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The Role of Indian Traditional Medicine in Alzheimer's Disease Treatment: A Scientific Perspective

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Abstract: *Cognitive impairment, caused by aging, stress, high blood pressure, and neurodegenerative diseases like epilepsy and Parkinson's, is a serious health issue. This review covers Alzheimer's disease (AD), the leading cause of cognitive decline. Progressive memory loss, linguistic impairments, agitation, sadness, mood swings, and psychosis define it. AD is characterized by β-amyloid plaques, neurofibrillary tangle formation, and cholinergic dysfunction, but other neurotransmitter dysfunction, high AGO levels, oxidative damage, neuroinflammation, and genetic and environmental factors are also factors. Due to this complicated etiopathology, reactions to widely prescribed medications like memantine, galantamine, rivastigmine, and donepezil are unpredictable and often unsatisfactory. Herbal remedies are recommended due to their cholinesterase inhibitory and nonspecific antioxidant and anti-inflammatory properties. Growing awareness of herbal medicines' efficacy, safety, and cost is driving their popularity. This article reviews the experimental and clinical evidence for several Indian herbal medicines that may treat cognitive impairment, including Centella asiatica, Bacopa monnieri, Curcuma longa, Clitoria ternatea, Withania somnifera, Celastrus paniculatus, Evolvulus alsinoides, Desmodium gangeticum, Eclipta alba, Moringa oleifera, and Convolvulus pluricaulis. Several popular Indian herbal memory-impairing formulations were reviewed.*

Keywords: Ayurvedic herbs, Traditional formulations.

I. INTRODUCTION

Ayurveda lists Dhi (acquisition/learning), Dhuti (retention), and Smriti (recall) as mental skills [1]. A defect in learning, memory, or recall is dementia. Dementia affects 40 million seniors [2, 3]. Dementia affects 3.7 million Indian seniors, and it will triple by 2050 and treble by 2030 [4]. Epilepsy, Parkinson's, and AD are connected to dementia.

Since AD accounts for roughly two thirds of dementia cases, this review examines herbal AD therapy [5,6].

Memory, executive functioning, language, visuospatial functioning, and attention are the main cognitive functions affected by AD. Several hypotheses explain AD's genesis. The first theory, the cholinergic hypothesis, blames ACh deficiency [7]. Current AD treatments are based on this notion [8]. The most compelling theory [9-12], the β-amyloid hypothesis, underpins innovative AD therapy techniques [13]. Histologically, AD is characterized by neuritic plaque and brain NFTs [14]. High levels of oxidative damage, neuroinflammation, and advanced glycation end products may also contribute to AD neurodegeneration (Figure 1). Free radicals and inflammation contribute to AD pathogenesis, suggesting antioxidants and anti-inflammatory medications may be beneficial [15]. Research indicates that antioxidants may prevent neuronal damage from Aβ [16, 17]. FZS, a herbal drug, has been found to protect the brain by inhibiting Aβ (25–35)-induced activation of cyclin-dependent kinase 5, calcium influx, calpain activation, and tau hyperphosphorylation [18]. Also, an aqueous extract of Ceylon cinnamon (C. zeylanicum) suppresses tau aggregation and filament formation [19].

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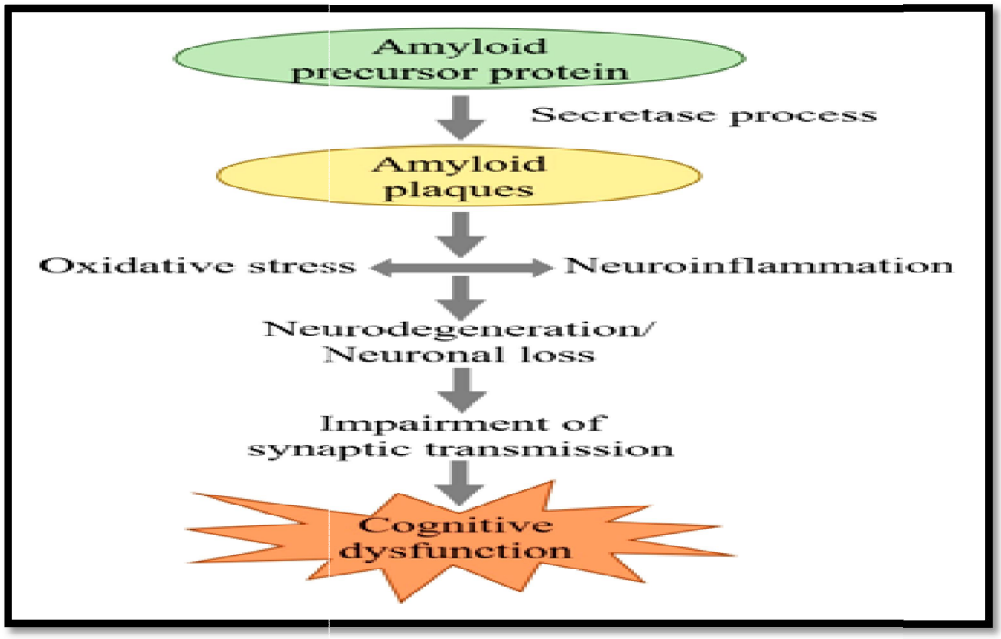

Figure 1. General pathogenesis of Alzheimer's disease (APP, amyloid precursor protein).

