(RESEARCH ARTICLE)

Check for updates

Sedative and anticonvulsant activities of aqueous and ethanol dried leaf extracts of *Solenostemon monostachyus* in mice

Ayokunmi Stephen Olusa * and Idris Ajayi Oyemitan

Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria.

Abstract

This study evaluated the sedative, and anticonvulsant activities of the aqueous (AESM) and ethanol (EESM) dried leaf extracts of *Solenostemon monostachyus*. The sedative effect of the extracts was evaluated with ketamine-induced hypnosis (100 mg/kg, *i.p.*). Also, the anticonvulsant activity was evaluated using pentylenetetrazole (PTZ)-induced convulsion (85 mg/kg, *i.p.*), strychnine-induced convulsion (2 mg/kg, *i.p.*) and maximal electroshock (MES)-induced convulsion models. The AESM (200 mg/kg, *p.o.*) gave 66.67% protection, while EESM (800 mg/kg, *p.o.*) gave 100% protection against the hind limb tonic extension on the MES. The AESM only at 200 mg/kg, *p.o.* caused a significant change (p < 0.01) in the convulsion latency and time of death in PTZ –induced convulsion. The AESM and EESM (200, 400 and 800 mg/kg, *p.o.*) significantly (p < 0.05 – 0.01) shortened sleep latency. At 400 and 800 mg/kg, *p.o.*, AESM prolonged (p < 0.05) total sleeping time while EESM at 800 mg/kg, *p.o.* significantly (p < 0.05) prolonged total sleeping time relative to vehicle. The study concluded that the aqueous leaf and ethanol dried leaf extracts of S. *monostachyus possessed* sedative and mild anticonvulsant activities.

Keywords: *Solenostemon monostachyus*; Leaf Extracts; Sedative; Anticonvulsant

1. Introduction

It is believed by many that herbal therapy can be used to treat a variety of diseases that require lifetime pharmaceutical treatment, which poses a challenge of side effects. Traditional medical practitioners also feel that the phytoconstituents found in herbal medicine are more compatible with the human system [1]. According to the World Health Organization (WHO), herbal medicine is used by 60% of the world's population, and about 80% of the people in developing nations rely on it nearly entirely for their basic health care requirements. Phytocompounds and their chemical analogs have produced a plethora of clinically relevant medications for the treatment of both chronic and acute illnesses. Herbal phytochemicals are being studied for direct medicinal application as well as prototype lead compounds for the development of novel synthetic or semisynthetic medicines [1]. The herb *Solenostemon monostachyus* sp. Beauv (Lamiaceae) is a valuable West and Central African plant. Its common name is Monkey's potato, but also known as African dead nettle. The Efik calls it Ntorikwot and Awakmmon; Aranpolo by the Yorubas and Sankwo by Hausas. It's a valuable herb that thrives in both anthropogenic and rocky savannah environments [2]. Convulsions, fever, headache, and cough, especially in children, are treated with the leaf sap, which is sedative and stomachic. Dysmenorrhoea, haematuria, female infertility, rheumatism, foot infections, and snakebites are conditions treated with the leaves [3]. Some pharmacological activities of the plant include hepatoprotective, antioxidant, analgesic, antipyretic, anti-inflammatory, antiulcer, prolacting-reducing and high blood pressure-reducing activities [4-8]. This study aimed at evaluating the sedative and anticonvulsant activities of the extracts to provide scientific information on its folkloric use.

* Corresponding author: Ayokunmi Stephen Olusa E mail: ayokunmiolusa@oauife.edu.ng Contact No. +2348059734264
Department of Pharmacology, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria.

2. Material and methods

2.1. Plant collection, identification, authentication and preparation

The plant, *S. monostachyus* was collected in Obafemi Awolowo University, Ile-Ife, Nigeria, 7.4968^o N, $4.5172^{o\ E}$ and herbarium specimen number IFE-17638 was issued after authentication at the Botany Department, Faculty of Science, Obafemi Awolowo University, Ile-Ife.

The fresh leaves were detached from the stalk, air dried under shade for about two weeks. The *S. monostachyus* dried leaves were powdered with laboratory mill. The powdered leaf (500 g) was weighed and the aqueous extraction done using soxhlet extraction method for about 48 h. The extract was then dried in an oven maintained at 40 °C before being kept in the desiccator until use.

For the ethanol extraction, the powdered leaf (500 g) was macerated with 3 L of 80 % ethanol for 72 h. The mixture was filtered and the filtrate concentrated to dryness *in vacuo* using a rotary evaporator at 40 °C. The extract was subsequently kept in the desiccator until use. The percentage yield of AESM was 3.55% while that of EESM was 2.63%.

