Sahel Journal of Life Sciences FUDMA (SAJOLS)
September 2026 Vol. 4(3): 621-627
ISSN: 3027-0456 (Print)
ISSN: 1595-5915 (Online)
DOI: *https://doi.org/10.33003/sajols-2026-0403-66*

Research Article

Evaluation of Anticonvulsant and Central Nervous System Depression Effects of Multi-Herbal Extracts against Chemoconvulsants Induced Epilepsy in Murines

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ABSTRACT
Convulsion is one of the most common neurological disorders affecting millions of population globally. Though there are several effective drugs for treating convulsion, most drugs are associated with side effects and drug interactions. *Combretum hypopilinum* and *Bombax buopozense* used in Nigerian traditional medicine have proven locally to possess antiepileptic and sedative properties. This study aimed to evaluate the anticonvulsant and central nervous system depressant effects of *Combretum hypopilinum* and *Bombax buopozense* against Pentylenetetrazole (PTZ) and Strychnine-induced seizure in murine. This study was carried out using murine model of epilepsy. Thirty animals were randomly divided into five groups of six mice each: Group 1 received distilled water, group 2, 3 and 4 received 100, 200 and 400 mg/kg extract of *Combretum hypopilinum* and *Bombax buopozense* extracts in separate and then similar designed was used for combined extracts. All the animals were induced with PTZ. The subsequent set of animals were induced with strychnine and similar dosing pattern was adopted. For the central nervous system depression, diazepam induced sleep and walk beam assay models was used. The acute toxicity studies revealed no mortality. The *Combretum hypopilinum* and *Bombax buopozense* attenuated the PTZ amd strychnine-induced seizures in a dose-dependent manner in separate extract and combined extracts intervention. The combined extracts showed central nervous system depressant effect by increasing duration of sleep in diazepam induced sleep. The findings of our study showed the anticonvulsant and central nervous system depressant properties of the combined extracts.

Keywords: *Bombax buonopozense; Combretum hypopilinum;* Convulsion; Nervous system; Pentylenetetrazole; Strychnine

Citation: Ibrahim, Y.A., & Usman, N. (2026). Evaluation of Anticonvulsant and Central Nervous System Depression Effects of Multi-Herbal Extracts against Chemoconvulsants Induced Epilepsy in Murines. *Sahel Journal of Life Sciences FUDMA*, 4(3): 621-627. DOI: *https://doi.org/10.33003/sajols-2026-0403-66*

INTRODUCTION

Convulsion is one of the most common neurological disorders and sometimes symptoms of other disorders after stroke and is characterized by recurrent seizures due to abnormal excessive or synchronous neural activity in the brain (Katzung *et al.,* 2012). Seizure arises due to excessive neuronal excitation or loss of inhibition in the brain (Stafstrom, 2010). Although there are many anticonvulsant drugs in the market, not all patients with epilepsy can be treated, and one-third of patients suffer from recurring epilepsy despite using different antiepileptic drugs and multidrug regimens (Mohanraj and Brodie, 2006). Moreover, more than 50% of epileptic patients show side effects of anti-epilepsy drugs during treatment (Krug *et a*l., 1997). So, it is necessary to conduct further studies to develop more effective anti-epilepsy drugs with the minimum side effects. Ethnopharmacology and

medicinal plants are considered new fields of interest in this area.

Using animal models is a proper way to establish epileptic models and identify the mechanisms involved in such diseases, evaluate novel antiepileptic medications and finally reach efficient therapeutic approaches in epileptic patients (Löscher, 2002). Pentylenetetrazole (PTZ) is one of the derivatives of tetrazole and acts as an antagonist of Gamma-Aminobutyric Acid (GABA), which can lead to epilepsy in animal models through the inhibition of the GABA receptors and blockade of chloride inflow (Naseeret *et al*., 2009). Strychnine on the other hand is a known chemoconvulsant that antagonize glycine and other inhibitory receptors.

