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ANTICONVULSANT PROPERTIES OF THE METHANOL STEM BARK EXTRACT OF *ACACIA ALBIDA* DEL.

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ABSTRACT

Acacia albida (Mimosoideae) is used in traditional medicine for the management of epilepsy. The methanol stem bark extract of *Acacia albida* was studied for its anticonvulsant effects in mice and chicks. The test systems selected were the maximal electroshock test (MEST) in chicks, Pentylenetetrazole (PTZ) and Strychnine (STN) induced seizure tests in mice. The effect of the extract on diazepam induced sleep in mice and preliminary phytochemical screening were also conducted. The extract (50, 100, 200 mg/kg) significantly ($p< 0.001$) shortened onset of sleep compared to normal saline (control) from 4.8±0.2 to 2.2±0.3, 2.0±0.0 and 2.0±0.3, respectively. The methanol stem bark extract of *Acacia albida* also increased total sleeping time from 58.2±14.0 to 201.0±23.9, 111.4±16.1 and 89.6±22.5 at 50, 100 and 200 mg/kg, respectively. The increase was significant ($p< 0.001$) at 50 mg/kg. *Acacia albida* stem bark extract at 200 mg/kg protected 50% of the mice against STN induced seizure with 63.3% survival rate. There was no protection against STN induced seizure at 50 and 100 mg/kg of the extract but a 16.3% and 33.3% protection against mortality was observed respectively. The extract was also able to delay, though insignificantly the onset of seizure at all the doses tested. In the PTZ induced seizure test, the extract did not protect the mice against seizure nor mortality but there was a significant ($p< 0.05$) delay in onset of seizure at 100 and 200 mg/kg. Similarly the extract of *Acacia albida* did not protect chicks against MEST. However there was a non significant dose dependent shortening of recovery time at the doses tested. Preliminary phytochemical studies of the stem bark extract of *Acacia albida* revealed the presence of tannins, saponin triterpenes and steroids. The intraperitoneal LD_{50} in mice was estimated to be 1131.4 mg/kg. Our results suggest that the methanol stem bark extract of *Acacia albida* may contain psychoactive principles that are relevant to the management of epilepsy (*petit mal*).

Key words: *Acacia albida*, *petit mal*, traditional medicine, *PTZ, MEST, STN*.

INTRODUCTION

Epilepsy is a major neurological disorder characterized by recurrent seizures with a lifetime prevalence of 5% (Sander and Shorvon, 1996; Raza *et al.,* 2001). Common causes include infectious, traumatic, metabolic or tumoural conditions or it may be idiopathic, that is unrelated to any underlying cause other than a possible hereditary predisposition (Engel, 2001). Falciparum malaria however is a common cause of seizures in children living in malaria endemic areas (Ogutu and Newton, 2004). In cases of cerebral malaria over 80% of children are admitted with a history of convulsions (Molyneux *et al.,* 1989). Furthermore, seizures in malaria are associated with a poor outcome. Prolonged seizures in children with malaria are associated with a neurological, cognitive and language deficits and the development of epilepsy (Holding *et al.,* 1999; Carter *et al.,* 2003). It can be postulated therefore, that sub-Saharan Africa may have a higher prevalence of epilepsy being malaria endemic.

Patients with epilepsy fail to experience adequate control of their seizures despite optimal use of available antiepileptic drugs-AEDs (Stables and Kupferberg, 1997). Synthetic AEDs are effective only in approximately 50% of patients and many refractory cases of epilepsy still remain highly resistant to their treatment (Heinemann *et al.,* 1994; Shorvon, 1996). Furthermore, AEDs are associated with side effects, including teratogenicity and adverse effects on cognition and behavior (Samren *et al.,* 1997; Raza *et al.,* 2001).

According to Meldrum (1997), plant extracts can be an important source of natural and safer drugs for the treatment of epilepsy. Extracts, fractions and pure compounds from several medicinal plants have been used in traditional medicine for the treatment of epilepsy and have demonstrated anticonvulsant properties that need to be further investigated (Raza *et al.,* 2001). *Acacia albida* also known as *Faidherbia albida* family *Mimosoideae* is commonly known among Hausa people in Northern Nigeria as *Gawo*. The stem bark is acclaimed to be effective in the management of epilepsy in traditional medicine (Hajiya Ummi personal communication). *Acacia*

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albida is a large tree 8-15 m high in Senegal and up to 5 m in Nigeria, bole straight to about a third of the overall height by 1m or more in diameter of the dry savanna, but favouring damp sites, often river banks and swamps, common and gregarious from Senegal to Northern Nigeria and extending across Sub-Saharan Africa to Egypt and in East Africa (Burkill, 2000). It is the largest of the African acacias. It shows anthropogenic characters, being common around villages and in past or present areas of cultivation when bush is cleared for agriculture it is left standing.

