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Ayurvedic Drugs in Prevention and Management of Age Related Cognitive Decline: A Review

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ABSTRACT
Age related cognitive decline is a term reserved for abnormal cognitive function less severe than dementia in person older than 50. It is considered as a prior condition to senile dementia. The term dementia signifies cognitive deterioration so severe that social and occupational functioning of an individual is markedly impaired to such an extent that he can no longer remain a fully independent and productive citizen. As the disease progresses, the personality of an individual also changes and subsequently, social withdrawal take a hold. Advanced dementia is characterized by progressive loss of personality and increasing disability to perform even a simplest task. According to World Health Organization, it is estimated that 5% of men and 6% of women of above 60 years of age affected with Alzheimer's type of dementia worldwide. According to Alzheimer's Disease International there are 35.6 million people living with dementia worldwide in 2010, increasing to 65.7 million by 2030 and 115.4 million by 2050. Degeneration of the cerebral neurons is one of the commonest and important causes of dementia with advancing age which leads to deterioration of quality of life in elderly. Therefore it is of prime importance to curb this progress of cognitive decline before it crosses the threshold to dementia. Ayuveda is full of evidences regarding use of single drugs or formulations in age related cognitive decline. The drugs either mentioned as Medhya rasayanas specifically or other having Medhya activity can be potentially used for prevention and management of age related cognitive decline.

Keywords: Ayurveda, Medhya rasayana, cognitive deficits, dementia, Alzheimer's disease, learning and memory

INTRODUCTION

Age related cognitive decline is a term reserved for abnormal cognitive function less severe than dementia in person older than 50. It is considered as a prior condition to senile dementia. The term dementia signifies cognitive deterioration to such an extent that social and occupational functioning of an individual is markedly impaired to such an extent that he can no longer remain a fully independent and productive citizen. [1] Degeneration of the cerebral neurons is one of the commonest and important causes of dementia with increasing age which leads to deterioration of quality of life in elderly. Advanced dementia is characterized by progressive loss of personality and increasing disability to perform even a simplest task. As the disease progresses, the personality of an individual also changes and subsequently, social withdrawal take a hold. According to World Health Organization, it is estimated that 5% of men and 6% of women of above 60 years of age affected with Alzheimer's type of dementia worldwide.[2] According to Alzheimer's disease International there are 35.6 million people living with dementia worldwide in 2010, increasing to 65.7 million by 2030 and 115.4 million by 2050. [3] Therefore it is of prime importance to curb this progress of cognitive decline before it crosses the threshold to dementia.

Ayurveda is full of evidences regarding use of single drugs or formulations in age related cognitive decline. The drugs either mentioned as Medhya rasayanas specifically or other having Medhya activity can be potentially used for prevention and management of age related cognitive decline. The drugs like Mandookparni (*Centella asiatica)*, Shankhapushpi (*Convolvulus pluricaulis*), Guduchi (*Tinospora cordifolia*) and Madhuyashti (*Glycyrrhiza glabra*) are known as Medhya rasayanas [4], which directly promote the cognition. Other drugs as Brahmi (*Bacopa monnieri*) [5] and Jyotishmati (*Celastrus panniculatus*) [6] are also known for their intellect promoting activity. Vidanga (*Embelia ribes*) is specifically indicated for increasing grasping and retention power. [7] Ashwagandha (*Withania somenifera*) [8] one of the most utilized rasayana drugs in Ayurveda is also scientifically proven to reverse the

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behavioral deficits and pathology seen in Alzheimer's disease models through up regulation of liver lipoprotein receptor-related protein (LRP) in brain microvessels and the Aβ-degrading protease neprilysin (NEP). This review sums up clinical and experimental studies to illustrate evidences regarding the indication for use of these drugs in cognitive decline and thereby improving their quality of life and making them socially accepted.

Our objective is to provide an overview of evidences of various Ayurvedic drugs which can be used for the prevention of age related cognitive decline and check the progress to the advanced stage known as senile dementia. We searched extensively on Pubmed and Medline databases with key words- Ayurveda, medhya rasayana, dementia, cognitive deficit, learning and memory. All the available texts published from 2000 to June 2012 were considered for the review. A total of 30 articles were selected for review.

