

Full Length Research Paper

Novelty-induced behavior and memory enhancing activities of aqueous and ethanol extracts of *Solanum incanum* Linn. fruits in mice

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The present study investigated novelty-induced behavior, learning and memory enhancing activities of aqueous and ethanol fruit extracts of *Solanum incanum* Linn. using mice models. The mice were divided into sixteen (16) groups of five (5) mice each and treated with distilled water (10 ml/kg, i.p); 7.5, 15, 30 mg/kg (i.p) of both aqueous and ethanol fruit extracts; scopolamine (0.4 mg/kg) and scopolamine (0.4 mg/kg, i.p) plus pramiracetam (100 mg/kg, i.p), 7.5, 15, 30 mg/kg, (i.p) of both aqueous and ethanol fruit extracts. On the 8th day of the experiment, the animal's locomotor, rearing, grooming, percentage alternation, transfer latency and escape latency were measured. Intraperitoneal administration of *S. incanum* fruit extracts showed a significant decrease in locomotion, rearing and grooming when compared with distilled water. *S. incanum* fruit extracts at the tested doses significantly increased the percentage of spontaneous alternation and attenuated the learning and memory impairment induced by scopolamine as indicated in reduction of the transfer latency and escape latency. In conclusion, both aqueous and ethanol extracts of *S. incanum* fruit significantly improved learning and memory in mice and this could justify the ethnomedicinal use of this plant.

Key words: *Solanum incanum*, novelty-induced behaviour, learning, memory, albino mice

INTRODUCTION

Dementia is the development of multiple cognitive deficits that interfere with daily activities such as: social and professional functioning (Duong et al., 2017). The cognitive deficits are characterized with memory impairment, aphasia, apraxia, agnosia or disturbances in

executive functioning (Etindele Sosso et al., 2017). The pharmacological treatment strategies used in memory impairments as a result of neurodegenerative diseases include: diseases modifying therapies (use of anti-oxidants e.g. vitamin E) and compensation mechanism

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of neurotransmitters (cholinesterase inhibitors e.g. rivastigmine; antagonist of N-methyl-D-Aspartate [NMDA] receptor e.g. memantine). The available conventional drugs for treatment of memory impairments such as: donepezil, rivastigmine, galantamine and memantine, aim at inhibiting acetylcholine esterase in the central nervous system (CNS). This acts to elevate the levels of the neurotransmitter acetylcholine or antagonizing NMDA glutamate receptors to prevent an abnormal neuronal stimulation (Jianjun et al., 2013; Kumar et al., 2017). However, these synthetic drugs show modest and transient effects in improving memory impairments and could hardly prevent, or avert the disease progression. In addition, most of them have undesirable side effects (Jivad and Rabiei, 2014). Thus, long duration of treatment and shortage of effective or curative treatments bring a great emotional and financial burden on patients, their families and society. Therefore, there is an urgent need to develop an alternative approach for treatment of numerous diseases that result from the malfunctioning of the Central Nervous System (CNS). Exploration of medicinal herbs/plants for treatment of memory impairments has attracted substantial attention worldwide. Medicinal plants show potential efficacy and drug-drug synergistic interactions as compared with the synthetic drugs (Kumar et al., 2017). They also exert multiple synergistic effects in improving cognitive and cholinergic functions (Anand et al., 2014). Use of medicinal plants in the treatment of memory impairments has been gaining ground due to inadequacies of the synthetic/conventional medicines (Kelly and Knopman, 2008). One of such plants used is *Solanum incanum* L. (Solanaceae) with other names, bitter garden egg, apple of Sodom or bitter apple (English Language), "ikan" or "igba" (Yoruba Language) and "gautandaacii" (Hausa Language). It is an herb or soft wooded shrub used ethnomedicinally in tropical Africa to treat several conditions including CNS malfunctions (Habtamu et al., 2014). The leaves, fruits and roots of *S. incanum* are being used as memory enhancer in the South-West of Nigeria (Oladele et al., 2012; Olatunji et al., 2016) with limited scientific evidence. Thus, studies are needed to establish the memory enhancing activities of the plant. Hence, this study was designed to investigate the novelty-induced behaviour (NIB), learning and memory enhancing activities of the plant fruit extracts.

METHODOLOGY

Plant collection, identification and authentication

Fresh fruits of *S. incanum* Linn. were collected from Mulbiya in Hawul Local Government Area, Borno State, Nigeria. The plant was identified and authenticated by a plant taxonomist, Professor S. S. Sanusi of the Department of Biological Sciences, Faculty of Science, University of Maiduguri and voucher specimen (Voucher No. DCPT 014) deposited in the Pharmacology Laboratory, Department of Clinical Pharmacology and Therapeutics, Faculty of

Basic Clinical Sciences, College of Medical Sciences, University of Maiduguri, Maiduguri, Borno State.

