Alzheimer's Disease: An Review

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Abstract- *Although dementia has been described in ancient texts over many centuries (e.g., "Be kind to your father, whether or not his mind fail him." – Old Testament: Sirach 3:12), our knowledge of its underlying causes is no quite a century old. Alzheimer published his now famous case study only 110 years ago, and our modern understanding of the disease that bears his name, and its neuropsychological consequences, really only began to accelerate within the 1980s. Since then we've witnessed an explosion of basic and translational research into the causes, characterizations, and possible treatments for Alzheimer's disease (AD) and other dementias. We review this lineage of labor beginning with Alzheimer's own writings and drawings, then jump to the fashionable era beginning within the 1970s and early 1980s and supply a sampling of neuropsychological and other contextual work from each ensuing decade. During the 1980s our field began its foundational studies of profiling the neuropsychological deficits related to AD and its differentiation from other dementias (e.g., cortical vs. subcortical dementias). The 1990s continued these efforts and commenced to spot the precise cognitive mechanisms stricken by various neuropathologic substrates. The 2000s ushered in an exceedingly concentrate on the study of prodromal stages of neurodegenerative disease before the full-blown dementia syndrome (i.e., mild cognitive impairment). the present decade has seen the increase of imaging and other biomarkers to characterize preclinical disease before the event of serious cognitive decline. Finally, we propose future directions and predictions for dementia-related research and potential therapeutic interventions.*

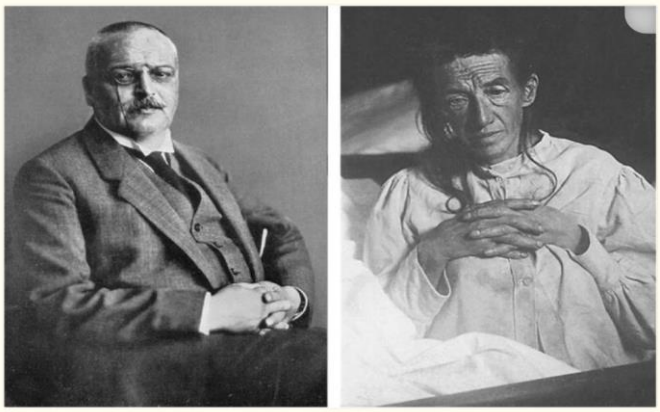
Keywords- Alzheimer, Management, Diagnosis, Treatment .

I. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and is clinically characterized by a progression from episodic memory problems to a slow general decline of cognitive function. In 2013, ~44 million of the world-wide population was estimated to be affected by dementia and a steep rise to ~136 million has been predicted by 2050 2.To date, there are no treatments with proven disease-modifying effects and AD remains the largest unmet medical need in neurology. A AD pathology presents a complex interplay between several biochemical alterations, including changes in amyloid precursor protein metabolism, phosphorylation of the tau protein, oxidative stress, impaired energetics, mitochondrial dysfunction, inflammation, membrane lipid dysregulation and neurotransmitter pathway disruption. Most of these pathological features can be directly linked to metabolic abnormalities and it is now clear that metabolic dysfunction is an important factor in AD.[4]For example, impaired cerebral glucose uptake occurs decades prior to the onset of cognitive dysfunction and is an invariant feature of AD. The well-documented neurotoxicity associated with Aβ42 is thought to participate in impaired neuronal energetics through initiating a cascade of pathological events; interaction between Aβ42 and mitochondrial enzymes leads to increased release of reactive oxygen species (ROS), affecting glycolysis, the TCA cycle and mitochondrial respiratory-chain activity through the accumulation of deleterious intermediate metabolites in the mitochondria. Alzheimer's disease is a chronic progressive neurodegenerative disorder characterised by three primary groups of symptoms. The first group (cognitive dysfunction) includes memory loss, language difficulties, and executive dysfunction (that is, loss of higher level planning and intellectual coordination skills). The second group comprises psychiatric symptoms and behavioural disturbances—for example, depression, hallucinations, delusions, agitation—collectively termed non-cognitive symptoms.2 The third group comprises difficulties with performing activities of daily living (deemed "instrumental" for more complex activities such as driving and shopping and "basic" for dressing and eating unaided). The symptoms of Alzheimer's disease progress from mild symptoms of memory loss to very severe dementia (figure). Increasingly, the coexistence of vascular disease and Alzheimer's disease is being recognised clinically, pathologically, and epidemiologically Population studies of ageing and cognition suggest that impairment in multiple cognitive domains is observable several years before a clinical diagnosis of observable several years before a clinical diagnosis of Alzheimer's disease is made.5 This observed cognitive dysfunction is not qualitatively different from that seen in normal ageing, suggesting continuity rather than discontinuity in the shift from normal ageing to preclinical dementia.6 Global cognitive deterioration, affecting memory and other aspects of cognitive functioning (verbal ability, visuospatial skills, attention, and perceptual speed), is almost always a presenting symptom.w1 There is considerable overlap in

cognitive performance between normal ageing and this stable phase,w2 and little evidence exists as yet that these changes are detectable in clinical encounters. A person with symptoms of Alzheimer's disease is about 30% more likely to display the clinical features of dementia if they have coexisting symptoms of vascular disease

The worldwide prevalence of dementia is estimated to be over 45 million people. Alzheimer's disease (AD) is the most common cause of dementia, responsible for 60-80% of cases [1]. An estimated 5.8 million Americans ages 65 and older have AD, a number which could grow to 13.8 million by 2050. As the number of people suffering from AD increases, so does the economic burden of care. Payments for healthcare and hospice services for Americans 65 and older with dementia are estimated to be $305 billion in 2020 . The neuropathology of AD consists of extracellular beta amyloid plaque depositions and intracellular neurofibrillary tangles of hyper phosphorylated tau. AD remains a clinical diagnosis, although cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers can increase diagnostic accuracy . Current treatments, including cholinesterase inhibitors and memantine, improve quality of life but do not modify or slow the disease course. Current research aims to treat underlying pathology of active AD as well as identify and stage interventions in those with preclinical, or asymptomatic, AD.



Historical Background

Alois Alzheimer, a German physician, reported the primary case of Alzheimer's disease in 1907 . He first saw Auguste Deter, a 51-year-old woman, in 1901. Auguste's husband Karl brought her to a infirmary after she began exhibiting unusual behavior, including hiding items, threatening neighbors, and accusing her husband of adultery. She also lost the power to try to to daily activities like cooking and housework. Auguste came under Alzheimer's care at a hospital in Frankfurt. There he observed and recorded her behavioral patterns: she could speak but not write her own name, she could name objects like a pencil but not the food she was eating, she was polite sometimes but loud and offensive at other times. He diagnosed Auguste with "presenile dementia" . Upon her death in 1906, Alzheimer's biopsy of her brain revealed diffuse cortical atrophy and "particular changes in cortical cell clusters" [. Alzheimer described plaques and tangles of nerve fibers which researchers would identify within the 1980's as beta amyloid plaques and neurofibrillary tangles of tau . That year, Alzheimer gave a presentation on Auguste at a German psychiatry conference, asserting these cortical lesions to be the reason for her symptoms. He published a quest paper the subsequent year, and a psychiatry textbook in 1910 named the disorder 'Alzheimer's disease.' The clinical diagnostic criteria for AD were standardized within the U.S. in 1984. They were revised in 2011 and 2018 to form separate diagnoses for the preclinical, mild cognitive impairment (MCI) and dementia stages of AD and to acknowledge the role of biomarkers in AD diagnosis