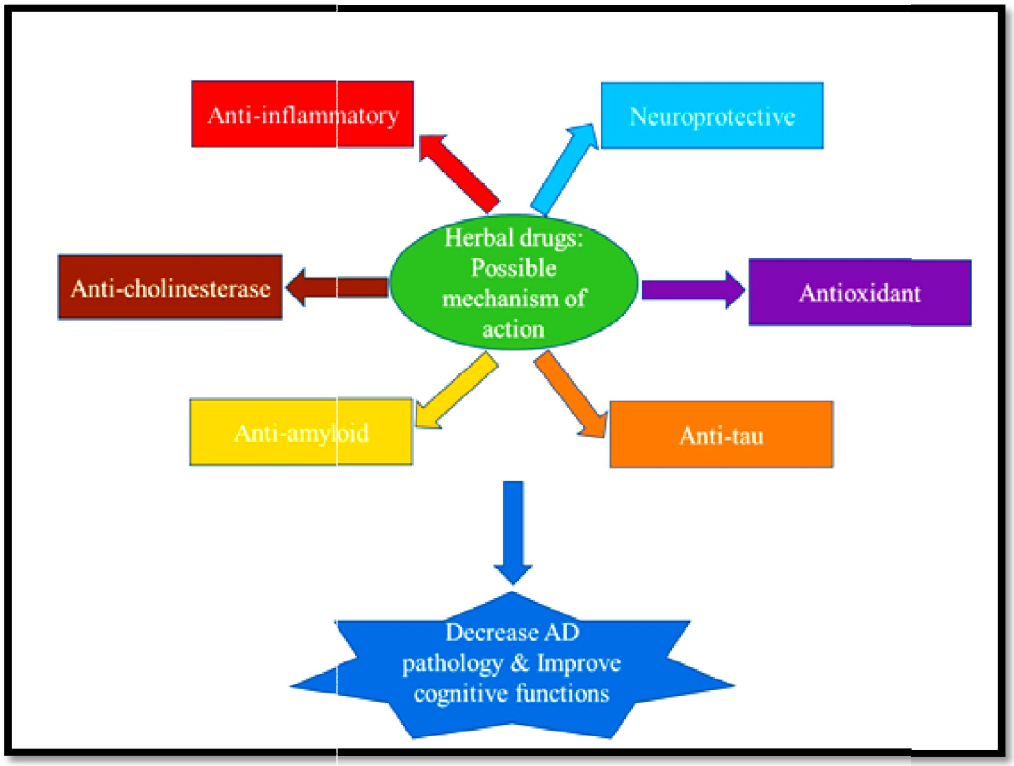

Figure 2. Multipronged approach of herbal medicines in Alzheimer's disease.

Thus, this study evaluates many AD-treatment-related herbal drugs and formulations.

Experimental and Clinical Evidence for Alzheimer's Herbal Remedies

Herbal treatments and complementary therapies have addressed neurological issues since ancient times. Many herbal medicines cure neurodegenerative illnesses worldwide. Europeans have used Salvia lavandulaefolia (Spanish sage) and

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Salvia officinalis (common sage) to improve memory since the 16th century, and clinical evidence supports these claims. Bacopa monniera, or water hyssop, has been used in Indian Ayurveda to improve memory and cognition since ancient times. Milk and Centella asiatica (Asian pennywort) improve memory. In Ayurveda, the revitalizing tonic root Withania somnifera improves memory. Due to their safety, affordability, and effectiveness, herbal treatments are becoming more popular. Herbal therapies for memory problems are just now being supported by science.

In experimental models of AD, CNS-active Indian herbal treatments including Withania somnifera, Centella asiatica, Celastrus paniculatus, and Bacopa monnieri enhance cognitive function as preventative medications [43–48]. Gingko biloba extract and donepezil were equally beneficial in AD patients with neuropsychiatric difficulties in a randomized, double-blind exploratory study. The combination outperformed donepezil monotherapy in safety and efficacy [49].

Centella asiatica

Centella asiatica (C. asiatica), also known as mandukparni or jalbrahmi, is a small, annual Apiceae plant that thrives in India. It bears tiny oval fruit, fan-shaped green leaves, and white, light purple-to-pink, or white blossoms. The Ayurvedic tradition has historically employed mandukparni leaves to improve memory. Traditional Chinese and African medicine utilize it too. It is taken with milk to boost memory, delay aging, and prevent memory issues.

C. asiatica's main chemicals include madecassoside, madasiatic acid, asiatic acid, and asiaticosides. Other chemical compounds from C. asiatica include centelloside, isothankuniside, thankuniside, brahmoside, and brahminoside.

C. asiatica has many pharmacological properties, including wound healing, antipsoriatic, antiulcer, hepatoprotective, antidepressant, nootropic, immunostimulant, antiviral, antibacterial, insecticidal, and antifungal, as well as anti-inflammatory, antioxidative stress, antiapoptotic, and neuroprotective effects.

Preclinical research: An aqueous C. asiatica extract given orally at 100, 200, and 300 mg/kg for 14 days improves normal rats' cognitive capacities dose-dependently. Pretreatment with the extract for 21 days reversed cognitive impairment caused by streptozotocin. The scientists attributed C. asiatica's benefits to its antioxidant activity, which increased glutathione, catalase, superoxide dismutase, and malondialdehyde suppression. Rao et al. found that C. asiatica at 200 mg/kg from day 15 to day 30 postpartum improved rats' learning and memory for at least six months. They also found increased hippocampal CA3 neuron dendritic arborization, which may enhance brain function. Another study found that 500 mg/b.i.d dried was superior for senior individuals' cognitive performance.