Drugs and chemicals

Scopolamine hydrobromide was purchased from Sigma Aldrich, United States of America (USA) and Pramiracetam was purchased from AK Scientific, Union City USA. All drugs and extracts were freshly prepared in distilled water on the day of experiments. All chemicals were of analar grades.

Preparation of extracts

The unripe fruits of *S. incanum* were washed and cleaned. They were cut into small pieces, air-dried at room temperature and pulverized into a coarse powder. Extraction was done using cold maceration method as described by Bandar et al. (2013). Afterwards, the solution was sieved and filtered. The filtrates were dried in an oven at 40°C. The dried mass was stored and kept in the refrigerator until further use for one (1) month.

Experimental animals

Mature male albino mice (15-25 g) were obtained from the Department of Clinical Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Medical Sciences, University of Maiduguri and Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine, University of Maiduguri, Nigeria. The mice were housed in groups of five in plastic cages and subjected to a standard 12-h light:12-h dark light cycle at room temperature. Food and water were available *ad libitum* and the houses were cleaned regularly. The animals were housed in the animal house of the department. All behavioral tasks were conducted after at least one-week acclimatization to the laboratory conditions and each animal was tested only once. All rules applying to animal safety and care were duly observed in accordance with the Principles of Laboratory Animal Care and the Animal Care and Use Guidelines of Biomedical Research Involving Animals (CIOMS and ICLAS, 2012).

Assessment of learning and memory enhancing activities of the extracts

Novelty-induced behaviors of the extracts were assessed using an open field apparatus while learning and memory were assessed with three behavioral paradigms viz. Y-maze model, elevated plus maze and morris water maze. The treatment was done for both aqueous and ethanol extracts of the plant and each mouse was tested only once for each of the tests carried out.

Open field test (OPT) to assess the novelty-induced behavior

The spontaneous open field test effect was measured in the arena of a rectangular structure (Open field apparatus) that is composed of a hard board floor (26 × 26 × 40 cm) and made of white painted wood. The floor is divided by a permanent red mark into 16 equal squares at the bottom. After acclimatization, each mouse was introduced into the field and the total locomotion (number of floor units entered with all paws), rearing frequency (the vertical locomotion activity when the animal stands on its hind leg while raising up its forearm in the air or placed on the wall of the cage) (Onigbogi et al., 2000) and frequency of grooming (number of body

cleaning with paws, picking of the body and pubis with mouth and face washing actions) (Adebisi et al., 2016) were determined within 30 min. The behavioral activities of each mouse were scored and recorded (Suarez et al., 1996; Ajayi and Ukponmwan, 1994). After a mouse has been studied for its novelty-induced behavior, the box was cleaned with cotton wool, soaked with ethanol to prevent interference of any odor with the subsequent mouse to be studied. The behavioral tests were commenced on each mouse after 45 min of treatment with the *S. incanum* fruit extracts.

Y-Maze model (spontaneous alternation)

Y-maze model was used to assess the effects of the extracts on spatial working memory. The Y-maze is composed of three equally spaced arms (120° apart; 41 cm long × 15 cm high × 5 cm wide). In Y-maze, each mouse was placed in one arm of the compartments and allowed to move freely for 6 min. The following parameters defined were used to determine the percentage alternation:

- (i) An arm entry was defined as the body of the mouse (except for its tail) completely entering into an arm compartment.
- (ii) Alternation was defined as entering three different arms consecutively (Krebs-Kraft et al., 2009)
- (iii) The maximum spontaneous alternation is the total number of arms entered minus two (2) (Nasri et al., 2012).

The spontaneous alternation percentage (SA %) is defined as a ratio of the arm choices that differed from previous two choices (successful choices) to total choices during the run (total entry minus two) (Sarter et al., 1988; Heo et al., 2003; Mamiya et al., 2004).

Elevated plus maze (EPM) test

The elevated plus maze was used as the behavioral model to evaluate learning and memory in mice. The apparatus consists of two open arms and two covered arms (16 cm × 12 cm × 5 cm) extended from a central platform (5 cm × 5 cm) elevated to height of 25 cm from the floor. On the first day of the experiment, each mouse was placed at the end of an open arm, facing away from the central platform (Joshi and Megeri, 2008). The transfer latency (TL), defined as the time taken by the mouse to move from her original position with its four legs to one of the covered arms, was recorded on the 7th day. When the animal did not enter into one of the covered arms within 90 s, it was gently pushed into one of the two covered arms and the TL was recorded as 90 s (Milind et al., 2004). After each session, each mouse was allowed to explore the maze for 10 s and returned to its cage. Memory retention was examined after 24 h (Itoh et al., 1990; Parle and Dhingra, 2003; Dhingra et al., 2004; Joshi and Megeri, 2008).