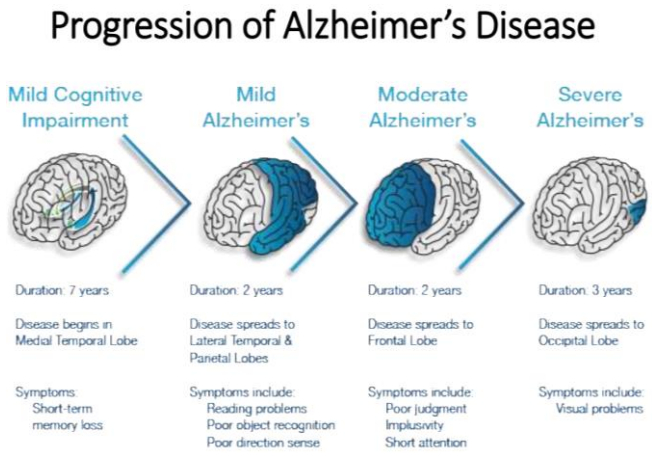
Case Study on Alzheimer's Disease

Alzheimer's disease is that the most widespread type of dementia which has been discovered and explained in 1906 by the German psychotherapist Alois Alzheimer. As a rule Alzheimer's disease is discovered among the elderly people that reach their 65 year of life, but there also are cases of the first Alzheimer's disease which occurs among the younger people. per the statistics of the year 2006 the quantity of the people littered with Alzheimer's disease within the world is adequate to over 26 million people. Every patient has his own peculiarities of the disease, but there are common symptoms which differentiate the disease from the others. At the very beginning there are disorders with the immediate memory. Unfortunately, this symptom is commonly not paid attention to, because this problem touches upon many elderly people thanks to stress. so as to detect the disease the patient is seriously monitored, his behaviour and memory is analyzed with the assistance of various methods.With the further development of the disease there's the loss of the remembering

Pathogenesis

The pathological hallmark of Alzheimer's disease is that the presence of Amyloid plaques and Neurofibrillary tangles (NFT). there's diffuse atrophy of the cerebral mantle and secondary Dilatation of the ventricles. The deposits are found more at the hippocampus, temporal cortex And nucleus basalis of Meyernet. there's loss of neurons because of the pathological changes Leading on to

reduced levels of neurotransmitters especially acetylcholine causing cognitive Deficits in these patients. the fundamental pathological reason behind Alzheimer's disease isn't fully understood and lots of Research is being done to elucidate the essential biological process. With this Understanding many hypothesis are put forth for the pathogenesis of AD may be a complex, multifactorial, neurodegenerative disease, resulting from complicated interactions of one's genetic makeup, education, age, and environment. Many hypotheses have laid the inspiration to realize understanding of the etiology of the disease, with one among the oldest being the cholinergic hypothesis. This hypothesis is predicated upon the very fact that AD patients show reduction in activity of choline acetyltransferase and acetylcholinesterase within the cerebral mantle compared with the traditional brain . Post-mortem brain tissue from patients with AD confirmed the reduced neurotransmitter pathway activity, revealing that degeneration of cholinergic neurons and loss of cholinergic neurotransmission significantly contributes to the cognitive impairment seen in those with AD . The Tau hypothesis has also been proposed, considering AD histopathology reveals intraneuronal neurofibrillary lesions made from tau proteins. Tau proteins are mainly found in neurons and are involved within the assembly and



stabilization of the neuronal microtubule network. Tau protein becomes pathological when the phosphorylation regulation becomes unchecked and hyper phosphorylated tau proteins polymerize into filaments and become neurofibrillary tangles. This results in malfunction of the structural and regulatory actions of the cytoskeleton so ends up in abnormal morphology, axonal transport, and synaptic function of neurons, thus resulting in neurodegeneration . These prior theories paved the thanks to the widely accepted hypothesis for the pathogenesis of AD: the amyloid cascade hypothesis. This theory attributes clinical sequelae of the disease to the overproduction or decreased clearance of amyloid beta (Ab) peptides, which then ends up in increased deposition of Ab, furthermore, resulting in neuronal damage . The length of Ab varies looking on the posttranslational cleavage pattern of the transmembrane amyloid precursor protein (APP). Ab is generated by cleavage of APP via either b- or g-secretases, leading to the infamous insoluble Ab fibrils . Two main varieties of Ab polymers play a right away role within the pathology of AD: Ab40 and Ab42. Ab40/Ab42 then oligomerizes, travels to synaptic clefts, and interferes with synaptic signaling. These eventually further polymerize into insoluble amyloid fibrils that aggregate into amyloid plaques . Within AD remains a clinical diagnosis and is reliant on an in depth history, cognitive assessment and physical exam. Structural imaging is additionally a very important component of the assessment for AD. Atrophy of the medial temporal lobes on resonance imaging (MRI) is taken into account a diagnostic marker for the mild cognitive impairment stage of AD . Similarly, hypo metabolism within the parieto-temporal association cortex, posterior cingulate and precuneus on fluorodeoxyglucose PET imaging is related to AD In 2012, the Food and Drug Administration approved the primary beta-amyloid tracer, florbetapir, to be used in PET scans of suspected Alzheimer's patients. In one study, florbetapir PET imaging was shown to possess a 92% sensitivity and 100% specificity for detecting moderate to frequent plaques in patients with an autopsy within 2 years of the scan . The amyloid PET tracers florbetaben and flutemetamol have also been approved and show similar sensitivity and specificity . However, amyloid PET scans have had limited clinical impact because of lack of insurance reimbursement, and that they are currently used primarily in research trials.

Treatment

Currently, Alzheimer's disease cases worldwide are reported to be around 24 million, and in 2050, the overall number of individuals with dementia is estimated to extend 4 times. although AD may be a public health issue, as of now, there's only two classes of medicine approved to treat AD, including inhibitors to cholinesterase enzyme (naturally derived, synthetic and hybrid analogues) and antagonists to N-methyl D-aspartate (NMDA). Several physiological processes in AD destroy Ach-producing cells which reduce cholinergic transmission through the brain. Acetylcholinesterase inhibitors (AChEIs), which are classified as reversible, irreversible, and pseudo-reversible, act by blocking cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, which ends in increasing ACh levels within the synaptic cleft. On the opposite hand, over activation of NMDAR ends up in increasing levels of influxed Ca2+, which promotes death and synaptic dysfunction. NMDAR antagonist prevents over activation of NMDAR glutamate receptor and

hence, Ca2+ influx, and restores its normal activity. Despite the therapeutic effect of those two classes, they're effective only in treating the symptoms of AD, but don't cure or prevent the disease . Unfortunately, only some clinical trials on AD are launched within the last decade and their outcome was an enormous failure. Several mechanisms are proposed to know AD pathology so as to switch its pathway and develop successful treatments, which include abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and radical damage . On the opposite hand, most AD modifiable risk factors like cardiovascular or lifestyle habits is prevented without medical intervention. Studies showed that physical activity can improve the brain health and reduce AD by activating the brain vascularization, plasticity, neurogenesis, and reducing inflammation by decreasing Aβ production, which all end in improving cognitive function in older people. Moreover, the Mediterranean diet (MD), intellectual activity, and better education all may reduce the progression of AD and amnesia and increase the brain capacity and cognitive functions. Several studies revealed that multi-domain intervention which incorporates lifestyle (diet, exercise, and cognitive training), depression of AD symptoms, and controlling cardiovascular risk factors, can increase or maintain cognitive function and forestall new cases of AD in older people . Herein, we summarize the currently available drugs and theories for the event of recent therapies for AD.

Symptomatic Treatment of AD

6.1.1. Cholinesterase Inhibitors in line with the cholinergic hypothesis, AD is thanks to the reduction in acetylcholine (ACh) biosynthesis. Increasing cholinergic levels by inhibiting acetylcholinesterase (AChE) is taken into account one amongst the therapeutic strategies that increases cognitive and neural cell function. AChEIs are accustomed inhibit acetylcholine degradation within the synapses, which ends up in continuous accumulation of ACh and activation of cholinergic receptors. Tacrine (tetrahydroaminoacridine) was the primary FDA (Food and Drug Administration)-approved cholinesterase inhibitor drug for the treatment of AD, which acts by increasing ACh in muscarinic neurons, but it exited the market immediately after its introduction thanks to a high incidence of side effects like hepatotoxicity and an absence of advantages, which was observed in several trials. Later on, several AChEIs were introduced, like donepezil , rivastigmine , and galantamine , and are currently in use for the symptomatic treatment of AD

1. Donepezil is an indanonebenzylpiperidine derivative and a second generation of AChEIs and is taken into account the leading drug for AD treatment. Donepezil binds to acetylcholinesterase reversibly and inhibits acetylcholine hydrolysis, which ends up in the next concentration of ACh at the synapses. The drug is well-tolerated with mild and transient cholinergic side effects which are associated with the gastrointestinal and nervous systems. It should be noted that donepezil is employed to treat symptoms of AD like improving cognition and behavior without altering the AD progression. Rivastigmine

2. Rivastigmine could be a pseudo irreversible inhibitor of AChE and butyrylcholinesterase (BuChE) that acts by binding to the 2 active sites of AChE (anionic and estearic sites), which ends up in preventing ACh metabolism. BuChE is found mostly in glial cells with only 10% of AChE activity within the normal brain, whereas within the AD brain, its activity is increased to 40–90%, while ACh activity is reduced simultaneously, which suggests that BuChE action may indicate a moderate to severe dementia. Rivastigmine dissociates more slowly than AChE, which is why it's called a pseudo-irreversible, and it undergoes metabolism at the synapse by AChE and BuChE. The drug is employed in mild to moderate AD cases. It improves cognitive functions and existence activities. Oral administration of the drug is related to adverse effects like nausea, vomiting, dyspepsia, asthenia, anorexia, and weight loss.

