EVALUATION OF NOOTROPIC ACTIVITY OF POLYHERBAL FORMULATION SR-105 IN EXPERIMENTAL ANIMALS

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ABSTRACT
The main objective of the proposed work is to evaluate the beneficial effect of SR-105 on CNS mainly for its locomotor and nootropic activities in different experimental animal models like passive paradigm, sodium nitrite induced amnesia, lithium induced head twitches. Also evaluate anticholinesterase activity on rat's brain. The LD_{50} of SR-105 was found more than 2000 mg/kg as OECD guidelines no-425. No significant alteration in motor activity was observed with all the doses of formulation tested on Actophotometer. In case of passive avoidance paradigm all dose of polyherbal formulation have shown an increased step-down latency (SDL), decreased time spent in shock zone and no of errors. SR-105 also reverse sodium nitrite induced amnesia and decreases lithium induced head twitches. In the present study. Polyherbal formulation SR-105, showed elevation of acetylcholine level by significant reduction of cholinesterase activity in rat's brain and ultimately improved memory. In the light of above, it may be worthwhile to explore the potential of this formulation in the management of Alzheimer patients.
KEYWORDS: Polyherbal formulation, Locomotor activity, Nootropic activity, anticholoinesterase activity.

INTRODUCTION

Dementia is generally defined as the "loss of intellectual abilities (medically called cognitive dysfunction) of sufficient capacity to interfere with social or occupational functioning". The most common cause of dementia is Alzheimer's disease.[1]

Alzheimer's disease (pronounced AHLZ-hi-merz) is a neurodegenerative disorder that destroys cells in the brain. The disease is the leading cause of dementia, a condition that involves gradual memory loss, decline in the ability to perform routine tasks, disorientation, difficulty in learning, loss of language skills, impairment of judgment and personality changes.[2] As the disease progresses, people with Alzheimer's become unable to care for themselves and the loss of brain cells eventually leads to the failure of other systems in the body.[3]

The Indian system of medicine is replete with medicinal plants claimed to promote learning, memory and intelligence, Plants like Glycyrrhiza glabra,[1] Bacopa monniera,[4] Azadirachta indica,[5] Albizzia lebbeck,[6] Vitis vimifera,[7] Ginseng[8] as well as Ocimum sanctum[9] have been investigated for their effect on cognitive functions of the brain. These plants have been grouped under the general class of rejuvenators i.e., drugs that counter the degenerative changes associated with ageing. Additionally, some of these plants act specifically in augmenting the cognitive functions of the brain termed as "Nootropic agents".

In recent years, several attempts have been made to develop drugs for treatment of dementia and attention deficit disorders to improve memory in these condition and the agents which are used for improving memory, mood and behavior. Piracetam is one of the widely used nootropic agents, but the resulting chemophobia associated with it and other similar agents has made their use limited. So it is worthwhile to explore medicines from the traditional system in the treatment of these cognitive disorders.

We and SHRUSHTI a Herbal Pharma Industry of Bangalore study the effectiveness of polyherbal formulation, SR-105 in improving the memory in experimental animals. The reversal effect of SR-105 against memory deficits induced by sodium nitrite was evaluated on elevated plus-maze as well as phenytoin passive avoidance in animals, a protection against lithium- induced head twitches and also evaluates the anticholinesterase activity of herbal formulation SR-105. The Polyherbal formulation SR-105 consisting of plant ingredients like Shankhpusphi (*Convolvulus miorophyllus*), Jyothishmati (*Celastrus paniculata*), Vacha (*Acorus calamus*) and Brahmi (*Bacopa monniera*).

METHODS AND MATERIALS

Drugs and Chemicals

Piracetam ('Neurocetam syrup', Brown & Burk. India), Lithium carbonate ('Licab' Torrent, Solan, India.), Phenytion PHT (Sigma, USA), Sodium Nitrite (Ranbaxy Lab Ltd India) and SR-105 (SHRUSHTI a Herbal Pharma Industry of Bangalore) in the form of tablets. All drugs were dissolved in distilled water and administered orally.