Brahmi (*Bacopa monnieri*)

1. In a study, 10 days old neonatal rat pups were given different doses of BM (*Bacopa monnieri*) extract orally for different periods of time. These rats were then subjected to spatial learning (T-Maze) and passive avoidance tests along with the age matched normal rats fed with gum acacia. The result showed improvement in spatial learning and enhanced memory performance in neonatal rats treated with extract of BM. The result provides evidence that treatment with BM extract during growth spurt period of neonatal rats enhances learning and memory. [9]
2. A study was carried on 61 aged subjects of both sexes aged 62-75 years. Out of 61 persons 28 had cognitive deficits particularly the memory loss whereas 21 were normal. The subject of both group were treated with organic extract of *Bacopa monnieri* in effective doses continuously for six months and evaluated on various neuropsychological parameters. The results obtained at the end of six months revealed beneficial effect in improving memory attention span and behavioral problems among demented elderly people. The neuro-chemical loss was checked and enhanced in senile dementia cases. Result showed that the test drug has potential to improve memory and other cognitive deficits among the aged persons suffering from dementia and associated behavioural problems. [10]
3. A study was conducted with an objective to study the effect of *B. monnieri* on scopolamine-induced amnesia. Morris water maze scale was employed to test the amnesic effect of scopolamine and its reversal by *B. monnieri.* Rota rod test was conducted to screen muscle coordination activity of mice. Scopolamine significantly impaired the acquisition and retrieval of memory producing both anterograde and retrograde amnesia. *Bacopa monnieri* extract was able to reverse both anterograde and retrograde amnesia. Thus it is concluded that *B. monnieri* effects on cholinergic system may be helpful for developing alternative therapeutic approaches for the treatment of Alzheimer's disease. [11]
4. In an open label, prospective, uncontrolled, non-randomized study, the effect of *Bacopa monnieri* on cognitive functions in Alzheimer's disease patients was evaluated. Study population included all newly diagnosed patients of Alzheimer's disease aged 60-65 years from the Psychiatry Outdoor Patient Department. Baseline scores on Mini Mental State Examination Scale (MMSES) were recorded for all patients. Subsequently all patients took 300 mg of *Bacopa monnieri* standardized extract orally twice a day for 6 months. MMSES scores were recorded again after the completion of trial. Study patients showed statistically significant improvements in various components of MMSES. The improvements were observed in orientation (of time, place & person), attention and in language components (reading, writing & comprehension) at the end of trial. The patients involved in this trial also reported improvement in their quality of life, and decrease in the irritability and insomnia. The results of clinical trial showed that *Bacopa monnieri* standardized extract 300 mg twice a day orally for 6 months resulted in improvement in some aspects of cognitive functions in geriatric patients suffering from Alzheimer's disease. [12]
5. A study evaluated the effect of alcoholic extract of *Bacopa monnieri* on cognitive function and neurodegeneration in animal models of Alzheimer's disease induced by ethylcholine aziridinium ion (AF64A). Male Wistar rats were given the alcoholic extract of *Bacopa monnieri* at doses of 20, 40 and 80 mg/kg BW orally via feeding needle for a period of 2 weeks before and 1 week after the intracerebroventricular administration of AF64A bilaterally. Rats were tested for spatial memory using Morris water maze test and the density of neurons and cholinergic neurons was determined using histological techniques after 7 days 0f AF64A administration. *Bacopa monnieri* 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. These findings suggested that *Bacopa monnieri* is a potential cognitive enhancer and neuroprotectant against Alzheimer's disease. [13]
6. An experimental study was conducted to investigate the efficacy of *Bacopa monnieri* in inhibiting aluminium toxicity in the cerebral cortex. Male Wister rats (8 months old) were administered with $AlCl_3$ orally at a dose of 50mg/kg/day in drinking water for 1 month. Experimental rats were given $AlCl_3$ along with *Bacopa monnieri* extract at a dose of 40 mg/kg/day. One group of rats was treated with l-deprenyl at a dose of 1mg/kg/day along with $AlCl_3$ treatment. Observations showed that *Bacopa monnieri* prevented accumulation of lipid and protein damage significantly induced by aluminium intake. It also inhibited decline in the activity of endogenous antioxidant enzymes associated with aluminium administration .The potential of *Bacopa monnieri* to inhibit Al-induced oxidative stress was observed to be similar to that of l-deprenyl. The potential of *Bacopa monnieri* extract to prevent aluminium neurotoxicity was reflected at the microscopic level as well. The results are suggestive of its neuroprotective effects. These findings strongly implicate that *Bacopa*

