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**Anticonvulsant, Anxiolytic, and Sedative Properties of The Fruit of  
*Sarcocephalus Latifolius* In Rats.**

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**ABSTRACT**

This study was conducted to evaluate the anticonvulsant and the sedative anxiolytic activity of the fruit extract of *Sarcocephalus latifolius* (synonym, *Nauclea latifolia*) Smith (Rubiaceae) in rats. The ethanolic extract of the plant fruit was screened for its anxiolytic activity using simple activity meter. Anticonvulsant activities of the extract was evaluated on four experimental animal models at doses of 200, 400 and 800 mg/kg,i.p in rats using maximal electroshock seizure (MES) test, pentylenetetrazole (PTZ) test, picrotoxin (PIC) and strychnine (STR) - induced seizures test. Sodium valproate (400 mg/kg) was used as a reference anticonvulsant drug for all models. The plant showed marked sedative - anxiolytic effect and significant decrease in the motor activity ( $p < 0.001$ ) since the first dose (200 mg/kg) in a dose-dependent manner. The doses 400 and 800 mg/kg of the extract significantly ( $p < 0.01$  -  $p < 0.001$ ) reduced the duration of seizures induced by maximal electroshock (MES) and delayed the onset of tonic- clonic seizures produced by strychnine respectively. All the tested doses significantly protected the animals up to 100% from pentylenetetrazole and picrotoxin- induced seizures. Results of the present study concluded that the ethanolic extract of the fruit of *S. latifolius* possess sedative, anticonvulsant and anxiolytic properties. So it is recommended for the treatment of insomnia anxiety and epilepsy.

**المستخلص**

اجريت هذه الدراسة لتقييم النشاط المضاد للتشنج والمزيل للقلق والمهدئ للمستخلص الكحولي من ثمرة نبات الكرمودودة لدى الجرذان. تم استخدام جهاز كشف النشاط البسيط لتقييم الاثر المزيل للقلق لثمرة النبات كما تم تقييم الاثر المضاد للتشنج على اربع نماذج اجريت على حيوانات التجارب باستخدام نموذج الصعق الكهربائي، مادة البنتالين تترازول ومادة البيكروتوكسين ومادة الاستركنين المشنجه. استخدم فالبوريت الصوديوم الدواء المضاد للتشنج كدواء ضابط ايجابي مع كل النماذج. تم اختبار ثلاث تراكيز مختلفة من مستخلص ثمرة النبات وهي 200 و400 و800 ملغ/كجم حقنت علي غشاء البريتون في الجرذان. اظهرت النتائج اثر مزيل للقلق وانخفاض كبير في النشاط الحركي منذ اعطاء الجرعة الاولى من المستخلص 200ملغ/كجم بدلاله معنويه اقل من 0.001 مقارنة مع مجموعة الضابط الايجابي. كما استطاعت الجرعتين 400 و800 ملغ/كجم تخفيض مدة نوبة التشنج الناجمة عن الصعقة الكهربائية على نمودجي الصعق الكهربائي وتأخر بدء ظهور النوبات التشنجية الناتجة عن مادة الاستركنين بدلالة معنويه 0.01 و0.001 على التوالي في حين إن كل الجرعات التي تم اختبارها قامت بحماية الحيوانات من النوبات التشنجية الناجمة عن مادتي البنتالين تترازول والبيكروتوكسين بشكل ملحوظ يصل

إلى 100%. خلصت الدراسة الى ان ثمرة نبات الكرمودودة والمستخدمة في الطب التقليدي السوداني لعلاج القلق والاراق والصرع تمتلك مركبات لها خواص مضادة للتشنج ومهدنه ومزيلة للقلق لدى الجرذان.

**KEYWORDS** Epilepsy, *Sarcocephalus latifolius*, Seizures, Traditional medicine, Pentylene-tetrazole, Picrotoxin, Strychnine .

