on Indian families are considerable, encompassing financial strain, psychological challenges societal consequences.

CAUSES OF AD

AD is a multifaceted neurodegenerative condition with numerous risk factors that contribute to its onset and progression. The likelihood of AD is greatly increased by vascular risk factors. An increased risk of AD is associated with the combination of vascular risk factors, including diabetes, hypertension, heart disease, and current smoking. When used alone or in combination, the two largest risk factors for AD are diabetes and current smoking.[2] Interestingly, the effect of vascular risk factors on AD risk and development varies by gender and genetic susceptibility. For example, obesity raised the risk of AD in females but not in males, but diabetes enhanced the probability of arterial dementia in females despite adjustments. Modifiable vascular risk variables offer chances for intervention and prevention. The intricate interplay of genetic predisposition, vascular health, and lifestyle variables emphasises the need for a multimodal approach to AD prevention and therapy. Future studies should focus on identifying the particulars causal pathways of these risk variables. Considering its interactions with gender and genetic factors allows for more focused strategies for AD detection and treatment.[3] Furthermore, the existence of the APOE4 allele, an inheritable risk factor, could communicate with vascular risk factors, influencing AD progression.[4] In

conclusion, while age remains the most significant risk factor for AD.[5]

1. Protein abnormalities
Amyloid plaques – An excessive buid up of amyloid beta proteins results in plaque formation outside neurons, interfering with cell to cell transmission.

2. Age
The condition is more frequent in elderly persons, and a bigger proportion of over 85 year of age have it relative of over 65 s.

3. Genetic factors
Even while most cases are not hereditary, some genes can raise the risk.

4. Health and lifestyle factors
Condition such as diabetes, obesity and poor dietary habits, together with a sedentary lifestyle, might increase the risk of cardiovascular diseases.

5. Family History
Getting AD in family is related with greater risk. After age, this is the major risk factor.

6. Life style
7. Environmental Toxins
8. Infectious diseases
Certain brain infections can lead to dementia, including chronic fungal meningitis, chronic HIV, and chronic syphilis.

9. Hypertension
10. Smoking and alcohol Use
11. Other Factors: High Blood Pressure, High Cholesterol Levels.

SYMPTOMS OF AD
A variety of cognitive, operational, and psychological signs that worsen with time are hallmarks of AD. The main symptoms are memory loss that interferes with day-to-day activities, trouble with language, disorientation, poor judgment, and difficulties with abstract thought.[6] Patients notice a loss in cognitive abilities, such as reasoning, problem-solving, and verbal or mathematical skills, as the condition worsens.[7] Interestingly, AD can manifest with atypical symptoms, occasionally called "atypical AD," which can complicate diagnosis. Moreover, symptoms of AD can sometimes start suddenly, making it more difficult to distinguish AD from other types of dementia.[8] To summarize, AD symptoms include behavioral abnormalities, functional disability, and cognitive decline. Together, these symptoms diminish patients' ability to live independently, which has an impact on caregivers as well as patients.[9] Primary sign of AD is memory loss. Memory loss from recent discussions or experiences is one of the early warning signals. But as the illness worsens memory deteriorates and new symptoms appear. Furthermore, behavioral alterations are prevalent and varied in AD. Apathy, impatience, and difficulty focusing are examples of early, mild personality changes. Aggression, agitation, and inhibited actions are examples of later phases.[10]

Individual suffering Alzheimer`s may
1. Rephrase questions and comments several times.
2. Forget activities and meetings, become lost in areas they used to be familiar with.
3. Names of regular things and family people eventually slip your mind.

Thinking and Measuring
AD impairs one`s ability to focus and think clearly, particularly when it comes to abstract ideas like numbers. Managing multiple task at once is very challenging.