monnieri has potential to protect brain from oxidative damage resulting from aluminium toxicity. [14]

7. In a study, effects of *Bacopa monnieri* whole plant standardized dry extract was evaluated on cognitive function and its safety and tolerability in healthy elderly study participants. The study was a randomized, double-blind, placebo-controlled clinical trial with a placebo run-in of 6 weeks and a treatment period of 12 weeks. Volunteers were recruited from the community to a clinic in Portland, Oregon by public notification. Fifty-four (54) participants aged 65 or older (mean 73.5 years), without clinical signs of dementia, were recruited and randomized to Bacopa or placebo. Forty-eight (48) completed the study with 24 in each group. Standardized *B. monnieri* extract 300 mg/day or a similar placebo tablet orally for 12 weeks. The primary outcome variable was the delayed recall score from the Rey Auditory Verbal Learning Test (AVLT). Other cognitive measures were the Stroop Task assessing the ability to ignore irrelevant information, the Divided Attention Task (DAT), and the Wechsler Adult Intelligence Scale (WAIS) letter-digit test of immediate working memory. Affective measures were the State-Trait Anxiety Inventory, Center for Epidemiologic Studies Depression scale (CESD)-10 depression scale, and the Profile of Mood States. Vital signs were also monitored. Controlling for baseline cognitive deficit using the Blessed Orientation–Memory–Concentration test, Bacopa participants had enhanced AVLT delayed word recall memory scores than placebo. Stroop results were similarly significant, with the Bacopa group improving and the placebo group remaining unchanged. CESD-10 depression scores, combined state plus trait anxiety scores, and heart rate decreased over time for the Bacopa group but increased for the placebo group. No effects were found on the DAT, WAIS digit task, mood, or blood pressure. The dose was well tolerated with few adverse events (Bacopa n = 9, placebo n = 10), primarily stomach upset. This study provided further evidence that *B. monnieri* has potential for safely enhancing cognitive performance in the aging. [15]
8. A study was conducted to evaluate the neuroprotective potential of *Bacopa monnieri* (BM), against cognitive impairment, in colchicine-induced dementia. Intracerebroventricular administration of colchicine (15µg/5µl) induced cognitive impairment in rats as assessed by elevated plus maze. This was accompanied by a significant increase in oxidative stress in term of enhanced levels of lipid peroxidation and protein carbonyls. Concomitantly, decrease in activity of antioxidant enzymes was also observed in colchicine treated animals. BM (50 mg/kg body weight) supplementation reversed memory impairment in the colchicine treated rats. *Bacopa monnieri* administration attenuated oxidative damage, as evident by decreased LPO and protein carbonyl levels and restoration in activities of the antioxidant enzymes. *Bacopa monnieri* supplementation was able to restore the altered activity of membrane bound enzymes (Na^+K^+ ATPase and AChE) as compared to the controls. The results suggested therapeutic potential of *Bacopa monnieri* in the treatment of AD associated cognitive decline. [16]

Mandukaparni (*Centella asiatica*)

