ORIGINAL ARTICLE

Evaluation of nootropic activity of *Sida cordifolia* in mice

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Abstract

Introduction: In the present study, nootropic effect of aqueous and hydroethanolic extracts of *Sida cordifolia* (AESC and EESC, respectively) was investigated in mice using transfer latency (TL) and step-down latency (SDL) tests. *S. cordifolia* is a well-known Ayurvedic plant which has been administered anciently for the various nervous disorders including loss of memory. **Materials and Methods:** Varying doses (50, 100, 250 mg/kg; p.o.) of AESC and EESC were administered along with standard drug (donepezil; 5 mg/kg) for 15 successive days to different groups. They were subjected TL and SDL tests on the 16th day. **Results:** EESC dose dependently increased the SDL and decreased the TL in mice as compared to control group, and this effect was comparable to the standard drug. No significant effect on TL and SDL was observed following varying dose treatment of AESC. **Conclusion:** These findings suggest the nootropic effect of EESC and predict its scope in the possible treatment of diseases associated with memory dysfunctions such as Alzheimer's disease.

Key words: Nootropic activity, *Sida cordifolia*, step-down latency, transfer latency

INTRODUCTION

Dementia is considered to be one of the important cause of severe morbidities and mortalities worldwide.[1] It is one of the most prevalent symptoms of Alzheimer's disease (AD). This dementia is due to the loss of cholinergic neurons in the basal forebrain region of brain.[2] It is considered that certain factors such as abnormality in the phosphorylation of protein tau, oxidative stress, changes in calcium metabolism, abnormal energy metabolism, neuroinflammation, and abnormal protein processing (unwanted Aβ generation and accumulation) are considered to be important factors in AD pathology.[3] Neurotransmitter acetylcholine, which is secreted in cortical and hippocampal area of brain, plays an important role in the process of learning and memory.[4] Agent modulating the activity of acetylcholine can affect learning and memory.

Currently available treatment for dementia includes cholinesterase inhibitors which are mostly associated with cholinergic side effects and hepatotoxicity. Another anti-dementia drug category include N-methyl-D-aspartate receptor antagonists such as memantine which is also associated with lack of neuroprotective activity.[5] Therefore, there is need to find a drug that should have minimum side effects and must exerts multiple protective actions, such as prevention of neurodegeneration through its antioxidant actions along with cholinergic effects.[5]

A number of Indian medicinal plants have been used for thousands of years in the Ayurveda system of medicine for various diseases. Among these, there are plants used for the management of neurodegenerative diseases such as Parkinson's, Alzheimer's, loss of memory, degeneration of nerves, and other neuronal disorders by the ayurvedic practitioners. Ayurvedic pharmacology classifies medicinal plants into different groups according to their actions, one of these is the "Rasayana" group. Rasayana drugs act inside the human body by modulating the neuroendocrino-immune systems and have been found to be a rich source of antioxidants. These Rasayana plants are said to prevent

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ageing, reestablish youth, strengthen brain, prevent diseases, and promote health longevity.[6]

There are several Rasayana plants which have been extensively used in the Ayurveda system of medicine for the management of various neurodegenerative diseases, for example, *Mucuna pruriens* for the management of PD;[7] *Withania somnifera* and *Melocanna bambusoides* for the management of AD.[8] To contribute further to the knowledge of Indian traditional plants, one of such rasayana plants, *Sida cordifolia*, has been evaluated for the first time for their memory enhancing effect.

S. cordifolia is one of the important Rasayana category plants of Ayurvedic system of medicine, belonging to the family Malvaceae. It have different pharmacologically important chemical constituents which include ephedrine, asparagin, hypaphorine, vasicine, vasicinone, vasicinol, mucin and phytosterols.[9] It is reported to possess significant *in vitro* antioxidant activity.[10] The plant also reported to have anti-inflammatory and antiperoxidative effect in quinolinic acid-induced neurotoxicity.[11] In the Ayurvedic literature, this plant have been reported to be useful for various nervous disorders such as hemiplegia, facial paralysis,[12] and PD.[13] Therefore, the objective of the present study was designed to investigate the nootropic of *S. cordifolia* using mice.

