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Convolvulus pluricaulis as a Cognition Booster: Relevance to Alzheimer's Disease

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ABSTRACT

The herbal medicinal plant, *Convolvulus pluricaulis*: a rasayana drug has been primarily advocated for use in mental stimulation and rejuvenation therapy. In ancient systems of Indian medicine, Ayurveda, the plant is also known by the name Shankhpushpi and has been shown to act as a prominent memory improving drug, a psychostimulant and tranquiliser. The plant displays its biological activity due to the presence of several alkaloids, flavanoids and coumarins as active chemicals. Previous reports by us and others have demonstrated beneficial effect of extracts of this plant in an *in-vitro* and *in-vivo* models of Alzheimer's disease (AD). Justification of its potential for an ancient brain tonic has been provided recently by clinical studies on polyherbal formulation of this plant. This review attempts to compile information on *Convolvulus Pluricaulis* in order to establish this herbal drug as a potent natural therapeutic agent to combat AD related symptoms.

Keywords: Alzheimer's disease; Acetylcholine esterase inhibitors; Amyloid beta, *Convolvulus pluricaulis*.

INTRODUCTION

Alzheimer disease (AD) constitutes the most prevalent form of dementia affecting the older individuals. AD is characterized by changes in brain anatomy, biology, and slow deterioration of the memory processes. [1] It is a condition that is linked with huge psychological and emotional distress for patients and their care takers. [2] The prevalence rates of AD vary between regions [3], with an estimated 31 million people suffering from this disease around the globe and according to one estimate this number will grow to 81.1 million cases worldwide by 2040. [4-5]

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This age related disorder is mainly characterized by excessive accumulation of two major proteinaceous aggregates; senile plaques composed of aggregated amyloid beta (Aβ) derived from the β-amyloid precursor protein (AβPP), and neurofibrillary tangles enriched with hyperphosphorylated tau which later are responsible for synaptic loss in the brain resulting in dementia. [6-7] Genetics implicates mutation in three genes; AβPP, presenilin 1 (PSEN 1), presenilin 2 (PSEN2) the onset of the familial early onset (<65 years) autosomal form of AD (EOAD), while on the other hand late onset AD (LOAD) represents over 90% of the cases (>65 years) is sporadic in nature and has no genetics association. [8]

Since the etiology of AD remains obscure, it hampers the development of proper therapeutic intervention. Despite many approaches and efforts, to date no researchers have been successful in developing a cure

or at least a modality to check the disease, and most of the therapies only provide functional relief. Evidence suggests that immense oxidative stress, free radical formation, genetic susceptibility, and programmed cell death all have a role in the development of AD. [9] The neuropathology of the disease is based on severe degeneration of the cholinergic neurons, projecting from the basal forebrain to cortical and hippocampal areas. [10] The effective drugs currently approved for the treatment of AD are the inhibitors of acetylcholine esterase (AChE), such as Aricept and Tacrine. [11] From their clinical trials and later therapeutic use in AD patients, it is clear that these drugs can alleviate memory and cognitive problems in AD patients; however the benefits are generally modest. [12]

Recently studies have shown that natural compounds have an advantage over conventional drugs, because being constituents of living system they may be less toxic and hence more acceptable for human application. [13] Herbal medicine provides alternatives to modify the progress and symptoms of AD. Recently drug preparation based on medicinal plants appears to gain momentum in heath related areas. There has been a new trend in the preparation and marketing of drugs based on medicinal plants, and their scientific and commercial significance appears to be gathering momentum in health-relevant areas. These plant-derived products are carefully standardized, and their efficacy and safety for a specific application have been demonstrated. [14-15] The present review attempts to put together reports on *Convolvulus Pluricaulis* (CP) portraying it as an alternative medicine capable of reversing the symptoms and pathological manifestations associated with Alzheimer's disease.