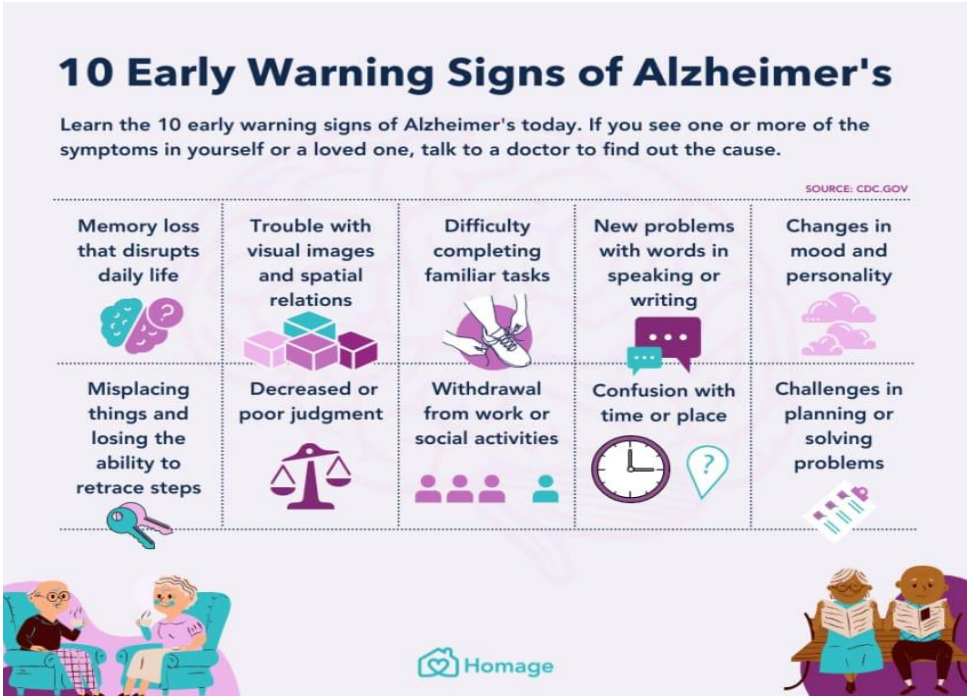
Making judgments and Decision
Decision making and judgment in daily life become increasingly difficult as one gets AD. For instance a person might dress inappropriately for the weather or make bad decision in social situation.

Alteration in behavior and Personality
AD realted brain abnormalities can have an impact on behavior and mood. Issues could consist of the following:
Depression.
A Decline in activity interest.
Mood swings.
Mistrust of other people.
Hostility Or Furry.
Alterations in sleeping pattern.
Loss of self control.

Preventive Major
There are not verified prevention strategies for alzheimers. There are may be study proof that healthfull way of life habits such as diet, workout and no longer smoking may additionally play a function in lowering your threat of alzheimers.

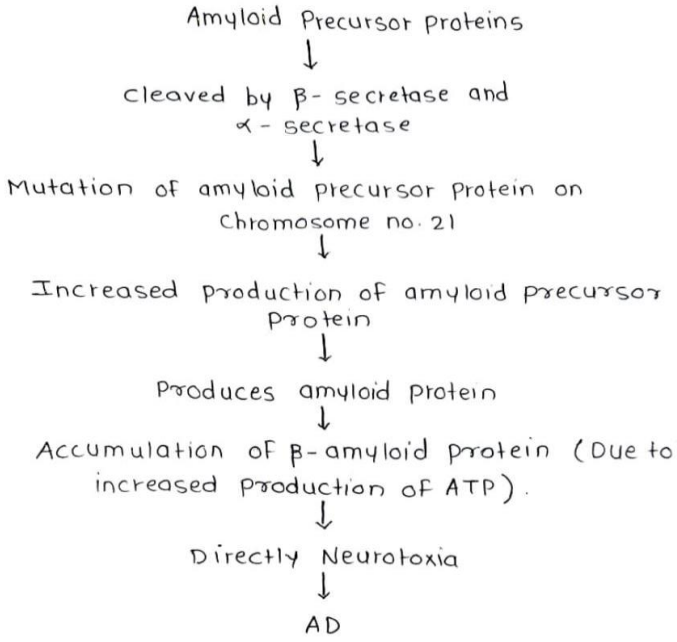
The following actions encourages optimal brain health overall.
1. Steer clear of smoking.
2. Manage vascular risk factors such as Diabetes, high cholesterol and blood pressure.
3. Consume well balanced diet like Mediterranean a diet heavy in fruits and vegetables and high in protein, especially sources of omega 3 fatty acids.
4. Engage in social and physical activities.
5. Sustain healthy weight.
6. Ensure your emotional wellbeing.
7. Prevent injuries to the head.
8. Restrict alcohol intake.
9. Healthy Eating: Consuming a lot of whole grains, fruits, veggies, and healthy fats, such as the DASH or Mediterranean diets, may reduce risk.

