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Review Article

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Review of Alzheimer's Disease: From a Pathophysiology, Diagnostics, and Indian Medicinal Herbs as a Pharmacological Approach

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ABSTRACT

The central nervous system, which is made up of the brain, spinal cord, and other major organs, is the principal organ of the human body. The most prevalent type of dementia, Alzheimer's disease, is a neurological ailment that affects the older population and progresses irreversibly. By 2030, there will be approximately 1 billion people on the planet, up from 420 million in 2000 and with an increase in the percentage of elderly people from 7% to 12%. The cause of AD is yet unknown, pathophysiology of AD, including low levels of the neurotransmitter Ach, aggregation of the amyloid beta peptide, accumulation of hyperphosphorylated tau protein, dyshomeostasis of biometals, oxidative stress, mitochondrial dysfunction, and neuroinflammation. The slow and steady decline in memory that affects language, personality, or cognitive control is the result of all these variables. There is no reliable diagnostic procedure; a brain autopsy is the only way to make a conclusive diagnosis of AD. Physicians can, however, accurately diagnose AD using medical history, cognitive testing, and neuroimaging methods. Due to the perceived effectiveness, safety, and affordability of herbal medications, their popularity is also rising. The experimental and clinical evidence for several Indian herbal remedies, including Centella asiatica, Bacopa monnieri, Curcuma longa, Clitoria ternatea, Withania somnifera, Celastrus paniculatus and Evolvulus alsinoides has been reviewed in the current study. The goal of the current study is to review the epidemiology, pathophysiology, signs, symptoms, diagnosis, and experimental and clinical evidences on herbal treatments of Alzheimer's disease with a focus on the research.

Keywords: Alzheimer's disease, Cholinergic hypothesis, Amyloid beta peptide, Tau protein, Oxidative Stress, Metal ion, Diagnosis, Symptomatology, Herbal medicine

INTRODUCTION

Human brain

The primary organ of the human body is the central nervous system, which includes the brain and spinal cord, and

other important organs. The majority of bodily processes, such as sensory perception, motor control, regulation of vital systems, language, cognition, emotion, etc., are controlled by the brain. Aging, microbial infections, autoimmunity, traumatic brain damage, toxic metabolites, and spinal cord injury is all factors that can lead to neuronal disorders or inflammation, a disease of the nervous system. The central nervous system's neurons can lose their form and function over time, even dying, a process known as neurodegeneration. The acute and chronic neurodegenerative diseases include multiple sclerosis, stroke, trauma, Huntington's disease, Alzheimer's disease, and Parkinson's disease. The term "neuro protection" refers to the techniques and the corresponding systems that can protect the Central Nervous System (CNS) against neuronal damage caused by both acute and chronic neuronal diseases [1].

Alzheimer's Disease (AD)

The most typical dementia subtype, Alzheimer's disease, is an illness of the nervous system that affects the older population and progresses irreversibly. Many intracellular and extracellular molecular alterations that lead to neuronal death are its hallmarks. The principal clinical aspects of AD, along with the loss of cholinergic neurons in the basal forebrain, include an elevation of beta Amyloid (A) protein through the presence of external Senile Plaques (SP), and the formation of cytoplasmic Neuro Fibrillary Tangles (NFTs), which are caused by tau protein hyperphosphorylation. The etiology and circumstances causing the disease's progression are still unknown, in addition to the cure [2].

History of AD

Dr. Alois Alzheimer, a German neurologist and psychiatrist, made the discovery of Alzheimer's disease in 1906. The disease was first identified in Auguste D., a 51 year old woman. Her demeanor and behavior had changed, and in 1901, someone brought her to see Dr. Alzheimer. She was said to have memory issues, speaking difficulties, and comprehension issues. Later, Dr. Alzheimer classified it as exhibiting an aggressive form of dementia that showed problems in memory, language, and conduct. Dr. Alzheimer recorded a wide range of unusual symptoms, such as speech problems, agitation, and confusion. Dr. Alzheimer conducted an autopsy after she passed away, and he discovered atrophied brain cells, fatty deposits in blood vessels, and a severe shrinking of the cerebral cortex. He identified senile plaques and neurofibrillary tangles, which are now recognised as symptoms of Alzheimer no's Disease (AD). Alzheimer's disease was first mentioned in medical literature in 1907, and it was given that name in 1910 [3].

Prevalence

By 2030, there will be approximately 1 billion people on the planet, up from 420 million in 2000 and with an increase in the percentage of elderly people from 7% to 12%. The proportion of the population who are older will rise most dramatically in developing nations. As a result, the proportion of the world's ageing population that comes from developing countries will rise from 59% to 71%. It is projected that Alzheimer's Disease (AD) will present enormous problems to public health and senior care systems throughout the world because AD incidence is significantly correlated with advancing age. In the industrialized world, 50%-60% of all dementia cases are caused by Alzheimer's disease. Dementia prevalence rises with age, from 1% in those 60 to 64 years old to between 24 and 33% in those 85 years or older (globally). As life expectancy increases, the number of persons with dementia is anticipated to double every 20 years, reaching 81.1 million in 2040 from the estimated 24.3 million in 2001. Western Europe, the USA, and China are the most affected nations and areas in the world. 55.7% of the world's impacted population will reside in these nations and regions by 2040.

Alterations to the AD brain's structure

- The cortex, entorhinal cortex, and hippocampus are the three primary regions involved in remembering. The primary sign of AD is memory loss, particularly an inability to recall recent events (short term memory loss).
- The entorhinal cortex, which connects the hippocampus (liable for the creation of the two main types of memory), and cerebral cortex, where preclinical AD first manifests itself.

- As the brain shrinks, the cerebrospinal fluid covers the empty space that the brain tissue once occupied.
- Mild to severe Alzheimer's is characterized by considerable cognitive impairment, ongoing cerebral cortical atrophy, and a variety of common symptoms, including short term memory loss, trouble remembering familiar faces and locations, changes in mood and personality.
- The regions of the brain that regulate speech, reasoning, conscious thoughts, and sensory processing exhibit substantial cortical atrophy in the severe stage and late stage of Alzheimer's disease.

The severity of symptoms, such as long-term memory impairment, where people can distinguish between familiar and unfamiliar faces but struggle to recall the name of a spouse or career, can be seen due to the higher level of atrophy. People also lose their ability to react to their surroundings [4].

LITERATURE REVIEW

Factors and etiopathogenesis

Cause of Alzheimer's disease is yet unknown. Numerous elements have been proposed to play significant roles in the pathogenesis of AD, including small amounts of a neuropeptide termed Ach, the amyloid beta molecule aggregating together, amount of tau protein that has been hyperphosphorylated, abnormal bio metal homeostasis, reactive damage, malfunction in the mitochondria, additionally to adult neurogenesis. Many theories have been proposed to explain the pathophysiology of AD based on these significant characteristics [5].

Cholinergic theory

The cholinergic system has a role in physiological functions like thought, memory, stress response, attentiveness, sleep, and tactile perception. Many facets of cerebral and memory functions, as well as neurobehavioral processes, can be affected by deficits in neurotransmitter acetylcholine and conduction in the central nervous system. Acetyl-CoA and choline are metabolized into ACh through choline acetyltransferase. Then enters the synapse and binds to postsynaptic nicotinic and muscarinic receptors. The protein Acetylcholinesterase (AChE) quickly hydrolyzes the ACh present at the synapses to produce the presynaptic receptors then reprocess acetic acid with choline [6].