MATERIALS AND METHODS

Collection, identification, and authentication of plant

The plant was collected in the month of November from Sagar, Madhya Pradesh, India. The plant was identified and authenticated at Department of Botany, Dr. Hari Singh Gour Central University, Sagar, Madhya Pradesh, India, and a voucher specimen have been deposited in the herbarium of the same department.

Preparation of plant extracts

The fresh whole plant was first washed with water, dried in shade, finely powdered, and then passed through sieve (400 µm). The whole powdered material was defatted with petroleum ether at 50°C using Soxhlet apparatus till no oily spot remains on filter paper. Then, the defatted plant material was subjected to extraction with 70% ethanol using Soxhlet apparatus. This 70% ethanol extract of *S. cordifolia* (EESC) was lyophilized and stored at 4°C for the preliminary pharmacological screening.

Standardized aqueous whole plant extract (dry powder) of *S. cordifolia* (AESC) was procured from Amsar Pvt. Ltd., Indore, India. The extract was stored in a tightly closed container at 4°C for the preliminary pharmacological screening. Aqueous and hydroethanolic extracts were selected for the evaluation in the present study based on literature which suggest the use of these two extracts for nootropic evaluation.[14]

The previous studies have shown low toxic profile of *S. cordifolia* in different studies. Franzotti *et al*. reported low acute toxicity of aqueous extracts of *S. cordifolia* leaves in mice.[15] Rao and Mishra reported that the LD_{50} value for *S. cordifolia* was higher than 10 g/kg in rats.[16] The hydroalcoholic extract of its leaves was found to be toxic at high i.p. doses. The LD_{50} values were 2639 mg/kg b.w. with 95% confidence limits of 2068-3367 mg/kg b.w. for i.p. administration but the oral administration of the extract was found to be safe.[17] Asdaq *et al*. also reported that the methanolic extract of this plant was safe up to 5 g/kg dose.[18] The aqueous plant infusions were found to be safe when tested in cytotoxicity study on PC12 cell line using MTT (3-4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide) test.[10] Hence, based in these previous toxicity and pharmacological studies, three dose levels (50, 100, and 250 mg/kg) were selected for pharmacological evaluation in the present study, as per the OECD guidelines.

Qualitative phytochemical analysis

Both the extracts (AESC and EESC) were subjected to various qualitative tests to detect the presence of various categories of plant constituents, that is, alkaloids, carbohydrates, glycosides, steroids, flavonoids, saponins, fixed oils, fats, tannins, phenolic compounds, proteins, amino acids, gums, and mucilage by following standard tests and all the tests were compared with a control.[19,20]

Animals

Female Swiss albino mice (3-4 months old) weighing 20-30 g were used for the nootropic activity. The animals were obtained from the National Institute of Nutrition, Hyderabad. They were housed in standard cages and maintained at an ambient temperature with natural day-and-night cycles (12:12 h light and dark cycles). Lights of the animal room were put on at 6 AM and were put off at 6 PM Animals were allowed free access to food (standard laboratory rodent's chow) and water during study. All experiments were carried out between 09:00 and 16:00 h. They were allowed a one-week habituation period to the animal room before testing. They were acclimatized with the laboratory conditions by handling them at least once a day during this period. All procedures were conducted as per guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals. The protocol for the use of animals for this study was approved by the Institutional Animal Ethics committee, Dr. Hari Singh Gour Central University, Sagar, Madhya Pradesh, India.

Evaluation of nootropic activity

The mice (n = 6/group) were divided into different groups for evaluating nootropic activity. Group 1 served as

vehicle (0.5% carboxymethyl cellulose [CMC] solution; 5 mL/kg)-treated control group. Group 2 served as donepezil (5 mg/kg)-treated positive control group. Group 3 to 8 served as EESC and AESC (50, 100, 250 mg/kg)-treated groups, respectively. All the treatments were administered orally (p.o.) for 15 days. After 1 h of the administration of the last dose of different treatments (on 15th day), mice were exposed to the training session for acquisition using elevated plus maze and passive avoidance apparatus. Retention (memory) of this learned behavior was recorded after 24 h (on 16th day). Donepezil, EESC, and AESC were suspended in 0.5 CMC% solutions. Memory was evaluated by transfer latency (TL) and step-down latency (ADL) tests using elevated plus maze and passive avoidance apparatus respectively.

