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Review Article

Rasayana Herbs of Ayurveda to Treat age Related Cognitive Decline: An Update

Reena Kulkarni[1*], Suhas Kumar Shetty[2], Rajarajeshwari N M[3], Prasanna Narasimha Rao[4] and Nayan J[5]

[1]Department of Kaumarabhritya, SDM College of Ayurveda, Tanniruhalla, Hassan-INDIA.
[2]Department of Manasa Roga, SDM College of Ayurveda, Tanniruhalla, Hassan-INDIA.
[3]Department of Samhita and Siddhanta, SDM College of Ayurveda, Tanniruhalla, Hassan-INDIA.
[4]Department of Shalya Tantra, SDM College of Ayurveda, Tanniruhalla, Hassan-INDIA.
[5]Department of Agada tantra, Sri Kalabairaveshvara Swamy Ayurveda Medical College, RPC layout, Vijayanagar, Bengaluru-40, Karnataka, INDIA.

ABSTRACT

Introduction: Cognitive decline associated with aging could be minor or major neuro-cognitive disorder presenting with progressive intellectual deterioration interfering with day to day activities. Behaviour and personality changes may complicate the life in due course. Significant increase in global prevalence of people aged above 60 years has raised concerns on effective management of old age problems. Age related cognitive deficits and dementia raise to the level of epidemics and established management is yet underway. Principles of preventive health and rasayana (rejuvenative) herbs of Ayurveda are being extensively researched up on for their effectiveness in dementia. In this fourteen such herbs with anti dementia property are discussed with relevant research update. **Methods:** Herbs like amalaki (*Emblica officinalis*), hareetaki (*Terminalia chebula*), haridra (*Curcuma longa*), manduka parni *(Centella asiatica)*, aindri *(Bacopa monniera)*, yastimadhu (*Glycirrhiza glabra*), guduchi (*Tinospora cordifolia*), shankhapushpi (*Convolvulus pleuricaulis*), vacha (*Acorus calamus*), jyotishmati (*Celastrus panniculata*), kushmanda (*Benincasa hispida*), Jatamamsi (*Nardostachys jatamamsi*), ashvagandha (*Withania somnifera*) and kapikacchu (*Mucuna pruriens* (*Linn.*)) are already proven of their efficacy in experimental and preclinical levels. The contents and research evidences are collected from ayurveda database on medicinal plants used in Ayurveda and Siddha and other authentic literature, Google scholar, Science direct, online and print journals. **Discussion:** The herbs in discussion mostly act on reactive oxygen species and oxidative stress injury by antioxidant properties and neuroprotective activity. Acetylcholine esterase inhibition, N-Methyl-D-Aspartate antagonism, Dopaminergic activity, Anti-amyloidogenic activity, Inhibition of Tau aggregation, neuroprotection and immune modulation are activity path ways. Tridosha namely Kapha, Pitta and Vata may be viewed to be categorically predominant in initial, middle and final stage of dementia. Selected herbs thus can be specific based on the pathology and relevant dosha predominance. **Conclusion:** Rasayana herbs with current updates and inferences can serve as an eye-opener for further researches at molecular and clinical aspect.

Key-words: Ayurveda, cognitive decline, Dementia, Herbs, Medhya, Rasayana.

Key Messages: Rasayana herbs of Ayurveda are a ray of hope to prevent and treat age related cognitive decline. Study on pharmacokinetics of rasayana herbs is the need of hour.

Corresponding author: Dr. Reena Kulkarni, Associate Professor, Department of Kaumarabhritya, SDM College of Ayurveda, Tanniruhalla,Hassan-INDIA.

Phone no: +91 9480478639

Email: drreenakulkarni@gmail.com
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INTRODUCTION

Cognitive decline and dementia are emerging to be the greatest challenge to the mankind in recent years. The WHO 2012 Report "Dementia: a public health priority"[1] estimates that there are at present 35.6 million people living in dementia worldwide. As the world's population ages, the frequency is expected to double by 2030 and triple by 2050.[2] Dementia is a disease of aging grouped under neuro-cognitive disorder presenting with progressive deterioration in multiple cognitive domains that is severe enough to interfere with daily functioning.[3] The current estimate of 7.7 million new cases per year is an important benchmark, globally and regionally, particularly given the relatively low levels of heterogeneity between studies.[1] Enormous researches in the field of medicine and new drug discovery have revolutionized management of old age problems. Unfortunately these developments have failed to impart substantial cure to dementia related issues. Some of the newer drugs and diet researched though documented significant results seem to be either too costly or cumbersome to adapt. Still these results are not translated into health indices. The total global societal costs of dementia were US$ 604 billion in 2010 (Annex 6.11.5).[1] 2030 worldwide societal costs will have increased by 85%.[1] These facts have urged to look towards traditional health systems like Ayurveda (the Indian system of medicine) to reinvent the possibilities of healthy ageing and better quality of life for elderly. Ayurveda emphasises on healthy living through ahara (diet) and charya (regimen) based on dinacharya (daily requirement of the body) as well as to suit the ritu (seasonal variations). Periodical shodhana (cleansing), use of rasayana (rejuvenation) therapy go a long way in delaying the complications of ageing and deficits associated with it. Rasayana comprise of therapeutic procedures or preparation that on regular practice will boost nourishment, health, memory, intellect, immunity and hence longevity. Rasayana preparations include single herbs in various medicinal forms and poly herbal combinations specifically aimed to target general health and specific body tissues or attributes. Thus they could be ayushkameeya (to boost general health and longevity) rasayana,vayasthapana(anti-aging), medhya (nootropic or intellect boosters) rasayana, vyadhipratyaneeka (disease specific) rasayana. Rasayana herbs that aid to prevent age specific complications and boost cognitive faculty is the scope of this paper. Evidences used are mostly facts from researches on animal model or on bioactive principles with some of preclinical works on human system. The contents and cross references are collected from ayurveda database on Medicinal plants used in Ayurveda and Sidha and authentic literature, Google scholar, Science direct, online and print journals