2.2. Laboratory materials

2.2.1. Drugs

Diazepam (Roche, Basel, Switzerland), pentylenetetrazole (Sigma, Chemical Co, St Louis, USA), Ketamine (Mark Pharmaceuticals, Lagos, Nigeria), strychnine (Sigma, Marin-Epagnier, Switzerland) and Phenytoin sodium (Pharma-deko, Ogun, Nigeria).

2.2.2. Laboratory animals

The study employed the use of adult male and female albino mice (18-25 g) from the Animal House, Department of Pharmacology, Faculty of Pharmacy, OAU, Ile-Ife. Food and drink were freely available to them. Oral route of administration of extracts and test substances (*p.o.*) was adopted. The animal studies followed a procedure approved by the Obafemi Awolowo University, Ile-Ife, Nigeria's committee on animal use and care.

2.2.3. The choice of route of administration

The oral route of administration was adopted to imitate the traditional way of administration. Working doses of 200, 400, and 800 mg/kg, *p.o.* were utilized, which were less than half of the LD_{50} values (3808 and 2154 mg/kg, *p.o*) for the aqueous and ethanol extracts respectively.

Effect of aqueous and ethanol dried leaf extracts of *S. monostachyus* on ketamine-induced sleeping time

Ketamine (100 mg/kg, *i.p.*) was used for the induction of sleep in the mice [9,10]. The mice in each of the groups (n=6) were pre-treated with the vehicles, extracts (200, 400 and 800 mg/kg, *p.o.,* respectively) and diazepam (2 mg/kg, *p.o.*) for the positive control groups [11] 1h before administering ketamine. Each of the animals was observed for sleep latency (SL) which is also the onset of sleep (duration for the loss of righting reflex from the time of injection); and the total sleeping time (TST) or the duration of sleep which is the time from loss of righting reflex to regaining it.

Effects of aqueous and ethanol dried leaf extracts of *S. monostachyus* on chemo - and electro - induced convulsion

The anticonvulsant activity of the leaf extracts of *S. monostachyus* was investigated via oral route using chemo-convulsion (pentylenetetrazole and Strychnine-induced convulsion) and electro-convulsion (maximal electro convulsion) models.

Effect of aqueous and ethanol dried leaf extracts of *S. monostachyus* on electro-induced convulsion**.**

Electroconvulsive shock was used to induce hind limb tonic extension (HLTE). The electrical stimulus (50 Hz, 50 mA, 0.2 s) was applied through the ear lobes by electrode clamp, using an electroconvulsiometer. Mice were divided into five groups for each of aqueous and ethanol extracts (n=6 per group). Group 1 was administered with the vehicle; groups 2-4 (test groups) were given 200, 400 and 800 mg/kg, *p.o.* of the extracts respectively while group 5 was treated with Phenytoin (25 mg/kg, *p.o.*). After being pre-treated for 1 h each mouse was subjected to the MES test. Protection against HLTE indicated anticonvulsant activity [12].

Effect of aqueous and ethanol dried leaf extracts of *S. monostachyus* on strychnine (STR)-induced convulsion

The mice groupings in section (a) above was repeated for the STR-induced convulsion. Strychnine (2 mg/kg, *i.p.*) was used as the proconvulsant and diazepam (5 mg/kg, *p.o.*) as the positive control. The onset of clonic and tonic-clonic convulsion as well as time of death was assessed after 1 h of pre-treatment before injection with strychnine (2 mg/kg, *i.p.*) [13]. Animals which survived more than 30 min were classified as protected.

Effect of aqueous and ethanol dried leaf extracts of *S. monostachyus* on pentylenetetrazole (PTZ)-induced convulsion

The mice groupings in section (b) above was repeated for the PTZ-induced convulsion. The proconvulsant used was PTZ (85 mg/kg, *i.p.*) [13] and diazepam (2 mg/kg, *p.o.*) as a positive control. The onset of clonic and tonic-clonic convulsion as well as time of death and mortality was observed. Animal that did not convulse within the 30 minutes of observation was qualified protected [14].

2.3. Statistical analysis

The results were expressed as Mean ± SEM and analysed using one-way analysis of variance (ANOVA) followed by post hoc test using Dunnett's comparison test and Student-Newman-Keuls test. The level of significance was set at 95% confidence interval ($p < 0.05$) for all treatments carried out compared to control groups. Graph pad prism, version 5.0 (UK) was used.

3. Results

3.1. Effects of the dried leaf extracts of *S. monostachyus* on ketamine-induced hypnosis

3.1.1. Effect of AESM on ketamine-induced sleep latency (SL) in mice

The AESM at 200, 400 and 800 mg/kg, *p.o.* and diazepam (2 mg/kg, *p.o*) caused a significant [$p < 0.05 – 0.01$, $F_{(4, 25)} = 7.380$] reduction in the sleep latency (SL) induced by ketamine (100 mg/kg, *i.p.*) compared to the vehicle (normal saline, at 0.1 ml/10g, *p.o.*). This result is shown in Figure 1A.