TL test

TL test on elevated plus-maze served as the exteroceptive behavioral model to evaluate memory in mice. The procedure, technique, and end point for testing memory were followed using the parameters described by the earlier investigators with little modification.[21,22] The elevated plus maze for mice consisted of two open arms (16 × 5 cm) and two covered arms (16 × 5 × 12 cm) extended from a central platform (5 × 5 cm), and the maze was elevated to a height of 25 cm from the floor. Mice were exposed to the training session for acquisition by placing each mouse at the end of an open arm, facing away from the central platform, and TL was recorded on the 1st day (training session) for each animal. TL was defined as the time (in s) taken by the animal to move from the open arm into one of the covered arms with all its four legs. Cut-off time for TL observation was 90 s.

The mouse was allowed to explore the maze for another 2 min and then returned to its home cage. Retention of this learned-task (memory) was examined 24 h after the treatment. Significant reduction in TL value of retention indicated improvement in memory.

SDL test

Passive avoidance behavior based on negative reinforcement was used to examine the long-term memory.[21,22] The step-down paradigm apparatus consisted of a box (27 × 27 × 27 cm) having three walls of wood and one wall of Plexiglass, featuring a grid floor (made up of 3 mm stainless steel rods set 8 mm apart), with a wooden platform (10 × 7 × 1.7 cm) in the center of the grid floor. The box was illuminated with a 15 W bulb during the experimental period. Electric shock (20 V, AC) was delivered to the grid floor. Mice were exposed to the two training session for acquisition by placing each mouse gently on the wooden platform set in the center of the grid floor. When the mouse stepped-down, placing all its paws on the grid floor, shock was delivered for 15 s and the SDL, which was defined as the time (in s) taken by the mouse to step down from the wooden platform to grid floor with all its paws on the grid floor, was recorded. Animals showing SDL in the range of 2-15 s during the first test were used for the second session and the retention test. The second session was carried out 90 min after the first test. During second session, if the animals stepped down before 60 s, electric shocks were delivered once again for 15 s. During the second test, animals were removed from shock-free zone, if they did not step down for 60 s and were subjected to retention test. Retention (memory) was tested after 24 h of the treatment in a similar manner, except that the electric shocks were not applied to the grid floor observing an upper cutoff time of 300 s. Significant increase in SDL value indicated improvement in memory.

Statistical analysis

All the results were expressed as mean ± standard error of the mean. The data were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's test (Sigma Stat Software, 3.5). P <0.05 were considered as statistically significant for all comparisons.

RESULTS

Qualitative phytochemical analysis

Preliminary qualitative phytochemical tests are very important screening tests. These tests give us a rough phytochemical image of the extract related to the presence or absence of biologically important class of phytoconstituents. Results of the qualitative phytochemical analysis of 70% ethanolic (EESC) and AESC showed the presence of alkaloids, carbohydrates, glycosides, flavonoids, saponins, tannins, phenolic compounds, proteins, and amino acids. Sterols, fixed oils, and fats were present in EESC and absent in AESC. Gums and mucilage were present in AESC and absent in EESC. The results of qualitative phytochemical analysis of both the extracts were summarized in Table 1.

Effect on TL

The EESC showed dose-dependent decrease in TL ($F_{(7,40)}$= 15.55, P < 0.001) of mice at different doses, that is, 50 mg/kg (16.09 ± 0.90; P < 0.001), 100 mg/kg (12.97 ± 0.78; P < 0.001), and 250 mg/kg (18.91 ± 1.14; P < 0.05), when compared to control group (25.10 ± 1.41). The maximum effect was observed at 100 mg/kg dose (12.97 ± 0.78) which was comparable (P > 0.05) to the effect of donepezil (13.84 ± 0.93), used as standard drug. No significant change in TL was observed for the AESC-treated groups (24.04 ± 1.80, 22.94 ± 1.35, 25.03 ± 1.57) as compared to the control group (25.10 ± 1.41; Figure 1 and Table 2).

