ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 12, Issue 6, 2019

Online - 2455-3891
Print - 0974-2441

Review Article

AN UPDATED REVIEW ON HERBAL DRUGS: NOOTROPIC ACTIVITY AND POSSIBLE MECHANISMS

DEBARATI MAITY, RAJENDRA SANDUR V*

Department of Pharmacology, Krupanidhi College of Pharmacy, Bengaluru, Karnataka - 560 035, India. Email: drrajendra1972@gmail.com

Received: 20 March 2019, Revised and Accepted: 25 April 2019

ABSTRACT

Nootropic drugs are those which are proclaimed to direct toward boosting the cognitive capabilities. Memory encodes, decodes, and stores information. Cognitive deficits or memory impairment that is present with neuropsychiatric conditions insists adoption of nootropics to improve cognitive abilities. At present, there is an enormous impulse to analyze medicinal plants worldwide for bettering cognitive behavior due to their minimal adverse effects. This paper is a review to refurbish knowledge on therapeutic and pharmacological actions along with major chemical constituents, safety, and conceivable mechanism of action of the chosen herbs from ayurvedic pharmacopoeia. Simultaneously, it comes up with further investigation and standardization on nootropic herbs.

Keywords: Neurobiology of memory, nootropic herbs, cognitive deficit, dementia.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i6.33164

INTRODUCTION

Dementia and cognitive deficit turn up to be a huge threat to the humankind in recent times and according to the WHO 2012 report, it was estimated that there are around 35.6 million populations getting adversely affected by dementia in the entire world [1]. Dementia is a gradual process of neurocognitive disorder and distinct by the evolution of numerous cognitive deficits such as aphasia, memory impairment, and also inability to initiate complex behaviors which is seriously sufficient to hamper the normal regular functioning. The present evaluation of 7.7 million different cases every year is a crucial benchmark worldwide, especially given the approximately low heights of heterogeneity among studies [2].

The massive analyses in the territory of medicine and new drug exploration have reformed management of old age complications. Sadly, these advancements have failed to convey considerable cure to dementia associated problems. A few of the newer medications and nutritional therapy was investigated, but the cited notable results seem either too expensive or inconvenient to adapt. The above-mentioned facts have aided to move toward conventional medication systems to renovate the chances of normal aging and improved condition of life for the aged persons. Rejuvenation (Rasayana) is the therapy which helps in procrastinating the complexities of aging and deficits correlated with it. It includes curative methods or preparation that on routinely practice will improve memory, immunity, strength, fitness, and thus increases life span. Rasayana preparations consist of individual herb in different medicinal forms and polyherbal mixture directed to target general health and targeted body tissues or aspects. Hence, they could be different types, Ayushkameeya Rasayana (the general health boosters and in long run improves the life span), Vayasthapana Rasayana (the one which delays the aging process), Medhya Rasayana (which shows nootropic actions), and Vyadhipratyaneeka Rasayana (its actions are disease specific) [3]. Rasayana herbs that assist to inhibit age-related complexities and improve that cognitive faculty is the scope of this paper. Informations used are facts from investigations on animal models or on bioactive conventions with some of preclinical works on humans.

NEUROBIOLOGY OF MEMORY

Process of memory formation

During learning procedures and memory formation, brain goes through both physical and chemical changes which are addressed as synaptic plasticity. It shows engrossment of different signal transduction pathways, induction of gene expression which concludes in production of new synapses among nerve cells [4]. This method goes through a steady refurbishing along with time and new experiences [5]. Memory can be branched into primarily three types, short-term memory (lasts for seconds or at the most minutes), intermediate long-term memory (lasts for days to weeks), and long-term memory (once gathered, can be recollected up to years or even a lifetime later). The procedure of memory formation (Fig. 1) associates the binding of neurotransmitter to the N-methyl D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor which triggers the torrent of molecular events which causes activation of CREB and PKC pathways, leading to the development of new proteins, i.e., receptors and some structural proteins that cement the synaptic connection among two frequently communicating neurons which basically lead to the formation of long-term memory [4-6]. A couple of evidence display the engrossment of the NF-kB/Rel pathway in the regulation of synaptic plasticity and it is also revealed that the inhibition of NF-kB activity in neurons results in enhanced cognitive functions [7].

During the initial stage of long-term potentiation (LTP) calcium influx into the NMDA receptor channel which causes activation of Ca^{2+}/calmodulin-dependent protein kinase and phosphorylation of previously existing AMPA glutamate receptor subtypes and infusion into postsynaptic membrane of the newly formed AMPA receptors to glutamate. AMPA receptors respond instantly by opening Na^{2+} and K^{+} ion channels which depolarizes the cell membrane. NMDA receptors don't respond to glutamate alone it requires adjuvant membrane depolarization which causes opening of Ca^{2+} ion channel. This NMDA receptor-dependent influx of Ca^{2+} promotes LTP, which is manifested as an increase in the postsynaptic response to glutamate release. Ca^{2+} influx activates release of arachidonic acid as well as NO and they act as retrograde messengers working presynaptically nurturing synaptic activity. Continuous large number of electrical stimuli develops LTP. CREB mediated transcription process leads to synapse-specific structural changes.

Cognitive dysfunction

Cognitive dysfunction, a large-scale health issue in the 21st century, one of the most functionally debilitating features of various neuropsychiatric as well as neurodegenerative disorders, for example, Alzheimer's disease (AD) dementia, schizophrenia, depression, seizure, cerebrovascular impairment, Parkinsonism, and head injury [8]. Aging is an important reason causing cognitive dysfunction, i.e., age-related memory impairment by leading to deterioration of LTP induction and synaptic plasticity [9].

Enhancement of cognition

Various schemes are projected to enhance cognition. Most interventions aim disease pathologies or the procedures concealing fundamental cognition, particularly synaptic plasticity. Treatment procedures in memory and cognition enhancement are as follows:

- Environmental embellishment and exercise
- Nutrients
- Herbal drugs
- Pharmaceutical drugs.

In this article, the role of herbal drugs in memory and cognition enhancement has been discussed in detail with evidence-based approach.

