A REVIEW ON MEDICINAL PLANTS WITH POTENTIAL NOOTROPIC ACTIVITY ALONG WITH ANIMAL MODELS NEEDED FOR THEIR SCREENING

ABSTRACT

Dementia is a brain disorder marked by cognitive dys functioning which causes loss of learning , thinking and memory .Various drugs that possess nootropic activity are used for treatment of dementia but emerges side effects. To overcome these side effects plants with medicinal importance came into existence. India has wide variety of medicinal plants (*Centella asiatica, Clitoria ternatea ,Ginkgo biloba, Curcuma longa etc*) that has been claimed for nootropic activity with limited side effects. Nootropic activity of medicinal plants can be screened with various animals models that has been able to identify chemicals with potential therapeutic efficacy. The current review article rehabilitates knowledge of medicinal plants with nootropic action, as well as the animal models needed to screen them.

Key words : Dementia, medicinal plants, nootropic activity, animal models.

1. INTRODUCTION

Dementia is a brain disorder that causes cognitive deficit which leads to gradual decline of mental health in an individual[1]. Much of the study on dementia has previously focused on the amyloid hypothesis, with amyloid beta (A) being thought to be important in the start and progression of cognitive deficits[2]. The pathogenesis of Alzheimer's disease (AD) was captured in a hypothetical biomarker model in 2010, with an update in 2013, the sequence in the pathology of Alzheimer's disease was recorded in hypothetical biomarker model where A-beta that was the first biomarkers of brain showed abnormalities followed by measures of neurodegeneration with progression of symptoms occurred over time [3].

Dementia was reported in patients suffering from Parkinson's disease that has been investigated in a Parkinson's disease population made up of all traceable individuals living in a designated area (Table 1)[4]. The total incidence of substantial mental illness in sufferer with Parkinsonism was 25%, majority of instances occurred in this group that shows symptoms of cerebral arteriosclerosis (Table 2) . The presence of these basic indicators, such as inactivity, twitching , rigidness, decreased muscular movement or disbalance in posture movements, was used to diagnose Parkinson's disease [4]. People with arteriosclerosis was found to be more prone to dementia as compare to the people without the disease. Demented persons made up 56.4 percent of arteriosclerotic patients and 18.2 percent of non-arteriosclerotic patients. When overall factors such as twitching, stiffness, and decreased muscular movements were examined in various phase of dementia , a significant optimistic connection was discovered in between the severity of the cardinal symptoms and degree of the Dementia. However, this link between rigidity and hypokinesia was substantially stronger than the link between tremor and rigidity [5].

There are about 18 million persons living with dementia worldwide and no of adults that provide support and care to relatives with dementia is growing [6]. Dementia incidence is predicted to rise dramatically as the world's population ages, with more than 130 million individuals expected to be affected by 2050. When examining the prevalence of mental illness or dementia in males and females (Table 3), feminine were somewhat found to be more likely than males to be demented, with 30.9 percent and 25.3 percent. Nevertheless, the presence of dementia was evaluated independently in both males and females, the precise proportions of demented individuals in both sexes were found to be relatively similar[7].There is already a significant influence on dementia patients, their families, and society at large. According to a recent report by WHO the relatives and family members spent on average 5 hours per day providing care for people living with dementia. Caring and cherishing cost for demented people have a money making impact on the medical management and communal services system as a result of the "greying of the globe" and the increasing number of people suffering from dementia. In 2003, the global expenditures of dementia care were predicted to be US$156 billion and it has been questioned whether all people with dementia can be cared for and treated

[8]. In the coming decades, the existing load and global yearly costs of $818 billion USD are likely to rise dramatically [9].

Table 1 : Agewise occurrence, disability in Parkinson's disease patients

Age (years) mean ± SEM	Age at onset (years) mean ± SEM	Duration (years) mean ± SEM	Disability stage 1	2	3	4	5
Idiopathic= 67.9 ± 0.4 (N = 421)	61.6 ± 0.5	7.2 ± 0.3	38*	246	86	29	22
Postencephalitic= 62.6 ± 1.8 (N = 23).	36.2 ± 3.4	27.5 ± 3.4	3	8	6	6	0

*No of patients

Table 2 : Disability stage, arteriosclerosis, demented and non demented

	Disability stage 1	2	3	4	5	Total
Without clinical arteriosclerosis						
Non-demented	33+(100.0)*	169(88.5)	45(69.2)	9(50)	5(41.7)	261(81.8)
Demented	0 (0.0)	22(11.5)	20(30.8)	9(50)	7(58.3)	58(18.2)
With clinical arteriosclerosis						
Non-demented	7(87.5)	34(54.0)	9(33.3)	3(17.7)	1(11.1)	54(43.6)
Demented	1(12.5)	29(48.0)	18(66.7)	14(82.3)	8(88.9)	70(56.4)

+No of patients.