3. N-methyl d-aspartate (NMDA) Antagonists NMDAR is believed to own a dominant role within the pathophysiology of AD. NMDAR stimulation leads to Ca2+ influx which activates signal transduction and as a consequence, it triggers gene transcription essential for the formation of a long-term potentiation (LTP), which is very important for synaptic neurotransmission, plasticity, and memory formation. Over-activation of NMDARs causes an abnormal level of Ca2+ signaling and overstimulation of glutamate, which is that the primary excitatory aminoalkanoic acid within the CNS, which ends up in excitotoxicity, synaptic dysfunction, neuronal necrobiosis, and a decline in cognitive functions. Several NMDAR uncompetitive antagonists are developed and entered clinical trials, however, most of them failed thanks to low efficacy and side effects.

4. Memantine may be a low-affinity uncompetitive antagonist of the NMDAR, a subtype of glutamate receptor that stops over-activation of the glutaminergic system involved within the neurotoxicity in AD cases. Memantine is employed for the treatment of moderate to severe AD alone or together with AChEI. The drug is safe and well-tolerated, it blocks the excitatory receptor without interfering with the conventional synaptic transmission thanks to memantine's low affinity, where it's displaced rapidly from NMDAR by high concentrations of glutamate, thus avoiding a chronic blockage.

The latter is related to high side effects, especially on learning and memory

Disease-Modifying Therapeutics (DMT)

Disease-modifying treatment or therapy (DMT) alter the progression of AD by functioning on several pathophysiological mechanisms. this is often in contrast to symptomatic therapy which works on improving the cognitive functions and decreasing symptoms like depression or delusions without affecting or modifying the disease. DMTs, either immunotherapies or small molecules, are administrated orally and are being developed to stop AD or decrease its progression. Several DMTs are developed and entered the clinical trials, like AN-1792, an artificial Aβ peptide (human Aβ1–42 peptide of 42-amino acids with the immune adjuvant QS-21) and also the first active immunotherapy for AD which entered phase II clinical trials and discontinued because of a meningoencephalitis side effect in 6% of the patients. Other drugs were also developed and failed within the clinical trials, including the anti-Aβ antibody (solanezumab and bapineuzumab), γ-Secretase inhibitors (semagacestat , avagacestat , and tarenflurbil) and β-secretase inhibitors (BACE) (Lanabecestat , verubecestat , and atabecestat DMTs failures are thanks to several factors, like starting therapy too late, giving treatment for the incorrect main target, use of inappropriate drug doses, and misunderstanding of the pathophysiology of AD. Several immunotherapies described in are developed over decades, including: CAD106, an energetic Aβ immunotherapy that induces Aβ antibodies in animal models and consists of multiple copies of Aβ1–6 peptide coupled to Qβ coat protein, a virus-like particle, and remains in clinical trials, and CNP520 (umibecestat,) , alittle molecule that inhibits beta-scretase-1 (BACE-1) and thus inhibits Aβ production. CNP520 was found to scale back Aβ plaque deposition and Aβ levels within the brain and CSF in rats, dogs, and healthy adults ≥ 60 years old, and continues to be under clinical trials. Furthermore, aducanumab, gantenerumab, and crenezumab are all human Aβ antibody that bind with high affinity to aggregated Aβ, and that they are still under study within the clinical phases with other DMTs described in

Disease modifying agents for the treatment of Alzheimer's disease in clinical trials.

Disease Modifying Agents	Mechanism of Action
Phase 3 Clinical Trials	
Aducanumab	Monoclonal antibody—targets β-amyloid and removes it.
Gantenerumab	Monoclonal antibody—binds and removes β-amyloid.
CAD106b	Amyloid vaccine—stimulates production of antibodies against β-amyloid.
BAN2401	Monoclonal antibody—reduces protofibrillar β-amyloid.
TRx0237 (LMTX)	Tau protein aggregation inhibitor.
AGB101	Low-dose levetiracetam—improves synaptic function and reduces amyloid-induced neuronal hyperactivity
ALZT-OP1 (cromolyn + ibuprofen)	Mast cell stabilizer and anti-inflammatory—promotes microglial clearance of amyloid
Azeliragon	RAGE (Receptor for Advanced Glycation End-products) antagonist—reduces inflammation and amyloid transport into the brain
BHV4157 (troriluzole)	Glutamate modulator—reduces synaptic levels of glutamate and improves synaptic functioning
Masitinib	Tyrosine kinase inhibitor—modulates inflammatory mast cell and reduces amyloid protein and tau phosphorylation

Herbal Medicines for Alzheimer's Disease, Experimental and Clinical Evidence

Herbal drugs and complementary medicines are used since earlier period for treatment of neurological disorders. Several herbal medicines worldwide are used for neurodegenerative disorders. as an example, Salvia lavandulaefolia (Spanish sage) and sage (common sage) are getting used for improving memory in Europe since the 16th century and are supported by clinical trials .Bacopa monniera (water hyssop) has been employed in the Indian Ayurvedic system to enhance memory and intellectual functions as an immemorial custom. Centella asiatica (Asiatic pennywort), another Ayurvedic remedy, is given together with milk to boost memory . Withania somnifera root, a rejuvenative tonic, is additionally utilized in Ayurveda to reinforce memory. Herbal medicines are getting popular thanks to their perceived effectiveness, safety and affordability. Indeed, only recently, scientific studies have started providing evidence and support for the utilization of herbal medicines in memory related disorders. Various CNS active Indian herbal medicines like Withania somnifera, Centella asiatica, Celastrus paniculatus and Bacopa monnieri have shown cognitive improvement in experimental models of AD when given as prophylactic treatment. A randomized, double-blind exploratory trial reported comparable efficacy of a Gingko biloba extract and donepezil in AD patients with associated neuropsychiatric problems. the mix was reported to be superior to donepezil monotherapy in terms of both safety and efficacy .

Centella asiatica

Plant description: Centella asiatica (C. asiatica), a small, annual herb belonging to the family Apiceae is found throughout India and commonly referred to as mandukparni or jalbrahmi. it's small fan-shaped green leaves with white or light purple-to-pink or white flowers and it bears small oval fruit . The leaves of mandukparni are used as a memory enhancer within the Ayurvedic system of drugs . Its use has also been described within the African system of drugs, and traditional Chinese medicine. it's accustomed delay ageing, prevent memory related disorders and is given with milk to reinforce memory

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Main chemical constituents: the most chemical constituents of C. asiatica are asiaticosides, asiatic acid, madecassoside and madasiatic acid. Other chemical compounds isolated from C. asiatica are brahmoside and brahminoside, isothankuniside, thankuniside and centelloside . Pharmacological activities: C. asiatica is well-known for its broad pharmacological activities such anti-inflammatory, antioxidative stress, antiapoptotic effects, neuroprotective effects, wound healing, antipsoriatic, antiulcer, hepatoprotective, antidepressant activity, nootropic activity, anticonvulsant, sedative, immunostimulant, cardioprotective, antidiabetic, cytotoxic and antitumor, antiviral, antibacterial, insecticidal and antifungal .

Preclinical studies: Aqueous extract of C. asiatica in 100, 200 and 300 mg/kg doses given orally for 14 days has been reported to dose-dependently improve cognitive functions in normal rats . Pretreatment with the extract for 21 days significantly reversed streptozotocin induced cognitive impairment . The authors attributed the beneficial effect of C. asiatica to antioxidant activity as evidenced by a decrease in malondialdehyde, increase in glutathione, catalase and enzyme levels. A study by Rao et al. demonstrated that 15 days treatment with C. asiatica at a dose of 200 mg/kg from day 15 to 30 postpartum stimulated learning and memory in rats, which lasted for a minimum of 6 months postpartum. They also observed a rise in dendritic arborization of hippocampal CA3 neurons, which can be one reason for improvement in brain function. Another study showed improved cognitive outcome in elderly subjects following prescribed dose of 500 mg/b.i.d dried C. asiatica for a 6-month period . Dhanasekaran et al. found that an 8 month treatment with 2.5 mg/kg of aqueous extract of C. asiatica significantly decreased amyloid beta 1-40 and 1-42 levels within the hippocampus of PSAPP transgenic mice expressing “Swedish” amyloid precursor protein and M146L presenilin 1 mutations, which lead to spontaneous amyloid beta plaque formation. a discount in azo dye stained fibrillar amyloid plaques was detected on the long-term treatment with 5.0 mg/kg dose.

