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Research Article

Psychopharmacological effects of ethanol leaf extract of *Setaria megaphylla* in mice

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Background: *Setaria megaphylla* (Steud) Dur & Schinz (Poaceae), a perennial grass used traditionally in the treatment of various diseases including central nervous system disorders.

Objective: To evaluate the *Setaria megaphylla* ethanol leaf extract for psychopharmacological effects in mice.

Materials and Methods: Antidepressant activity was evaluated in mice using open field, force swimming and tail suspension tests as well as phenobarbitone-induced sleeping time. Anticonvulsant activity was also tested against pentylenetetrazol and aminophylline-induced convulsions.

Results: The leaf extract (200-600 mg/kg) increased significantly ($p<0.05$- 0.001) the line crossing, walling and rearing activities in open field test and reduced significantly ($p<0.05$-0.001) the immobility time in force swimming and tail suspension tests. The leaf extract antagonized the hypnotic effect of phenobarbitone sodium and offered no protection to animals against convulsions induced by pentylenetetrazol and aminophylline in mice.

Conclusion: The leaf extract of *S. megaphylla* has prominent antidepressant and CNS stimulatory activities which is due to the activities of its phytochemical constituents.

Keywords: Antidepressant, *Setaria megaphylla*, CNS stimulant

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1. Introduction

Setaria megaphylla (Steud) Dur & Schinz (Poaceae) is a tall, robust, tufted, perennial grass used mainly as pasture grass. It is also called broad leafed brittle grass and occurs in tropical and subtropical areas of Africa, America and India where there is high rainfall (Van Oudtshoorn, 1999, Lowe, 1989). The plant is use traditionally by the Ibibios in Akwa Ibom State, Nigeria in the treatment of various ailments such as malaria, inflammation and diabetes (Okokon et al, 2007). The plant leaves have been reported to possess antiplasmodial activity in vitro (Clarkson et al, 2004) and in vivo (Okokon et al, (2007). Hypoglycaemic and antidiabetic (Okokon and Antia, 2007; Okokon et al, 2007), anti-inflammatory and analgesic (Okokon et al, 2006), cytotoxic, immunomodulatory and antileishmanial (Okokon et al, 2013) activities have also been reported on the leaf extract of this plant.

The leaf extract as reported by Okokon and Antia, (2007) contains flavonoid, carbohydrate, terpenes, saponins, tannins, anthraquinones and cardiac glycosides with LD_{50} of 2.4 ± 0.5g/kg. GCMS analysis of the n-hexane fraction of the leaf revealed the presence of 8,11,14-eicosatrienoic acid (Z,Z,Z), phthalic acid, diisooctyl ester, Vitamin E, $^{\gamma}$-Elemene, Urs-12-ene, bicyclogermacrene, α-muurolene, germacrene- A, and guaiol among others (Okokon et al, 2013). Considering the ethnomedical records of this plant in herbal medicine and the few reported biological activities, we reported the antidepressant activity of the leaf extract which has not been evaluated previously to provide information on medicinal potentials of this plant.

2. Materials and Methods

2.1 Plant material

The plant was identified at the Department of Botany, University of Uyo, Uyo. The leaves were collected from Anwa forest, Uruan in Akwa Ibom State, Nigeria in August, 2016 and were authenticated. A voucher specimen (**FPHUU. 221**) of the plant was deposited at hebarium of Department of Pharmacognosy and Traditional Medicine, University of Uyo, Uyo.

2.2 Extraction

The leaves were shade dried for 2 weeks. The dried leaves were further chopped into small pieces and reduced to powder using electric grinder. The powdered material was soaked in 50% ethanol for 72 hours. The liquid filtrate was concentrated and evaporated to dryness in vacuo 40°C using rotary evaporator. The dried extract was stored in a refrigerator at - 4°C until use for the proposed experiment.

2.3 Animals

The animals (Swiss albino mice) both male and female that were used for these experiments were obtained from University of Uyo animal house. The animals were housed in standard cages and were maintained on a standard pelleted Feed (Guinea Feed) and water *ad libitum*. Permission and approval for animal studies were obtained from College of Health Sciences Animal Ethics committee, University of Uyo.