Natural products are essential components of ancient traditional medicine systems, examples are Chinese medicine and Egyptian medicine. There are about 3.3 billion people in developing world who depend on plant-based traditional medicine, and this represent about 87 of the world's inhabitants, who rely mainly on traditional medicine for their primary health care. *Combretum hypopilium* and *Bombax buonopozense* have been used individually by traditional medicine practitioners in Zuru, Kebbi State of Nigeria for the treatment of some epileptic symptoms.

In recent years, plenty of studies have been conducted on medical plants, and *Combretum hypopilinum* and *Bombax buopozense* are among the Nigerian traditional medicine with traditional claims to have central nervous system effects (Kumar & Bhat, 2014). These plants have shown many therapeutic features such as anti-oxidative (Saeedi *et al*., 2008), sedative, anti-inflammatory (Delfan *et al*., 2014), anti-anxiety (Rabbani *et al*., 2005), antidiarrheal (Bahmani *et al*., 2014) and analgesic (Hajhashemi, *et al*., 2007). It is proposed that the mentioned properties may be attributed to the presence of flavonoid, propanoid, and terpenoid components (Monji *et al* 2011). Overall, considering the anti-anxiety, analgesic, and sedative effects of the *Combretum hypopilinum* and *Bombax buopozense*, it might possess anti-convulsive effects, too. Therefore this study, we explored the effect of oral administration of *Combretum hypopilinum* and *Bombax buopozense* methanolic leaf extracts.

MATERIALS AND METHODS

Experimental Animals

Five to six weeks old, male and female Swiss albino mice weighing (20–33 g), six to eight weeks old, Wister rats weighing (160-200g) were obtained from animal house of the Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria and delivered to animal house of the Department of Pharmacology and Toxicology, Usmanu Danfodiyo University Sokoto.

Plant Collection and Extraction

A sample of each plant of *Combretum hypopilinum* and *Bombax buonopozense* were collected from Safana Local Government, Katsina State, Northwestern Nigeria. It was taken for authentication and extraction using maceration technique at the Department of Pharmacognosy and ethnopharmacy, Faculty of Pharmaceutical Sciences, Usmanu Danfodiyo University Sokoto.

Acute toxicity study

The acute toxicity testing was performed using two phases protocol. Three (3) groups of three (3) mice were treated with the combined extract of *Combretum hypopilinum and Bombax buonopozense* at doses of 10, 100, and 1000 mg/kg body weight orally, and observed for signs of toxicity and death within 24 hours.

Anticonvulsant Studies on the Methanol Stem Bark Extract of *C. hypopilinum* and *B. buonopozense*

Pentylenetetrazole-induced seizure (PTZ) test in mice

Animals were divided into five (5) groups of six (6) each. Groups II, II and IV received *C. hypopilinum* methanol extract 100, 200 and 400 mg/kg, per oral respectively. Groups V and I received diazepam (1 mg/kg) and distilled water (10 ml/kg) intraperitoneum, respectively. Seizure was induced by administering 90 mg/kg of PTZ, subcutaneous as modified by Vogel (1997). Methanol stem bark extract of *C. hypopilinum* was administered orally, 1 hour before the PTZ administration. Absence of an episode of clonic spasm of at least 5 seconds duration, hind limb extension or death indicated the extract's ability to stop the effect of pentylenetetrazole on seizure threshold. Similar protocol will be adopted for strychnine induced seizure and anticonvulsant effect was evaluated.

Another set of thirty-six animals were divided into five (5) groups of six (6) each. Groups II, III and IV received *B. buonopozense* methanolic extract 100, 200 and 400 mg/kg, *p.o* respectively. Groups V and I received diazepam (1 mg/kg) and distilled water (10 ml/kg) *p.o*, respectively. Seizure will be induced by administering 50 mg/kg of strychnine, *sc*. Methanol stem bark extract of *B. buonopozense* will be administered orally, 1 hour before the PTZ administration. Absence of an episode of clonic spasm of at least 5 seconds duration, hind limb

extension or death indicated the extract's ability to abolish the effect of strychnine on seizure threshold