It is widespread in semi-arid Africa on a wide range of soil types and in different climates. The tree is in full leaf during dry season and so reduces ambient air temperature and evaporation during this time. The bark exudes a gum which is sometimes collected in Nigeria. It is a form of gum Arabic and has limited medicinal use as an emollient and emulsifier. A fanciful aphrodisial application by *pulaar* folk is reported in Senegal in which the gum is taken with the meat of a bull, preferably the testicles for impotence.

Bark of the trunk is rich in tannins 28-30% and is widely used for tanning skins (Burkill, 2000). An infusion or decoction is made with other drug plants in Senegal to treat *diangara cayor*, an inclusive term covering many diseases. In Nigeria an infusion is taken for fevers and cough and to assist in child birth. Similar use is reported in Senegal and in the case of childbirth it is mixed with palm oil. In Tanganyika and South-West Africa a decoction is taken for diarrhoea and as an emetic in fever. The bark in decoction is used to cleanse new wounds, having an action akin to that of potassium permanganate. It is used for kidney pain and with other drugs for madness **(**Burkill, 2000**).**

To the best of our knowledge, scientific evidence for the use of *Acacia albida* in treatment of epilepsy is lacking, and therefore this study was conducted to evaluate these claims. Three models of epilepsy were used including maximal electroshock test (MEST), pentylenetetrazole (PTZ) induced seizure and strychnine (STN) induced seizure tests.

MATERIALS AND METHODS

Animals. Swiss albino mice (18-25 g) of either sex maintained at the animal house of the Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria, Nigeria were used. In addition, day old white ranger cockerels obtained from the National Animal Production and Research Institute Shika, Zaria were used. They were housed under standard conditions of temperature (25±2°C), 12/12 hour light/dark cycle and fed on standard diet (Feeds Masters Plc. Ilorin, Nigeria) and given water *ad libitum*. All experiments performed in this study followed the principles of laboratory animal care outlined by the ethical committee of the faculty.

Plant Material. *Acacia albida* Del stem bark was collected in Zaria City, Kaduna State, Nigeria. It was identified and authenticated by a taxonomist, Mall. Umar Shehu Gallah, with the Department of Biological Sciences, Ahmadu Bello University Zaria, Nigeria by comparing with a voucher specimen (No. 900334) deposited for reference at the herbarium section of the Department.

Preparation of the Extract. The stem bark was carefully removed washed and cut into pieces. The bark was air dried and ground into powder form using mortar and pestle and then sieved. The powdered material was macerated in methanol solution with occasional shaking for 24 h and then filtered. The filtrate was then evaporated to dryness *in vacuo* at 60 °C.

Test Drugs and Chemicals. Hydroalcoholic stem bark extract, pentylenetetrazole (Sigma Chem. Comp., USA), strychnine (Sigma Chem. Comp., USA), sodium valproate (Sanofi synthelabo) were prepared by dissolving the powder in deionised water prior to administration. Phenobarbitone and Phenytoin were supplied in ampoules and appropriate dilutions were made with deionised water prior to use.

Preliminary Phytochemical Screening. The phytochemical analysis of the methanol stem bark extract of *Acacia albida* was conducted using standard qualitative methods as described by Trease and Evans (1983) and Sofowora (1993).

Acute Toxicity Studies. The intraperitoneal median lethal dose **(**LD_{50}) was evaluated in mice using the method of Lorke (1983). In the initial phase the mice were divided into three groups of three mice each and administered with 10,100 and 1000 mg/kg of the stem bark extract of *Acacia albida* respectively and observed for signs and symptoms of toxicity and death for 24 hours. In the final phase the mice were divided into four groups of one mouse each and treated with the extract at doses of 200, 400, 800 and 1600 mg/kg i.p respectively. The LD_{50} value was determined by calculating the geometric mean of the lowest dose that caused death and the highest dose for which the animal survived.

