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Multi-Target Strategy Of Traditional Herbs For The Prevention And Treatment Of Alzheimer's Disease - A Review

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ABSTRACT

The incidence of Alzheimer's disease (AD)rises from the ages of 65 to 70 years and ranges from 1-4 percent of the population per year.This progressive neurodegenerative disease is characterised by changes in the brain such as damage and loss of nerve cells and their connections, tangled fibers, protein clumps, and inflammation which are considered to be the hallmarks of the disease.Though researchers believe the combination of several factors such as genetic, familial, environmental factors, age, lifestyle, diet, etc, its pathogenesis has been considered to be highly complex.Presently more than 200 promisingpharmaceuticalproducts have been tested on subjects with Alzheimer's disease (AD). The mainfocus of treatment is to augment the acetylcholine in the brain to compensate the loss of cholinergic function but the outcomes are often unsatisfactory as there is a lack of cure or to prevent the disease progression. According to Siddha system, the nervous system disorders are considered to occur due to imbalances of vatham(Biological air humor), the energy that moves through the brain and the nerves.This system classifies 80 types of vatha disease and the Alzheimer's disease is one among its types.In this scenario, traditional herbs are now gaining worldwide attention due to its antioxidant, anti-inflammatory and cognitive enhancing potential. The present article reviews selected herbs such as Bacopa monnieri(Brammi), Withaniasomnifera(Amukkara), Clitoriaternaetea(Kaakataan), Centella asiatica(Vallaarai), Curcuma longa(Manjal), Glycyrrhiza glabra(Athimadhuram), Tinospora cordifolia (Seenthil)that have been indicated in siddha literature for brain and neurodegenerative diseases (Narambu uramaki) for their neuroprotective and multitargeted roles towards Alzheimer's disease (AD). The review concludes that medicinal plants can have great potential for prevention and treatment of Alzheimer's disease (AD)

Key words: Alzheimer's disease (AD),Narambuuramaki,Siddha, Traditional medicine, Neuroprotective

INTRODUCTION

Alzheimer's disease is a neurodegenerative progressive disease of brain and often shortened to "Alzheimer's" or "AD".Though the greatest single risk factor for AD is considered to be advanced age (usually begin after age 60), it is not a normal part of ageing. Perl DPMt Sinai J Med. 2010 Jan-Feb; 77(1):32-42.After 65 years, the number of people affected couples every five years and nearly half of all people over 85. According to World Alzheimer's Report 2015, global prevalence of dementia rose from 30 million (2010) to 46.8 million and global expenditure on dementia rose from US$ 604 million (2010) to US$ 818 million (2015). In India, the prevalence of dementia was 33.6 in every 1,000 people of which 54% were cases of AD. [1]Usually, AD commences deep in the brain, as many as 10 to 20 years earlierto the appearance of symptoms, and gradually spreads to other parts of the brain. Alzheimer's disease causes impaired memory initially followed deterioration in intellect, recall, and dialectal, personality changes, and gradually get worse over time and affect the motor system.[2] Eventually the disease results in the aptitude loss to carry out the basic daily routines. Hence it is noteworthy to discover drugs that can prevent the brain damage and disease development.

The pathophysiological manifestations of AD in brain are formation of an Aβ peptide that are Neuritic plaquesforming spheroid-like microscopic lesions. The increased concentration of Aβ peptides favours the formation of oligomers, which have neurotoxic properties.[3] The other manifestation of AD in brain is the formation of neurofibrillary tangles that are fibrillary intracytoplasmatic structures formed by a protein called Tau. Physiologically Tau stabilizes the axonal microtubules and presents a certain number of phosphate molecules attached to it. In AD an alteration in phosphorylation of mechanics of Tau occurs and the detached hyper-phosphorylated Tau proteins tend to assemble to form filamentous structuresresulting in aggregation of neurofibrillary tangles.[4]The granulo-vacuolar degeneration is yet another pathological observation in AD. This degeneration is likely associated to the cognitive decline However, the mechanisms behind are not fully determined. [5]

MATERIALS AND METHODS

This article involved literature reviewing of herbs with tri-humoural balancing action with anti-vatha properties as per Siddha literature that has been indicated for similar symptoms of Alzheimer's disease. The same herbs were investigated for the role of neuroprotective action for relevance of subject matter. The search included PubMed Central, Scopus, and Google Scholar databases and research and review articles were collected and validated for the treatment of AD.