*Percentages of patients.

Table 3 : Prevalence of dementia in various age groups by sexes

	Age group (years)				
	-59	60-69	70-79	80-	Total
Male	5+	18	15	5	43
(N =169)	(15.2)*	(22.0)	(32.6)	(62.5)	(25.4)
Female	6	25	35	19	85
(N= 275)	(20.0)	(21.9)	(33.3)	(73.1)	(30.9)

+No of demented patients in both age group.

*percentage of demented patients in both age group.

Various risk factors are associated with dementia such as oxidative damage, insufficient blood supply to brain and some other coexisting brain disorders such as Alzheimer's and Parkinson's disease [10]. Impairment of learning capacity, cognitive dys functioning, disorientation and lack of thinking ability are some of the common manifestation of dementia [11].

2. NEUROBIOLOGICAL PROCESS OF MEMORY FORMATION

Brain goes through physcial and chemical changes during learning procedures and memory formation that are addressed as synaptic plasticity. Induction of gene expression and engrossment of different signal transduction pathways includes in production of new synapses among nerve cells[61]. Memory can be categorized mainly into three parts, short-term memory(remains for seconds), long-term memory(remains for long time), intermediate long-term memory(remains for days to weeks). The formation of long term memory includes the binding of neurotransmitter to the N-methyl D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor which triggers the molecular events that causes activation of CREB and PKC pathways, leading to formation of new proteins that cement the synaptic connection among two communicating neurons leads to production of long-term memory[62]. Various evidences display the engrossment of NF-kB in the regulation of synaptic plasticity which also revealed the inhibition of NF-kB activity in neurons leads to enhanced cognitive functions[63]. At the initial stage of long-term potentiation (LTP) influx of calcium into NMDA receptor causes activation of calmodulin-dependent protein kinase and

phosphorylation of pre-existing of AMPA glutamate receptor and infusion into the postsynaptic membrane of newly formed AMPA recpetors to glutamate. Receptors of AMPA responds instantly by opening of Na^{2+} and K^{+} ion channels that depolarizes cell membrane. Continuity of large number of electrical stimuli develops LTP. CREB mediated process of transcription leads to synapse-specific structural changes.

3. CURRENT TREATMENT FOR DEMENTIA AND ITS LIMITATIONS

Some nootropics that are currently been used for curing dementia are :- a)Cholinestrase inhibitors such as donepezil, galantamine, and rivastigmine b) NMDA receptor antagonist like memantine, amantadine[12] . These standard drugs are effectual but usually associated with life threatening side effects which diverted the focus towards utilizing the medicinal plants with minimal side effects[13]. These nootropics can help manage the disease to some extent, but they are only used in the short term because they are not a permanent treatment. India contains a large number of medicinal plants that can be utilized for a long time with no negative side effects[14]. Several medicinal plants (*Centella asiatica, Clitoria ternatea, Ginkgo biloba, Curcuma longa*, and others) has been claimed to have nootropic potential with little adverse effects[15].

Memory enhancers are hypothesized that functions by modifying the accessibility of chemicals that are present in neurons (acetylcholine, adrenaline , various enzymes, and the hormones) that are present in brain, improves the oxygen transportation in the brain, or encouraging development in neuron. Herbal medications are the safest types of cognitive enhancers, and they come in supplement form, with micronutrients, saturated fatty acids, certain antioxidants, various amino acids, some minerals, and other natural substance [16]. This practice of using medicinal plants was known to arose initially from India and then followed by China. The world is now progressing towards the implementation of medicinal plants to combat the diseases [17].

