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Medicinal Plants with Potential Nootropic Activity: A Review.

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ABSTRACT

Alzheimer's disease (AD) is an age-related neurodegenerative disease increasingly recognized as one of the most important medical problems affecting the elderly. Although a number of drugs, including several cholinesterase inhibitors and an NMDA receptor antagonist, have been approved for use, they have been shown to produce diverse side effects and yield relatively modest benefits. To overcome these limitations of current therapeutics for AD, extensive research and development are underway to identify drugs that are effective and free of undesirable side effects. In traditional practices of Ayurvedic, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer's disease (AD). An ethnopharmacological approach has provided leads to identifying potential new drugs from plant sources, including those for cognitive disorders. Various other plant species have shown pharmacological activities relevant to the treatment of cognitive disorders, indicating potential for therapeutic use in disorders such as AD. This article reviews some of the plants and their active constituents that have been used in traditional systems of medicine for their reputed cognitive-enhancing or anti-ageing effects. Plants and their constituents with pharmacological activities that may be relevant for the treatment of cognitive disorders, including enhancement of cholinergic function in the central nervous system (CNS), anti-inflammatory and antioxidant activities, are discussed.

Keywords: Dementia, Alzhiemer's Disease, Acetylcholinesterase inhibitors, Nicotine, Plants, Anti-aging

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INTRODUCTION

The incidence of age related dementia and brain disorders is dramatically on the rise as life expectancy increases. Alzheimer's disease (AD) is a complex, multifactoral, progressive, neurodegenerative disease primarily affecting the elderly population which is estimated to account for 50–60% of dementia cases in persons over 65 years of age [1]. According to the World Health Organisation (WHO, 2006), around 35 million people in industrialized countries will suffer from AD by 2010. The disease is characterized by loss of memory and impairment of multiple cognitive and emotional functions [2]. The pathological attributes in AD are amyloid plaques, neurofibrillary tangles, inflammatory processes and disturbance of neurotransmitters [3.4]. Basically brain cells wither away and die, causing disorientation, dementia and severe changes in personality and social interactions. There is currently no cure for most forms of dementia including AD.

Pharmacotherapy is focussed on symptomatic benefit and slowing disease progression [5], but a number of possible disease intervention strategies based on current understanding of AD pathophysiology are under investigation[6,7]. Some AChE inhibitors have been approved for clinical use to treat mild to moderate AD cases, but their effect is only to alleviate symptoms and they do not achieve any permanent improvement. The synthetic drug tacrine (Cognex) was the first AChE inhibitor to be licensed, but its routine use has been restricted largely due to its hepatotoxicity[8,9]. The use of tacrine has been eclipsed by the newer AChE inhibitors such as donepezil (Aricept, Eisai, Pfizer, UK), rivastigmine (Exelon, Novartis, UK) and galantamine (Reminyl, Shire, UK). The use of anti-inflammatory agents has also been suggested to delay the progression of AD. Several studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of developing AD, and that patients with rheumatoid arthritis, who often use NSAIDs, have a lower incidence of AD[10,11]. Thus, the use of anti-inflammatory drugs has been proposed as a therapeutic target in AD. Also implicated in the pathology of many diseases, including neurodegenerative diseases such as AD, are free radical reactions, which are reported to initiate cell injury [12]. Consequently, the use of antioxidants has been explored in an attempt to slow AD progression and neuronal degeneration.

In traditional practices of medicine, plants have been used to enhance cognitive function and to alleviate other symptoms associated with AD. Plant constituents may not only act synergistically with other constituents from the same plant but may also enhance the activity of compounds, or counteract toxic effects of compounds, from other plant species. This approach has been used in various practices of traditional medicine, including ayurveda where a combination of plants is frequently prescribed. An ethno-pharmacological approach may be useful in providing leads to identify plants and potential new drugs that are relevant for the treatment of cognitive disorders, including AD.

Several milestones in the history of drug therapy have been discovered from ethnomedical knowledge, such as atropine, pilocarpine, cardiac glycosides, curare, and reserpine. Exploring the different Sources for ethno-medical information may also be useful as a starting point for the discovery of new drugs for the treatment of AD and cognitive disorders.