Experimental Animals

Albino mice of either sex weighing between 18-22 gm were used in this study. All the animals were procured from Shri Venkateswara Enterprises, Bangalore for experimental purpose. After procuring the animals were acclimatized for 7 days and housed in groups of six under standard husbandry condition[10,11] like room temperature 26 ± 2^0C, relative humidity 45-55% and light/ dark cycle of 12 hours. All the animals were fed with synthetic standard diet (Amrut Laboratories Pranava Agro Industries Ltd. Sangli) and water was supplied ad libitum under hygienic conditions. After obtaining permission from Institutional Animal Ethical Committee (IAEC) of V. L. College of pharmacy Raichur (Karnataka), animal studies were performed as per rules and regulations in accordance to guidelines of CPCSEA with registration number 557/02/C/CPCSEA. Animals were fasted overnight prior to vehicle/standard/extract administration and during the experiment. All experiments were carried out during the light period (8:00 to 16:00 hour).

Determination of LD_{50}

The acute toxicity formulation was determined by using female albino mice (20-30g) those maintained under standard husbandry conditions. The animals were fasted 3 hrs prior to the experiment, up and down procedure (OECD guideline no. 425) of CPCSEA was adopted for toxicity studies[17]. Animals were administered with single dose of formulation and observed for its mortality during 48 hours study period (short term) toxicity. Based on short-term profile of drug, the dose of the next animals was determined as per as OECD guideline 425. The LD_{50} of the test extract was calculated using AOT 425 software provided by Environmental protection agency, USA.[12,13]

Locomotor Activity

Albino mice (18-22 g) of either sex were divided into five groups of six mice in each group. Animals are fasted overnight prior to the test but water was supplied ad libitum. Group I was served as vehicle treated control; group II receive piracetam, group III, IV and V received polyherbal formulation in a dose of 100, 200 and 400 mg/kg respectively. One hour after above treatment, each mouse was placed individually in Photoactometer (INCO, Ambala, India) for a period of 10 min and locomotor activity was measured in terms of scores.[14]

Nootropic Activity

Passive Avoidance Paradigm

Group of adult Swiss male albino mice 24-32g, each consisting of 6 animals was divided into following groups. Animals are fasted overnight prior to the test but water was supplied ad libitum. The memory- impairing dose of phenytoin 25mg/kg daily for 14 days and the selected dose of polyherbal formulation SR-105 for 07 days i.e. on 8th to 14th day and the parameters mentioned below were noted. Group I was maintained as control (phenytoin alone) (25 mg/kg p.o.) daily once for 14 days. Group II receive piracetam (200 mg/kg p.o.) which served as standard, Groups III, IV, V were treated with different doses of SR-105 (100, 200 and 400 mg/kg p.o.) a polyherbal formulation respectively daily once for 7 days as mentioned above.[15]

Passive-avoidance task is a method widely used for screening drugs affecting learning and memory. The method described by Papazova et al**.** was modified as follows[16]. An inverted petridish placed in the centre of the grid floor of a continuous avoidance apparatus (Techno, Lucknow) was used. The petridish served as the shock-free zone (SFZ). Mice were placed in the SFZ and up on stepping down from the SFZ were given an electric shock (20 V) through the grid floor. Animals were trained to remain on the SFZ for at least 60 sec and mice which did not meet these criteria in five trials were rejected. Observations were made for acquisition i.e. the number of trials required to reach the learning criteria and for retention of learning for 10 min at 2 h and 24 h post-training. The following retention parameters like step-down latency (SDL) in seconds, step-down error (SDE) as the number of times the animal stepped down from the SFZ and the time spent in the shock zone (TSZ) in seconds are noted.[17]

Sodium Nitrite-induced Amnesia

Group of adult Swiss male albino mice 18-25g, each consisting of 6 animals was divided into following groups. Animals are fasted overnight prior to the test but water was supplied ad libitum. Group I was maintained as normal control which was given with distilled water only, Group II receive Sodium nitrite alone (25mg/kg s.c.), Groups III receive piracetam (200 mg/kg p.o.) which served as standard, Groups IV, V and VI were treated with different doses (100, 200 and 400 mg/kg) of polyherbal formulation SR-105 respectively. All groups were treated according to protocol for a period of 7 days and sodium nitrite 25 mg/ kg was given s.c. route 90 minutes after the last dose of formulation to induce

amnesia. There after using Elevated Plus maze (EPM) Transfer latency (TL) will be recorded at 45 minutes and 24 hrs after administration of Sodium nitrite. The inflexion ratio was calculated by the formula as follows[18].