BOTANY AND MEDICINAL VALUE OF *CONVOLVULUS PLURICAULIS*

The plant *Convolvulus pluricaulis* (CP) of the Ayurvedic Pharmacopeia of India (English name: Bindweed, Hindi: Shankhpushpi) belongs to the family *Convolvulaceae.* It is a perennial herb which grows under xerophytic conditions of northern India. The herb produces flowers during the months of September and October which are white to light pink in colour and their appearance is mostly resembles a "Shankh" (a marine shell), hence the name given to this plant is Shankhpushpi (Pushpa meaning flower) (Figure 1). [16] Beside *Convolvulus,* other plants namely *Evolvulus alsinoides* Linn, *Clitorea ternatea* Linn and Canscora are recognized by same name. A number of publications by Indian council of Medical Research have allotted standards for CP. [17] The plant has been found to be effective in reducing different types of stress including psychological, chemical and traumatic. The roots of CP have been used to reduce total serum cholesterol, triglycerides, phospholoipids and also been reported to increase brain protein content. [17] It has been recently reported that the extract of this plant is a potential cognitive enhancer.

Fig. 1: Pictorial representation of plant *Convolvulus Pluricaulis*.

CLASSIFICATION (Taxanomic) (Figure 1) [18]
Kingdom: Plantae, plants
Sub kingdom: Tracheobionta, vascular plants
Super division: Spermatophyta, seed plants
Division Magnoliophyta: flowering plants
Class Magnoliopsida: dicotyledons
Sub class: Asteridae
Order: Solanales
Family: Convulvulaceae
Genus: *Convolvulus*
Species: *pluricaulis*

ETIOLOGY OF AD

The neurodegenerative disease, AD is the most common form of dementia affecting the ageing individuals. Beside, cell loss, accumulation of senile plaques (SP), neurofibrillary tangles (NFT) in the neo cortex and hippocampus (including entorhinal cortex) AD is characterized neurochemically by a decrease in cholinergic neurotransmission, particularly affecting cholinergic neurons in the basal forebrain. [19] This is exemplified by reductions in Choline acetyltransferase (ChAT) activity and acetylcholine (ACh) synthesis which are strongly correlated with the cognitive impairment in patients with AD. [20] A decline of 90% in basal forebrain cholinergic neurons has been observed in AD patients. [21] Moreover, in comparison to significant decline of acetylcholine content in cholinergic target areas in AD brain, other transmitters such as serotonin, norepinephrin, and dopamine do not depict the same reduction. [22] While it has long been accepted that cholinergic neurons are pivotal for cognition, experimental evidences have shown that agents that block muscarinic cholinergic receptors cause transient loss of short term memory while agents that potentiate enhance memory and reduce any deficiencies induce by muscranic blockers. [23] These finding indicate that ACh plays a key role in normal cognition and memory. Dysfunction of cortical cholinergic neurotransmission has been found to contribute to Aβ plaque pathology in AD by affecting expression and processing of the AβPP. Moreover, low level of soluble Aβ has been observed to inhibit cholinergic synaptic function. [24] More emphasis has been given towards this particular deposition of AChE together with Aβ as it represents an early step in the development of senile plaques. [25] *In-vitro* studies by

Inestrosa and coworkers demonstrated that when a mixture of Aβ peptide and AChE are incubated for duration of 24 h it potentiates the formation of aggregates as compared to Aβ alone. [26] Seminal studies by Dinamarca and colleagues reported that treatment of rat hippocampal neurons with Aβ-AChE complexes induced neurite network dystrophia and apoptosis to a larger extend as compared to Aβ. They further reported that Aβ-AChE complexes induced a sustained increase in intracellular Ca^{2+} as well as a loss of mitochondrial membrane potential. [27] Moreover, studies have also found that other proteins do not promote amyloid formation, thus indicating the effect of AChE on amyloid formation to be specific. [28] Although, previous studies have determined the correlation between Aβ peptides and increased AChE levels, recent studies have revealed that increase in AChE is also associated with tau hyperphosphorylation. [29] Seminal *in-vivo* investigation by Silveyra and coworkers observed frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17), in transgenic mice (Tg VLW mice) over-expression of P-tau. These changes were also associated with increased activity of the T-transcript of AChE, thus suggesting that the early increase in AChE expression that occurs around NFT is due to disturbed tau phosphorylation. [29] Accumulating evidence also suggest that unlike Aβ transgenic models in which only one specific molecular form of AChE increases, in P tau transgenic mice, all major molecular forms of AChE were increased, including the tetrameric species. [30] Research reports from our lab have also shown that intra-peritoneal administration of cholinergic antagonist, scopolamine, to rodents results in elevation of Aβ 42 levels and Tau phosphorylation. [31]

