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Nootropic potential of *Alternanthera sessilis* and *Clerodendrum infortunatum* leaves on mice

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ABSTRACT

Objective: To ascertain the nootropic potential (memory enhancing effects) of the leaves of *Alternanthera sessilis* (Amaranthaceae) and *Clerodendrum infortunatum* (Verbenaceae) using rectangular maze and Y maze (interoceptive behavioral models) **Methods:** Methanolic extracts of leaves *Alternanthera sessilis* and *Clerodendrum infortunatum* dosed at 100 and 200 mg/kg each were administered to adult Swiss albino Wistar mice and the effect on acquisition, retention and retrieval of spatial recognition memory was determined. *Bacopa monniera* extract was used as the standard drug while Scopolamine hydrobromide served as the amnestic agent. **Results:** The higher doses of both the extracts exhibited a more promising nootropic potential. Maximal response was observed in the 200 mg/kg dose of *Clerodendrum infortunatum* methanolic extract, which closely approximated the results for the standard drug Brahmi. Both the higher doses elicited greater responses in both the models studied and were comparable to that achieved with the standard drug. **Conclusions:** The methanolic extracts of *Clerodendrum infortunatum* afforded greater memory enhancing effects in comparison to *Alternanthera sessilis* extract, the higher dose evoking pronounced alteration behavior and better learning assessments.

1. Introduction

According to the world health report (WHO 2001) approximately 450 million people suffer from a mental or behavioral disorder, yet only a small minority of them receive even the most basic treatment this amount to 12.3% of the global burden of disease and will rise to 15% by 2020.[1] Drug acting in the central nervous system were among the first to be discovered by the primitive human and are still the most widely used group of pharmacological agents. The CNS acting drugs are invaluable therapeutically, because they can produce specific physiological and psychological effects from the vast array of Materia Medica of the indigenous system so many plants have been reported to have activity against CNS disorders and thus act as very useful remedies for the alleviation of human suffering.[2] In the search of new therapeutic product for the treatment of neurological disorder medicinal plant research worldwide has progressed constantly, demonstrating the pharmacological effectiveness of different plant species in a variety of animal models.[1]

Clerodendrum infortunatum (Verbenaceae) commonly known as Bhat is an important and widely used medicinal plant, reported to contain active bitter substance like clerodin, has been widely used as tonic and anthelmintic agent in the countryside's of North India.[3] As reported in Ayurveda, the plant has a bitter pungent taste and is tonic, aphrodisiac, antipyretic, anthelmintic, also useful in biliousness, "kapha", "tridosha", leucoderma, thirst, burning sensations, foul odor and diseases of blood. *Alternanthera sessilis* (Amaranthaceae) commonly known as Gudari saag, Matsyaakshi, distributed in warmer parts of India ascending to an altitude of 1200m is a herbaceous branched weed possessing significant medicinal value. It is used as lactogogue, galactogogue, abortifacient and febrifuge.[4] The plant is rich in saturated hydrocarbons, aliphatic ester, stigmasterol and ß-sitosterol.[5] Petroleum ether extract of plant was reported to yield nonacosane, 16-hentriacontane, ß-sitosterol, stigmasterol and handianol.