3.1.2. Effect of AESM on ketamine-induced total sleeping time (TST) in mice

The AESM (400 and 800 mg/kg, *p.o.*) and diazepam (2 mg/kg, *p.o.*) caused a significant [$p < 0.01$; $F_{(4, 25)} = 12.575$] increase in the total sleeping time (TST) induced by ketamine (100 mg/kg, *i.p.*) compared to the vehicle (normal saline, at 0.1 ml/10g, *p.o.*). This result is shown in Figure 1B.

3.1.3. Effect of EESM on ketamine-induced sleep latency (SL) in mice

EESM (200, 400 and 800 mg/kg, *p.o.*) and diazepam (2 mg/kg, *p.o*) caused a significant ([$p < 0.05 - 0.01$, $F_{(4, 25)} = 4.073$] reduction in the sleep latency (SL) induced by ketamine (100 mg/kg, *i.p.*) compared to the vehicle (5% Tween 80, at 0.1 ml/10 g, *p.o.*). This result is shown in Figure 2A.

3.1.4. Effect of EESM on ketamine-induced total sleeping time (TST) in mice

EESM at 800 mg/kg, *p.o.* and diazepam (2 mg/kg, *p.o.*) caused a significant [$p < 0.05 - 0.01$, $F_{(4, 25)} = 6.658$] prolongation in the total sleeping time (TST) induced by ketamine (100 mg/kg, *i.p.*) compared to the vehicle (5% Tween 80, at 0.1 ml/10 g, *p.o.*). This result is shown in Figure 2B.
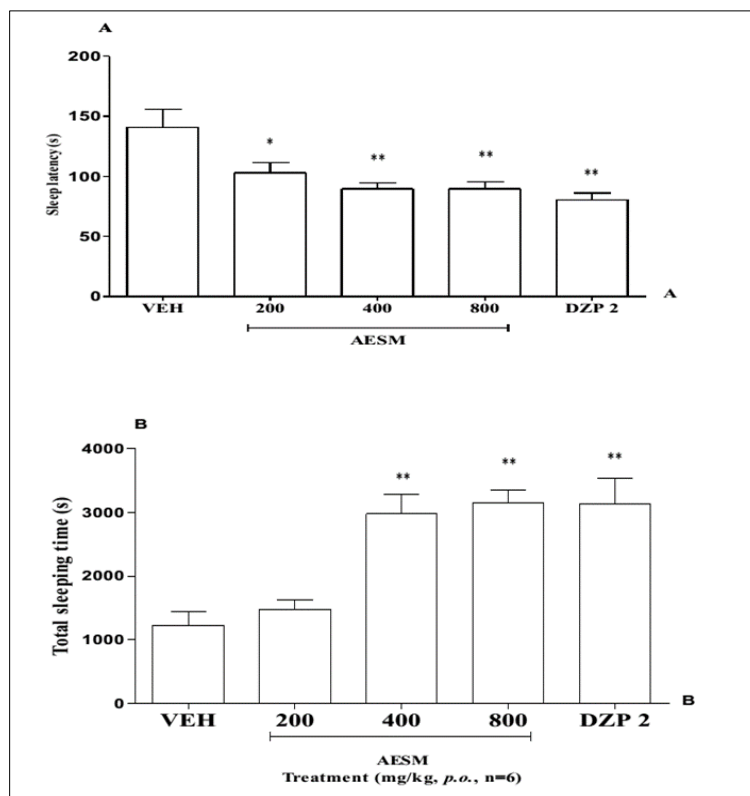
Bars represent mean values with error bars (n=6). VEH, AESM and DZM represent vehicle (normal saline), aqueous dried leaf extract of *S. monostachyus* and diazepam respectively. *p < 0.05, **p < 0.01 statistically lower than vehicle (ANOVA, Dunnett's comparison test).