Morris water maze (MWM) test

The Morris water maze test was used to assess spatial memory (Asi et al., 2011; Asadbegi et al., 2017). A black circular pool (180 cm in diameter and 60 cm in height) was filled with water (22 ± 1°C) to a depth of 25 cm. The pool was divided into four quadrants. A flat escape platform was submerged 1 cm below the water level in the center of the northern quadrant. The animals were placed in the water at one of the four randomly selected positions and the time between entry into the water and escape onto the platform (escape latency) was measured. Each animal was trained for six days of 60 s trials each at approximately the same time each day (10:00 a.m-12:00 p.m) for six consecutive days. The animals spent 30 s on the platform between each trial and were allowed to rest for 5 min. If an

animal failed to locate the platform within 60 s, it was gently placed on the platform and allowed to stay there for 30 s. A video camera (Samsung) was mounted directly above the pool to record the escape latency. On the 8th day, memory impairment was induced in mice with scopolamine (0.4 mg/kg, i.p.) 60 min after administration of the extracts and the standard drug, the time taken to find the hidden platform (latency) was recorded (Zarrinkalam et al., 2016).

Statistical analyses

Data obtained were expressed as mean ± standard error of mean (SEM) and subjected to statistical analyses using computer software GraphPad® InStat version 5.01 (2007). Differences among means were shown as P-values. Values of p≥0.05 were considered non-significant.

RESULTS

Novelty-induced behavior (NIB) effects of the fruit extracts

Locomotor activity

The effect of aqueous and ethanol fruit extracts of *S. incanum* on locomotor activity of mice in total session of 30 min were shown in Figure 1. The results showed a significant decrease in the locomotor activities of mice treated with both aqueous and ethanol extracts when compared with mice treated with distilled water (p<0.05). However, there was no difference in locomotor activities of mice treated with distilled water and 30 mg/kg of aqueous fruit extract (p>0.05).

Rearing activity

The effect of aqueous and ethanol fruit extracts of *S. incanum* on rearing activity of mice in total session of 30 min after intraperitoneal administration were presented in Figure 2. The rearing activities of the mice treated with all the 3 doses of both aqueous and ethanol extract were significantly lower (p<0.05) than the rearing activities of mice treated with distilled water (control).

Grooming activity

The effect of aqueous and ethanol fruits extracts of *S. incanum* on grooming activity of mice in total session of 30 min after intraperitoneal administration were presented in Figure 3. The mice treated with both aqueous and ethanol extracts at dosage of 15 and 30 mg/kg had significant (p<0.05) lower grooming activities than the control group treated with distilled water.

