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Anticonvulsant and Depressant Activities of Ethanol Leaf Extract of *Solanum Anomalum* (Solanaceae)

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ABSTRACT

The ethanol leaf extract of *Solanum anomalum* (70-210 mg/kg) was evaluated for anticonvulsant activity in mice using pentylene tetrazol and aminophylline models as well as depressant activity using open field, forced swimming and Tail suspension tests. The leaf extract significantly ($p<0.005$-0.001) inhibited convulsions induced experimentally in all the models tested in a dose-dependent fashion. The leaf extract further caused increases in the frequencies of line crossing, walling and rearing activities of mice. The immobility time of mice during forced swimming and tail suspension tests was also increased. The findings of this study show that the leaf extract possesses anticonvulsant and depressant activities which confirms its use in traditional medicine in the treatment of CNS disorders.

Keywords: *Solanum anomalum*, anticonvulsant, Depressant, medicinal plant

INTRODUCTION

*Solanum anomalum*Thonn. ex Schumach. (family *Solanaceae*) is a shrub growing up to 2 metres tall. The stem, branches and midribs of the leaves are usually armed with prickles up to 5 mm long. The edible fruits are gathered from the wild and consumed locally. Both the fruits and the leaves are used medicinally. The plant is sometimes cultivated or semi-cultivated for its fruits. It is found in West tropical Africa - Sierra Leone to southern Nigeria, Cameroon and DR Congo. It is Known as 'children's tomatoes', they are more commonly used as a condiment in soups and sauces and the fruits are eaten raw or cooked (Burkill, 2000). The sap from the leaves and fruits is drunk, or taken as enema 1 - 2 times daily, as a treatment for leprosy and gonorrhoea (Burkill, 2000). The fruits are used as a laxative and digestive (Burkill, 2000). They are also served ground up in soups and sauces as an appetizer for sick persons, sometimes mixed with fruits of Parkia (Burkill, 2000). The crushed fruits are applied to maturate inflammations on fingers or toes (Burkill, 2000). The fruit juice is applied to sores on the ears to alleviate pain (Bukenya and Hall, 1988). Offor and Ubengama (2015) reported the antidiabetic activity of the fruit of this plant. The anti-inflammatory activity of the leaf extract has been reported (Okokon*et al*., 2017). Although there is a little information on the biological activity of the leaves of this plant, we report in this study the anticonvulsant and depressant activities of the leaf extract of the plant.

MATERIALS AND METHODS

Plants collection

The plant material *Solanum anomalum* (leaves) were collected in compounds in Uruan area, Akwa Ibom State, Nigeria in August, 2018. The plant was identified and authenticated by Prof Margaret Bassey, a taxonomist in the Department of Botany and Ecological Studies, University of Uyo, Uyo, Nigeria. Hebarium specimen was deposited at Department of Pharmacognosy and Natural Medicine Herbarium.(UUH:No 75(a))

Extraction

The plant parts (leaves) were washed and shade-dried for two weeks. The dried plant materials were reduced to powder using mortar and pestle. The powdered material (1 kg) was soaked in 50% ethanol (5 L). The liquid filtrate was concentrated and evaporated to dryness in vacuo 40˚C using rotary evaporator and stored in a refrigerator at - 4˚C.

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Animals

Albino Swiss mice (19 – 28g) of either sex were obtained from the University of Uyo animal house. They were maintained on standard animal pellets and water *ad libitum*. Permission and approval for animal studies were obtained from the College of Health Sciences Animal Ethics committee, University of Uyo.

Determination of Median Lethal Dose (Ld_{50})

The median lethal dose (LD_{50}) of the extract was estimated using albino mice by intraperitoneal (i.p) route employing the method of Lorke (1983). This involved intraperitoneal administration of different doses of the extract (100 -1000 mg/kg) to groups of three mice each. The animals were observed for manifestation of physical signs of toxicity such as writhing, decreased motor activity, decreased body/limb tone, decreased respiration and death. The number of deaths in each group within 24 hours was recorded. The LD_{50} was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b).

$LD_{50} = \sqrt{ab}$

Evaluation of 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 orally with 70, 140 and 210 mg/kg of the leaf extract respectively, phenobarb, 40 mg/kg, p.o 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 orally treated with 70, 140 and 210 mg/kg of the extract respectively and phenobarb, 40 mg/kg p.o, 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.
Number of mice dead/alive at 24 hours.