HERBAL NOOTROPIC DRUGS

Convolvulus pluricaulis (*Shankhapushpi*)

Shankhapushpi (*Convolvulaceae*) is a perennial herb (Fig. 2). The major active components (Shankhapushpin, microphyllic acid, and 3, 4-dihydroxycinnamic acid) of this plant show neuroprotection action, protect the brain from oxidative damage, free radical damage or neurotoxicity, and act as cognitive enhancer [10]. Hippocampal area linked with the learning and memory functions exhibits dose-dependent elevation in AChE activity in CA1 with AS and CA3 region with *Shankhapushpi* extracts treatment. This mechanism of the action of *Shankhapushpi* contributes to its antioxidant, neuroprotective, and cholinergic properties [11]. According to the investigation BR-16A (Mentat), a polyherbal mixture consisting *Shankhapushpi* considerably inversed the solitude stress affected amplification of onslaught and inhibition in pentobarbitone caused sleepiness, elevated overall motor actions, and stress affected antinociception. A mixture consisting *Brahmi, Shankhpushpi*, and *Vacha* called as Ayushman-8 proved to be productive on mental disorders or retardation, i.e., Manasa Mandata [12]. Investigators consider that *Shankhpushpi* soothes the nerves by balancing the body's synthesis of the cortisol, stress hormones, and adrenaline [13]. The full plant extract demonstrates the maximal inhibited action toward the microbes, especially *Helicobacter muridarum* [14]. The aqueous extract of the plant possesses neuroprotection action which is used in lessening side effects caused due to scopolamine [15].

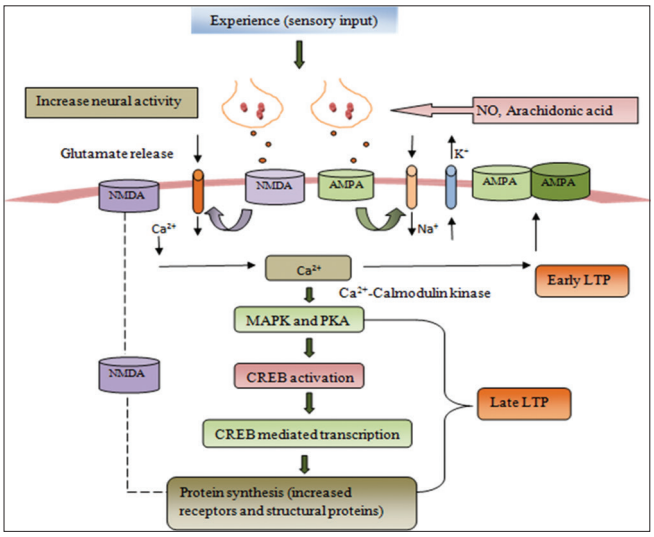

Fig. 1: Neurobiology of memory

Fig. 2: Shankhapushpi

Emblica officinalis (*Amalaki*)

Amalaki (*Phyllanthaceae*) fruits (fresh and dried), flowers, seeds, roots, leaves, and barks show medicinal activity (Fig. 3). *Amalaki* is profoundly witnessed as vayasthapana and recommended to be incorporated in regular nutritional therapy [16]. It consists of two hydrolysable tannins of less molecular weight called emblicanin A (2,3-di-o-galloyl-4,6-(S)-hexahydroxydiphenoyl-2-keto-glucono-d-lactone) and emblicanin B (2,3,4,6-bis-(S)-hexahydroxydiphenoyl-2-eto-glucono-d-lactone) as well as other tannins such as pedunclagin (2,3,4,6-bis-(S)-hexahydroxydiphenoyl-D-glucose) and punigluconino (2,3-di-O-galloyl-4,6-(S)-hexahydroxydiphenoylgluconic acid) display heavy antioxidant activity. The two emblicanins A and B conserve erythrocytes in opposition to oxidative stress caused by asbestos,

Fig. 3: Amalaki (dried fruit)

Fig. 4: Brahmi

which generates of superoxide radical [17,18]. *Amalaki* Rasayana increases the expression $\beta_1/_2$-adrenergic receptor genes in the rat heart which plays a role in hippocampal synaptic plasticity by stimulating extracellular signal-regulated kinase/mitogen-activated protein kinase, leading to activation of CREB (cAMP response element-binding protein) that mediates protein transcription and thereby strongly supports persistent long-term memory [19,20]. The fruit extract also shows antiviral activity and antimutagenic, improves the immune defense, and shows hypolipidemic and hepatoprotective activity [21,22]. Nutritional therapy consisting an organometallic ash prepared from mercury and sulfur (rasa sindoora) or a preparation from Indian gooseberry (Amalaki Rasayana) interrupted aggregation of inclusion bodies and heat shock proteins, concealed apoptosis and neurodegeneration, and inflated the heights of heterogeneous nuclear rib nucleoproteins [19].

Bacopa monnieri (*Brahmi*)

Brahmi (*Scrophulariaceae*) is the most popularly used nootropic drug (Fig. 4). The plant extract acts as cognitive and memory enhancer, reactive oxygen species (ROS) scavenging and sedative actions are also shown by the extract [23,24]. *Brahmi* extract (alcoholic) is rich in a saponin and bacosides which is the major cause of nootropic properties [25]. Extraction of new components (bacopasaponin G, bacopasides III, IV, and V, and phenyl-ethyl alcohol) has been reported [26]. *Brahmi* acts on cholinergic system, i.e., it affects the neurotransmitter acetylcholine or the areas of nervous system that uses acetylcholine which is a coordinator of memory formation [27]. Cognitive actions in the brain are enhanced by improving the availability of this neurotransmitter [28]. On rats, the plant extract (alcoholic) improves cognition and retention capability, protects cognitive deterioration affected by phenytoin, and reduces retrograde amnesia [29]. Recent investigation has determined antioxidant actions of bacosides toward persistent toxin effected oxidative catastrophe in rat brain [30] and thyroid T4 hormone appealing actions in animals in elevated doses [31]. *Brahmi* extract could prove to be a potent memory analeptic agent in the treatment of amnesia [32]. *Brahmi* reduces the degree of forgetting gathered information [33].