Age dependent oxidative stress is another risk factor which has the potential to influence the pathogenesis and progression of AD. Oxidative stress is caused by an imbalance between pro-oxidant and antioxidant and it is increased with advancing age due to an excessive production of reactive oxygen species (ROS) or their derivatives. [32] Compared to other tissues the central nervous system (CNS) is vulnerable to free radical damage due to its high oxygen consumption rate, its abundant lipid content, and the relative paucity of antioxidant enzymes. [9] Numerous studies have reported increased oxidation of DNA, RNA, proteins, and lipids in AD brains. [33-34] Studies have found lower levels of antioxidants enzymes, such as catalase and glutathione peroxidase, in AD brains [35-36]; moreover individuals with mild cognitive impairments also display altered levels of antioxidants. [37] Considerable amount of evidence is accumulating that show a correlation between dyshomeostasis of the redox-active biometals, and oxidative stress. Previously elements such as aluminum (Al), mercury (Hg), and iron (Fe) have received the most attention in AD investigations. [38] *In-vivo* studies from our lab have shown that rats exposed to Aluminum (Al) resulted in the elevation of the antioxidants levels in brain frontal cortex. [39] Additional studies from our lab also showed increased lipid per oxidation increased immunoreactivity of bcl-associated X protein (BAX) in rat frontal cortex which were exposed to Al (Figure 2). [39] Moreover studies have shown that besides neurotoxicity associated with aggregation of Aβ; its aggregation produces free radicals. It has been shown that Aβ causes H_2O_2 accumulation in cultured hippocampal neurons and in neuroblastoma cultures. [40-41]

At present, the only available drugs for the treatment of AD have symptomatic effect only and are associated with adverse reactions in patients thereby having limited scope for the treatment of patients of Alzheimer's syndrome. [42] In recent years herbal remedies for AD have gained immense popularity due to their ability to slow down the brain's degeneration. There beneficial effect on AD have been evaluated by various research groups, the results have been very promising and the use of some medicinal herbs have been touted to extend beyond that of modern prescription drugs.

CONVOLVULUS PLURICAULIS AS AD THERAPEUTICS

The neurodegenerative disease, AD is the leading cause of dementia among the elderly individuals and has emerged as a major challenge for modern researchers. Increased levels of AchE have been detected around NFT and Aβ and its inhibition has been considered as an effective tool to treat AD and related dementia. [43] Tacrine, a known AChE inhibitor displays its pharmacological activity by increasing the level of ACh in rodent brain, but is also associated with side effects. [44] Hence, the AChE inhibitory potential of plant extract indicates their potential in the development of natural therapeutics for AD and related problems. The traditional Ayurvedic system of medicine which has evolved in India, involve a number of plants that are used for the treatment of variety of diseases. Over the several centuries, Ayurvedic medical practitioners have been using some of the plants which have been classified as "medhya rasayanas" or nootropic cerebral activators for treating disorders of the central nervous system (CNS) and also to improve the memory and intellect. Various scientific studies have described the use of various Ayurvedic medicinal plants termed 'nervines' and their constituents to strengthen the functional activity of the nervous system and restoration of memory. [45-46] Among the various plants of Ayurvedic importance, CP is regarded as the most reputed as it being effective during anxiety and neurosis. Phytochemical studies have shown the presence of alkaloid (Shankhapushpine), triterpenoids, flavanoids, glycosides, anthocyanins, and steroids, these metabolites show a wide range of pharmacological activity including its nootropic and memory-enhancing properties. [47-48]