Memory enhancing effects of the fruits extracts

Spontaneous alternation

The effects of administration of *S. incanum* aqueous and

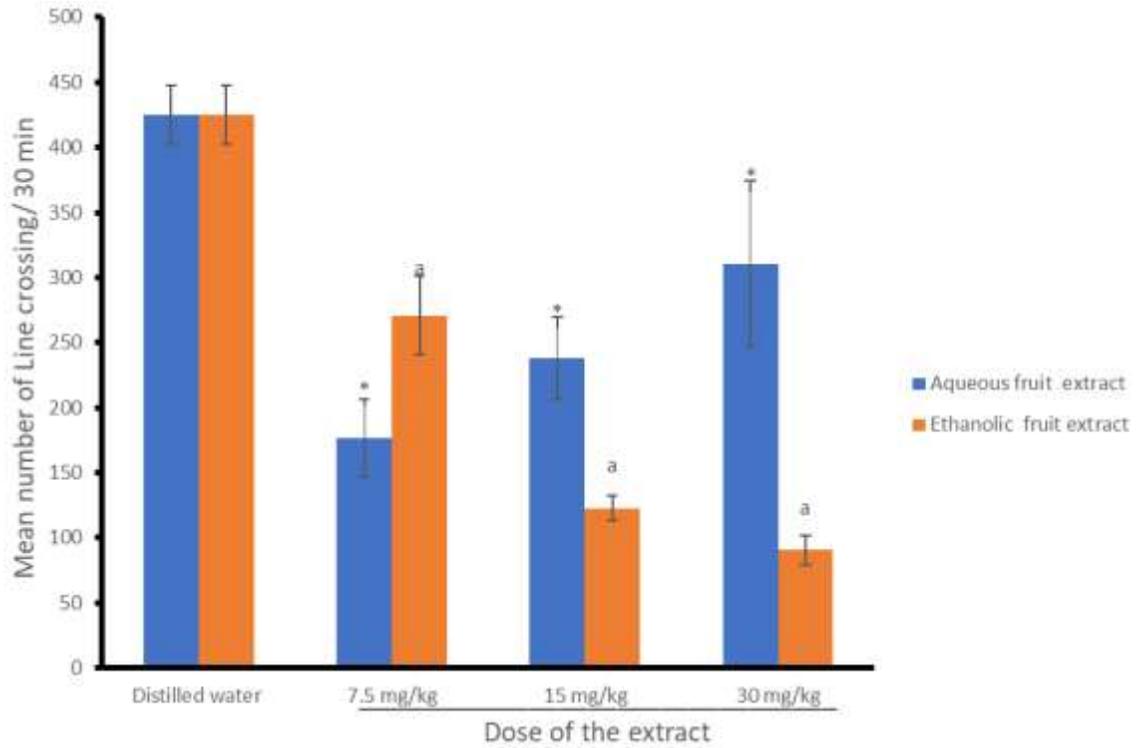


Figure 1. The effect of ethanol and aqueous fruits extracts of *S. incanum* on locomotor activity of mice in total session of 30 min. * $p < 0.05$ and ^a $p < 0.05$ when compared with the control.

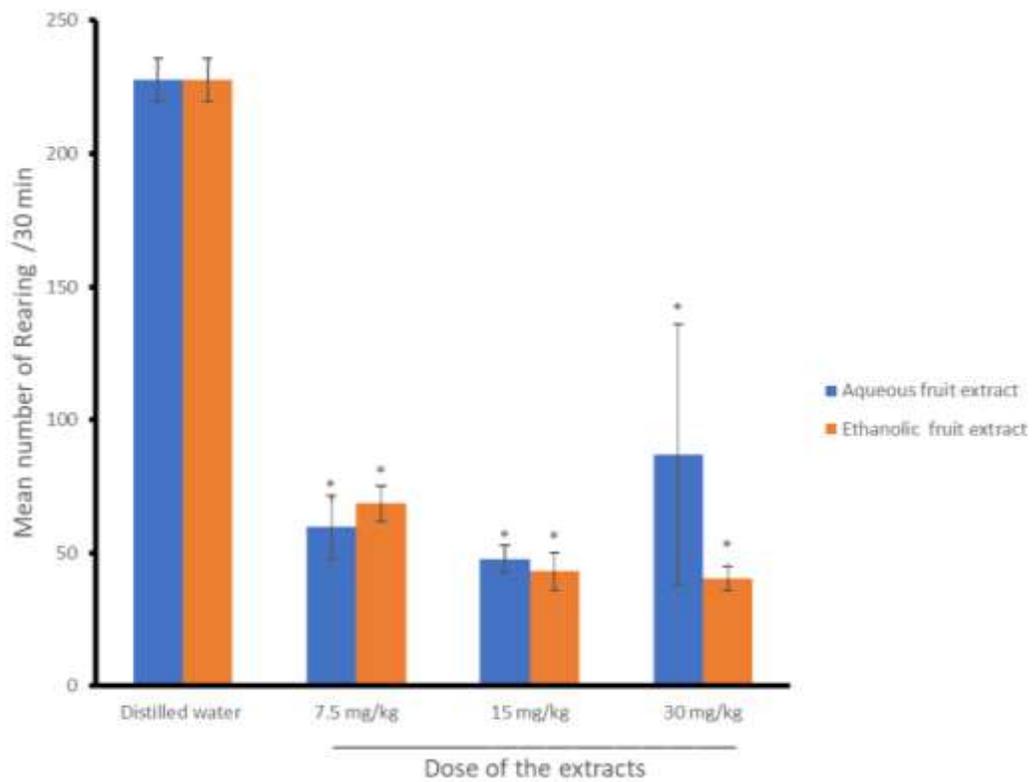


Figure 2. The effect of ethanol and aqueous fruits extract of *S. incanum* on rearing activity of mice in total session of 30 min. * $p < 0.05$ when compared with control.