C. asiatica for six months. Dhanasekaran et al. found that 2.5 mg/kg of C. asiatica aqueous extract reduced amyloid beta 1-40 and 1-42 in the hippocampus of PSAPP transgenic mice with M146L presenilin 1 mutations and "Swedish" amyloid precursor protein, which causes spontaneous plaque formation, after 8 months. Congo red-stained fibrillar amyloid plaques decreased after long-term 5.0 mg/kg treatment.

C. asiatica aqueous leaf extract enhanced rats' learning and memory and affected their brain dopamine, noradrenaline, and 5-hydroxytryptamine (5-HT) systems. The leaf extract also had cholinomimetic, sedative, and antidepressant activities, suggesting it might treat AD-related depression, anxiety, and cognitive impairment. The leaf extract enhanced rat axonal regeneration, stimulated rat brain dendrites, and elongated human SH-SY-5Y neurites. Phosphorylated cyclic AMP's response element binding property (CREB) affects memory formation. Both AD patients and experimental models have low phosphorylated CREB. In vitro prolonged exposure of cortical primary cells to exogenous Aß and neuroblastoma cells, which generate inducible Aß, to C. asiatica leaf aqueous extract elevated CREB phosphorylation. In rats, the extract increased neuronal dendritic arborization and axonal regeneration.

The principal active element in C. asiatica's ethanolic extract is triterpenoids, including asiatic acid, mecadessic acid, asiaticoside, scentellin, asiaticin, and centellicin. Aspartic acid and its derivatives may improve memory by increasing ACh production. Hoechst Aktiengesellschaft patented it for dementia treatment and cognitive enhancement. It is unclear which plant component boosts cognition. Research suggests that the leaf's triterpene saponins may improve cognition by modifying brain neurotransmitters.

Clinical evidence: A randomized, double-blind, placebo-controlled study gave healthy volunteers 250–750 mg of C. asiatica extract once a day for two months. High doses enhanced working memory and mood.

Thus, clinical and experimental data confirms C. asiatica's memory-boosting effects.

Its AD treatment efficacy is currently being evaluated.

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Asiaticoside and C. asiatica extract were well-tolerated in experiments. Atcoside was safe up to 1 g/kg oral. The subacute toxicity experiment showed no harm at 10–1000 mg/kg, however the acute toxicity trial showed no toxicity at 10 g/kg. A six-month chronic toxicity experiment in Wistar rats showed no significant toxicity at 1200 mg/kg/day. One study found that albino rats fed 1000 mg/kg/day dried C. asiatica orally for 30 days developed hepatotoxicity.

Explain Bacopa monnieri: Bacopa monnieri is a small, perennial Scrophulariaceae creeper. It has numerous branches, short, oblong leaves, and white or light purple blooms. In India, Brahmi is known for its nootropic and revitalizing effects, which boost memory and cognition. For thousands of years, Indian traditional healers have used bacopa to cure several diseases.

Main chemical elements: The main chemical components of B. monniera are triterpenoid saponins, or bacosides. This plant contains herpestine, nicotine, and brahmine. New saponins, bacopasides I–XII, were found.

Pharmacological functions: This herb has hepatoprotective, bronchodilatory, immunostimulatory, anticonvulsant, antidepressant, anxiolytic, analgesic, anti-inflammatory, antioxidant, antimicrobial, antiulcerogenic, and anti-Helicobacter pylori properties.

An animal model of AD established by bilateral intracerebroventricular injection of AF64A was tested for cognitive performance and neurodegeneration with an alcoholic Bacopa extract at 20, 40, and 80 mg/kg. Copa decreased cholinergic neuron density loss and increased Morris water maze escape latency. Oral Bacopa extract at 40 mg/kg/day for five weeks protected aluminum chloride-exposed rats against neurotoxicity. Standardized Bacopa extract reduced the cognitive deficit caused by intracerebroventricular (ICV) injection of cholchicine and ibotenic acid into the nucleus basalis magnocellularis by reversing ACh depletion, reducing ChAT activity, and decreasing muscarinic cholinergic receptor binding in frontal cortex and hippocampus. Holcomb et al. found that administering Bacopa leaf ethanolic extract to mice at 40 and 160 mg/kg for two and eight months reduced Aβ 1–40 and 1–42 levels in their cortex. Bacopa's antioxidant properties restored AChE and Na+K+ATPase function at 50 mg/kg in the colchicine dementia model. Bacopa may improve memory by stimulating neuronal dendritic growth.

clinical proof A double-blind, placebo-controlled investigation found that 300 mg B. monniera extract (containing 55% combined bacosides A and B) did not substantially affect cognitive function at two hours in 38 healthy volunteers (ages 18–60). In healthy adults aged 40–65, a six-week double-blind, randomized, placebo-controlled Bacopa administration regimen (300 mg for subjects under 90 kg and 450 mg for subjects over 90 kg, equivalent to 6 g and 9 g dried rhizome, respectively) improved new information retention. Despite the same information acquisition rate.

Stough et al. found that 300 mg of Bacopa daily for 12 weeks improved verbal learning, memory consolidation, and early information processing in 46 healthy volunteers aged 18–60. Bacosides make up 55% of this Bacopa. Bacopa's antioxidant and/or cholinergic system-influencing properties may have delayed the benefits' onset, which occurred five weeks following treatment. In another randomised, double-blind, placebo-controlled investigation, 54 older volunteers (mean age 73.5 years) with equivalent Bacopa medication performed better on an auditory verbal learning test, delayed word recall memory scores, and a stroop test]. Over-55 memory-impaired individuals received 125 mg of standardized Bacopa extract twice a day for 12 weeks in a double-blind, placebo-controlled trial. Mental control, logical memory, and paired-related learning improved. In a healthy older Australian population, 300 mg/kg bacopa extract daily for 12 weeks improved memory acquisition and retention.