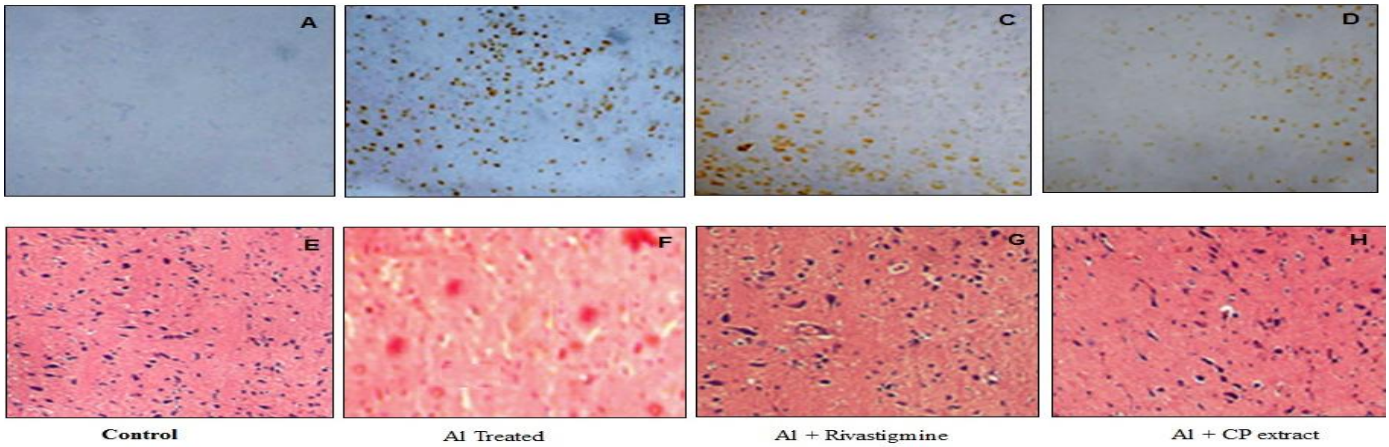

Fig. 2: Pictograph show neuroprotective effect of the CP extract on the aluminum chloride induced neurotoxicity. (A-D) represents Bax immunoreactivity and (E-H) represent hisopathological changes [H and E 40×] in the rat cerebral cortex in different group: Control group (A &E), Aluminum chloride treated group: (B and F), Aluminum chloride + rivastigmine (C and G), Aluminum chloride + CP extract (150 mg/kg) (D and H).

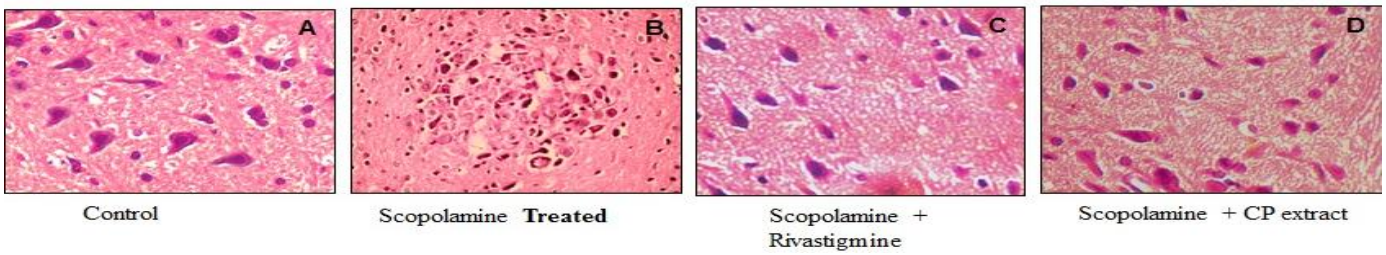

Fig. 3: Photographs (A-D) showing histopathological changes in cerebral cortex in different groups. (A) Control group (distilled water), (B) Scopolamine treated group, (C) Scopolamine + rivastigmine tartrate treated group, (D) Scopolamine + CP extract [H and E 40×]