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[6] In Ayurveda, traditional practitioners like Charak and Shushruta have used various plants, or their combinations to study their effect on C.N.S. or on memory, also modern writers like Sukhdev and Khare have also discussed such plants in their books, further there are reports of role of ß sitosterol in overall health like improving cardiovascular efficiency and memory. [7] β – sitosterol and its glycoside in *Alternanthera sessilis* possess potent anti-inflammatory and antipyretic activity.[8] Also *A.sessilis* is a potential source of natural antioxidant. [9] Antioxidant carotene is found in large amounts in *Alternanthera sessilis*, useful in night blindness. Siddha literature mentioned *Alternanthera sessilis* as Kaya Kalpa drug (i.e. drug which prevents and cures chronic diseases and rejuvenates the body) and as compatible diet. The Antidiabetic activity of *A. sessilis* can be attributed to the presence triterpenoids, phytosterols and glycosides. [10] Ethanolic extract of *Alternanthera sessilis* produced significant ($P<0.01$) memory enhancing activity when evaluated by elevated plus maze model. [11] Both aqueous and ethanolic extracts of aerial parts of *Alternanthera sessilis* Linn. possess significant nootropic potential in the view of its facilitatory effect on the retention of acquired learning and retention. [12] The preliminary phytochemical screening carried out on *Clerodendron infortunatum* Linn root indicated the presence of carbohydrates, starch, mucilage, saponins, flavanoids, tannins, phenolic compounds. [13] Methanol extract of *C. infortunatum* Linn. Exhibited anticonvulsant activity. [14] Saponin from the leaves of *C. infortunatum* has analgesic and anticonvulsant effects in mice. [15] Saponins isolated from aqueous extract of leaves of *Clerodendron infortunatum* has potential anticonvulsant activity in swiss albino mice. [16] The ethanolic extract of the leaves of *Clerodendrum infortunatum* Linn. possess antioxidant activity due to flavonoids. [17] Ethanolic and hexane fractions of *Alternanthera sessilis* has a potent hepatoprotective action against CCl_4 induced hepatic damage in rats. [18] There are few synthetic medicines, e.g., tacrine, donepezil and the natural product – based rivastigmine and galatamine to treat cognitive dysfunction and memory loss associated with Alzheimer's disease. These approved drugs are limited in use due to their adverse side effects such as gastrointestinal disturbances and bioavailability problems. [12] Both these medicinally important plants i.e. *Alternanthera Sessilis* and *Clerodendrum Infortunatum* find mention in the traditional texts, of possessing nootropic properties. However the same is of little use in the absence of scientific validation. Therefore an attempt has been made to evaluate the learning and memory potential of methanolic extracts of *Clerodendrum infortunatum* and *Alternanthera sessilis* leaves on the interoceptive behavioral model (scopolamine induced amnesia producing transient memory impairment).

Materials and methods

1. Experimental animals

Adult Swiss albino Wistar mice of either sex weighing between 25-30 g procured from our animal house were housed under standard environmental conditions (25± 1 ℃, 55±5% humidity and 12 h/12 h light/dark cycle). The animals were allowed free access to tap water and standard laboratory rat food. The care and handling of mice were in accordance with the internationally accepted standard guidelines for use of animals, and the protocol was approved by our Institutional Animal Ethics Committee under the CPSCEA. (BBDNITM/IAEC/02/2010).

2. Drugs and chemicals

Bacopa monniera extract (Brahmi, Himalaya Herbal Healthcare, Bangalore, India), Scopolamine hydrobromide (Sigma Aldrich, USA), Normal saline (used as vehicle for Scopolamine HBr)

3. Plant material & preparation of extracts

The plant materials were collected from local areas of Lucknow, Uttar Pradesh and were authenticated from National Botanical Research Institute, Lucknow by depositing a herbarium (Ref No. NBRI/PH/4-5-1/51) and was identified as *Alternanthera sessilis* and *Clerodendrum infortunatum*. The leaves were shade dried at room temperature for more than two weeks and were powdered finely for extraction. The dried powdered drug (leaves) 200 g was Soxhlet extracted for a 72 hour cycle with methanol and the yields were 12.32% and 22.312% for *Alternanthera sessilis* and *Clerodendrum infortunatum*. The methanolic extracts were subjected to phytochemical tests, which showed the presence of steroids, terpenoids, fats and flavonoids which were confirmed by TLC.

4. Experimental protocol

55 mice of either sex were trained on rectangular maze for assessment of learning and memory (Day1-Day5). Those with lower scores were selected and randomly grouped. Seven groups of six mice each were used to evaluate their responses on rectangular maze.

Group-1: Positive control; Vehicle; equivolume p.o.