## INTRODUCTION

Traditional medicine in many areas of the world relies on the use of a wide variety of plant species. Only 10% of plants have been studied for their pharmacological properties<sup>(1)</sup>. *S. latifolius* is one of the medicinal plants used in Africa and Sudan. The stem bark, the leaves, the roots, and the fruit of this plant are used to treat various types of diseases<sup>(2,3)</sup>. In Sudan and many African countries, *S. latifolius* is used in the treatment of fever, yellow fever, malaria, and diseases of the central nervous system like epilepsy<sup>2</sup>. According to herbalist, the plant is also used in the treatment of anxiety and agitation. Previous experiments have shown that if the aqueous extract of *S. latifolius* is administered intraperitoneally, it lowers the rectal temperature of guinea pigs and also exhibits analgesic, antidiabetic, and hepatoprotective properties<sup>(4, 5)</sup>. The extracts of the roots, leaves and bark possess antibacterial and antiplasmodial activities<sup>(6,7)</sup>. Recently, Amos *et al*<sup>(8)</sup>, Taiwe *et al*<sup>(9)</sup> showed that the aqueous extract of the root of *S. latifolius* possesses antidepressant, myorelaxant and anti-anxiety effects, decreases spontaneous motor activity and exploratory behaviour in mice, increases pentobarbital-induced sleep time in rats and attenuates the intensity of apomorphine-induced stereotypies in mice. As *S. latifolius* is used to treat diseases of the nervous system such as anxiety and epilepsy and also to tranquilize agitated patients, this study was intended to investigate the anticonvulsant, anxiolytic and sedative

properties of this medicinal plant in rats.

## MATERIALS and METHODS

### Plant material

*Sarcocephalus latifolius* fruits were purchased from its natural homeland at Nubba Mountains area, southwest Sudan.

The fruits were manually cleaned to remove all foreign matter, then sliced with a clean knife into thin slices. They were allowed to dry in open air for 7 days. The dried plant material was ground into a fine powder using clean, dry electric blender.

Ethanol extraction process was followed according to Pavia *et al*<sup>(10)</sup>.

### Chemicals

Pentylene-tetrazole, sodium valproate, picrotoxin and strychnine (Sigma Chemical, USA).

### The experimental animals

Adult males, Wistar Albino Rats (WAR), weighting 110-125 g were housed in standard polypropylene cages in the Laboratory Animal House of the Aromatic Plants Research Institute (MAPRI), National Centre for Research (NCR), Sudan (from February 2012 to May 2013). The animals were acclimatized for 7 days under standard environmental conditions (*i.e.*, relative humidity: 40-60%, temperature: 24±2°C, and 12 h light-dark cycle), and fed with mash feed consisting of flour, meat, edible oil, sodium chloride, vitamins, minerals and tap water *ad libitum*. Supply of food was withdrawn 12 h prior to the commencement of the experiment; however, the rats were allowed for free access to water always. All the experiments were

carried out by using five animals in each group. The experiments were carried out between 8 am and 12 noon<sup>(11)</sup>. Twenty five rats were used in each experiment, divided into five groups; each group received 3 different single doses (200, 400 and 800 mg/kg. i.p) of the plant fruit extract. One group was given 400 mg/ kg. i.p sodium valproate as a reference drug (positive control). The last group was given 10ml/kg. i.p distill water (negative control). This study was approved by the Scientific Research Committee of the College of Pharmacy, OIU in accordance with good clinical practice and international guidelines for animal use in experimentations.

#### **Phytochemical screening**

Preliminary phytochemical characterization of the extract was done using methods already described for the determination of alkaloids, anthraquinones, flavonoids, glycosides, phenols, saponins and tannins by Harbone<sup>(12)</sup>.

#### **Experiment 1**

##### **Measurement of anxiolytic activity in rats**

An anxiety model, simple activity meter test, was used to explore the anti-anxiolytic effect of the tested extract<sup>(13)</sup>. The simple activity meter is a box composes of two glassy and two wooden sides stand on 625 cm<sup>2</sup> wooden plane board divided to 25 squares, each square was 25 cm<sup>2</sup>. A rat was placed on the center of the board and left to move freely for a period of 5 minutes. The number of movements between the squares were counted in the consecutive 5 minutes. Decrease in number of movements/5 minutes was taken as an indication of anti-anxiety activity. Decrease in motor activity reflected the sedative effect of the extract.