Evidence based approach

Amalaki (*Emblica officinalis Gaertn.*). Emblica is a medium to large deciduous tree. Dried fruit and fresh fruit, seed, leaves, root bark, flowers are used for medicinal purpose (Figure 1).[4] Amalaki is highly regarded as vayasthapana and prescribed to be included in daily diet.[5] It contains two hydrolysable tannins with low molecular weight (B1000), called emblicanin A (2,3-di-o-galloyl-4,6-(S)-hexahydroxydiphenoyl-2-keto-gluco-no-d-lactone) and emblicanin B (2,3,4,6-bis-(S)-hexahydroxydiphenoyl-2- eto-glucono-d-lactone) along with other tannins like punigluconino (2,3-di-O-galloyl-4,6-(S)-hexahydroxydiphenoylgluconic acid) and pedunclagin (2,3,4,6-bis-(S)-hexahydroxydiphenoyl-D-glucose) exhibit strong antioxidant action. The two emblicanins A and B have been found to preserve erythrocytes against oxidative stress induced by asbestos, generator of superoxide radical. Fruit extract has been shown to have an anti-mutagenic activity in Ames test.[6,7] Recently fruits have been tested for their antiviral activity, particularly for inhibiting reverse transcriptase in the replication of retroviruses like HIV-1. Fruit enhances the immune-defence[8] and has a hypolipidemic[9-11] and hepatoprotective activity.[12] Dietary supplement of either of amalaki rasayana (a preparation from Indian goose berry) and rasa sindhoora (an organo-metallic ash prepared from mercury and sulphur) during larval period substantially suppressed neurodegeneration in fly models of polyQ and Alzheimer's disorders without any side effects. Dietary Amalaki Rasayana or Rasa Sindoor prevented accumulation of inclusion bodies and heat shock proteins, suppressed apoptosis, elevated the levels of heterogeneous nuclear ribonucleoproteins and cAMP response element binding protein and at the same time improved the ubiquitin proteasomal system for better protein clearance in affected cells.[13]

Hareetaki (*Terminalia chebula Ketz.*) is a large tree seen all over India. Fruits (myrobalans) are used in almost all the ailments (Figure 2). In 'Ayurveda', myrobalans are used in fevers, cough, asthma, urinary diseases, piles and worms. It is also useful in chronic diarrhea and dysentery, flatulence, vomiting, colic and enlarged spleen and liver.[14] Phytochemical gallic acid, ellagic acid,tannic acid, ethyl gallate, chebulic acid, chebulagic acid, corilagin, mannitol, ascorbic acid (vitamin C),[15] tannin,[16] polyphenols, saponins, flavonoids and alkaloids.[17] Chebulic myrobalans are extensively used in combination with belleric and embelic myrobalans under the name of 'Triphala' and also as adjuncts to other medicines in numerous diseases.[18] 3 g of 'Haritaki' is used in the morning in empty stomach for body strengthening and anti-aging.[19] *Terminalia chebula* showed maximum inhibition in the TBARS formation, restore antioxidant enzyme SOD from the radiation-induced damage.[20] *Terminalia chebula* exhibited antioxidant activity at different magnitudes of potency for anti-LPO, anti-superoxide radical formation and free radical scavenging activities.[21] Intra peritoneal administration of ethanol extract of *Terminalia chebula* enhanced the learning and memory recall ability in male mice in an inverse dose-dependent manner. The pattern of changes of learning & memory induced by TC extract was similar to those of donepezil, is a golden standard medicine for curing the AD.[22] Water, methanol, and 95% ethanol extracts of the air-dried fruit of *T. chebula* Retzius demonstrated chemiluminescence antioxidant activities, and neuro-protective effects. The methanol and water extracts exhibit neuro-protective activities against H_2O_2-induced toxicity toward PC12 cells and are potential candidates for the treatment of H_2O_2- induced neurodegenerative disease.[23]

Haridra (*Curcuma longa linn*), is a perennial herb regarded as master of Indian kitchen. Rhizome is widely used daily in food as well as medicine owing to its multi fold benefits (Figure 3). Rhizome piece or fine powder is added in culinary curry and used as a coloring agent in food. Biologically it is vishaghna (anti toxic), varnya (complexion promoter) and pramehaghna (anti diabetic).[24] Traditional Indian medicine considered this polyphenolic compound as an effective therapy for several pathological conditions, ranging from asthma to epilepsy, from gall stone to diabetic wound healing.[25] Ganguli and co-workers found Indians who regularly used cucrumin in curry in food reported lower prevalence of Alzheimer dementia.[26] Yet another study reported that elderly healthy individuals who consumed it in curry showed better cognitive performance.[27] Preclinical studies on curcumin reported anti-oxidant and neuro-protective activity of curcumin which was reported to be greater than tocopherol. In particular, curcumin protects neuron-like PC12 rat cells and umbilical endothelial cells against Aβ toxicity and reduces tau hyperphosphorylation[28] promotes Aβ uptake from macrophages of AD patients[29] and dose-dependently reduces fibril formation and extension, also destabilizing preformed Aβ fibrils[30-32] Additionally, curcumin decreased levels of Aβ-induced radical oxygen species[33] and inhibits APP cleavage.[34] Dietary curcumin (2000 ppm) succeeded in reducing oxidative damage and increased microglial reaction near Aβ deposits. Additionally, low doses of curcumin (160 ppm) avoided the occurrence of spatial memory impairment in rat treated with Aβ infusion. In a study conducted in Tg2576 mice showed that curcumin reduced Aβ oligomer and fibril formation.[32] Oral administration of a low dose of dietary curcumin (160 ppm) to an Alzheimer transgenic mouse model (Tg2576) for six months reported reduced inflammation and oxidative stress in the brain.[35-37] Dietary curcumin (2000 ppm) succeeded in reducing oxidative damage and increased microglial reaction near Aβ deposits. Additionally, low doses of curcumin (160 ppm) avoided the occurrence of spatial memory impairment in rat treated with Aβ infusion. Intravenous administration of curcumin (7.7 mg/kg/day) for 7 days demonstrated an enhanced clearance of Aβ deposit in mouse brain.[38] Oral administration of curcumin in a range of 500 to 12000 mg did not report any serious adverse events. curcumin nanoparticles were effective in Alzheimer Tg2576 transgenic mouse model.[39] Similar increases in bioavailability were observed if curcumin-phospholipid complex or polymeric micellar curcumin were administered[40-41] Oral administration of aqueous extracts of rhizome exhibited antidepressant activity in mice which was associated with inhibition of brain MAO type A.[42] Curcumin (10–80 mg/kg, i.p.) dose dependently inhibited the immobility period, increased serotonin (5hydroxytryptamine, 5HT) as well as dopamine levels (at higher doses), and inhibited the monoamine oxidase enzymes (both MAOA and MAOB higher doses) in mice.[43] Human studies using curcumin inconclusive or deficient evidences in dementia which in large could be due to poor plasma concentration bioavailability of curcumin alone after oral administration. According to its pharmaco-dynamic properties, curcumin seems to act more as a neuro-protective agent than as a reversal medication.[44] The neuro-protective activity is attributed to curcuminoids namely curcumin, demethoxycurcumin, and calabin-A.[45,46] Majority of these results are reported to be from anti-oxidant and anti-inflammatory activity.[47-51]