Group-2: Negative control; Scopolamine (amnestic agent); 0.4 mg/kg i.p, dissolved in Normal Saline.

Group-3: Standard; *Bacopa monniera* extract (Himalaya Herbals); 40 mg/kg p.o.

Group-4: Methanolic extracts of *Alternanthera sessilis*; 100 mg/kg p.o., dissolved in double Distilled water

Group-5: Methanolic extracts of *Alternanthera sessilis* 200

mg/kg p.o., dissolved in double distilled water

Group-6: Methanolic extracts of *Clerodendrum infortunatum*; 100 mg/kg p.o., dissolved in double distilled water.

Group-7: Methanolic extracts of *Clerodendrum infortunatum*; 200 mg/kg p.o., dissolved in double Distilled water

The dosing commenced on day 6 for a period of 7 days and on the day-13, amnesia was induced by administration of scopolamine (0.4 mg/kg i.p.) to Groups 2-7. The negative control group (group 2) received just one dose of scopolamine on day-13 itself. 45 mins after the administration of amnestic agent, trials were taken on rectangular maze and the retention was observed 24 hours after.

The same experimental protocol was followed on the same experimental animals after one month of rehabilization for assessment of learning and memory by Y-maze model.

5. Acute toxicity studies

The acute toxicity studies were performed in accordance with the OECD (Organization for Economic Co-operation and Development) guidelines no. 425 (Up and Down Procedure) [19]. No death was observed till the end of the study. The test samples were found safe upto the dose of 2000 mg/kg and from the results 200 mg/kg was chosen as the maximum dose for further experimentation on mice in the present study.

6. Assessment of learning and memory using hebb's william maze (rectangular maze)

The Hebb William maze (Medicraft Rectangular Maze Model No. 511 ER)

The maze consists of completely enclosed rectangular box with an entry (A) and reward chamber (B) appended at opposite ends. The box is partitioned with wooden slats into blind passages leaving just twisting corridor (C) leading from the entry (A) to the reward chamber (B) [20] . The learning assessment for control and treated mice was conducted at end of treatment. On the first day, all the mice were familiarized with the Hebb William maze for a period of ten minutes. From the 2nd to 5th day the mice received four consecutive trials of training per day in the maze. In each trial the mice were placed in the entry chamber and the timer was activated as soon as the mice leave the chamber. The time taken by the mice to reach the award chamber was taken as the learning score of the trial. The average of four trials was taken as the learning score for the day. Lower scores of assessment indicate efficient learning while higher scores indicate poor learning in animals. During learning assessment the animals were exposed to food and water ad libitum only for 1 hour after the maze exposure for the day was completed to ensure motivation towards reward area (B).

7. Assessment of learning and memory using y maze apparatus

The Y-maze is a simple two-trial recognition test for measuring spatial recognition memory, it does not require learning of a rule, and thus is useful for studying memory in rodents, and in particular for the study of genetic influences on the response to novelty and recognition processes.

Y-maze made of wood, consists of three arms with an angle of 120° between each of the two arms. The arm dimensions are 8 cm x 30 cm x 15 cm (width x length x height). The three identical arms were randomly designated: start arm, in which the mice started to explore (A), novel arm (B, with food stimuli), and the other arm (C) [21].

Mice tend to explore the maze systematically, entering each arm in turn. The ability to alternate requires that the mice know, which arm they have already visited. On the first day, all the mice were allowed to explore the Y maze apparatus for a period of ten minutes each. From the 2nd to 5th day the mice received four consecutive trials of training per day in the maze of 5 min duration. In each trial the mice were placed in the entry chamber (A) and the series of arm entries in all the three arms, including possible return into the same arm was recorded visually. Alteration is defined as the number of successive entries into the three arms on overlapping triplet sets. The percentage of alteration is calculated as the total number of arm entries minus two, and multiplied by 100. Pretreatment with amnestic agent 30 min prior to trials induces a marked decrease in spontaneous alteration performance with a concomitant increase in the total number of arm entries. Administration of agents that possesses memory enhancing effects is expected to reverse the changes. During learning assessment the animals were exposed to food and water ad libitum only for 1 hour after the maze exposure for the day was completed to ensure motivation towards reward area (B) [22].