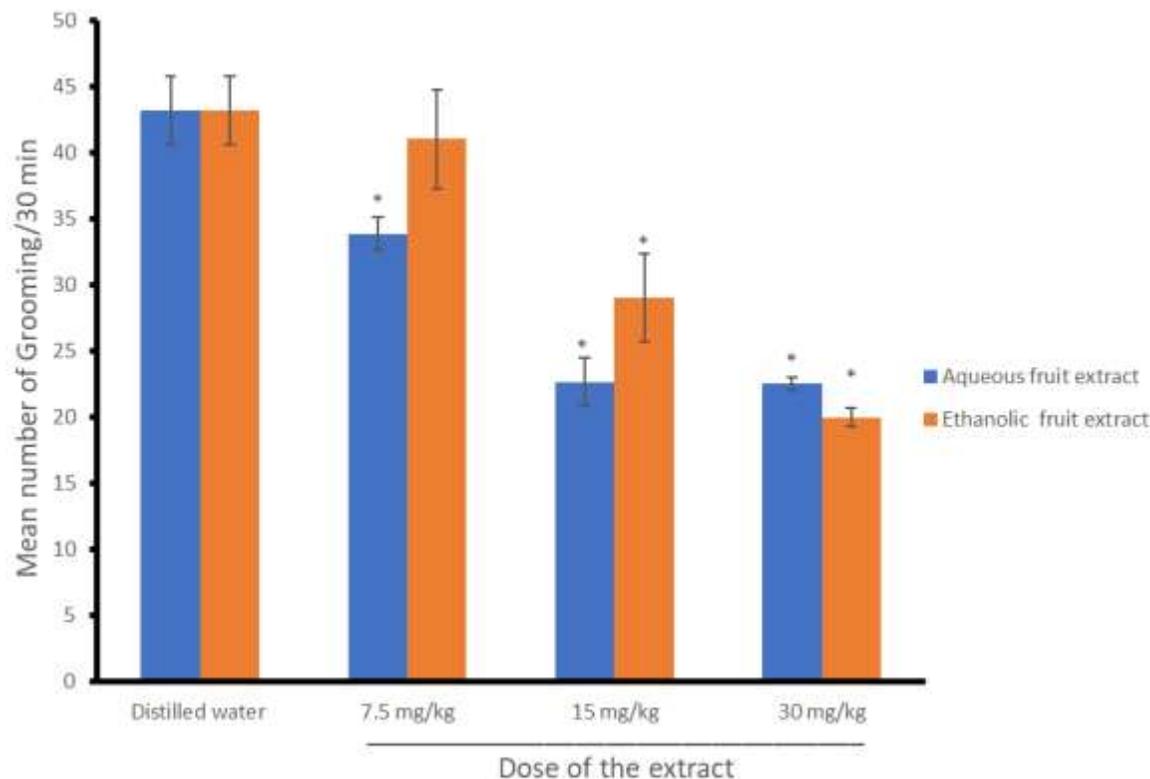


Figure 3. The effect of ethanol and aqueous fruits extracts of *S. incanum* on grooming activity of mice in total session of 30 min. * $p < 0.05$ when compared with control.

ethanol fruits extracts on learning and memory using the Y-maze paradigm are summarized in Figure 4. The results obtained showed that *S. incanum* fruits extracts caused a significant ($p < 0.05$) reverse in the amnesia induced by scopolamine followed Dunnetts post hoc analysis.

Transfer latency in elevated plus maze

Effects of aqueous and ethanol *S. incanum* fruits extracts on reflected retention of information or memory [Transfer latency (TL)] using elevated plus maze (Tables 1 and 2). Aqueous and ethanol extracts of *S. incanum* and pramiracetam (100 mg/kg) administration for 7 days significantly decreased TL on the second days, indicating significant improvement of learning and memory. Scopolamine (0.4 mg/kg, i.p.) injected before training impaired learning significantly as indicated by increased TL.

Escape latency in Moris water maze

The effects of the aqueous and ethanol extracts of *S. incanum* fruits on special learning and memory process

were assessed by Morris water maze test. The escape latency for finding the hidden platform is presented in Tables 3 and 4. The control group mice showed a marked reduction in escape latencies from days 7 and 8 (Tables 3 and 4). After acquisition time in the first six days, the administration of scopolamine in the 7th day resulted in a significant ($p < 0.05$) increase of the escape latency on the 8th compared to normal control group. The different doses of aqueous and ethanol *S. incanum* fruits extracts significantly ($p < 0.05$) decreased the escape latency induced by scopolamine on the 8th day. Likewise, piramitacetam (100 mg/kg) also significantly ($p < 0.05$) decreased the escape latency.