Various models of animals in the history has played important role in drug development to check memory. Memory is a procedure in which acquisition of knowledge and retentivity of that knowledge takes place[18]. To overcome these problem of neurodegenerative disorders it is necessary that each drug needs to be appraise in a precise manner to ensure their superior convincingness. This could be feasible only when appropriate animal models are selected for their screening. Therefore various animal models can be used to screen the nootropic activity of medicinal plants that has been able to identify chemicals with potential therapeutic efficacy [19].

The understanding of several medicinal plants that has been claimed to have nootropic action, as well as the numerous animal models necessary to screen them, will be Highlighted in this current review article.

4. MEDICINAL PLANTS WITH NOOTROPIC ACTIVITY

4.1 *Centella asiatica*

Centella asiatica L. is a perennial plant commonly known as gotu kola belongs to Apiaceae family. This whole fresh plant is utilised as a cognitive enhancer for therapeutic purposes [20]. *Centella asiatica* is the herb that has the tendency to boost awareness interval, concentration, and revitalize peripheral nervous system and cerebrum. [21]. *Centella asiatica* hinders memory impairment induced by scopolamine through the inhibition of AChE [22].

Fig :- 1 *Centella asiatica*

4.2 *Ginkgo biloba*

Ginkgo biloba belongs to Ginkgoaceae family, also called as kew tree [23]. *Ginkgo biloba* serves as an antioxidant by removing free radicals, helps to increase oxygen supply and improves behavioral modification for memory enhancement. In vitro study has shown that extract of ginkgo has anti amyloid effect[24]. This extract also believed to increases transthyretin RNA levels which is a part of beta-amyloid transport mechanism that inhibits further amyloid deposition in brain [25].

Fig :- 2 *Ginkgo biloba*

4.3 *Clitoria ternatea*

Clitoria ternatea of Fabaceae family is commonly known as butterfly pea [26]. Dose of 100mg/kg of aqueous root extract when administer to young adult rat groups for 30 days period and to neonatal raised the content of Ach in hippocampus when compare to aged match control groups[27]. Increased content of Ach in hippocampus may also consider as a basis of neurochemical for their upgrade learning process and memory [28].

Fig :- 3 *Clitoria ternatea*

4.4 *Emblica officinalis*

Emblica officinalis is a transient plant of family Phyllanthaceae also called as amla . Ayurvedic composition of *Emblica officinalis* acquire some evidences that shows their memory enhancing effects and has been demonstrated as effective cure in the Alzheimer's disease management. Therefore amla acts as potent memory enhancer that ascribe to its quality of reducing brain cholinesterase activity[29].

Fig :- 4 *Emblica officinalis*

4.5 *Sesamum indicum*

Sesamum indicum is also known as sesame belongs to Pedaliaceae family. Extensively distributed all around the world and is harvested for its palatable seeds that grows in shell. Some plentiful glycosides that are mostly found in *Sesamum indicum* are sesaminol glycosides which is a lignan glycosides that shows their presence in the seeds of seasame. The protective factor against Abeta-induced learning and memory deficits in morris water maze test was dietary sesaminol. [30].

Fig :- 5 *Sesamum indicum*

4.6 *Evolvulus alsinoides*

Shankhpushpi is another name of *Evolvulus alsinoides* belongs to Convolvulaceae family .This herb is used as nootropic as it possesses memory potentiating, anxiolytic and tranquilizing properties. In a study this has been claimed that various extracts of *Evolvulus alsinoides* improves learning an memory in rats [31].

Fig :- 6 *Evolvulus alsinoides*

4.7 *Bacopa monnieri*

Bacopa monnieri commonly called as brahmi is one of the members of the Scrophulariaceae family . This plant is known for its various therapeutics aspects such as memory enhancer, hepatoprotective, cognitive enhancer and tranquilizing effects. Presence of saponin triterpenoid which is also called as bacosides are responsible for memory enhancement [32].

Fig :- 7 *Bacopa monnieri*

4.8 *Celastrus paniculatus*

Celastrus paniculatus , also known as jyotishmati belongs to Celastraceae family [33]. Aqueous seed extract of *Celastrus paniculatus* improves memory and cognitive function . This plant has shown antiarthritic and antioxidant effects in rat model [34].

Fig :- 8 *Celastrus paniculatus*

4.9 *Curcuma longa*

Curcuma longa belongs to Zingiberaceae family, also known as haldi .*Curcuma longa* possess various therapeutic aspects such as anti-depressant, anti-cancer , hepatoprotective, anti-tumor and anti viral [35]. Extracts of *Curcuma longa* as aqueous reported antidepressant activity in reduction of brain monoamine oxidase type A [36].