Effect on SDL

The EESC showed dose-dependent increase in SDL ($F_{(7,40)}$= 13.36, P < 0.001) of mice at 50 mg/kg (212.06 ± 11.98; P < 0.05) and 100 mg/kg dose (238.87 ± 14.52; P < 0.001),

Table 1: Results of the qualitative phytochemical analysis of 70% EESC and AESC

Test	Inference	
	70% Ethanolic extract	Aqueous extract
Test for alkaloids		
Dragendorff's test	+	+
Meyer's test	+	+
Hager's test	+	+
Wagner's test	+	+
Test for carbohydrates		
Molisch's test	+	+
Fehling test	+	+
Benedict's test	+	+
Test for glycoside		
Legal's test	+	+
Baljet's test	+	+
Kellar–killiani test	+	+
Borntrager's test	+	+
Test for sterols		
Liebermann–Burchard's test	+	-
Salkowski test	+	-
Test for flavonoids		
Fluorescence test	+	+
Ferric chloride test	+	+
Shinoda test	+	+
Sodium hydroxide test	+	+
Test for saponins		
Foam test	+	+
Test for fixed oils and fats		
Spot test	+	-
Saponification test	+	-
Test for tannins and phenolic compounds		
Lead acetate solution	+	+
Ferric chloride test	+	+
Potassium dichromate test	+	+
Test for protein and amino acids		
Biuret test	+	+
Ninhydrin test	+	+
Xanthoproteic test	+	+
Millon's test	+	+
Test for gums and mucilage		
Absolute alcohol test	-	+

+: Means present, -: Means absent, EESC: Ethanolic extract of *Sida cordifolia*, AESC: Aqueous extract of *Sida cordifolia*

Table 2: Effect of varying doses of extracts on TL and SDL of mice in exteroceptive memory model

Treatment group	TL (in s)	SDL (in s)
Control	25.10±1.41	151.37±8.54
Donepezil (Dpl)	13.84±0.93***	226.43±15.22***
EESC (50 mg/kg)	16.09±0.90***	212.06±11.98*
EESC (100 mg/kg)	12.97±0.78***	238.87±14.52***
EESC (250 mg/kg)	18.91±1.14*	202.93±12.32
AESC (50 mg/kg)	24.04±1.80	141.74±10.64
AESC (100 mg/kg)	22.94±1.35	133.12±7.85
AESC (250 mg/kg)	25.03±1.57	149.24±9.41

*P<0.05, ***P<0.001 significant as compared to control group. Data are represented as mean values±SEM. EESC: Ethanolic extract of *Sida cordifolia*, AESC: Aqueous extract of *Sida cordifolia,* TL: Transfer latency, SDL: Step-down latency

when compared to control group (151.37 ± 8.54). The maximum effect was observed at 100 mg/kg dose (238.87 ± 14.52) which was comparable (P > 0.05) to the effect of donepezil (226.43 ± 15.22), used as standard drug. The increase in SDL of mice was not significant at 250 mg/kg dose of EESC (202.93 ± 12.32) as compared to control group (151.37 ± 8.54). Varying doses of AESC did not show significant change in SDL (141.74 ± 10.64, 133.12 ± 7.85, 149.24 ± 9.41) as compared to the control group (151.37 ± 8.54; Figure 2 and Table 2).

DISCUSSION

In this preliminary screening, EESC at varying doses showed significant nootropic activity in the memory model using TL and SDL as evaluation tests. On the other hand, varying doses of AESC failed to show any nootropic activity in these tests. This effect of AESC might be due to the absence of specific pharmacologically active phytoconstituents in this extract which are associated with the nootropic activity. These phytoconstituents might be present in the AESC, which showed significant nootropic activity in the present study.