Mandukaparni (*Centella asiatica Linn.*) is a prostrate, stoloniferous perennial herb rooting at nodes (Figure 4).[52] Fresh whole plant juice is used for therapeutic purposes as Medhya (cognitive enhancer).[53] Major constituents are saponin (medacoside, asiaticoside, medacassoside, asiatic acid, a new triterpenic acid.[54] They act on behaviour besides being neuro-protective[55] and brain growth promoter.[56] Dendritic arborization is supposed to be the neuronal basis for improved learning and memory.[57] Anti-seizure activity may result from direct or indirect modulation of ATPase activity.[58] *Centella asiatica* inhibits the memory impairment induced by scopolamine through the inhibition of AChE.[59] BR-16A (Mentat), a formulation containing *Centella asiatica* proved for its anti-stress effects.[60] Methanol extract of *Centella asiatica* showed highest free radical scavenging activity that can be attributed to the presence of polyphenols and flavonoids as this fraction contains maximum amount of these secondary metabolites (0.07 mg/ml). It also exhibited DNA

damage protection activity on pRSETA plasmid DNA in TE buffer (10 mM Tris-Cl and 1 mM EDTA) pH 8.0. Chloroform extract of Centella showed highest poly phenolic activity followed by methanol extracts (9.04 µg/mg, 7.7 µg/mg, 6.76 µg/mg Gallic acid equivalents respectively); while flavonoids were abundant in water extracts, followed by chloroform extracts. These two namely poly phenols and flavonoids are responsible for potent anti-oxidant and terminate free radicals.[61] Rats treated with *C. asiatica* in another study showed a dose dependent increase in both cognitive and behaviour paradigms. A significant decrease in MDA and an increase in glutathione and catalase levels were observed only in rats treated with 200 and 300 mg/kg *C. asiatica*. The results indicated that an aqueous extract of *C. asiatica* is effective in preventing the cognitive deficits, as well as oxidative stress, caused by i.c.v. STZ in rats.[62] The rat pups (7-days-old) were fed with 2, 4 and 6 ml/kg body of fresh leaf juice of CeA for 2, 4 and 6 weeks showed significant increase in dendritic length (intersections) and dendritic branching points along the length of dendrites of the amygdaloid neurons of rats treated with 4 and 6 ml/kg body weight/day of CeA for longer periods of time (i.e. 4 and 6 weeks). The study indicated that constituents/active principles present in CeA fresh leaf juice has neuronal dendritic growth stimulating property; hence it can be used for enhancing neuronal dendrites in stress and other neurodegenerative and memory disorders.[63] Total triterpenes from *Centella asiatica* exhibhited anti-depressant activity in mice on forced swimming test.[64] Administration of *Centella asiatica* at 1,000 mg/kg b.wt for a period of 30 days in albino rats, showed organ specific toxicity.[65]

Aindri (*Bacopa monniera*) commonly called as brahmi belongs to Scrophulariaceae family.[66] It is a small, creeping marshy herb grown throughout India (Figure 5).[67] Most beneficial therapeutic form is macerated whole plant juice. Properties are said to be similar to that of Mandukaparni.[68] *Bacopa monniera* is a well-known nootropic plant reported for its tranquilizing,[69] sedative action,[70] cognitive enhancer,[71] hepato-protective,[72] memory enhancer[73] and antioxidant actions.[74-76] Neuro-protective activity may be ascribed to having its reactive oxygen species scavenging property.[77] *Bacopa monniera* is a saponin rich plant.[78] Bacosides are the main active nootropic principle present in the alcoholic extract of the plant.[79]

Isolation of a new saponin, a jujubogenin, named bacopasaponin G, and a new glycoside, phenylethyl alcohol was reported.[80] Three new saponins designated as bacopasides III, IV and V isolated.[81] Apart from memory enhancer activity these bacosides have the potential to modulate the activities of heat stock protein (Hsp70) expression, cytochrome P450 and superoxide dismutase in the rat brain.[82] On rats, alcoholic extract increases both cognitive function and retention capacity, decreases retrograde amnesia and protects from phenytoin -induced cognitive deficit.[83] It is mainly utilized in the treatment of memory and attention disorders.[84] Recent studies have indicated antioxidant effect of bacosides (triternoid saponin isolated from *Bacopa monniera*) against chronic toxin induced oxidative damage in rat brain[85] and thyroid T_4 hormone stimulating activity in animals in high doses.[86]