10. Frequent Exercise: Performing aerobic exercises for 150 minutes a week or more can enhance brain function.
11. Mental Stimulation: Reading, solving puzzles, and picking up new abilities are all beneficial for preserving cognitive function.
12. Sufficient Sleep: Getting 7-8 hours of sleep per night promotes brain health.



PATHOPHYSIOILOGY OF AD

AD pathophysiology is comprised of several interrelated pathways. The condition progresses as a result of gliosis, persistent neuroinflammation, and deficiencies in cholinergic function.[11] Furthermore, apoptosis, excitotoxicity, and oxidative stress all play significant roles in neurodegeneration.[12] Remarkably, current studies have demonstrated how metal ion dyshomeostasis—specifically, that of copper, iron, and zinc—plays a role in AD pathogenesis. Moreover, it has been suggested that deregulation of cholesterol metabolism plays a role in the development of AD, indicating a possible connection between altered brain cholesterol metabolism and metal dyshomeostasis.[13]



STAGES OF AD

STAGE 1: Normal outward behaviour

AD normally begins silently with brain abnormalities that begin years before anybody sees a problem. They will not have any visible symptoms. Only PET scan, an imaging tool that shows how the brain is behaving, can tell whether they have Alzheimer`s.

STAGE 2: Very mild changes

Individuals with stage 2 AD, commonly known as moderate cognitive impairment (MCI), suffer relatively mild deficits in memory and thinking ability. These changes are frequently modest and can involve occasional amnesia, such as putting away objects or forgetting basic words. While these symptoms may be evident to close relatives and friends, they rarely disrupt daily activities or social interactions. This stage can endure for a while and may be an onset to more serious cognitive decline.

STAGE 3: Mild Decline

During the early stages of AD, individuals may exhibit changes in thinking and reasoning, that includes – forgetting recently read information. Repeatedly asking same question. Experiencing difficulties with planning and organisation. As well as remembering names of new acquaintances.

STAGE 4: Moderate decline

During this stage, problems with thinking and reasoning become more noticeable and new issues arises such as – Forgetting personal details, Difficulty putting the correct date and amount on bill, Forgetting month or period, Not grasp what is spoken to them.

STAGE 5: Moderately severe decline

The patient began to lose track of where they were and what time it was. They may struggle to remember their home, phone no. or school location, They may become confused about what attire to wear for the day or season.

STAGE 6: Severe decline

As Alzheimer develops, sufferers may recognise faces but forget names. They may also confuse a person for another, Delusions may set in, It may be difficult to communicate, but you can still connect with them through the senses. May persons with AD like listening to music, being read to, or looking over old photos. During the late stages of AD, patients may experience difficukty in eating, swallowing, depression, depression, weight loss and skin infection; Symptoms may include pneumonia, difficulty walking and sleep disturbance.

Classes Of Drugs Used In Treatment Of AD

AchE Inhibitors

The cholinergic system is engaged in cognitive process. Reduced cholinergic, the use of AchE inhibitors is based on synaptic activity produced by reduction in actions of choline acetyl transferase, an enzyme engaged for ach production in the nucleus basalis of meyer.[14]

According to the cholinergic hypothesis of AD, the cholinergic system in the basal forebrain is disrupted early in the disease process, resulting in memory loss and degeneration of other cognitive and non-cognitive processes, such as signs of neuropsychiatric disorders.

This includes loss of Ach neurons and lack of enzyme activity for ach synthesis and degradation.