C. asiatica aqueous leaf extract showed improvement in learning and memory in rats, and modulated dopamine, 5-hydroxytryptamine (5-HT) and noradrenaline systems within the rat brain in-vivo . The leaf extract also had sedative, antidepressant and cholinomimetic activities suggesting its suitability for treatment of AD associated cognitive dysfunction and depression and anxiety. The leaf extract stimulated dendrites of neuronal cells within the rat brain and induced neurite elongation in human SH-SY-5Y cells and accelerated axonal regenerate in rats . Cyclic AMP response element binding property (CREB) and its phosphorylated form are involved in memory formation . Reduced level of phosphorylated CREB has been reported in AD patients and experimental models of AD. The aqueous extract of C. asiatica leaves enhanced phosphorylation of CREB in both neuroblastoma cells, which express inducible Aß and in cortical primary cells, which were chronically exposed to external Aß in-vitro. The extract increased neuronal dendritic arborization and axonal regeneration in rats. Triterpenoids are the most important active component of ethanolic extract of C. asiatica, which consists of the many chemical constituents like asiatic acid, mecadessic acid, asiaticoside, scentellin, asiaticin and centellicin. Asiatic acid and its derivatives have shown a promising memory improving effect by improving ACh synthesis . it's been patented (Hoechst Aktiengesellschaft) for the treatment of dementia and as a cognition enhancer. the precise constituent answerable for cognition enhancing effects of the herb remains to be established. However, studies suggest that perhaps triterpene saponins present within the leaf improve cognitive function by influencing central neurotransmitters.

Clinical evidence: in an exceedingly randomized, double-blind placebo-controlled, study, C. asiatica extract was administered to healthy volunteers as 250–750 mg once daily dose for two months. The high dose enhanced memory and improved self-rated mood .

Thus, clinical and experimental studies support memory enhancing potential of C. asiatica. However, its use for treatment of AD remains to be evaluated. **Toxicity:** C. asiatica extract and asiaticoside were found to be tolerated in experimental studies. Asiaticoside didn't cause any toxicity up to 1 g/kg oral dose . In acute toxicity study, C. asiatica extract up to 10 g/kg failed to shown any sign of toxicity whereas within the subacute toxicity study, no toxicity was observed when the extract was administered at the doses of 10–1000 mg/kg. within the chronic toxicity study, doses up to 1200 mg/kg/day for 6 months failed to lead to significant toxicity in Wistar rats However, in one study, oral administration of 1000 mg/kg/day

dried C. asiatica for 30 days caused hepatotoxicity in albino rats .

Plant description: Bacopa monnieri (B. monniera), belonging to the Scrophulariaceae family may be a small, perennial creeping herb with numerous branches, small oblong leaves and light-weight purple or white flowers. In India, it's commonly called Brahmi and is thought for its revitalizing, Medhya rasayana and nootropic activities because it strengthens memory and intellect (Medhya). Bacopa has been used for the treatment of assorted ailments for thousands of years by the practitioners of the normal system of medication of India.

Main chemical constituents: the most chemical compounds of B. monniera are triterpenoid saponins called bacosides. The alkaloids brahmine, nicotine and herpestine have also been reported during this plant. Novel saponins called bacopasides I–XII have also been identified Pharmacological activities: This medicinal herb possesses various biological activities like anticonvulsant, antidepressant, anxiolytic, analgesic, anti-inflammatory, antioxidant, antimicrobial, antiulcerogenic, anti-Helicobacter pylori, adaptogenic, antineoplastic, bronchodilatory, hepatoprotective and immunostimulatory

Preclinical studies: The extract of B. monniera has been reported to contain several beneficial bioactive components like alkaloids, flavonoids, glycoside, triterpenoids saponins and alcohols. The alcoholic extract of B. monniera improved acquisition, consolidation and retention of memory within the foot shock motivated brightness discrimination test, active conditioned avoidance response test and Sidman continuous avoidance responses in rats .Bacosides A and B (a mixture of two saponins) is also answerable for its facilitatory effect on learning and memory. Besides, bacosides has been proven for its antioxidant and anti inflammatory effects bacosides also attenuated the blackout produced by immobilization induced stress, electroconvulsive shock and scopolamine . They enhanced protein kinase activity and increased the protein content within the hippocampus, which can also contribute to their memory enhancing effect. Administration of bacosides (200 mg/kg) for 3 months in middle-aged and aged rats exerted a protective effect against age associated alterations within the neurotransmission system, behavioral paradigms, hippocampal neuronal loss and oxidative stress markers . The involvement of the microRNA 124-CREB pathway and serotonergic receptor within the memory enhancing mechanism of standardized extract of B. monniera (BESEB CDRI-08) has also been reported. The effect of alcoholic extract of Bacopa has been evaluated at the dose of 20, 40 and 80 mg/kg on cognitive functions and neurodegeneration within the animal model of AD induced by bilateral intracerebroventricular administration of AF64A. They found that Bacopa improved the escape latency within the Morris water maze test and prevented the reduction in cholinergic neuron density. Besides, oral administration of 40 mg/kg/day of the Bacopa extract for five weeks prevented neurotoxicity in rats exposed to aluminium chloride. Cognitive deficit induced by intracerebroventricular (ICV) injection of cholchicine and ibotenic acid into the nucleus basalis magnocellularis was attenuated by standardized Bacopa extract by reversing the depletion of ACh level, reduction in choline acetyl transferase (ChAT) activity and reduce in muscarinic cholinergic receptor binding in cortical region and hippocampus . Holcomb et al. reported that administration of ethanolic extract of Bacopa leaves at doses of 40 and 160 mg/kg for two and eight months reduced Aβ 1–40 and 1–42 levels within the cortex of PSAPP mice. Bacopa, at the dose of fifty mg/kg, demonstrated the neuroprotective effect within the colchicine model of dementia through its antioxidant effect and restored the activity of Na+K+ATPase and AChE . The neuronal dendritic growth stimulating property of Bacopa has also been reported which can be answerable for its memory enhancing property

Clinical evidence: in an exceedingly double-blind, placebo-controlled trial in 38 healthy volunteers (ages 18–60 years), single dose of 300 mg B. monniera extract (containing 55% combined bacosides A and B) didn't cause any significant change in cognitive function at 2 h . However, six week Bacopa administration (300 mg for subjects under 90 kg, and 450 mg for subjects over 90 kg, adore 6 g and 9 g dried rhizome, respectively) during a double-blind, randomized, placebo controlled fashion was related to significant improvement in retention of latest information in 40–65 year old healthy adults. Though there was no difference within the rate of acquisition of knowledge . Stough et al. reported significant improvement in verbal learning, memory consolidation and speed of early science following Bacopa administration (containing 55% combined bacosides) for 12 weeks at a dose of 300 mg daily during a double-blind placebo-controlled study in healthy volunteers (age 18–60 years, n = 46). Since the results weren't observed until five weeks of treatment, the slow onset of action could also be attributed to Bacopa's antioxidant properties and/or its effect on the cholinergic system. In another randomized, double-blind, placebo-controlled trial in 54 elderly participants without clinical signs of dementia (mean age 73.5 years), similar Bacopa treatment enhanced an auditory verbal learning test, delayed word recall memory scores and a stroop test relative to the placebo . In subjects above 55 years old with memory impairment,

standardized Bacopa extract 125 mg was given twice daily for 12 weeks in a very run, placebo-controlled manner. There was a big improvement in mental control, logical memory and paired associated learning . Furthermore, Bacopa extract at the dose of 300 mg/kg, daily for 12 weeks improved memory acquisition and retention in healthy older Australians population