SIDDHA ASPECT ON THE TRIHUMOURAL THEORY OF ALZHEIMER DISEASE

As it is well known, Alzheimer's disease is primarily caused by neuronal loss, damage to memory centres and its network of nervous system. According to Siddha system, nerve impulse is considered to be the wind/air one among the component of trihumours (vatham) that controls both voluntary and involuntary functios of the body.Tridhosham and Thirigunam are the bioenergies to regulate the physiological and psychological functions of human body. Disruptions in these will have negative impact in Indiriyam(Cognitive and motor organs), Manam (Psychological mind) and Buddhi (Intellectual mind). Hence creating an environment of balanced state of trihumoural balance is essential for the effective management of Alzheimer's disease. The ancients considered nerve impulse to be the kind of wind or air travelling through the body controlling both voluntary and involuntary functions.[6] Among the three dosham, vatham is the motivating force behind the other dosham (pitham and kapam). Increase in the vatham dosha leads to tissue decrease of the brain cells leading to pathological condition similar to that of AD. [7,8]

According to Siddha system the treatment for diseases (Derranged humours) is based on the choice of herbs which is able to correct the deranged humour by its nature of opposite action due to its suvai (taste), Veeryam (Potency) and Taste after digestion (Vipaakam). Each taste is the combination of two basic elements of nature such as earth, water, fire, air and space that are panchabootham. Our human body is also made up of these similar elements of panchabootham. Hence substituting suitable herbs with selective tastes to balance these humours is the basic treatment tool in Siddha system of medicine. In this aspect, the selected herbsBacopa monnieri(Brammi), Withaniasomnifera (Amukkara), Clitoriaternaetea (Kaakataan), Centella asiatica (Vallaarai), Curcuma longa (Manjal), Glycyrrhiza glabra (Athimadhuram), Tinospora cordifolia (Seenthil) have been analysed for their taste and Siddha pharmacokinetics on their action on trihumours. The search results on their tri-humoural balancing potential has been tabulated in Table-1.[9]

Table-1. Siddha concept on Trihumoural balancing potential of selected herbs for AD

S.No	Bot name	Tamil Name	Taste	Potency	Action on trihumours
1	Bacopa monnieri	Brammi	Sweet Astringent	Cold	Balances vatham, pitham and kapam
2	Withaniasomnifera	Amukkara	Bitter	Hot	Balances vatham and kapam
3	Clitoriaternaetea	Kaakattan	Bitter Sweet Astringent	Hot	Treats vatham, pitham and kapam

4	Centella asiatica	Vallarai	Astringent Bitter Sweet	Cold	Balances kapam and pitham
5	Curcuma longa	Manjal	Hot Bitter	Hot	Balances vatham and kapam
6	Glycyrrhiza glabra	Athimathuram	Sweet	Cold	Balances vatham, pitham and kapam
7	Tinospora cordifolia	Seenthil	Bitter	Hot	Balances vatham, pitham and kapam

Scientific analysis of selected herbs for AD

1.Bacopa monnieri

Bacopa monnieri (L.) is an important medicinal plant in Indian traditional medicine.[10]

It is also known as Brahmi and Aindri in Sanskrit, is classified into the Scrophulariaceae family.[11]Bacopa is a small tropical, creeping, succulent, marshy herb which is short, with petiolated, oblong leaves, rooting at nodes.The genus Bacopa has 146 aquatic herbal species dispersed throughout the subtropical regions of the globe, including plains of Southeast Asia, tropical Asia, sub-tropical United States, tropical Africa, and Australia.[12]and abundantly grown in wetlands and marshes of warmer districts. [11].