#### **Experiment 2**

##### **Pharmacological tests & Assessment of anticonvulsant activity: Pentylenetetrazole (PTZ) -induced seizure test:**

Myoclonic jerks seizures were induced in male rats by subcutaneous injection of 70 mg/kg pentylenetetrazol (PTZ)<sup>(14, 15, 16 and 17)</sup>. The protective effect of the three tested doses of the extract was recorded. The tested extract was given 45 minutes before PTZ injection. The positive control group received 400mg/kg. ip sodium valproate 15 minutes before PTZ injection. One group received 10ml/kg.i.p distilled water and served as a negative control group.

#### **Experiment 3**

##### **Picrotoxin (PIC) - induced seizure test:**

This model acts to disrupt the inhibition/excitation balance and creates an epileptogenic focus<sup>(18)</sup>.

Clonic seizures were induced in male rats by subcutaneous injection of 10 mg/kg/i/p picrotoxin. The three various doses of the extract were given 45 minutes before picrotoxin administration while sodium valproate was given 15 minutes before picrotoxin injection. Another group received 10ml/kg.i.p distilled water and served as a negative control group. The protective percentage was then recorded.

#### **Experiment 4**

##### **Maximal electroshock test (MES)**

Tonic convulsions of the hind extremities of mice were induced by passing an alternating electrical current (50 mA, of 100 Hz frequency (pulse/sec.) for 0.5 sec. duration through ear electrodes<sup>(16,17,18, and 19)</sup>.

The three tested doses of the extract were given 45 minutes before the induction of the MES while sodium valproate was given 15 minutes before

the induction. One group of five rats received 10ml/kg.i.p distilled water and served as a negative control group. The number of animals protected from tonic hind limb extension was determined in each dose group.

### Experiment 5

#### Strychnine (STR) test

Convulsions followed by death were induced in male mice by the subcutaneous injection of 2.5 mg/kg strychnine (STR) nitrate. The protective effect of the different intraperitoneal treatments were given 45 minutes prior to STR was recorded. The positive control group received 400 mg/kg.ip sodium valproate 15 minutes before the STR administration while the last group received 10ml/kg.i.p distilled water and served as a negative control. Animals that survived more than 10 minutes were qualified as protected. <sup>(14,16 and 20)</sup>

#### Statistical analysis

The values are expressed as mean  $\pm$  SEM and the data were analyzed using one way ANOVA followed by Tukey-

Kramer test. The level of significance was set at

$P < 0.05$ . Median anticonvulsant dose ( $ED_{50}$ ) was calculated according to the method of Litchfield and Wilcoxon <sup>(21)</sup>. A computer program was used to calculate 95% confidence limit of  $ED_{50}$ .

## RESULTS

### Phytochemical characterization

Chemical characterization showed that the extract of *Sarcocephalus latifolius* contained alkaloids, anthraquinones, flavonoids, glycosides, phenols, saponins, and tannins.

### Experiment 1

#### The effects of *Sarcocephalus latifolius* extract on the motor performance in the simple activity meter test

The plant showed marked sedative - anxiolytic effect and significant decrease in the motor activity ( $p < 0.001$ ) since the first dose (200mg/kg) in a dose-dependent manner (Table 1).

Table 1: The effects of *Sarcocephalus latifolius* extract on the motor performance in the simple activity meter test

Dose (mg/kg) i.p		200 (mg/kg)	400 (mg/kg)	800 (mg/kg)
Movements count/5 minutes (Mean $\pm$ SEM)	-ve control group	26.0 $\pm$ 1.90	26.0 $\pm$ 1.90	26.0 $\pm$ 1.90
	Treated group	10.4 $\pm$ 1.21***	4.0 $\pm$ 1.30***	1.20 $\pm$ 0.56***

Treatment was compared with negative control group. \*\*\*  $p < 0.001$ .

### Experiment 2

#### Effect of *S. latifolius* on pentylenetetrazol-induced seizures

*Sarcocephalus latifolius* and sodium valproate also protected rats against PTZ-induced seizures. 200 mg/kg. ip of the plant extract showed 60% protection against PTZ, whereas 400

and 800 mg/kg, ip as well as sodium valproate (400mg/kg. ip) showed 100% immunity against PTZ in the treated groups (Table 2).