2.4 Evaluation of antidepressant activity

Open field test

Rats were randomly divided into groups of 5 rats each and treated as follows for 5 days before open field test; control (normal saline, 2 ml/kg *p.o.*), imipramine (5.0 mg/kg, *p.o.*) and ethanol leaf extract of *Setaria megaphylla* (200,400, and 600 mg/kg, *p.o.*). The open-field arena was made of acrylic (transparent walls and black floor, 30 × 30 × 15 cm), divided into nine squares of equal areas. The open field was used to evaluate the exploratory activity of the animal (Archer, 1973). The observed parameters were the number of squares crossed (with the four paws) and number of walling and rearing activities, recorded for 5 min testing period.

Forced swimming test

Mice were randomly divided into groups of 5 mice each and treated as follows for 5 days before the behavioural test; control (normal saline, 2 ml/kg *p.o.*), imipramine (5.0 mg/kg, *p.o.*) and ethanol leaf extract of *Setaria megaphylla* (200,400, and 600 mg/kg, *p.o.*). For assessing antidepressant activities, we employed the method described by Porsolt et al, (1977; 1978). The development of immobility when mice were placed inside an inescapable cylinder filled with water reflects the cessation of persistent escape-directed behavior. Briefly, mice were individually placed in a circular tank (46 cm tall × 20 cm in diameter) filled with tap water (25 ± 1°C) to a depth of 20 cm and left there for 5 min. During this period, the behavior of the animals was recorded by an observer. Mice were considered immobile when remained floating without struggling and making only slight movements necessary to maintain the head above the water.

Tail suspension test (TST)

Mice of either sex were randomly divided into groups of 5 mice each and treated as follows for 5 days before tail suspension test; control (normal saline, 2 ml/kg *p.o.*), imipramine (5.0 mg/kg, *p.o.*) and ethanol leaf extract of *Setaria megaphylla* (200,400, and 600 mg/kg, *p.o.*). The total duration of immobility induced by tail suspension was measured according to the methods described by Steru et al, (1985). Briefly, mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period. Mice were considered immobile only when they hung passively and were motionless.

2.5 Anticonvulsant activity

Pentylenetetrazol -induced convulsion

Anticonvulsant effect of the extract was assessed using a modified method of Vellucci and Webster (1984) on overnight fasted mice. The mice were divided into five groups of six animals each and treated with 200, 400 and 600 mg/kg of the leaf extract respectively, phenytoin, 40 mg/kg one hour before induction of convulsion. Seizure was induced in each set of mice with pentylenetetrazol (PTZ) (70 mg/kg i.p). Control group received normal saline. The onset of Clonic/tonic convulsion and the mortality rate was recorded and compared with the respective control group. The ability of the plant extract to prevent or delay the onset of the hind limb extension exhibited by the animals was taken as an indication of anticonvulsant activity (Amabeoku and Chikuni, 1993).

Aminophylline-induced Convulsion

The extract was evaluated for activity against aminophylline –induced convulsion using the method of Juliet et al, (2003). The mice were divided into 5 groups of six animals each and treated with 200, 400 and 600 mg/kg of the extract respectively and phenytoin, 40 mg/kg one hour before induction of convulsion. Seizure was induced using aminophylline (280 mg/kg, i.p). The animals were observed for 120 mins after the administration of aminophylline and the following parameters were noted: time to onset of myoclonic jerks in mins; time to onset of tonic convulsions in mins; time to death during experimental time of 120 mins; and number of mice dead/alive at 24 hours.

2.6 Effect on phenobarbitone–induced sleeping time of rats

The crude ethanolic extract was evaluated for effect on phenobarbitone sodium sleeping time of rats. The rats were divided into five groups of five rats each (n=5). The extract (200, 400 and 600 mg/kg) was administered to various groups of rats, diazepam (2 mg/kg) was given to the reference group and the control group was given distilled water (10 ml/kg).