The central nervous system contains two different kinds of Cholinesterase Enzymes (ChEs), acetylcholinesterase and butyrylcholinesterase. Through is hydrolyzed by the neurotransmitter acetylcholine, both of these enzymes, which are members of the carboxylesterase family of enzymes, contribute significantly to cholinergic transmission. AchE and Butyrylcholinesterase are produced by several genomes, but their active sites share more than 65% of similarities, making them highly homologous. AchE contains two primary subsites for bonding: Catalytic Active Site (CAS) and Peripheral Anionic Site (PAS). Cholinergic neurotransmission is actively maintained by the CAS of the enzyme. The production of -amyloid fibrils, which are linked to plaque deposition, is facilitated by PAS. AchE blockers that prevent both CAS and PAS. The production of -amyloid fibrils, which are linked to plaque deposition, is facilitated by PAS. AchE inhibitors that simultaneously block CAS and PAS can improve intellectual symptoms by raising Ach concentrations in Patients with Alzheimer's disease. They also have the ability to treat the disease by preventing the growth of amyloid plaques. In healthy brains, AchE is much more effective than BuChE and also can solubilize approximately 80% of total of Ach. Recent studies have demonstrated that as the disease advances, BuChE capability raises by 40%-90% and AchE capability falls in the hippocampal and frontal cortical areas of the brain. BuChE has a variety of functions in both neural and non-neural processes. According to clinical evidence, extracellular amyloid beta protein deposition and tau protein aggregates are two significant AD hallmarks that are correlated with high cortical BuChE levels. This highlights the crucial significance played by cholinesterase as well as the requirement to create unique there are medications that could affect both of these ChEs. Among the four FDA-Acetylcholinesterase Inhibitors (AChEIs), which are legal anti-AD medications, act by stopping the AchE in its tracks [7].

Neuritic tangles of tau protein that has been hyperphosphorylated, also known as neurofibrillary tangles, and extracellular Amyloid plaques, also known as senile plaques, are two prominent clinical characteristics observed inside the brains of Alzheimer's patients. Both deposits were first described over a century ago, but University of California pathologist George Glenner, isolated Amyloid for the first time in 1984. Glenner also stated that the protein known as precursor protein for amyloid (APP) is the source of Amyloid. The proteases can cleave the integral membrane glycoprotein APP in two different ways, namely the non-amyloidogenic pathway and the amyloidogenic pathway. Most of the time, the alpha and Gama secretases in the alpha path cleave APP sequentially. The APP is first broken down by alpha secretase into soluble extracellular APP fragments (sAPP-) and C83 fragments, which are then broken down further by Gama secretase into p3 fragments. The p3 fragment's precise physiological function is still not entirely understood. As amyloid beta is not released by the alpha mechanism, it is recognized as such non-amyloidogenic pathway. The beta secretase initially generates the C-terminal fragment (C99) and a soluble extracellular fragment (sAPP-) of APP in the beta pathway (BACE-1).The intracellular C-terminal domain with 38-43 amino acid peptides known as amyloid beta are produced from the C99 segment by additional cleavage by the Gama secretase (AICD) [8].

The two primary amyloid beta peptide isoforms produced by this amyloidogenic pathway are amyloid beta 1-40 and amyloid beta 1-42. Whereas amyloid beta 1-42 is more fibrillogenic in nature, amyloid beta 1-40 is the main result of the proteolytic cleavage. The misfolding and aggregation of these amyloid beta monomers results in the formation of extracellular plaques and amyloid fibrils. These aggregates start the pathogenic cascade, which ultimately leads to dementia and neuronal death. The inflammatory mediators TNF alpha and IL-6 are constantly activated by the amyloid beta plaques produced by amyloid beta 1-42 and are neurotoxic. Moreover, amyloid beta 1-42 itself has the potential to produce Reactive Oxygen Species (ROS), which have a direct impact on neurocytes' usual physiological processes [9].

Thus, the hypothesis states that there is a flaw in the way that amyloid beta gets cleared from the brain, in its creation, or maybe in both, and that this flaw ultimately causes AD.

Tau protein hypothesis

Tau protein, a completely soluble Microtubule Associated Protein (MAP), regulates the integrity and motility of Microtubules (MTs), axonal transportation, and neuritis growth in the normal phosphorylation state. The primary processes for regulating the tau protein include Post-Translational Modifications (PTMs) involving truncation, phosphatase, acetylation, glycation, and methylation. Tau's most prevalent PTM is phosphorylation.

Tau's functions and isoform expression are altered by overexpression of GSK-3 beta, which causes hyperphosphorylation. Because tau is three times more phosphorylated in the AD brain than in the healthy brain, the MTs are disrupted and filaments develop. Hyperphosphorylated tau degrades microtubules and forms coupled helical filament tangles with normal tau, ubiquitin, MAP-1, and MAP-2 (PHFs). These unstable structures block axonal transports, conflict with cytoplasmic processes, and lead to cell death [10].

Oxidative stress

According to research, oxidative damage develops earlier any other symptoms of Alzheimer. Under normal conditions, Reactive Oxygen Species (ROS) develop, and their levels are regulated by an intricate equilibrium among the rates at which they generate and eliminated by antioxidants, associated enzymes like superoxide dismutase as well as catalase, and some antioxidant substances like ascorbic acid and glutathione, and vitamin E. As such, the redox equilibrium of the cell changes in favour of oxidative variation and higher ROS generation. Additionally, it might lead to a decreased antioxidant mechanism. Additionally, it has been noted that, through Fenton like reactions, the redox active metal ions Cu (I/II) and Fe (II/III) form reactive oxygen species, or ROS, when associated with amyloid beta.

ROS can cause the breakdown of biomolecules such proteins, lipids, and nucleic acids. This could cause tissue damage as a result of apoptosis and necrosis in cells.

Metal ion hypothesis

Enzymes and many intracellular signaling proteins depend on metals to function properly. The concentrations of these metals are tightly controlled in a healthy person. Age related decline or a degenerative neurological state can interfere with these equilibrium processes, which can lead to the diversion of metal dependent enzyme functioning, mitochondrial malfunction, and the creation of ROS, all of which are well-known causes of Alzheimer. Coordination of the Cu^{2+} ion to the amyloid beta precursor protein (APP) at its amino terminus, which results in the export of neuronal Cu^{2+}, is what causes the metal mediated amyloid beta aggregation. Reduced cellular Cu^{2+} levels cause APP mRNA to be expressed, which results in an excess of APP being produced. Then, beta and gama secretase sequentially cleave it to create amyloid beta 40-42. The beta form of amyloid binds to copper and zinc immediately, but not with iron or additional metal ions. In order to interact with superoxide dismutase-1, Secretase have Cu^{2+} binding point in its cytoplasmic C-terminus. The activity of secretase has also been shown to be inhibited by low Zn^{2+} concentrations. The Cu/Zn metals and amyloid beta peptides combine to form complexes that, in various ways, cause neuronal cell toxicity. The metal Aβ complex increases Aβ fibrilization, which results in formation of senile plaques, increases Aβ oligomerization, which impairs synaptic functions, and produces ROS, which results in oxidative stress. The tau protein also contributes to the alterations associated to metal seen in Alzheimer's. Tau protein undergoes a conformational change as a result of its Cu^{2+} binding, which is pH and stoichiometric dependent. Cu also affects the cyclin-dependent kinase (CDK)5/p25 complex and GSK-3β, which is essential for development of PHFs and hyperphosphorylated tau protein. This causes the tau protein to aggregate, which results in the development of neurofibrillary tangles, which directly cause cell death. In addition to the cholinergic, Aβ, tau, oxidative stress, and metal hypotheses, other factors, such as excitability, apoptosis, neurological inflammation, etc., are reported to play crucial roles in the complex pathology of AD [11].

