



A Review on Medicinal Plants with Potential Nootropic Activity along with Animal Models Needed for their Screening

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Dementia is a brain disorder marked by cognitive dysfunctioning 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 animal 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.

Keywords: 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

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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 , rigidity, 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

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

+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 (N=169)	5 ⁺ (15.2)*	18(22.0)	15(32.6)	5(62.5)	43(25.4)
Female (N=275)	6(20.0)	25(21.9)	35(33.3)	19(73.1)	85(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 dysfunctioning, disorientation and lack of thinking ability are some of the common manifestation of dementia [11].

2. NEUROBIOLOGICAL PROCESS OF MEMORY FORMATION

Brain goes through physical 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 [12]. 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 [13]. 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 [14]. 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 receptors to glutamate. Receptors of AMPA responds instantly by opening of Na²⁺ 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)Cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine b) NMDA receptor antagonist like memantine, amantadine [15]. 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 [16]. 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[17]. Several medicinal plants (*Centella asiatica*, *Clitoria ternatea*, *Ginkgo biloba*, *Curcuma longa*, and others) has been claimed to have nootropic potential with little adverse effects [18].

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 [19]. 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 [20].

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 [21]. 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 [22].

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 [23]. *Centella asiatica* is the herb that has the tendency to boost awareness interval, concentration, and revitalize peripheral nervous system and cerebrum. [24]. *Centella asiatica* hinders memory impairment induced by scopolamine through the inhibition of AChE [25].



Fig. 1. *Centella asiatica*

4.2 *Ginkgo biloba*

Ginkgo biloba belongs to Ginkgoaceae family, also called as kew tree [26]. *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 [27]. 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 [28].



Fig. 2. *Ginkgo biloba*

4.3 *Clitoria ternatea*

Clitoria ternatea of Fabaceae family is commonly known as butterfly pea [29]. 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 [30]. Increased content of Ach in hippocampus may also consider as a basis of neurochemical for their upgrade learning process and memory [31].



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 [32].



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 sesame. The protective factor against Abeta-induced learning and memory deficits in morris water maze test was dietary sesaminol [33].



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 [34].



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 [35].



Fig. 7. *Bacopa monnieri*

4.8 *Celastrus paniculatus*

Celastrus paniculatus , also known as jyotishmati belongs to Celastraceae family [36]. Aqueous

seed extract of *Celastrus paniculatus* improves memory and cognitive function. This plant has shown antiarthritic and antioxidant effects in rat model [37].



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 [38]. Extracts of *Curcuma longa* as aqueous reported antidepressant activity in reduction of brain monoamine oxidase type A [39].



Fig. 9. *Curcuma longa*

4.10 *Prunus amygdalus*

Prunus amygdalus 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 [40]. In rats *Prunus amygdalus* reduced the brain cholinesterase activity. *Prunus amygdalus* demonstrated as a useful memory restoring agent. The potential of this plant would be explore further for the management of Alzheimer's disease [41].



Fig. 10. *Prunus amygdalus*

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 [40]. The extract of the seed part of *Vitis vinifera* was evaluated for antistress activity in stress induced rats and normal rats [41]. 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 [42].



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 [43].



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) [44].



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 [45].



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 [46]. *Eclipta alba* has potential neuropharmacological activity as a nootropic also having the property of attenuating stress induced alterations [47].

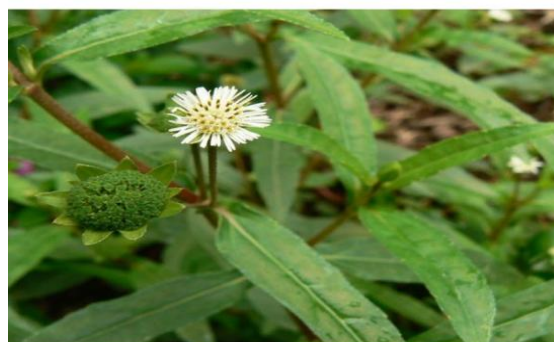


Fig. 15. *Eclipta alba*

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[48]. 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 [49]. 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 [50]. 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 [50].

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 [51]. 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 [52]. 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 [53]. 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 [54].

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 x 1.8 cm) in the midpoint of the ground [55]. Compartment that was painted white was lightened 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 [56]. When all the paws of mouse goes down on grid floor the shocks were transferred for 20 sec during that time the latency of going down was determined [57]. 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 [58].

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 [59].

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 lightened 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 lightened up with lamp, maximized distance from door and dormancy to enter the compartment of dark side was measured [60]. Instantly when the animals entered the dark compartment the gate was closed spontaneously and unpreventable foot shock was transferred. Finally during learning phase the time taken to step-through was examined and time utilized during retention was determined [61].

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 [62]. 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 remunerated 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 [62].

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 acquainted 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 [63].

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.

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