***Terminalia chebula* (*Hareetaki*)**

According to Ayurveda, fruits (Fig. 5) of *Hareetaki* (Combretaceae) are useful in the treatment of asthma, fevers, cough, worms, urinary diseases, and piles; it also shows usefulness in dysentery and chronic diarrhea, vomiting, enlarged liver, and spleen [16]. The phytochemical constituents present are tannic acid, gallic acid, ethyl gallate, chebulagic acid, ascorbic acid [22], mannitol, tannin, polyphenols, flavonoids, saponins, and alkaloids [34]. *Hareetaki* is a potential nootropic agent and acts as centrally acting reversible acetylcholinesterase inhibitor, and the kind of variations of learning and memory produced by *Terminalia chebula* extract was same to that of donepezil, is one of the best medicines for the treatment of AD [35]. It has shown signs of anti-aging and body strengthening if taken regularly [36]. *Hareetaki* demonstrated maximal suppression in the TBARS (thiobarbituric acid reactive substance) formation, rehabilitates antioxidant enzyme SOD (superoxide dismutase) from the radiation-induced impairment. The methanol, water, and ethanolic extracts (dried fruit of *Hareetaki*) exhibit antioxidant activity and neuroprotective effect toward H_2O_2 (Hydrogen peroxide)-induced toxicity [37].

Glycyrrhiza glabra (*Yashtimadhu)*

Yashtimadhu (*Fabaceae*) is harvested all over India (Fig. 6). The major effective constituents are glycyrrhizine [38], flavanones [39], and glycyrrhetenic acid [40]. Pseudoaldosteronism [41], hyperkalemia [42], and hypertension [43,44] are the side effect for long-term usage of *Yashtimadhu* as it is cytotoxic in nature. The rhizomes and roots extract of *Yashtimadhu* reported to possess free radical scavenging [45], cognition [46], as well as antioxidant efficiency against low-density lipoprotein oxidation [47]. The antihypoxic effects are enhanced by the aqueous extract mostly due to the plant's antioxidant properties [48]. The plant extract given orally (25 and 50 mg/kg) enhances the cognition in diabetic and healthy rats; thus, the anticholinesterase and neuroprotective properties of the plant prove inhibition of ruining effect caused by diabetes on cognition [49]. *Yashtimadhu* shows anticholinesterase activity on the brain and according to an experiment piracetam (4 mg/kg) and *yashtimadhu* extract (2 mg/kg) considerably inhibits dementia produced through scopolamine (0.5 mg/kg; i. p.); thus, it proves that *yashtimadhu* is an effective competitor for the treatment of AD [50].

Curcuma longa (*Haridra*)

The rhizomes of *Haridra* (*Zingiberaceae*) show extensive importance in various food preparations used as food coloring agents and even it has medicinal benefits (Fig. 7). Therapeutically, it acts as antidiabetic, antitoxic, and complexion promoter [51]. It also shows considerable therapeutic effect in epilepsy, asthma, and gallstone diabetic wound healing and shows neuroprotective as well as antioxidant activity [52]. Regular consumption of *curcumin* (in food) recorded reduced pervasiveness of AD [53]. In an appropriate way, *curcumin* preserves umbilical endothelial cells and neuron (PC12, i.e., Paracetamol rat cells) adjacent to amyloid-β-protein (Aβ) toxicity as well as boosts Aβ uptake from macrophages of AD patients [54] and decreases hyperphosphorylation [55] also dose dependently decreases fibril construction along with expansion, additionally destabilizing prearranged Aβ fibrils [56,57]. *Curcumin* also reduces heights of Aβ caused radical oxygen species [58] as well as constraints amyloid precursor protein cleft [59]. Moreover, lower doses of *curcumin* (160 ppm, i.e., parts per million) evade the incident of spatial memory deterioration in rat administered with Aβ admixture [58]. In a study, it was found that to Alzheimer mice (transgenic model) treated orally with the lower doses of comestible *curcumin* (160 ppm) for 183 days and reduced oxidative damage and decreased the inflammation in the brain as well as improved microglial reaction adjacent to Aβ

Fig. 5: Hareetaki

Fig. 6: Yashtimadhu

depositions [59-61]. Mice treated with *curcumin* (7.7 mg/kg/day) intravenously for a week proved to improve clearance of Aβ deposition in the brain [62]. The acute oral toxicity studies were performed which proved that *curcumin* dose 500–12000 mg/kg orally administered was not harmful (no mortality or no major adverse events) and the nanoparticles of *curcumin* were useful in Alzheimer mice (transgenic model) [63]. Aqueous extracts of *curcumin* rhizome (orally administered) displayed antidepressant activity in mice linked with reduction of brain monoamine oxidase type A [64]. *Curcumin* oral administration in human studies was ambiguous or insufficient conformation in dementia that could be probably due to poor plasma concentration bioavailability. As per the pharmacodynamic properties of *curcumin*, it behaves as a neuroprotective agent better than as a reversal medication [65]. The presence of the active constituents (curcuminoids) of *curcumin,* especially calabin-A, curcumin, and demethoxycurcumin, shows neuroprotective activity [66,67].

Withania somnifera (*Ashwagandha*)

Ashwagandha (*Solanaceae*) is mostly used in the Ayurveda system of medicine (Fig. 8). Active components comprise steroidal lactones (withaferin and withanolides), saponins, and alkaloids (anaferine, isopelletierine, anahygrine, and cuseohygrine) [68]. *Ashwagandha* has been proclaimed assuring contestant for anticancer drug due to its cytotoxic properties [69], apoptotic [70], antiangiogenesis [71], and antimetastatic [72]. This plant is found to have therapeutic effect on the CNS (central nervous system)-related disorders in rodents, for example, cognitive and memory deterioration, stress, Parkinson's disease (PD), Huntington's disease, excitotoxicity, for AD, sleep disturbance in mice, used in epilepsy and in oxidative stress induced by copper, rotenone, and streptozotocin [73]. Withaferin (active component of the plant) is claimed to possess hepatoprotective potential (10 mg/kg), anti-inflammatory (2.15 mg/kg), anticancer (3.5 mg/kg), and antiparasitic activity (0.3 mg/kg) [74] and withanolide (active component of the plant) has shown neuropharmacological activity (4.7 mg/kg) [75]. *Ashwagandha* (withanolide) thus proves to be a paramount contestant for the treatment of neurodegenerative disorders (PD, AD, cognitive deterioration, and convulsions) because it has the capacity to reassemble neural chains [76]. Glucosides and sitoindosides present in *Ashwagandha* reported to show antistress and antidepressant effect as well as have therapeutic effect on the cognitive deterioration as well as on dementia [77]. According to the investigation, root extracts of *Ashwagandha* orally administered for 1 month inversed behavioral deterioration, aggregation of Aβ, and plaque pathology in AD brain (transgenic mice) [78]. *Ashwagandha* proved fruitful reduction of neurobehavioral deformities caused by various chemical and physical incentives on oxidative stress in brain (rodent) as well as considerably reduced the elevated protein carbonyl, AchE, and nitrite heights in various section of rodent brain [79].