The elements mentioned earlier work together to create a sophisticated cell network. The aetiology of AD is so complicated that it is classified as a multifactorial or multifaceted disease.

Symptomatology

When the symptoms progress to a severe level and there is a long, steady decline in speech, character, and mental functioning are all impacted by mental capacity, Alzheimer's is frequently a primary cause of dementia in senior individuals. Due to issues including dementia, reliance, and disability, AD has significant negative medical, economic, and social effects. 3 stages of Alzheimer's can be distinguished: early stage, in which memory loss is discrete, limbic system cholinergic neurons are impaired, and the hippocampus experiences a 25% volume reduction. According to Seidl, the middle phase, which is characterized by difficulties in distinguishing between different persons and connecting with them, can continue anywhere between two and 10 years. Neuronal damage is linked to it because they are in charge of both short and long term memory. Then, some neurons, including those in the ventral telencephalon, which is usually related to long term memory and knowledge storage, experience a decline in acetylcholine levels. The last phase occurs when the patient is completely incapacitated, totally dependent, unable to perform daily tasks. Also, because the condition interferes with the limbic system, information retrieval is impossible. Degeneration of cholinergic neurons throughout the cerebral cortex is linked to the loss of long-term memories. The individual forgets his past, his friends, and his family. The patient's death marks the end of this period, which typically lasts one to three years. According to Petronilho, this syndrome is primarily brought on by a reduction in Acetylcholine (ACh) levels in the synapse mechanism because this chemical messenger is directly linked to mental, motor, and behavioral activities. There are common behavioral changes in earlier stages of Alzheimer's, such as irritation and disinterest in the family activities and amusement. Individuals exhibit changes in personality, a lack of concentration, confusion, wrath, and depression. Agitation is associated with volume reduction in several different parts of the brain, including the frontal lobe, Anterior Cingulate Cortex (ACC), Posterior Cingulate Cortex (PCC), insula, amygdala, and hippocampal. Agitation in AD can be explained by two separate mechanisms: executive function deficiencies and deficits in

emotional regulation (emotional reactions) (problem solving). It's crucial to note that each patient's course of treatment may differ from another. A lack of interest, agitation, nervousness, sorrow, illusions, confusion, abnormal behavior, irritation, insomnia, problems with eating, excitement, or disinterest are symptoms that about 90% of patients experience over time. Many people who experience Alzheimer's at some point in the development of dementia also experience mood problems. Between 40 and 50% of patients experience depressive symptoms, while 10 to 20% of patients experience depressive disorders. Although major depressive disorder has received substantial research as a potential neurocircuitry issue and depressed symptoms are highly common in AD, there are currently very few neuroimaging studies that have been published that focus on depression in AD. Patients with AD experience a nagging cognitive loss that worsens over time and becomes incapacitating in later stages of the illness. These terrible symptoms severely reduce the patients' quality of life, resulting in complete dependence, institutionalization, and unavoidable death [12].

AD diagnostic exams and tests

The treatment of AD at its earliest stages slows the disease's progression and keeps the patient out of the hospital as long as possible. For these reasons, an early diagnosis of AD is crucial. The only way to positively diagnose AD is through a brain autopsy; there is no reliable diagnostic technique. Medical professionals may, however, diagnose AD with 90% accuracy using physical, behavioral, and mental testing.

Medical history

The patient's medical history is gathered as the first stage in making a diagnosis. The medical professional will find out whatever signs and symptoms appear, when they first appeared, and the evolution of each throughout age. The medical record of relatives is crucial [13].

Testing for neuropsychology

In addition to assessing cognitive functioning, the doctor will look for behavioural and behavioural changes and compare the patient's performance to that of people their own age. Only by comparison with a typical control group that is matched for age, sex, and local educational attainment can performance be assessed. The Mini-Mental State Test for mental examination, the blessed dementia scale for neurological signs and interaction with others, the hamilton depression scale for the extent of anxiety, the current state assessment for mood disorders, hallucinations, and illusions, and the Hachinski Scale for predicting the possibility of multiple strokes are among the other tests that are also performed.

Testing in a laboratory

Hypothyroidism, which has been linked to sadness, irritability, and slowed thought processes, may be discovered by thyroid function tests. Although hematological defects are not always present, vitamin B12 deficiency can nonetheless result in myelopathy, with or without neuropathy, and mental symptoms. Only individuals who appear to be at particular risk for this etiology should have tests for HIV or a sexually transmitted disease, which can also cause mental symptoms in addition to dementia.

Brain imaging methods

PET

Positron Emission Tomography (PET) has been used to investigate the metabolic uptake of fluorine 18 (18F) labeled Fluorodeoxyglucose (FDG) and blood flow among individuals with memory loss. Positron Emission Tomography (PET) creates a 3-D, colored representation of the human anatomy using radioactive impulses. Introduced into the human body, 18F-labeled Fluorodeoxyglucose (FDG) flows through systems that need that specific molecule for energy. The molecule undergoes positron emission during metabolism. PET (Positron Emission Tomography) scanning, which transforms the input into an image, detects the energy from these positrons. By displaying how well

the radiotracer is broken down, this graphic depicts how the patient's body functions. The spectrum of colors and brightness's created by the amount of emitted positron energy reflects the amount of activity in the mind. The nervous system's metabolic processes, blood flow, and neuronal connections can all be detected by a Positron Emission Tomography (PET) scan. Moreover, another radiolabeled substance known as Pittsburg compound B (11C-PIB), which is also called as 6-hydroxy-2-(4-N-(11C) methylaminophenyl-1, 3-benzothiazole, is being used to bond with cerebrovascular amyloid plaques [14].

Tomography using a Computer (CT)

The method can quantify cerebral weight, cardiac terms of size, anatomical density levels, and cerebrospinal proportion as well as characterize gyri and sulci. The ventricular system volume and third ventricle width are expanded, the gyri are narrowed, and the sulci are widened in Alzheimer's disease; nevertheless, these common trends might not be very useful as diagnostic standards in particular patients.

Imaging using Magnetic Resonance (NMR)

Investigations into disorders that demyelinating have been successful using MRI, or proton Nuclear Magnetic Resonance (NMR) images, which reveal the contrast between the brain's gray and white matter. In both human and double transgenic Dementia animals, the 125I-labeled A40 (125I-A40) and gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) have excellent binding affinity to the amyloid deposits, and they showed T2 contrasting that matched the signal on T1 spin echo [15].