1. A study was conducted to investigate the underlying mechanisms of neuroprotective effects of asiatic acid (AA), a pentacyclic triterpene in *Centella asiatica*, in vivo & in vitro. Human neuroblastoma SH-SY5Y cells were used for in vitro study and cell viability was determined with the MTT assay. Hoechst 33342 staining and flow cytometry were used to examine the apoptosis. The mitochondrial membrane potential (MMP) and reactive oxygen species (ROS) were measured using fluorescent dye. PGC-1α and Sirt1 levels were examined using Western blotting. Neonatal mice were given monosodium glutamate (2.5 mg/g) subcutaneously at the neck from postnatal day (PD) 7 to 13, and orally administered with AA on PD 14 daily for 30 d. The learning and memory of the mice were evaluated with the Morris water maze test. HE staining was used to analyze the pyramidal layer structure in the CA1 and CA3 regions. Pretreatment of SH-SY5Y cells with AA (0.1-100 nmol/L) attenuated toxicity induced by 10 mmol/L glutamate in a concentration-dependent manner. AA 10 nmol/L significantly decreased apoptotic cell death and reduced reactive oxygen species (ROS), stabilized the mitochondrial membrane potential (MMP), and promoted the expression of PGC-1α and Sirt1. In the mice models, oral administration of AA (100 mg/kg) significantly attenuated cognitive deficits in the Morris water maze test, and restored lipid peroxidation and glutathione and the activity of SOD in the hippocampus and cortex to the control levels. AA (50 and 100 mg/kg) also attenuated neuronal damage of the pyramidal layer in the CA1 and CA3 regions. Study indicated that AA attenuates glutamate-induced cognitive deficits of mice and protects SH-SY5Y cells against glutamate-induced apoptosis *in-vitro*. [17]
2. An investigation was undertaken to evaluate the nootropic effect of *Centella asiatica*. Three months old male Swiss albino mice were injected orally with graded doses (200, 500, 700, 1000 mg/kg body weight) of *C. asiatica* aqueous extract for 15 days to select an effective dose for nootropic studies. Animals were tested in radial arm maze to assess the learning and memory performance. Based on the results, mice were treated orally with 200 mg/kg of C. asiatica for 15 days from day 15 to day 30 post partum (p.p.). The nootropic effect was evaluated on the 31st day and 6 months p.p. The behavioral (open field, dark/bright arena, hole board and radial arm maze tests), biochemical (acetylcholine esterase activity) and histological studies (dendritic arborization) were carried out. Performance of juvenile and young adult mice was significantly improved in radial arm maze and hole board tests, but locomotor activity did not show any change compared to control. Treatment resulted in increased acetylcholine esterase activity in the hippocampus. Dendritic arborization of hippocampal CA3 neurons was also increased in terms of intersections and branching points, both at one month and 6 months of trial. Results of the

present investigation indicated that treatment during postnatal developmental stage with *C. asiatica* extract can influence the neuronal morphology and promote the higher brain function of juvenile and young adult mice. [18]

3. In a study, the effect of aqueous, methanolic and chloroform extracts of *Centella asiatica* were investigated on cognitive functions in rats. Male Wistar rats of 200-250 g were used to study the effect on learning and memory by using shuttle box, step through, step down and elevated plus maze paradigms. Only the aqueous extract of whole plant (200 mg/kg for 14 days) showed an improvement in learning and memory in both shuttle box and step through paradigms. Therefore, further experiments were conducted with aqueous extract using 100, 200 and 300 mg/kg doses in different paradigms of learning and memory. All doses of aqueous extract increased the number of avoidances in shuttle box and prolonged the step through latency in step through apparatus in a dose dependent manner, while only two doses 200 and 300 mg/kg of aqueous extract showed significant increase in the step down latency in step down apparatus and transfer latency (TL) in elevated plus maze. Among doses of aqueous extract tested on oxidative stress parameters, only 200 and 300 mg/kg showed a significant decrease in the brain levels of malondialdehyde (MDA) with simultaneous significant increase in levels of glutathione. There were significant increase in the levels of catalase at the 300 mg/kg but no significant changes in superoxide dismutase (SOD) levels were observed. The results indicated that the aqueous extract of *C. asiatica* has cognitive enhancing effect and an antioxidant mechanism is involved. [19]
4. The effect of an aqueous extract of *Centella asiatica* (100, 200 and 300 mg/kg for 21 days) was investigated in i.c.v. STZ-induced cognitive impairment and oxidative stress in rats. Male Wistar rats were injected with STZ (3 mg/kg, i.c.v.) bilaterally on the days 1 and 3. Cognitive behavior was assessed by using passive avoidance and elevated plus-maze paradigms on the days 13, 14 and 21. Rats were killed on the day 21 for estimation of oxidative stress parameters (malondialdehyde (MDA), glutathione, superoxide dismutase and catalase) in the whole brain upon completion of the behavioral task. Rats treated with *C. asiatica* showed a dose-dependent increase in cognitive behavior in both 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. [20]
5. A study evaluated the role of *Centella asiatica* (CeA) fresh leaf juice treatment during growth spurt period of rats on dendritic morphology of amygdaloid neurons, one of the regions concerned with learning and memory. The study was conducted on neonatal rat pups. 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. After the treatment period, the rats were killed, brains removed and amygdaloid neurons impregnated with Silver nitrate (Golgi staining). Amygdaloid neurons were traced using camera lucida and dendritic branching points (a measure of dendritic arborization) and intersections (a measure dendritic length) quantified. The data were compared with those of age-matched control rats. The findings indicated a 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. [21]
6. A study was conducted to evaluate the antidepressant activity of total triterpenes from *Centella asiatica* in forced swimming test. Mice were randomly divided into control group, model group and treatment group. The effect of total triterpenes from *Centella asiatica* on the immobility time in forced swimming mice and concentration of amino acid in mice brain tissue was observed. Imipramine and total triterpenes from *Centella asiatica* reduced the immobility time and ameliorated the imbalance of amino acid levels. The study concluded that the total triterpenes from *Centella asiatica* had antidepressant activity. [22]