For the treatment of individuals with mild to severe AD, this medicine is indicated when used alone since it inhibits the catabolic enzyme ache, delaying the levels of ach.

Three AchE are available to treat AD. These includes Donepezil, Galantamine and, Rivastigmine.

It has been suggested to use CIs to postpone the breakdown of ach between synaptic clefts in order to improve cholinergic transmission.

These medications are thought to be the gold standard and initial line of treatment for AD.

BACE Inhibitors

The build up of amyloid in brain parenchyma is caused by defective BACE activity.[15] Hypothetically, BACE inhibition would decrease the generation of A beta.[16] Despite being tried in recent clinical trials, ceratin BACE inhibitor were unable to reduces the course of AD.

CNP520, an long lasting, selective oral BACE 1 inhibitor was investigated in two phase 2 / phase 3 investigations.

N-Methyl-D-Aspartate Antagonist

For additional therapy to treat moderate to severe AD, Memantine is used.

This medication is a moderate affinity, Uncompetitive NMDAs antagonist that may shield neurons from excititoxicity.

In memantine trials, headaches, dizziness and disorientation were the most commonly reported side effects. An isolated group of patients may become agitated.[17]

Anti-Tau Therapy

An inhibitor of Tau aggregation is TRX 0237. To lessen Tau related neuronal damage, it lowers the amount of aggregated tau proteins.[18] October 2012 saw the start of the TRX 0237 experiment which examined the effectiveness of TRX0237in moderate advertising and conclude in May 2016. The two scales, the ADAS-Cog 11 and the ADCS-ADL 23, were the primary studies ometrics for such clinical outcomes.

Compared to amyloid pathology, tau pathology is more strongly linked to clinical and cognitive deterioration, and tau may build up in vulnerable areas sooner than amyloid.[19] Zagotenemab it is one type of immunotherapy. The purpose of this anti-tau antibody is to bind and neutralise tau clusters. The most common way that tau pathology is observed in the brain is as NFTs, which are present in both AD and other neurodegenerative illness.

Butyrylcholine Esterase

BuChE is an enzyme that catalyses the breakdown of acetylcholine into acetate and choline, further contributing to the maintenance of the neuronal communication process.

As a result, lowering BuChE activity is an effective treatment for AD symptoms. Currently, the medications used to treat the symptoms of AD work by inhibiting the hydrolysis of synaptic Ach.

Certain Drugs With Their Effects In AD

DRUGS	EFFECTS
CIs and Memantine	Potentially impact behavioural symptoms. These anti-dementia medications might not be as helpful as they once were when BPSD got worse, thus additional medications would have to be used.
Serotonin Reuptake Inhibitors (SSRIs) (Fluoxetine, Sertraline, Fluvoxamine, Paroxetine	When treating comorbid depression in AD dementia, SSRIs are widely regarded as among of the most effective antidepressant.
BDZPs	BDZPs sre used to calm anxiety and agitation. But they can also make elderly people even more agitated.
Anticonvulsant (Carvamazepine)	Lower BPSD in AD in to the certain extent.

Recent Developments in AD`s Early Detection

Early identification of AD is essential for implementing interventions and slowing its progression. Over the past decade, numerous machine learning and deep learning algorithm have been developed to enhance automated detection of the disease.[20] PET Imaging for assessing microglial activation, astrocyte reactivity, and synaptic degeneration remains a relatively new technique primarily utilized in research. Further studies are necessary to confirm its applicability in the clinical diagnosis of AD.[21]

Neuroimaging Technique

These days, imaging is frequently used to identify AD; early in its structural brain shrinkage particularly in areas like the hippocampus, can be shown on MRI and may be an early indicator of AD.

FDG PET

Identifies decreased glucose metabolism and brain cell activity in region crucial for memory and cognitive function.