In children (age 6–8 years), Bacopa syrup (350 mg Bacopa powder), when administered 3 times daily for 3 months, resulted in significant improvement as compared to the placebo . However, this study wasn't blinded. Negi et al. applied a double-blind, randomized, placebo-controlled trial in 36 children diagnosed attentively deficit/hyperactivity disorder (mean age 8.3–9.3 years). Nineteen children received Bacopa extract (standardized to contain 20% bacosides) at a dosage of fifty mg twice daily for 12 weeks. As compared to placebo, a big improvement in cognitive function was observed in Bacopa-treated children at 12 weeks as evidenced by improvement in sentence repetition, logical memory and paired associate learning tasks, which was maintained at 16 weeks (after four weeks of placebo administration). **Toxicity**: The LD50 of orally administered Bacopa extracts in rats was 5 g/kg for aqueous extract and 17 g/kg of the alcoholic extract . The intraperitoneal LD50 was 1000 mg/kg for aqueous extract and 15 g/kg for alcoholic extract . A double-blind, placebo-controlled trial in healthy male volunteers reported safety and tolerability of bacosides in single (20–30 mg) and multiple (100–200 mg) daily doses over a four-week period . A randomized, double-blind, placebo-controlled trial reported that Bacopa treatment (300 mg/kg, daily) for 12 weeks caused increased stool frequency, abdominal cramps and nausea, which can flow from to either an upregulation of ACh level or saponin-mediated GI tract irritation, or both .

Curcuma longa

Plant description: herb (C. longa) Linn may be a perennial herb belonging to the Zingiberaceae. it's grown for commercial use in South and geographical region. Curcumin, also called turmeric, is obtained from the rhizome of the plant, and is usually utilized in India as a food flavoring and coloring agent. Several preparations of the plant are used for hundreds of years within the Ayurvedic system of drugs .

Main chemical constituents: Curcuminoids are main chemical constituents of turmeric, which include mainly curcumin (diferuloyl methane), demethoxycurcumin and bisdemethoxycurcmin. Other chemical compounds reported during this plant are alpha- and beta-tumerone, artumerone, alpha- and gamma-atlantone, curlone, zingiberene and curcumol Pharmacological activities: Previous studies reported the varied pharmacological properties of curcuminoids like neuroprotective, analgesic, antiproliferative, anti-inflammatory, anticancer, antidiabetic, hypocholesterolemic, antithrombotic, antihepatotoxic, antidiarrheal, carminative, diuretic, antirheumatic, hypotensive, antimicrobial, antiviral, antioxidant, larvicidal, insecticidal, antivenomous and antityrosinase effects.

Preclinical studies: it's also one among the foremost systematically studied plants for various diseases . it's been reported in various experimental studies to possess large choice of biological and pharmacological activities including antioxidant, anti-inflammatory and cholesterol-lowering properties, all three of which are key processes involved within the pathogenesis of AD. Water insolubility could be a major limitation for curcumin, which has been overcome, to some extent, by synthesis of biodegradable poly (lactic-co-glycolic acid) (PLGA) coated curcumin nanoparticles. These nanoparticles were found to be able to destroy amyloid aggregation and exhibit antioxidative activity without a cytotoxic effect . Nanoliposomes of curcumin have high affinity for Aβ1-42 fibrils and were found to inhibit the formation of fibrillar and oligomeric Aβ in-vitro . Apolipoprotein E3 mediated poly(butyl) cyanoacrylate nanoparticles containing curcumin (ApoE3-C-PBCA) provided photostability, enhanced the cellular uptake of curcumin and increased its efficacy against Aβ induced cytotoxicity. Curcumin also demonstrated a protective effect against Aβ neurotoxicity by decreasing Aβ production through downregulation of presenilin 1 (PS1) and GSK-3-β expression and accelerating Curcumin has been shown to scale back both in-vivo and in-vitro Aβ plaque deposition . Curcumin treatment for 6 months significantly decreased the elevated levels of oxidized protein and proinflammatory interleukin-1β within the transgenic Epps mouse brain (Tg2576). Plaque formation and also the concentration of insoluble and soluble Aβ were also lowered by curcumin within the same study. Pre-treatment with curcumin (10, 20 and 50 mg/kg, p.o for 21 days) ameliorated memory impairment within the sporadic AD model in mice. Furthermore, curcumin in diet form improved the spatial memory, oxidative stress and synaptophysin loss via reducing Aβ deposits. Significant cognitive improvement was documented at low (160 ppm) and high (1000 ppm) doses of curcumin after administration for the 6-month period within the double transgenic AD model (APP/PS1). In-vivo, curcumin may protect cells from beta amyloid attack and subsequent oxidative stress-induced damage. Curcumin can inhibit Aβ aggregation or promote its disaggregation at low concentrations (IC50 = 0.81–1 μM). Monomeric Aβ formed

fewer aggregates within the presence of curcumin, whereas increasing doses of curcumin promoted disassembly of preformed Aβ aggregates. Structurally, curcumin is analogous to azo dye and might prevent oligomer formation after binding to plaques and recognize secondary structure in fibrillar and oligomeric Aβ. Low dose curcumin significantly lowered the soluble Aβ levels, insoluble amyloid and plaque burden by nearly 40. Additionally, curcumin treatment for 7 days caused reduction in plaques burden and reversed structural changes in dystrophic dendrites in APPswe/PS1dE9 mouse model of AD.
Impaired insulin or insulin-like growth factor-1 (IGF-1) signaling is related to AD. It ends up in hyperphosphorylation of the tau protein, mitochondrial dysfunction, oxidative stress and necrosis, and contributes to cognitive impairment .Curcumin significantly improved cognitive function by improving the IGF-1 level within the intracerebroventricular (ICV)-streptozotocin (STZ) model of sporadic AD . It also suppressed IL-1 and glial fibrillary acidic protein, reduced oxidative damage and plaque burden and decreased the number of insoluble amyloid. Another experimental study showed that curcumin treatment restored learning and memory functions within the STZ model of AD by reducing the oxidative stress, enhancing ChAT activity and restoring insulin receptor protein .

Curcumin suppressed the microgliosis in neuronal layers, but it did not reduce within plaques microgliosis and even significantly increased microgliosis immediately adjacent to plaques, raising the chance that it should stimulate microglial phagocytosis of amyloid. Other possible mechanisms for curcumin induced neuroprotective effects include inhibition of IL-1-induced increase in alpha-1-antichymotrypsin (α1ACT) and NFκB-mediated transcription of apolipoprotein E (ApoE). Both α1ACT and ApoE are shown to be proamyloidogenic in APP transgenic mice. Curcumin can even reduce two other proamyloidogenic factors, oxidative damage and raised cholesterol levels . The neuroprotective effect of curcuminoid mixture and its individual components on inflammatory and apoptotic organic phenomenon in AD using an Aβ plus ibotenic acid-infused rat model has also been reported . Additionally, Ahmed and colleagues also reported that a curcuminoids mixture (bisdemethoxycurcumin, demethoxycurcumin and curcumin) treatment improved memory function in amyloid fragment induced AD-like conditions in rats . Nonetheless, chronic treatment with curcumin also prevented the colchicine induced cognitive impairment in rats by reducing the oxidative stress . Chronic stress induces impairment of spatial cognition, neuroendocrine and plasticity abnormalities because of a rise in serum corticosterone levels. Curcumin exerts its neuroprotective effect by normalizing the corticosterone response, leading to downregulating of calcium/calmodulin kinase II and glutamate receptor (NMDA-2B) levels . The protective effect of curcumin on a Aβ1–40 AD model was documented by Wang et al. and Yin et al. , where treatment with 300 mg/kg curcumin reversed spatial learning and memory impairment in the midst of hippocampal regeneration. Evidence also suggests that metals are concentrated within the AD brain and curcumin chelates iron and copper (but not zinc) sure to beta amyloid potentially contributing to amyloid reduction . a distinct approach was followed by McClure et al. , where aerosol-mediated treatment of young 5XFAD mice with curcumin averted Aβ buildup and memory deficits in adulthood as compared to the untreated mice.
Thus, this multitarget compound may be a promising therapeutic agent for AD and associated cognitive decline. However, despite intensive curcumin related research in various diseases, there's an absence of clinical data on the efficacy of curcumin in AD.
Toxicity: in a very clinical test trial with 25 healthy subjects, curcumin up to 8000 mg/day for 3 months didn't show any toxicity . In an acute toxicity study, ethanolic extract of rhizome of C. longa at the doses of 0.5, 1.0 and 3.0 mg/kg failed to cause any sign of toxicity in mice. Moreover, no toxicity was found at 100 mg/kg/day within the 90-day toxicity study in mice .