***Tinospora cordifolia* (*Guduchi*)**

Guduchi (*Menispermaceae*) is harvested all over India (Fig. 9). *Guduchi* extract (full plant) clinically acts as Medhya [80,81]. Antimalarial and antileprotic actions are possessed by the roots of the plant [40]. Glycosides, alkaloids, steroids, phenolics, sesquiterpenoid, and polysaccharides are the major chemical constituents of the plant [82]. Zinc and copper (trace elements) present in the plant preserves cells from harmful properties of oxygen radicals developed in the time of immune arousal and it also acts as antioxidants [83]. The plant also proved to possess the lead scavenging action [84]. Learning and memory improving therapeutic power is also present in the plant [85]. Amplified synthesis of acetylcholine and immune stimulation boosts the mechanism of cognitive action [86]. Alcoholic extracts (200 mg/kg) and aqueous extracts (100 mg/kg) administration for half a month improved cognition in healthy rats as well as rats with memory deterioration caused by cyclosporine [87]. According to the clinical studies, aqueous extract (500 mg) administration by oral routes to 30 normal volunteers of age groups 18–30 years improved cognitive

Fig. 7: Haridra

Fig. 8: Ashwagandha

Fig. 9: Guduchi

Fig. 10: Kushmanda

activity [88]. Considerable antidepressant action was also shown by the plant through expanding brain monoamines [89].

Benincasa hispida (*Kushmanda*)

Kushmanda (*Cucurbitaceae*) is also called as "winter melon" (Fig. 10). It is a wide-ranging crawling herb harvested all over India [90]. The plant gives large cylindrical fruits which are camouflaged with waxy coating [53]. Steroids, flavonoids, saponins, and alkaloids are the major phytochemical constituents of *Kushmanda* [91]. Antioxidant effective agent and ROS scavenger activity are shown by *Kushmanda* [92]. It has a tissue defensive effect on AD caused by colchicine by antioxidant activity [93].

Celastrus paniculatus (*Jyotishmati*)

Jyotishmati (*Celastraceae*) is also called "black oil plant" (Fig. 11). Seed oil of the plant majorly used for enhancing memory and cognitive function [40,94]. This seed oil consists of terpenoids (b-sitosterol, b-amyrin, paniculatadiol, celastrol, and pristimerin), esters, and sesquiterpenoids [95]. *Jyotishmati* seed oil improves the memory as well as cognitive function, and the plant is also reported to possess antiarthritic and antioxidant activity (decreased the level of lipid peroxidation) in rat model [96]. In navigational memory task performed on adult rats, the seed oil of *Jyotishmati* inversed scopolamine-induced deterioration [97]. *Jyotishmati* boosts learning and memorizing ability by selectively reversing the deterioration in spatial memory caused through acute central muscarinic receptor blockade, but it is not linked to an anticholinesterase-like action. It also shows free radical scavenging capacity, takes care of DNA cleavage as it has a defensive effect on DNA damage and cytotoxicity [98].

Nardostachys jatamansi (*Jatamansi*)

Jatamansi (Valerianaceae) is a rhizomatous plant (Fig. 12). Rhizome finds therapeutic importance in improvement of cognition and in the treatment of psychiatric disorders [99]. The plant also possesses the capacity to treat cardiovascular disorders, insomnia, and neural diseases [100]. Major chemical components are nardostachysin I, terpenoids, coumarins, and sesquiterpenes [101]. Enhancement of biogenic amine actions [102] and cognition [103] was found in the rhizome extract. Administration of alcoholic extracts to mice of all ages considerably enhanced cognition and inversed aging amnesia caused by scopolamine and diazepam [104]. According to the investigation, rhizome extract (hydroalcoholic) of *Jatamansi* proved AChE inhibition activity (IC50 value = 130.11612 mg/ml) [105,106]. Ethanolic and acetone extract of the plant showed dose-related therapeutic improvement of the anti-Parkinson activity [107] and considerable decrease of oxidative stress [108], respectively.

Mucuna pruriens (*Kapikacchu*)

Kapikacchu (*Fabaceae*), in Ayurveda, different parts (roots, seeds, leaves, and hairs) of the plant (Fig. 13) are commonly known to be used as nervine, aphrodisiac, and rejuvenating tonic [109]. It is a great supplier of L-3, 4-dihydroxyphenyl alanine as a result, it is therapeutically important in the treatment of PD [110]. It was found to improve semen secretion and it functions as a curative in sexual dysfunction attributed to weakness or loss of sexual power [110]. Seeds of *Kapikacchu* show lipid-lowering capacity, hypoglycemic, antioxidant, and neuroprotective activity which could be due to the dopaminergic and antioxidant potentials [111]. The seeds consist of the active constituents such as mucunine, mucunadine, mucunadinine, prurienidine, nicotine, b-sitosterol, vernolic acid, gallic acid as well as alkaloids, alkyl amines, tryptamine, steroids, flavonoids, and metals such as iron, manganese, magnesium, copper, and zinc [112]. After the treatment of *Kapikacchu,* the nigrostriatal section of mouse brain who is suffering from Parkinson disorder displayed considerable increase in the heights of malondialdehyde (MDA), nitrite, and decrease rate of catalase as well as improved the behavioral deformities [113].

CONCLUSION

Ayurveda an integrated science arranges solutions for memory and cognitive disorders in a beneficial way. From the discussion, herbal nootropic drugs find beneficial usefulness in achieving adequate results in memory disorders. Thus, the effort has been made to consider rationally in the prospect of memory enhancement in a view to explore greener pastures.