All the affected animals were recovered and no incidence of mortality was recorded.

*Table 2: The Effect of S.latifolius on Pentylenetetrazole (PTZ) – induced convulsions*

Treatment	Sodium valproate	<i>S. latifolius</i>
ED <sub>50</sub>	162	171.29
(95% C.L.), mg/kg	(140-185)	(107.91 – 341.37)

ED<sub>50</sub> (in mg/kg).

### Experiment 3

#### The effect of *Sarcocephalus latifolius* against picrotoxin (PIC)-induced convulsion

The plant extract proved a potent anticonvulsant activity against PIC-induced seizures. A dose of 200 mg/kg, ip appeared 40% protection against PIC- induced seizures while the

protection ratio increased up to 80% after the administration of 400mg/kg,ip. 100% protection was observed in the group that administered 800 mg/kg, ip. (Table 3). All the affected animals were recovered and no incidence of deaths was observed.

*Table 3: The effect of S. latifolius against Picrotoxin (PIC)- induced convulsion*

Treatment	Sodium valproate	<i>S. latifolius</i>
ED <sub>50</sub>	192.6	209.1
(95% C.L.),mg/kg	(159-207)	(117.17 – 373.15 )

ED<sub>50</sub> (in mg/kg).

### Experiment 4

#### Effect of *S.latifolius* on maximal electroshock (MES) -induced seizures

The anticonvulsant compound sodium valproate completely protected rats against MES-induced seizures (P < 0.001).

The dose of 800 mg/kg showed 60% protection in the tested group and significantly (p< 0.001) decreased the recovery period by (14.60±9.33)

compared to the positive control group (174.20 ± 23.01 sec ). 400 mg/kg appeared 40% protection against the MES with significant (p <0.01 ) decrease in the recovery period by(30.40±14.49sec) compared to the control. 200 mg/kg of the extract did not show significant protection against the test and the mean of recovery time was (129.60±4.96 sec) (Table 4 ). All the animals were recovered and no deaths were observed.

Table 4: The effect of *S. latifolius* extract on maximal electroshock (MES)- induced seizures

Type of treatment	Dose rate (mg/kg)	Protection rate against MES %	Time (sec) for duration of recovery (Mean $\pm$ SEM)	Recovery/ death
Saline (- ve control)	( 1 ml/rat)	0 %	174.20 $\pm$ 23.01	Recovery
Standard valproate	400	100%	0.00 $\pm$ 0.00***	Recovery
<i>S. latifolius</i>	200	0 %	129.60 $\pm$ 4.96	Recovery
	400	40 %	30.40 $\pm$ 14.49**	Recovery
	800	60 %	14.60 $\pm$ 9.33***	Recovery

\*\*p < 0.01 most significant, \*\*\*p < 0.001 highly significant (compared with the respective negative control).

### Experiment 5

#### Effect of *S. latifolius* on strychnine (STR)-induced seizures

Sodium valproate completely protected the rats against STR-induced seizures (p< 0.001). In the same way, *S. latifolius* significantly increased the number of protected rats by increasing the delay of convulsions occurrence

induced by strychnine. 800mg/kg, ip of the plant extract appeared significant (p< 0.001) increase in the latency of seizures by (38.20 $\pm$ 1.77 min) compared to the negative control (3.20  $\pm$ 0.86 min), whereas, 400mg/kg significantly (p<0.05) increased the latency of seizures by (20.90 $\pm$  1.50 min. 200 mg/kg failed to protect the animals against STR effect (Table 5).

Table 5: The effect of *S. latifolius* extracts on strychnine (STR)- induced seizures

Type of treatment	Dose rate (mg/kg)	Protection rate against (2.5mg/kg.ip) STR %	Time (Min) of the latency of convulsions (Mean $\pm$ SEM)	Survive/ death
Saline (-ve control)	( 1 ml/rat)	0 %	3.20 $\pm$ 0.86	Death
Standard sodium valproate	400	100%	0.00 $\pm$ 0.00***	Survive
<i>S. latifolius</i>	200	0%	7.20 $\pm$ 1.02	Death
	400	20%	20.90 $\pm$ 1.50*	Death
	800	60%	38.20 $\pm$ 1.77***	Death

\*p < 0.05 significant, \*\*\*p < 0.001 highly significant (compared with the respective negative control).