Madhuyashti (*Glycyrrhiza glabra*)

1. A study was undertaken to investigate the effects of *Glycyrrhiza glabra* (popularly known as liquorice) on learning and memory in mice. Elevated plus-maze and passive avoidance paradigm were employed. Three doses (75, 150 and 300 mg/kg; *p.o.*) of aqueous extract of *Glycyrrhiza glabra* were administered for 7 successive days in separate groups of animals. The dose of 150 mg/kg of the aqueous extract of liquorice significantly improved learning and memory of mice. Furthermore, this dose significantly reversed the amnesia induced by diazepam (1 mg/kg; *i.p.)* and scopolamine (0.4 mg/kg; *i.p.*). Since scopolamine-induced amnesia was reversed by liquorice, it is possible that the beneficial effect on learning and memory was due to facilitation of cholinergic-transmission in mouse brain. The study showed that *Glycyrrhiza glabra* has potential as a memory enhancing agent. [23]
2. In a study, the effect of chronic treatment with glabridin (5, 25 and 50 mg/kg; *p.o.*) on cognitive function in control and streptozotocin (STZ)-induced diabetic rats was investigated. Animals were divided into untreated control, glabridin-treated control (5, 25 and 50 mg/kg), untreated diabetic and glabridin treated diabetic (5, 25 and 50 mg/kg) groups. Treatments were started at the onset of hyperglycemia. Passive avoidance learning (PAL) and memory was assessed 30 days later. Diabetes caused cognition deficits in the PAL and memory paradigm. Oral glabridin administration (25 and 50 mg/kg) improved learning and memory in non-diabetic rats, it also reversed learning and memory deficits of diabetic

rats. Low dose glabridin (5 mg/kg) did not alter cognitive function in non-diabetic and diabetic groups. Glabridin treatment partially improved the reduced body weight and hyperglycemia of diabetic rats although the differences were not significant. The combination of antioxidant, neuroprotective and anticholinesterase properties of glabridin may all be responsible for the observed effects. The result showed that glabridin prevented the deleterious effects of diabetes on learning and memory in rats. [24]