Combined *C. hypopilinum* and *B. buonopozense* extracts effect on PTZ and Strychnine-induced seizure was tested using the following protocol: Thirty-six animals were divided into five (5) groups of six (6) each. Groups II, III and IV received combined extracts of *B. buonopozense* and *C. hypopilinum* methanol stem bark extracts at doses of 100, 200 and 400 mg/kg, per oral respectively. Groups V and I received diazepam (5 mg/kg) and distilled water (10 ml/kg) per oral, respectively. Seizure was induced by administering 50 mg/kg of strychnine subcutaneously. Combined methanol stem bark extracts was administered orally, 1 hour before the strychnine administration. The same protocol was used for PTZ induced seizure. Absence of an episode of clonic spasm of at least 5 seconds duration, hind limb extension or death indicated the extract's ability to abolish the effect of strychnine or PTZ on seizure threshold

Central Nervous System (CNS) Depressant Effect of Combined Extracts of *Combretum hypopilinum* and *Bombax buonopozense*

Diazepam-induced sleep test in mice

Combined extract of *Combretum hypopilinum* and *Bombax buonopozense* was investigated for their central nervous system (CNS) depressant effect using the diazepam-induced sleep test. Mice were divided into 4 groups of 6 each. Group (II-IV) were treated with 100, 200 and 400 mg/kg doses of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense*. Group IV (control group) was treated with distilled water (10 mL/kg, *p.o*). One hour after receiving combined extract formulation of *Combretum hypopilinum* and *Bombax buonopozense* each, animal was injected with Diazepam 5 mg/kg *i.p*. The criterion for sleep was the loss of righting reflex onset and duration of sleep was recorded.

Beam walking assay

The method described by Stanley *et al.*, (2005) was used for this study. Mice were be trained to walk from a start platform along a ruler (80 cm long, 3 cm wide) elevated 30 cm above the bench by a metal support to a goal box. Three trials were performed for each mouse. The mice were grouped into 5 groups of 6 mice each. Mice in the first group were given distilled water per oral; second, third and fourth groups received graded doses of the combined extract formulation, and the fifth group was given diazepam at the dose of 01 mg/kg per oral. After one hour, each mouse was placed at one end of a beam (60 cm long, 8 mm in diameter and elevated 30 cm above the bench by a metal support) and allowed to walk to the goal box at the other end. The number of foot slips, which is a sensitive measure of motor coordination deficit was recorded for each mouse using a tally counter.

RESULTS

Acute Toxicity Studies

There was no mortality observed upon administration of *Combretum hypopilinum* and *Bombax buonopozense* combined extract in the first and second phases of acute toxicity study (Table 1).

Effects of *Combretum hypopilinum* extract on pentylenetetrazole-induced convulsion in mice

The extract significantly ($p<0.05$) increased the latency and shortened the duration of seizure across all the doses employed indicating potential antiepileptic effect (Table 2).

Effect of *Bombax buonopozense* extract of on pentylenetetrazole-induced seizure in mice

The extract significantly ($p<0.05$) increases the latency and shorten the duration of seizure across all the doses employed indicating potential antiepileptic effect (Table 3).

Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on pentylenetetrazole-induced convulsion in mice

The combined extracts has significantly ($p<0.05$) increases the latency, increases the animals survival and shorten the duration of seizure across all the doses used indicating possible synergistic effects of the combined extract in ameliorating seizure induced by pentylenetetrazole (Table 4).

Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on Strychnine-induced convulsion in mice

The combined extracts significantly ($p<0.05$) increased the latency, increases the animals survival and shortened the duration of seizure across all the doses used indicating possible synergistic effects of the combined extracts in ameliorating seizure induced by strychnine (Table 5).

Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on Diazepam induced Sleep in Mice

The combined extracts at the doses of 100, 200 and 400 mg/kg significantly increased the duration of sleep induced by diazepam and shortened its onset (Table 6).

Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on Walk beam Assay for motor coordination

The combined extracts at the doses of 100, 200 and 400 mg/kg significantly increased the number of foot slip on walk beam apparatus indicating motor incoordination and central nervous system depression (Table 7).

