

Research Article***Sphaeranthus indicus* enhances memory and protects against amnesia in rodent models**

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Abstract

Objective: To evaluate anti-amnesic activities in rodents and phytochemical analysis of leaves of *Sphaeranthus indicus*. **Material and methods:** The four leaves extracts of *S. indicus* in Soxhlet's apparatus method using low polar to high polar solvent and used to screen the preliminary phytochemicals. The elevated plus maze (EPM) models and Cook and Weidley's pole apparatus were employed to evaluate learning and memory activity. Acute toxicity studies were performed as per OECD guidelines. **Results:** The results indicate that the methanolic extract of *S. indicus* in doses of 150 and 300 mg/kg p.o. significantly reversed the amnesia induced by scopolamine (0.4 mg/kg i.p.) using elevated plus maze and Cook and Weidley's pole apparatus for a period of 7 days augment both the acquisition as well as the retention of memory of learned task. Nootropic activity was compared using piracetam (100 mg/kg p.o.) as the standard. **Conclusion:** The observation suggested that methanol extract of *Sphaeranthus indicus* showed significant effects on learning behavior and memory enhancement as evidenced from the experiments performed. The activity may be attributed to the presence of 7-hydroxyeudesmanolides and sesquiterpenoids.

Keywords: *Sphaeranthus indicus*, elevated plus maze (EPM), Cook and Weidley's pole apparatus

Introduction

Term "Cognition" is defined in various ways by researchers a combination of processes uses to manage information, including attention, acquisition, encoding of material, rehearsal and praxis (skilled motor behaviors) are important determinants of memory ability. In daily life, persons regularly complain that their memory is insufficient or that they cannot give attention cognitively challenging circumstances (Whitehouse et al., 1997). Cognitive dysfunction due to pathologic condition like neurodegenerative diseases, anxiety, depression, hypoxia, cardiovascular surgery, tumors and normal aging. Numerous neuromodulators play significance role in learning and memory are acetylcholine, dopamine, serotonin, epinephrine, nor-epinephrine, histamine, neuropeptides, angiotensin converting enzymes, platelets activating factor, insulin, oxygen free radical, and neurotrophic factors etc.

Learning and memory are like two sides of a coin. Learning is the understanding of new information whiles the upholding of

learned information is known as memory. The Indian ayurvedic system is replete with medicinal plants asserted to enhancing memory and learning plants like *Bacopa monniera* (Vollala et al., 2010), *Embllica officinalis* (Vasudevan et al., 2007), *Centella asiatica* (Hoang Loc et al., 2013), as well as *Canscora decussata* (Sethiya et al., 2011) have been investigated for their effect on cognitive functions of the brain. These plants have cognitive enhancement is amplification or extension of core capacities of the mind through improvement or augmentation of internal or external information processing system. Therefore, the purpose of this study was to test the effectiveness of specific memory technique training on adult learners and to evaluate the possible successes of such training. *Sphaeranthus indicus* Linn. (Family: Asteraceae) also called as Gorakmundi in Hindi is abundantly in the plains all over India, ascending to an attitude of 1500 m in the hills, especially as a weed grows in the rice fields (Gogate et al., 2000).

It is widely used in indigenous Indian system of medicine to treat chronic skin diseases as antisyphilitic, urethral discharges, jaundice and nervine tonic (Kirtikar et al., 1987). The aerial parts of *S. indicus* have been widely used to treat variety of common and stress related disorders.