Computerized Single-Photon Emission Tomography (SPECT)

A popular method for determining brain perfusion with a rotating gamma camera is Brain uptake of a technetium 99 m based dissolved in lipid radioisotope like ethyl cysteinate dimer or hexamethylpropylene amine oxime provides the basis for brain SPECT imaging.

Genetic identifiers

There are several markers that can be used to undertake genetic testing. Defects in the PS-1, PS-2, and a precursor protein for amyloid genes, which are found on the chromosome 1, 14, and 21, are associated with early development of the hereditary and very uncommon form of AD. The chromosome 19 Apo lipoprotein APOE 4 allele, which amongst the other two variants is linked to a high risk of Alzheimer's disease, while the 2 allele may be a preventive measure, is the only useful marker for the more common late onset (sporadic type) dementia. It's believed that the 3 allele doesn't indicate any changed risk. The 4 allele is missing in roughly 30%-40% of AD patients and is present in about 30%-40% of healthy individuals. In order to identify oxidative stress, a pathophysiologic imbalance between oxidants and antioxidants in favor of the former, with potential damage, has been seen in the blood, Cerebro Spinal Fluid (CSF), and brain of neurologic patients with probable AD. These biomarkers include the super oxide dismutase enzyme, the antioxidant system, oxidation of proteins, Nucleotide oxidation, and peroxidation of lipids [16].

RESULTS AND DISCUSSION

Experimental and clinical evidence on herbal treatments for Alzheimer's disease

Since ancient times, neurological problems have been treated using herbal medications and complementary therapies. Many herbal remedies have been utilized throughout the world for neurodegeneration disorders. For instance, *Salvia officinalis* (common sage) and *Salvia lavandulaefolia* (Spanish sage) are being utilized since the time of the 16th century across Europe to enhance memory; additionally, they are backed through medical research. Water hyssop, or *Bacopa monniera*, has been utilized in Indian Ayurvedic medicine. As a timeless tradition, a system exists to enhance

mental and memory abilities. *Asiatic centella* (Asiatic pennywort), a different Ayurvedic treatment, is administered with milk to enhance recall. Ayurveda also uses the rejuvenating tonic *Withania somnifera* root to improve recall. Ayurveda perceived efficacy, safety and cost, herbal medications are growing in popularity. In fact, the use of herbal medications for diseases connected to memory has only recently begun to get support and evidence from scientific investigations. *Withania somnifera, Centella asiatica, Celastrus paniculatus*, and *Bacopa monnieri* are a few CNS active Indian herbal remedies that, when administered as a preventative measure, have been proven to improve cognition in animal models of AD. A randomized, double blind exploratory research found that donepezil and a *Gingko biloba* extract both had equivalent efficacy in treating AD patients with co-occurring neuropsychiatric issues. According to reports, the combination was more effective and safe than donepezil monotherapy [17].

Centella asiatica

Centella asiatica, also known as mandukparni or jalbrahmi, is a tiny, annual plant that is native to India and is a member of the Apiceae family. It has tiny green leaves in the shape of a fan, white, produces small, oval in shape, pale purple to pink or white blooms. In Ayurveda medical system, mandukparni leaves has employed to improve brain. Traditional Chinese medicine and the African medical system have both mentioned its use. It is administered with milk to improve memory and is employed to delay age and avoid memory issues.

Madecassoside and madasiatic acid, asiatic acid, and asiaticosides make up the majority of *C. asiatica's* chemical makeup. The chemical substances Centelloside, isothankuniside, and brahmoside as well as brahminoside were also isolated from *C. asiatica*.

Pharmacological technologies: The medicinal uses of *C. asiatica* are widely recognized. Cardio protective, antipsoriatic, antiulcer, hepatoprotective, anti-inflammatory, antioxidant, toxic to cells, cancer prevention, anti-apoptotic, and wound heal, antibacterial, insecticidal and antiviral, antifungal, neuroprotective effects, sedative, antidepressants, anticonvulsant and nootropic [18].

Preclinical research has shown that aqueous extract of *Centella asiatica* administered orally for 14 days 100, 200, and 300 mg/kg dosages improved cognitive skills in normal rats in a dose dependent manner. Significant cognitive impairment caused by streptozotocin was significantly reversed by 21 days of exposure using the extract. The reduction in malondialdehyde and rise in the level of superoxide dismutase, the enzyme catalase and levels of glutathione were used by the authors as evidence of *C. asiatica's* protective effects. Based on the research conducted by Rao and colleagues, rats received a 15-day medication with *C. asiatica* at a dose of 200 mg/kg from the 15th day to day 30 following delivery, which increased learning and memory and lasted for at least 6 months after delivery. They also noticed a rise in hippocampal CA3 neurons' dendritic arborization, which may contribute to the enhancement of brain activity. Another investigation found that giving older participants a daily 500 mg dosage of dried *Centella asiatica* for six months enhanced their cognitive outcomes. Dhanasekaran et al., reported that PSAPP transgenic mice expressing "Swedish" amyloid precursor protein and M146L presenilin 1 mutations, which cause spontaneous amyloid beta plaque formation, had significantly lower levels of amyloid beta 1-40 and 1-42 after an 8-month treatment with 2.5 mg/kg of aqueous extract of *Centella asiatica*.

On the long term 5.0 mg/kg dosage treatment, there was a decrease in the plaques of fibrillar amyloid stained with Congo red. Rat learning and memory were improved by *C. asiatica* aqueous leaf extract, this also altered the rat brain's *in vivo* dopamine, 5-HT, and noradrenaline systems. Additionally, the leaf extract showed sedative, depressant, and cholinomimetic properties. Pointing to its appropriateness for treating depression, anxiety, and cognitive dysfunction linked to AD. The leaf extracts increased neuritis elongation in human SH-SY-5Y cells, activated the neuronal cell dendrites in the rat skull and sped up axonal regeneration in rats. Memory formation involves CREB, a phosphorylated version of the cyclic AMP response element binding characteristic. Both AD patients and experimental AD models have been found to have lower levels of phosphorylated CREB. The aqueous extract of *C. asiatica* leaves benefited both neuroblastoma cells, which produce inducible Aß, and cortical primary cells, which were chronically exposed to exogenous Aß *in-vitro*. The extract promoted axonal regeneration and neuronal dendritic arborization in rats. Triterpenoids, which include scentellin, asiaticin, mecadessic acid, asiaticoside, and centellicin,

are the main active ingredients in the ethanolic extract of *Centella asiatica* (*C. asiatica*). By enhancing Ach production, the use of asiatic acid and its analogs has demonstrated a potential improvement in cognition. It has a patent from Hoechst Aktiengesellschaft for both dementia treatment and cognitive enhancement. The particular ingredient that gives the herb its capacity to improve cognition is still unknown. However, research suggests that triterpene saponins in the leaf may improve memory capacity by influencing neurotransmitters in the brain [19].

Evidence from science: Healthy volunteers received 250–750 mg of *C. asiatica* extract once daily for two months in a double blind study, randomized, controlled trial using a placebo. The high dose increased self-rated mood and worked memory. Thus, *C. asiatica's* potential to improve memory is supported by clinical and experimental studies. Its efficacy in treating AD, however, has to be further studied.