Table 1: Acute toxicity studies of methanolic extracts of *Combretum hypopilinum* and *Bombax buonopozense*

Dose (mg/kg) PO	Number of animals dead/used	% Mortality
Phase I		
10	0/3	0
100	0/3	0
1000	0/3	0
Phase II		
1000	0/1	0
1600	0/1	0
2900	0/1	0
5000	0/1	0

Table 2: Effect of *Combretum hypopilinum* extract on PTZ-induced seizure

Treatment/ dose	Latency of clonic seizure (s)	Duration of seizure (s)	% Mortality
Distilled water10 ml/kg	22.30 ± 2.50	79.43 ± 3.30	95
Extract 100 mg/kg	26.81 ± 2.41	81.72 ± 5.25*	96
Extract 200 mg/kg	58.60 ± 1.10	26.50 ± 3.91*	25
Extracts 400 mg/kg	67.46 ± 4.21	18.30 ± 2.34*	5
Diazepam 1mg/kg	77.56 ± 2.11	12.65 ± 1.95*	0

Data presented as mean ± standard error of mean, * =significance at p<0.05 one way analysis of variance followed by dunnet post-hoc test.

Table 3: Effect of *Bombax buonopozense* extract of on PTZ-induced mice

Treatment/ dose	Latency of clonic seizure (s)	Duration of seizure (s)	%Mortality
Distilled water10 ml/kg	21.22 ± 1.51	97.21 ± 2.01	100
Extract 100 mg/kg	24.71 ± 1.52	98.10 ± 2.20*	100
Extract 200 mg/kg	65.40 ± 2.20	35.21 ± 2.83*	30
Extracts 400 mg/kg	72.41 ± 2.20	17.21 ± 1.28*	15
Diazepam 1mg/kg	76.21 ± 1.10	14.31 ± 2.30*	0

Data presented as mean ± standard error of mean, * =significance at p<0.05 one way analysis of variance followed by dunnet post-hoc test.

Table 4: Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on pentylenetetrazole-induced convulsion in mice

Treatment/ dose	Latency of clonic seizure (s)	Duration of seizure (s)	% Mortality
Distilled water10 ml/kg	22.10 ± 1.51	86.21 ± 2.28	100
Extract 100 mg/kg	39.76 ± 2.62	63.12 ± 4.10*	25
Extract 200 mg/kg	78.40 ± 2.20	35.21 ± 2.83*	5
Extracts 400 mg/kg	97.33 ± 4.23	11.24 ± 1.30*	0
Diazepam 1mg/kg	98.15 ± 3.40	14.31 ± 2.30*	0

Data presented as mean ± standard error of mean, * =significance at p<0.05 one way analysis of variance followed by dunnet post-hoc test.

Table 5: Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on Strychnine-induced convulsion in mice

Treatment/ dose	Latency of clonic seizure (s)	Duration of seizure (s)	%Mortality
Distilled water10 ml/kg	14.26 ± 2.88	102.51 ± 4.31	100
Extract 100 mg/kg	36.10 ± 1.31	83.20 ± 2.11*	75
Extract 200 mg/kg	93.50 ± 6.55	46.10 ± 5.31*	15
Extracts 400 mg/kg	101.21 ± 4.21	9.23 ± 2.76*	0
Diazepam 1mg/kg	115.15 ± 3.40	10.22 ± 1.67*	0

Data presented as mean ± standard error of mean, * =significance at p<0.05 one way analysis of variance followed by dunnet post-hoc test.

Table 6: Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on Diazepam-induced Sleep in Mice

Treatment/ dose	Onset of sleep (s)	Duration of sleep (s)
Distilled water10 ml/kg	124.21 ± 1.83	105.22 ± 1.31
Extracts 100 mg/kg	58.12 ± 2.22	117.13 ± 1.12*
Extracts 200 mg/kg	43.50 ± 1.22	126.25 ± 2.71*
Extracts 400 mg/kg	21.24 ± 1.60	139.22 ± 1.49*
Diazepam 1mg/kg	11.20 ± 1.81	160.35 ± 2.53*

Data presented as mean ± standard error of mean, * =significance at p<0.05 one way analysis of variance followed by dunnet post-hoc test.