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Clitoria ternatea

Plant description: Clitoria ternatea (C. ternatea) may be a perennial tropical climber herb with slender downy stem, found throughout the tropical regions of India, growing wild and in gardens, bearing white or blue flowers. C. ternatea belongs to family Leguminosae commonly called “butterfly”. it's a commonly used Ayurvedic medicine. C. ternatea is termed Aparajit (Hindi), Aparajita (Bengali) and Kakkattan in Indian traditional medicine. The extracts of C. ternatea are utilized in Ayurveda, as an ingredient in “Medhya rasayana”.

Main chemical constituents: Various

phytocomponents like 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, aparajitin, beta-sitosterol, malvidin-3ß-glucoside, kaemphferol, p-coumaric acid, etc., are isolated from C. ternatea.

Pharmacological activities: In previous studies, various biological activities including nootropic, anticonvulsant, antidepressant, antianxiety, antistress, antioxidant, anti-inflammatory, antihyperlipidemic, antidiabetic, antiasthmatic, analgesic, immunomodulatory, cytotoxicity, platelet aggregation inhibitory, antimicrobial, gastroprotective and hepatoprotective of C ternatea are documented .

Preclinical studies: The nootropic activity of methanolic extract of aerial parts of C. ternatea (100 mg/kg, p.o) has been reported by using elevated plus maze and therefore the beholding test in rats . Taranalli and Cheeramkuzhy evaluated the ethanolic extracts of roots and aerial parts of C. ternatea at the dose of 300 and 500 mg/kg, p.o in amnesia induced by submaximal electroshock . They also estimated the ACh level within the whole brain and different parts of it. The aerial parts extract resulted in improved memory retention and increased brain ACh content, which was more at 300 mg/kg as compared to the five hundred mg/kg dose. the foundation extract exhibited similar but more marked effects, which were almost equal at both doses. Rai et al. described the training and memory enhancing effect of the C. ternatea root extract during the expansion spurt period in rats. They intubated 7-day old neonatal rats and administered 50 and 100 mg/kg of the aqueous root extract of C. ternatea for 30 days. The extract improved retention within the passive avoidance task and spatial performance within the T-maze test. The behavioral changes were reported to be long lasting as indicated by a 30 days post-treatment evaluation. A previous study also showed that the aqueous root extract (50 and 100 mg/kg, p.o for 30 days) enhanced dendritic arborization of amygdala neurons in rats . This cognition enhancing effect was hypothesized to ensue to the presence of proteins kind of like the brain derived neurotrophic factor or nerve growth factor. Increase in hippocampus acetylcholine content could also be one amongst the explanations for nootropic activity of C. ternatea root. additionally, Rai reported that the C. ternatea root extract exhibited the neurogenesis-promoting sequel on the anterior subventricular zone of neural stem cells. More recently, Damodaran et al. documented the neuroprotective effect of the C. ternatea root extract in reversing chronic cerebral hypoperfusion-induced neural damage and memory impairment at doses of 200 and 300 mg/kg. In another study, Mehla and colleagues showed anti-AD effects of C. ternatea in ICV-STZ induced AD-like conditions in rats . These observations suggest that C. ternatea extract exerts its beneficial effect by preventing the progression of cognitive deterioration in AD. However, the potential of C. ternatea extract still has to be systematically evaluated for human use. Toxicity: Ethanolic extract of aerials parts and root of C. ternatea are studied at 200–3000 mg/kg, p.o in mice. A cathartic effect of root extract was observed. Mice treated with a dose above 2000 mg/kg had ptosis and were lethargic. The extract wasn't lethal orally but resulted in severe CNS depression and death when used intraperitoneally at dose of 2900 mg/kg and above . Taur and Patil reported LD50 of ethanolic extract of C. ternatea root to be quite 1300 mg/kg.

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Withania somnifera

Plant description: *Withania somnifera* (*W. somnifera*) is a small woody shrub belonging to the family Solanaceae and is widely grown in India. It is commonly called Indian ginseng or winter cherry or ashwagandha. Its flowers are greenish or yellowish in color and about one centimeter long . Ashwagandha is mentioned in ancient Sanskrit writings from India as a “Medhya rasayan”. It is also known as Indian ginseng and is widely used in Ayurveda. It is an ingredient in many formulations prescribed as a general tonic to increase energy, improve overall health and longevity.

Main chemical constituents: The major phytoconstituents of *W. somnifera* are isopellertierine, anferine, withanolides, withaferins, sitoindoside VII and VIII and withanoloides. Other chemical compounds are withanine, somniferine, somnine, somniferinine, withananine, pseudo-withanine, tropine, pseudo-tropine, 3-a-gloyloxytropane, choline and cuscohygrine .

Pharmacological activities: *W. somnifera* exhibits a broad range of biological activities like anti-inflammatory, antioxidant, neuroprotective, antischemic, anti-Parkinson’s, antiepileptic, anxiolytic, antidepression, antiarthritic, cardioprotective, antidiabetic, anticancer, antistress, nephroprotective, heptoprotective, antihypoxic, immunomodulatory, hypolipidaemic and antimicrobial.

Preclinical studies: Total alkaloid extract (ashwagandholine, AG) of *W. somnifera* root has been studied for its effects on CNS . *W. somnifera* attenuated the memory loss induced by STZ through the antioxidant mechanism . The root preparation has been shown to have protective effects in neurodegenerative disorders by reducing stress induced degeneration in the brain hippocampus of rats . The extract containing sitoindosides VII–X and withaferin A (50 mg/kg, p.o for two weeks) reversed ibotenic acid-induced cognitive

deficit and reduction in cholinergic markers (e.g., ACh and ChAT) in rats . Sitoindosides VII-X and withaferin differentially (40 mg/kg for 7 days) but favorably altered the AChE activity and enhanced M_1- and M_2-muscarinic receptor-binding in various brain regions . Withaferin A and Withanolide A suggested to have a potent immunomodulatory effect in BV-2 microglial cells by triggering the Nrf2 pathway, leading to production of the neuroprotective protein, such as heme oxygenase-1 .

Withanoside IV, another chemical constituent of *Withania*, when administered orally at the dose of 10 micromol/kg prevented cognitive impairment in the experimental model of AD [44]. Sominone (1 microM) a metabolite of Withanoside IV, induced axonal and dendritic regeneration and synaptic reconstruction in cultures of rat cortical neurons damaged by the amyloid peptide, Aβ(25–35) . Therefore, withanoside IV may act as a prodrug, with sominone as the active component. The enhancement of spatial memory by sominone may be attributed to neuritic outgrowth, which is mediated by the neurotrophic factor receptor, RET . Methanolic root extract dose dependently enhanced in-vitro dendrite formation in human neuroblastoma cells . A study carried out by Jayaprakasam et al. stated that withanamides (A/C) present in *W. somnifera* fruits protect pheochromocytoma-(PC-12) from β-amyloid induced toxicity. In the same study, β-amyloid fibril formation was prevented, possibly due to the presence of a serotonin moiety in both withanamide compounds.

Treatment with *Withania* root extract (1 g/kg, p.o for 30 days) reversed the AD pathology by upregulating the low-density lipoprotein receptor-related protein, which enhanced the Aβ clearance and ameliorated the cognitive deficit in middle-aged and old APP/PS1 mice. Alcoholic extract of the *Withania* leaf and its component withanone was neuroprotective against scopalmine induced changes in the brain . An in-vitro, inhibitory effect on the fibril formation by Aβ peptide has also been reported. The increase in cortical muscarinic ACh receptor capacity might partly explain the cognition-enhancing and memory-improving effects of *Withania*. The root extract and their chemical constituents such as glycowithanolides also possess anxiolytic, antidepressant, anti-inflammatory and antioxidant activities, which may be relevant in AD treatment. Furthermore, withanone, a chemical constituent from root extract of *W. somnifera* showed improvement in cognitive functions by inhibiting amyloid processing and reducing the elevated levels of proinflammatory cytokines and oxidative stress markers. *W. somnifera* (20 mg/mL) treatment mitigated the Aβ toxicity and mediated longevity in the AD model of *Drosophila melanogaster*.