Inflexion ratio (IR) = $(L_0 - L_1)/ L_0$, where L_0 is the initial TL (s) on first day and L_1 is the TL (s) on the 2nd day.

Lithium- induced Head Twitches (5-HT Mediated Behavior)

Group of adult Swiss male albino rats 125-150g, each consisting of 6 animals was divided into following groups. Animals are fasted overnight prior to the test but water was supplied ad libitum. Lithium induced head twitching is used to assess the effect of drugs influencing second messenger system like Phosphatidylinositol (IP) pathway (5-HT receptor).[19] Rats was treated with vehicle/formulation SR-105/Piracetam 30 min before i.ply administration of 190mg/kg of lithium carbonate. The prevention of head twitches due to standard drug and polyherbal formulation SR-105 was recorded upto 60 min after lithium treatment. Group I was maintained as control which was given with Lithium alone (190mg/kg i.p.), daily once for 7 days Group II receive piracetam (200 mg/kg, p.o.) which served as standard, Groups III, IV, V were treated with different doses of SR-105 (100,200 and 400 mg/kg p.o.) a polyherbal formulation respectively daily once for 7 days as mentioned above.[6, 20]

Estimation of Acetylcholinesterase Activity in Rat's Brain

Albino rats (250-300 g) of either sex were divided into five groups of six rats in each group. Animlas are fasted overnight prior to the test but water was supplied ad libitum. Group I serve Normal control (distilled water 10ml/kg, p.o.), Group II as Piracetam (200 mg/kg, p.o.), Group III as SR-105 (100mg/kg, p.o.), Group IV as SR-105 (200 mg/kg, p.o.) and Group V as SR-105 (400 mg/kg, p.o.).

Experimental Procedure

1. Dissection: Adult Male Wistar rats (250-300g body weight) are used for the experiment. The rats are decapitated after 60 min of treatment with vehicle, piracetam (200 mg/kg) and SR-105 (100, 200, 400 mg/kg); brains are removed quickly and placed in ice-cold saline. Frontal cortex, hippocampus and septum (and any other regions of interest) are quickly dissected out on a petri dish chilled on crushed ice.

2. The tissues are weighed and homogenized in 0.1M Phosphate buffer (pH 8).

3. 0.4ml aliquot of the homogenate is added to a cuvette containing 2.6 ml phosphate buffer (0.1M, pH 8) and 100µl of DTNB.

4. The contents of the cuvette are mixed thoroughly by bubbling air and absorbance is measured at 412 nm in a photoelectric colorimeter (H2 grade). When absorbance reaches a stable value, it is recorded as the basal reading.

5. 20 ml of substrate i.e., acetylthiocholine is added and change in absorbance is recorded for a period of 10 mins at intervals of 2 mins. Change in the absorbance per minute is thus determined.[21]

Calculations

The enzyme activity is calculated using the following formula;

$R = 5.74 \times 10\text{-}4 \times A/CO$

Where,

R = Rate in moles of substrate hydrolyzed / minute / gm tissue

A = Change in absorbance / min

CO = Original concentration of the tissue (mg / ml).

Statistical Analysis

Values are expressed as mean ± SEM. Statistical differences between means were determined by performing one-way ANOVA followed by Dunnet's 't' test. $P < 0.05$ were considered as significant. All the statistical analysis was performed using demo version of Instat® software (Graph pad Inc., Santabarbara, CA)

RESULTS

Determination of Acute Toxicity (LD$_{50}$)

The mice treated with a polyherbal formulation, SR-105 at a dose of 2000 mg/kg, p.o. exhibited normal behaviour, without any signs of passivity, stereotypy and vocalization. Their motor activity and secretory signs were also normal and no sign of depression. Further the formulation even upto the dose level of 2000 mg/kg body weight did not produce any behavioural symptoms or mortality. So 1/20th, 1/10th and 1/5th doses of 2000 mg/kg were selected as low, medium and high doses and were tested in the present study to explore nootropic activity.