The TL test is a neutral behavioral model used to assess learning and memory in mice.[21,23] The principle of the TL test is based on the assumption that mice prefer the closed arms over the open arms. It has been reported that the aversive quality of the open arms is not apparent until the mice enter them.[24] The SDL test can be used to measure three stages of memory (learning acquisition, memory retention, and retrieval) process depending on drug-treatment schedule.[25]

The nootropic drugs belong to the category of psychotropic agents with selective facilitatory effect on intellectual performance, learning, and memory. The decrease in TL and increase in SDL by EESC at varying doses showed that EESC possessed nootropic activity. The maximum effect was

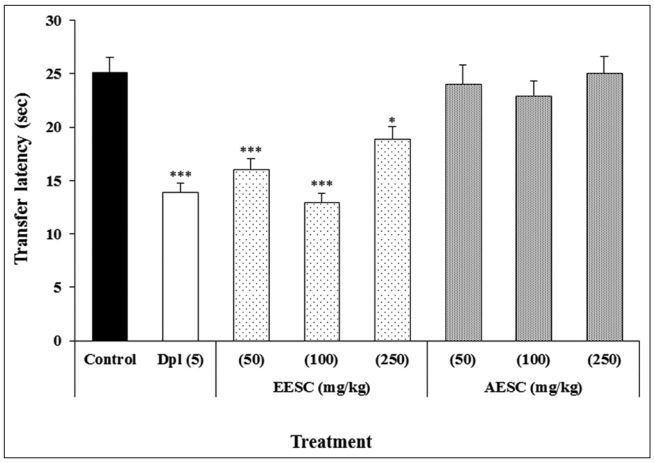

Figure 1: Effect of varying doses of ethanolic extract of *Sida cordifolia*, aqueous extract of *Sida cordifolia* and donepezil (Dpl) on transfer latency of mice. **P* < 0.05, ****P* < 0.001 significant as compared to control group. Data are represented as mean values ± standard error of the mean

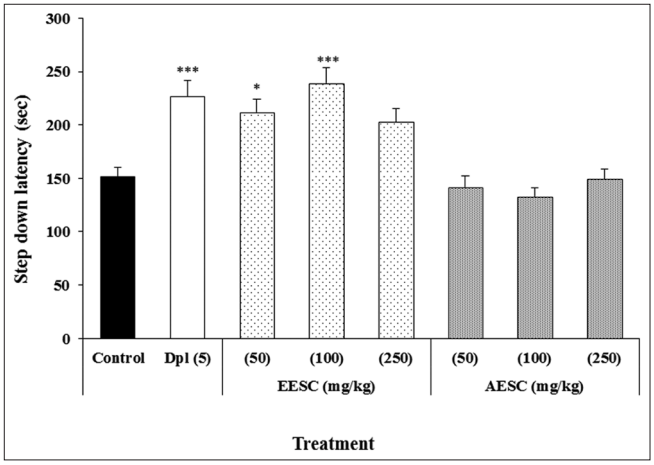

Figure 2: Effect of varying doses of ethanolic extract of *Sida cordifolia*, aqueous extract of *Sida cordifolia*, and donepezil (Dpl) on step-down latency of mice. **P*<0.05, ****P*<0.001 significant as compared to control group. Data are represented as mean values ± standard error of the mean

observed at 100 mg/kg dose of EESC which was comparable with the donepezil-treated positive control group. Thus, the EESC meets a major criterion for nootropic activity.[21] These results could be further extrapolated for possible utility of EESC in poor learning individuals to meet the competitive demands of life, as well as in the management of cognitive deficit, which is another prime target for nootropics.

There is dose-dependent effect of EESC on memory, showing inverse U dose-response relationship which is a typical characteristic of drugs acting on CNS, particularly nootropic and anxiolytic agents.[21,26,27] The possible reason for this effect may be due to dose-dependent modulation in various neurotransmitters involved in learning and memory.

The AESC treatment failed to show any effect in this model. The observed nootropic effect by EESC over AESC in both models might be due to the presence of some specific phytoconstituents present in EESC, which could be responsible for its nootropic effect. The effect may be due to AChE inhibition, antioxidant effect, and/or increase in cholinergic transmission by the EESC. Hence, it is further suggested that its further detailed evaluation should be carried out to reveal its mechanism of beneficial effect.

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