Fig :- 9 *Curcuma longa*

4.10 *Prunus amygladus*

Prunus amygladus commonly called as (Badam) used as cognitive enhancer. Various parameters like memory and learning, total cholesterol levels and cholinesterase activity were determined using elevated plus maze[51]. In rats *Prunus amygladus* reduced the brain cholinesterase activity. *Prunus amylgladus* demonstrated as a useful memory restoring agent. The potential of this plant would be explore further for the management of Alzheimer's disease [52].

Fig :- 10 *Prunus amygladus*

4.11 *Vitis vinifera*

Aerial parts of the plant *Vitis vinifera* have been used in Ayurveda system for the treatment of various stress related disorders[51]. The extract of the seed part of *Vitis vinifera* was evaluated for antistress activity in stress induced rats and normal rats[53]. The methanolic resin extract of *Vitis vinifera* at a dose of 30 mg/kg significantly exhibit nootropic activity in elevated plus maze and in passive shock avoidance[54].

Fig :- 11 *Vitis vinifera*

4.12 *Thespesia populnea*

Indian tulip tree is another name of *Thespesia populnea* a large tree mainly found in coastal forests of India and in tropical regions. Several parts of *Thespesia populnea* possess medicinal properties such as antibacterial, anti-inflammatory and antifertility. By using passive avoidance and elevated plus maze various learning and memory parameters are assessed. Bark of *Thespesia populnea* showed powerful memory enhancing activity in mice[55].

Fig :- 12 *Thespesia populnea*

4.13 *Hibiscus sabdariffa*

Aqueous extract of calyces of *Hibiscus sabdariffa* at 100 and 200 mg/kg showed nootropic activity in mice. As the latency transfer and increased step down latency are decreased in aged mice and in amnesic mice treated with scopolamine. Acetyl cholinesterase activity also decreased when compared with piracetam (200 mg/kg)[56].

Fig :- 13 *Hibiscus sabdariffa*

4.14 *Rubia cordifolia*

Rubia cordifolia is also known as Indian madder. Alcoholic root extract of *Rubia cordifolia* possess the enhancement in brain gamma-amino-n-butyric acid (GABA) levels and decrease in plasma corticosterone and brain dopamine levels. Scopolamine induced learning and memory impairment are also antagonised[57].

Fig :- 14 *Rubia cordifolia*

4.15 *Eclipta alba*

Eclipta alba (Bhringraj) contains a wide variety of phytoconstituents which includes glycosides, polyacetylenes, flavonoids, triterpenoids and alkaloids. *Eclipta alba* is widely used as it possess various medicinal properties like nootropic, muscle-relaxant, sedative, anti-stress and anxiolytic activities[58]. *Eclipta alba* has potential neuropharmacological activity as a nootropic also having the property of attenuating stress induced alterations[59].

Fig :- 15 *Eclipta alba*

5. VARIOUS ANIMAL MODELS TO SCREEN NOOTROPIC ACTIVITY

5.1 Morris water maze test

The assembly of maze contains a pool which was circular (121 cm diameter, 52 cm height) and has a inner surface that was filled with water. Water present in the pool was pigmented with black dyes that was non toxic and were used to conceal the position of platform[37]. When the rat was placed on the position of the stage could climb the stage to get away from the essential of floating. During 4 consecutive days the rats were trained with the platform in their place for 120 sec and were allowed to stay on the platform for 30 s [38]. The rats that were failed to stay on the stage are detached from the maze. Individually rats were subjected to a trial session for 5 days and latency time during each trial was determined [39]. According to Lakkireddy et al. aqueous leaves extract of *Spinacia oleracea* at a dose of 200 mg/kg and 400 mg/kg showed improvement of learning and memory respectively[39].