Figure 1A and B Effects of AESM on ketamine-induced sleep latency (SL) and total sleeping time (TST) in mice
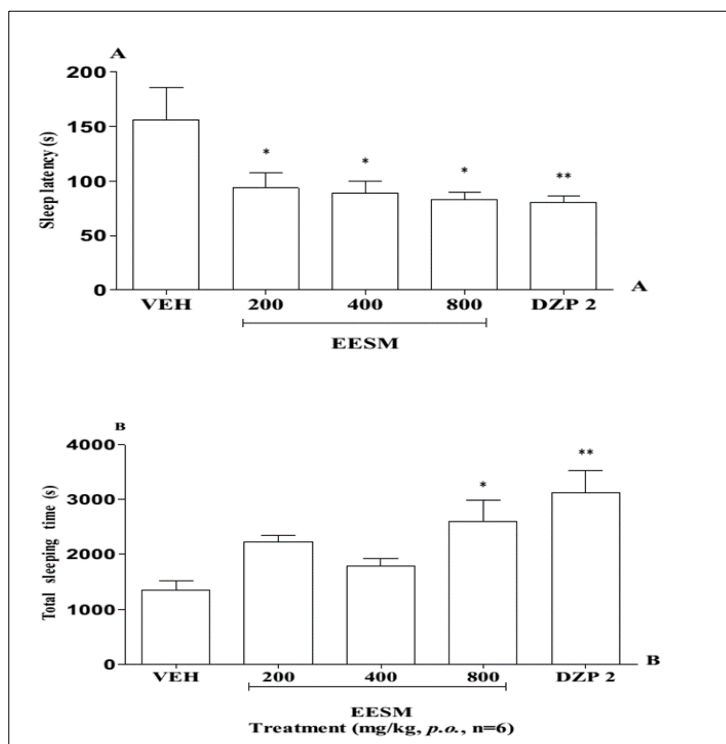
Bars represent mean values with error bars (n=6). VEH, EESM and DZM represent vehicle (normal saline), ethanol dried leaf extract of *S. monostachyus* and diazepam respectively. *p < 0.05, **p < 0.01 statistically lower than vehicle (ANOVA, Dunnett's comparison test).

Figure 2A and B Effects of EESM on ketamine-induced sleep latency (SL) and total sleeping time (TST) in mice

3.2. Anticonvulsant evaluation

3.2.1. Effects of AESM on pentylenetetrazole (PTZ)-induced convulsion test

The AESM (200, 400, and 800 mg/kg, *p.o.*) caused no significant change in the convulsion latency (CL) compared to the vehicle (normal saline, 0.1 ml/10g, *p.o.)* respectively, while diazepam (2 mg/kg, *p.o.*) caused a significant (p < 0.05) increase in CL compared to the vehicle. The AESM (800 mg/kg, *p.o.*) and diazepam (2 mg/kg, *p.o.*) caused a significant (p < 0.05) increase in the time of death (TD) compared to the vehicle. However, The AESM (200 and 400 mg/kg, *p.o.*) showed no significant change in TD compared to the vehicle. Furthermore, the AESM at 400 and 800 mg/kg, *p.o.* offered 16.67% and 33.33% protection against PTZ-induced convulsion respectively while Diazepam 2 mg/kg, *p.o.* gave a protection of 66.67% (Table 1).

Table 1 Effects of AESM on pentylenetetrazole-induced convulsion in mice

Treatment *p.o.* (n=6)	Convulsion Latency (CL) (Mean ± SEM) (s)	Time of Death (min) (Mean ± SEM)	% protection against convulsion
VEH 0.1 ml/10 g	75.83 ± 14.61	4.67 ± 0.55	0.00
AESM 200 mg/kg	97.50 ± 21.92	10.5 ± 3.09	0.00
AESM 400 mg/kg	99.00 ± 22.35	12.83 ± 3.71	16.67
AESM 800 mg/kg	115.00 ± 24.75	16.5 ± 4.42*	33.33
DZM 2 mg/kg	243.00 ± 62.42*	21.83 ± 5.18*	66.67

VEH, AESM and DZM represent vehicle (normal saline), aqueous dried leaf extract of S. monostachyus and diazepam respectively.
*p < 0.05 statistically significant compared to the vehicle (ANOVA, Dunnett's test).

3.2.2. Effects of AESM on strychnine-induced convulsion test

The AESM (400 and 800 mg/kg, *p.o.*) and diazepam (5mg/kg, *p.o.*) did not produce significant change in the convulsion latency (CL) and time of death (TD)compared to the vehicle (normal saline). However, at 200 mg/kg, *p.o.* AESM caused a significant change in CL (p < 0.01) and TD (p < 0.05) (Table 2).

Table 2 Effect of AESM on strychnine-induced convulsion in mice

Treatment *p.o.* (n=6)	Convulsion Latency (CL) (Mean ± SEM) (s)	Time of Death (min) (Mean ± SEM)	% Protection against convulsion
VEH 0.1 ml/10 g	211.33 ± 14.52	4.67 ± 0.33	0.00
AESM 200 mg/kg	393.83 ± 28.17**	7.17 ± 0.40*	0.00
AESM 400 mg/kg	298.33 ± 42.14	4.83 ± 0.65	0.00
AESM 800 mg/kg	206.83± 9.65	4.83 ± 0.65	0.00
DZM 5 mg/kg	276.67 ± 42.62	6.00 ± 0.68	0.00

VEH, AESM and DZM represent vehicle (normal saline), aqueous dried leaf extract of S. monostachyus and Diazepam respectively.   **p < 0.05 – 0.01 statistically significant compared to the vehicle (ANOVA, Dunnett's test).