PET Imaging

PET Imaging detects early Alzheimer`s changes before structural damage by binding to Tau or beta amyloid proteins. PET, a revolutionary imaging system, has great Reliability and precision in diagnosing AD study. Using multiple molecular imaging probes, distinct pathophysiological facts about AD can be illustrated.[22]

MRI

In order to make a prognosis, magnetic resonance imaging has become indispensable, with neural networks used to analyse various image datasets for disease categorisation and progression evaluation.[23] Various MRI techniques have demonstrated potential in detecting AD by measuring brain structures, particularly the hippocampus and related regions.[24] These techniques include diffusion-weighted imaging (DWI), arterial spin labelling (ASL), perfusion-weighted imaging (PWI), and functional MRI (FMRI).[25] Advanced image processing methods, such as principal component analysis (PCA), and artificial neural networks (ANN), have been utilized to enhance the accuracy of AD classification from MRI data. One study achieved nearly 92% accuracy in diagnosing AD using these advanced techniques.[26]

BIOMARKRS

In vitro diagnostic biomarkers are useful not only for the early clinical diagnosis of AD but also for pathophysiology research, disease progression prediction, and monitoring the effects of novel therapy candidates in clinical trials. The complex pathophysiology of AD, the limitations of individual biomarkers, and the limitations of clinical detection methods have hindered the development of efficient, cause-effective, and convenient diagnostic methods and standards, despite the fact that there are many biomarkers associated with AD diagnosis.[27]

Biosensors

Biosensors utilising nanotechnology are being created to enable the precise and sensitive detection of neurodegenerative biomarkers, including Tau proteins, which could facilitate early identification and predicting disease progression.[28]

Functional 1H Magnetic Resonance Spectroscopy (fMRS)

Functional 1H Magnetic Resonance Spectroscopy is a derivative of MRS Imaging.[29] Another promising technology, fMRS, has the potential to detect lactate as a new diagnostic and prognostic marker for AD.

Blood Based Biomarkers

Promising non-invasive methods for early AD prediction comprise blood based biomarkers blood tests. Identifying biomarkers is essential because traditional method like cerebrospinal fluid analysis, and neuro Imaging are often invasive, costly, or not readily available.[30] However, proteomic, techniques have demonstrated potential in discovering protein signatures in blood that could act as viable biomarkers for AD.[31] The identification of novel proteins like ALZAS and the related autoimmune responses in AD patients present a promising opportunity for developing blood-based markers.[32] A panel of plasma biomarkers has been identified that effectively differentiates individuals with AD from healthy controls, demonstrating high sensitivity and specificity across various cohorts.[33] However, despite these advancements, research for dependable blood biomarkers is ongoing, as some studies have yielded inconsistent results. The development of additional biomarkers may enhance diagnostic accuracy.[34]