AUTHORS' CONTRIBUTIONS

The first author contributed in conceptualization of the article along with the collection of data and preparation of manuscript. Corresponding author provided expertise and feedback.

COMPETING INTERESTS

We declare that we have no conflicts of interest.

Fig. 11: Jyotishmati

Fig. 12: Jatamansi

Fig. 13: Kapikacchu

REFERENCES

1. Blennow K, Zetterberg H, Rinne JO, Salloway S, Wei J, Black R, *et al.* Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. Arch Neurol 2012;69:1002-10.
2. Waring SC, Rosenberg RN. Genome-wide association studies in Alzheimer disease. Arch Neurol 2008;65:329-34.
3. Wimo A, Jönsson L, Bond J, Prince M, Winblad B, Alzheimer Disease International. *et al.* The worldwide economic impact of dementia 2010. Alzheimers Dement 2013;9:1-1000.
4. Tully T, Bourtchouladze R, Scott R, Tallman J. Targeting the CREB pathway for memory enhancers. Nat Rev Drug Discov 2003;2:267-77.
5. Ingole SR, Rajput SK, Sharma SS. Cognition enhancers: Current strategies and future perspectives. CRIPS 2008;9:42-8.
6. Lynch G. AMPA receptor modulators as cognitive enhancers. Curr Opin Pharmacol 2004;4:4-11.
7. Qin ZH, Tao LY, Chen X. Dual roles of NF-kappaB in cell survival and implications of NF-kappaB inhibitors in neuroprotective therapy. Acta Pharmacol Sin 2007;28:1859-72.
8. Cesková E. Cognitive dysfunction and its therapy. Cas Lek Cesk 2005;144:801-4.
9. Rosenzweig ES, Barnes CA. Impact of aging on hippocampal function: Plasticity, network dynamics, and cognition. Prog Neurobiol 2003;69:143-79.
10. Kassab RB, Bauomy AA. The neuroprotective efficency of the aqueous extract of clove (*Syzygium aromaticum*) in aluminium induced neurotoxicity. Int J Pharmacy Pharm Sci 2014;6:503-8.
11. Bhatnagar M, Sisodia SS, Bhatnagar R. Antiulcer and antioxidant activity of *Asparagus racemosus* Willd and *Withania somnifera* Dunal in rats. Ann N Y Acad Sci 2005;1056:261-78.
12. Kumar A, Kulkarni SK. Protective effect of BR-16A, a polyherbal preparation against social isolation stress: Possible GABAergic mechanism. Phytother Res 2006;20:538-41.
13. Sethiya NK, Nahata A, Mishra SH, Dixit VK. An update on shankhpushpi, a cognition-boosting ayurvedic medicine. Zhong Xi Yi Jie He Xue Bao 2009;7:1001-22.
14. Kumar V. Potential medicinal plants for CNS disorders: An overview. Phytother Res 2006;20:1023-35.
15. Vimal SK, Sharma D, Bhatnagar M. Anti-bacterial activity of herbal extracts, EuMiL® and antibiotics against *Helicobacter muridarum*. Pharm J 2010;2:436-41.
16. Mahadev B, Ram GS, Subhose V, Maheswar T, Babu G. Critical review of medhya rasayana drugs mentioned in ayurveda-traditional indian medicine. Int J Ayurveda Pharm Res 2016;4:47-53.
17. Bhandari PR, Kamdod MA. *Emblica officinalis* (Amla): A review of potential therapeutic applications. Int J Green Pharm 2012;6:6-16.
18. Sowmya MN, Nanjammanni N. An phyto-chemical analysis of seedless amalaki fruit (*Emblica officinalis*) Churna. Int J Pharm Sci Invent 2017;6:9-12.
19. Kumar V, Aneesh KA, Kshemada K, Ajith KGS, Binil RSS, Deora N, *et al.* Amalaki rasayana, a traditional Indian drug enhances cardiac mitochondrial and contractile functions and improves cardiac function in rats with hypertrophy. Sci Rep 2017;7:8588.
20. Hagena H, Hansen N, Manahan-Vaughan D. β-adrenergic control of hippocampal function: Subserving the choreography of synaptic information storage and memory. Cereb Cortex 2016;26:1349-64.
21. Mirunalini S, Vaithiyanathan V, Krishnaveni M. AMLA: A novel Ayurvedic herb as a functional food for health benefits a mini review. Int J Pharm Pharm Sci 2013;5 Suppl 1:1-4.
22. Dwivedi V, Tripathi BK, Mutsuddi M, Lakhotia SC. Ayurvedic amalaki rasayana and rasa-sindoor suppress neurodegeneration in fly models of Huntington's and Alzheimer's diseases. Curr Sci 2013;104:1711-23.
23. Vasundhara S, Hafsa A, Rajiv G. Memory enhancing effects of *Ficus carica* leaves in hexane extract on interoceptive behavioral models. Asian J Pharm Clin Res 2013;6:109-3.
24. Rehni AK, Pantlya HS, Shri R, Singh M. Effect of chlorophyll and aqueous extracts of *Bacopa monniera* and *Valeriana wallichii* on ischaemia and reperfusion-induced cerebral injury in mice. Indian J Exp Biol 2007;45:764-9.
25. Maciuk A, Bouchet MJ, Mazars G, Um BH, Anton R. Nootropic (medhya) plants from ayurvedic pharmacopoeia. Etudes Chim Pharmacol 2002:402-11.
26. Achliya GS, Barabde U, Wadodkar S, Dorle A. Effect of bramhi ghrita, an polyherbal formulation on learning and memory paradigms in experimental animals. Indian J Pharmacol 2004;36:159.