Bacopa monnieri

A little, creeping annual herb with many branches, tiny oval leaves, and bright purple or white blooms, *Bacopa monnieri* (*B. monniera*) is a member of the Scrophulariaceae family. It is known for its energizing, Medhya rasayana, and nootropic properties in India, where it is frequently referred to as Brahmi. It also boosts memory and intelligence (Medhya). Indian traditional system experts of medicine have been using bacopa for thousands of years to cure a variety of illnesses.

Triterpenoid saponins, also known as bacosides, are *B. monniera's* primary chemical constituents. It has also been reported that this plant contains the alkaloids brahmine, nicotine, and herpestine. Bacopasides I–XII, new saponins, have also been discovered [20].

Pharmacological effects: This medicinal plant has a number of biological effects, including those listed below: adaptogenic, antineoplastic, anti-oxidants, antiseptic, anti-Helicobacter pylori, soothing, anticonvulsant, antidepressant, anxiolytic, analgesic, broncho dilatory, hepatoprotective, and immunostimulatory.

Preclinical research has shown that *B. monniera* extract contains a number of advantageous bioactive substances, including alkaloids, flavonoids, glycosides, triterpenoids, saponins, and alcohols. The alcoholic extract of *B. monniera* improved the Sidman continuous avoidance responses, the active conditioned avoidance test, and the foot shock motivated bright discrimination test in rats. Its facilitative impact on learning and memory may be due to two saponins known as bacosides A and B together. In addition to its demonstrated antioxidant and anti-inflammatory properties, bacosides have been shown to lessen the dementia imposed on by scopolamine, electroconvulsive shock, and stress brought on by immobilization. Their ability to improve memory may possibly be attributed to the fact that they increased activity of the protein kinases. As well as the amount of the hippocampal protein. Middle aged and elderly rats were fed bacosides (200 mg/kg) for three months, and they showed protection against age related changes in the neurotransmission system, behavioral paradigms, loss of hippocampal neurons, and indications of oxidative stress. It has also been reported that the serotonergic receptor and the the CREB pathway and microRNA 124 play a role in standardized *B. monniera* extract (BESEBCDRI-08 ability)'s to improve memory. The impact of the alcoholic extract of *Bacopa* at dosages of 20, 40, and 80 mg/kg on cognitive functioning and neurodegeneration has been evaluated in the animal model of AD produced by bilateral intracerebroventricular infusion of AF64A. Morris water maze test, they discovered that *Bacopa* increased escape latency and stopped the loss of cholinergic neuron density. Moreover, rats exposed to aluminum chloride were protected from neurotoxicity for 5 weeks by receiving 40 mg/kg of *bacopa* extract each day orally. Standardized *Bacopa* extract reduced the mental deficits resulting from Intracerebroventricular (ICV) injection of cholchicine and ibotenic acid through the nucleus basalis magnocellularis by changing Ach level depletion, decreased Choline Acetyl Transferees (ChAT) activity, and decreased muscarinic the cholinergic binding to receptors in the frontal lobe and the Hippocampus. According to Holcomb et al., giving PSAPP mice an 40 and 160 mg/kg of an ethanol based extract of bacopa plants over 2 and 8 months. Decreased the levels of A 1-40 and 1-42 in their cortex. By exerting an antioxidant impact and restoring In the colchicine mouse model of memory loss, the activities of Na+K+ATPase with Ache, bacopa, as a dosage of 50 mg per kg, revealed the protective for neurons effect. It has also been suggested that *Bacopa's* ability to enhance memory may be due to its ability to stimulate neuronal dendritic development.

Clinical evidence: 300 milligrams of *B. monniera* powder taken once, which contains 55% of the total amount of bacosides A and B didn't significantly alter cognitive function at 2 hours in a double blind, placebo controlled trial involving 38 healthy volunteers (ages 18–60). However, a randomised, placebo controlled, a double blind trial found that the giving healthy adults aged 40 to 65 the herb *Bacopa* for six weeks (For people under 90 kilograms, the dosage is 300 milligrams, and for those over 90 kg, it is 450 milligrams, which is comparable to six grams and 9 grams of dried out roots, accordingly) significantly improved their ability to remember new information. Despite the fact that there was no variation in the rate of information collection. With the placebo controlled, a double blind trial involving 46 participants in good health (aged 18 to 60), Stough et al., found that taking Bacopa (which contains 55% total bacosides) at an amount of 300 milligrams each day for 12 weeks. Significantly improved verbal learning, memory consolidation, and the speed of early information processing. The gradual beginning of action could linked to *Bacopa's* antioxidant capabilities either is impact on systems acetylcholine because the effects were not noticed until five weeks into treatment. Additional 54 senior people, randomly allocated, double blind in placebo controlled trial (mean age 73.5 years) who did not exhibit any clinical symptoms of dementia found that a *Bacopa* treatment similar to this one improved a comparison with the untreated group on a stroop test, an extended words memory test, and an auditory language acquisition testing. Standardized herbal extract of *Bacopa* with the dose 125 mili gram was administered twice each day for a period of 12 weeks in a double blind, placebo controlled study to subjects older than 55 who had memory impairment. Logic memory, mental control, and paired related learning were significantly improved. *Bacopa* extract, given daily for 12 weeks at a dose of 300 mg/kg, also improved memory acquisition and retention in the population of healthy older Australians. When given daily for a period of three months, every day to youngsters (age 6 to 8), 350 mg of *Bacopa* powder, *Bacopa* syrup produced a substantial improvement compared to the placebo. However there was no blinding in this study. An attention deficit disorder with hyperactivity diagnosis was present in 36 kids, Negi et al., conducted a double blind, randomized, placebo controlled experiment (age range 8.3 to 9.3 years). 19 kids was given 50 mg of herb extract of *Bacopa* twice daily for 12 weeks. The extract was standardized to contain 20% bacosides. Children receiving *Bacopa* showed a significant improvement in cognitive function compared to placebo at 12 weeks, which was supported by improvements in tasks requiring repetition of sentences, logical memory, and learning with paired associates. This improvement persisted the 16^{th} week (after 4 weeks of placebo administration).

Curcuma longa

Description of the plant: The herb turmeric (*C. longa*) is perennial from Zingiberaceae family. Southeast and South Asia are where it is cultivated for commercial use. Turmeric, also known as curcumin, is a common food flavoring and coloring ingredient in India. It is produced from the plant's rhizome. The Ayurveda medical system has been using various plant based treatments for ages.

The primary chemical components of turmeric are curcuminoids, which are mostly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcumin. Curlone, zingiberene, alpha- and beta-tumerone, artumerone, alpha- and gamma atlantone, and curcumol are additional chemical substances found in this plant.

Curcuminoids have a wide range of pharmacological effects, including analgesic, anti-inflammatory, anti-cancer, hypocholesterolemic, antithrombotic, anti-hepatotoxic, anti-diarrheal, carminative, diuretic, anti-rheumatic, hypotensive, larvicidal, insecticidal, antivenomous, and anti-tyrosinase effects, according to previous studies.

Pre-clinical studies: It is also among the plants that have been thoroughly examined for a variety of disorders in preclinical scenarios 133. In numerous experimental studies, it has been claimed to have a wide range antioxidant, anti-inflammatory, and cholesterol lowering properties all of which are significant pathophysiological processes in the development of AD among other biological and pharmaceutical effects.