### DISCUSSION

The results of the current study indicate that *S. latifolius* (synonym, *Nauclea latifolia*) have potential

anxiolytic-sedative properties. This potentiation of anti- anxiety suggests the presence of anxiolytic-sedative properties in the extract of *S.*

*latifolius*<sup>(20, 22)</sup>. This is in accordance with the results obtained by Amos *et al*<sup>(8)</sup> and Ngo Bum *et al*<sup>(20)</sup> who showed that the aqueous and the ethanolic extract of the roots of *S. latifolius* prolongs pentobarbital-induced sleep in rats. Taiwe *et al*<sup>(9)</sup> reported similar results that *S. latifolius* root extract induced reduction of mobility and displayed anxiolytic property in a similar way to that of fluoxetine. These anxiolytic properties could be mediated by some components in the extract interacting with the benzodiazepine/GABAA receptors as agonists, with the 5-HT1A receptors as agonists<sup>(20)</sup>. The sedative properties found here could explain the use of this plant in traditional medicine in Africa, particularly in Sudan, in the treatment of the nervous system diseases such as insomnia, anxiety and epilepsy and also to tranquilize agitated patients. *Sarcocephalus latifolius* also showed significantly anticonvulsant properties by inhibiting convulsions induced chemically or electrically. The extract protected rats against PTZ, PIC and STR-induced seizures in a dose-dependent manner. As PTZ has been shown to interact with the GABA neurotransmitter<sup>(11)</sup>, the antagonism of PTZ-induced seizures suggests that *S. latifolius* interacts with GABAergic neurotransmission since PTZ is a selective blocker of the chloride ionophore complex to the GABA-A receptor. Picrotoxin (PIC)- induced seizures is known to be a non-competitive GABA antagonist, exerting its effect by blocking the chloride channel in the GABA<sub>A</sub> receptor complex<sup>(23, 24 and 25)</sup>. It is used to induce acute simple partial seizures and generalized tonic-clonic seizures<sup>(26)</sup>. The antagonism of PIC-induced seizures suggests the interaction of the plant extract with the GABA-ergic neurotransmission.

The inhibition of STR-induced seizures by *S. latifolius* extract suggests that it possesses anticonvulsant properties<sup>(27,28)</sup> and that glycine neurotransmission is involved<sup>(29)</sup>. *S. latifolius* completely antagonized MES-induced seizures probably by prolonging the inactivation of sodium channels<sup>(17)</sup>. The previous results are in correspondence with Taiwe *et al*<sup>(9)</sup> and Ngo Bum *et al*<sup>(20)</sup> who reported that the root extract of *S. latifolius* possesses antidepressant, myorelaxant and anticonvulsant activity by interacting with the GABA-ergic neurotransmission and inactivation of sodium channels.

Among the tests used, the PTZ, PIC and MES tests are of predictive relevance with respect to the clinical spectrum of activity of experimental compounds. They are assumed to identify anticonvulsant drugs effective against absence epilepsy, partial seizures, generalized tonic-clonic and myoclonic seizures<sup>(16, 17, 26 and 30)</sup>.

Besides, the phytochemical screening of tested extract revealed the presence of alkaloids, tannins, triterpenes, flavonoids, phenols, saponins and glycosides. The phytochemicals such as tannins, triterpenes and glycosides were reported as active substances for anticonvulsant activity<sup>(31, 32)</sup>. Also, many animals models showed that flavonoids exerted their effects through the central benzodiazepine receptors as well as GABAA receptor ligands<sup>(33, 34 and 35)</sup>. Hence, these phytochemicals might be contributing to the anticonvulsant activity of the tested extract. The effect of the extract in these tests could therefore suggest anticonvulsant efficacy against the aforementioned seizure types in humans.

**CONCLUSION**

In conclusion, it could be suggested that *S. latifoliosa* possess sedative, anticonvulsant and anxiolytic properties in rats. These properties could explain the use of this plant in traditional medicine in Africa, especially in Sudan, in the treatment of insomnia, anxiety and epilepsy.

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