5.2 Elevated plus maze

This apparatus was used to detect the retention of learning and memory . This assembly contains 2 arms that was open (15 cm x 5 cm) along with arms that has two covers (16 cm x 5 cm x 13 cm). From the central platform the arms were extended (11 cm x 11 cm) and was uplifted to a height of 25 cm from the ground that gives the apparatus a plus sign appearance [40]. In the beginning of first day towards the end of the open arm each mouse was placed that was apart from the centre stage. When the mouse move into any one of the cover arms along with its all 4 legs that time was considered as latency transfer[41]. The mouse was permitted to analyze the maze for 20 sec and then get back to their cage. Retention of memory was determined after 24 hours for the first day trial and on the second day [42]. According to M.Bhanumathy et al. the extract of *Celastrus paniculatus* at a dose of (350 and 1050 mg/kg) when administered to rats showed enhancement of cognitive functions in rats[40].

5.3 Passive avoidance test

The avoidance behavior was examined using apparatus that was light dark and consists of a box (26 cm x 26 cm x 26 cm) having three walls of wood and one wall of plexiglass featuring a wooden platform (11 cm x 6 cm x1.8 cm) in the midpoint of the ground [43]. Compartment that was painted white was lighten up with 10 W bulb, inside the chamber was painted black. The wooden platform that was located in the centre of the grid floor each mouse was gently placed on that platform[44]. When all the paws of mouse goes down on grid floor the shocks were transfered for 20 sec during that time the latency of going down was determined [45]. Another time animals need to test were eliminated from the zone that was shock free if they do

not goes down for 60 sec. Retention was tested after every 24 hours in a similar manner. According to Vikas Kumar et al. the ethanolic extract of Indian *Hypericum perforatum* Linn. at a dose of 200 mg/kg causes significant reversal of scopolamine impaired Piracetam retention in rats[44].

5.4 Radial arm maze task performance

In this experiment radial arm maze was employed. This apparatus was uplifted 50 cm exceeding the floor consists a centre 36 cm in diameter that contains eight radial arms. Each and every arm has dimension (44 cm x 15 cm x 12 cm) the total diet at which mouse was maintained was 85% and regularly was revealed to the maze ,the food pellet was present in the fixed arm succeed for 7 days for drug treatment. After each trial the apparatus was cleaned to avoid the presence of evidences. On 7 day the appraisal was carted out after 60 minutes of drug treatment. The measurement of memory that was working can be evaluated on the basis of the time that has been taken by mouse in search of food [46].

5.5 Step through

This method contains a chamber that was small in size connected to bigger chamber which was dark inside through doorway . The chamber that was small in size was lighten up with 12 V lamp. Animals to be tested was given acquirement trial along with maintenance trial after 24 hours. In the acquirement trial animals were placed in the chamber that was lighten up with lamp, maximized distance from door and dormancy to enter the compartment of dark side was measured [47]. Instantly when the animals entered the dark compartment the gate was closed spontaneously and unpreventable foot shock was transfered. Finally during learning phase the time taken to step-through was examined and and time utilized during retention was determined [48].

5.6 Olfactory learning

In this model 48 h before training the animals were fasted and meanwhile during the test they received water for time period of 30 min[49]. This assembly contains of a box which was rectangular in shape (31 cm x 31 cm x 56 cm) along with light sensitive cell placed on uppermost of outlet. Responses towards positive odor was renumerated with presence of water and feedback towards negative odor was marked as light flash. The experiment was terminated when the rat makes 99 % correct choices. Final result was reported in terms of % correct responses [50].

5.7 Rectangular maze test

This method was carried out with a rectangular box which has an entrance and a reward chamber that was separated with wooden band that splits into unseen passages departing a corridor from the entrance to reward chamber . In the beginning for a time period of 20 min all the mice were acquaint with rectangular maze. This was considered as tutoring session. On the 3 day the mice was positioned in the entrance chamber and the time was actuated immediately after the exit of mouse from maze. The time period by which the rats grasp to the reward chamber was considered as latency time. Higher scored indicates poor learning in animals while lower scored indicate efficient learning. According to Lakkireddy et al. *Spinacia oleracea* significantly improved the tasks of learning and retained the stored information when compared with previous studies[39,60].