After 30 min the groups were treated with phenobarbitone sodium (40 mg/kg,i.p). The onset and the duration of sleep were noted and recorded in minutes.

2.7 Statistical analysis and data evaluation

Data obtained from this work were analyzed statistically using ANOVA (One-way) followed by a post test (Tukey-kramer multiple comparison test). Differences between means were considered significant at 5% level of significance ($P \leq 0.05$).

3. Results

Open field test

Administration of leaf extract of *S. megaphylla* (200 – 600 mg/kg) for 5 days caused significant ($p<0.05$ – 0.01) non dose-dependent increase in the frequency of line crossing with the low doses of the extract (200 and 400 mg/kg) having highest effect when compared to control. The standard drugs, imipramine (5 mg/kg), caused a significant ($p<0.001$) increase in the locomotor activity of the rats as evident in the frequency of the line crossing (**Table 1**).

Setaria megaphylla leaf extract (200 – 600 mg/kg) caused prominent increase in walling frequency of the mice which was significant ($p<0.05$) in the middle dose (400 mg/kg) when compared to control. These effects were non dose-dependent. The standard drug, imipramine (5 mg/kg), produced a significant ($p<0.001$) increase in the walling frequency of the animals. The leaf extract of the *S. megaphylla* (200 – 600 mg/kg) caused significant ($p<0.001$) non dose–dependent increase of the rearing frequency of mice administered with the extract for five days. Similarly, the standard drug, imipramine (5 mg/kg), exerted a significant ($p<0.001$) increase in the rearing frequency when compared to control (**Table 1**).

Effect on Force Swimming Test

Administration of the ethanol leaf extract of *S. megaphylla* (200 – 600 mg/kg) to mice for five days significantly ($p<0.05$-0.01) reduced immobility duration though in non dose-dependent fashion in mice during force swimming test when it was compared to control. The standard drug, imipramine (5 mg/kg) similarly produced a significant ($p<0.001$) reduction in the immobility time of the rats when compared to control (**Table 2**).

Effect on Tail Suspension Test

Administration of the ethanol leaf extract of *S. megaphylla* (200 – 600 mg/kg) to mice for five days significantly ($p<0.001$) reduced immobility duration during tail suspension test when it was compared to control. The lowest dose (200 mg/kg) exerted the most prominent reductions in the immobility time which was higher than that of the standard drug. The standard drug, imipramine (5 mg/kg), exerted a significant ($p<0.001$) reduction of the immobility time of the rats when compared to control (**Table 3**).

Table 1: Effect of ethanol leaf extract of *Setaria megaphylla* on locomotive behavior of mice during open field test.

Treatment	Dose (mg/kg)	Line Crossing	Walling	Rearing
Control normal saline	-	35.25 ±3.53	10.75 ± 1.50	1.25±0.25
Imipramine	5	93.75 ±5.72^{c}	20.25 ± 1.25^{a}	7.50±0.53^{c}
Crude extract	200	73.25±3.88^{c}	19.0 ± 1.68	7.25±0.25^{c}
	400	70.25 ± 4.80^{c}	21.25 ± 1.20^{a}	4.25±0.62^{c}
	600	55.50 ± 5.60^{a}	13.75±4.09	0.50±0.01

Data are expressed as MEAN ± SEM, Significant at $^{a}p < 0.05$, $^{c}p<0.001$, when compared to control. (n=6).

Table 2: Effect of ethanol leaf extract of *Setaria megaphylla* on behavior of mice during forced swimming test.

Treatment	Dose (mg/kg)	Episode of immobility	Latency of immobility	Duration of immobility
Control normal saline	-	6.25 ±0.85	70.0 ± 3.72	130.0±5.53
Imipramine	5	4.25 ±1.03	77.25 ± 5.19	106.25±3.33^{a}
Crude extract	200	3.25±0.75	115.25± 3.35^{c}	100.50±2.46^{b}
	400	5.0 ± 0.70	93.25 ± 3.81^{b}	99.50±2.42^{b}
	600	5.0 ± 0.70	66.0±4.49	99.25±9.49^{b}

Data are expressed as MEAN ± SEM, Significant at $^{a}p < 0.05$, $^{b}p<0.01$, $^{c}p<0.001$, when compared to control. (n=6).