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These herbs and its species are widely distributed in tropical Asia, Africa and Australia. All parts of the plant possess medicinal uses and have been reported to have beneficial effects on several ailments. The juice of the plant is styptic and diuretic and it is said to be useful against liver and gastric disorders. Roots and seeds are used as stomachic and anthelmintic. It is reported that flowers are highly alterative, depurative, cooling and tonic. They are also used as blood purifiers in skin diseases. Dried and powdered leaves of plant are useful in the treatment of chronic skin diseases, urethral discharges and jaundice (Nadkarni et al., 1976). Extract of *Sphaeranthus indicus* has been reported for the inhibition of hyaluronidase (Nanba et al., 1995) and exhibited excellent antibacterial activity against Gram positive as well as Gram negative bacteria (Naqvi et al., 1998). The phytochemical analysis of the plant showed that it contains eudesmanolide type of sesquiterpene possessing immunostimulating (Shekhani et al., 1990) and anti-inflammatory activities (Heinrich et al., 1998). It also reported to possess Anxiolytic activity (Ambavade SD et al., 2006, Galani VJ et al. 2010) Neuroleptic activity (Mhetre NA et al., 2006), analgesic, anti-inflammatory (Jain et al., 2003, Nanda et al., 2009), Antioxidant activity (Shirwaikar et al., 2006) activity, Wound healing activity (Jha et al., 2009), thus based on these characteristics, we believe that *S. indicus* can be a safe nutraceutical for the treatment of neurodegenerative disorders.

The aim of the present study is to justify the traditional claims by investigating its use in cognitive enhancement with the help of various validated models.

Materials and methods

Plant material

The whole plants of *S. indicus* were collected from the garden of Garpahra temple Sagar, Madhya Pradesh, India, in the month August 2016 and were authenticated by botanist Dr. P. K. Khare, Professor of Botany, Dr. Harisingh Gour Vishwavidyalaya, Sagar, India. A herbarium specimen bearing voucher No. Bot/Her/02/2017 has been deposited in the Department of Botany, Dr. H.S. Gour Vishwavidyalaya, Sagar, India.

Animals

Healthy Wistar albino rats of weighing 180–200 g and Swiss albino mice weighing 20–25 g of either sex in standard household conditions of temperature, humidity and light were used. They were feed with standard rodent diet and water ad libitum. The Institutional Animal Ethical Committee of BTPC, Sagar, India (0604/IAEC/2017/252), approved the study.

Preparation of extracts

The shade-dried leaves of the plant were powdered and subjected to extraction. 70 g of the dried leaf powder was extracted using petroleum ether, chloroform, methanol and

water in succession using Soxhlet's apparatus. The four extracts were concentrated under reduced pressure and used for the neuropharmacological investigation.

Drugs

The drugs used in this study were obtained from following drug stores. Piracetam, (Cerecetam, 400 mg/tablet, Intas Laboratories, India), Scopolamine hydrobromide (Sigma-Aldrich, USA) and tween 80 (oxford laboratory, India) were used in this study. The solvents used were of analytical grade.

Phytochemical investigation

The petroleum ether, chloroform, methanol and water are subjected to phytochemical analysis using conventional protocol (Khandelwal et al., 2008).

Acute toxicity and effect on gross behavior

The acute toxicity test was carried out according to the OECD-425 guidelines (Up and Down Procedure). Various plant extracts were administered orally in doses to Swiss mice (n = 3) of either sex selected by random sampling technique were employed in this study. The animals were fasted for 4 h with free access to water only (Ecobichon et al., 1997). The test samples were found safe up to the dose of 2000 mg/kg and from the results 300 mg/kg was chosen as the maximum dose for further experimentation on mice in the present study. (Dixon et al., 1965)

Pharmacological evaluation

General behavioral tests

Swiss albino mice were divided into five groups (3 in each group). The first four groups were received with petroleum ether, chloroform, methanol and water extracts with 300 mg/kg dose each and fifth received tween 80 as vehicle. The activities were recorded at 30-min intervals in the first hour and at hourly intervals for the next 4 h for the following parameters.

Spontaneous activity, awareness and alertness: These were evaluated by placing a mouse in a bell jar. It usually shows a moderate degree of inquisitive behavior. Sound responses: Mice normally utter no sound, so that vocalization may point to a noxious stimulus. Touch responses: It was noted when the animal was touched with a forceps at various parts (ie. on the side of the neck, on the abdomen and on the groin). Pain response: This response was graded when a small artery clamp was attached to the base of tail.