Locomotor activity

The effect of SR-105 on locomotor activity was tested using actophotoactometer. The polyherbal formulation, SR-105 and piracetam both failed to produce any significant reduction in locomotor activity as compared to control (Table 1).

Nootropic activity

Effect of SR-105 on Passive Avoidance Learning and Retention in Mice

Effect of SR-105 on learning and retention was tested using passive avoidance paradigm apparatus. Statistically significant increase in SDL and reduction in TSZ and no. of errors were observed with piracetam and different doses of polyherbal formulation SR-105 (Table 2).

Effect of SR-105 on Inflexion Ratio in Mice (Sodium Nitrite-induced Amnesic Model)
Sodium nitrite treated group has shown decrease in IR as compared to normal control group, which indicates the induction of amnesia. Piracetam and all the doses of SR-105 treated groups had shown increased IR and a significant reduction in TL. It indicates SR-105 reversed the sodium nitrite-induced amnesia (Table 3).

Effect of SR-105 on Lithium-induced Head Twitches in Rats
Lithium treated group had shown 20.333 ±1.308 head twitches. Prior treatment with piracetam decreased the number of head twitches to 3.167 ±0.3073 and all doses of SR-105 100, 200 and 400mg/kg, had showed significant reduction in head twitches i.e. 13.33 ±1.116, 8.500 ±0.6708 and 4.167 ±0.3073 respectively. A significant nootropic effect was observed with piracetam and different doses of SR-105 treated groups. Amitriptyline had reduced the head twitches to 1.833±0.4773 (Table 4).

Anti-acetylcholinesterase Activity in Rat's Brain
Vehicle treated group had shown 7.837×10^{-7} µmol/min/g tissue of acetyl Cholinesterase activity in rat's brain. Prior treatment with piracetam and different doses of SR-105 100, 200, 400 mg/kg had showed decreased the acetyl Cholinesterase activity 4.249×10^{-7}, 5.979×10^{-7}, 5.065×10^{-7}, 4.363×10^{-7} respectively. However, a significant effect was observed with piracetam and all doses of SR-105 as compared control group (Table 5).

DISCUSSION
The concept and definition of a "**nootropic drug**" was first proposed in 1972 by C.E. Guirgea and coined the term "nootropic" from the italic words "noos" (mind) and "tropein" (to turn toward), to mean enhancement of learning and memory.[22]
Nootropics, popularly referred to as "smart drugs", are substances, which boost human cognitive abilities (the functions and capacities of the brain). Typically these are thought to work by increasing the brain's supply of neurochemicals (neurotransmitters, enzymes and hormones) improving brain's oxygen supply or by stimulating nerve growth.
Alzheimer's disease (AD) is characterised by degenerative changes in the brain accompanied by loss of memory, expressly for recent events. The learning and memory is closely associated with the functional status of the central cholinergic system. The basal forebrain provides the major source of cholinergic inputs to the neocortex and hippocampus. The main cholinergic pathways in the mammalian forebrain are the projection from the medial septal nucleus and the nucleus of the vertical limb (diagonal band of Broca) to the hippocampus via the fimbria-fornix and the projection from nucleus basalis cellularis to the neocortex.[23] Despite the severity and high prevalence of this disease, Allopathic system of medicine is yet to provide a satisfactory remedy. Therefore, we were motivated to explore the Indian traditional system to come up with a promising solution to manage this deadly disease (AD).
In the present study, we have focused upon exploring the potential of an Indian ayurvedic poly-herbal formulation, "SR-105" for its efficacy in reversing the memory deficits and for its improving acquisition and memory retention in experimental animals. Locomotor activity considered as an index of alertness and a decrease in it would indicate sedative activity. However, all the dose of polyherbal formulation SR-105 has no effect on locomotor activity. Moreover, the lack of effect on locomotor activity works to the advantages of the polyherbal formulation SR-105 demonstrating nootropic activity.
The passive avoidance is a classic model for the assessment of cognitive performance after brain lesions or pharmacological manipulation. In this the avoidance cage consists of single box without any compartments that prevents inter-compartment transfers. A sequence of stimuli is presented during which the animal has the freedom to transfer onto a safe area within the compartment. Failure to transfer or the latency to transfer to a shock-free area indicates the passive bevavior. Which is used as a short-term memory task.[24]
The polyherbal formulation SR-105 and piracetam, when given along with PHT in the second week of the 2 week regimen significantly reversed PHT-induced impairment both on acquisition and retention. A protection was observed with all the parameters tested to step-down latency (SDL), time spent in shock zone (TSZ) and step-down error (SDE). This indicates the polyherbal formulation SR-105 and piracetam have shown with significance in consolidation and retention of memory.
Sodium nitrite impaired memory was through the cholinergic innervation i.e. it causes hypoxia leading to decreased oxygen content in the brain as suggested by Koziar et al.[25,26] The protective effect existing by polyherbal formulation SR-105 and piracetam against sodium-nitrite-induced amnesic model may be due to enhanced brain metabolism by increased oxygen content in brain.
It has been reported that an increase in serotonergic transmission in the median raphe of mid brain interferes with learning acquisition and memory consolidation.[27] Diverse evidence suggests that serotonin $(5\text{-HT})_{1A}$ receptors involved in learning and memory process.[6,20] In our study we observed that polyherbal formulation SR-