Diazepam Induced Sleep Test in Mice. The method described by Rakotonirina *et al*., (2001) was used. Twenty mice were divided into four groups of five mice each. The first group was treated with normal saline 10 ml/kg i.p, the second, third and fourth groups received graded doses of the extract, 50, 100 and 200 mg/kg i.p respectively. Thirty minutes post treatment,

mice in all the groups received diazepam at 20 mg/kg i.p. The time observed between the disappearance and the recovery of the righting reflex was measured as the sleeping time (Miya *et al.*, 1973). The interval between the times of administration of diazepam to loss of the righting reflex was recorded as the onset of sleep, while the time from the loss to regaining of the righting reflex as the duration of sleep (Soulimani *et al*., 2001).

Maximal Electroshock Test in Chicks. The method described by Swinyard and Kupfferberg (1985) as described by Sayyah *et al.* (2002) was employed in this study. Fifty day old cockerels were randomly divided into five groups, each containing 10 chicks. The first group was administered normal saline at 10 ml/kg *i.p*. while the second, third and fourth groups received 50, 100 and 200 mg/kg of *Acacia albida* extract *i.p*. respectively which represents 20-30% of the LD_{50} dose. The last group received phenytoin 20 mg/kg *i.p*. Thirty minutes after drug treatment, maximal electroshock was administered to induce seizure in the chicks using Ugo Basile electroconvulsive machine (model 7801) with corneal electrodes placed on the upper eyelids of the chicks. The shock duration, frequency and pulse width were set and maintained at 0.6 s, 100 pulse/second and 0.6 m/s, respectively. A current of about 80 mA, which produced tonic seizures of the hind limb in 80% of control chicks was used throughout the study. Seizures were manifested as hind limb tonic extension (HLTE) in the mice (Swinyard, 1969). The ability to prevent this feature or shorten the recovery from the HLTE was considered an indication of anticonvulsant activity (Swinyard, 1969; Sayyah *et al.,* 2002).

Subcutaneous Pentylenetetrazole Induced Seizure Test in Mice. The method of Swinyard et al. (1989) was employed. Thirty mice were divided into five groups of six mice each. The first group received normal saline 10 ml/kg while the second, third and fourth groups received graded doses of *Acacia albida* bark extract at 50, 100 and 200 mg/kg *i.p*. respectively. The fifth group served as positive control and received valproic acid at a dose of 200 mg/kg *i p*. Thirty minutes later, mice in all groups were injected with a convulsive dose of pentylenetetrazole (90 mg/kg) subcutaneously and observed over a period of 30 minutes. Absence of an episode of clonic spasm of at least five seconds duration or ability to prolong mean onset of seizure is an indication of the compound's ability to reverse the effect of PTZ (Raza *et al*., 2001).

Subcutaneous Strychnine Induced Seizure Test in Mice. The method of Porter *et al*. (1984) was adopted. Thirty mice were divided into five groups of six mice each. The first group received normal saline 10 ml/kg *i.p*. while the second, third and fourth groups received graded doses of *Acacia albida* bark extract at 50, 100 and 200 mg/kg *i.p*. respectively. The fifth group received phenobarbitone 20 mg/kg as positive control. Thirty minutes post treatment, mice in all the groups received strychnine 1 mg/kg subcutaneously. The proportion of mice presenting convulsion and the onset of tonic convulsion were recorded. Abolition of tonic extension jerks of the hind limb within 30 minutes after strychnine administration was regarded as an indication that the extract could prevent strychnine- induced convulsion (Raza *et al*., 2001).

Statistical Analysis . The onset of sleep, duration of sleep and onset of seizure were expressed as mean± SEM. The mean value of control groups were compared to the mean values of groups treated with *Acacia albida* extract using student's *t-test.* Values of $p<0.05$ were considered significant.

RESULTS

Phytochemical analysis

The preliminary phytochemical analysis of the methanol stem bark extract of *Acacia albida* revealed the presence of tannins, saponins, triterpenes and steroids. Other phytochemicals such as glycosides, alkaloids and flavonoids were not detected (Table 1).

Acute toxicity studies

The calculated intraperitoneal median lethal dose (LD_{50}) of the stem bark extract of *A. albida* in mice was estimated to be 1131.4 mg/kg.

Diazepam induced sleep test in mice

The methanol stem bark extract of *Acacia albida* at doses of 50, 100 and 200 mg/kg significantly ($p<0.001$) shortened onset of diazepam induced sleep in mice compared to normal saline (from 4.8±0.2 min to 2.2±0.37, 2.0±0.00 and 2.0±0.32 min respectively). The duration of sleep was also significantly ($p<0.001$) prolonged, though inversely, compared to normal saline from 58.2±14.79 to 201.6±23.96, 111.4±23.5 and 89.6±22.5 minutes at 50, 100 and 200 mg/kg respectively (Fig. 1). The extract at doses below 50 mg/kg did not produce any significant effect on diazepam-induced sleep.