Curcumin's inability to dissolve in water is a significant drawback, but it has been partially solved by the creation of curcumin nanoparticles coated with biodegradable Poly (Lactic-co-Glycolic Acid, or PLGA). These nanoparticles were reported to have antioxidative activity and the ability to inhibit amyloid aggregation without having any harmful effects. Curcumin Nano liposomes have been discovered to suppress the synthesis of oligomeric fibrils an *in vitro* due

to their strong affinity for A1-42 fibrils.

Curcumin containing poly (butyl) cyanoacrylate nanoparticles delivered by apolipoprotein E3 (ApoE3-C-PBCA) offered photo stability, improved cellular absorption, and increased curcumin's effectiveness prevent the cytotoxicity caused by Aβ. Additionally, turmeric demonstrated that it protects over Aβ neurodegeneration by accelerating the transformation of Aβ into fibrils and lowering the production of Aβ by reducing the expression of Presenilin 1 (PS1) and GSK- 3β.

Aβ plaque can form in both *in vivo* and *in vitro* conditions have been demonstrated to be reduced by curcumin. In cerebral cortex of the transgenic APPSw mouse (Tg2576), curcumin administration within a six month period dramatically reduced increased amount of oxidized amino acids and inflammatory interleukin-1141. Curcumin was also found to reduce plaque development and levels of both soluble and insoluble Aβ in the same study. In the sporadic AD model in mice, Turmeric (10, 20 and 50 mg/kg, p.o. for a period of 21 days) pretreated reduced memory deterioration. Moreover, curcumin supplementation enhanced synaptophysin loss, oxidative stress, and spatial memory by lowering Aβ deposits. Significant cognitive improvement was observed at low (160 ppm) and high (1000 ppm) doses of curcumin after administration for six months in the twin transgenic AD mouse (APP/PS1). Curcumin may defend against beta amyloid assault and consequent Cell death brought on by the effects of oxidative stress *in vivo*. At low doses, curcumin can prevent Aβ from aggregating or encourage it to do so (IC50=0.81-1) sence of curcumin, monomeric Aβ generated fewer aggregates, whereas increasing doses of curcumin encouraged disassembly of preformed A aggregates. Curcumin shares structural similarities with Congo red, which, when bound to plaques, can prevent the development of oligomers and reveal secondary structure in fibrillar and oligomeric Aβ. A low dose of curcumin lowered the levels of soluble c, insoluble amyloid, and plaque burden by around 40%. In the APPswe/PS1dE9 mouse model of AD, curcumin therapy for 7 days reduced the load of plaques and restored structural alterations in dystrophic dendrites.

AD is linked to insulin or the Insulin like Growth Factor-1 (IGF-1) signaling dysfunction. It causes mitochondrial malfunction, oxidative stress, necrosis, hyperphosphorylation of the tau protein, and cognitive impairment. In the sporadic Alzheimer model using Intracerebroventricular (ICV)-Streptozotocin (STZ), curcumin markedly increased cognitive performance *via* raising the IGF-1 level. Moreover, it reduced plaque load and oxidative damage, decreased levels of insoluble amyloid, glial fibrillary acidic protein, and IL-1. A second research examination showed that turmeric treatment enhanced memory and cognitive function in the STZ model of Alzheimer by reducing oxidative damage, enhancing ChAT activity, and restoring insulin receptor protein.

Curcumin considerably boosted microgliosis immediately close to plaques while dramatically decreasing microgliosis in neuronal layers, supporting the notion that it may drive microglial phagocytosis of amyloid. Alpha-1-Antichymotrypsin (1ACT) suppression and NF-B mediated transcription of apolipoprotein E are two additional potential pathways for Curcumin's neuroprotective benefits (ApoE). In APP transgenic mice, 1ACT and ApoE have both been demonstrated to be proamyloidogenic. In addition, oxidative stress and elevated cholesterol levels, two additional proamyloidogenic variables, can be decreased by curcumin. The protective impact of the turmeric blend and each of its parts on 163 and apoptosis gene expression in Dementia was investigated using an Aβ plus ibotenic acid-infused rat model. According to Ahmed and colleagues, treatment of a curcuminoids in mixture (bisdemethoxycurcumin, demethoxycurcumin, and curcumin) enhanced retention of information in rat models of AD created by amyloid fragments. Nevertheless, curcumin therapy given repeatedly also protected mice from cognitive damage brought on by colchicine by lowering oxidative stress.

Due to a rise in serum corticosterone levels, chronic stress causes aberrant neuroendocrine and plasticity processes that impair spatial cognition. By restoring normal corticosterone response, curcumin reduces levels glutamate receptor, calcium/calmodulin kinase II, and (NMDA-2B), which has neuroprotective effect. According to Wang et al. and Yin et al., therapy Turmeric 300 mg per kilogram improved spatial retention and learning deficits along with hippocampus regeneration in an Aβ1–40 AD model. There is evidence that the AD brain has high levels of metals, and turmeric chelates copper and iron attached to beta amyloid (but not zinc), which may help reduce amyloid. McClure et al., used a different strategy, treating young 5XFAD mice with curcumin through aerosol in a manner that

prevented Aβ accumulation compared to untreated mice, mature animals have cognitive and memory issues. Such multi target substances are potentially effective treatment of Alzheimer's and the resulting cognitive deterioration. There are, however, little clinical studies on the effectiveness of curcumin in treating AD despite extensive study on the drug's effects on a number of disorders.

Clitoria ternatea

Tropical annual climbing herb *Clitoria ternatea* (*C. ternatea*) has a thin, downy consistency branch that can be grown in gardens and in the wild across tropical India. It has white or blue blooms. *C. ternatea* is a member of the Fabaceae, also known as the "butterfly" family. It is an Ayurvedic drug that is frequently utilized. In Indian traditional medicine, *C. ternatea* is known by the names Aparajit (Hindi), Aparajita (Bengali), and Kakkattan. Ayurveda has employed *C. ternatea* extracts as a component of "Medhya-rasayana."

The principal chemical substances are: Numerous phytochemicals are isolated from *C. ternatea*, including taraxerol, teraxerone, ternatins, delphinidin-3, delphinidin-3ß-glucoside, malvidin-3ß-glucoside, 3-monoglucoside, 3-rutinoside, 3-neohisperidoside, 3-o-rhamnosyl Glycoside, kaempferol-3-o-rhamnosyl 172.

Medicinal techniques: Earlier investigations have shown that *C. ternatea* has a wide range of biological properties, including nootropic, anticonvulsant, antidepressant, antianxiety, antistress, antioxidant, anti-inflammatory, antihyperlipidemic, antidiabetic, antiasthmatic, analgesic, immunomodulatory, cytotoxicity, platelet aggregation inhibitory, antimicrobial, gastroprotective, and hepatoprotective properties.

Pre-clinical studies: The nootropic effect of methanol derived extracts of apical parts of *C. ternatea* (100 mg/kg, p.o.) has been noted, using elevated plus maze and the object recognition test using rats. Taranalli and Cheeramkuzhy studied the effects of ethanolic extracts of the roots and apical parts of *C. ternatea* at doses of 300 and 500 mg/kg, per oral. on dementia induced by submaximal electroshock. Also, they calculated the Ach levels throughout the entire brain and various regions of it. Better memory retention and more Ach were found in the brain when the aerial parts extract was given as compared to 500 milligrams per kilogram, and 300 mg/kg.