Bacopa syrup (350 mg of bacopa powder) enhanced children's health compared to a placebo when administered three times a day for three months (92, 93). However, this study was not blinded. Negi et al. tested 36 children (mean age 8.3–9.3 years) with ADHD in a double-blind, randomized, placebo-controlled trial. 19 children received 50 mg twice a day of Bacopa extract (standardized to 20% bacosides) for 12 weeks. Children treated with Bacopa had significantly better cognitive performance than placebo after 12 weeks. Despite four weeks of placebo, phrase repetition, logical memory, and paired association learning tasks improved after 16 weeks.

Toxicology: Bacopa aqueous and alcoholic extracts had LD50s of 5 and 17 g/kg in rats. Aqueous extract had 1000 mg/kg intraperitoneal LD50, whereas alcoholic extract had 15 g/kg. In a double-blind, placebo-controlled investigation with healthy male volunteers, bacosides at 20–30 mg and 100–200 mg daily doses were tested for safety and acceptability for four weeks. A 12-week randomized, double-blind, placebo-controlled research found that bacopa (300 mg/kg, daily) increased stool frequency, stomach cramps, and nausea. Saponin-mediated gastrointestinal tract irritation or ACh overexpression may cause these adverse effects.

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Curcuma longa

Curcuma longa Linn is a perennial Zingiberaceae plant. South and Southeast Asia grow it for commerce. Indians utilize turmeric, or curcumin, from the plant's rhizome as a coloring and flavoring. The Ayurvedic medical system has long used plant remedies.

Main chemical elements: Curcuminoids—mainly curcumin (diferuloyl methane), demethoxycurcumin, and bisdemethoxycurcummin—make up turmeric. Alpha- and beta-tumerone, artumerone, alpha- and gamma-atlantone, curlone, zingiberene, and curcumol are also identified in this plant.

Pharmacological activities: Curcuminoids are anti-inflammatory, anti-proliferative, anti-cancer, antidiabetic, hypocholesterolemic, antithrombotic, antihepatotoxic, carminative, diuretic, antirheumatic, hypotensive, antimicrobial, antiviral, antioxidant, larvicidal, insecticidal, antivenomous, and antityrosinase.

Preclinical research: It has been extensively studied for several diseases. Many studies have demonstrated that it has a wide variety of biological and pharmacological benefits, including cholesterol-lowering, antioxidant, and anti-inflammatory actions, which are critical to Alzheimer's disease.

Curcumin's insoluble characteristic has been partly addressed by biodegradable nanoparticles coated with poly (lactic-co-glycolic acid). Antioxidative nanoparticles may inhibit amyloid aggregation without harm. Curcumin nanoliposomes inhibit fibrillar and oligomeric Aβ in vitro and exhibit strong affinity for Aβ1-42 fibrils. Apolipoprotein E3-mediated curcumin-containing poly(butyl) cyanoacrylate nanoparticles (ApoE3-C-PBCA) enhanced photostability, cellular absorption, and Aβ-induced cytotoxicity. Curcumin also protects against Aβ neurotoxicity by converting Aβ fibrils faster and lowering Aβ generation by downregulating GSK-3-β and PS1 expression.

Research indicates that curcumin reduces Aβ plaque formation in both in vivo and in vitro. After six months of curcumin treatment, the transgenic APPSw mouse brain (Tg2576) significantly reduced proinflammatory interleukin-1β and oxidized protein levels.

Plaque formation

Curcumin also decreased insoluble and soluble Aβ levels in the study. Curcumin (10, 20, and 50 mg/kg, p.o. for 21 days) enhanced cognition in sporadic AD rats. Additionally, curcumin in the diet improved spatial memory, oxidative stress, and synaptophysin loss by reducing Aβ deposits. After 6 months, low (160 ppm) and high (1000 ppm) curcumin therapy improved cognition in the double transgenic AD animal (APP/PS1). Curcumin may protect cells against beta amyloid and oxidative damage in vivo. Curcumin effectively prevents or disaggregates Aβ at low dosages (IC50 = 0.81-1 μM). Increasing curcumin doses deconstructed Aβ aggregates, whereas monomeric Aβ reduced clumping. Curcumin, like Congo red, suppresses oligomer formation by binding to plaques and identifying secondary structure in fibrillar and oligomeric Aβ. Curcumin was shown to lower soluble Aβ, insoluble amyloid, and plaque burden by 40% at low dosages. Curcumin treatment for 7 days decreased plaque burden and repaired dystrophic dendritic structural changes in APPswe/PS1dE9 mice model of AD.

AD is connected to insulin/IGF-1 dysregulation. It induces tau protein hyperphosphorylation, mitochondrial dysfunction, oxidative stress, necrosis, and cognitive impairment. In the intracerebroventricular (ICV)-streptozotocin (STZ) model of sporadic AD, curcumin boosted IGF-1 and cognitive function. Also decreased were IL-1, glial fibrillary acidic protein, oxidative damage, plaque burden, and insoluble amyloid. In the STZ model of AD, curcumin decreased oxidative stress, enhanced ChAT activity, and restored insulin receptor protein, enhancing learning and memory. Microgliosis was suppressed in neuronal layers but increased adjacent to plaques, indicating curcumin may promote microglia amyloid phagocytosis. Curcumin may protect the brain by suppressing IL-1-induced α1ACT upregulation and NFκB-mediated apolipoprotein E transcription. In APP transgenic mice, both α1ACT and ApoE are proamyloidogenic. High cholesterol and oxidative damage are further proamyloidogenic factors curcumin lowers. A rat model with Aβ and ibotenic acid demonstrated the neuroprotective effects of curcuminoid mixture and its components on inflammatory and apoptotic gene expression in AD. Ahmed and colleagues also observed that bisdemethoxycurcumin, demethoxycurcumin, and curcumin improved memory in rats with amyloid fragment-induced AD-like conditions. However, ongoing curcumin treatment decreased oxidative stress and restored colchicine-induced cognitive impairment in rats.