6. CONCLUSION

Dementia is characterized as brain disorder that causes loss of learning, memory impairment, disorientation. Different risks are marked such as oxidative damage , insufficient blood supply to brain. Treatments available for this disorder are cholinesterase inhibitors, N-methyl-D-aspartate antagonist. These nootropics can manage the disease to a certain extent and could be effectual but are associated with certain limits and side effects. Naturally occurring medicinal plants could be economically feasible treatment to a great extent. The medicinal plants that has been claimed for nootropic activity could be used for long term because of their memory enhancing effects. Various models of animals in the history has played important role in drug development to check memory. This current review article expressed strong evidences that shows the different extracts of these medicinal plants would possibly act as the treatment of dementia and an endeavor has been made to accumulate all the accessible knowledge about various methods used to determine memory enhancing activity therefore would be helpful for the investigators to gain all the needed knowledge at one place during their research about these methods.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Blennow K, Zetterberg H, Rinne JO, Salloway S, Wei J, Black R. Effect of immunotheraphy 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. Jack CR, Jr, Knopman DS, Jagust WJ . Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013;12(2): 207-216.

4. Hoehn, MM, MD Yahr. Parkinsonism: onset, progression and mortality. Neurology Minnep .1967;17:427-442.

5. Garron, DC, HL Klawans, F Narin. Intellectual functioning of persons with idiopathic parkinsonism. J.nerv.ment.Dis.1972;154(6):445-452.

6. Torti FMJ, Gwyther LP, Reed SD, Friedman JY, Schulman KA. A multinational review of recent trends and reports in dementia caregiver burden. Alzheimer Dis Assoc Disord.2004;18 : 99–109.

7. RJ Marttila, UK Rinne.Epidemiology of Parkinson's disease—An overview.1981;51:135-148.

8. Larissa Schwarzkopf, Petra Menn, Simone Kunz . Cost of Care for Dementia Patients in Community Setting : An Analysis for Mild and Moderate Disease Stage. Value in Health.2011; 14 : 827-835.

9. Wimo A, Jonsson L, Winblad B . An Estimate of the worldwide prevalence and direct costs of dementia in. Dement Geriatr Cogn Disord.2003; 21: 175–81.

10. Devesh Tewari, Adrian M Stankiewicz, Andrei Mocan, Archana N Sah, Nikolay T Tzvetkov, Lukasz Huminiecki, Jaroslaw O Horbanczuk, Atanas G Atanasov. Ethnopharmacological Approaches for Dementia Therapy and Significance of Natural Products and Herbal Drugs. Front. Aging Neurosci. 2018;10(3):1-24.

11. Sangeeta Paul, Balawant Rajawat, Rishu Tiwari . Plants with nootropic activity : A Review. World J. Pharm. Res. 2015;4(6):591-607.

12. Preksha Dwivedi, Richa Singh, Mohd Tabish Malik, Talha Jawaid. A Traditional approach to Herbal Nootropics Agent: An Overview.IJSR.2012;3(3):630-636.

13. Sagarika Biswas, Deeksha Kaloni, Debolina Ckakraborty . A review on the efficacy of phytomedicines for Rheumatoid arthritis. AJMP.2020; 8(12):179-190.

14. Nabi NU. Natural remedies for improving learning and memory-Review. Int.J. Pharmaceutical and phytopharmacological Research.2014;3(2):161-165.

15. MD Sahab, Bijo Mathew, George E Barreto . Nootropic and Anti-Alzheimer's actions of medicinal plants : Molecular Insight Therapeutic Potential to Alleviate Alzheimer's Neuropathology. Mol. Neurobiol. 2019;56 : 4925-4944.

16. Joshi Pranav C . A review on natural memory enhancers (Nootropics). UJEAS. 2013;1(1): 8-18.

17. Pandey M, Debnath M , Gupta S, Chikara S . Phytomedicine : An ancient approach turning into future potential source of therapeutics. J. Pharmacogn. Phytother. 2011;3(2): 27-37.

18. Crawely Behavioural J.N. phenotyping of transgenic and knockout mice: experimental design and evaluation of general health , sensory functions, motor abilities and specific behavioural test. Brain Res.1999;57:61-64.

19. Avneet Gupta, Hemraj, Sunny Jalhan, Anil Jindal, Neeraj Upmanyu . Various Animal Models to Check Learning and Memory – A Review: Int. J. Pharm. Pharm. Sci. 2012;4(3): 91-95.

20. Reena Kulkarni, Girish KJ, Abhimanyu Kumar . Nootropic herbs (Medhya Rasayana) in Ayurveda : An update. Pharmacogn. Rev.2012; 6(12) : 147-153.

21. Brinkhaus B, Lindner M, Schuppan D, Hahn EG . Chemical, pharmacological and clinical profile of the East Asian medical plant Centella Asiatica. Phytomedicine 2000;7(5): 427-448.