27. Gohil KJ, Patel JA. A review on *Bacopa monniera*: Current research and future prospects. Int J Green Pharm 2010;4:303-4.
28. Chakravarty AK, Garai S, Masuda K, Nakane T, Kawahara N. Bacopasides III-V: Three new triterpenoid glycosides from *Bacopa monniera*. Chem Pharm Bull (Tokyo) 2003;51:215-7.
29. Chowdhuri DK, Parmar D, Kakkar P, Shukla R, Seth PK, Srimal RC, *et al.* Antistress effects of bacosides of *Bacopa monnieri*: Modulation of hsp70 expression, superoxide dismutase and cytochrome P450 activity in rat brain. Phytother Res 2002;16:639-45.
30. Vohora D, Pal SN, Pillai KK. Protection from phenytoin-induced cognitive deficit by *Bacopa monniera*, a reputed Indian nootropic plant. J Ethnopharmacol 2000;71:383-90.
31. Anbarasi K, Vani G, Balakrishna K, Devi CS. Effect of bacoside a on brain antioxidant status in cigarette smoke exposed rats. Life Sci 2006;78:1378-84.
32. Kar A, Panda S, Bharti S. Relative efficacy of three medicinal plant extracts in the alteration of thyroid hormone concentrations in male mice. J Ethnopharmacol 2002;81:281-5.
33. Joshi H, Parle M. Brahmi rasayana improves learning and memory in mice. Evid Based Complement Alternat Med 2006;3:79-85.
34. Govindarajan R, Vijayakumar M, Pushpangadan P. Antioxidant approach to disease management and the role of "Rasayana" herbs of ayurveda. J Ethnopharmacol 2005;99:165-78.
35. Kapoor LD. Handbook of Ayurvedic Medicinal Plants: Herbal Reference Library. London: Routledge; 2017.
36. Kulkarni R, Shetty SK, Rajarajeshwari NM, Rao PN, Nayan J. Rasayana herbs of ayurveda to treat age related cognitive decline: An update. Pharmacogn J 2016;8:411-23.
37. Cheng HY, Lin TC, Yu KH, Yang CM, Lin CC. Antioxidant and free radical scavenging activities of *Terminalia chebula*. Biol Pharm Bull 2003;26:1331-5.
38. Palaksha MN, Satish S. The effects of ethanolic extract in dried fruits of *Terminalia chebula* on learning and memory in mice. Asian J Biomed Pharm Sci 2013;3:???.
39. Goswami S, Saoji A, Kumar N, Thawani V, Tiwari M, Thawani M. Effect of *Bacopa monnieri* on cognitive functions in Alzheimer's disease patients. Int J Collaborat Res Int Med Public Health 2011;3:285-93.
40. Lavekar GS, Padhi MM, Mangal AK, Joseph GV, Raman KG, Selvarajan S, *et al.* Database on Medicinal Plants used in Ayurveda and Siddha. Vol. 5. India: Central Council for Research in Ayurveda and Siddha; 2001.
41. Hatano T, Shintani Y, Aga Y, Shiota S, Tsuchiya T, Yoshida T, *et al.* Phenolic constituents of licorice. VIII. Structures of glicophenone and glicoisoflavanone, and effects of licorice phenolics on methicillin-resistant *Staphylococcus aureus*. Chem Pharm Bull (Tokyo) 2000;48:1286-92.
42. Kuroda M, Mimaki Y, Sashida Y, Mae T, Kishida H, Nishiyama T, *et al.* Phenolics with PPAR-gamma ligand-binding activity obtained from licorice (*Glycyrrhiza uralensis* roots) and ameliorative effects of glycyrin on genetically diabetic KK-A(y) mice. Bioorg Med Chem Lett 2003;13:4267-72.
43. Kanda H, Sakurai M, Arima K. Licorice of "shakuyaku kanzou tou" induced pseudoaldosteronism. Hinyokika Kiyo 2004;50:215-7.
44. Yoshida S, Takayama Y. Licorice-induced hypokalemia as a treatable cause of dropped head syndrome. Clin Neurol Neurosurg 2003;105:286-7.
45. Sigurjónsdóttir HA, Franzson L, Manhem K, Ragnarsson J, Sigurdsson G, Wallerstedt S, *et al.* Liquorice-induced rise in blood pressure: A linear dose-response relationship. J Hum Hypertens 2001;15:549-52.
46. Ravichandra V, Devi A, Adiga S, Rai KS. Evaluation of the effect of *Glycyrrhiza glabra* Linn root extract on spatial learning and passive avoidance response in rats. Indian Drugs 2007;44:214-9.
47. Gupta D, Agrawal S, Sharma JP. Effect of preoperative licorice lozenges on incidence of postextubation cough and sore throat in smokers undergoing general anesthesia and endotracheal intubation. Middle East J Anaesthesiol 2013;22:173-8.
48. Zhan C, Yang J. Protective effects of isoliquiritigenin in transient middle cerebral artery occlusion-induced focal cerebral ischemia in rats. Pharmacol Res 2006;53:303-9.
49. Muralidharan P, Balamurugan G, Babu V. Cerebroprotective effect of *Glycyrrhiza glabra* Linn. Root extract on hypoxic rats. Bangladesh J Pharmacol 2009;4:60-4.
50. Dhingra D, Parle M, Kulkarni SK. Memory enhancing activity of *Glycyrrhiza glabra* in mice. J Ethnopharmacol 2004;91:361-5.
51. Hasanein P. Glabridin as a major active isoflavan from *Glycyrrhiza glabra* (Licorice) reverses learning and memory deficits in diabetic rats. Acta Physiol Hung 2011;98:221-30.