The polyphenols, and sulfhydryl compounds that are suggested to have antioxidant activity. [13] Bacopa has additional useful components which includes apigenin, cucurbitacin, alkaloids brahmine, monnierin, hersaponin, monnierasides I-III, plantain side B, d-mannitol, herpestine, and nicotine.[11]Bacopa monnieri is commonly used as Ayurvedic medicine and act as a nerve tonic, cardiotonic, diuretic and as therapeutic agent against asthma, insomnia, epilepsy, and rheumatism.[13]The chemical compound that has neuropharmacological properties and pseudo-jujubogenin moieties, is aglycone units, called Bacoside A. This compound contains bacopaside III, bacopaside X, bacoside A3, and bacopasaponinC.[11]Bacosides prevent Aß aggregation and formation of fibrils as well as protect neurons against Aβ-induced toxicity. The bioactive constituent, bacoside A, present in the B monnieri extract (BME) treated rat serum and could directly or indirectly interact with the neurotransmitter systems to improve memory and learning ability. [11]Oxidative stress is one of the vital factor in the process of aging and age-related illnesses. The main role of EBm as an antioxidant is to increase concentration of GSH and enzymatic antioxidants

like SOD, CAT, and GPx and as free radical scavenging agent. Hence, its administration in recommended doses may act as a remedy for age-associated memory and cognitive decline in AD.[12]

The neuropharmacological effects and nootropic actions were extensively investigated with BM extracts of the plant. BM enhances protein kinase activity that may contribute to its nootropic action in the hippocampus of the brain and also inhibited cholinergic degeneration and displayed a cognition-enhancing effect in a rat model of AD. A team of researchers also reported that, cognitive deficits which was induced by intra cerebro-ventricularly administered colchicines and ibotenic acid into the nucleus basalis magnocellularis,was effectively reversed by standardized extract of BM, which also reversed the (a) depletion of acetylcholine, (b) reduction in choline acetyltransferase activity, and (c) decrease in muscarinic cholinergic receptor binding in the frontal cortex and hippocampus of the brain. By suppressing cellular acetylcholinesterase activity, BM extracts protected neurons from beta-amyloid-induced cell death. Additionally, BM extract-treated neurons expressed a lower level of reactive oxygen species, indicating Brahmi restrained intracellular oxidative stress. [14]In Alzheimer model of rat, B. monnieri inhibited cholinergic degeneration and showed enhanced cognition effect in a toxic free safe manner. It was reported that a standardized B. monnieri extract reversed the cognitive deficits induced by colchicines and ibotenic acid into the nucleus basalis magnocellularis also reversed the acetylcholine depletion, choline acetyltransferase activity reduction, and reduce the muscarinic cholinergic receptor binding in frontal cortex of hippocampus and mainly it protected the neurons from β- amyloid induced cell death by repressing cellular acetylcholinesterase activity which are the major activities that increase symptomatic effects of Alzhemers. [15]

The study conducted by Sireeratawong et al, reported that 5000mg/kg dose of B. monnieri extract was safe, did not cause any observable signs or symptoms of toxicity and also neither gross nor histopathological abnormalities were observed in any of the internal organs, including the liver and kidney of B. monnieri-treated rats. With this result the study states that B. monnieri extract is nontoxic at a dose of 5,000 mg/kg. Eventhough dose of B. monnieri extract used in this study is approximately 1,000 times higher than that generally used in humans (5 mg/kg/day), there was no toxicity which indicates that B. monnieri is quite safe for human use. [16]Upon the promising neuroprotective effect of B monnieri in in-vitro and in-vivo studies, numerous clinical studies on human subjects have been performed for cognitive improvement. [11]The standardized extract of B monnieri (Bacognize) has been proven to improve some aspects of cognitive functions in a 6-month trial in geriatric Alzheimer patients. In this study, all patients who took 300 mg of Bacognize orally twice a day showed a statistically significant improvement in various components of Mini-Mental

State Examination Scale (MMSES) including orientation of time, place and person, attention, and their language ability in terms of reading, writing, and comprehension at the end of trial. [11]A clinical study reported the standardized extract of B monnieri (150 mg) on 60 medical students from Government Medical College, Nagpur, India over a period of 15 days revealed significant improvement in biochemical analyses, that is, significant elevation in serum calcium levels and enhanced memory test. Another research reported that individual doses of B monnieri and Sideritisscardica extracts in 10 mild cognitive impairment subjects from Germany (mean age: 61.88 ± 6.69 years) resulted in improvement in the d2-concentration test. However, the study conducted in Australia, in Swinburne University reported that, treatment with B monnieri (2 × 150 mg) for 90 days in 107 participants (between ages 18 and 60 years) led to an improved performance in a structural working remembrance task in healthy participants with no history of neurological diseases, gastrointestinal disorders, as well as chronic infections and none of the healthy participants took any cognitive- enhancing drugs. Not only cognitive improvement, B monnieri can also enhance learning capability. A study stated that, Consumption of B monnieri for 3 months in 76 human subjects between 40 and 65 years of age in University of Wollongong, Australia had significant effects on retention of new information. Other study concluded that, the consistent consumption of BME (300 mg/day) for 84 days in participants without dementia aged 65 years and above in University of Catania, Italy showed improvement in their performance in a restraint recall and Stroop Task, that is, evaluating the capability to bypass unnecessary input. In another study, Significant enhancement in prompt memory and response performance was recorded when Bacopa was administered in the form of syrup (proportionate to 10 g dried Bacopa daily) in 40 school children aged between 6 and 8 years for 90 days from rural India. [11]