22. Russo A, Borrelli F. Bacopa monniera, a reputed nootropic plant : An overview. Phytomed. 2005;12(4) : 305-17.

23. Bharti Goel, Neelesh Kumar Maurya . Memory Booster Herb (natural cognitive enhancers) – An Overview. Int. J. Physiol. 2019;4(1): 975-979.

24. Mattioli L , Perfumi M. Effects of a Rhodiola rosea L.extract on acquisition and expression of morphine tolerance and dependence in mice. J Psychopharmacol.2011;25:411-420.

25. Rathee P, Chaudhary H, Rathee S, Rathee D . Natural memory boosters. Phcog. Rev.2008; 2 (4): 249-56.

26. Piya Kosai, Kanjana Sirisidthi, Kanitta Jiraungkoorskul, Wanne Jiraungkoorskul. Review on Ethnomedicinal uses of memory boosting herb, butterfly pea, clitoria ternatea. J. Natural Remedies.2015;15(2):71-76.

27. Pulok K Mukherjee, Venkatesan Kumar, N Satheesh Kumar, Michael Heinrich.The Ayurvedic medicine Clitoria ternatea--from traditional use to scientific assessment.J. Ethnopharmacol. 2008;120(3) : 291-301

28. Rai KS, Murthy KD, Karanth KS, Rao MS . Clitoria ternatea (linn) root extract treatment during growth spurt period enhances learning and memory in rats. Indian J. Physiol. Pharmacol.2001; 45(3) : 305-313.

29. Singh HK, Dhawan BN . Neuropsychooharmacological effects of the Ayurvedic nootropic Bacopa monniera linn (Brahmi). Indian J. Pharmacol. 1997;29 : 359-65.

30. Woodruff-Pak DS, Wenk GL . Galantamine : effect on nicotinic receptor binding, acetylcholinesterase inhibition and learning. Proc. Natl. Acad. Sci. USA.2001; 98(4) : 2089-94.

31. Lee D, Park J, Yoon J, Kim MY ,Choi HY, Kim H . Neuroprotective effects of Eleutherococcus senticosus bark on transient global cerebral ischemia in rats. J. Ethnopharmacol.2012; 139 (1): 6-11.

32. Jatwa V, Khirwadkar P, Dashora K . Indian traditional memory enhancing herbs and their medicinal benefits. IJRPB. 2014;2(1): 1030-1037.

33. Yong QT, Yao ZC, Da GW, Xian MZ, Xiao JH . Sesquiterpenoids from Celastrus paniculatus. J. Nat. Prod. 1993;56 : 122-5.

34. Kumar MH, Gupta YK . Antioxidant property of Celastrus paniculatus willd. A possible mechanism in enhancing cognition. Phytomedicine. 2002;9(4) : 302-11.

35. Ashraf K, Sultan S .A Comprehensive Review on Curcuma Longa: Phytochemical, Pharmacological and Molecular Study. Int. J. Green Pharm.2017;11(4): S671-685.

36. Perry E, Howes MJ, . Medicinal plants and dementia therapy : Herbal hopes for brain aging. CNS. Neurosci. 2011;17(6): 683-98.

37. Pawar Madhuri S, Gurav Kunal, Karandikar Yogita, Wele Asmita . Assessment of Nootropic activity of Vachadi Ghrita, A medicated ghee formulation using animal models. World J. Pharm. Pharm Sci. 2016;5(1) : 629-638.

38. Morris R . Development of water maze procedure for studying spatial learning in the rat. J. Neurosci. Meth. 1984;11(1): 163-169.

39. Lakkireddy Rachana Reddy, Kulandaivelu Umasankar, Bandaru Sheshagiri Sharavana Bhava, Eggadi Venkateshwarlu . Evaluation of Nootropic activity of Spinacia oleracea in Scopolamine Induced Cognitive Decline Mice. Rees. J. Med. Plants. 2019;13(4): 155-161.

40. M Bhanumathy, MS Harish, HN Shivaprasad, G Sushma . Nootropic activity of Celastrus paniculatus seed. Pharm. Biol.2010; 48(3): 324-327.

41. Verma A, Kulkarni S.K. Effect of a herbal psychotropic preparation, BR-16A(Mentat), on performance of mice on Elevated plus maze. Ind.J. Experimental biology.1991;29:1120.