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PLANTS USED TRADITIONALLY FOR COGNITIVE DISORDERS

For thousands of years plants and other naturally occurring substances have been used, and continue to be used, for medicinal purposes with advantageous results. Throughout various cultures (namely China and India) the development of plant and animal based materia medica has been thoroughly developed. Historically, several different plant sources have been used to combat learning and memory associated deficits. More recently, a growing interest has reemerged regarding the value and use of these herbal resources for their efficacy in the treatment and amelioration of cognitive impairments, Alzheimer's disease (AD) and its associated pathologies.

Celastrus paniculatus Willd.

Seeds and seed oil of *Celastrus paniculatus* (Celastraceae) have been used in Ayurvedic medicine for ‘‘stimulating intellect and sharpening the memory’’ [13,14]. Upon oral administration of the seed oil decreased levels of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) in the rat brain, which was correlated with an improvement in learning and memory processes; in addition, the oil was not shown to be neurotoxic [15]. The nootropic effect of *Celastrus paniculatus* was not mediated by the anti-AchE but it could reverse the scopolamine induced amnesia [16]. However, Methanolic extract of *Celastrus paniculatus* seeds failed to alter N-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) receptor binding and nerve growth factor (NGF) at significant extent. Water Soluble extract of *Celastrus paniculatus* seeds protected neuronal cells against glutamate-induced toxicity by modulating glutamate receptor function [17]. Flowers from *C. paniculatus* could have possible implication in the management of the neurodegenerative disorder as it exhibited anti-inflammatory actions [18]. The aqueous extract of *Celastrus paniculatus* seed has dose-dependent cholinergic activity, thereby improving memory performance in the sodium nitrite induced amnesia rodent model. The mechanism by which *Celastrus paniculatus* enhances cognition may be due to increased acetylcholine level in rat brain [19]. The studies conducted to date regarding this plant have not identified the active constituents, nor has any therapeutic potential been established for use in AD patients.

Centella asiatica L.

One primeval Ayurvedic remedy is *Centella asiatica* (Umbelliferae), which is known to restore youth, memory and longevity [20]. For example, an Ayurvedic formulation comprising of four herbs, including *Centella asiatica,* is used to impede the ageing process and prevent dementia, and the herb combined with milk is given to improve memory [21]. *Centella asiatica* has also been used to treat rheumatic disorders, which suggests it may have anti-inflammatory effects. The essential oil (0.1% of the plant) extracted from *Centella asiatica* leaf contains monoterpenes, including bornyl acetate, α-pinene, β-pinene and γ-terpinene [22, 23], which are reported to inhibit AChE [24, 25]. However, monoterpene AChE inhibitors are weaker phytochemicals compared to the anti-ChE alkaloid, physostigmine [25]. The pharmacological basis to explain the reputed anti-amnesic effects of *Centella asiatica* has been explored experimentally. The tranquillising properties exhibited by the alcoholic extract of *Centella asiatica* was attributed to a triterpene, brahmoside [20]. Further the extract of *Centella asiatica* leaf was proved to be sedative,

antidepressant and potentially cholinomimetic in vivo [26]. These findings suggest that *Centella asiatica* may be appropriate to treat symptoms of depression and anxiety in AD, and that it may also influence cholinergic activity, and thus cognitive function.

Cognitive-enhancing effects have been observed in rats following oral administration of an aqueous extract of *Centella asiatica*. This effect was associated with an antioxidant mechanism in the CNS [27]. An aqueous extract of *Centella asiatica* leaf modulated dopamine, 5-HT and noradrenaline systems in rat brain and improved learning and memory processes in vivo which might be corrected the alteration in other neurotransmitter systems which have been linked with AD pathology [28, 29]. Glutamate may induce neuronal degeneration by overstimulation of NMDA receptors. Memantine, an NMDA receptor antagonist, is licensed for the treatment of moderately severe to severe AD and it is therapeutically effective [30, 31]. The triterpene asiatic acid (found in *Centella asiatica*) and its derivatives have been shown to protect cortical neurons from glutamate-induced excitotoxicity in vitro [32]; thus, further research regarding the clinical potential of these compounds may be necessitated. Water extract of *Centella asiatica* is known to attenuate β-amyloid-associated behavioral abnormalities in the Tg2576 mouse, a murine model of AD with high β-amyloid burden. Further, In vitro, *Centella asiatica* protected SH-SY5Y cells and MC65 human neuroblastoma cells from toxicity induced by exogenously added and endogenously generated β-amyloid, respectively. *Centella asiatica* prevented intracellular β-amyloid aggregate formation in MC65 cells [33]. *Centella asiatica* treatment alters amyloid-β pathology in the PSAPP Alzheimer's disease mouse model after prolonged treatment, although the alterations did not significantly affect Y-maze or open field behaviors. It was shown that *Centella asiatica* displayed antioxidant properties such as free radical scavenging, decreased lipid peroxidation and protection from DNA fragmentation due to oxidative stress, providing multiple mechanisms to alter pathology in Alzheimer's brain [34].