Maximal electroshock test in chicks

The methanol stem bark extract of *Acacia albida* did not protect chicks against maximal electroshock induced convulsion at the doses tested (50, 100 and 200 mg/kg). The mean recovery time at doses of 100 and 200 mg/kg was shortened but not significantly compared to normal saline (Table 2). The standard antiepileptic agent, phenytoin protected 90% of the chicks.

Pentylenetetrazole induced seizure test in mice

The methanol stem bark extract of *Acacia albida* at doses of 50, 100 and 200 mg/kg did not protect mice against subcutaneous PTZ induced seizure. There was however, a significant ($p<0.05$) delay in the onset of convulsion at 100 and 200 mg/kg of the extract (Fig. 2). Sodium valproate (200 mg/kg), the standard antiepileptic drug used as control, protected 66.67% of mice against subcutaneous PTZ induced seizure.

Subcutaneous strychnine induced seizure test in mice

The methanol stem bark extract of *Acacia albida* at the dose of 200 mg/kg showed 50% protection against seizure induced by strychnine. It also exhibited 66.67% protection against mortality. However at doses of 50 and 100 mg/kg the extract offered no protection against seizure but showed 16.33% and 33.33% protection against mortality respectively (Table 3). A insignificant delay in the onset of seizure compared to normal saline was also observed. Phenobarbitone (20 mg/kg) protected 83.33% of the mice against seizure and showed 100% protection against mortality.

DISCUSSION

Generally, the data presented here suggested that the methanol extract of *Acacia albida* contain psychoactive principles that may be useful in the management of epilepsy. Preliminary phytochemical screening of *Acacia albida* revealed the presesnce of tannins, flavonoids and saponins amongst others. Phytocostituents such as tannins, flavonoids and saponins have been shown to modulate central nervous system activities. For example tannins identified from the aqueous fraction of the stem bark extract of *Xeromphis nilotica* was believed to be responsible for the behavioural effects observed in mice (Danjuma *et al.*, 2009). Similarly, the central nervous system activities of the stem bark extract of *Randia nilotica* was believed to be due to saponins present in larger quantity than other fractions (Danjuma *et al.*, 2008). Also, the saponin present in *Baccopa moniera* was reported to be responsible for the observed anticonvulsant activity of the plant (Ray, 2004). The estimated LD_{50} value of the stem bark extract of *Acacia albida* suggested that it is

Table 1: Phytochemical constituents of the methanol stem bark extract of *Acacia albida*

Constituent	Inference
Carbohydrates	+
Glycosides	_
Steroids	+
Saponins	+
Flavonoids	_
Tannins	+
Alkaloids	_
Triterpenes	+

Key: + = present
_ = negative

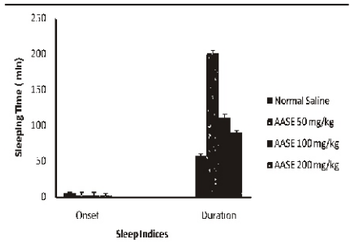

Fig 1: Effect of methanol stem bark extract of *Acacia albida* (AASE) on Diazepam induced sleep in mice results are presented as means SEM. and analyzed using student's t-test, all value are significant at $p<0.001$, n=6 in each group

Table 2: Effect of methanol stem bark extract of *Acacia albida* (AASE) on maximal electroshock induced convulsion in chicks.

Treatment mg/kg	Mean Recovery Time (min) ± S.E.M	Quantal Protection	% Protection	% Mortality
Normal Saline (10 ml/kg)		2/10	20	0
AASE 50	6.78 ± 0.57	1/10	10	0
AASE 100	5.80 ± 0.59	0/10	0	0
AASE 200	5.50 ± 0.67	0/10	0	0
Phenytoin 20	1.0 ± 0.00*	9/10	90	0

Student *t-test* followed by Dunnet's post hoc analysis.

N=10 in each group. * = significant value at $p<0.05$ compared to normal saline.

moderately toxic (Lorke, 1983). LD_{50} values give an idea of the degree of toxicity of compounds (van Brummelen, 2000).