105 and piracetam (200mg/kg) and amitriptyline i.e. 5-HT uptake inhibitor reduced the lithium induced head twitches, the behavior which is mediated by 5-HT.

Neuropathologic changes in Alzheimer's disease (AD) include cerebral atrophy, neuritic plaques, and neurofibrillary tangles. Neurons that use acetylcholine are critical to memory and learning, and it is primarily cholinergic neurons that show changes and degeneration in Alzheimer's disease. The decrease in cholinergic function correlates closely with cognitive deficits in patients. However, the primary pathologic process that causes Alzheimer's disease is still unknown. In the present study Polyherbal formulation SR-105, showed elevation of acetylcholine level by significant reduction of cholinesterase activity in rat's brain and ultimately improved memory.

The results of the study concluded that polyherbal formulation SR-105, has exhibited nootropic activity in absence of cognitive deficit. Due to bacopa monniera is an ingredient of polyherbal formulation, the phytoconstituent like saponins (bacosides A and B) is present, it has been suggested that the bacosides induce membrane dephosphorylation, with a concomitant increase in protein and RNA turnover in specific brain areas.[28] Further, BM has been shown to enhance protein kinase activity in the hippocampus which could also contribute to its nootropic action.[29,30] The celastrus paniculata is another ingredient of formulation, which improving learning and memory by decreasing the lipid peroxidation. The mechanism by which Celastrus paniculata enhances cognition can be attributed at least in part to antioxidant properties. In addition the serotonergic receptor antagonist property[31] or ability to decrease the levels of norepinephrine, dopamine and serotonin and its metabolites in the brain.[32,33]

In the light of above, it may be worthwhile to explore the potential of this formulation in the management of Alzheimer patients.

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Table 1. Effect of SR-105 on Locomotor activity in mice (Actophotometer)

Group No.	Treatment	Dose (per Kg)	Scores
I	Control (vehicle)	10ml p.o	202.50±28.073
II	Piracetam	200 mg p.o.	170.50ns±32.610
III	SR-105	100 mg p.o.	132.25ns±17.679
IV	SR-105	200 mg p.o.	190.75ns±4.732
V	SR-105	400 mg p.o.	199.75ns±55.138
One-way ANOVA		F	0.8080
		df	19

n=4 in each group. Data is expressed as mean ±SEM. Statistical analysis by one-way ANOVA followed by Dunnett's 't' test. Significance at $P<0.05^*$, $P <0.01^{**}$ and ns-not significant vs control group.