Anticonvulsant activity *Setaria megaphylla* leaf extract on aminophylline- induced convulsion

The administration of *Setaria megaphylla* leaf extract (200 – 600 mg/kg) did not provide any protection for the mice against seizure induced by aminophylline. There was no significant difference ($p>0.05$) in the onset of myoclonic, onset of tonic and time of death of treated animal when compared with the control. The standard drug, phenytoin offered 100% protection to the animals treated with it (**Table 4**).

Anticonvulsant activity of *Setaria megaphylla* leaf extract on PTZ- induced convulsion

The pre-treatment of mice with leaf extract of *Setaria megaphylla* (200-600 mg/kg) did not protect the mice against tonic–clonic convulsion induced by the administration of pentylenetetrazol. The prolongation produced by the highest dose of the extract (600 mg/kg) was more than that of the standard drug, phenytoin. (**Table 5**).

Effect of *Setaria megaphylla* leaf extract on phenobarbitone induced sleeping time of rats

Administration of the leaf extract of *S. megaphylla* (200–400 mg/kg) to rats reduced the effect of phenobarbitone in producing sleep in mice. All the mice treated with the extract did not sleep throughout the duration of the experiment. The standard drug, diazepam, shortened significantly ($p<0.05$) the onset of sleep and also prolonged significantly ($p<0.05$) the duration of sleep when compared to control (**Table 6**).

Table 3: Effect of ethanol leaf extract of *Setaria megaphylla* on behavior of mice during Tail climbing test.

Treatment	Dose (mg/kg)	Latency of immobility	Duration of immobility
Control normal saline	-	140.5 ± 6.93	147.25±8.56
Imipramine	5	186.5 ± 8.76 [c]	78.75±6.28 [c]
Crude extract	200	155.0± 8.38	68.0±5.00 [c]
	400	179.75 ± 3.40 [b]	97.25±3.40 [c]
	600	146.76±6.79	81.25±6.57 [c]

Data are expressed as MEAN ± SEM, Significant at [b]$p<0.01$; [c]$p< 0.001$, when compared to control. (n=6).

Table 4: Effect of ethanol leaf extract of *Setaria megaphylla* on Aminophylline-induced convulsion

Treatment	Dose (mg/kg)	Onset of myoclonic	Onset of Tonic	Time of death	No. of death
Control normal saline	-	8.54 ±1.02	23.00 ± 1.67	31.11±7.20	6/6
Phenytoin	5	4.63 ±0.86	15.05 ± 1.17	0.00±0.00	6/6
Crude extract	200	7.19 ±0.82	18.71 ± 3.91	27.51±2.53	6/6
	400	2.22 ± 0.46	30.81 ±11.10	31.70±18.73	6/6
	600	7.59 ± 2.86	24.88±7.26	31.86±7.21	6/6

Data are expressed as MEAN ± SEM, Significant at [a]$p < 0.001$, when compared to control. (n=6).

Table 5: Effect of ethanol leaf extract of *Setaria megaphylla* on Pentylene tetrazol-induced convulsion

Treatment	Dose (mg/kg)	Onset of myoclonic	Onset of Tonic	Time of death	No. of death
Control normal saline	-	1.09 ±0.21	4.63 ± 0.66	10.77±4.08	6/6
Phenytoin	5	1.23 ±0.24	4.71 ± 0.53	13.17±1.61	6/6
Crude extract	200	1.49 ±0.18	3.86 ± 0.44	11.48±4.53	6/6
	400	1.46 ± 0.22	3.89 ± 0.94	3.89±2.66	6/6
	600	2.19 ± 0.08	3.99±2.53	4.64±2.72	6/6

Data are expressed as MEAN ± SEM, Significant at [a]$p < 0.001$, when compared to control. (n=6).