Clitoria ternatea L.

The roots of the *Clitoria ternatea* (Leguminosae) have been reported for its promoting intellect [14, 35]. A study investigating both the aerial parts and roots of *Clitoria ternatea* showed alcoholic root extracts to be more effective in attenuating memory deficits in rats compared to aerial parts [36]. Upon oral administration of *Clitoria ternatea* root extract enhanced memory retention which was associated increased ACh levels in rat hippocampus and it was hypothesised that this effect may be due to an increase in ACh synthetic enzymes [37]. Further studies are necessary to establish the mechanism of action to explain the observed effects of the root extract on the CNS and to identify the compounds responsible for activity.

Curcuma longa L.

Curcuma longa (Zingiberaceae), known in English as 'turmeric,' has also been used for culinary purposes. Much research has focused on curcumin, a curcuminoid from *Curcuma longa* rhizomes. In particular, numerous studies are reported that curcuminoids are associated with antioxidant and anti-inflammatory activities, but studies with particular attention to cognitive disorders and any clinical effects are lacking. In addition, further evaluation of potentially active compounds from *Curcuma longa*, other than the

curcuminoids, may contribute to the understanding of the traditional uses of this herb. The antioxidant activity of curcumin is well documented [38, 39, 40, 41]. Curcumin was shown to be neuroprotective against ethanol-induced brain injury in vivo following oral administration; an effect that was related to a reduction in lipid peroxide levels and enhancement of glutathione in rat brain [42]. Some compounds from *Curcuma longa*, including curcumin, demethoxycurcumin, bisdemethoxycurcumin and calebin-A (and some of its synthetic analogues), were shown to protect PC12 cells from β-amyloid insult in vitro [43, 44]; this activity was also suggested to be due to an antioxidant effect [44]. Curcumin is also reported to have anti-inflammatory actions [39] and has been suggested to modulate eicosanoid biosynthesis and to inhibit cyclooxygenase (COX)-1, COX-2 and lipoxygenase (LOX) [45, 46, 47]. Another activity that is perhaps relevant to the management of symptoms of cognitive-related disorders is antidepressant activity. An aqueous extract of C. longa demonstrated antidepressant activity in mice following oral administration, which was associated with inhibition of brain monoamine oxidase (MAO-A) [48] (Yu et al., 2002).

Butea monosperma

Butea monosperma (Family: Scrophulariaceae) a traditional Ayurvedic medicinal plant has been used for centuries as a memory-enhancing, anti-inflammatory, analgesic, antipyretic, sedative, and antiepileptic agent. Preclinical studies have reported cognitive enhancing effects with various extracts of *Butea monosperma*, but the exact mechanism of its actions is still uncertain, as its multiple active constituents make its pharmacology complex. It has been suggested that *Butea monosperma* exhibits neuroprotective and cognitive enhancing effects, in part due to its, capacity to modulate the cholinergic system [49] and to contrast oxidative stress [50, 51, 52]. Although pre-clinical animal studies have shown that *Butea monosperma* has nootropic effects in established learning and memory models, few clinical studies have been performed to complement these findings. Literature data reported that *Butea monosperma* given chronically improved early information processing and verbal learning and memory consolidation in humans [53]. Moreover, other clinical studies have to be encouraged, also to evidence any side effects and possible interactions between this herbal medicine and synthetic drugs.