2. Withaniasomnifera

Withaniasomnifera called as Ashwagandha belonging to the family of Solanaceae. Generally its root is utilized for medicinal purposes. It is ordered as a Rasayana (rejuvenating) and is accepted and approved to have cell reinforcement movement, free radical rummaging action, and a capacity to bolster a solid resistant framework. [17] Ashwagandha contains several bioactive compounds of great interest, such as ergostane-type steroidal lactones, including withanolides A-Y, dehydrowithanolide-R, withasomniferin-A, withasomidienone, withasomniferols A-C, withaferin A, withanone, and others. Other constituents include the phytosterols sitoindosides VII-X and beta-sitosterol and alkaloids. [18]The alkaloid-rich fraction of the Withania root showed soothing action on the CNS of many mammals, signifying its role to create relaxation. In the commencement and advancement of AD, the withanamides consisted of glucose and serotonin, and the long-chain hydroxyl fatty acid moieties have been seen to scavenge unobstructed radicals produced during the

disease progression. Withanamides was found to obstruct the activated neuronal cell death by amyloid plaques. The aqueous extract of Ashwagandha was found to improve the cholinergic action, which helped to stimulate the acetylcholine amount and choline acetyltransferase activity in mice, which might be the perception of enhancing memory activity. In human neuroblastoma cells, Ashwagandha methanol extract was found to trigger the growth and development of the neuronal network. In a study done by Sehgal et al., described that per-oral intake of Withania root extract overturned behavioral shortages and Aβ plaque formation in validated AD mice. These effects of Ashwagandha were associated with the upregulation of the low-density lipoprotein receptor-linked protein in the liver. By boosting cellular immunity along with neutralizing the lethal mediators of the cytotoxic cascade (cytokines and reactive oxygen species (ROS)), the roots of Ashwagandha advance the defense mechanism of the body in case of chronic disease. [17] Simulation studies have reported that withanamides- A and –C may bind to the active motif of (Aβ25–35) in a distinctive fashion and may protect cells from Aβ-induced toxicity by avoiding fibril formation

Glycowithanolides and sitoindosides VII-X solated from the root extract of Withaniasomnifera (L.) have proved to significantly reverse the ibotenic acid-induced cognitive impairments in animal models of AD. [20,21]Oral doses of Withaniasomnifera (L.) in mice has shown to reduce the neurite atrophy, modulate synaptic integrity and improve memory promisingly. The active constituents Withanolide-A, Withanoside IV, VI have been reported to preserve axons and dendrites.[22]Withanamides and aqueous extract of Withaniasomnifera (L.) has shown to deliver PC-12 cells against H2O2 and Aβ(1-42)-induced toxicity. [23] In this in-vitro study it ws proved that, the cells treated with 100 and 50 µg/mL concentrations showed 100% cell survival and indicated that at these concentrations WA completely protected PC-12 cells from cell-death caused by BAP.[19]

Withanamides effectively blocked the Neuronal cell death triggered by amyloid plaques in alzheimers disease. The capacity of withanamides A and C uniquely binding to the active motif of beta-amyloid (Aβ 25-35) and preventing fibril formation was studied in Molecular modeling studies. Reports suggests that, In the CNS, Amukkara has potency to increase memory and learning. Increase in cholinergic activity, such as increases in the acetylcholine content and cholineacetyl transferase activity was found to be prominent in aqueous extracts of this herb and this property of the herb might partly explain the cognition-enhancing and memory-improving effects in rats. [24]Successively treatment with a methanol extract of Amukkara initiated significant regeneration of both axons and dendrites (reconstruction of pre- and postsynapses in the neurons)and also reversed amyloid peptide-induced memory deficit in mice. [22]