DISCUSSION

The extracts of aqueous and ethanol extracts of *S. incanum* were investigated for NIB, learning and memory enhancing activities by determining NIB (locomotor activity, rearing and grooming) using an open field test, percentage alternation using Y-maze, TL using elevated plus maze and escape latency using Moris water maze (Adebiyi et al., 2016). Animals placed in a novel environment show anxiety and fear, with alteration in all or some parameters such as: locomotion, rearing and

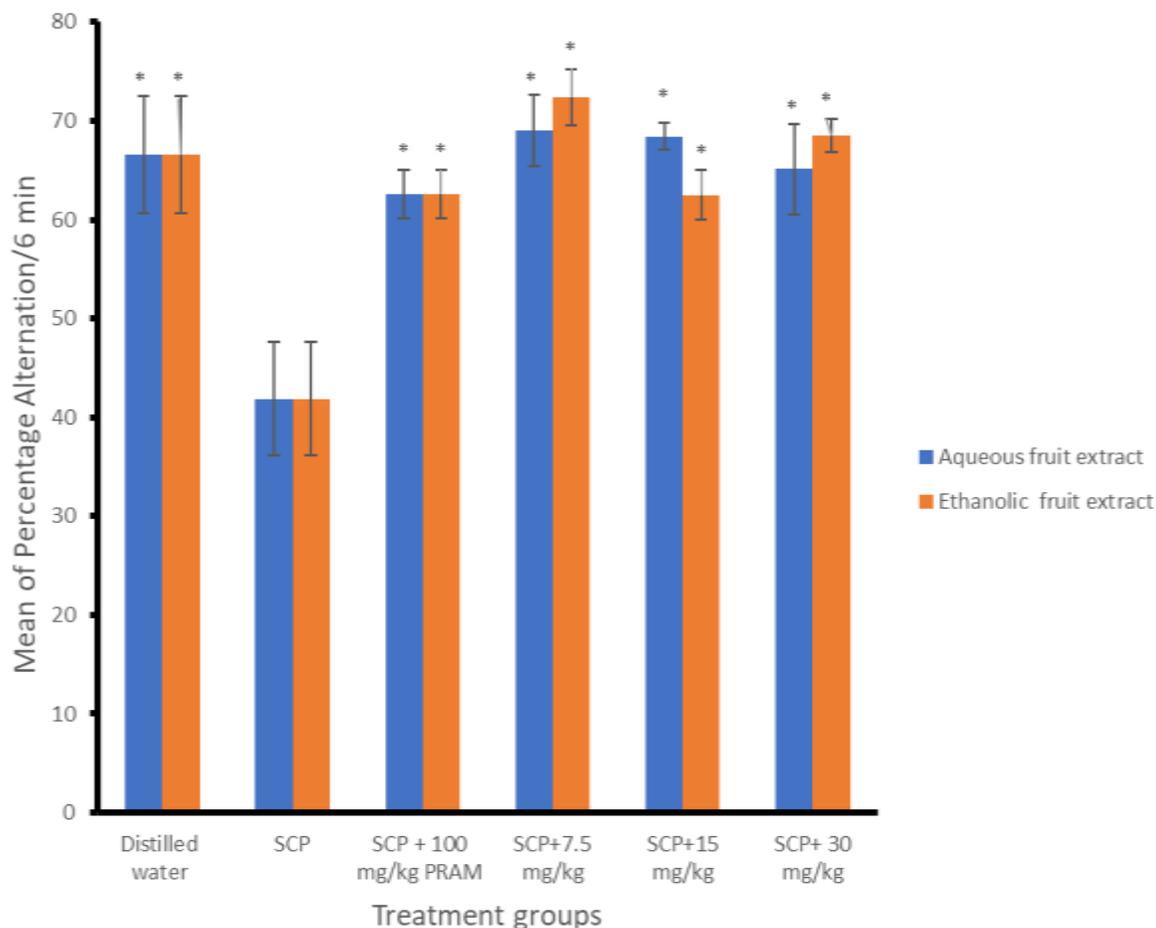


Figure 4. The effect of ethanol and aqueous extract of *S. incanum* on memory of mice in Y-maze. Data are presented as group mean \pm SEM. * $p < 0.05$ when compared with scopolamine.

Table 1. Effect of ethanol extract of *S. incanum* fruits on transfer latency of mice using elevated plus maze.