Evaluation of depressant Activity

Open Field Test

Swiss albino mice of either sex were randomly divided into groups of 5 mice 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 *Solanum anomalum* (70, 140, 210 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 grooming and rearing, recorded for 5 min testing period.

Forced Swimming Test

Swiss albino mice of either sex 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 *Solanum anomalum*ethanol leaf extract (70, 140, 210 mg/kg *p.o.*). For assessing depressant activity, the method described by Porsolt*et al.*, (1977; 1978) was employed. 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 they 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 *S anomalum* (70, 140, and 210 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.

RESULTS

Determination of Median lethal dose (LD_{50})

The median lethal dose (LD_{50}) was calculated to be 724.56 mg/kg. The physical signs of toxicity included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which was followed by death.

Effect of extract on PTZ –induced Convulsion

Administration of leaf extract of *S. anomalum* (70-210 mg/kg) provided a considerable degree of protection for the mice against seizure induced by pentylene tetrazol. The extract protected the mice against onset of myoclonic convulsion in a dose-dependent fashion which was significant ($p<0.001$) and comparable to that of the standard drug, Phenobarb (Table 1). Similarly, there was a significant ($p<0.05$-0.01) prolongation of time for onset of tonic convulsion in a dose-dependent manner (Table 1). The standard drug, phenobarb also offered 100% protection to the animals treated with it.

Table 1: Effect of ethanol leaf extract of *Solanum anomalum* on Pentylenetetrazol-induced convulsion

TREATMENT	DOSE	Onset of myoclonic (min)	Onset of Tonic(min)	No. of death
	mg/kg			
Control normal saline	-	0.49 ±0.07	1.14 ± 0.02	6/6
Phenobarb	40	1.26 ±0.28[b]	0.00±0.00[c]	6/6
Crude extract	70	0.53 ±0.02	3.38 ± 0.55	6/6
	140	0.47 ± 0.01	8.35± 0.58 [a]	6/6
	210	1.27 ± 0.12[b]	26.31±2.67[b]	6/6

Data are expressed as MEAN ± SEM, Significant at [a]$p< 0.05$;[b]$p<0.001$, when compared to control. (n=6).

Table 2: Effect of ethanol leaf extract of *Solanum anomalum*on Aminophylline-induced convulsion

TREATMENT	DOSE	Onset of myoclonic	Onset of Tonic	No. of death
	mg/kg	(min)	(min)	
Control normal saline	-	6.23±0.90	8.26 ± 1.11	6/6
Phenobarbitone	40	23.00±1.20[b]	0.00 ± 0.00[b]	6/6
Crude extract	70	13.71±0.96	22.74±1.15[b]	6/6
	140	16.29±0.63[b]	39.57±1.29[b]	6/6
	210	19.49±0.62[b]	16.90±2.79[a]	6/6

Data are expressed as MEAN ± SEM, Significant at [a]$p< 0.05$;[b]$p<0.001$, when compared to control. (n=6).

Determination of Depressant Effect

Table 3: Effect of ethanol leaf extract of *Solanum anomalum* 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
Immipramine	5	93.75 ±5.72[b]	20.25 ± 1.25[a]	7.50±0.53 [b]
Crude extract	70	113.6±6.43 [b]	33.33 ± 2.90[b]	7.00±1.46 [b]
	140	85.66 ± 7.33 [b]	16.0 ± 2.00[a]	2.66±0.66 [a]
	210	53.66 ± 10.83 [a]	20.33±2.02[a]	4.00±0.57

Data are expressed as MEAN ± SEM, Significant at [a]$p< 0.05$, [b]$p<0.001$, when compared to control. (n=6).

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Table 4: Effect of ethanol leaf extract of *Solanum anomalum* on behavior of mice during forced swimming test.

TREATMENT	DOSE	Episode of immobility	Latency of immobility	Duration of immobility
	mg/kg			
Control normal saline	-	6.25 ±0.85	70.0 ± 3.72	130.0±5.53
Immipramine	5	4.25 ±1.03	77.25 ± 5.19	106.25±3.33 [a]
Crude extract	70	8.0±1.00	175.0± 9.15 [c]	145.33±5.49 [a]
	140	4.66± 0.88	159.66± 10.32[b]	133.0±12.00
	210	5.33 ± 0.88	86.33±3.18	162.66±7.51 [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).

Table 5: Effect of ethanol leaf extract of *Solanum anomalum* on behavior of mice during Tail suspension test.