Organic extract of *Bacopa monniera* in effective doses continuously for six months revealed beneficial effect in improving memory attention span and behavioural problems among demented elderly people.[87] *Bacopa monniera* extract was able to reverse both anterograde and retrograde amnesia in mice with scopolamine induced amnesia. Thus it was concluded that *B. monniera* effects on cholinergic system may be helpful for developing alternative therapeutic approaches for the treatment of Alzheimer's disease.[88] A study evaluated the effect of orally administered alcoholic extracts of *Bacopa monniera* (at doses of 20, 40 and 80 mg/kg) on cognitive function and neuro-degeneration in animal models of Alzheimer's disease induced by ethylcholine aziridinium ion (AF64A). *Bacopa monniera* extract improved the escape latency time ($p<0.01$) in Morris water maze test. Moreover, the reduction of neurons and cholinergic neuron densities were also mitigated. The study suggests that *Bacopa monniera* is a potential cognitive enhancer and neuro-protectant against Alzheimer's disease.[89] Yet another study in experimental rats with oral administration of $AlCl_3$ and *Bacopa monniera* extract 50 mg/kg/day in drinking water for 1 month prevented accumulation of lipid and protein damage significantly induced by aluminium intake. Activity was similar to that of l-deprenyl. It also inhibited decline in the activity of endogenous antioxidant enzymes associated with aluminium administration. Results suggest that *B. monniera* has potential to protect brain from oxidative damage resulting from aluminium toxicity.[90] *B. monniera* (50 mg/kg body weight) supplementation reversed memory impairment in the colchicine treated rats by attenuating oxidative damage, as evident by decreased LPO and protein carbonyl levels and restoration in activities of the antioxidant enzymes. Also, Bacopa monnieri supplementation was able to restore the altered activity of membrane bound enzymes (Na^+K^+ ATPase and AChE) as compared to the controls.[90] In adult swiss mice extracts of Bacopa monnieri produced anti-dementic activity against scopolamine induced dementia and a dose dependent antiAChE activity.[91,92] special BM extract (CDRI-08) ameliorated amnesic effect of scopolamine by decreasing acetyl cholinesterase activity and drastically up regulating the mRNA and protein expression of BDNF, Arc, and GFAP in mouse cerebrum. Study also provides first molecular evidence for anti-amnesic potential of CDRI-08 via enhancement of CREB mediated basal transcriptional machinery of memory linked both neuronal and glial plasticity markers.[93]

In a randomized, double-blind, placebo-controlled clinical trial on elderly participants aged 65 or older (mean 73.5 years) without clinical signs of dementia, *B. monniera* extract (300 mg/day per oral) enhanced Rey Auditory Verbal Learning Test(AVLT) delayed word recall memory scores and Stroop Task assessing the ability to ignore irrelevant information. Study also showed reduction in Center for Epidemiologic Studies Depression scale (CESD-10) depression scores, combined state plus trait anxiety scores, and heart rate over time.[94] In an open label, prospective, uncontrolled, nonrandomized study on human participants newly diagnosed Alzheimer's disease, Bacopa monnieri standardized extract 300 mg twice a day orally for 6 months resulted in improvement in orientation (of time, place & person), attention and in language components (reading, writing & comprehension) of cognitive functions using Mini Mental State Examination Scale (MMSES). The trial also reported improvement in their quality of life, and decrease in the irritability and insomnia.[95]

Yastimadhu (*Glycirrhiza glabra Linn*.) is a hardy herb or under shrub belonging to Fabaceae family.[96] Fine powder of dried root is used internally with milk for therapeutic purpose as Medhya (Figure 6). Active ingredients are glycyrrhizine, flavonones,[97] is oflavones, glycyrrhetenic acid,[98] six phenolic compounds.[99] Multidimensional activities of *Yashtimadhu* may be attributed to glycyrrhizine and flavonones. *Yashtimadhu* is cytotoxic and its prolonged use may lead to pseudoaldosteronism,[100] hyperkalemia,[101] and hypertension.[102,103] The roots and rhizomes of *G. glabra* has been studied with respect to spatial learning and passive avoidance[104] preliminary free radical scavenging[105] cerebral is chemia[106] and antioxidant capacity towards LDL oxidation.[107] *Glycyrrhiza glabra* aqueous extract markedly improves antihypoxic effects induced by sodium nitrite in rats and this effect may be mediated by its antioxidant properties.[108,109] The roots and rhizomes of *Glycyrrhiza glabra* is an efficient brain tonic; it increases the circulation into the CNS system and balance the sugar levels in the blood.[110] Liquorice has significant action on memory enhancing activity in dementia.[111] It significantly improved learning and memory on scopolamine induced dementia. Oral glabridin administration (25 and 50 mg/kg) improved learning and memory in

Figure 1: Amalaki (*Emblica officinalis*) fruit (dried).

Figure 2: Hareetaki (*Terminalia chebula*).

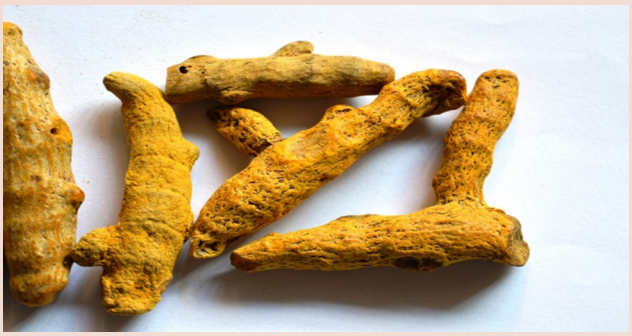

Figure 3: Haridra (*Curcuma longa linn*).

Figure 4: Mandukaparni (*Centella asiatica Linn.*).

Figure 5: Aindri (*Bacopa monniera*).

Figure 6: Yastimadhu (*Glycirrhiza glabra Linn.*).

Figure 7: Guduchi (*Tinospora cordifolia*).

Figure 8: Shankhapushpi (*Convolvulus pleuricaulis*).

Figure 9: Jyotishmati (*Celastrus panniculata*).

Figure 13: Ashvagandha (*Withania somnifera*).

Figure 10: Kushmanda (*Benincasa hispida*).

Figure 14: Kapikacchu (*Mucuna pruriens (Linn*.).

Figure 11: Vacha (*Acorus calamus*).

Figure 12: Jatamamsi (*Nardostachys jatamamsi*).

non-diabetic rats, it also reversed learning and memory deficits of diabetic rats. The study concluded that glabridin prevented the deleterious effects of diabetes on learning and memory in rats by combination of antioxidant, neuroprotective and anticholinesterase properties.[112] The higher doses (2 and 4 mg/kg; p.o.) of glabridin and piracetam significantly antagonized the amnesia induced by scopolamine (0.5 mg/kg; i.p.) in an experimental model. Furthermore, both glabridin (2 and 4 mg/kg; p.o.) and metrifonate (50 mg/kg; i.p.), used as a standard drug, remarkably reduced the brain cholinesterase activity in mice compared to the control group. The study indicated that glabridin can be a promising candidate for memory improvement and can be used in the management of Alzheimer patients.[113]