NATURAL REMEDIES FOR TREATING AD

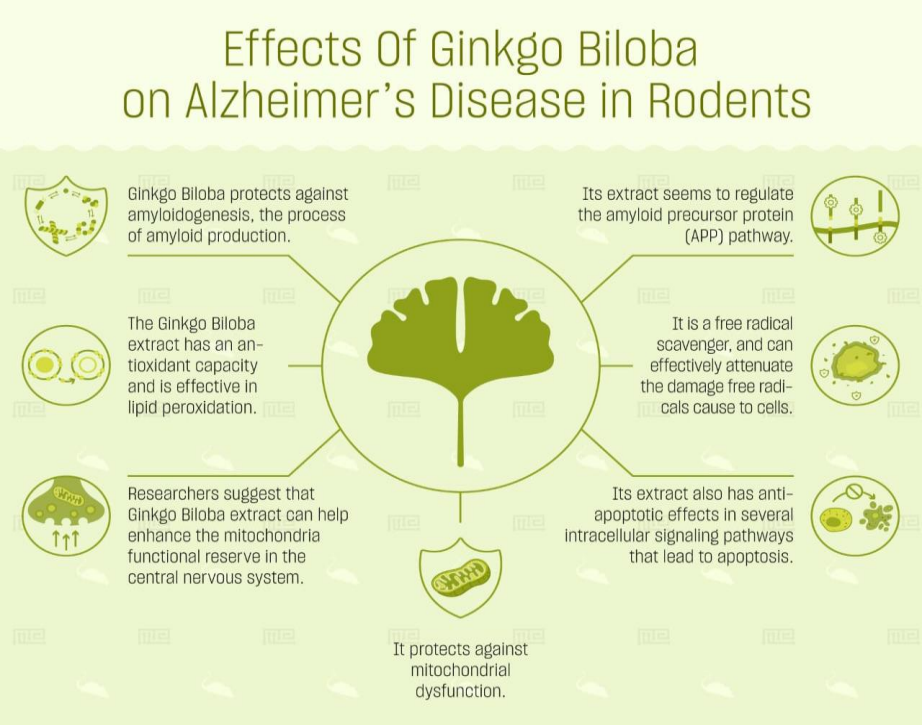
Natural and herbal remedies, often referred to as "alternative" or "complementary" medicines, have seen significant growth in popularity over the past two decades, becoming an integral part of healthcare and overall wellness globally. Their widespread availability over the counter, along with their generally favourable safety and tolerability, has contributed to this trend, allowing many individuals to benefit from these treatments.[35] The management AD symptoms and possible deceleration of the illness's course have been demonstrated using natural therapies. Herbal remedies with anti-inflammatory, antioxidant, and neuroprotective qualities include Withania somnifera, Bacopa monnieri, Ginkgo biloba, and Curcuma longa.[36] For example, ginkgo biloba extract plus transcranial magnetic stimulation markedly improved the neuropsychological, behavioral, and cognitive condition of patients with AD.[37] Certain substances made from plants could be able to lessen and perhaps stop the severe neurodegeneration seen in AD.[38] The best strategy might be an integrated one that combines lifestyle modifications and conventional therapies with herbal medications. Given that AD is complex, this could involve mind-body therapies, dietary changes, physical activity, and stress-reduction methods that support overall health.[39]

CURCUMIN

Turmeric comprising of rhizomatous plants, turmeric is a perennial found in tropical and subtropical countries and belongs to the zingiberaceae family. The biological effects of turmeric are mostly attributed to its three main chemical constituents: Curcumin, Demethoxycurcumin, and Bisdemethoxycurcumin.[40] AD a form of neurodegenerative condition marked by cognitive loss and dementia, may benefit from the use of curcumin, a polyhenolic substance obtained from turmeric plant. In light of its anti-inflammatory, antioxidant, anti-apoptotic, and Neuroprotective qualities, curcumin`s function in AD has been investigated. These abilities may help to reverse neurodegenerative damage and slow the onset of dementia. Curcumin is not the only curcuminoid having advantageous properties, despite the fact that it is frequently emphasized for its therapeutic potential. Demethoxycurcumin and bisdemethoxycurcumin, two additional components of the curcuminoid combination, are known to have important functions in the pharmacological profile of turmeric and may be responsible for some of its therapeutic efficacy.[41] Furthermore, curcumin's medicinal potential is further highlighted by its capacity to alter cellular pathways via epigenetic mechanisms.[42] The primary ingredients of the leaf's rhizome are alfa-, beta-, and arturmerone. Turmeric's health benefits include antimicrobial activity, antioxidant activity, gastrointestinal effects, anticancer effects, cardiovascular and antidiabetic effects, photoprotector activity, hepatoprotective and renoprotective effects, and suitability for the treatment of Alzheimer's disease and inflammatory and edematic disorders.[41] Dietary polyphenol curcumin has the capacity to modify a number of targets connected to the etiology of chronic illness. Therapeutic promise for neurodegenerative illnesses, such as AD and PD, has been demonstrated by curcumin.[43]

Ginkgo Biloba

The possible use of ginkgo biloba extract in the treatment of AD, a progressive neurodegenerative disease, has been investigated. The Ginkgo biloba tree's leaves are used to make an extract that contains terpenoids and flavonoid glycosides, which are thought to have antioxidant qualities and may guard against free radical damage to cells. Nonetheless, there is ongoing debate and research over the effectiveness of GBE, particularly when used in conjunction with traditional antidementia therapies.[44]According to certain research, GBE may help AD patients with their daily living activities and cognitive performance. The meta analysis revealed a moderate but noteworthy improvement in the AD assessment scale along with a tiny but significant effect of GBE on cognitive performance in AD. subtest of cognition.[45]