Table 6: Effect of ethanol leaf extract of *Setaria megaphylla* on Sleeping time of rats

Treatment	Dose (mg/kg)	Onset of Sleep	Time of wakefulness	Duration of sleep
Control normal saline	-	92.30±13.15	120.35 ± 35.10	30.57±7.47
Diazepam	2	34.07 ±13.18 [a]	130.97 ± 22.58	99.56±26.29 [a]
Crude extract	200	0.00 ±0.00	0.00 ± 0.00	0.00±0.00
	400	0.00 ± 0.00	0.00 ± 0.00	0.00±0.00
	600	0.00 ± 0.00	0.00±0.00	0.00±0.00

Data are expressed as MEAN ± SEM, Significant at [a]$p < 0.05$, when compared to control. (n=6).

4.0 Discussion

In this study, evaluation of the effect of ethanol leaf extract of *Setaria megaphylla* on central nervous system was carried out in mice using different models; Open field test, tail suspension test and force swimming test. The leaf extract (200 – 600 mg/kg) was found to cause significant non dose-dependent increases in the frequency of line crossing, walling and rearing activities of the pre-treated mice. It also reduced significantly the immobility time of the mice in force swimming and tail suspension tests.

Monitoring of locomotor activity of animals has been used in assessing effect of drug on the CNS. An increased movement is a measure of the level of excitability of the CNS (Ozturk et al, 1996) and its decrease may be intimately related to sedation resulting from depression of the CNS (Kolawole et al, 2007). Central nervous system stimulants are known to increase locomotor activity, while agents with depressant activity cause reduction in movements (Yadav et al, 2008). The leaf extract was found to increase significantly line crossing, walling and rearing activities during open field test suggesting stimulatory effect on the CNS

The CNS stimulatory effect of the leaf extract was further supported by its potential to reduce immobility time of mice during force swimming and tail suspension tests. Forced swimming and tail suspension tests are two of the most commonly used animal models of depression for antidepressant screening. In the forced swimming test, the development of immobility when mice are placed into an inescapable cylinder of water reflects the cessation of persistent escape-directed behaviour (Lucki, 1997). The tail suspension test is based on the fact that animals subjected to the short-term, inescapable stress of being suspended by their tail, will develop an immobile posture. Various antidepressants are able to reverse the immobility and promote the occurrence of escape related behaviour. Both models of depression are widely used to screen new antidepressants (Porsolt et al, 1977, 1978; Steru et al, 1985). These tests are quite sensitive to major antidepressant drugs including tricyclics, serotonin-specific reuptake inhibitors, MAO inhibitors, and atypical antidepressant (Porsolt et al, 1977; Steru et al, 1985; Detke et al, 1995).

Forced swimming and tail suspension tests which represent the behavioural despair model, claimed to reproduce a condition similar to human depression (Porsolt et al, 1977; Willner, 1984; Steru et al, 1985). The tests are based on the observation that animals, following initial escape oriented movements, develop an immobile posture when placed in an inescapable chamber. The immobility is thought to reflect either a failure of persistence in escape-directed behaviour (i.e. behavioural despair) or the development of passive behaviour that disengages the animal from active forms of coping with stressful stimuli (Lucki, 1997). It is well known that clinically effective antidepressants (such as imipramine) typically increase the swimming efforts of the animal seeking a solution to the problem and, therefore, they decrease the duration of immobility in the forced swimming test (Porsolt et al, 1977). This was observed in this study.