Guduchi (*Tinospora cordifolia (Wild) Miers*) is a large glabrous, deciduous, climbing shrub of Menispermaceae family found throughout tropical India (Figure 7).[114] Juice of whole plant is used therapeutically as *Medhya*.[53] It is also used in the form of decoction, powder and *Satwa* (starch extract of stem). Its root is known for its anti-stress, anti-leprotic and anti-malarial activities.[115,116] Chemical constituents' classes are alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides.[117] Neuroprotective and ameliorative properties are due to their antioxidant and trace element contents.[118] *Tinospora cordifolia* is known to be a rich source of trace elements (Zinc and Copper) which act as antioxidants and protects cells from the damaging effects of oxygen radicals generated during immune activation.[119] It increases the blood profile and has lead scavenging activity.[120] *Tinospora cordifolia* has been claimed to possess learning and memory enhancing,[121] antioxidant,[122,123] and anti-stress activity.[124] *Tinospora cordifolia* enhanced the cognition in normal and cognition deficits animals in behavioural test Hebb William maze and the passive avoidance

task.[125] Mechanism of cognitive enhancement is by immune-stimulation and increasing the synthesis of acetylcholine, this supplementation of choline enhances the cognition.[126] Myriad actions of Guduchi may be attributed to its antioxidant[127,128] and immune-modulatory properties.[129] Administration of aqueous and alcoholic extracts of Tc (100 and 200 mg/kg respectively) for 15 days in an experimental model enhanced cognition (learning and memory) in normal rats and rats with cyclosporine induced memory deficit. It also provided hippocampal protection in normal rats as against cyclosporine treated rats showed neurodegenerative changes on histopathological study.[130] Oral administration of Tinospora cordifolia (500 mg aqueous extract) for 30 healthy volunteers (age 18-30 years) in a double blind, randomized and placebo controlled design enhanced verbal learning and memory and logical memory (of immediate and short term type).[131] Tc also showed significant antidepressant activity by increasing brain monoamines.[132] The most likely antidepressant mechanisms involve inhibiting reuptake of mines in the brain, improved levels of norepinephrine (NE), serotonin (5hydroxytryptamine or 5HT), and dopamine (DA), and decreased levels of gammaaminobutyric acid (GABA).[133]

Shankhapushpi (*Convolvulus pleuricaulis Chois*) is a perennial, prostate or sub erect spreading hairy herb (Figure 8),[134] found throughout India.[135] Recommended therapeutic form is fine paste of whole plant. Highly regarded as *Medhya* (intellect promoter).[53] Important chemical principles are microphyllic acid, shankhapushpin, kaempferol-kaempferol-3-glucoside, 3, 4 dihydroxycinnamic acid, sitosterols. Neuro-protective and intellect promoting activity implicated to free radical scavenging and antioxidant property.[136] BR-16A (Mentat), a poly herbal combination containing *Shankhapushpi* significantly reversed the social isolation stress-induced prolongation of onset and decrease in pentobarbitone-induced sleep, increased total motor activity and stress-induced antinociception in experimental model.[137]Ayushman-8 (containing *Shankhpushpi, Brahmi* and *Vacha*) reported to be effective on *Manasa-mandata* (mental retardation).[138] *Shankhapushpi compound* containing *Shankhapushpi, Sarpagandha*, and *Gokshura* in equal quanitities studied to be effective in *Chittodvega* (anxiety disorders).[139] Sanjay Parsania[140] reported *Shankhapushpi* to be effective in relieving signs and symptoms of *Chittodvega* (anxiety disorders). Herbalists believe that *Shankhpushpi* calms the nerves by regulating the body's production of the stress hormones, adrenaline and cortisol.[141] Few investigations reports that Shankhpushpi has potent depressive action in mice.[142]

In an experimental study, a dose dependent enhancement of memory was observed with Convolvulus pluricaulis and Asparagus racemosus. Hippocampal regions associated with the learning and memory functions showed dose dependent increase in AChE activity in CA1 with AS and CA3 area with CP treatment. The underlying mechanism of these actions of CP and AE may be attributed to their antioxidant, neuro-protective and cholinergic properties.[143] Daily administration of CP (150 mg/kg) for 3 months along with aluminium chloride (50 mg/kg) decreased the elevated enzymatic activity of acetylcholine esterase and also inhibited the decline in Na^+/K^+ATPase activity aluminium intake. Beside, preventing accumulation of lipid and protein damage, changes in the levels of endogenous antioxidant enzymes associated with aluminium administration were also improved. Oral administration of CP preserved the mRNA levels of muscarinic receptor 1 (M1 receptor), choline acetyl transferase (ChAT) and Nerve Growth Factor- Tyrosine kinase A receptor (NGF-TrkA). It also ameliorated the up regulated protein expression of cyclin dependent kinase5 (Cdk5) induced by aluminium. The potential of CPE to inhibit aluminium induced toxicity was compared with rivastigmine tartrate (1 mg/kg), which was taken as standard. The potential of the extract to prevent aluminium-induced neurotoxicity was also reflected at the microscopic level, which indicated its neuro-protective effects.[144]

Oral administration of CP extract (150 mg/kg) to scopolamine treated rats reduced the increased protein and mRNA levels of tau and AβPP levels followed by reduction in Aβ levels compared with scopolamine treated group.[145]

Jyotishmati (Celastrus panniculata) is a large, woody, climbing shrub with ovate or obvovate leaves found all over India (Figure 9).[146] Seed oil (*Jyotishmati Taila*) is known for *Medhya* action.[147] This oil contains several terpenoids like paniculatadiol, b-sitosterol, celastrol, b-amyrin, pristimerin, but its most investigated components are its many sesquiterpenoids, dihydroagarofuran-type polyols or esters.[148] *Celastrus paniculata* showed antioxidant activity by decreasing the lipid peroxidation[149] and anti-arthritic activity in rat model.[150] Seed oil of *Celastrus panniculata* (*Malkangni*) reversed scopolamine-induced deficits in navigational memory task in young adult rats.[151] study revealed an increased cholinergic activity of brain is noted resultant up on decreased in AChE activity assayed from hypothalamus, frontal cortex and hippocampus of the rat brain treated with 400 mg/kg body weight. No side effects were observed with administration of the seed oil.[152]