Elevated plus maze test

Elevated plus-maze served as the exteroceptive behavioral model to evaluate learning and memory processes in mice by measuring transfer latency. The maze was constructed of two open arms (30 × 05 cm), with central platform (5×5 cm) and

two enclosed arms (30 × 05 × 25 cm). From day 1 to 6, each mouse was placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) was considered as the time taken by the mice to move into any one of the covered arms with all its four legs. TL was recorded for six successive days as training module. If the mice did not enter into one of the covered arms within 90 s, it was gently pushed into one of the two covered arms and TL was assigned as 90 s. The mice were allowed to explore the maze for 10 s and then were returned to its home cage. Memory retention was examined 24 h after the sixth day. The animals were divided into eleven groups containing six animals in each group. Group I received the vehicle only. Group II received a single dose of scopolamine on day 7. Group III received piracetam (100 mg/kg p.o.) as positive control and group IV–XI received different *S. indicus* extracts (150 and 300 mg/kg p.o.) were administered for 7 successive days orally. Scopolamine (0.4 mg/kg) was injected i.p. to mice at 60 min after administration of extract on day 7. TL was recorded 30 min after injection and after 24 h (Sharma et al., 1992; Parle et al., 2004).

Assessment of nootropic activity

The nootropic activity was determined by using the active avoidance paradigm (Cook and Weidley, 1957). The apparatus consisted of a soundproof chamber with a grid floor which could be electrified and with a prerequisite for a buzzer tone. Experimental chamber had a clear perspex front sliding door, through which the animal could be introduced. A wooden pole, attached the inner surface of the lid of the chamber acted as the shock-free zone. The stimulus provided was a foot shock of 6 mA given for a period of 10 s from the electrified grid floor for assessment of nootropic activity. Rats were initially trained to escape the foot shock by climbing on to wooden pole. Preliminary trial was carried out by having three trial sessions interspersed with an interval of 10 s. Only those rats were selected in the study, which were sensitive to the foot shock and

could climb the pole. The animals were divided into ten groups, each group containing six animals. Group II received piracetam (100 mg/kg p.o.) as standard reference drug for comparison. Group III–X received *S. indicus* extracts (150 and 300 mg/kg p.o.) were administered for a period of 7 days following which the training trial (TT) was conducted. This consisted of 10 trial sessions interspersed with an interval of 30 s. During each trial, the rats were permitted to explore the apparatus for 10 s, followed by a buzzer tone (conditioned stimulus) of 50 Hz for 10 s. This was followed by the foot shock for 10 s. The rat learned to combine the buzzer tone with the impeding foot shock and was seeking of avoiding the foot shock on hearing the buzzer warning. Avoidance responses (AR) mean jumping onto the wooden pole, before the shock period. One day later, a relearning trial (RT) composed of 10 trials was carried out and the number of ARs in the 10 trial sessions was computed.

Statistical analysis

The results are given as mean±S.E.M. The data obtained was analysed by one-way analysis of variance (ANOVA) followed by Dunnett's test. *P <0.05, **P <0.01 were considered significant.

Results

Acute toxicity study

No mortality was observed following oral administration of *S. indicus* extracts even with the highest dose (2000 mg/kg). They were behaving normal grooming, touch response and pain response. There were no signs of passivity, stereotypy or vocalization. Their motor activity and secretory signs were also normal.