3. In an experimental study, Glabridin was isolated from the roots of *Glycyrrhiza glabra* and its effects on cognitive functions and cholinesterase activity were investigated in mice. Glabridin (1, 2 and 4 mg/kg; *p. o.*) and piracetam (400 mg/kg; *i.p.*), a clinically used nootropic agent, were administered daily for 3 successive days to different groups of mice. 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.*) 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. [25]
4. A study was undertaken to investigate the effects of *Glycyrrhiza glabra*s on learning and memory. The elevated plus-maze and passive avoidance paradigm were employed to evaluate learning and memory. Three doses (75, 150, and 300 mg/kg; *p.o.*) of aqueous extract of *G. glabra* were administered for 7 successive days in separate groups of mice. The dose of 150 mg/kg of the aqueous extract of liquorice significantly improved learning and memory of mice. This dose reversed the amnesia also,induced by diazepam (1 mg/kg; *i.p.*), scopolamine (0.4 mg/kg; *i.p.*), and ethanol (1 g/kg; *i.p.*). Since scopolamine-induced amnesia was reversed by liquorice, it is possible that the beneficial effect on learning and memory may be because of facilitation of cholinergic transmission in brain. Investigation showed that *G. glabra* has shown promise as a memory enhancer in both exteroceptive and interoceptive behavioral models of memory. [26]

Shankhapusphi (*Convolvulus pluricaulis*)

1. In an experimental study, a dose dependent enhancement of memory was observed with *Convolvulus pluricaulis* (CP) and *Asparagus racemosus* (AR) treatment as compared to control group. When tested on second day, CP and AR at the dose of 200 mg/kg; *p.o.* showed significantly higher percent retentions, than piracetam. Multiple treatment with CP and AR for 3 days also demonstrated significant dose dependent increase in percent retentions as compared to control group. The effect was more prominent with CP as compared with piracetam and AR. A significantly lower percent retention in aged mice was observed as compared to young mice. Aged mice (18-20 months) showed higher transfer latency (TL) values on first and second day (after 24 hours) as compared to young mice, indicating impairment in learning and memory. Pretreatment with CP and AR for 7 days enhanced memory in aged mice as significant increase in percent retention was observed with CP (200 mg/kg; *p.o.*) as compared with piracetam (10 mg/kg; *p.o.*). Post trial administration of CP and AR extract demonstrated significant decrease in latency time during retention trials. Hippocampal regions associated with the learning and memory functions showed dose dependent increase in AGhE 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, neuroprotective and cholinergic properties. [27]
2. In an experimental study, ethanolic extract of *Convolvulus pluricalis* (CP) and its ethyl acetate and aqueous fractions were evaluated for their memory enhancing properties. Cook and Weidley's Pole Climbing Apparatus, passive avoidance paradigms and active avoidance tests were used to test learning and memory. Two doses (100 and 200 mg/kg; *p.o.*) of ethyl acetate and aqueous fractions of the ethanolic extract were administered in separate groups of animals. Both the doses of all the extracts of CP significantly improved learning and memory in rats. [28]
3. An experimental study investigated the neuroprotective effects of aqueous extract from *Convolvulus pluricaulis* (CP) against aluminium chloride induced neurotoxicity in rat cerebral cortex. 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 which resulted from 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 upregulated protein expression of cyclin dependent kinase5 (Cdk5) induced by aluminium. The potential of CPE to inhibit aluminium induced toxicity was compared with rivastigmine tartrate (1mg/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 neuroprotective effects. Therefore it was proved that *Convolvulus pluricaulis* possesses neuroprotective potential, thus validating its use in alleviating toxic effects of aluminium. [29]

Guduchi (*Tinospora cordifolia*)

1. In a double blind, randomized and placebo controlled design, thirty healthy volunteers of age 18-30 years received *Tinospora cordifolia* (500 mg of pure aqueous extract) or a matching placebo for 21 days. Learning and memory was assessed by subjecting the volunteers to a battery of psychological tests that aimed at studying visual memory, logical memory, verbal memory, attention span and concentration.