Table 7: Effects of combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* on Walk beam assay

Treatment/ dose	Number of foot slip
Distilled water10 ml/kg	7.01 ± 2.15
Extracts 100 mg/kg	18.11 ± 1.35*
Extracts 200 mg/kg	23.56 ± 0.87*
Extracts 400 mg/kg	51.21 ± 1.71*
Diazepam 1mg/kg	62.11 ± 1.0*

Data presented as mean ± standard error of mean, * =significance at p<0.05 one way analysis of variance followed by dunnet post-hoc test.

DISCUSSION

The preliminary phytochemical screening of the methanolic combined extract of *Combretum hypopilinum* and *Bombax buonopozense* revealed the presence of tannins, saponins, flavonoids, steroids, alkaloids, carbohydrates and reducing sugar. Large varieties of plants containing a wide variety of phytochemicals as their bioactive principles have been reported to alter central nervous system activities. Median lethal dose (LD_{50}) was found to be greater or equal to 5000 mg/kg. In Toxicolgy, 1mg/kg is considered highly toxic, 10 mg/kg is considered toxic, 100 mg/kg is moderately toxic, 1000 mg/kg is slightly toxic and 5000 mg/kg is considered not toxic. The result of 5000 mg/kg reported in this work indicates that large dose of the extract could be relatively no toxic upon oral administration.

This study revealed methanolic that combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* have an anticonvulsant effect that attenuated the PTZ-induced seizures in a dose-dependent manner. Administration of methanol stem-bark combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* increased the latency period of clonic seizure initiation and shorten the duration of seizure and decreased mortality rate compared to the distilled water treated group. This may indicate possible interaction of the phytochemicals of these extracts with GABA A or glycin receptors in elicitin their anticonvulsive effects. In addition, the administration of methanol stem-bark combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* reveals increased duration of sleep and decrease onset in the diazepam induced sleep model, indicating possible central nervous system depressant effect of these combined extract likely by stimulating the inhibitory pathways or suppressing the excitatory neurons. In this study, the administration of 400 mg/kg methanol stem-bark combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* increased the latency period of clonic seizure initiation and the delay duration of tonic-clonic initiation and decreased mortality rate just like 1 mg/kg dose of diazepam as a positive control treatment group. Similar to our study, Bahramnejad et al. 2018 reported that peritoneal injection of diazepam could increase the delay time of clonic and tonic-clonic seizure initiation in mice. Also, the mortality rate reached following the injection of the effective dose of diazepam, which was following the results of Nejad et al, (2017). Some studies reported that methanol stem-bark extracts of *Combretum hypopilinum* and *Bombax buonopozense* extract has certain phytochemical components such as flavonoid, propanoid, and terpenoid, which contribute to their central nervous system depression and anticonvulsant effects. The significant effects of these plants on anxiety have been approved comparable to diazepam (Monji et al., 2011; Neshat et al., 2017). Because flavonoids have a similar structure to GABAA receptor ligands (Wasowski & Marder, 2012), thus the plant may have a modulatory effects toward GABA A and glycine receptors. This effects of methanol stem-bark combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* can be mediated by benzodiazepines receptors via hyperpolarization of neural resting membrane hyperpolarization.

Flavonoids as found enormous in the methanol stem-bark combined extracts of *Combretum hypopilinum* and *Bombax buonopozense* as an important category of natural antioxidant components as all our inducing agents such as the pentylenetetrazole and strychnine were known to provoke release of free radicals ad causes oxidative stress (Hajhashemi et al., 2007).

CONCLUSION

This study showed the anti-convulsive and central nervous system depressant activities of methanol stem-bark combined extracts of *Combretum hypopilinum* and *Bombax buonopozense*. These effects might be due to the impact of the phytochemical components of these extracts on the central inhibitory and excitatory pathways coordinated by gamma aminobutyric acid and glutamate respectively.

Ethical Considerations and Compliance with ethical guidelines

Ethical clearance was sort and it was approved by the Ethical committee on experimental animals use of the Usmanu Danfodiyo University Sokoto
Ethics Committee of Guilan University of Medical Sciences
(Approval Number: AREC.FPS.UDUS.0013).

Funding

Funding for this study was provided by the Institutional Based Research Grant, IBR Batch 10
Usmanu Danfodiyo University, Sokoto

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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