TREATMENT	DOSE mg/kg	Duration of immobility
Control normal saline	-	120.5 ± 6.93
Immipramine	5	78.66± 7.88 [b]
Crude extract	70	130.13± 7.33[a]
	140	142.12 ± 5.17[b]
	210	159.33±6.33[b]

Data are expressed as MEAN ± SEM, Significant at [a]p< 0.05; [b]p< 0.001, when compared to control. (n=6).

Effect Of Extract on Aminophylline-induced Convulsion

Administration of the leaf extract of *S. anomalum* (70-210 mg/kg) caused a significant (p<0.05-0.001) delay in the onset of seizure induced by aminophylline. The delay was more prominent at the lower doses (70 and 140 mg/kg) of the extract than the highest dose (210 mg/kg) (Table 2). The standard drug, Phenobarb offered a more significant (p<0.001) protection to the mice treated with it.

Open Field Test

Administration of leaf extract of *Solanum anomalum*(70-210 mg/kg) for 5 days caused significant (p<0.05 - 0.01) non dose-dependent increase in the frequencies of line crossing, rearing and walling activities when compared to control. The standard drugs, imipramine (5 mg/kg), caused a significant (p<0.001) increase in the locomotor activity of the mice as evident in the frequency of the line crossing, walling and rearing activities (Table 3).

Effect on Force Swimming Test

Administration of the ethanol leaf extract of *Solanum anomalum*(70-210 mg/kg) to mice for five days significantly (p<0.001) increased latency and duration of immobility in mice during force swimming test when compared to control. These increases were non dose-dependent.. The standard drug, imipramine (5 mg/kg) similarly produced a significant (p<0.001) reduction in the immobility time of the mice when compared to control (Table 4). The effect of the extract (70-210 mg/kg) was higher than that of the standard drug, imipramine

Effect on Tail Suspension Test

Administration of the ethanol leaf extract of *S. officinarum*(70 – 210 mg/kg) to mice for five days significantly (p<0.01-0.001) increased immobility duration dose-dependently during tail suspension test when it was compared to control. The standard drug, imipramine (5 mg/kg), exerted a significant (p<0.001) reduction of the immobility time of the mice when compared to control (Table 5).

DISCUSSION

Solanum anomalum leaf is used to treat central nervous system disorders traditionally by the ibibios. The leaf extract of *Solanum anomalum* was evaluated for anticonvulsant and depressant activities in mice using various experimental models. The leaf extract was found to exert significant anticonvulsant and depressant activities in mice.

The median lethal dose (LD_{50}) was determined to be 724.56 mg/kg which shows that the extract is moderately toxic (Homburger, 1989)

The extract was found to prolong the latency of tonic and clonic convulsion in aminophylline-induced convulsions. 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 amminophylline. Although the exact mechanism of action of the extract is not known but it is likely to be related to the antioxidant activity of its phytochemical constituents.

According to De Sarro *et al.,* (1999), pentylene tetrazol (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. anomalum* was able to delay PTZ – induced convulsion, it may in part result from its ability to enhance GABA-mediated inhibition in the CNS.This also confirms its CNS depressant effect.

In this study, evaluation of the depressant effect of ethanol leaf extract of *Solanum anomalum* on central nervous system was also carried out in mice using different models; Open field test, tail suspension test and force swimming test. The leaf extract (70-210 mg/kg) was found to cause significant dose-dependent increases in the frequency of line crossing, walling and rearing activities of the pretreated mice (Table 1). It also increased significantly the immobility time of the mice in force swimming and tail suspension tests.

Monitoring of locomotor activity of animals has been used to assess the effect of drug on the CNS. An increased movement is a measure of the level of excitability of the CNS (Ozturk *et al*., 1996), while its decrease may be 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 leaf extract further demonstrated CNS depressant effect by its potential to increase 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 behavior (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 behavior. 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 depressant activity with a strong psychomotor stimulation. The leaf extract was reported to contain chemical constituents such as alkaloids, flavonoids, tannins, terpenes, saponins, anthraquinones, reducing sugars, phenol, and cardiac glycosides (Okokon et al., 2017). These phytochemical constituents may be responsible for the observed activities of the leaf extract in this study

The results of this study show that ethanol leaf extract of *Solanum anomalum* possesses anticonvulsant and depressant activities which justifies its use in ethnomedicine for the treatment of central nervous system disorders.

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