Similarly, the results of this study suggest that the leaf extract exhibited significant antidepressant activity with a strong psychomotor stimulation. Phytochemical constituents such as flavonoids have been implicated in antidepressant action on the CNS (Hossain et al, 2009), while polyphenols especially flavonoids like quercetin and rutin have also been reported to exhibit antidepressant effect (Nolder and Schotz, 2002). The leaf extract of *S. megaphylla* have been reported to contain 8,11,14-eicosatrienoic acid (Z,Z,Z), phthalic acid, diisooctyl ester, Vitamin E, $^{\gamma}$-Elemene, Urs-12-ene, bicyclogermacrene, α-muurolene, germacrene- A, and guaiol among others (Okokon et al, 2013). These phytochemical constituents may be responsible for the observed activity of the leaf extract in this study

The evaluation of anticonvulsant activity of *S. megaphylla* was also carried out in this study. Pre-treatment of the mice with the leaf extract of *S. megaphylla* (200 – 600 mg/kg) was found to offer no protection for the animal against onset of tonic/clonic convulsions and time of the death of the treated mice against pentylenetetrazol and aminophylline-induced convulsions. Further confirming the CNS stimulatory action of the extract.

The exact mechanisms of seizures induced by aminophylline appear to be diverse, multiple and complex, and also unclear. Evidence suggests that seizures induced by aminophylline, could be the result of adenosine receptor antagonism or due to inhibition of cerebral nucleotidase activity (Chu, 1981; Jensen et al, 1984) , which lower the adenosine content in the brain and eventually lead to a process of disinhibition. However, report has it that di-phenylhydantoin a potent inhibitor of adenosine uptake was ineffective in preventing these seizures (Sharma and Sandhir, 2006). Apart from non-specific adenosine receptor antagonism (Daval et al, 1991), aminophylline is thought to have

inhibitory influence on adenosine synthesis. At higher doses inhibition of phosphodiesterase activity including mobilization of intracellular calcium ions from labile stores are said to be implicated in aminophylline-induced seizures (Neering et al, 1984; Tutka et al, 1996). However, a report by Ray et al, (2005), has implicated oxidative stress due to the generation of free radicals and reactive oxygen species to be responsible for the seizures induced by aminophylline.

Setaria megaphylla leaf extract which was observed to exert antidepressant and CNS stimulatory activitites, has been reported to contain 8,11,14-eicosatrienoic acid (Z,Z,Z), phthalic acid, diisooctyl ester, Vitamin E, $^{\gamma}$-Elemene, Urs-12-ene, bicyclogermacrene, α-muurolene, germacrene- A, and guaiol among others (Okokon et al, 2013). These compounds may be responsible for the observed antidepressant activity of the plant.

According to De Sarro et al,*(*1999), pentylenetetrazol (PTZ) is suggested to exert its anticonvulsant effect by inhibiting the activity of gamma aminobutyric acid (GABA) at $GABA_A$ receptors. Gamma aminobutyric acid is the major inhibitory neurotransmitter which is implicated in epilepsy. The enhancement and inhibition of the neurotransmission of GABA will attenuate and enhance convulsion respectively (Gale, 1992; Westmoreland et al,1994). Phenobarbitone and diazepam, standard epileptic drugs,have been shown to exert their antiepileptic effects by enhancing GABA-mediated inhibition in the brain (Porter and Meldrum, 2001; Rang et al,2003). These drugs are reported to antagonise PTZ-induced convulsion (Amabeoku et al, 2007) by enhancing GABA neurotransmission. Phenytoin was unable to prevent PTZ- induced seizure because it is thought to exert its antiepileptic effect by blocking sodium ions into brain cells thus inhibiting generation of repitative action potential (Porter and Meldrum, 2001). Since the leaf extract of *S. megaphylla* was unable to delay PTZ – induced convulsion,this also confirm its CNS stimulatory effect.

The ethanol leaf extract of *S. megaphylla* was found to significantly antagonise phenobarbitone sodium-induced hypnotic effect, which was observed in the lack of sleep in mice following its administration suggesting a stimulatory activity on the CNS. Substances which possess CNS depressant activity either decrease the time for onset of sleep or prolong the duration of sleep or both (Nyeem et al, 2006; Raquibul et al, 2009).

5.0 Conclusion

From the results of this study, the leaf extract possesses significant CNS stimulatory and antidepressant activities. It will be interesting to isolate and characterised the active ingredient in this extract

Conflict of Interest declaration

The authors declare no conflict of interest.

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