Preliminary phytochemical screening

Preliminary phytochemical results in *S. indicus* revealed the

Table 1. Qualitative analysis of various extract of *S. indicus* leaves

Phyto Constituents	Phyto chemical Test	Reagent	Methanol Extract (SIME)	Water Extract (SIWE)	Chloroform Extract (SICE)	Pet. Ether Extract (SIPE)
Carbohydrates	Molisch test	1% α -Naphthol+ H ₂ SO ₄	+ve	+ve	-ve	-ve
	Fehling test	Fehling's (A+B)				
Proteins	Biurate test	1% CuSO ₄ + 10 % NaOH	+ve	+ve	-ve	-ve
Amino acid	Million's test	Hg(NO ₃) ₂ + 1% NaNO ₂	+ve	+ve	-ve	-ve
Tannins	Ferric chloride Test	5% FeCl ₃	+ve	+ve	-ve	-ve
	Hager test	Picric acid	+ve	-ve	+ve	-ve
Alkaloids	Wagner test	I ₂ +KI				
	Saponins	Foam test	Water	-ve	+ve	-ve
Flavonoids	Lead acetate test	Pb (CH ₃ COO) ₄	+ve	+ve	+ve	-ve
Glycosides	Hydroxyanthraquinone test	10% KOH	-ve	-ve	-ve	-ve
Steroid	Liebermann Burchard test	(CH ₃ CO) ₂ O + Con.H ₂ SO ₄	+ve	-ve	-ve	+ve
Terpenoid	Salkowski Test	CHCl ₃ + Con.H ₂ SO ₄	+ve	-ve	-ve	+ve

presence as well as absence of certain photochemical constituents in the extracts such as alkaloids, flavonoids, steroids, tannins, glycosides, carbohydrates, saponins and terpenoids etc. in various leaves extracts (Table 1).

Effect on Elevated plus maze test

Significant reduction in transfer latency (TL) value of retention indicated improvement in memory. Piracetam (100 mg/kg, p.o.) and *S. indicus* extracts (150 and 300 mg/kg, p.o.) showed dose-dependent reduction in TL of 7th day and 8th day in mice when compared to control groups. The methanol extract showed more significant in both dose as compare to standard drug piracetam. High dose of petroleum ether extract showed significantly enhanced the learning and memory of mice rather than

chloroform and water extracts reflected by marked decrease in scopolamine hydrobromide (0.4 mg/kg, i.p.) injected before testing (Table 2).

Test for nootropic activity

The Cook and Weidley's pole apparatus was evaluated the percentage AR as an index for studying the nootropic activity in *S. indicus* extracts (150 and 300 mg/kg, p.o.) and piracetam (100 mg/kg po). Our result showed that the methanolic extract administered for 7 days showed dose dependent a statistically significant increase in the percentage AR in the TTs as well as in the RTs, the results are given in table 3.

Table 2. Effect of different extracts of *S. indicus* and piracetam on transfer latency of mice on elevated plus maze apparatus

Groups	Treatment	Dose mg/Kg	Transfer latency 1 st day (score±SEM)	Transfer latency 2 nd day (score±SEM)
I	Control	Vehicle	28.32±0.3	22.14±1.7
II	Scopolamine	0.4	42.35±2.0	38.5±3.8
III	Piracetam + Scopolamine	100	16.57±0.9**	13.62±0.7**
IV	Pet. Ether extract	150	29.17±1.0	27.05±3.8
V	+ Scopolamine	300	23.94±3.6*	21.13±1.3*
VI	Methanol extract	150	18.94±1.3*	18.37±2.7*
VII	+ Scopolamine	300	16.41±2.3**	14.85±1.3**
VIII	Chloroform extract +	150	32.43±1.9	30.46±1.9
IX	Scopolamine	300	31.10±3.7	28.11±0.3
X	Water extract	150	37.22±2.1	35.92±1.8
XI	+ Scopolamine	300	34.98±1.4	31.88±2.3

Values are expressed in mean ± SEM (n = 6). *p < 0.05, **p < 0.01 as compared to control (vehicle treated), scopolamine (SCP), plant extract groups respectively

Table 3. Effect of the different extracts of *S. indicus* and piracetam on nootropic activity in rats administered for a period 7 days using Cook and Weidley's pole apparatus

Groups	Treatment	Dose (mg/kg)	% Avoidance responses in TT (mean±S.E.M.)	% Avoidance responses in RT (mean±S.E.M.)
I	Control	Vehicle	21.62 ± 3.07	24.16 ± 1.03
II	Piracetam	100	68.34 ± 2.10**	79.25 ± 3.21**
III	Pet. Ether extract	150	30.86 ± 3.15	32.18 ± 3.01
IV		300	31.23 ± 2.18	33.12 ± 1.24
V	Methanol extract	150	48.32 ± 1.10*	59.23 ± 2.22*
VI		300	60.64 ± 3.07**	73.46 ± 2.10**
VII	Chloroform extract	150	21.34 ± 2.14	23.13 ± 3.04
VIII		300	23.12 ± 4.02	25.45 ± 2.14
IX	Water extract	150	23.15 ± 1.16	26.12 ± 2.25
X		300	27.12 ± 2.14	29.23 ± 1.18

Values are expressed in mean ± SEM (n = 6). *p < 0.05, **p < 0.01 One-way ANOVA followed by Dunnett's test.