3.2.3. Effects of the AESM on Maximal Electroshock (MES) – induced convulsion test

The results obtained on the MES test showed that all the mice in the vehicle (normal saline) group displayed spontaneous hind limb tonic extension (HLTE), However, the animal groups pretreated with the AESM (200, 400 and 800 mg/kg, *p.o.*) and phenytoin (25 mg/kg, *p.o.*) in the MES test showed 66.67%, 33.33%, 33.33%, and 100.00 % protection respectively. There was 16.67% mortality in the groups pretreated with the vehicle and AESM 200 mg/kg *p.o.* respectively. However, no mortality was recorded in all the other treatment groups (Table 3).

Table 3 Effects of AESM on Maximal Electroshock-induced convulsion

Treatment *p.o.* (n=6)	Number of mice with MES- induced HLTE	Duration of HLTE (s) Mean ± SEM	Protection against HLTE (%)	Mortality (%)
VEH 0.1 ml/ 10 g	6/6	111.50 ± 2.87	0	16.67
AESM 200 mg/kg	2/6	49.67 ± 16.42**	66.67	16.67
AESM 400 mg /kg	4/6	58.50 ± 20.06**	33.33	0
AESM 800 mg/ kg	4/6	0.00 ± 0.00*	33.33	0
PHNY 25 mg/ kg	0/6	0.00 ± 0.00**	100.00	0

VEH, AESM and PHNY represent vehicle (normal saline), aqueous dried leaf extract of S. monostachyus and Sodium valproate respectively. **p < 0.05 – 0.01 statistically significant compared to the vehicle (ANOVA, Dunnett's test.)

3.2.4. Effects of EESM on pentylenetetrazole (PTZ)-induced convulsion test

The EESM (200, 400 and 800 mg/kg, *p.o.*) caused no significant increase in the convulsion latency (CL) compared to the vehicle (5% Tween 80, 0.1 ml/10g, *p.o.*) respectively. However, diazepam (2 mg/kg, *p.o.*) caused a significant (p < 0.05) increase in CL compared to the vehicle. The EESM (200, 400 and 800 mg/kg) did not cause significant change in the time of death (TD) but diazepam (2 mg/kg, *p.o.*) caused a significant increase (p < 0.05) in TD compared to the vehicle. Furthermore, it was found that, the extract at 400, and 800 mg/kg, *p.o.* offered 16.7% and 33.33% protection respectively while at 200 mg/kg, *p.o.* it had no protection (0%). Diazepam 2 mg/kg, *p.o.* offered 66.67% protection to the animals (Table 4).

Table 4 Effect of EESM on pentylenetetrazole -induced convulsion in mice

Treatment *p.o.* (n=6)	Convulsion Latency (CL) (Mean ± SEM) (s)	Time of Death (min) (Mean ± SEM)	% Protection against convulsion
VEH 0.1 ml/10 g	79.33 ± 8.57	4.67 ± 0.56	0.00
EESM 200 mg/kg	85.17 ± 16.62	8.67 ± 2.43	0.00
EESM 400 mg/kg	126.33 ± 29.20	13.17 ± 3.60	16.67
EESM 800 mg/kg	147.33 ± 20.54	16.50 ± 4.42	33.33
DZM 2 mg/kg	243.00 ± 62.42*	21.83±5.18*	66.677

Vehicle, EESM and DZM represent vehicle (5% Tween 80), ethanol dried leaf extract of S. monostachyus and diazepam respectively. *p < 0.05 statistically significant compared to the vehicle (ANOVA, Dunnett's test.)

3.2.5. Effects of EESM on strychnine-induced convulsion test

The EESM (200, 400 and 800 mg/kg, *p.o.*) did not cause a significant change in the convulsion latency (CL) and time of death (TD) compared to the vehicle (5% Tween 80). Diazepam (5 mg/kg, *p.o.*) did not cause significant change in CL but there was significant change in TD compared to the vehicle (5% Tween 80). (Table 5).

3.2.6. Effects of EESM on Maximal Electroshock (MES) – induced convulsion test

The results obtained on the MES test showed that all the mice in the vehicle (5% Tween 80) group displayed spontaneous hind limb tonic extension (HLTE) and went unconscious. However, all the animals pretreated with the EESM (200, 400 and 800 mg/kg, *p.o.*) had a percentage protection of 33.33%, 33.33% and 100.00% respectively against HLTE. Phenytoin (25 mg/kg, *p.o.*) had 100.00% protection against HLTE. There was no mortality in all the treatment groups except the vehicle group (16.67%). (Table 6).