8. Statistical analysis

All results were expressed as mean ±standard error of mean (S.E.M.). Data was analyzed using one-way ANOVA followed by Dunnett's' test. $P < 0.05$ was considered as statistically significant.

Results

The up and down procedure for the acute toxicity studies indicated a reasonably good safety potential for both the parts employed in the study i.e. leaves and stem bark and on this basis 200 mg/kg was chosen as the maximum dose for further experimentation on mice in the present study.

Assessment of learning and memory using Hebb's William Maze (Rectangular Maze):

The learning scores (time in seconds) obtained by each

Table 1

Learning Scores of mice on Day 13 (45 min post amnesia) and Day 14 (24 hours after amnesia)

Group	Treatment	Dose	Learning Scores (Time in seconds) Day 13	Learning Scores (Time in seconds) Day 14
1	Positive control; Vehicle	Equivolume p.o.	200.125±0.421	175.75 ±0.236
2	Negative control; Scopolamine (amnestic agent)	0.4 mg/kg i.p.	95.25±0.547	127.75 ±0.119
3	Standard; *Bacopa monniera* extract + Scopolamine	40 mg/kg p.o., 0.4 mg/kg i.p	80±0.360	73.6±0.457
4	Methanolic extracts of *Alternanthera sessilis* + Scopolamine	100 mg/kg p.o., 0.4 mg/kg i.p	119.75±0.672	213.5±0.399
5	Methanolic extracts of *Alternanthera sessilis* + Scopolamine	200 mg/kg p.o., 0.4 mg/kg i.p	90.5±0.361	90±0.254
6	Methanolic extracts of *Clerodendrum infortunatum* + Scopolamine	100 mg/kg p.o., 0.4 mg/kg i.p	108.8±0.346	85.2±0.268
7	Methanolic extracts of *Clerodendrum infortunatum* + Scopolamine	200 mg/kg p.o., 0.4 mg/kg i.p	87.75±0.549	84.75±0.742

Values represent mean ±SEM; n= 6; P< 0.05

group as presented in Table 1, are suggestive of the fact that the mice took lesser time on Day 14 (i.e. 24 hours after amnesia) than Day 13. Group 2 (Negative control group) showed an increase in learning score on Day 14 due to the memory deficit induced by scopolamine, however in Groups 3–7 , there was a significant decrease in learning scores on Day 14, thus elaborating the drugs responses to overcome the learning deficits produced by scopolamine. The higher doses of both the test drugs i.e. *Alternanthera sessilis* and *Clerodendrum infortunatum* afforded better learning scores as compared to the lower doses. The higher dose of *Clerodendrum infortunatum* methanolic extract closely approximated the learning scores obtained for the standard drug *Bacopa monniera*. On the basis of the data obtained the following order of nootropic potential can be traced.

Bacopa monniera extract (40 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (200 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (200 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (100 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (100 mg/kg)

Assessment of learning and memory using Y Maze Model:

Y maze model used in the present study proved to be a sensitive measure of spatial recognition memory. The effect on alteration behavior was studied on two parameters, % alteration (Table 2 a) and No. of arm entries (Table 2 b).

Effect on % alteration: Normally mice exhibit an alteration of around 60–70% as exhibited by the positive control group (Group 1). Group 2 exhibited a marked decrease in spontaneous alteration, elaborating the amnestic effects of scopolamine, however in Groups 3–7; there was a significant increase in % alteration thus supporting their memory enhancing effects to reverse the effects of scopolamine. The greatest alteration was achieved by the standard *Bacopa monniera* extract followed by the higher doses of both the test drugs i.e. *Alternanthera sessilis* and *Clerodendrum infortunatum* methanolic extracts. The higher dose of *Clerodendrum infortunatum* closely approximated the alteration response of the standard *Bacopa monniera*. Assuming generalization % alteration on Day 14 was found to be greater than that observed on Day 13 in all groups thus elucidating the retention characteristics of the purported nootropics. A stacked view of % alteration on the two different trials across all treatment groups is demonstrated in Figure 1. The purported order of activity as evident from % alteration is as follows:

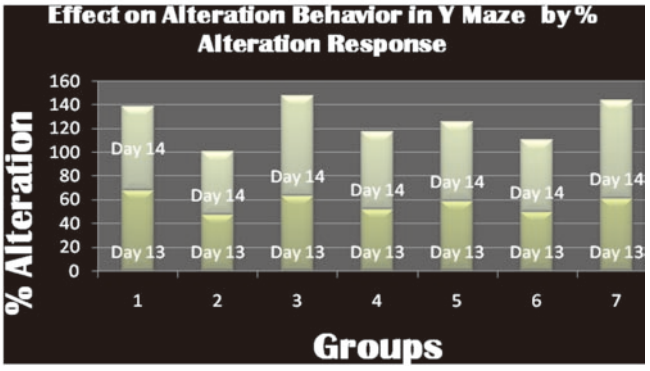

Figure 1

Bacopa monniera extract (40 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (200 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (200 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (100 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (100 mg/kg)

Effect on No. of arm entries: Normally mice tend to make 20–25 entries in a five minutes trial on the Y maze, as exhibited by the positive control group (Group 1). There is a significant increase in the no. of arm entries in presence of amnesia. This behavior was well evident in Group 2 because of the amnesic effects of scopolamine, resulting in transient memory impairment. However presence of memory enhancing effects in a drug tends to reverse the effects brought about by an amnestic agent, as exhibited by Groups 3–7. There was a dramatic decrease in the no. of arm entries, the maximum being showcased by *Bacopa monniera* extract, which is a proven nootropic. The higher doses afforded close proximity to the results observed for the standard Brahmi. Out of the two test drugs the methanolic extracts of *Clerodendrum infortunatum* afforded better results. Assuming generalization the no. of arm entries on Day 14

Table 2

Effect on Alteration Behavior in Y Maze in mice (a) % Alteration Response (b) No. of arm entries

Table 2 (a)

Group	Treatment	Dose	% Alteration on Day 13	% Alteration on Day 14
1	Positive control; Vehicle	Equivolume p.o.	67.50±0.344	71.25±0.110
2	Negative control; Scopolamine (amnestic agent)	0.4 mg/kg i.p.	47.38±0.594	53.33±0.259
3	Standard; *Bacopa monniera* extract + Scopolamine	40 mg/kg p.o., 0.4 mg/kg i.p	63.33±0.723	84.52±0.674
4	Methanolic extracts of *Alternanthera sessilis* + Scopolamine	100 mg/kg p.o., 0.4 mg/kg i.p	50.0±0.595	65±0.349
5	Methanolic extracts of *Alternanthera sessilis* + Scopolamine	200 mg/kg p.o., 0.4 mg/kg i.p	58.76±0.417	66.66±0.351
6	Methanolic extracts of *Clerodendrum infortunatum* + Scopolamine	100 mg/kg p.o., 0.4 mg/kg i.p	52.0±0.543	60±0.428
7	Methanolic extracts of *Clerodendrum infortunatum* + Scopolamine	200 mg/kg p.o., 0.4 mg/kg i.p	61.33±0.155	82.67±0.286

Values represent mean ±SEM; n= 6; $p < 0.05$

Table 2(b)