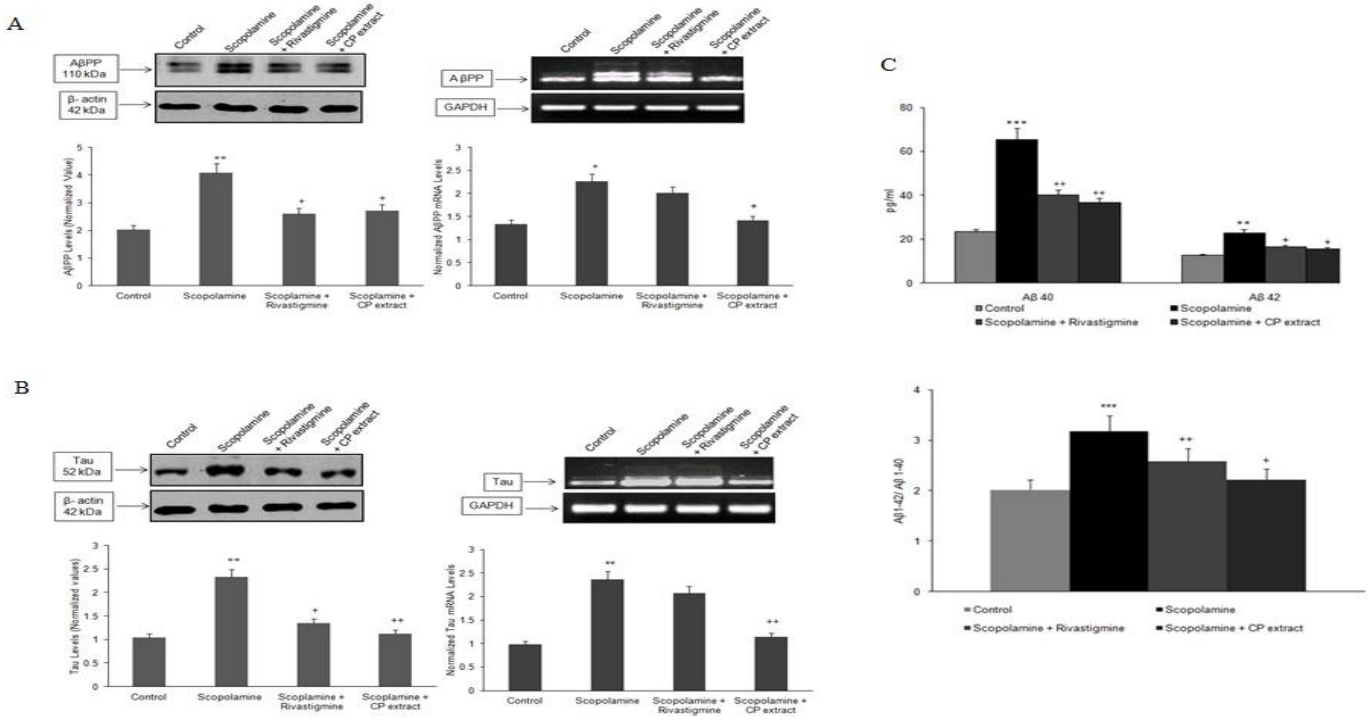

Fig. 4: Effect of CP extract on AD biomarkers. (A and B) represents western blotting and RT-PCR performed to examine the effect of CP extract and rivastigmine tartrate on the increased protein and mRNA levels of AβPP and tau induced by administration of scopolamine. (C) Cortical Aβ1-40 and Aβ1-42 levels were measured by an ELISA assay.