Considering the safety of W. somnifera use, no serious adverse events were reported in any of the previous studies, and no biochemical abnormalities (complete blood count, renal function, liver

function tests, and lipid profile) were found at the end of a 29-day study period. [25] Acute and subacute studies of W. somnifera administered to Wistar rats, even at the highest tested concentration of 2,000 mg/kg, it was found to be safe and Hematological and serum chemistry parameters were within the normal limits, and postmortem histopathological examinations did not reveal any abnormalities.[26]

In a prospective, randomized, double-blind, placebo-controlled pilot study involving 50 subjects with mild cognitive impairment, ashwagandha treatment group demonstrated significant improvements in both immediate and general memory tests compared to the placebo group. Furthermore, significant improvement was seen in executive function, sustained attention, and information-processing speed. [27,28]A detailed analysis in 50 human subjects with symptoms of MCI revealed that daily treatment with ashwagandha for a period of eight weeks produced significant enhancement versus placebo in a battery of cognitive tests designed to assess memory (p 0.05), executive function (p 0.03), and attention and information-processing speed ($p < 0.01$). In a study,treatment with ashwagandha was associated with significant enhancement in auditory immediate and declarative memory compared with placebo, as seen in the logical memory I and II and verbal paired associates I and II subtest scores after eight weeks ($p < 0.05$).[29]

3. Clitoriaternaetea

Clitoriaternatea L. (Fabaceae), commonly named as Shankapushpi, also called Aparajit (Hindi), Aparajita in Bengali and Kakkattan is used traditionally for various ailments. Roots, seeds and leaves of C. ternatea are used in the Ayurvedic system of medicine. In Kerala (India) and in Philippines C. ternatea young shoots, leaves, flowers and tender pods are eaten as vegetable. In Malaysia, the food colours are prepared from the flowers to impart a bright blue color to rice cakes and the leaves to impart a green color to food. [30,31]Clitoriaternatea (C. ternatea) is a perennial tropical climber herb with slender downy stem, found throughout the tropical regions of India, growing wild and in gardens, bearing white or blue flowers.[31]Clitoria comprises 60 species distributed mostly within the tropical belt with a few species found in temperate areas. The plant originated from tropical Asia and later was distributed widely in South and Central America, West Indies, China and India As the plant is well adapted to various climates.[32]

In the previous study by Linggam Kamilla et al, it states that, the general toxicity activity was considered weak when the LC50 was between 500 and 1000 µg/mL, moderate when the LC50 was between 100 and 500 µg/mL, and designated as strong when the LC50 ranged from 0 to 100 µg/mL against the Brine shrimps and they stated that this preliminary toxicity results show that leaf extract is not toxic to brine shrimps after short period of exposure. [30] Recently with the study conducted

by Damodaran et al., it was documented that neuroprotective effect of the C. ternatea root extract in reversing chronic cerebral hypoperfusion-induced neural damage and memory impairment at doses of 200 and 300 mg/kg. [33]The toxicological evaluation of a leaf extract seeks to determine its safe use. In some studies, There were no significant differences in the mean organ weight between control and animals treated with 50, 300, and 2000 mg/kg body weight as per toxicity guidelines.The acute toxicity study indicated that, acute minimum fatal dose of C. ternatea leaf extract for mice is higher than 2000 mg/kg body weight which indicates some high level of safety margin in oral formulation and Gross examination at autopsy and histopathological evaluations of the various organs stained with hematoxylin and eosin revealed no significant for both sexes.[30]

4. Centella asiatica

Centella asiatica belongs to Apiaceae family and found throughout India, Sri Lanka and Bangladesh. It contains various bioactive compounds including triterpenes, asiatic acid, asiaticoside, adecassoside, sapogenins, glycosides, madecassic acid, vellarin, and centelloside. [34] C. asiatica has been reported to contain a vast number of compounds belonging to different chemical classes of which major chemical class found in this plant is triterpene saponosides, asiatic acid, madecassic acid (6-hydroxy-asiatic acid), asiaticoside, madecassoside, and madasiatic acid, betulinic acid, thankunic acid, and isothankunic acid. [35]