Withania somnifera

Roots of *Withania somnifera* (Solanaceae) are one of the most highly reputed herbs in Ayurvedic medicine and of similar status of ginseng in Traditional Chinese Medicines. They are classed among the Rasayanas rejuvenating tonics used for treating age associated decline in cognitive function [54]. Steroid lactones have been isolated from the root and leaf [55]. The phytosterols were found, alongside the alkaloids. The presence of nicotine has been associated with cognitive enhancement and protection against AD development [56]. There have been numerous studies regarding the cognitive enhancing activities of *Withania somnifera*. Withanoside IV or VI produced dendritic outgrowth in normal cortical neurons of isolated rat cells, whereas axonal outgrowth was observed in the treatment with withanolide A in normal cortical neurons [57]. Neuritic regeneration or synaptic reconstruction was induced by withanolide A, withanoside IV and VI in amyloid-β (25–35)-induced damaged cortical neurons. In addition, these components also facilitated the reconstruction of post-synaptic and pre-synaptic regions in neurons, where severe synaptic

loss had already occurred. *Withania somnifera* extract, containing the steroidal substances sitoinodosides VII–X and withaferin A augmented learning acquisition and memory in both young and old rats [58]. It enhanced AChE activity in the lateral septum and globus pallidus and decreased it in the vertical diagonal band. Receptor binding on the muscarinic M1 receptor was enhanced in the lateral and medium septum and in the frontal cortices. M2 receptor binding increased in cortical regions but did neither affect γ-aminobutyric acid ($GABA_A$), benzodiazepine, nor NMDA receptor binding. The extract reversed ibotenic acid induced cognitive deficit and reversed the reduction in cholinergic markers, such as acetylcholine [59].

***Bacopa monnieri* L.**

Bacopa monnieri L.(Scrophulariaceae) is very widely recommended for the management of a range of mental conditions including anxiety, poor cognition and a lack of concentration [60], as a nerve tonic, for memory and intelligence improvement [54] for an intellect promoting effect and helpful in cases of general debility [14]. The effects *Bacopa monnieri* (40 mg/kg) on learning performance in rats were studied in shock-motivated brightness discrimination reaction and in conditioned fight reaction. In both schedules the treated groups showed a shorter reaction time than the control group. In addition, the rats improved learning capability confirmed by a maze-learning experimental method [55]. The saponins bacoside A and B have been claimed to be the active principles regarding enhancement of cognitive function [60, 61]. They, apart from facilitating learning and memory in normal rats, inhibited the amnesic effects of scopolamine, electroshock and immobilization stress. Furthermore, *Bacopa monnieri* has been shown to enhance protein kinase activity in the hippocampus, which could also contribute to its nootropic action. When *Bacopa monnieri* was administered along with phenytoin for 2 weeks, it significantly reversed phenytoin-induced impairment in rats [55]. *Bacopa monnieri*, administered for 2 weeks, reversed the depletion of acetylcholine. Further, it reduced the choline acetylase activity and decreased muscarinic, cholinergic receptor binding in the frontal cortex and hippocampus, induced by neurotoxins, such as colchicine [60]. *Bacopa monnieri* has proven to be an effective antiamnesic agent against diazepam-induced amnesia [62] In studies examining diazepam-induced amnesia control group mice showed a significant decrease in escape latency time (ELT), with successive acquisition trials at days 1–6; however, after administration of diazepam at 1.75 mg/kg i.p. 30 min before acquisition trials, ELT was significantly altered suggesting diazepam produced anterograde amnesia. Oral administration of *Bacopa monnieri* (optimal dose 120 mg/kg) reversed diazepam-induced increases in ELT [62, 63]. The mechanism of diazepam's action on $GABA_A$ receptors is well known for its inhibitory effects in the CNS. These results suggest that *Bacopa monnieri* elicits some actions through the GABAergic system.

In a double blind placebo-controlled trial, 76 participants, aged 40–65, received capsules of *Bacopa monnieri* extract equivalent to 6–9 g of dried rhizome. Effects on anxiety and memory functions were tested. The results did not show any significant effect on measures of short-term memory, working memory, attention, or the retrieval of information from long-term memory acquired pre-experimentally. No effects on subjective measures of psychological state as depression, anxiety and stress, or everyday memory were observed. There was, however, an activity measured in a task requiring the retention

of new information, recalling unrelated word pairs after a short delay (Roodenrys et al., 2002).