Table 5 Effect of EESM on strychnine-induced convulsion in mice

Treatment *p.o.* (n=6)	Convulsion Latency (CL) (Mean ± SEM) (s)	Time of Death (min) (Mean ± SEM)	% protection against convulsion
VEH 0.1 ml/10 g	213.83 ± 24.54	3.83 ± 0.31	0.00
EESM 200 mg/kg	267.00 ± 18.56	4.83 ± 0.40	0.00
EESM 400 mg/kg	219.17 ± 44.21	4.00 ± 0.73	0.00
EESM 800 mg/kg	231.17 ± 29.00	4.50 ± 0.50	0.00
DZM 5 mg/kg	276.67 ± 42.62	6.00 ± 0.68*	0.00

VEH, EESM and DZM represent vehicle (5% Tween 80), ethanol dried leaf extract of S. monostachyus and diazepam respectively *p < 0.05 statistically significant compared to the vehicle (ANOVA, Dunnett's test.)

Table 6 Effect of EESM on maximal electroshock- induced convulsion

Treatment *p.o.* (n=6)	Number of mice with MES- induced HLTE	Duration of HLTE (s) Mean ± SEM	Protection against HLTE (%)	Mortality (%)
VEH 0.1 ml/ 10 g	6/6	96.83 ± 7.03	0	16.67
EESM 200 mg/kg	4/6	36.00 ± 15.15**	33.33	0
EESM 400 mg /kg	4/6	25.17 ± 11.35**	33.33	0
EESM 800 mg/ kg	0/6	0.00 ± 0.00**	100.00	0
PHNY 25 mg/ kg	0/6	0.00 ± 0.00**	100.00	0

VEH, EESM and PHNY represent vehicle (5% Tween 80), ethanol dried leaf extract of S. monostachyus and phenytoin respectively. **P < 0.01 statistically significant compared to the vehicle (ANOVA, Dunnett's test).

4. Discussion

The sleep-like state of the mice observed during the acute toxicity test, the behavioural activity assessment also in mice during the open field test after administration of the extracts [15] and the sedative property associated with CNS depressants pushed for the evaluation of the sedative property of the extracts. This was however evaluated using ketamine. Ketamine which is known to cause hypnosis is an antagonist of NMDA receptor, an excitatory receptor which plays a role in seizures. Results from the effect of the extracts on ketamine-induced sleeping time showed that AESM and EESM reduced sleep latency significantly (p < 0.05 – 0.01) at 200 and 400 and 800 mg/kg, *p.o.* in mice compared to the vehicle. Both extracts prolonged the total sleeping time. AESM significantly prolonged the total sleeping time (p < 0.01) at 400 and 800 mg/kg, *p.o.* while EESM significantly prolonged the total sleeping time (p < 0.05) at only 800 mg/kg, *p.o.* Reduction of sleep latency and prolongation of total sleeping time indicate sedative activity [9,16,17]. In agreement with the previous reports, diazepam 2 mg/kg, *p.o.* significantly prolonged ketamine-induced sleeping time. Various neurotransmitters and endogenous molecules are involved in regulation of sleep and wakefulness. The sleep-promoting neurons located in the anterior hypothalamus release gamma-aminobutyric acid (GABA) to suppress activity of wake-inducing areas of the brain [18]. Ketamine has been established to exhibit agonist properties on $GABA_A$ receptors [19] hence, it suggests a possible involvement of the GABAergic pathway in the eliciting of the sedative activity of the extracts [20].

Some medicinal plants have been observed to interact with GABAergic system for the inducement of their sedative or hypnotic effect [21]. Previous studies have reported that the presence of the different phytochemical compounds such as terpenes, flavonoids and saponins are responsible for the hypnotic activity of medicinal plants [22]. Flavonoids bind with high affinity to benzodiazepine site of the $GABA_A$ receptor [23] hence, these phytochemical compounds may be part of the components of the extracts eliciting a sedative activity. This therefore, established the ethnomedicinal use of the *S. monostachyus* as a sedative.

Global CNS depressants like benzodiazepines are used as anticonvulsants. The extracts, having displayed CNS depressant effect were therefore evaluated for anticonvulsant property. In the PTZ-induced convulsion model, there was no significant change in the convulsion latency of AESM at all the three dose levels (200, 400, 800 mg/kg, *p.o.*) when

compared with the vehicle but diazepam (2 mg/kg, *p.o.*) showed a significant ($p < 0.05$) increase in the convulsion latency. There was however a significant ($p < 0.05$) delay in the time of death by AESM only at a dose of 800 mg/kg, *p.o.* Diazepam (2 mg/kg, *p.o.*) also delayed the time of death significantly. EESM (200, 400, 800 mg/kg, *p.o.*) did not cause significant change in PTZ-induced convulsion latency and time of death compared to the vehicle.