Treatment	Dose (mg/kg)	Transfer latency (s)	
		7th day	8th day
Distilled water (10 ml/kg)	-	7.8 \pm 1.40	7.6 \pm 1.63 ^a
Scopolamine	0.4	54.6 \pm 24.85	63.0 \pm 20.89
ESIF for 7 days+ SCP	7.5	38.8 \pm 7.33	11.2 \pm 1.93 ^a
ESIF for 7 days+ SCP	15	31.4 \pm 5.18	15.2 \pm 2.60 ^a
ESIF for 7 days+ SCP	30	40.8 \pm 5.27	12.2 \pm 1.50 ^a
Pramiracetam for 7 days+ SCP	100	30.8 \pm 12.97	16.6 \pm 4.86 ^a

SCP: Scopolamine, ESIF: ethanol extract of *S. incanum* fruits, $n=5$ in each group. Data are presented as group mean \pm SEM. Superscript letters a indicate $P < 0.05$ compared with scopolamine (Analysis was done by one way analysis of variance followed by Dunnett's multiple comparison test).

grooming (Hogas et al., 2011; Mutiu and Abidemi, 2013). Comparisons of the effect of *S. incanum* fruits extracts on locomotor activity revealed a significant decrease in locomotor activity with both extracts compared with the

distilled water. The decreased motor activity obtained in the present study may suggest that both aqueous and ethanol extracts of *S. incanum* fruits had some CNS depressant activities. Locomotor activity has been

Table 2. Effect of aqueous extract of *S. incanum* fruits on transfer latency of mice using elevated plus maze.

Treatment	Dose (mg/kg)	Transfer latency (s)	
		7th day	8th day
Distilled water (10 ml/kg)	-	7.8±1.40	7.6±1.63 ^a
Scopolamine	0.4	54.6±24.85	63.0±20.89
ASIF + SCP	7.5	29.8±6.61	15.2±1.56 ^a
ASIF + SCP	15	29.4±7.55	11.0±2.85 ^a
ASIF + SCP	30	30.0±5.73	12.4±2.66 ^a
Pramiracetam + SCP	100	30.8±12.97	16.6±4.86 ^a

SCP: Scopolamine, ASIF: aqueous extract of *S. incanum* fruits, n=5 in each group. Data are presented as group mean ± SEM. Superscript letters a indicate P<0.05 compared with scopolamine (Analysis was done by one way analysis of variance followed by Dunnett's multiple comparison test).

Table 3. Effect of ethanol extract of *S. incanum* fruits on escape latency of mice using Moris water maze.

Treatment	Dose (mg/kg)	Trial (s)	Test (s)
Distilled water (10 ml/kg)	-	39.6±6.0	15.0±1.2 ^a
Scopolamine	0.4	21.6±2.4	31.5±9.3
ESIF for 7 days+ SCP	7.5	29.3±1.1	12.8±2.9 ^a
ESIF for 7 days+ SCP	15	35.5±4.3	11.6±1.2 ^a
ESIF for 7 days+ SCP	30	38±6.5	10.2±3.1 ^a
Pramiracetam for 7 days + SCP	100	44.0±4.1	15.2±3.1 ^a

SCP: Scopolamine, ESIF: ethanol extract of *S. incanum* fruits, n=5 in each group. Data are presented as group mean ± SEM. Superscript letters a indicate P<0.05 compared with scopolamine (Analysis was done by one way analysis of variance followed by Dunnett's multiple comparison test).

Table 4. Effect of aqueous extract of *S. incanum* fruits on escape latency of mice using Moris water maze.

Treatment	Dose (mg/kg)	Trial (s)	Test (s)
Distilled water (10 ml/kg)	-	39.6±6.0	15.0±1.2 ^a
Scopolamine	0.4	21.6±2.4	31.5±9.3
ASIF + SCP	7.5	34.7±3.4	10.4±2.9 ^a
ASIF + SCP	15	36.7±8.1	10.7±1.7 ^a
ASIF + SCP	30	33.5±6.7	11.6±1.4 ^a
Pramiracetam + SCP	100	44.0±4.1	15.2±3.1 ^a

SCP: Scopolamine, ASIF: aqueous extract of *S. incanum* fruits, n=5 in each group. Data are presented as group mean ± SEM. Superscript letters a indicate P<0.05 compared with scopolamine (Analysis was done by one way analysis of variance followed by Dunnett's multiple comparison test).

reported to represent a broad class of sensory, motor and integrative processes and mediated through dopamine and other neurochemical pathways (Rang et al., 2001; Aderibigbe et al., 2010). Extracts of *S. incanum* fruits showed a dose dependent decreased in rearing, indicating sedative effect of *S. incanum*. The fruits extracts of *S. incanum* also reduced novelty-induced grooming suggesting that the fruits extracts have ability to depress the CNS. Sedative activities and stimulation of