CP is believed to regulate the production of stress hormones, adrenaline, and cortisol which in turn calms the nerves. [48] Previous reports from our lab have shown that CP reversed the effect of aluminum in rat brain by decreasing the elevated enzymatic activity of AchE. The neuroprotective potential of the plant was also evident by its potential in preventing accumulation of lipid and protein damage. Also, changes in the levels of endogenous antioxidant enzymes associated with Al administration were also attenuated by administration of CP extract as compared to standard drug for AD, rivastigmine. [39] Oral administration CP extract also ameliorated the up-regulated protein expression of cycline dependent kinase5 (Cdk5) and also preserved

the mRNA levels of muscarinic receptor 1 (M1 receptor), choline acetyl transferase (ChAT) and Nerve Growth Factor-Tyrosine in rat brain exposed to Al. CP also displayed its neuroprotective potential by rectifying the histopathological perturbations and enhanced Bax immunoreactivity in the cerebral cortex of rat induced by Al exposure (Figure 2). [39] An improvement in memory was clearly identified in behavioral test such as elevated plus maze (EPM) and in Morris Water maze (MWM) paradigm, wistar rats pretreated of with aqueous extract of CP displayed significant reduction in scopolamine-induced increase in the total latency in EPM, these rats also the other improved the scopolamine induced impairment of spatial memory. Biochemical studies showed decline in the activity of the AchE in the cerebral cortex and hippocampus of rats pretreated with scopolamine. [49] These changes were also associated by reduction of lipid per oxidation and protein oxidation as well as normalization of anti-oxidant levels viz reduced glutathione (GSH), superoxide dismutase (SOD) and glutathione peroxidase (GPx). [49] Oral administration of CP extract to rat for four weeks reversed the toxic effect of scopolamine which was reflected at microscopic level also (Figure 3). Comparison of the neuroprotective potential of CP against rivastigmine was also scrutinized at molecular level. Western blot and RT-PCR studies by us revealed significant reduction in the scopolamine induced increase in the mRNA and protein levels of APP and tau in CP treated animals. CP treatment was also able to reduce the Aβ burden in these animals (Figure 4). [31]

We postulate that CP display its neuroprotective activity due to the interactions of its constituents of the extract with the cholinergic nerve terminal or trans-synaptically by mechanisms such as the modulation of AβPP secretion at one side of the synaptic cleft, which in turn can result in activation of neighboring cells and synaptic constituents. Mathew and colleagues using thioflavin T fluorescence assay investigated the influence of extracts from various herbal plants including CP on preventing the aggregation of Aß and its subsequent dissociation. There results revealed that extract of only few species including CP exhibited promising activity by preventing Aβ fibril formation/ retention thus identifying Aß as the molecular target for their action. [50] Recently Kaur and coworkers studied the neuroprotective effect of four sub-fractions from a cocktail of chloroform and ethyl acetate fraction. They studied the neuroprotective activity of these fraction on rats treated with 3-Nitropropionic acid (3-NP). Their results revealed that only one fraction was able to attenuate the loss in body weight, improved the locomotor activity, grip strength, and gait abnormalities. It also attenuated the increased MDA and nitrite levels, and restored SOD and reduced GSH enzyme activity in the cortex of 3-NP-treated groups, thus suggesting that CP exhibits a neuroprotective effect by accelerating brain antioxidant defense mechanisms. Further purification of the fraction gave pure compound, scopoletin. [51] Seminal studies Malik and his associates found that daily administration of ethyl acetate and butanol sub-fractions of hydro-methanol extract of CP extract for 10 and 15 days reversed 3-NP induced reduction in locomotor activity, grip strength, memory, body weight, and oxidative defense. [52] Subsequently the same research group by using column chromatography managed to isolate pure compounds from chloroform and ethyl-acetate fractions, these included scopoletin, ayapanin and scopolin. [53] They further evaluated the memory-enhancing potential of these isolated compounds against scopolamine-induced amnesia using elevated plus maze and step down paradigms. Scopoletin and scopolin, in both the paradigms, significantly and dose dependently attenuated the scopolamine-induced amnesic effect. Moreover, dosage of extract at 10 mg/kg and 15 mg/kg also attenuated increased activity of AChE activity in mice brain, the extract was observed to exhibit activity comparable to that of standard drug, donepezil. [54] Although there is a lot of experimental evidence which reveal a beneficial aspect of herbal medicine in alleviating AD associated symptoms. The use of herbal treatment in AD should be considered equivalent to pharmacological treatment currently in use.