A in-vitro study suggested possible role in Alzheimer's disease treatment and β-amyloid toxicity prevention was due to asiatic acid and asiaticoside, which showed reduce hydrogen peroxide-induced cell death, decline concentration of free radicals, and β-amyloid cell death inhibition. Centella asiatica extract reversed the β-amyloid pathology in mice brains and modulated oxidative stress response components and is an important plant for nerve and brain cells capable of enhancing intellect, memory and longevity.[15] In our quantitative study on C. asiatica of Turkish origin by HPLC, we reported existence of several phenolic acids, for example, p-hydroxybenzoic acid, vanillic acid, p-coumaric acid, o-coumaric acid, and transcinnamic acid [48]. On the other hand, only a few studies have described the chemical composition of the essential oils obtained from C. asiatica from Japan, South Africa, and Thailand, which mainly consisted of monoterpene and sesquiterpene derivatives. In a study conducted by Orhan et al., examined the essential oil composition of C. asiatica cultivated in Turkey by GC-MS for the first time and identified α-copaene as the major component. [35]Reduce hydrogen peroxide-induced cell death, decrease free radical concentrations, and inhibit betaamyloid cell death in vitro which was exhibited by Asiaticoside derivatives, such asasiaticacid and asiaticoside, suggested a possible role for Vallarai in the treatment and prevention of AD and beta-amyloid toxicity. As stated in previous studies, Vallarai extracts was able to reverse the beta-amyloid pathology in the brains.[36]

In another study conducted by Rao et al., enhancing effect of C. asiatica extract on learning and memory was examined during 15 days at 200, 500, 700, and 1000 mg/kg (b.w.) doses by oral administration to mice displayed improving effect in radial-armed labyrinth test, whereas it did not cause any change in locomotor activity, on the other hand, increase in AChE activity and dendritic arborization in CA3 neurons located in hippocampus was found with extract administration. In a similar study, the fresh leaf extract of C. asiatica given to adult mice at 2, 4, and 6mL/kg doses during 2, 4, and 6 weeks, respectively which pointed out to the evidence that the extract given at 6mL/kg dose during 6 weeks had significant augment in dendritic arborization in neurons when the removed brains of mice were investigated under microscope. These authors came to another similar conclusion that, enhanced dendritic arborization was seen in mice which was administered with the juice obtained by pressing the fresh leaves of C. asiatica.[35]

The results of an early double-blind clinical study on the children with mental deficiency in 3rd and 6th months following administration of C. asiatica, showed a statistically significant improvement. In other study, possible effect of the capsulated aqueous extract of C. asiatica standardized to contain 29.9mg/g tannic acid, 1.09 mg/g asiaticoside, and 48.89 mg/g asiatic acid was determined in a randomized, double-blind, and placebo-controlled clinical study on 28 healthy and elder volunteers consisting of 4 men and 24 women with once a day dose of 250, 500, and 750 mg during 2 months, revealed that the highest dose of C. asiatica extract tested in this study possessed a cognitive enhancing effect. In a similar study, Dev et al. investigated effect of the capsulated C. asiatica extract on cognitive performance conducted with a total 41 of middle-age healthy subjects with doses as once a day during 2 months revealed remarkably positive influence on all of the subjects with the cognitive performance measured using Woodcock-Johnson Cognitive Abilities Test III (WJCAT III). In a clinical study consisting of 60 elderly subjects with average age of 65 with mild cognitive deficiency indicated that C. asiatica extract administered at 500 mg dose twice per day during 6 months led to a significant cognitive improvement according to Mini Mental State Examination (MMSE) scoring.[35]

5. Curcuma longa

Curcuma longa belongs to Zingiberaceae family and possesses anti-inflammatory activity. In studies the word “curry spice” is used for turmeric and curcumin. Southeast Asian countries utilize turmeric frequently in diet and there are 4.4-fold lower cases of Alzheimer.[36] There is a long list of compounds that have been isolated from turmeric include curcumin, bisdemethoxycurcumin, demethoxycurcumin, eugenol, dihydrocurcumin, azulene, borneol, D-camphene, caprylic acid, cineol, turmerone, and zingiberene (Duke, 1992). Also reported to contain β-caryophyllene, β-bisabolene, and β- squiphell and renendrene (Qin et al., 2007).Comparitive study on

tetrahydrocurcumin and curcumin showed that only curcumin was effective in reducing plaque burden (Begum et al., 2008). A recent study has showed protection particularly against Aβ-oligomer-induced toxicity by tetrahydrocurcumin. [37] A study conducted on tetrahydrocurcumin, shown to reduce the neuroinflammation but ineffective in reducing plaques and insoluble Aβ. [38] Ferulic acid (an Antioxidant) inhibited fibril Aβ formation and extension from amyloid beta-peptide in a dose-dependent manner.[39]