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Chronic stress raises serum corticosterone, affecting spatial cognition, neuroendocrine, and plasticity. Curcumin stabilizes corticosterone and downregulates calcium/calmodulin kinase II and NMDA-2B to protect neurons. According to Wang et al. and Yin et al., 300 mg/kg curcumin treatment improved spatial learning, memory impairment, and hippocampal regeneration in an Aβ1–40 AD model Curcumin may lower beta amyloid by chelating iron and copper (but not zinc) [134]. Metals abound in AD brains. McClure et al. discovered that aerosol-mediated curcumin treatment in early 5XFAD mice decreased Aβ buildup and memory issues in adulthood compared to untreated animals

Thus, this multitarget chemical may cure AD and cognitive decline. Despite significant curcumin research in other illnesses, AD has little clinical proof of its benefits.

A phase I study of 25 healthy individuals reported no damage from curcumin up to 8000 mg/day for 3 months. Ethanolic C. longa rhizome extract at 0.5, 1.0, and 3.0 mg/kg did not affect mice in an acute toxicity study. A 90-day mouse toxicity study found no damage at 100 mg/kg/day.

Clitoria ternatea

C. ternatea is a perennial tropical climber plant that grows wild and in gardens. It blooms blue or white on delicate, downy stalks. It is found across tropical India. Fabaceae—"butterflies."—include C. ternatea. This is standard Ayurvedic medicine. C. ternatea is called Aparajit, Aparajita, and Kakkattan in Indian traditional medicine. C. ternatea extracts are utilized in Ayurvedic "Medhya rasayana."

Main chemical elements: C. ternatea produces taraxerol, teraxerone, ternatins, delphinidin-3, 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,.

Pharmacy-related activities: C. ternatea has been shown to be nootropic, anticonvulsant, antidepressant, antianxiety, antistress, antioxidant, anti-inflammatory, antihyperlipidemic, antidiabetic, antiasthmatic, cytotoxic, antimicrobial, gastroprotective, and hepatoprotective.

Preclinical research: The elevated plus maze and object recognition test were employed to assess the nootropic effects of a methanolic aerial C. ternatea extract (100 mg/kg, p.o.) on rats. Taranalli and Cheeramkuzhy investigated 300 and 500 mg/kg, p.o. ethanolic extracts of C. ternatea roots and aerial parts in submaximal electroshock-induced amnesia. They also assessed ACh levels in many brain areas and the total brain. At 300 mg/kg, aerial parts extract increased brain ACh and memory retention compared to 500 mg/kg. The root extract had similar but stronger effects at both doses.

Rai et al. examined how C. ternatea root extract affected rat growth spurt learning and memory. They fed 7-day-old neonatal rats 50 and 100 mg/kg C. ternatea aqueous root extract for 30 days after intubating them. The extract improved T-maze spatial performance and passive avoidance retention. A 30-day post-treatment assessment showed long-lasting behavioral changes. A previous study found that parenteral aqueous root extract at 50 and 100 mg/kg for 30 days increased amygdala neuron dendritic arborization in rats. Growth factors like nerve growth factor or brain-derived neurotrophic factor may have caused this cognitive benefit. The nootropic effect of C. ternatea root may be attributed to increased hippocampus acetylcholine. Rai found that C. ternatea root extract promoted neurogenesis in neural stem cell anterior subventricular zones. Recently, Damodaran et al. found that 200 and 300 mg/kg C. ternatea root extract may protect against chronic cerebral hypoperfusion-induced neuronal damage and memory impairment. Mehla and colleagues showed C. ternatea's anti-AD effects in rats with ICV-STZ-induced AD. These data suggest that C. ternatea extract slows AD patients' cognitive impairment. C. ternatea extract's human use potential needs more evaluation.

Toxicity: An ethanolic extract of C. ternatea aerial parts and root was given to mice at 200–3000 mg/kg p.o. Root extract was cathartic. Ptosis and sluggishness in mice occurred at > 2000 mg/kg. The extract was not deadly when given orally at 2900 mg/kg and higher intraperitoneally, although it caused significant CNS depression and death. Taur and Patil found an LD50 of almost 1300 mg/kg for the C. ternatea root ethanolic extract.

Withania somnifera

Plant description: Withania somnifera, a small woody shrub of the Solanaceae family, grows throughout India. Known as ashwagandha, winter cherry, or Indian ginseng. Its one-centimeter flowers are green or yellow. Ancient Indian Sanskrit literature call ashwagandha "Medhya rasayan." Indian ginseng is used in Ayurveda. It is included in various general tonics that promote energy, health, and lifespan.

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Main chemical constituents: Isoletertierine, anferine, withanolides, withaferins, sitoindoside VII and VIII, and withanoloides are W. somnifera's primary phytoconstituents Other compounds include 3-a-gloyloxytropane, choline, cuscohygrine, withanine, somniferine, somnine, somniferinine, withananine, and pseudo-withanine.

Pharmacological activities: W. somnifera has anti-inflammatory, antioxidant, neuroprotective, antischemic, anti-Parkinson's, antiepileptic, anxiolytic, antidepressant, antiarthritic, cardioprotective, antidiabetic, anticancer, antistress, nephroprotective, heptoprotective, immunomodulatory, hypolipidaemic, and antimicrobial properties.