CNS effects of medicinal plants can be assessed through the modification and measurement of the frequency of rearing and grooming in mice (Vogel, 2002). Drugs with stimulating activities on the CNS increase rearing and grooming behavior, while those with depressive activities on the CNS inhibit rearing and grooming behavior (Aderibigbe et al., 2010). Gray (2001), Owens et al. (2012), Storbeck (2012), and Luck and Vogel (2013) reported that cognitive performance can be affected by

emotional state and anxiety. These two factors are involved in the impairment of cognitive performance (Sandi, 2013; Maloney et al., 2014; Moran, 2016). Anxiety is associated with an increase in overall sensory sensitivity due to uncertainty or conflict (Gray, 2001; Grillon, 2002; Cornwell et al., 2007; Eysenck et al., 2007; Grupe and Nitschke, 2013). In an open field, individual testing and agoraphobia trigger anxiety behavior (Crawley, 1985; Doukkali et al., 2016).

Multiple neurotransmitter system such as: gamma-aminobutyric acid (GABA), cholinergic, adrenergic, opioid, serotonin, glutamate and dopamine receptors have been reported to regulate the novelty-induced rearing and grooming behavior response in animals (Adebiyi et al., 2016). Reduction of rearing and grooming behaviors by the fruits extracts of *S. incanum* suggests its antagonizing activities on dopamine, serotonin, glutamate or cholinergic neurotransmission and potentiation of GABA as reported by Leggio et al. (2011) and Adebiyi et al. (2016). Thus, further studies are required to ascertain the mechanism of action of the fruit extracts.

In the present study, memory-enhancing activity of both aqueous and ethanol fruits extracts of *S. incanum* were investigated in mice models. Exhaustion of stored acetylcholine (ACh) is the major cause of memory loss in progressive neurodegeneration diseases in the ageing population. Drugs or plants that show anticholinesterase activity are thus useful in the treatment of neurodegenerative disorders e.g. AD (Agrawal et al., 2009). In Y-maze model, the similarity between the percentage alternation in mice that received distilled water alone, extracts and pramiracetam is an indication that the extracts possess memory enhancing activity. This result suggests that both aqueous and ethanol extracts of *S. incanum* fruits used in this study display an improved effect on spatial working memory within the Y-maze task. The possible underlying mechanism of the aqueous and ethanol extracts action could be an increase in the brain cholinergic receptor sensitivity or the decrease of the acetylcholinesterase (AChE) activity.

In EPM, TL is distinctly reduced if the animal had been previously exposed to an open and closed arms and this has been found to be associated with memory processes (Bhanumathy et al., 2010). On the first day, TL reflected learning behavior of animals, whereas TL of second day reflected retention of information or memory (Itoh et al., 1990; Achliya et al., 2004). In the present study, the animals treated with extract of *S. incanum* fruits extracts showed a significant decrease in transfer latency as comparable to that of pramiracetam, this indicates its cognitive enhancing activity in mice.

MWM is designed to validate and evaluate the neurocognitive disorders and neurocognitive treatments in the investigation of spatial learning and memory in rodents (D'Hooge and De Deyn, 2001; Ju et al., 2020). It was observed that administration of *S. incanum* fruits extracts showed a significant decreased escape latency value as compared to the scopolamine treated group and

this effect is comparable to that of pramiracetam (Pahuja et al., 2012). The previous studies showed a correlation between reduced cholinesterase activity and impaired learning and memory functions in different rat models (Adebiyi et al., 2016; Akinyemi et al., 2017; Rubio et al., 2017; Opeyemi et al., 2018). Therefore, the ability of pretreated *S. incanum* fruits extracts to inhibit scopolamine-induced impaired spatial working memory could be correlated with their anti-ChEs activities (Kwon et al., 2010; Shi et al., 2010; Azizi-Malekabad et al., 2012; Opeyemi et al., 2018), suggesting the possible mechanism of action of *S. incanum*. Saponins and tannins found in the fruits have been reported to have nootropic activities (Chintawar et al., 2002; Elufioye et al., 2012). Moreover, it was reported that diet with more carbohydrate, fibre and mineral such as: Mg²⁺, Ca²⁺ and Zn²⁺ improve cognitive performance (Ortega et al., 1997; Huskisson et al., 2007; Piechal et al., 2016).

In conclusion, the aqueous and ethanol extracts of *S. incanum* fruits exert memory-enhancing effects in a scopolamine induced memory loss in mice model. It exhibited a cognitive-enhancing effect by reversing scopolamine-induced learning and memory deficits as demonstrated with Y-maze, elevated plus maze and Morris water maze. These therapeutic properties could be attributed to the phytochemicals in the fruit extracts.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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