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Research Paper

The Extract of *Bombax Costatum* Bark Improves Depression and Epileptic Seizures in Rats

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ABSTRACT

Background: The plant *Bombax costatum* (BC) has been used traditionally in Nigeria for the management of various ailments. The chloroform extract of BC bark was investigated for its potential effects against the induced seizures and depression in rats.

Methods: Thirty Wistar rats were divided into five groups of six. Group I received normal saline, group II received pentylenetetrazole (PTZ, 35 mg/kg), group III received diazepam (5 mg/kg) plus PTZ at 35 mg/kg, group IV received 250 mg/kg of the BC extract, and group V received 500 mg/kg of the same extract. The above protocol was repeated on alternate days from the first to twenty 5th days.

Results: Tukey's post hoc test revealed a statistically significant increase in the seizure scores after using PTZ (3.38±0.29, P<0.0001), in contrast to a decrease in the seizures after treatment with the BC extract (250 mg/kg; 2.72±0.25, P=0.0001). The analysis of variance for forced swimming test showed a significant decrease in immobility time if treatment with the extract (250 mg/kg; 125±5.59; P=0.01). The immobility duration increased with the PTZ treatment (163.8±12.03). The brain's dopamine and serotonin levels under PTZ effect significantly decreased to 140.2±15.66 and 26.38±1.16, respectively, when the rats were treated with the extract at 500 mg/kg.

Conclusion: The findings of this study suggest that the BC extract has anticonvulsive and anti-depressive properties, thus it offers neuro-protection against both conditions, induced by PTZ in rats.

Keywords: *Bombax costatum* extract, Depression & epilepsy, Diazepam, Dopamine & serotonin, Pentylenetetrazole

Introduction

Epilepsy is a chronic neurological disorder, characterized by the spontaneous and recurrent bursts of seizures due to neuronal hyperactivity. It generally arises in the restricted regions of the brain and may affect people of all ages [1, 2]. Epileptic seizures occur due to excessive electrical discharges in the brain [3]. These abnormal events are synchronized, localized, or widely distributed in the brain, which may remain confined to the area of origin, i.e. focal or partial seizures, or spread across cerebral hemispheres, i.e. generalized seizures [4]. This can also be explained by episode of neurologic dysfunction due to abnormal neuronal firing, causing changes in sensory perception, motor control,

behavior or autonomic function [5]. Epilepsy affects about 50 million people worldwide, making it one of the most common neurological disorders [6]. In Nigeria, the estimated prevalence of epilepsy is 8 per 1000 individuals, causing a substantial burden on the healthcare economy [7].

Depression is one of the most predominant psychiatric comorbidities in patients with epilepsy, due to physiological or biological causes [8]. Depression affects, general health, quality of sleep, eating habits and subsequently disrupts physiological and neurological homeostasis [9]. Further, depression is associated with the state of sadness, loneliness, irritability, despair, confusion and shame. Studies are in progress to elucidate the pathophysiological relationship between depression and epilepsy [10]. Many mechanisms with bidirectional relationship have been suggested as the causes, including structural abnormalities in the brain nuclei. In this context, monoamine pathways, cerebral glucose metabolism, hypothalamic-pituitary-adrenal (HPA) axis, and interleukin-1 levels are involved in the pathogenesis of these conditions [11].

Both epilepsy and depression are associated with an imbalance between excitation and inhibition in specific brain circuitries and neurotransmitter systems [12]. Quantitative changes in neurotransmitter system at several brain regions are involved in the development of many psychiatric and neurodegenerative diseases [13, 14]. Monamine activity is associated with 5-hydoxytrptamine, dopamine, and norepinephrine levels as the modulation indices of the brain [15]. These neurotransmitters regulate principal functions and behaviors, such as mood swings, emotions, sleep and wakefulness [16], which have been scientifically proven to also modulate seizure-like events in the brain [16].

Bombax costatum is mostly found in grassland areas of West Africa [17]. This family of plants, especially its Pellegr and Vuillet species, is known as red-flowered silk cotton tree in English, while in the local dialects in Nigeria, it is known as “Gurjiyaa”, “Joohi” and “Akpu”, in Hausa, Fulani and Igbo areas, respectively [18]. In Nigeria and other countries of West Africa, different parts of the plant is consumed as food and in the treatment of various conditions, such as tiredness, epilepsy, insanity, headache, yellow fever, wounds and convulsion [19, 20]. The phytochemical screening conducted on the hydromethanolic extract of BC bark has revealed the presence of alkaloids, tannins, flavonoids, phytosterols, glycosides and saponins [21].

Pharmacological studies have reported that the plant has hepatoprotective, anti-oxidant and anti-inflammatory properties [22, 23]. These studies also suggest that the aqueous root extract has anxiolytic effect in mice by up-regulating the gamma aminobutyric acid (GABA) level while decreasing the activity of 4-aminobutyrate transferase in the brain [22, 23].

In many communities in the developing countries, people inherently resort to readily available and familiar folk medicines for the management of epilepsy and the associated neurological disorders [24, 25]. The majority of the plants used in African traditional medicine have shortage of scientific data to support their efficacy in the management of epilepsy-induced depression. Given the background information, the main research question of this study was whether the chloroform extract of the stem bark of BC plant could ameliorate depression associated with epilepsy, induced by PTZ in rat model.

Aim of the study: This study aimed at evaluating the potential mitigating effects of *B. costatum* extract against the seizures induced by PTZ, and the subsequent depressive behavior in experimental rats.