Group	Treatment	Dose	No. of arm entries on Day 13	No. of arm entries on Day 14
1	Positive control; Vehicle	Equivolume p.o.	25±0.411	20±0.428
2	Negative control; Scopolamine (amnestic agent)	0.4 mg/kg i.p.	28.5±0.343	19.5±0.298
3	Standard; *Bacopa monniera* extract	40 mg/kg p.o.	14±0.591	10±0.761
4	Methanolic extracts of *Alternanthera sessilis*	100 mg/kg p.o.	22.5±0.365	18±0.481
5	Methanolic extracts of *Alternanthera sessilis*	200 mg/kg p.o	16±0.691	13.5±0.833
6	Methanolic extracts of *Clerodendrum infortunatum*	100 mg/kg p.o.	20.5±0.354	14±0.480
7	Methanolic extracts of *Clerodendrum infortunatum*	200 mg/kg p.o	15±0.420	12±0.387

Values represent mean ±SEM; $n= 6$; $P < 0.05$

was found to be lesser than that recorded on Day 13 in all groups thus serving as an index of their transfer latencies, acquisition and retrieval of spatial recognition memory. A clustered coloumn view of the no. of arm entries made by all treatment groups on two different trial occasions (Day13 and day 14) are demonstrated in Figure 2.

The purported order of activity as evident from no. of arm entries is as follows:

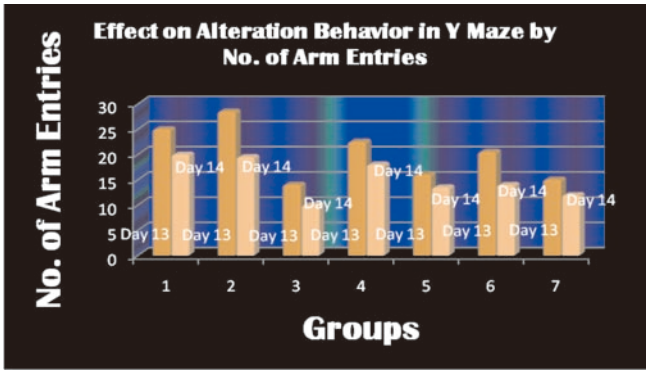

Figure 2

Bacopa monniera extract (40 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (200 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (200 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (100 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (100 mg/kg)

A 3 D cone display of the cumulative alteration behavior based on both the % alteration and no. of arm entries, indexed as a measure of acquisition and retrieval of spatial recognition memory is presented in Figure 3.

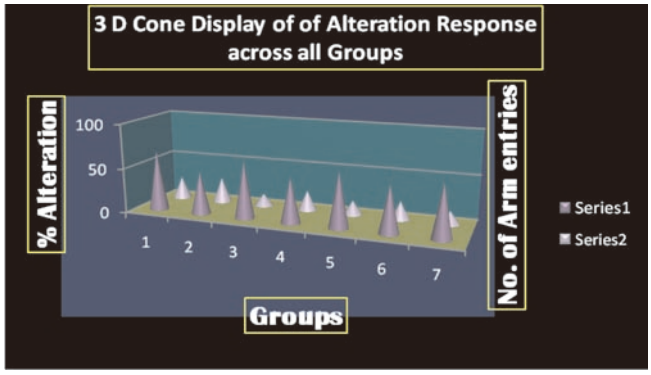

Figure 3

Discussion

The findings from the present study are suggestive of the fact that results obtained for the memory enhancing effects of *Alternanthera sessilis* and *Clerodendrum infortunatum* and also the standard nootropic agent i.e. *Bacopa monniera* provide enough scientific promise to validate the claims on their nootropic potentials as proven by two different interoceptive models having different parameters and methods of evaluation. The learning scores in the rectangular maze and the % alteration and arm entries criterion in the Y-maze models (Figure 3) present similar results. *Bacopa monniera* the standard nootropic gave the most prominent results in both models, followed by *Clerodendrum infortunatum* and *Alternanthera sessilis*. The study reveals a dose dependant effect in both the plants, the higher doses being able to produce better results and even giving a closer comparison with the standard. The

cumulative order of activity based on both the models is as follows: *Bacopa monniera* extract (40 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (200 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (200 mg/kg) > Methanolic extracts of *Clerodendrum infortunatum* (100 mg/kg) > Methanolic extracts of *Alternanthera sessilis* (100 mg/kg).

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