Comparable yet greater pronounced impacts that are practically comparable at both doses were seen in the root extract. In rats going through a growth spurt, Rai, et al., demonstrated how the *C. ternatea* root extract improved learning and memory. Neonatal rats who were 7 days old were intubated for 30 days, they gave them doses of 50 and 100 mg/kg of *C. ternatea's* aqueous root extract. The extract enhanced spatial performance in the T-maze test and retention in the passive avoidance task. A 30 day post-treatment evaluation revealed that the behavioral modifications were long lasting. In a previous study, it was also demonstrated that the aqueous root extract (50 and 100 mg/kg, p.o. for 30 days) improved the neuronal dendritic arbor in the rat amygdala. The presence of growth factors like nerve growth factor or brain derived neurotrophic factor was speculated to be the cause of this effect on cognition. One of the causes of the nootropic action of *C. ternatea* root may be an increase in hippocampal acetylcholine content. Additionally, Rai reported that 3 promoting consequence on the *C. ternatea* root extrac showed up in the anterior subventricular zone of brain stem cells. In a previous study, it was also demonstrated that the aqueous root extract (50 and 100 mg/kg, p.o. for 30 days) enhanced dendritic arborization of rat amygdala neurons. Its effect on cognition was thought to be caused by the presence of growth factors such as brain derived neurotrophic factor or nerve growth factor. One of the potential causes of the nootropic effects of *C. ternatea* root is a rise in the choline level of the cerebral cortex. In addition, Rai noted that 3 encouraging sequel on the *C. ternatea* extract of root was found in the brain stem cells' anterior subventricular zone. Recently, Damodaran et al., reported the brain protective properties of the *C. ternatea* roots extract in correcting continuous brain function hypoperfusion induced neuronal injury and loss of memory at doses of 200 and 300 mg/kg. In a different investigation, Mehla and associates showed that *C. ternatea* has anti-AD effects in ICV-STZ. Rats were subjected to circumstances resembling AD. These results suggest that C. *ternatea* extract's positive benefits are brought about through slowing the progression of AD's mental loss. However, a thorough assessment of *C. ternatea* extract has potential for human use is still required.

The *Withania somnifera* plant (*W. somnifera*) is a small, woody shrub from the Solanaceae family that is widely cultivated in India. It goes by the name's Indian ginseng, winter cherry, and ashwagandha. Approximately one centimeter long, greenish or yellowish, are its flowers. Old Indian Sanskrit writings refer to ashwagandha as a "Medhya rasayana." It is frequently used in Ayurveda and goes by the name Indian ginseng. It is a component of numerous formulations recommended as a general tonic to boost energy, enhance all around health, and lengthen life.

The main phytoconstituents of (*W. somnifera*) are its main chemical ingredients. Examples of somnifera include isopellertierine, anferine, withanolides, withaferins, sitoindosides VII and VIII, and withanoloides. Other substances include withanine, somniferine, 3-a-gloyloxytropane, choline, cuscohygrine, withanine, pseudo-withanine, tropine, and pseudo-tropine.

Pharmacological actions: Wide ranging biological effects of *W. somnifera* include anti-inflammatory, antioxidant, neuroprotective, anti-ischemic, anti-parkinson's, antiepileptic, anxiolytic, antidepressant, antiarthritic, cardioprotective, antidiabetic, anticancer, antistress, nephroprotective, hepatoprotective, antihypoxic, immunomodulatory, hypolipidemic, and antimicrobial effects.

Pre-clinical investigations: The effects of *W. somnifera's* root whole an alkaloid derivative (ashwagandholine, AG) on the central nervous system have been researched. By acting as an antioxidant, W. somnifera reduced the lack of remembering resulting from STZ. By halting stress induced degeneration in the rat brain's hippocampus, the preparation of root systems has been demonstrated to be capable of preventing neurological conditions. The extract of a herb comprising sitoindosides VII-X and withaferin A was given to rats with ibotenic acid induced dementia and a decline in acetylcholine indications (such as Ach and ChAT) for a period of two weeks. Differentially, but favourably, Withaferin and stoindosides VII–X (40 milligram per kilogram for a period of seven days) changed Several regions of the brain exhibit increased M1 and M2 muscarinic receptor binding and the AchE activity. In BV-2 microglial cells, withaferin A and withanolide A may has a strong impact immune system modulation by activating the Nrf2 pathway, which results in the synthesis of neuroprotective proteins such heme oxygenase-1.

Withanoside IV, an alternative chemical constituent for withania, lessened dementia of the brain in an animal model of Alzheimer when administered orally at a level of 10 micromol/kg. Axonal and dendritic regeneration as well as synaptic rebuilding were stimulated Amyloid peptide A (25–35) damaged rat neurons in the cortex was cultivated, and with Withanoside IV metabolite sominone (1 microM). Using sominone as the active ingredient, withanoside IV might function being a prodrug. Semitone's ability to improve spatial memory might linked to A RET transmitter for Neurotrophic Factor (NF) is a mediator of neuritic expansion. Human neuroblastoma cells' ability to generate *in-vitro* dendrites was improved by methanolic root extract. According to a study of Jayaprakasam et al., withanamides found in *W. somnifera* fruit shield pheochromocytoma (PC-12) against toxicity caused by β-amyloid. The same study found that the two withanamide molecules contain a serotonin molecule inhibited the production of β -amyloid fibrils.

Through increasing the protein linked to a low density lipoprotein receptor, *Withania* root extract treatment 1 g/kg, orally for 30 days changed the pathogenesis of Alzheimer and lifted the cognitive deficit in APP/PS1 mice that were elderly and old. Withanone, an ingredient in the Ethanol *Withania* herb extract, proved neuroprotective against alterations in the brain caused by scopalmine. Aβ peptide has also been shown to have an inhibitory effect on fibril production *in vitro*. The effects of withania on cognition and memory may be partially explained by the ability of cortical muscarinic cholinergic receptors was raised. Anxiolytic, depressive, anti-inflammatory, and antioxidant properties of the rhizome herbal extract and its chemicals, like glycowithanolides, may be important in the treatment of AD. Moreover, withanone, a chemical component found in *W. somnifera* root extract, improved cognitive abilities by preventing the processing of amyloid and lowering increased proinflammatory cytokine concentrations and signs of oxidative damage. *W. somnifera* (20 mg/mL) was used for treating D. melanogaster, an Alzheimer model, which decreased the toxic effects of Aβ and improved lifespan.

Clinical evidence: Using ashwagandha an extract of roots during treatment (300 mg twice daily for eight weeks).

Improved executive function, focus, and data processing speed in people with mild cognitive impairment, as well as improved short and long term memory, according to a hypothetical, randomized, double blinded placebo controlled research. Ng and his colleagues reported herbal extract from *W. somnifera* improved executive functions and reduced cognitive impairment of people possessing a slight mental disorder in a systematic study. There is not much information available about using *Withania* for cognitive impairment in therapeutic settings.