Tinospora cordifolia showed a significant ($p < 0.05$) increase in the test scores for "verbal learning and memory" (control -1.2±1.9, drug 6.9±2.5) and "logical memory" (control 5.1±6.1, drug 26.6±6.7). No significant untoward effects were reported during *Tinospora cordifolia* administration. *Tinospora cordifolia*, 500 mg daily, enhanced verbal learning and memory and logical memory (of immediate and short term type) compared to placebo in healthy volunteers. [30]

2. To study the effect of *Tinospora cordifolia* (Tc) on learning and memory in normal and cyclosporine induced memory deficit rats, alcoholic and aqueous extracts of the whole plant of *Tinospora cordifolia* were administered orally for 15 days in two groups of rats. Cyclosporine 15, 25 mg/kg, *i.p.* was administered on alternate days for 10 days. Combination of cyclosporine 25 mg/kg, *i.p.* for 10 days and Tc alcoholic 200 mg/kg and Tc aqueous 100 mg/kg were administered in two different groups of rats. At the end of treatment, learning and memory was assessed using Hebb William maze and passive avoidance task. The locomotor activity was assessed using open field chamber. The immune status was studied using DNCB skin sensitivity test. Histopathological examination of hippocampus was also done. Both alcoholic and aqueous extracts of Tc produced a decrease in learning scores in Hebb William maze and retention memory indicating enhancement of learning and memory. However, cyclosporine at both the doses increased the learning scores in Hebb William maze and decrease in retention time in the passive avoidance task suggesting a memory deficit. The combination of cyclosporine and Tc produced a decrease in learning scores in Hebb William maze and increase latency in passive avoidance task compared to cyclosporine alone treated rats. The histopathological examination of hippocampus in cyclosporine treated rats showed neurodegenerative changes which were protected by the Tc. The study revealed that Tc enhances cognition (learning and memory) in normal rats and cyclosporine induced memory deficit was successfully overcome by Tc. [31]

Vidanga (*Embelia ribes*)

1. An experimental study investigated the neuroprotective effect of ethanolic extract of *Embelia ribes* Burm fruits on middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia in rats. Male Wistar albino rats were fed ethanolic *E. ribes* extract (100 and 200 mg/kg body weight; *p.o.*) for 30 days. After 30 days of feeding, all animals were anaesthetized with chloral hydrate (400 mg/kg; *i.p.*). The right middle cerebral artery was occluded with a 4-0 suture for 2 hours. The suture was removed after 2 hours to allow reperfusion injury. Ischemia followed by reperfusion in ischemic group rats significantly ($P < 0.001$) reduced the grip strength activity and non-enzymatic (reduced glutathione, GSH) and enzymatic [glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-*S*-transferase (GST)] antioxidant levels in hippocampus and frontal cortex compared to sham-operated rats. Also, serum lactate dehydrogenase (LDH) and thiobarbituric acid reactive substance (TBARS) levels in hippocampus and frontal cortex were significantly increased in ischemic group compared to sham-operated rats. Furthermore, ethanolic *E. ribes* extracts pretreatment significantly ($P < 0.001$) increased the grip strength activity, and GSH, GPx, GR and GST levels in hippocampus and frontal cortex with significant decrease in LDH levels in serum and TBARS levels in hippocampus and frontal cortex compared to MCAO + vehicle group rats. Thus the results suggest that chronic treatment with ethanolic *E. ribes* extract enhances the antioxidant defense against MCAO- induced focal cerebral ischemia in rats and exhibits neuroprotective activity. [32]
2. In an experimental study, the protective effects of embelin from *Embelia ribes* on global ischemia/reperfusion-induced brain injury in rats were investigated. Transient global ischemia was induced by occluding bilateral common carotid arteries for 30 min followed by 24-h reperfusion. Neurological functions were assessed using sensorimotor tests. Ischemia/reperfusion-induced neuronal injury was assessed by cerebral infarct area, biochemical and histopathological examination. Pretreatment of embelin (25 and 50 mg/kg; *p.o.*) significantly increased locomotor activity and hanging latency time and decreased beam walking latency when compared with ischemic control. The treatment also reduced significantly the lipid peroxidation and increased the total thiol content and glutathione-S-transferase activity in brain homogenates. The decreased cerebral infarction area in embelin-treated groups and histopathological observations confirmed the findings. The observations suggested that embelin is a neuroprotective agent and may prove to be useful adjunct in the treatment of stroke. [33]

Jyothismati (*Celastrus paniculatus*)