Discussion

Nootropics represent a new class of psychotropic agents with selective facilitatory effect on brain is particularly related to the telencephalic level of CNS, and improve learning capacity and memory. A number of drugs, including piracetam, have now been introduced in therapy to ameliorate cognitive deficits is a nontoxic compound and does not interfere with autonomic functions, general behavior, level of wakefulness, the limbic system, etc. (Giurgea et al., 1973). Recently, Itoh and workers (1990) demonstrated that the latency of mice to enter in enclosed arm from open arm (TL) and then exposure of apparatus for 10s or more shortened the TL when experiments were repeated on 2nd day. Therefore, the utilization of this parameter has been emphasized for evaluation of learning and memory mechanisms. In the present study, we for the first time report that methanolic extract of *S. indicus* administered orally for 7 days improved the memory of mice as reflected by diminished TL as compared to control animals. Furthermore, pretreatment with *S. indicus* extracts for 7 days protected the animals from memory deficits produced by scopolamine. These findings suggest the possible neuroprotective role for *Sphaeranthus indicus*. Acetylcholine is considered as the most important neurotransmitter involved in the regulation of cognitive functions. Dysfunction of cholinergic neurons in the central cholinergic system (CCS) contributes to the salient cognitive decline (Vinutha et al., 2007). Earlier studies conducted by various researchers have revealed that several medicinal plants possess memory enhancing drugs like *B.monnierea* (Joshi & Parle, 2006) and *A. recemosus* (Ojha et al., 2010) including Ayurvedic preparations such as Anwala churna (*E. officinalis*) have been reported to improve memory (Nahata et al., 2008) through augmentation of CCS function. The elevated plus-maze paradigm has been used for evaluating learning and memory in rodents.

Scopolamine, a known muscarinic antagonist, displayed temporary loss of memory by interfering with cholinergic transmission in the CNS (Kameyama et al., 1986. Kulkarni and Sharma, 1990). The increase in transfer latency as exhibited by time taken by animal to reach safe compartment was observed during our experiment.

The findings of the present study clearly indicate that the alcoholic extracts at a dose of 300 mg/kg significantly improve the acquisition and retention of memory of the learned task as was seen in the increase in the percent ARs, thus demonstrating nootropic activity.

Already, Yadava and Kumar (1998) have reported carbohydrates like arabinose, Carbohydrates such as arabinose, galactose, glucose, fructose, lactose, maltose, raffinose and rhamnose have been reported from leaves of *S. indicus*. A sesquiterpene lactone, 7-hydroxyeudesm-4-en-6, 12-olide, and a sesquiterpene acid, 2-hydroxycostic acid, along with the known compounds, β -

eudesmol and ilicic acid, have been isolated from the acetone extract of *S. indicus*. Three 7-hydroxyeudesmanolides and two sesquiterpenoids, cryptomeridiol and 4-epicryptomeridiol, have been isolated from this plant (Sohoni et al., 1988; Rojatkar et al., 1992).

For centuries, Gorakmundi has a medicinal plant widely used in Indian traditional system of medicine for curing memory disorders. Research on dementia treatments has gradually changed focus from organic compound synthesis to the development of natural compounds from herbs or plants that exert multiple actions.

Conclusion

Our studies thus support and validate the earlier findings for the use of as Gorakmundi a nervine tonic in traditional ayurvedic medicine is not invalid. The pharmacological actions of *Sphaeranthus indicus*, justify the therapeutic uses of the plant in mental disorders.

Conflicts of interest

The authors report that they have no potential conflicts of interest.

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