A study reported that low doses of Curcumin reduced Aβ level up to 40% in mice as compared to control drug with Alzheimer's disease. Another study correlated the anti-inflammatory property of turmeric with a decrease Alzheimer risk. [15]Curcuminoids or the curcuminoid mixture is known to contain three compounds that are found in turmeric in a specific ratio 3–5% bisdemethoxycurcumin, 15–20% demethoxycurcumin, and 75–80% curcumin (Ahmed and Gilani, 2009), which is known as a vital ingredient of turmeric. [40]The non-steroidal anti-inflammatory property of turmeric is well known to a reduced risk of AD. The amount of plaque deposition was significantly reduced with the use of Curcumin by the mechanism of reduced oxidative damage and reversed the amyloid pathology in an AD transgenic mouse. The mice with AD not only hampered further development of plaque but also reduced the plaque levels when the curcumin was directly injected into the brains. Curcumin's powerful antioxidant and anti-inflammatory properties also reduced AD symptoms characterized by inflammation and oxidation. Proinflammatory cytokine levels which are linked to the neuroinflammatory cascades involved in neuritic plaque pathogenesis was reduced with a low dose of turmeric (160 parts per million, or ppm). [41]

There are several studies which present the safe use of Curcumin in rats which demonstrated anti-inflammatory activities of curcumin, in which a In-vivo study using an AD rat model have shown that curcumin exerts a significant reduction in glial fibrillary acidic protein expression and astrocyte activity, contributing to the rescue of behavioral defects caused by Aβ intracerebral injection (Wang et al., 2013). [42]

To date there is one clinical study which has evaluated the sensitivity and specificity of curcumin fluorochrome in retinal Aβ imaging. This study obtained positive results which encouraged more clinical trials of curcumin-related Aβ probes in brain imaging. Curcumin shows potential beneficial effects on human health making it a life-long anti-aging nutraceutical, which may reduce risk factors of AD. Eventhough curcumin has showed promising biological activity in AD animal models, its treatment in AD patients remains a challenge, and development of early AD diagnosis and new curcumin formulations are an active area of research. [42]

6. Glycyrrhiza glabra

G. glabra is a typical herbaceous perennial, growing to 1 m in height, having pinnate leaves with a length of 7 to 15 cm and flowers are purple to pale whitish blue, arranged in a hermaphrodite inflorescence. [43]

The genus Glycyrrhiza (Fabaceae) consists of about 30 species, and like the other plants of Fabaceae, G. glabra is able to fix nitrogen, due to symbiosis with bacteria of the genus However, in the last years, different studies was carried out to study the phytochemical composition of G. glabra leaves, demonstrating that certain compounds present in the roots are also identified in leaves, although in smaller quantities (Hayashi &Sudo, 2009; Siracusa et al., 2011). [43] It is distributed in southern Europe, Syria, Iran, Afghanistan, Russia, China, Pakistan, and N. India. [44] Glycyrrhiza glabra contains various bioactive compounds which include linalool oxide, geraniol, benzoic acid, terpinen, tetramethyl pyrazine, propionic acid, ethyl linolenate, butanediol, feuferaldehyde, methyl ethyl ketone, furfuryl formate, trimethylpyrazine, glycyrrhizin, tannin, and glycyrrhizic acid.