Earlier studies have shown that benzodiazepines and barbiturates elicit their anticonvulsant effects on PTZ-induced seizures by enhancing GABA effect in the brain [24]. PTZ is one of the chemoconvulsants widely used to induce convulsions in experimental animals [25]. It is therefore, possible that the mild anticonvulsant effect against PTZ by AESM at 800 mg/kg *p.o.* might be due to the activation of GABA (major inhibitory neurotransmitter implicated in epilepsy) neurotransmission [26]. Studies have shown that activation of NMDA receptor plays a role in the initiation and spread of PTZ-induced siezures [27], hence suggesting a possible inhibitory activity of the extract on NMDA receptor.

For strychnine-induced convulsion, the AESM only at 200 mg/kg, *p.o.* caused a significant change ($p < 0.01$) in the convulsion latency (CL) and time of death (TD). The EESM however at all the three dose levels did not significantly change CL and TD compared to the vehicle (5% Tween 80). Diazepam (5 mg/kg *p.o.*) Caused significant ($p < 0.05$) prolongation in TD compared to the vehicle (5% Tween 80). Strychnine induces convulsion by directly antagonizing the inhibitory action of glycine at the spinal cord and brainstem hence, increasing spinal reflexes [28]. This induces excitatory response in the central nervous system. The result however revealed that the AESM may have an impact on glycinergic neurotransmission.

The effect of AESM (200, 400 and 800 mg/kg, *p.o.*) on Maximal Electroshock-induced (MES) convulsion, showed a 66.67%, 33.33% and 33.33% protection respectively against HLTE in mice. The EESM (200, 400 and 800 mg/kg, *p.o.*) offered 33.33%, 33.33% and 100.00% protection respectively against HLTE. Phenytoin (25 mg/kg, *p.o.*) offered 100.00% protection against HLTE. The maximal electroshock (MES) is a widely used tool to screen drugs for generalized tonic-clonic seizures. MES basically causes disruption of signal (impulse) transduction in the neurons, and damage cell due to facilitation of Ca^{2+} influx into the cell, thus resulting to prolongation of convulsion period [29]. Apart from Ca^{2+}, MES may also facilitate the influx of other positive ions like Na^+ which when blocked by drugs such as phenytoin is known to prevent MES-induced tonic hind limb extension [30]. Hence, the extracts may probably be acting through blockade of Ca^{2+} or Na^+ channels or both [24].

5. Conclusion

It is hereby concluded that the aqueous and ethanol dried leaf extracts of *Solenostemon monostachyus* displayed significant sedative and mild anticonvulsant effects in mice. Therefore, the various CNS effects of the extracts that have been shown in this research inferentially established the pharmacological basis for the use of the plant ethnomedicinally as sedative and for the treatment of convulsion and other related ailments.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest

Statement of ethical approval

The animal studies followed an approved procedure with the number: PHP14/15/H/0209 by the Postgraduate College on behalf of Obafemi Awolowo University, Ile-Ife, and research committee.

References

[1]   Mohd S, Ahmad K, Iqbal A. Herbal Medicine: Current Trends and Future Prospects. New Look to Phytomedicine. Academic Press. 2019, pp 3-13. ISBN 9780128146194.

[2]   Mba CE, Menut C. Aromatic plants of tropical Central Africa. Flav Frag J. 1994. 9(6):315–317.

[3]   Lemmens, RHMJ. *Solenostemon monostachyus* (P.Beauv.) Briq. *Solenostemon monostachyus* (P.Beauv.) Briq. In: Grubben, G.J.H. and Denton, O.A. (Eds). PROTA 2: Vegetables/Légumes. PROTA, Wageningen, Netherlands. pp.507.

[4]   Tebekeme O, Diepreye E. Antioxidant Activities of *Solenostemon monostachyus* Leaf Extract Using in Vitro Methods. Sci Res Essays. 2012. Feb 16;7(6):621-626.

[5]   Okokon JE, Louis UA, Lucky LN. Antidiabetic and hypolipidaemic activities of *Solenostemon monostachyus*. J Herbal Drugs. 2015. Article 3, Vol 6, Issue 2:85-92.

[6]   Okokon J, Koofreh AD, Bala AA. Antipyretic and antimalarial activities of *Solenostemon monostachyus*. Pharm Biol. 2016;54(4): 648-653.

[7]   Kpahe, Z.F., Konan, B.A., Datté, J.Y. and Offoumou, A.M. Action of hydroethanolic leaves extract of *Solenostemon monostachyus* (lamiaceae) on cardiovascular system of mammalians: Blood pressure lowering effects. Int J Pharm Bio Sci. 2012. 2(3):310-320.

[8]   Omoloye, A.A., Quasim, K. O., Johnson, S. O. and Murtala, A.A. Endocrine and metabolic effects of hydroethanolic extract of *Solenostemon monostachyus* on haloperidol induced hyperprolactinemia. J Pharm Pharmacol. 2015. Aug 28;3(8)391-399.