Preclinical studies: The CNS effects of W. somnifera root's entire alkaloid extract (ashwagandholine, AG) have been studied. W. somnifera reduced STZ-induced memory loss with its antioxidant mechanism. The root preparation reduces stress-induced hippocampus degeneration in rats, protecting against neurodegenerative disorders. An extract of sitoindosides VII–X and withaferin A (50 mg/kg, p.o. for two weeks) recovered rats' cognitive deficits and cholinergic markers such ACh and ChAT after ibotenic acid treatment. AChE activity and M1- and M2-muscarinic receptor binding in different brain regions were favorably affected by sitoindosides VII–X and withaferin (40 mg/kg for 7 days). Some study suggests that withaferin A and withanolide A induce the Nrf2 pathway in BV-2 microglial cells, which generates neuroprotective proteins such heme oxygenase-1 [158].

Withanoside IV, another chemical component of withania, decreased cognitive loss in AD animal models when administered orally at 10 micromol/kg [44]. In cultures of rat cortical neurons damaged by the amyloid peptide Aβ(25-35), sominone (1 microM) from Withanoside IV induced synaptic reconstruction, axonal and dendritic regeneration. Withanoside IV may be a prodrug since sominone is the active component. Sominone improves spatial memory by promoting neuritic outgrowth via the neurotrophic factor receptor (RET). Methanolic root extract dose-dependently boosted neuroblastoma cells' in vitro dendritic formation. Jayaprakasam et al. found that withanamides (A/C) in W. somnifera fruits protect PC-12 against β-amyloid-induced toxicity. The study found that both withanamide molecules include serotonin, which may reduce the development of β-amyloid fibrils.

Withania root extract (1 g/kg, p.o. for 30 days) reversed AD pathogenesis, increased Aβ clearance, and decreased cognitive decline in middle-aged and old APP/PS1 mice via upregulating the low-density lipoprotein receptor-related protein. An alcoholic extract of Withania leaf and its component withanone protects against scopalmine-induced brain changes. Research indicates that Aβ peptide inhibits fibril formation in vitro. Withania may improve cognition and memory by increasing cortical muscarinic ACh receptor capacity. The root extract and its chemical components, such as glycowithanolides, may treat AD due to its anxiolytic, depressive, anti-inflammatory, and antioxidant characteristics. Withanone, a compound in W. somnifera root extract, reduced proinflammatory cytokines, oxidative stress, and amyloid processing to enhance cognitive functions. In the Drosophila melanogaster AD model, W. somnifera (20 mg/mL) decreased Aβ toxicity and improved longevity.

Clinical proof In a prospective, randomized, double-blind, placebo-controlled research, ashwagandha root extract (300 mg twice day) improved immediate and general memory, executive function, attention, and information processing speed in people with moderate cognitive impairment. In a comprehensive research by Ng and colleagues, W. somnifera extract improved executive functioning and decreased cognitive impairment in mild cognitive impairment. Few studies have examined withania's cognitive impairment treatment.

Toxicity: Several W. somnifera root formulations and extracts were nontoxic after extended treatment. Ashwagandholine 2% suspension in propylene glycol had an LD50 of 465 mg/kg for rats and 432 mg/kg for mice. In contrast, mice given 1076 ± 78 mg/kg intraperitoneal aqueous-methanol root extract had 50% mortality. A single intraperitoneal injection of an equimolar combination of sitoindosides VII and VIII and withaferin-A (SG-2) had an LD50 of 1564 ± 92 mg/kg.

Celastrus paniculatus

Plant description: The Celastraceae family includes large climber Celastrus paniculatus. It grows in the sub-Himalayan slopes, Punjab, and South India's mountains. The common name, jyotismati, comes from the Sanskrit words "mati" (intelligence) and "jyoti teja," which signify mental fire and intellect. The bark and seeds have long been used as expectorants, stimulants, and brain tonics. Digestion and intellect have also been helped. C. paniculatus treats arthritis, leprosy, depression, paralysis, and fever in Ayurveda. Fruit and seed oils are used for their relaxing, tranquilizing, and wound-healing properties.

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Main chemical constituents: C. paniculatus contains sesquiterpenoid polyalcohols and esters (malkanguniol, malkangunin, polyalcohol A–D, and celapnin), alkaloids (paniculatine and celastrine), phenolic triterpenoids (celastrol and paniculatadiol), and agarofuran derivatives.

Desmodium gangeticum

Plant description: The Fabaceae family member Desmodium gangeticum (D. gangeticum), known as salpani in Hindi, is abundant in India. The perennial undershrub is 60–130 cm tall and angular-branched. Simple, ovateoblong or rounded leaves with 5-7 cm violet or white blooms. Traditional medicine uses it as a bitter tonic, febrifuge, antiemetic, digestive assistance, and vata-related inflammatory illness. In India's Satpuda hills, D. gangeticum powdered root and honey treat mouth ulcers. Uttat Pradesh uses aloe vera and D. gangeticum leaf paste to combat hair loss.

Main chemical constituents: D. gangeticum contains tryptamines, phenylethylamines, gangetin, desmodin, phospholipids, sterols, flavones, and glycosides.

Pharmacological activities: Antileishmanial, immunomodulatory, antioxidant, anti-inflammatory, antinociceptive, cardioprotective, antiulcer, antiamnesic, and hepatoprotective are just a few of the pharmacological actions it demonstrates.