52. Saleem M, Daniel B, Murli K. Antimicrobial activity of three different rhizomes of *Curcuma longa* and *Curcuma aromatica* on uropathogens of diabetic patients. Int J Pharm Pharm Sci 2011;3:273-9.
53. Lavhale MS, Mishra SH. Nutritional and therapeutic potential of *Ailanthus excelsa* a review. Pharmacogn Rev 2007;1:106-16.
54. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: The Indian solid gold. Adv Exp Med Biol 2007;595:1-75.
55. Park SY, Kim HS, Cho EK, Kwon BY, Phark S, Hwang KW, *et al.* Curcumin protected PC12 cells against beta-amyloid-induced toxicity through the inhibition of oxidative damage and tau hyperphosphorylation. Food Chem Toxicol 2008;46:2881-7.
56. Ng TP, Chiam PC, Lee T, Chua HC, Lim L, Kua EH, *et al.* Curry consumption and cognitive function in the elderly. Am J Epidemiol 2006;164:898-906.
57. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M, *et al.* Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer's disease patients. J Alzheimers Dis 2006;10:1-7.
58. Kim H, Park BS, Lee KG, Choi CY, Jang SS, Kim YH, *et al.* Effects of naturally occurring compounds on fibril formation and oxidative stress of beta-amyloid. J Agric Food Chem 2005;53:8537-41.
59. Ono K, Hasegawa K, Naiki H, Yamada M. Curcumin has potent anti-amyloidogenic effects for Alzheimer's beta-amyloid fibrils *in vitro*. J Neurosci Res 2004;75:742-50.
60. Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H. Epigallocatechin-3-gallate and curcumin suppress amyloid beta-induced beta-site APP cleaving enzyme-1 upregulation. Neuroreport 2008;19:1329-33.
61. Lin R, Chen X, Li W, Han Y, Liu P, Pi R, *et al.* Exposure to metal ions regulates mRNA levels of APP and BACE1 in PC12 cells: Blockage by curcumin. Neurosci Lett 2008;440:344-7.
62. Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM, *et al.* The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 2001;21:8370-7.
63. Kim J, Lee HJ, Lee KW. Naturally occurring phytochemicals for the prevention of Alzheimer's disease. J Neurochem 2010;112:1415-30.
64. Perry E, Howes MJ. Medicinal plants and dementia therapy: Herbal hopes for brain aging? CNS Neurosci Ther 2011;17:683-98.
65. Garcia-Alloza M, Robbins EM, Zhang-Nunes SX, Purcell SM, Betensky RA, Raju S, *et al.* Characterization of amyloid deposition in the APPswe/PS1dE9 mouse model of Alzheimer disease. Neurobiol Dis 2006;24:516-24.
66. Liu A, Lou H, Zhao L, Fan P. Validated LC/MS/MS assay for curcumin and tetrahydrocurcumin in rat plasma and application to pharmacokinetic study of phospholipid complex of curcumin. J Pharm Biomed Anal 2006;40:720-7.
67. Kulkarni SK, Bhutani MK, Bishnoi M. Antidepressant activity of curcumin: Involvement of serotonin and dopamine system. Psychopharmacology (Berl) 2008;201:435-42.
68. BAIS S, Chandewar A. Toxicological standardisation of marketed ashwagandha formulations by atomic absorption spectroscopy. Asian J Pharm Clin Res 2013;6:45-8.
69. Kim DS, Park SY, Kim JY. Curcuminoids from *Curcuma longa* L. (*Zingiberaceae*) that protect PC12 rat pheochromocytoma and normal human umbilical vein endothelial cells from βA (1-42) insult. Neurosci Lett 2001;303:57-61.
70. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): A review. Altern Med Rev 2000;5:334-46.
71. Yousuf SK, Majeed R, Ahmad M, Sangwan Pl, Purnima B, Saxsena AK, *et al.* Ring a structural modified derivatives of withaferin a and the evaluation of their cytotoxic potential. Steroids 2011;76:1213-22.
72. Mohan R, Hammers HJ, Bargagna-Mohan P, Zhan XH, Herbstritt CJ, Ruiz A, *et al.* Withaferin a is a potent inhibitor of angiogenesis. Angiogenesis 2004;7:115-22.
73. Thaiparambil JT, Bender L, Ganesh T, Kline E, Patel P, Liu Y, *et al.* Withaferin a inhibits breast cancer invasion and metastasis at sub-cytotoxic doses by inducing vimentin disassembly and serine 56 phosphorylation. Int J Cancer 2011;129:2744-55.
74. Kushwaha S, Soni VK, Singh PK, Bano N, Kumar A, Sangwan RS, *et al. Withania somnifera* chemotypes NMITLI 101R, NMITLI 118R, NMITLI 128R and withaferin A protect *Mastomys coucha* from *Brugia malayi* infection. Parasite Immunol 2012;34:199-209.
75. Kuboyama T, Tohda C, Komatsu K. Neuritic regeneration and synaptic reconstruction induced by withanolide A. Br J Pharmacol 2005;144:961-71.
76. Tohda C, Kuboyama T, Komatsu K. Search for natural products related to regeneration of the neuronal network. Neurosignals 2005;14:34-45.
77. Sehgal N, Gupta A, Valli RK, Joshi SD, Mills JT, Hamel E, *et al. Withania somnifera* reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. Proc Natl Acad Sci U S A 2012;109:3510-5.
78. Jayaprakasam B, Padmanabhan K, Nair MG. Withanamides in *Withania somnifera* fruit protect PC-12 cells from beta-amyloid responsible for Alzheimer's disease. Phytother Res 2010;24:859-63.
79. Kulkarni R, Rao PN, Shailaja U, Pujar M, Sharma G, Ghanti B. Formulation of swarnamritaprashana-a novel Ayurveda electuary. J Ayurveda Holist Med 2017;5:65-84.
80. Cui YM, Ao MZ, Li W, Yu LJ. Effect of glabridin from *Glycyrrhiza glabra* on learning and memory in mice. Planta Med 2008;74:377-80.
81. Sharma PC, Yelne MB, Dennis TJ, Joshi A, Billore KV. Database on medicinal plants used in Ayurveda. India: Central Council for Research in Ayurveda and Siddha; 2000.
82. Singh SS, Pandey SC, Srivastava S, Gupta VS, Patro B, Ghosh AC. Chemistry and medicinal properties of *Tinospora cordifolia* (Guduchi). Indian J Pharmacol 2003;35:83-91.
83. Rawal AK, Muddeshwar MG, Biswas SK. *Rubia cordifolia*, *Fagonia cretica* Linn and *Tinospora cordifolia* exert neuroprotection by modulating the antioxidant system in rat hippocampal slices subjected to oxygen glucose deprivation. BMC Complement Altern Med 2004;4:11.
84. Chulet R, Pradhan P. A review on Rasayana. Pharmacogn Rev 2009;3:229-34.
85. Sharma V, Pandey D. Protective role of *Tinospora cordifolia* against lead-induced hepatotoxicity. Toxicol Int 2010;17:12-7.
86. Yalla Reddy Y, Mohana Lakshmi S, Saravana KA. Review on effect of natural memory enhancing drugs on dementia. Int J Phytopharmacol 2010;1:1-7.
87. Manjrekar PN, Jolly CI, Narayanan S. Comparative studies of the immunomodulatory activity of *Tinospora cordifolia* and *Tinospora sinensis*. Fitoterapia 2000;71:254-7.
88. Bairy KL, Rao Y, Das SK, Kumar KB. Efficacy of *Tinospora cordifolia* on learning and memory in healthy volunteers: A double-blind, randomized, placebo controlled study. Iran J Pharmacol Ther 2004;3:57-60.
89. Agarwal A, Malini S, Bairy KL, Rao MS. Effect of *Tinospora cardifolia* on learning and memory in normal and memory deficit rats. Indian J Pharm 2002;34:339-49.
90. Lekha G, Kumar BP, Rao SN, Arockiasamy I, Mohan K. Cognitive enhancement and neuroprotective effect of *Celastrus paniculatus* Willd. Seed oil (Jyothismati oil) on male Wistar rats. J Pharm Sci Technol 2010;2:130-8.
91. Ali A, Umar D, Farhan M, Basheer B, Baroudi K. Effect of *Brahmyadi churna* (brahmi, shankhapushpi, jatamansi, jyotishmati, vacha, ashwagandha) and tablet shilajatu in essential hypertension: An observational study. J Adv Pharm Technol Res 2015;6:148-53.
92. Battu GR, Mamidipalli SN, Parimi R, Viriyala RK, Patchula RP, Mood LR. Hypoglycemic and anti-hyperglycemic effect of alcoholic extract of *Benincasa hispida* in normal and in alloxan induced diabetic rats. Pharmacog Mag 2007;3:101.
93. Bhalodia YS, Patel NJ, Patel RK, Vaghasiya JD, Jivani NP, Sheth NR. *Benincasa cerifera* ameliorates renal ischemia/reperfusion injury in hyperlipidemic rat. Pharmacog Res 2009;1:406.
94. Bihaqi SW, Singh AP, Tiwari M. Supplementation of *Convolvulus pluricaulis* attenuates scopolamine-induced increased tau and amyloid precursor protein (AβPP) expression in rat brain. Indian J Pharmacol 2012;44:593-8.
95. Chandra TR, Suresh C, Sanghamitra D, Kumar GR. Kanchnara (*Bauhinia variegata* Linn.): A critical review. Int J Ayurveda Pharm Res 2015;3:39-46.
96. Kumar MH, Gupta YK. Antioxidant property of *Celastrus paniculatus* Willd: A possible mechanism in enhancing cognition. Phytomedicine 2002;9:302-11.
97. Patil KS, Suryavanshi J. Effect of *Celastrus paniculatus* Willd. Seed on adjuvant induced arthritis in rats. Pharmacogn Mag 2007;3:177.
98. Arora N, Rai SP. *Celastrus paniculatus*, an endangered Indian medicinal plant with miraculous cognitive and other therapeutic properties: An overview. Int J Pharm Bio Sci 2012;3:290-303.
99. Yelne MB, Sharma PC, Dennis TJ. Database on Medicinal Plants used in Ayurveda. New Delhi: Central Council for Research in Ayurveda and Siddha; 2002. p. 4.
100. Sahu R, Dhongade HJ, Pandey A, Sahu P, Sahu V, Patel D. Medicinal properties of *Nardostachys jatamansi* a review. Orient J Chem 2016;32:859-66.
101. Chatterjee A, Basak B, Saha M, Dutta U, Mukhopadhyay C, Banerji J,