Kushmanda (*Benincasa hispida*) belonging to Cucurbitaceae an extensive trailing or climbing herb cultivated throughout the plains of India as a vegetable.[153] The fruit, broadly cylindrical, is covered with a waxy bloom (Figure 10).[154] Phytochemical analysis of *Benincasa hispida* shows presence of alkaloids, flavinoids, saponins and steroids.[155] *Benincasa cerifera* serves as ROS scavenger and an antioxidant effective agent.[156] It has a tissue protective preventive effect on colchicine induced Alzheimer's disease via direct and indirect antioxidant activity.[157]

Vacha (*Acorus calamus*) of Araceae family is a semiaquatic, perennial, aromatic herb with its rhizome being horizontal, rounded, somewhat vertically compressed, spongy and leaves grass like and sword shaped; grown all over India.[158] Rhizome is useful part having *Medhya* quality (Figure 11). It has been used in Indian and Chinese system of medicine for hundreds of years to cure diseases especially the central nervous system (CNS) abnormalities.[159-162] Active chemical principles are α-asarone, elemicine, cis-isoelemicine, cis and trans isoeugenol and their methyl ethers, camphene, P-cymene, bgurjunene, a-selinene, b-cadinene, camphor,terpinen-4-ol, aterpineol and a-calacorene, acorone, acrenone, acoragermacrone, 2-deca–4,7 dienol, shyobunones, linalool and preisocalamendiol. Acoradin, galangin, 2, 4, 5- trimethoxy benzaldehyde, 2,5- dimethoxybenzoquinone, calamendiol,spathulenol and sitosterol are also present.[163,164] It has been proved for its analgesic and anticonvulsant,[165] hepatoprotective,[166] antioxidant,[167,168] antimutagenic,[169] sedative and hypothermic effects[170] good in clearing speech to the children[171,172] and useful in schizophrenic psychosis.[173] *Acorus calamus* possesses a beneficial memory enhancing property for memory impairment, learning performance, and behavior modification. Essential oil from rhizome and β-asarone inhibits the acetylcholinesterase (AChE).[174,175] α-asarone inhibits the activity of hippocampal neurons and produces antiepileptic effect in central nervous system through enhancing tonic GABAergic inhibition.[176] Food and Drug Administration banned usage its oil in food formulations and in other therapeutic preparations[177] due carcinogenic and toxic properties of β-asarone compound.[178] Ethanolic extract demonstrated to possess potential anti-oxidative, anti-inflammatory as well as neuroprotective actions.[179-181] Experimentally, it has also been reported to decrease free radical generation via enhancement of anti-oxidant mechanisms such as increase in superoxide dismutase, catalase, reduced glutathione and glutathione peroxidise levels.[182] Additionally, it is shown to be a neuroprotective action against the hypoxic (ischemia) event and chemical (i.e. acrylamide) induced severe insult in nervous system.[183-185] *Acorus calamus* has also been shown to modulate calcium channel activity [186] thus attenuating CCI induced peripheral neuropathic pain.[187] Oral administration of

methanol extract of rhizome of *A. calamus* in rodents exhibited an anti-depressant-like activity, probably by modulating the central neurochemical as well as HPA axis in response to stress induced by FST.[188]

Jatamamsi (*Nardostachys jatamamsi*) is an erect perennial aromatic herb with long, stout, woody, greyish, rhizomatous, tail-like rootstock covered with reddish-brown hairs or tufted fibrous remains of the petioles of withered radical leaves,[189] and belongs to Valerianaceae family. Rhizome is used for medicinal purposes as it is *Bhutaghna* or *Manasa Doshahara* (relieves of psychiatric problems) and *Medhya* (Figure 12).[190] Roots and rhizomes of *N. jatamansi* are used to treat hysteria, epilepsy, and convulsions.[191] The decoction of the drug is also used in neurological disorders, insomnia and disorders of cardiovascular system.[192] Rhizomes contain a terpenoid ester, nardostachysin I[193] and variety of sesquiterpenes and coumarins.It is proven to improve learning and memory in mice[194] and also to enhance biogenic amine activity.[195] An alcoholic extract of this plant administered to both young and aged mice significantly improved learning and memory and also reversed aging induced amnesia due to diazepam and scopolamine.[196] Nardostachys jatamansi extract prevented chronic restraint stress-induced learning and memory deficits in a radial arm maze task.[197] In another study, hydroalcohol extract of Nardostachys jatamansi rhizome showed AChE inhibitory activity with an IC_{50} value of 130.11612 mg/ml.[198,199] An acetone extract of *N. jatamansi* has shown significant inhibition of benzoyl peroxide-induced cutaneous oxidative stress, toxicity, and ear oedema in mice.[200] Ethanolic extracts of NJ showed a dose dependent increase in the number of surviving neurons and anti-Parkinson effects.[201]