Withania Somnifera

Withania somnifera, widely recognised as Ashwagandha or Indian Ginseng, has demonstrated remarkable potential in the medical management of Alzheimer's disease by virtue of its neuroprotective, antioxidant, and memory-enhancing characteristics.[46] Ashwagandha's active components, especially withanolides, have showed multimodal positive benefits, including anti-inflammatory and rejuvenating qualities, which contribute to its neuroprotective powers in many neurological disorders, including AD.[47] According to research, phyto-compounds derived from Withania somnifera, including Pubesenolide, Acetyl Withaferin A, and Withanolide L, bind to particular amino acids in the AChE CAS site, PAS site, and mid-gorge area and show medium blood-brain barrier penetration. This binding raises the possibility of a therapeutic mechanism for ashwagandha in AD.[48] This binding raises the possibility of a therapeutic mechanism for ashwagandha in AD. To sum up, there is a great deal of promise for Withania somnifera as an AD treatment.[49] animal studies have shown that it can improve memory and learning. When paired with its antioxidant and neuroprotective qualities, it becomes a strong contender for additional study in the treatment of AD.[50]

Bacopa Monnieri

Through a number of different methods, the Indian herb bacopa monnieri, commonly referred to as brahmi, has demonstrated encouraging potential in the treatment of AD. Research has indicated that it can prevent Tau aggregation, lessen oxidative stress, and enhance cognitive performance in models of AD.[51] It has been noted that the ethanolic extract of Bacopa monnieri inhibits Tau aggregation in vitro and lowers the phospho-Tau load in cells stressed by formaldehyde. Moreover, it functions as an antioxidant, raising Nrf2 levels, lowering ROS, and decreasing caspase-3 activity in neural cells. Bacopa monnieri extract lessened the loss of cholinergic and neuronal densities in animal models and enhanced spatial memory.[52] Contrary to popular belief, a comprehensive analysis of clinical trials revealed very low certainty evidence, indicating that Bacopa monnieri and placebo or donepezil differ very little in their ability to treat AD or mild cognitive impairment. This is interesting because some research may demonstrate major enhancements in cognitive function and neuroprotection.[53]

Resveratrol

Natural polyphenolic chemical resveratrol is present in many plant sources and has demonstrated encouraging results in the medical management of AD. Studies reveal that resveratrol targets several pathogenic pathways implicated in AD to display neuroprotective effects.[54] It has been shown to reduce levels of the amyloid-beta peptides, both extracellular and intracellular, which are essential building blocks of the cerebral amyloid plaques that are indicative of AD.[55] AMP-activated protein kinase signaling is one of the main ways whereby resveratrol prevents the formation of amyloid plaques. This activation lessens the amount of Abeta that accumulates and deposits in the brain by encouraging autophagy and lysosomal breakdown.[56] Resveratrol is a good option for treating AD because of its diverse strategy for tackling AD pathogenesis, which includes its capacity to target Abeta buildup, Inflammation, oxidative stress, and tau protein phosphorylation.[57] Huperzine A, an alkaloid obtained from Huperzia serrata, or Chinese club moss, has demonstrated encouraging potential in the

management of AD. It enhances cognitive performance by raising acetylcholine levels in the brain since it is a strong, particular, and transient acetylcholinesterase (AChE) inhibitor. Clinical research have shown that AD patients' Mini-Mental State Examination scores improved by 1–5 points over the course of 8–12 weeks.[58] Huperzine A has also been shown to improve memory and learning in AD patients and animal models.[59] It's interesting to note that huperzine A's function in the management of AD goes beyond AChE inhibition. Numerous neuroprotective actions are demonstrated by it, such as controlling the metabolism of β-amyloid precursor protein, preventing Aβ-mediated oxidative stress and apoptosis, decreasing neuroinflammation, and modifying nerve growth factor production and signaling.[60]

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