42. Parle M, Dhingra D . Ascorbic acid : a promising memory enhancer in mice . J. Pharmacol. Sci. 2003;93(2): 129-35.

43. Joshi H, Parle M . Effects of piperine on memory and behaviour mediated via monoamine neurotransmitters. J. Trad Med. 2005;2: 39-43.

44. Vikas Kumar, PN Singh, AV Muruganandam, SK Bhattacharya. Effect of Indian Hypericum Perforatum Linn on animal models of cognitive dysfunction. J. Ethnopharmacol. 2000;72 : 119-128.

45. Parle M,Vasudevan M,Singh N. Swim everyday to keep dementia away.J. Sports Science and Medicine.2005;4:37-46.

46. Amir Farshchi, Globarg Ghiasi, Samireh Farshchi, Payman Malek Khatabi. Effects of Boswellia Papyrifera Gum Extract on Learning and Memory in Mice and Rats.2010;13(2):9-15.

47. King RA, Glasser RL . Duration of electro convulsive shock induced retrograde amnesia in rats. Physiol Behav . 1970;5(3): 335-339.

48. Jarvik ME, Kopp R . An improved one trial learning situation in mice. Psychol Rep. 1967;21(1): 221-224.

49. Vanover KE, Barrett JE. An automated learning and memory model in mice: pharmacological and behavioral evaluation of an autoshaped response.Beha Pharmacol.1998;9:273-283.

50. Roman FS, Simonetto I, Soumireu MB . Learning and memory of odor-reward association : selective impairment following horizontal diagonal band lesions. Behav. Neurosci. 1993;107: 72-81.

51. Mukesh Kumar, S.K. Singh, J.S. Tripathi, Y.B. Tripathi. Medicinal plants with nootropic effects : A Review. European j. biomed. Pharm. Sci. 2016; 3(8):128-132.

52. Kulkarni KS, Kasture SB, Mengi S. Efficacy study of Prunus amygdalus (almond) nuts in scopolamine induced amnesia in rats. Indian Journal of Pharmacology. 2010; 42(3): 168-73.

53. Satyanarayana Sreemantula, Srinivas Nammi, Rajabhanu Kolanukonda, Sushruta Koppula and Krishna M Boini. Adaptogenic and nootropic activities of aqueous extract of Vitis vinifera (grape seed): an experimental study in rat model BioMed Central .2005; 5(1):1-8.

54. Kakad VD, Mohan M, Kasture VS and Kasture SB. Effect of Vitis vinifera on memory and behaviour mediated by monoamines. Journal of Natural Remedies. 2008; 8(2): 164 – 172.

55. M. Vasudevan and M. Parle, Pharmacological actions of Thespesia populnea relevant to Alzheimer's disease. Phytomedicine. 2006; 13(9-10): 677-687.

56. Joshi H, Parle M. Nootropic Activity of Calyces of Hibiscus sabdariffa Linn. Iranian Journal of Pharmacology and Therapeutics.2006; 5(1): 15-20.

57. Patil RA, Jagdale SC, Kasture SB. Antihyperglycemic, antistress and nootropic activity of roots of Rubia cordifolia Linn. Indian Journal of Experimental Biology. 2006; 44(12): 987-92.

58. Wagner H. et al. Coumestans as the main active principles of the liver drugs Eclipta alba and Wedelia Calendulaceae. Planta Med.1986; 5: 370- 74.

59. V.D. Thakur and S.A. Mengi. Neuropharmacological profile of Eclipta alba (Linn.) Hassk. Journal of Ethnopharmacology. 2005; 102(1): 23-31.

60. Kouémou, N.E., G.S. Taiwe, F.C. Moto, S. Pale and G.T. Ngoupaye *et al*. Nootropic and neuroprotective effects of *Dichrocephala integrifolia* on scopolamine mouse model of Alzheimer's disease. Front. Pharmacol. 2017; 8.

61. Tully T, Bourtchouladze R, Scott R, Tallman J. Targeting the CREB pathway for memory enhancers. Nat Rev Drug Discov. 2003; 2 : 267-77.

62. Lynch G. AMPA receptor modulators as cognitive enhancers. Curr Opin Pharmacol. 2004; 4: 4-11.

63. 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.