Potentiation of total sleeping time by the stem bark extract of *Acacia Albida* indicated the presence of sedative compounds (Vogel and Vogel, 1997). Compounds that increase the duration of sleep in the diazepam induced sleep test are believed to have sedative properties (Rakotonirina *et al*., 2001).

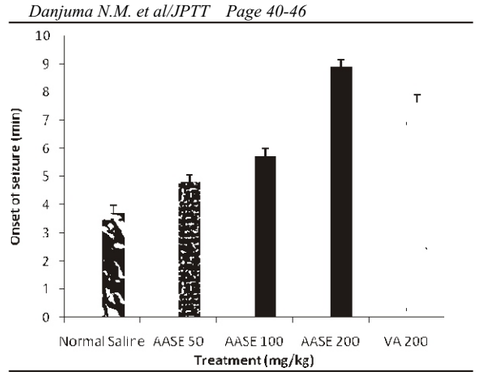

Fig. 2: Effect of Methanol Stem Bark Extract of Acacia albida (AASE) and Valproic Acid (VA) on Pentylenetetrazole Induced Seizure in Mice. N=6 in each group.

Table 3: Effect of methanol stem bark extract of *Acacia albida* (AASE) and phenobarbitone on strychnine induced seizure in mice. N=6 in each group.

Treatment (mg/kg)	Mean Onset of Seizure (min) Mean ± S.E.M	Quantal Protection	% Protection	% Mortality
Normal Saline	6.80 ± 0.58	1/6	16.33	83.33
AASE 50	9.5 ± 0.99	0/6	0	83.33
AASE 100	9.17 ± 0.75	0/6	0	66.67
AASE 200	9.67 ± 0.33	3/6	50	33.33
Phenobarbitone 20	12.0 ± 0.00*	5/6	83.33	0.00

Sedation results from activation of the benzodiazepines and or GABA receptors in the GABA receptor complex (Rang *et al*., 2003).

The results of the anticonvulsant studies with stem bark extract of *Acacia albida* revealed that the extract has activity on sc-PTZ and strychnine with little or no activity on MEST. Strychnine is a competitive antagonist of the inhibitory amino acid glycine (Larson, 1969). Compounds which reverse the action of strychnine (an antagonist to glycine) have been shown to have antiepileptic effects (Raza *et al.,* 2001). The ability of stem bark extract of *Acacia albida* to protect 50% of the animals against strychnine induced seizure suggested anticonvulsant property (Rogawski, 1992), involving glycine receptors, and interference with strychnine sensitive channels (Ogbonnia, 2003).

Pentylenetetrazole is a known convulsant and anticonvulsant activity in the sc-PTZ test identifies compounds that can raise seizure threshold in the brain (White *et al*., 1998). The PTZ induced seizures are similar to the symptoms observed in the *absence seizures* and drugs useful in the treatment of *absence seizures* suppress PTZ induced seizures (Mc Namara, 2006). PTZ has been shown to interact with GABA neurotransmitter and the GABA receptor complex (De Deyn *et al*., 1992). Ability of the extract of *Acacia albida* to increase the latency time to onset of seizure in the PTZ test suggested possible interaction of the extract with GABA-ergic neurotransmission and anticonvulsant activity against *petit mal* epilepsy (Vida, 1995).

The electroshock assay is used primarily as an indication for compounds which are effective in *grand mal* epilepsy while PTZ induced seizure test identifies primarily compounds that raise seizure threshold and is a fairly good index of effectiveness against absence seizures *petit mal* (Rang and Dale, 1995). Protection against HLTE in the MEST predicts anticonvulsant effect that prevents the spread of epileptic seizure discharge from an epileptic focus during seizure activity. Inhibition of HLTE is the common feature of maximal electroshock in rodents, cats, monkeys and humans and the response of rodent brain to the anticonvulsant is similar to that of humans (Swinyard, 1972). There are no false negatives in the MEST and all the currently available anti-epileptic drugs that are clinically effective in the treatment of generalized *tonic clonic* and *partial* seizures such as phenobarbitone, carbamazepine, oxcarbazepine and lamotrigine also suppress HLTE in MEST (Browning, 1992; Rho and Sankhar, 1999). The extract of *Acacia albida* was only able to shorten recovery period of the chicks, which was not significant and thus, has no effect on *grand mal* epilepsy.

The findings in this study showed that the stem bark extract of *Acacia albida* possesses both sedative and anticonvulsant properties, which may account for its use in traditional medicine in management of epilepsy, particularly *petit mal*.

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