Acorus calamus

Acorus calamus is originally native to Europe, but has been cultivated and naturalized throughout India and Sri Lanka. Sala et al. (1993) list the plant with traditional uses as an intellect-promoting agent against depression, mental disorders and general debility [65]. *Acorus calamus* is also combined with *Polygala* root to help maintain mental and intellectual health of the elderly [66]. When powdered, it can be of avail for depressed psychosis and dementia. Further indications include the loss of consciousness, confusion of the mind, forgetfulness, anorexia and epilepsy and as a traditional Ayurvedic medicine to treat memory loss [67]. *Acorus calamus* contains essential oil with the main components α-asarone and β-asarone. Other components found in the plant are caryophyllene, α-humulene and sekishone [66]. Methanolic extracts of the roots, which contain essential oil which the toxin α-asarone showed inhibitory effect on AChE with an IC50 value of 188 µg/ml [68]. *In vitro* and *in vivo* studies have shown *Acorus calamus* oil to induce malignant tumours, due to β-asarone. In mice, the root extract of *Acorus calamus* protected against acrylamide-induced neurotoxicity and reduced the incidence of paralysis [69]. *Acorus calamus* is registered in the Pakistani Materia Medica where both the roots and rhizomes are used for nervous diseases and disorders, whereas the rhizome is especially indicated in cases of neurological symptoms of the brain [70].

Convolvulus pluricaulis

Traditional indications were found for *Convolvulus pluricaulis* (Convolvulaceae), a plant common in southern India, where the whole plant is used in various formulae as a nervine tonic for improvement of memory and intellect. The leaves and flowers possess hypotensive properties used for treating anxiety neurosis. Furthermore, it is also recommended as a brain tonic to promote intellect and memory, eliminate nervous disorders and to treat hypertension [71]. Recent study indicated the extract of *Convolvulus pluricaulis* can lower Amyloid β(Aβ) generation by modulating APP processing in the N2a-SwedAPP Cell line [72]. In mice, the root extract of *Convolvulus pluricaulis* protected against aluminium-induced neurotoxicity and reduced the incidence of paralysis [73].

Other Medicinal Plants with the potential memory enhancing activity

The bark, leaves, flowers, fruits and pods of *Sesbania grandiflora* (Fabaceae) are used in Ayurvedic medicine. The pods are considered useful for promoting memory power and for resolving glandular tumours or enlargements [54]. *Canscora decusata* (Gentianaceae) is a notable Ayurvedic drug for improving memory and intellect. A paste is made of the whole pla nt, including the flowers, to be taken with milk as a nervine tonic and to alleviate memory problems [54]. *Gmelina arborea* (Verbenaceae) is used in Ayurvedic medicine to improve digestion, strengthen memory, to overcome giddiness and to treat fever, thirst, emaciation, heart diseases and nervous disorders [54]. The ripe fruit of *Terminalia chebula* (Combretaceae) is considered to possess the ability to promote memory,

intellect and to prolong life. It is also believed to improve eyesight and has the ability to delay aging. It is suggested that one ripe fruit should be eaten every morning to achieve the listed effects [74]. *Nardostachys jatamansi* (Valerianaceae) is a reputed medhya, an intellect-promoting herb, with various medicinal properties, especially on the nervous system. In order to assess the nootropic activity of plant, an elevated plus maze and a passive avoidance task were employed to evaluate learning and memory parameters. The ethanolic extract of plant (200 mg/kg) significantly improved learning and memory in young mice and also reversed amnesia induced by scopolamine and diazepam. It was also claimed to have reversed amnesia due to natural aging of mice [75].

CONCLUSION

Memory loss, confusion and forgetfulness in old age are recognized as expected part of life, or oftentimes dementia is attributed to madness caused by spiritual and supernatural causes. Also, dementias are diseases which occur at an advanced age which was rarely reached in countries with a low life expectancy. A small selection of herbs traditionally used for CNS disorders have been evaluated pharmacologically and regarding their active constituents in terms our modern understanding of brain functions, but so far very little clinical data is available. Many prescriptions that claim to prevent or restore cognitive and memory deficits have not shown any actions in established test systems. Research for new potential drugs, however, is restricted to the pathways known or assumed to be included in the progression of AD, which are frequently based on AChE inhibition. Several traditional remedies have demonstrated interesting *in vitro* and *in vivo* activities and provided promising components with potential as therapeutics for neurodegenerative disorders. Most *in vitro* studies have focused on inhibition of AChE, because this has so far been the most promising clinical approach for the treatment of AD. To date the pathophysiology of AD is not yet nearly clarified. Further research will provide better understanding of the molecular pathways involved and hereby lead to the development of additional pharmacological test systems, in which activities may yet be observed. Also, some traditional medical systems such as Ayurveda emphasize health maintenance and disease prevention over curative treatments. Hence, preclinical and clinical research into protective and preventive effects of herbals drugs should be carried out in the future.

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