Clinical evidence: A prospective, randomized, double-blind, placebo-controlled study reported that treatment with ashwagandha-root extract (300 mg twice daily for eight weeks) improved immediate and general memory functions and enhanced executive function, attention and information processing speed in adults with a mild cognitive impairment . In a systematic review, Ng and colleagues mentioned that *W. somnifera* extract ameliorated cognitive impairment and improved executive functions in adults with mild cognitive impairment . There is limited data available on the clinical use of *Withania* for cognitive impairment.

Toxicity: Different preparations and extracts of *W. somnifera* root did not cause any toxicity even on chronic treatment . Ashwagandholine 2% suspension in propylene glycol had a LD_{50} of 465 mg/kg in rats and 432 mg/kg in mice . Whereas intraperitoneal administration of aqueous-methanol root extract caused 50% lethality in mice at a dose of 1076 ± 78 mg/kg . Equimolar combination of sitoindosides VII and VIII and withaferin-A (SG-2) when administered once intraperitoneal, the LD_{50} was 1564 ± 92 mg/kg .

Celastrus paniculatus

Plant description: *Celastrus paniculatus* (*C. paniculatus*) is a large climber of the family Celastraceae. It grows throughout India, on sub-Himalayan slopes and the hilly regions of Punjab and South India. It is commonly known as jyotismati, which comes from the Sanskrit words "jyoti teja" or fire of mind and "mati"—intelligence. Traditionally, the bark and seeds have been used as a brain tonic, to promote intellect and to improve digestion, stimulant and expectorant . In Ayurveda, *C. paniculatus* has been used to treat many diseases like depression, leprosy, paralysis, fever and arthritis. The seed oil and fruit are commonly used for their tranquilizer, sedative and wound healing properties .

Main chemical constituents: *C. paniculatus* shows the presence of various phytoconstituents such as sesquiterpenoid polyalcohols and esters (malkanguniol, malkangunin, polyalcohol A–D and celapnin); alkaloids (paniculatine and celastrine); phenolic triterpenoids (celastrol and paniculatadiol); fatty acids (oleic, linoleic, linolenic, palmitic, stearic and lignoceric acid) and agarofuran derivatives .

Pharmacological activities: Various pharmacological activities such as hypolipidemic, neuroprotective, anti-infertility, antiarthritic, wound healing, anti-inflammatory, antioxidant, analgesic, antimalarial, antibacterial and fungicidal action of *C. paniculatus* have been reported

Preclinical studies: Celastrus seed extract and oil have been evaluated in different experimental models of cognitive impairment such as scopolamine and sodium nitrite induced amnesia. The aqueous, methanolic, chloroform and petroleum ether extracts of seeds of *C. paniculatus* were investigated for their effect on cognitive function in rats. The aqueous extract showed significant improvement in cognitive performance at the doses of 200 and 300 mg/kg, p.o for 14 days. In another study, methanolic extract reported to have memory-enhancing activity in rats at doses of 100, 200 and 400 mg/kg . The antioxidant activity of *C. paniculatus* may be involved in improving the cognitive function . The oil of *C. paniculatus* seeds when given for 14 days to Wistar rats at a dose of 400 mg/kg resulted in enhanced learning and memory in radial arm maze and decreased the AChE enzyme activity in hypothalamus, frontal cortex and hippocampus Karanth et al. also demonstrated a similar effect of *C. paniculatus* at the dose of 400 mg/kg for 3 days. In another study, rats treated with 850 mg/kg of *C. paniculatus* oil for 15 days had significantly improved retention in two passive avoidance tasks . The seed oil treatment for 14 days at the doses of 50, 200 and 400 mg/kg, p.o reversed scopolamine induced spatial memory impairment in the Morris water maze and increased locomotor activity without affecting AChE activity in rats . The aqueous seed extract improved memory performance in elevated plus maze and in sodium nitrite induced amnesia by reducing the AChE activity . Furthermore, *C. paniculatus* seed oil treatment showed memory improvement in scopolamine induced amnesia in mice . *C. paniculatus* has not undergone clinical trials for safety and efficacy. Animal toxicology data is also lacking to dat

Plant description: *Evolvulus alsinoides* L. (*E. alsionoides*, dwarf morning glory), belonging to the family Convolvulaceae, is a perennial herb with small woody and branched rootstock. *E. alsionoides* is a weed, found mainly in the swampy regions of tropical and subtropical regions of the world. It has numerous branches (greater than 30 cm) with long hairs. The leaves are small, acute, elliptical with small size and blue-colored flowers . It is locally known as Shankhpushpi and is very commonly used in Ayurveda. It is a key ingredient in majority of Medhya Rasayana formulations available in the Indian market. It is traditionally used as a memory enhancer in children and elderly and for neurological disorders like epilepsy.

Main chemical constituents: Major chemical constituents are octadecanoic acid, n-hexadecanoic acid, piperine, squalene, ethyl oleate and cholesterol.

Pharmacological activities: Studies indicate that *Evolvulus alsionoides* (*E. alsionoides*) possesses in-vitro antioxidant , immunomodulatory , adaptogenic, antiamnesic and antiulcer activities.

Preclinical studies: Nahata et al. reported learning and memory enhancing property of its ethanolic extract and ethyl acetate and aqueous fractions in rats. The ethanolic extract (100 mg/kg, p.o) also protected against scopolamine induced dementia in rats . Three days oral treatment with *E. alsionoides* (100 mg/kg) was effective in decreasing scopolamine induced deficit in adult male Swiss mice [. Pretreatment with hydro-alcoholic extract at the doses of 100, 300 and 500 mg/kg, p.o ameliorated the ICV-STZ induced cognitive impairment by decreasing the oxidative stress and rho kinase (ROCK II) expression in the rat brain . In-vitro, aqueous and hydroalcoholic extracts of *E. alsinoides* showed free radicals scavenging, anti-inflammatory and enzymes (cholinesterase, glycogen synthase kinase-3-β, Rho kinase (ROCKI I), prolyl endopeptidase, catechol-o-methyl transferase and monoglycerol lipase) inhibitory activity, all of which are involved in the pathophysiology of AD. Previous studies also indicated the memory enhancing effect of *E. alsionoides* in the experimental model of amnesia . The methanol and water extract of *E. alsinoides* documented to exhibit acetylcholinesterase activity, supporting its potential in reverting neuronal dysfunctions and thus in management of AD . *E. alsionoides* has not been studied systematically for clinical efficacy and toxicological effects.

Desmodium gangeticum

Plant description: *Desmodium gangeticum* (*D. gangeticum*), belonging to the family Fabaceae, commonly known as Salpani in Hindi and is found in abundance throughout India. It is a perennial undershrub, 60–130 cm high with somewhat angular branches. Its leaves are simple, ovateoblong or rounded with purplish or white flowers, 4–7 cm . It has been used in the traditional system of medicine as a bitter tonic, febrifuge, antiemetic, digestive and in various inflammatory conditions due to vata disorder . In Satpuda hills of India, powdered root of *D. gangeticum* is applied along with honey to treat a mouth ulcer. In Uttat Pradesh state of India, the leaf paste of *D. gangeticum* and aloe vera are applied to prevent hair fall .

Main chemical constituents: *D. gangeticum* shows the presence of alkaloids (tryptamines and phenylethylamines), pterocarpanoids (gangetin and desmodin), phospholipids, sterols, flavone and glycosides

Pharmacological activities: It shows various pharmacological activities including antileishmanial, immunomodulatory,

antioxidant, anti-inflammatory, antinociceptive, cardioprotective, antiulcer, antiamnesic and hepatoprotective .

Preclinical studies: Aqueous extract of *D. gangeticum* when administered orally at the dose of 50, 100 and 200 mg/kg for 7 days improved memory in mice. Scopolamine and ageing induced amnesias were also prevented in rats by pretreatment with the aqueous extract of *D. gangeticum*. Moreover, treatment of mice with the chloroform extract (400 mg/kg) and alkaloidal fraction (50 mg/kg) of *D. gangeticum* for 6 days alleviated the scopolamine-induced amnesia . Antioxidant, anti-inflammatory and AChE inhibitory activity of *D. gangeticum* has also been reported . These pharmacological properties indicate the potential of *D. gangeticum* in the management of AD related cognitive impairment. Yet, not much clinical evidence is available to this effect. Toxicity studies are also required to establish the safety of this potentially useful herb.