ADVANTAGES AND FUTURE PROSPECT OF HERBAL MEDICINE

There has been a tremendous increase in the use of herbal products among western societies and developing countries. Herbal medicine has been perceived as natural and safe treatment compared to those of synthetic drugs. Many natural products have been traditionally used as memory enhancers and provide promising results. Demand for traditional medicine in developed countries is also on rise and according to one estimate approximately 40%-50% people in Germany, 42% in USA, 48% in Australia are using traditional medicine. [55] There are around 49000 species of plants in the Indian subcontinent with around 20% is global species. Although around 3500 plants have been known for their medical values, but only 500 among them are only used by the Ayurvedic industry. The increasing popularity of herbal medicine becoming is due to toxicity and side effects of allopathic medicines. Several reports have suggested that almost 80% of drug molecules are of natural origin or inspired by natural origin. It has been estimated that almost 50% of drugs approved since 1994 are based on natural products. [56] Previous and also present ongoing studies on herbal plants have been able to make numerous claims for the treatment of many acute and chronic diseases and symptoms, the prevention of disease, and the improvement of quality of life. [57] Medicinal plants have been widely used to treat psychotropic and behavioral conditions as anxiety, depression, seizures,

poor memory, dementia, insomnia and drug intoxication. Accumulating evidence show memory herbs increase the level of neurotransmitters, particularly acetylcholine, and improve blood flow to the brain, thereby increasing its oxygen and nutrient supply, which will aid brain function and memory. Herbal remedies for AD have become more and more popular in the recent years. [58] This has been attributed to the benefits derived from using herbal treatments and in some cases have performed to extend beyond that of modern prescription drugs. [59] World health organization has estimated that around 80% of the world population is using herbal medicine, thus becoming drug of choice. [60] Although, numerous pharmaceutical companies are investing enormous resources in order to identify agents with potential to slow the progression of neurodegeneration which afflict numerous people around the globe. Sources of potentially beneficial agents, namely phytochemicals, have appeared to have significant benefits that have yet to be fully exploited. The valuable medicinal properties of different plants are due to presence of several constituents i.e. saponins, tannins, alkaloids, alkenyl phenols, glycol-alkaloids, flavonoids, sesquiterpenes lactones, terpenoids and phorbol esters. [61] The demand for herbal medicines is increasing globally, due to the growing recognition of these being mainly non-toxic, having lesser side effects, better compatibility with physiological flora, and availability at affordable prices. However, the use of herbal drugs through developed and developing countries as home remedies, over-the-counter drug products and raw materials for the pharmaceutical industry, and represent a substantial proportion of the global drug market. It is therefore essential to establish internationally recognized guidelines for assessing their quality. [62] In future also drug discovery will have strong association with biologically active natural products, as these will continue to serve as lead compounds for drug development and act as biochemical probes for the discovery of pharmacological and biochemical process. This association will also lead in development of structure–activity libraries due to incorporation of knowledge of traditional systems such as ayurveda with dramatic power of combinatorial chemistry generation. However, the main factor to remain competitive with the modern system of medicine includes continual improvements in the speed of dereplication, isolation, structure elucidation, compound supply processes and prudent selection of drug targets for the screening of natural product libraries.

The use of CP as memory booster has been increasing recognized in ayurvedic system of medicine. However, current evidence to support its use as therapeutic agent in alleviating AD and its associated symptoms is inconclusive or inadequate. Several studies currently underway or in early-stage development to evaluate herb mixtures will hopefully show promising results in the near future.

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