Ashvagandha (*Withania somnifera*) commonly known as Indian winter cherry or Indian ginseng is most used rasayana herb in Indian system of medicine. It is clinically used for the treatment of general debility, consumption, nervous exhaustion, insomnia, loss of memory, and so on.[202] finely powdered root is therapeutically used with water, milk, ghee (clarified butter) or honey. Root is extensively used for therapeutic purpose (Figure 13). Chemical constituents include alkaloids (isopelletierine, anaferine, cuseohygrine, anahygrine, etc.), steroidal lactones (withanolides, withaferins) and saponins.[203] Withania has been reported as promising anti-cancer drug candidate due to its cytotoxic,[204] apoptotic,[205] anti-metastatic[206] anti-mitotic[207] and anti-angiogenesis properties.[208] The herb is reported to possess beneficial effects in a wide range of central nervous system (CNS) pathology in rodents. These include catalepsy, cognitive and memory impairment, orofacial dyskinesia,[10] stress, Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), cerebral stroke, epilepsy, excitotoxicity, in sleep disturbed mice, chronic fatigue syndrome, streptozotocin induced oxidative stress, copper-induced oxidative stress and rotenone-induced oxidative stress.[209] Withaferin A was reported dose dependent anti-cancer (3.5 mg/kg), anti-inflammatory (2.15 mg/kg), anti-parasitic (0.3 mg/kg)[210] and hepatoprotective (10 mg/kg) potential.[211] Withanalide A has attracted interest due to its neuropharmacological properties of promoting synaptic and outgrowth reconstruction at a dose of 4.7_g/kg.[212] WLD is therefore an important candidate for the therapeutic treatment of neurodegenerative diseases, like Alzheimer disease (AD), Parkinson's disease (PD), convulsions, cognitive function impairment, as it is able to reconstruct neural networks.[213] The underlined molecular mechanisms studies on WA and WLD demonstrated modulation of multiple targets such as transcriptional factors, inflammatory cytokines, enzymes, growth factors, receptors and other targets suggesting promising drug candidates for cancer and neurological disorders[214] Withania Sitoindosides and acylsteryl glucosides in Ashwagandha are anti-stress agents. Widely researched and proven for its effect on age related cognitive decline and dementia. WSG also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim induced 'behavioural despair' and 'learned helplessness' tests.[215] In a study, a 30-days course of oral administration of a semipurified extract of the root of *Withania somnifera* consisting predominantly of withanolides and withanosides reversed behavioural deficits, plaque pathology, accumulation of β-amyloid peptides (Aβ) and oligomers in the brains of middle-aged and old APP/PS1 Alzheimer's disease transgenic mice. It was similarly effective in reversing behavioural deficits and plaque load in APPSwInd mice (line J20).[216] The cell death caused by beta-amyloid was negated by treatment with withanamide from withania fruits. Molecular modeling studies showed that withanamides A and C uniquely bind to the active motif of beta-amyloid (25-35) and suggest that withanamides have the ability to prevent the fibril formation.[217] Systematic review on *W. somnifera reveled* successful inhibition of neurobehavioural abnormalities produced by different physical and chemical stimuli on oxidative stress in rodent brain. It also significantly decreased the increased LPO, protein carbonyl, AchE and nitrite levels in different parts of rodent brain. The natural cellular antioxidants (SOD, catalase and GPx) and the non-enzymatic anti-oxidant like GSH, ChAT and Ach alteration in the neuropathological environment were also considerably restored to normal by *W. somnifera*.[209]

Kapikacchu *(Mucuna pruriens (Linn.))*DC is a herbaceous twinning annual plant found all over India. Useful parts are root, leaves, seed and hairs (Figure 14). Mostly used as aphrodisiac, rejuvinative and nervine tonic in Ayurveda.[218] it is extensively used in the treatment of parkinson's disease as it is a good source of L-3, 4 dihydroxyphenyl alanine (L-DOPA).[219,220] It is known to increase secretion of semen and it act as a restorative and aphrodisiac in sexual dysfunction characterized by weakness or loss of sexual power.[220] Seeds of M. pruriens possess anti-oxidant, hypoglycemic, lipid lowering and neuroprotective activities.[221] The neuro protective activity may be due to Antioxidant, Dopaminergic potentials.[222] Its seeds contain the alkaloids, mucunine, mucunadine, mucunadinine, prurienidine and nicotine, besides b-sitosterol, glutathione, lecithin, vernolic acid and gallic acid. Other bioactive substances include tryptamine, alkylamines, steroids, flavonoids, coumarins, cardenolides and metals like magnesium, copper, zinc, manganese and iron.[223] Treatment with M. pruriens significantly ameliorated psychological stress and seminal plasma lipid peroxide levels along with improved sperm count and motility.[224] The nigrostriatal portion of Parkinsonian mouse brain showed significantly increased levels of nitrite, malondialdehyde (MDA) and reduced levels of catalase besides improved the behavioral abnormalities as compared to the control.[225]

DISCUSSION

A review on selected rasayana herbs of Ayurveda revealed their potential to combat age related cognitive decline. The herbs reviewed were amalaki, hareetaki, haridra, manduka parni, anidri, *y*astimadhu, guduchi, shankhapushpi, vacha, jyotishmati, kushmanda, Jatamamsi, ashvagandha and Kapikacchu. Among them all herbs showed anti-oxidant and neuro-protective activities. Apart from anti-oxidant activity other factors that aid in anti-dementia and neuro protection are acetylcholine estarase inhibition, NMDA antagonism, Dopaminergic activity, removal of amyloidal plaques, inhibition of *Tau* aggregation, Folic acid, glutamic acid, Vitamin B etc. Rasayana herbs presenting with inhibition of AChE activity are hareetaki, amalaki, manduka parni, yashtimadhu, aindri, guduchi and ashvagandha. Predominant NMDA antagonist activity is shown by haridra, vacha, hareetaki and ashvagandha. Dopaminergic activity is seen in Kapikacchu, ashvagandha, guduchi and haridra. Reduction in amyloidal plaques and *Tau* aggregation is characteristic to shankhapushpi, haridra, hareetaki, amalaki, guduchi, ashvagandha and mandukaparni. Thus these rasayana herbs act by more than one way to break down the pathological path way in age related cognitive decline and hence can be potential contender in treatment of dementia. More-

over, rasayana drugs enhance digestion, tissue metabolism, nutritional quality of plasma (rasa) and micro circulation.[226] Besides this, most of the drugs discussed are medhya (nootropic) in nature with specific action as medhya (specific to nervous system) as well as their multi-dimensional utility.[227] by virtue of the trace elements present in them. Getting deep into characteristics of drugs it may be postulated that regular usage of haridra, hareetaki,[228-230] amalaki, vacha will go a long way to prevent Dementia & related complications. Early usage of Aindri, mandukaparni, jyotishmati, jatamamsi, ashvagandha & shankapushpi as single herb or in combination are beneficial in neuro degenerative condition, 1st & 2nd stage of Dementia and Lewy bodies pathology for secondary prevention. Kapichacchu, Ashvagandha, Jatamamsi & Haridra singly or in combination are better choice in treating dementia associated with Huntington's disorder. Guduchi, Vacha, Ashvagandha, Kushmanda, Yastimadhu and Haridra are helpful in vascular dementia. Yastimadhu, Aindri, Guduchi and Kushmanda are favourable in dementia due to toxic pathology like aluminium toxicity, food toxicity and radiation hazards etc. Kushmanda, Aindri, Guduchi, Yastimadhu, Jatamamsi and Ashvagandha are useful in dementia associated with anxiety, depression and personality changes.