[9]   Oyemitan IA, Emmanuel O, Adebola OO. Neuropharmacological profile of ethanol dried seed extract of Persea Americana in mice. Afr J Pharm Pharmacol. 2016. Vol. 10(22):480-492.

[10]   Mimura MA, Namiki R, Kishi TI, Miyake H. Antagonistic effects of physostigmine on ketamine-induced anaesthesia. Psychopharmacology. 1990.102(3):399-403.

[11]   Adeyemi OO, Akindele AJ, Yemitan OK, Aigbe FR, Fagbo FI. Anticonvulsant anxiolytic and sedative activities of the aqueous root extract of Securida longepedunculata. J Ethnopharmacol. 2010. Jul 20;130(2):191-195.

[12]   Pourgholami MH, Kamalinejad M, Javadi M, Majzoob S, Sayyah M. Evaluation of anticonvulsant activity of essential oil of Eugenia caryophyllata in male mice. J Ethnopharmacol. 1999. Feb;64(2):167-171.

[13]   Bilkel-Gorzo A, Gyertyan I. Some doubts about the basic concept of hole board test. Neurobiology (Bp). 1996. 4(4):405-15.

[14]   Komorowska J, Pellis SM. Regulatory mechanisms unmderlying novelty-induced grooming in laboratory rat. Behav Processes. 2004. Sep 30;67(2):287-93.

[15]   Olusa AS, Oyemitan IA. Acute toxicity test and behavioural activity of aqueous and ethanol dried leaf extracts of *Solenostemon monostachyus* in mice. NJPR. 2022 Apr 5;17(S):1-14.

[16]   Ayoka, AO, Akomolafe RO, Iwalewa EO, Akanmu MA, Ukponmwan OE. Sedative, antiepileptic and antipsychotic effects of Spondias mombin L. (Anacardiaceae) in mice and rats. J Ethnopharmacol. 2006. Jan 16;103(2):166–175.

[17]   Imoru JO, Oriola AO, Oyemitan IA, Akanmu MA. Sedative, hypothermic, anxiolytic effects and rapid radical scavenging property of aqueous leaf extract of Vitex doniana (Lamiaceae) in mice. IJTCM. 2020. 5:32.

[18]   Datta S. Cellular and chemical neuroscience of mammalian sleep. Sleep Med. 2010. May;11(5):431-40.

[19]   Henschel O, Gipson KE, Bordey A. GABA receptors, anesthetics and anticonvulsant in brain development. CNS Neurol Disord Drug Targets. 2008. Apr 7(2):211- 224.

[20]   Sivam SP, Nabeshima T, Ho IK. Acute and chronic effects of pentobarbital in relation to postsynaptic GABA receptors: a study with muscimol. J Neurosci.Res. 1982. 7(1):37-47.

[21]   Nogueira E, Vassilieff U S. Hypnotic, anticonvulsant and muscle relaxant effects of Rubus brasiliensis. Involvement of GABAA system. J Ethnopharmacol. 2000. Jun;70:275-280.

[22]   Jiang J, Huang X, Chen J, Lin Q. Comparison of sedative and hypnotic effects of flavonoids, saponins, and polysaccharides extracted from Semen Ziziphus jujube. Nat Prod Res. 2007. Apr;21(4):310-320.

[23]   Wasowski C, Marder M. Flavonoids as GABAA receptor ligands: the whole story. J Exp Pharmacol. 2012. Feb;4:9-24.

[24]   Hedge K, Thakker SP, Joshi AB, Shastry CS, Chandrashetchar KS. Anti-convulsant activity of Carissa carandas Linn. Root extract in experimental mice. Trop J Pharm Res. 2009. Apr; 8:117-125.

[25] McNamara JO. Development of new pharmacological agents for epilepsy: lessons from the kindling model. Epilepsia. 1989. 30, S13-S18; discussion S64-8.

[26] Ozbakis-Dengiz G, Bakira A. Anticonvulsant and hypnotic effects of amiodarone. J Zhejiang Uni Sci. 2009. Apr10:317-322.

[27] Nevins ME, Arnolde SM. A comparison of the anticonvulsant effects of competitive and non-competitive antagonist of the N-methyl-d-aspartate receptor. Brain Res. 1989. Nov27;503(1):1-4.

[28] Sayin U, Cengiz S, Altug T. Vigabatin as an anticonvulsant against pentelenetetrazole seizures. Pharmacol Res. 1993. Dec; 28:325-331.

[29] Inan SY. Buyukafsar K. Antiepileptics effects of two Rho-kinase inhibitors, Y-27632 and fasudil in mice. Br J Pharmacol. 2008. Sep;155:41-51.

[30] MacDonald RL, Kelly KM. Antiepileptic drug mechanisms of action. Epilepsia.1995.36: Suppl 2:S2-S12.