Preclinical studies: An aqueous D. gangeticum extract administered orally at 50, 100, and 200 mg/kg for seven days improved mice's memory. The aqueous extract of D. gangeticum also prevented age- and Scopolamine-induced amnesias in rats. After 6 days of treatment with D. gangeticum chloroform extract (400 mg/kg) and alkaloidal fraction (50 mg/kg), mice showed decreased scopolamine-induced amnesia. Antioxidant, anti-inflammatory, and AChE inhibitory properties of D. gangeticum have been reported. These pharmacological properties imply D. gangeticum may treat AD-related cognitive impairment. There is little clinical evidence for this. To assess the safety of this potentially useful herb, toxicology testing are needed.

Other Plants with Potential Memory Enhancing Activity

Several additional botanicals may help AD and cognitive function. However, there is little information about each plant. Acorus calamus (vach), Prunus amygdalus (badam), Orchis mascula (salap), Syzygium aromaticum (lavang), Mukta pishti (pearl), Tinospora cordifolia (guduchi), Picrorrhiza kurroa (kutki), Zingiber officinale (sonth), Boerhaavia diffusa (punarnava), Commiphora wightii (guggal), Piper longum (pippali), Carum copticum

Methodology

Search criteria: Dementia, herbal products/drugs/medicine, Alzheimer's disease, and complementary and alternative therapies were searched in PUBMED and GOOGLE SCHOLAR. The search was limited to plants or plant products listed in online English-language and Indian Ayurvedic literature for dementia treatment.

Inclusion criteria: This review includes the following studies: (1) in-vitro and in-vivo preclinical investigations; (2) clinical studies; and (3) regional or Hindi-named herbal medication.

Indian Herbal Formulations Studied in Alzheimer's Disease

Mentat

Ayurveda uses compound formulations because they have synergistic medicinal benefits with little side effects. An Ayurvedic polyherbal compound called Medhya Rasayana, BR-16A (Mentat), improves memory and cognitive deficiencies caused by chronic disease and aging. Brahmi, Mandookaparni, Ashwagandha, Shankapushpi, Jatamansi, Vach, Tagar, Badam, Salap, Lavang, Pearl, Malkangni, and Brahmi are in BR-16A.

Mentat improved learning and retention in rats and prevented cognitive deficits caused by prenatal undernutrition, postnatal environmental impoverishment, sodium nitrite hypoxia, aluminum, age, and electroconvulsive shock-induced antero-grade and retro-grade amnesia. In elderly rats, 100 mg/kg/day aluminum extended the reduced step-through latency and increased learning retention for 20 days. Rats given BR-16A on the Hebb Williams complex maze learned and remembered better than controls, according to Ramteke et al.. In rats with scopolamine-induced amnesia, BR-16A improved learning and memory dose-dependently. When given for 2 weeks, mentat restored the cognitive loss and cholinergic dysfunction caused by colchicine and ibotenic acid in AD.

Clinical evidence: It enhanced memory quotient in normal participants of various ages, expanded memory span and reduced attention fluctuations in normal adults, and improved learning capacity in children with behavioral issues or moderate brain injury.

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An acute toxicity investigation found no harm in Mentat up to a dosage of 1.5 g/kg. LD50 was 1.75 g/kg intraperitoneally and 2400 mg/kg orally.

Trasina

Ayurveda classifies several Indian medicinal herbs as Medhya rasayana, and Trasina is a polyherbal preparation of these plants. It contains 10 mg of Eclipta alba, 10 mg of Tinospora cordifolia, 10 mg of Picrorrhiza kurroa, 80 mg of Withania somnifera, 190 mg of Ocimum sanctum, and 20 mg of Shilajit. When given for 21 days at doses of 200 and 500 mg/kg, p.o., it had a substantial nootropic effect in patients with colchicine- and ibotenic acid-induced cognitive impairment. In the frontal cortex and hippocampus of rat brains, trassina therapy enhanced, in a dose-dependent manner, both memory and cholinergic indicators such as acetylcholine concentration, choline acetyl transferase activity, and muscarinic cholinergic receptor binding, after 14 and 21 days. Therefore, the repair of cholinergic dysfunction may be the cause of its nootropic effect.

Memorin

Mandookparni, Shankhpushpi, Jatamansi, Yashtimadhu, and Smruti sagar make up Memorin. Andrade, 1998 found that memorin improved memory in older people. In passive avoidance learning paradigms like the shuttle box and T-maze test, memorin (200 mg/day/kg) reduced retrograde and anterograde amnesia in rats.

Bramhi Ghrita

This polyherbal Ayurvedic recipe contains 20% Evolvulus alsinoids, 20% Acorus calamus, 20% Saussurea lappa, and 40% Bacopa monneri in 750 mL cow's ghee. It traditionally boosted memory. Achliya et al. tested the formulation's memory and learning effects at 30, 50, and 100 mg/kg oral doses. At 50 and 100 mg/kg, p.o., Bramhi Ghrita decreased escape and transfer latency in the Morris water maze and raised plus maze, respectively. It also increased rats' memory and learning, indicating nootropic activity.