1. Ethanol extract of *Celastrus paniculatus* was administered at the rate of 2 g/kg body weight orally for 16 days before trial experiment in male Wister albino rats of 3, 12 and 20 months old age. They were studied for learning and memory process as well as for any change in the serum biochemistry. All animals were trained on Y-maze. Each animal received a daily session of 10 trials for 5 days i.e. a maximum of 50 trials. Increase in response of 5th session as compared to 1st session was taken as criteria of learning and memory. There was a significant increase in learning and memory in the treated group compared to its control. Results showed that *Celastrus paniculatus* preferentially affects learning and recall of memory and also regulate the serum biochemistry. [34]
2. In a study, Jyothismati oil from seeds of *Celastrus paniculatus* (CP) was used to determine its effect on the learning process in the adult male Wistar rats. Radial arm maze paradigm was used to study effect on learning and memory. The data indicated enhancement in radial arm maze acquisition with chronic administration of CP oil (400 mg/kg body weight). A decrease in AChE activity was noted in the treated animals leading to increased cholinergic activity in the brain. There was significant decrease in the 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. [35]

Ashwagandha (*Withania somnifera*)

1. A study investigated the anxiolytic and antidepressant actions of the bioactive glycowithanolides (WSG), isolated from *Withania somnifera* (WS) roots, in rats. WSG (20 and 50 mg/kg) was administered orally once daily for 5 days and the results were compared by those elicited by the benzodiazepine lorazepam (0.5 mg/kg; *i.p.*) for anxiolytic studies, and by the tricyclic anti-depressant, imipramine (10 mg/kg; *i.p.*), for the antidepressant investigations. Both these standard drugs were administered once, 30 min prior to the tests. WSG induced an anxiolytic effect, comparable to that produced by lorazepam, in the elevated plus-maze, social interaction and feeding latency in an unfamiliar environment, tests. Also, both WSG and lorazepam, reduced rat brain levels of tribulin, an endocoid marker of clinical anxiety, when the levels were increased following administration of the anxiogenic agent, pentylenetetrazole. WSG also exhibited an antidepressant effect, comparable with that induced by imipramine, in the forced swim-induced 'behavioural despair' and 'learned helplessness' tests. These investigations support the use of WS as a mood stabilizer in clinical conditions of anxiety and depression. [36]
2. 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 behavioral 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 behavioral deficits and plaque load in APPSwInd mice (line J20). The temporal sequence involved an increase in plasma Aβ and a decrease in brain Aβ monomer after 7 days, indicating increased transport of Aβ from the brain to the periphery. Enhanced expression of low-density lipoprotein receptor-related protein (LRP) in brain microvessels and the Aβ-degrading protease neprilysin (NEP) occurred 14-21 days after a substantial decrease in brain Aβ levels. However, significant increase in liver LRP and NEP occurred much earlier, at 7 days, and were accompanied by a rise in plasma sLRP, a peripheral sink for brain Aβ. In *Withania somnifera* treated mice, the extract induced liver, but not brain, LRP and NEP and decreased plasma and brain Aβ, indicating that increase in liver LRP and sLRP occurring independent of Aβ concentration could result in clearance of Aβ. Selective down-regulation of liver LRP, but not NEP, abrogated the therapeutic effects of the extract. The remarkable therapeutic effect of *W. somnifera* mediated through up-regulation of liver LRP indicated that targeting the periphery offers a unique mechanism for Aβ clearance and reverses the behavioral deficits and pathology seen in Alzheimer's disease models. [37]
3. In a study, two major withanamides A (WA) and C (WC) present in *Withania somnifera* fruit were tested for their ability to protect the PC-12 cells, rat neuronal cells, from beta-amyloid induced cell damage which plays a significant role in the development of Alzheimer's disease (AD). The cell death caused by beta-amyloid was negated by withanamide treatment. 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. Further, the understanding of the mechanism of action and in vivo efficacy of these withanamides may facilitate its development as a prophylaxis in Alzheimer's disease. [38]

The review of studies regarding Ayurvedic drugs reveals that these drugs can be used for both prevention and management of age related cognitive deficits and progress to senile dementia can be halted. Thus it can be concluded that based on these evidences these drugs have potential to check the cognitive decline in elderly and can be used to improve their quality of life and enjoy an independent socially productive life.

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