Memory enhancing activity of this plant was reported in studies with scopolamine induced dementia. Dhingra et al. reported that in mice Glycyrrhiza glabra enhances memory and three dose levels (75, 150, 300mg/kg) of plant extracts were administered to mice in seven successive days and dose at 150mg/kg was found effective in memory enhancement which could be helpful in the treatment of AD.[15] In Siddha and Ayurvedha, it is used mainly to relieve “Vata” (governs all movements/activities, Pitta governs heat/energy levels and regulates various transformations) and “Kapha” (controls growth, structural modifications and lubrication) inflammations.[45] In the first research finding showing enhancement of learning and memory by liquorice, 150 mg/kg of liquorice extract (equivalent to 5.19 g of dried plant material) administered orally for 7 days improved learning and memory of mice significantly. Furthermore, liquorice extract protected the animals from learning and memory impairment produced by interoceptive stimuli (scopolamine and diazepam) with pretreatment of 150 mg/kg for 7 days. The lethal effect of the extract was proved when the extract showed impairment of learning due to the highest dose (300 mg/kg) of the extract and this paradoxical effect could also be due to the sedative property of the drug.[45]

Immunohistochemical studies conducted in Alzheimer’s disease patients suggested the existence of chronic inflammation in certain regions of the brain, since inflammation can be damaging to host tissue, it was said that anti-inflammatory drugs might be inhibiting both the onset and the progression of Alzheimer’s disease. The antioxidant property by which brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function, thereby enhancing the memory may be possible with liquorice extract. Thus, a combination of anti-

inflammatory, antioxidant and neuroprotective role could all be leading to the net memory-enhancing effect of the Liquorice extract. [45]

7. Tinospora cordifolia

Tinospora cordifolia distributed throughout tropical Indian subcontinent and China, ascending to an altitude of 300 m is a large, glabrous, deciduous climbing shrub belonging to the family Menispermaceae. The plant is commonly known as Giloya in Hindi, also known as Guduchi or Amrita in India, is considered as "Heavenly elixir" due to its adaptogenic properties that have saved celestial beings from old age and kept them eternally young. [46].

Pharmacological activities of Tinospora cordifolia include anti-fertility, antioxidant and immunomodulating activities (Reddy and Rajasekhar, 2015). Tinospora cordifolia possesses a memory improving effect in animals which are memory deficits (Malve et al., 2014). The synthesis of acetylcholine and immunostimulation in Tinospora cordifolia improves memory (Asuthosh et al., 2000). Tinospora cordifolia increases the cognitive function in patients with AD. [47]

In a study, Ethanolic extract of T. cordifolia was found to improve the motor coordination and exert neuroprotection against 6-OHDA-induced degeneration of dopaminergic neurons by restoration of antioxidant levels. [48] Many extracts and polyherbal formulations containing T. cordifolia have been shown to exhibit anti-inflammatory activity in animal models of asthma and edema (Tiwari et al. 2014; Patgiri et al. 2014; Nipanikar et al. 2017; Philip et al. 2018). T. cordifolia exhibited anti-depressant activity, memory improvement, and anxiolytic activities in Oral administration of different extracts such as petroleum ether, aqueous ethanolic extracts. [45,37]
Antioxidant-rich nature of T. cordifolia is considered as the basis of anxiolytic potential of this herb. [46] A study done by Chandrasekaran et al,. reported that, In MN (rodent bone marrow micronucleus) and Comet assays, T. cordifolia was given as pre-treatment for 7 days at three dose levels (150, 200 and 250 mg/kg body weight) orally to male Balb/c mice and the results showed that TC treatment did not display clastogenicity and DNA damaging effect in bone marrow erythrocytes and p eripheral blood lymphocytes respectively.[47]

A study done by Chandrasekaran et al,. Stated that, In CA (chromosome aberration) assay, TC was not clastogenic to human peripheral blood lymphocytes up to a concentration of 3000 microg/ml. In another study done by Karkal, it was concluded that Tinospora cordifolia is safe at a dose of 500mg per day for a period 21 days in healthy volunteers for the parameters studied.[48]

CONCLUSION

Traditional medicinesaid as therapeutic choices to alleviate the various pathological cascades of AD. This review provides a spectrum of rejuvenating herbs and their mode of action towards the treatment of AD. These herbs have been validated in terms of trihumoural basics of AD according to Siddha pathologic concept for all human ailments as well as the scientific researches on phytocompounds to enhance memory, intellect, rejuvenate brain functions, and improve quality of life in subjects with AD. Thus, a sound knowledge in fundamentals of traditional system coupled with contemporary science may provide innovative leads for preventive and curative aspects of age-related neurodegenerative diseases like AD and may also favour new drug developmental process and researches.

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