Abana

Abana, another polyherbal Ayurvedic formulation, is available in tablet form consisting of Terminalia arjuna (30 mg), Withania somnifera (20 mg), Nepeta hindostana (20), Dashamoola (20 mg), Tinospora cordifolia (10 mg), Phyllanthus emblica (10 mg), Terminalia chebula (10 mg), Eclipta alba (10 mg), Glycyrrhiza glabra (10 mg), Asparagus racemosus (10 mg), Boerhaavia diffusa (10 mg), Shilajeet (20 mg), Centella asiatica (10 mg), Convolvulus pluricaulis (10 mg), Ocimum sanctum (10 mg), Nardostachys jatamansi (10 mg), Piper longum (10 mg), Carum copticum (10 mg), Zingiber officinale (10 mg), Shankh bhasma (10 mg), Makardhwaj (10 mg), Cyperus rotundus (5 mg), Acorus calamus (5 mg), Embelia ribes (5 mg), Syzygium aromaticum (5 mg), Celastrus paniculatus (5 mg), Santalum album (5 mg), Elettaria cardamomum (5 mg), Foeniculum vulgare (5 mg), Rosa damascena (5 mg), Cinnamomum cassia (5 mg), Jaharmohra (10 mg), Abhrak bhasma (5 mg), Akik pishti (5 mg), Yeshab pishti (5 mg), Yakut pishti (5 mg), Praval pishti (5 mg) and Crocus sativus (2 mg).

Abana was administered orally to young and elderly mice at 50, 100, and 200 mg/kg for 15 days. Retention memory was tested using the maze, raised plus, and passive avoidance tests. Amnesia caused by scopolamine and diazepam at the same doses was also tested. Abana dose-dependently decreased brain AChE activity. Abana may improve memory by lowering brain AChE activity, according to these studies. Oral and acute Abana administration to 2000 mg/kg mice was safe.

Herbal Drugs: Regulatory Status

Herbal medication laws differ by country. USFDA classifies herbal remedies as botanical pharmaceuticals and nutritional supplements. Safety and efficacy studies are not necessary to sell dietary supplements, but they should be labeled. Botanicals need product descriptions and human usage evidence. Criteria may alter for non-clinical research, clinical trials, and batch impact studies. The EU Committee on Herbal Medicinal Products (HMPC) provides scientific opinions on herbal substances and preparations. Depending on human exposure, regulatory methods include stand-alone or combination applications, well-established use marketing authorization, and conventional use registration.

The 1940 Drugs and Cosmetics Act and 1946 Regulations govern Indian herbal treatments. If they must be incorporated in the present medical system under the 2019 new drugs and clinical trials legislation, development is similar to synthetic pharmaceuticals [264]. Licencing, formulation, manufacture, labeling, packaging, and quality control are covered under Schedule T [265]. Safety and efficacy studies follow AYUSH GCP [266].

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Issues and Challenges with Herbal Drugs

Herbal medicine quality control is needed since extraction and processing might affect active component quantities. Herbal drugs' macroscopic and microscopic properties should be examined for quality control. Ash, heavy metals, pesticide residues, and microbiological pollution must be measured.

Interaction between drugs and herbs Herbal drugs used with prescriptions might cause serious negative effects. Herbal drugs include numerous unknown constituents, making interactions difficult to determine. Since herbal medicines are natural, they are frequently considered harmless, however numerous have been demonstrated to have harmful drug reactions [267]. Several studies [267–269] found that herb–drug interactions cause side effects. Dosage and usage variability makes medication interaction assessment difficult. CYP450 affects AD drug metabolism [270, 271]. Thus, herbal remedies' CYP450 inhibition must be assessed to avoid herb-drug interactions. Combined with donepezil, ginkgo biloba boosts AD effects via cholinergic activity. It activates CYP2C19, hence combining it with phenytoin causes breakthrough seizures. Curcumin inhibits intestinal CYP450 enzymes and p-glycoprotein, increasing celiprolol oral bioavailability [272]. Donepezil, a reversible cholinesterase inhibitor, and curcumin increased BBB permeability [274] and synergized oxidative stress and cognition [273]. We need more clinical and experimental study on herb-drug interactions. Patients' statement of concurrent use and physicians' understanding may prevent such interactions. Drug absorption, metabolism, and excretion are impaired in the elderly. Taking herbal drugs together may worsen impairment. Therefore, elderly adults should use herbal treatments cautiously.

Adulteration: Herbal remedies are routinely blended with or substituted with cheaper imitations. Herbs with volatile ingredients are commonly contaminated. Adulterants might not even because adverse effects, much alone be helpful. Quality assurance should be essential for herbal drugs.

Labeling herbal medicines: Labeling may reduce damage and misuse. The label should include the herbal medication's name, amount, active ingredients, intended use, storage, shelf life, side effects, and precautions. The pharmacovigilance of herbal treatments Modern pharmaceuticals rely more on meticulous study due to tight national and international rules. In contrast, traditional medical systems lack regulatory mechanisms. Because herbal treatments are natural, they are typically safe. As said, many herbal treatments have adverse effects, either alone or due to herb–drug interactions. Herbal drugs have inherent risks, but faulty labeling, composition, quality, adulteration, infection, improper use, or quackery may cause negative effects.

Alzheimer's disease patients in later stages are susceptible and unable to communicate negative events, making them a distinct category. This group needs special caution with side effects and drug interactions. Thus, national pharmacovigilance programs must include herbal and modern pharmaceutical pharmacovigilance.

II. CONCLUSIONS AND FUTURE PROSPECTUS

Alternative medicine has been used since ancient times, and numerous herbal formulas and medicinal plant extracts may cure AD. Medicinal plants are rich in chemical components and biological targets, making them a good source for medication research. Much effort remains to transform this potential into actual medicine. Standardizing plant extracts is crucial for natural medicine research. Pharmacological phytoconstituents must be identified, isolated, and rigorously tested. Multicenter clinical trials are needed to prove that these herbal therapies, alone or in conjunction with other drugs, cure AD. In this research, herbal treatments for AD were tested in clinical and experimental studies.

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