Celastrus paniculatus

Botanical description: *Celastrus paniculatus* (*C. paniculatus*) is a large climbing plant in the Euonymaceae family. It grows throughout India, on the slopes of the Sub-Himalayas, in the foothills in Punjab and south part of India. The term "Jyothismati" is derived from the Sanskrit phrases "Jyoti Teja" (spirit fire) and "Mati" (fire). (intelligence). The tree's bark and nuts have historically been employed as an energy booster and expectorant, as a cerebral tonic, to heighten cognition and enhance digestion. His *C. paniculatus* has been utilised in Ayurveda for the treatment of a wide range of illnesses, including anxiety, the leprosy, paralysis in humans, high temperatures, and gout. Because of their calming, relaxing, and wound-healing qualities, fruits and seed derived oils are frequently employed.

Chemical constituents: Sequiterpenoid polyalcohols including ester compounds, among other plant elements, are present in *C. paniculatus*. (markanniol, marcangunin, polyalcohol AD and serapnin). Paniculatin and celastrin is alkaline compounds. Celastrol and paniculatadiol are phenol triterpenoids. Oleic, linoleic, linolenic, palmitic, stearic and lignoceric acids.

Pharmacological activity: pharmacology of *C. paniculatus* including hypolipidemic, neuroprotective, antifertility, Analgesic, anti-bacterial, anti-inflammatory, antibacterial, anti-malarial, with wound healing and antifungal activities Activity has been reported.

Preclinical studies: Several research models of dementia, including sodium nitrite induced amnesia with scopolamine, have been tested on *Celastrus* seed extract and oil. Rats cognitive abilities were examined after being exposed to *C. paniculatus* seed extracts in methanolic, chloroform solution, petroleum based ether, and water. The aqueous extract significantly enhanced cognitive function when administered orally for 14 days at doses of 200 and 300 mg/kg. Methanolic extract was found to improve memory in rats when administered at dosages of 100, 200, and 400 mg/kg in another study. *C. paniculatus's* antioxidant activity may have a role in boosting cognitive function. The ability to learn and recall information in the radial arm maze were enhanced when Wistar rodents were fed 400 milligrams per kilogram of *C. paniculatus* oil from seeds every day for 14 days, and the production of the AchE enzyme in the brain regions of the hypothalamus, frontal lobe, and hippocampal was decreased. With a dose of 400 mg/kg for 3 days, Karanth et al., similarly showed that *C. paniculatus* had a comparable impact. Rats were given 850 mg/kg of *C. paniculatus* oiled to eat for a period of fifteen days in a different trial, and the rats memory in two passive avoidance tasks significantly increased. The morris water maze spatial memory impairment caused by scopolamine was reversed and enhanced locomotor activity Rats action on AchE was unaffected by the use of seed oil therapy for 14 days at doses of 50, 200, and 400 milligrams per kilogram, orally. The watery extract of seeds enhanced memory capacity in the raised plus maze and in sodium nitrite induced dementia *via* reducing AchE activity. Furthermore, scopolamine induced amnesia in rats was improved by *C. paniculatus* seed oil therapy. Clinical investigations for the safety and effectiveness of *C. paniculatus* have not been conducted.

Evolvulus alsinoides

Evolvulus alsinoides L., often known as the dwarf morning glory and a member of the Convolvulaceae family, possesses a small, branched, wooden root and is an annual plant. A weed called *E. alsionoides* is primarily present in swampy areas of worldwide tropical and subtropical areas. Possess several, beyond 30 centimeters long, hairy branches. Flower is blue in color, while the leaves are tiny, sharp, and elliptic. It is widely used in Ayurveda and is known locally as Shankhpushpi. The bulk compounds from the Medhya Rasayana sold at India contain this as a primary component. It has historically been used to treat neurological conditions including epilepsy and to improve memory in youngsters and the elderly.

Chemical components: The primary chemical constituents are cholesterol, n-hexadecanoic acid, piperine, squalene, as well as ethyl oleate.

Pharmacological activities: *Evolvulus alsionoides* (*E. alsionoides*) has been shown to have *in-vitro* antioxidant, immunomodulatory, adaptogenic, anti-amnesic, with antiulcer actions.

Pre-clinical studies: In rats, Nahata et al., observed that its water based, ethanolic, and extractive portions improved learning and memory. Rats exposed to scopolamine induced dementia were likewise protected by 100 milligrams per kilogram of the ethanol based extract, orally. *E. alsionoides* (100 mg/kg) oral therapy for three days was successful in reducing the deficit caused by scopolamine in adult male Swiss mice. The preliminary treatment with hydro-alcoholic extracts at dosages of 100, 300, and 500 milligrams per kilogram, p.o. decreased oxidative stress and rho kinase (ROCK II) activity in the rat brain's activity, which improved memory deficit brought on with ICV-STZ. Aqueous and hydroalcoholic extracts of *E. alsinoides* demonstrated anti-inflammatory, free radical scavenging, and enzyme inhibitory activity *in vitro*. These enzymes include cholinesterase, catechol-o-methyl transferase, prolyl endopeptidase, glycogen synthase kinase-3-, Rho kinases (ROCKI I), along with monoglycerol protease. In the experimental paradigm of amnesia, other investigations have shown that *E. alsionoides* improves memory. The acetylcholinesterase activity of the *E. alsinoides* methanol and water extract supports the plant's potential to reverse neuronal dysfunctions and hence aid in the treatment of AD.

CONCLUSION

In this paper we learn more detail about the pathophysiology and disease progression of AD and an insight into the potential therapeutic targets. Despite of the bulk of knowledge regarding this complex disease, only a fistful options are available for its management. Currently available drugs (AChEIs and memantine) for the treatment unfortunately target symptoms only and not the cause of the disease. So, the hope is now raised for the novel therapies that act at the root of the disease process.

REFERENCES

[1] Amor S, et al. *Immunology*. **2010**;129(2):154-169.
[2] Kumar Gp, et al. *Pharmacognosy Reviews*. **2012**;6(12):81.
[3] Scott A. *Neuron*. **2008**;60(4):534-542.
[4] Huang HC, et al. *J Alzheimers Dis*. **2009**;16(1):15-27.
[5] Ferri CP, et al. *Lancet*. **2005**;366:2112-2117.
[6] Fox NC, et al. *Lancet*. **2001**;358:201-205.
[7] Kaye JA, et al. *Neurology*. **1997**;48:1297-1304.
[8] Forstl H, et al. *Br J Psychiatry*. **1995**;167:737-746.
[9] Craig LA, et al. *Neurosci Biobehav Rev*. **2011**;35:1397-1409.
[10] Greig NH, et al. *Int Psychogeriatrics*. **2002**;14:77-91.
[11] Jing L, et al. *Drug Discov*. **2019**;24:629-635.
[12] Sussman JL, et al. *Science*. **1991**;253:872-879.
[13] Dinamarca MC, et al. *Mol Neurodegener*. **2010**;5.
[14] Ferrari GV, et al. *Biochemistry*. **2001**;40:10447-10457.
[15] Wang Y, et al. *Curr Neuropharmacol*. **2016**;14:364-375.
[16] Hartmann J, et al. *J Neurochem*. **2007**;100:1421-1429.
[17] Guillozet AL, et al. *Ann Neurol*. **1997**;42:909-918.
[18] Hardy JA, et al. *Science*. **1992**;256:184-185.
[19] Chu D, et al. *ACS Chem Neurosci*. **2019**;10:931-944.
[20] O'Brien RJ, et al. *Annu Rev Neurosci*. **2011**;34:185-204.