et al. Structure and stereochemistry of nardostachysin, a new terpenoid ester constituent of the rhizomes of *Nardostachys jatamansi*. J Nat Prod 2000;63:1531-3.
102. Ahmad M, Saleem S, Ahmad AS, Ansari MA, Yousuf S, Hoda MN, *et al.* Neuroprotective effects of *Withania somnifera* on 6-hydroxydopamine induced parkinsonism in rats. Hum Exp Toxicol 2005;24:137-47.
103. Joshi H, Parle M. *Nardostachys jatamansi* improves learning and memory in mice. J Med Food 2006;9:113-8.
104. Karkada G, Shenoy KB, Halahalli H, Karanth KS. *Nardostachys jatamansi* extract prevents chronic restraint stress-induced learning and memory deficits in a radial arm maze task. J Nat Sci Biol Med 2012;3:125-32.
105. Ahmeda F, Urooja A, KS R. *In vitro* antioxidant and anticholinesterase activity of *Acorus calamus* and *Nardostachys jatamansi* rhizomes. J Pharm Res 2009;2:830-3.
106. Ahmad M, Yousuf S, Khan MB, Hoda MN, Ahmad AS, Ansari MA, *et al.* Attenuation by *Nardostachys jatamansi* of 6-hydroxydopamine-induced parkinsonism in rats: Behavioral, neurochemical, and immunohistochemical studies. Pharmacol Biochem Behav 2006;83:150-60.
107. Ali A, Dua Y, Siddiqui AW, Sultana S, Rafiullah MR. Inhibition of benzoyl peroxide–induced cutaneous oxidative stress, toxicity, and ear edema in mice by *Nardostachys jatamansi*. Pharm Biol 2005;43:533-9.
108. Singh RH, Narsimhamurthy K, Singh G. Neuronutrient impact of Ayurvedic rasayana therapy in brain aging. Biogerontology 2008;9:369-74.
109. Farina E, Baglio F, Caffarra P, Magnani G, Scarpini E, Appollonio I, *et al.* Frequency and clinical features of lewy body dementia in Italian memory clinics. Acta Biomed 2009;80:57-64.
110. Manyam BV, Dhanasekaran M, Hare TA. Neuroprotective effects of the antiparkinson drug *Mucuna pruriens*. Phytother Res 2004;18:706-12.
111. Sharma H, Chandola HM, Singh G, Basisht G. Utilization of Ayurveda in health care: An approach for prevention, health promotion, and treatment of disease. Part 2 ayurveda in primary health care. J Altern Complement Med 2007;13:1135-50.
112. Misra L, Wagner H. Extraction of bioactive principles from *Mucuna pruriens* seeds. Indian J Biochem Biophys 2007;44:56-60.
113. Yadav SK, Prakash J, Chouhan S, Singh SP. *Mucuna pruriens* seed extract reduces oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in paraquat-induced parkinsonian mouse model. Neurochem Int 2013;62:1039-47.