In the first stage (1 to 2 year of onset) gradual onset of forgetfulness for recent events, become lost in familiar places, loss of track, time including day, month, year and season, difficulty in communication, finding words, making decisions, handling finance, mood changes, lack of interest and difficulty in carrying complex household activities. This stage at the onset is often overlooked as a part of normal aging process. Middle stage of the disease (2-5 years of the onset) presents with more precise progressive limitations and restrictions. Progressive forgetfulness for recent events and people's names, difficulty in comprehending time, date, place and events, may become lost in home and community, difficulty in speech, comprehension and communication. Assistance is required in personal care (toileting, washing and dressing). Inability to prepare food, cook, clean, shop, live alone safely without any assistance. Behaviour changes include inappropriate behaviours at home and community, wandering, repeated questioning, calling out, clinging, disturbed sleep and hallucinations. Last stage (after 5 yr of onset) is of nearly total dependence and inactivity. Memory disturbances are very serious and the physical side of the disease becomes more obvious. Usually unawareness of time, place, people and events happening around prevails. Progressive dependence in self-care, sphinctural incontinence, changes in mobility, behaviour (aggression and nonverbal agitation including kicking, hitting, screaming and moaning etc). Other features may vary based on the co-morbidities and pathology.[1]

1st stage of Dementia can be managed on the lines of Kapha Dosha. In this stage, Haridra and Jyotismati can be used. Second stage of dementia is ideally managed on the lines of Pitta Dosha. In this stage, Mandookaparni, Aindri, Haridra and Yastimadhu are the better choice. Last stage of Dementia can respond well to Vata dosha management like Yastimadhu, Vacha, Jyotismati. Herbs like Amalaki, Haritaki, Jatamamsi, Guduchi, Ashvagandha, Kapikacchu, Kushmanda, Shankhapushpi can be used in all 3 stages because of its ability to pacify all 3 doshas.

CONCLUSION

Ample of evidences through experimental and pre-clinical studies have proven the efficacy of Ayurveda herbs in age related cognitive decline. In spite of their effective clinical use through ages valid document is sparse. The need of hour is to study the molecular basis of these herbs in humans.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

ABBREVIATIONS USED

WHO: World health organization; **HIV:** Human Immunodeficiency virus; **cAMP:** cyclic adenosine monophosphate; **NMDA:** N- methyl -D -aspartate; **TBARS:** Thiobarbituric acid reactive substance; **SOD:** Superoxide dismutase; **AD:** Alzheimer's Disease; **Aβ:** amyloid-β-protein, **H_2O_2:** Hydrogen peroxide; **PC12:** Paracetamol; **Ppm:** parts per million; **MAO:** Monoamine oxidase; **MAOA:** Monoamine oxidase A; **MAOB:** Monoamine oxidase B; **ATPase:** Adenosine triphosphatase; **DNA:** Deoxy ribonucleic acid; **C. asiatica:** *Centella asiatica*; **MDA:** Methylene dioxy amphetamine; **CeA:** *Centella asiatica*; **Alcl2:** Aluminium chloride; Na+: Sodium; K^+: Potassium, **BDNF:** Brain derived neurotrophic factor; **GFAP:** Glial fibrillary acidic protein; **LDL:** Low density, lipoproteins, **CNS:** Central nervous system; **CP:** Convolvulus pleuricaulis; **mRNA:** Messenger ribo nucleic acid; **ABPP:** Amyloid precursor protein; **ROS:** Reactive oxygen species; **GABA:** Gamma amino butyric acid; **CCl:** Carbon tetra chloride; **HPA:** Hypothalamic pituitary adrenal; **FST:** Forced swimming test; **WLD:** Withanolide; **WA:** Withaferin A; **WSG:** glycosides in Withania somnifera; **APP/PS1:** Amyloid precursor protein; **GPx:** Glutathione; **GSH:** Growth stimulating hormone.

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SUMMARY

- Rasayana herbs of Ayurveda namely Amalaki (*Emblica officinalis*), Hareetaki (*Terminalia chebula*), Haridra (*Curcuma longa*), Manduka parni(*Centella asiatica*), Aindri (*Bacopa monniera*), Yastimadhu (*Glycirrhiza glabra*), Guduchi (*Tinospora cordifolia*), Shankhapushpi (*Convolvulus pleuricaulis*), Vacha (*Acorus calamus*), Jyotishmati (*Celastrus panniculata*), Kushmanda (*Benincasa hispida*), Jatamamsi (*Nardostachys jatamamsi*) and Ashvagandha (*Withania somnifera*) are beneficial in prevention and management of age related cognitive decline. Factors that aid in anti-dementia and neuro protection are acetylcholine estarase inhibition, NMDA antagonism, Dopaminergic activity, removal of amyloidal plaques, inhibition of *Tau* aggregation, Folic acid, glutamic acid, Vitamin B etc apart from antioxidant activity.

ABOUT AUTHORS

Reena Kulkarni: Is a practicing Ayurveda Pediatrician who has obtained Post Doctoral degree from Dr Sarvepalli Radhakrishnan Rajasthan Ayurveda University, Jodhpur in 2015 and is Masters in Clinical child development from university of Kerala, Thiruvananthapuram. She positioned as Associate professor at Sri Dharmasthala Manjunatheshwara College of Ayurveda & Hospital, Hassan, India. Dr Kulkarni is an expert in Ayurveda management of various childhood respiratory, allergic and developmental disorders. At present she is working on Medhya Rasayana their therapeutic applications in preventive pediatrics.

Suhas Kumar Shetty: Obtained his Ph. D. degree in Ayurveda from Rajiv Gandhi university of health Sciences Karnataka, Bangalore in 2016. He is positioned as Professor at Sri Dharmasthala Manjunatheshwara College of Ayurveda & Hospital, Hassan, India. Dr. Shetty is working on various aspects of Ayurvedic management of psychiatric disorders and engaged in finding preventive as well as therapeutic solutions from Ayurvedic principles. He is also an expert in Medical Statistics in the field of Ayurveda.

Prasanna Narasimha Rao: Obtained his Post Doctoral degree in 1994 from the prestigious Banaras Hindu University, Varanasi. He is currently positioned as Principal, Sri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Hassan, India. Dr Rao is an expert in Shalya Tantra (Surgery) has a vast experience of 21 years in Administration as well as Ayurveda practice. He has visited many overseas universities and engaged in various teaching and learning programmes and guiding Graduate, Post graduate and Doctoral scholars. He is also an active advisory board member to many Government and Non government organizations in the field of Ayurveda.