Table 2. Effect of SR-105 on passive avoidance learning and retention in mice

Treatment (per kg p.o.)	Trials required for acquisition (number)	Retention (2 h)			Retention (24 h)		
		SDL (sec)	SDE (number)	TSZ (sec)	SDL (sec)	SDE (number)	TSZ (sec)
Control (Phenytoin Alone) 25mg	6.0	19.833 ±3.544	5.333 ±0.4216	46.500 ±8.804	105.83 ±19.597	3.833 ±0.6540	17.667 ±2.060
Piracetam 200mg	6.0	91.000** ± 5.447	1.333** ±0.2108	13.667** ±2.348	277.67** ±11.203	0.5000** ±0.2236	2.000** ±0.9309
SR-105 100 mg	6.16	48.833* ±10.846	3.667* ±0.6146	25.833* ±4.110	194.33* ±35.333	1.500** ±0.3416	6.167** ±1.515
SR-105 200mg	6.5	71.333** ±5.142	2.000** ±0.4472	16.167** ±4.012	256.33** ±13.139	1.167** ±0.3073	4.500** ±1.648
SR-105 400mg	7.16	82.500** ±5.847	1.667** ±0.2108	10.500** ±2.487	271.50** ±9.725	0.8333** ±0.1667	2.667** ±0.7601
One-way ANOVA	F	18.694	16.645	8.687	12.952	12.171	19.124
	df	29	29	29	29	29	29

n=6 in each group. Data is expressed as mean ±SEM. Statistical analysis by one-way ANOVA followed by Dunnett's 't' test. Significance at $P<0.05^*$, $P <0.01^{**}$ and ns-not significant vs control group.

Table 3. Effect of SR-105 on inflexion ratio in mice (sodium nitrite-induced amnesic model)

Group No.	Treatment	Dose (per Kg)	Inflexion Ratio (Mean ± SEM)
I	Normal control (vehicle)	10 ml p.o.	0.2370±0.08373
II	Sodium nitrite alone	1.0 mg i.p.	0.4550±0.06283
III	Piracetam	200 mg p.o.	0.6585**±0.04064
IV	SR-105	100 mg p.o.	0.4837*±0.03842
V	SR-105	200 mg p.o.	0.5458**±0.06334
VI	SR-105	400 mg p.o.	0.5852**±0.01689
One-way ANOVA		F	6.902
		df	35

n=6 in each group. Data is expressed as mean ±SEM. Statistical analysis by one-way ANOVA followed by Dunnett's't' test. Significance at P<0.05*, P <0.01** and ns-not significant vs control group.

Table 4. Effect of SR-105 on Lithium-induce head twitches in rats

Group No.	Treatment	Dose (per Kg)	No. of Head Twitches for 60 min session (Mean ± SEM)
I	Normal control (vehicle)	10 ml p.o.	-
II	Lithium control	190 mg i.p.	20.333±1.308
III	Piracetam	200 mg p.o.	3.167**±0.3073
IV	Amitriptyline	20mg.p.o.	1.833**±0.4773
IV	SR-105	100 mg p.o.	13.333**±1.116
V	SR-105	200 mg p.o.	8.500**±0.6708
VI	SR-105	400 mg p.o	4.167**±0.3073
One-way ANOVA		F	94.308
		df	35

n=6 in each group. Data is expressed as mean ±SEM. Statistical analysis by one-way ANOVA followed by Dunnett's't' test. Significance at P<0.05*, P <0.01** and ns-not significant vs control group.

Table: 5. Effect of SR-105 on Acetyl Cholinesterase (AchE) activity in rat's brain

Group No	Treatment	Dose mg/kg	AchE Activity µmol/min/g tissue(Mean±SEM)
I	Normal control (vehicle)	10ml	$7.837 \times 10^{-7} \pm 0.1081 \times 10^{-7}$
II	Piracetam	200mg/kg	$4.249 \times 10^{-7}** \pm 0.1073 \times 10^{-7}$
III	SR-105	100 g/kg	$5.979 \times 10^{-7}** \pm 0.0700 \times 10^{-7}$
III	SR-105	200mg/kg	$5.065 \times 10^{-7}** \pm 0.0528 \times 10^{-7}$
IV	SR-105	400mg/kg	$4.363 \times 10^{-7}** \pm 0.0773 \times 10^{-7}$
One-way ANOVA		F	296.06
		df	29

n=6 in each group. Data is expressed as mean ±SEM. Statistical analysis by one-way ANOVA followed by Dunnett's't' test. Significance at P<0.05*, P <0.01** and ns-not significant vs control group.