Eclipta Species

Plant description: *Eclipta alba* (L.) Hassk (*E. alba*) is an annual erect or prostrate herb, belonging to the Asteraceae family. There are four major varieties of Eclipta based on the colors of flower like red, yellow, white and blue. The flowers of *E. alba* are white in color and largely harvested due to its therapeutic activity. Its stem is reddish-purple in color with up-turned hairs and roots are greyish with cylindrical shape . *Eclipta alba* (*E. alba*), commonly known as Bringharaj, is well known in the traditional system of medicine for its beneficial effects on learning and memory. Another species of Eclipta, commonly known as false daisy, is *E. prostrate*. It has also been traditionally used for treatment of memory related disorders, hepatic disorders and atherosclerosis .

Main chemical constituents: The major chemical constituents present in *E. alba* are coumestans, flavonoids, sterols, alkaloids, triterpenoid saponins and volatile oil.

Pharmacological activities: It has good antimicrobial properties like antibacterial, antifungal and antimalarial. It also shows antidiabetic, hepatoprotective, hypolipidemic, anticancer, hair growth promoting and memory enhancement and immunomodulatory properties .

Preclinical studies: The ethanolic extract of *E. alba* resulted in improvement in learning and memory abilities in passive avoidance and the elevated plus maze test in rats after both acute and chronic administration . Saponins, the main chemical constituent of butanol fraction of *E. prostrate*, prevented ethanol induced memory impairment in rats . Kim et al. also reported that butanol fraction increased ACh content, decreased MAO-B activity and reduced oxidative stress in the rat brain. Lipid lowering and antioxidant activities of *Eclipta* plants have also been reported . *E. alba* also possesses antiviral, antinociceptive, anti-inflammatory, bronchodilator, antibacterial, antipyretic, tonic, expectorant and hepatoprotective activity . Previous study also reported the improvement in learning and memory functions of rats] Based on the animal data available, the herb needs to be evaluated clinically.

Toxicity: An aqueous extract of *E. alba* did not cause any toxicity at a dose of 2.0 g/kg orally and 200 mg/kg by intravenous and intraperitoneal routes. The LD_{50} in mice were 7.841 g/kg, 302.8 and 328.3 mg/kg for oral and intravenous and intraperitoneal routes respectively .The alcoholic extract did not show any toxicity in rats and mice and the minimum lethal dose was found to be greater than 2.0 g/kg when given orally and intraperitonially in mice .

Moringa oleifera

Plant description: *Moringa oleifera* (*M. oleifera*) belonging to the family Moringaceae is the commonly distributed species of this family. This plant is native to India and the height of trees can reach up to 10 m. It has fragile branches and bipinnate or tripinnate leaves. It has yellowish white flowers 0.5–1 cm long and around 2 cm broad . It is commonly known as a drumstick. *M. oleifera* has shown antimicrobial activity and traditionally been used to clarify water due to its coagulant property. Oil of *M. oleifera* has high stability and contains a large amount oleic acid, hence used as an edible oil, biodiesel and lubrication of machinery .

Main chemical constituents: The major chemical constituents in *M. oleifera* are vitamins (vitamin A and C), polyphenols (flavonoids, chlorogenic acid and phenolic acids), alkaloids, glucosinolates, isothiocyanates, tannins and saponins .

Pharmacological activities: Various pharmacological activities like nootropic, anti-inflammatory, hypocholesterolemic, hypotensive and antioxidant effects of its leaves have been reported. Additionally, it has also shown hypolipidemic, antiobesity, antidiabetic, anti-inflammatory, immunomodulatory and anticancer effects. *M. oleifera* is a good source of vitamin, hence prevents night-blindness and delays cataract development.

Preclinical studies: Pretreatment with *M. oleifera* at an oral dose of 250 mg/kg prevented hypoxia induced memory impairment in rats by maintaining the monoamines levels in the brain . The ethanolic leaf extract at a dose of 250 mg/kg, p.o for 14 days provided protection against cognitive

impairment induced by ICV–colchicine. It restored colchicine induced changes in the brain norepinephrine, serotonin and dopamine levels . Improvement in learning and memory has been suggested to be due to its antioxidant effect. Other studies also demonstrated the protective effect of *M. oleifera* against memory impairment in experimental models of dementia. Intriguingly, *M. oleifera* was shown to mitigate hyperphosphorylation and Aβ pathology also in hyperhomocysteinemia-induced AD in rats .The mechanism of action, composition of the herb and difference between different extracts need to be established before it can be taken to clinical trials.

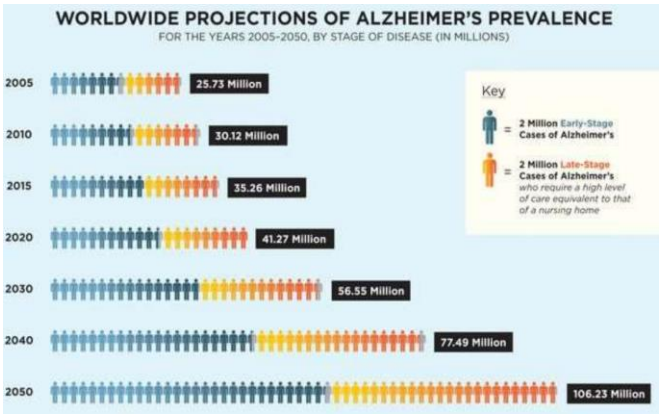
Toxicity: The aqueous leaf extract was found safe in rats after oral administration of 2000 mg/kg . The acute toxicity of aqueous and ethanolic extract of *M. oleifera* root was evaluated in mice with the LD_{50} of 15.9 g/kg and 17.8 g/kg, respectively .

Prevention

Modifiable risk factors for AD

Since AD develops over a long preclinical stage that can last for several decades, the extent to which risk factors assessed in late life or shortly before the onset of clinical symptoms are a result of pathological changes rather than having a causal relationship has been discussed intensively. Longitudinal studies that include participants in early mid-life have been crucial to assess the relationship between early or mid-life exposures and cognitive decline or AD later in life .

Observational studies have identified several modifiable risk factors for AD. Based on a comprehensive systematic review of the evidence related to risk factors for cognitive decline and AD, the US National Institutes of Health highlighted diabetes mellitus, smoking, depression, mental inactivity, physical inactivity and poor diet as being associated with increased risk of cognitive decline, AD, or both . Later on, this list was further extended to include hypertension, obesity and low educational attainment. Recently, an association was demonstrated between the presence of vascular risk factors in mid-life and amyloid deposition later in life , even though some of these factors are still under debate. It has been estimated that up to a third of AD cases are potentially attributed to these factors and, consequently, could be prevented .



II. CONCLUSION

Alzheimer's disease is now considered a world health concern; as a consequence, the National Institute on Aging—Alzheimer's Association reclassified and updated the 1984 NINCDS-ADRDA criteria for higher specificity, sensitivity, and early identification of patients at risk of developing AD. Several criteria have been proposed for a more accurate diagnosis of AD, including clinical biomarkers, bodily fluids, and imaging studies. Despite that, the treatment of AD remains symptomatic, without alteration in the disease's prognosis. Inhibitors to cholinesterase enzyme such as galantamine, donepezil, and rivastigmine, and NMDA antagonists such as memantine, improve memory and alertness but do not prevent progression. Several studies have shown that modification in lifestyle habits like diet and exercise can improve brain health and reduce AD without medical intervention and is considered as a first-line intervention for all AD patients. Recently, the research is focusing on targeting the pathological features of AD such as Aβ and p-tau. Future therapies such as disease-modifying treatment can alter the progression of AD by targeting the Aβ pathway, and many drugs have entered the clinical trials, like AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil, but failed in demonstrating efficacy in the final clinical stages. Other DMTs are still under investigation, such as those targeting Aβ and tau pathologies, such as aducanumab, gantenerumab, crenezumab, tideglusib, lithium, and others. Other promising compounds called chaperones like heat shock proteins and vacuolar sorting protein 35 (VPS35) function by assisting other proteins to function normally and to arrive at their destination in the cell safely, and therefore can be used as a treatment for neurodegenerative diseases. Moreover, the natural extracts used in folk Chinese medicine showed great potential in treating AD by acting on several mechanisms' pathways. In conclusion, the success of AD treatment depends on its early administration and patient monitoring for disease progression using biomarkers diagnosis. Future therapies that target tau

pathology and the use of combination therapy may have a potential to slow the progression of AD pathology. Designing a potent, selective, and effective drug is urgently needed to treat patients with AD and those at risk for developing the disease.

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