Materials and Methods

Plant Materials: *B. costatum* stem bark samples were collected from the Jere local government area in Borno State, Nigeria. The plant was authenticated by a taxonomist (voucher number UM/HAH/2021/002) and deposited at the herbarium section of the Department of Human Anatomy, University of Maiduguri, Nigeria. The bark samples were thoroughly washed with water, air dried at room temperature (28°C), and powdered, using a pestle and mortar.

Extract Preparation: The crude extract of the BC bark samples was achieved, using chloroform (JHD®) by maceration method. The powder was soaked in chloroform for 48 hours with occasional agitation at regular intervals. The supernatant was then filtered using Whatman filter paper No.1, and was evaporated to complete dryness at room temperature. The extract was then stored in sealed bottles at room temperature until further use. The extract was then dissolved at appropriate concentrations in distilled water and the rats were orally administered with a predetermined dosage of the extract per group, such that the volumes given were appropriate to their body weight and size.

Drugs and chemicals: Diazepam (Valium®) and pentylenetetrazole (PTZ; P6500) were purchased from Sigma Aldrich (St Louis, MO, USA) while 3,4-dihydroxyphenethylamine (DA), and 5-hydroxytyramine (5-HT) ELISA kits were obtained from Sigma-Aldrich (Northon, Germany). All chemicals and reagents used for the experiments were of analytical grades.

Animal handling: Adult healthy Wistar rats (n=30) weighing 150-220 grams were used for the experiments. The rats were housed at room temperature (28±3°C) under 12hr of light and dark cycles, in clean cages with metal cover lids and were bedded on soft wood shavings, which were renewed every three days. The rats were fed standard commercially available rat feed (Vital feed®, Jos) with free access to food and drinking water ad libitum. The animals were allowed to acclimatize for 14 days before they were subjected to the experiments. The study protocols were consistent with the international guide for the care and use of laboratory animals [26].

Experimental design

Epilepsy induction: Epilepsy was induced and confirmed by Racine scale. Forced swimming test was performed to evaluate the depressive-like behavior while alterations in serum serotonin and dopamine levels were also checked for further confirmation of the diagnosis.

Chemical kindling: Neurologically, kindling is the process of starting a seizure or making its recurrence more likely in experimental animals. On the day of the experiments, PTZ was weighed and dissolved in sterile normal saline. The rats' body weight was measured in grams, while the volume of PTZ solution was calculated based on the rats body weight, which determined the injection dosage. The kindling was carried out, using a sub-convulsive dose of 35 mg/kg body weight and pentylenetetrazole was administered intraperitoneally (IP). The rats were then monitored for 30 minutes after seizure induction with PTZ, while the latency and the stages of seizures were recorded. The above protocol was repeated on alternate days for 25 days. The seizure activity was then evaluated, using the following Racine scale without modification:

Stage 0: No response.

Stage 1: Restlessness and vibrissae twitching.

Stage 2: Head nodding, head clonus, and myoclonic jerks.

Stage 3: Unilateral forelimb clonus.

Stage 4: Rearing position with bilateral forelimb clonus.

Stage 5: Generalized tonic-clonic seizure with falling [27].

Kindling was considered complete when the rats exhibited seizures at score 4 or above after 3 consecutive PTZ administrations [28]. Behavioral tests were conducted 24 hours after the last PTZ injection. The same rats in each group were used for all of the behavioral assessments.

Animal groupings: Thirty rats (n=30) were randomly divided into 5 groups of six each as follows:

Group 1: Normal control, received normal saline.

Group 2: Model group, received normal saline followed by sub-convulsive dose of 35 mg/kg PTZ intraperitoneally after 30 minutes.

Group 3: Diazepam group, received diazepam at 5 mg/kg followed by 35 mg/kg PTZ intraperitoneally after 30 minutes.

Group 4: BC 250 group, received 250 mg/kg of the BC extract orally followed by 35 mg/kg PTZ intraperitoneally after 30 minutes.

Group 5: BC 500 group, received 500 mg/kg BC extract orally followed by 35 mg/kg PTZ intraperitoneally after 30 minutes.

Neurobehavioral assessment: Behavioral parameters were assessed by two trained observers blinded to the animals' treatment status in order to eliminate bias.

Forced swimming test: The forced swimming test (FST) was used to evaluate the depressive-like behavior in rats [29] without modification. A cylinder made of plastic (45 cm height & 35 cm diameter) was filled with water (26°C) up to 35 cm of its depth. The rats were placed in the water for six minutes, and the immobility time was recorded. Immobility was defined as the rat stopped climbing and their head floated above the water level. Longer immobility time (sec) indicated state of despair while the mobility time indicated active behavior. After the FST procedure, the rats were dried in towels and returned to their respective home cages.

Assessment of depressive biomarkers

Brain tissue: The rats were euthanized under ketamine anesthesia, 24 hours after the FST. The rat brains were harvested and prepared for biochemical assessments. The whole brain from each rat was homogenized in sodium phosphate buffer (0.1 M, pH 7.4), centrifuged for 10 min at 10,000g (4°C) and the supernatant was collected. The supernatants were used for the assessment of dopamine and serotonin concentrations. The total concentrations of dopamine and serotonin in each brain were measured by an ELISA kits (dopamine and serotonin research ELISA), Labor Diagnostika Nord (LDN), Northorn, Germany) according to the manufacturer's instructions.

Statistical analyses: The data obtained were expressed as Means±SEM. The results were analyzed by one-way analysis of variance (ANOVA) while the comparison of significance among the groups was performed by Tukey's post hoc test, using Graphpad prism software, version 8.0.2. Only the comparative values at $P<0.05$ were considered to be statistically significant.

Results

Effects on Seizure: The one way ANOVA showed a statistically significant difference in the seizure scores recorded during the 26-day kindling period among the rat groups [$F_{(4, 15)}$= 92.34, P=0.005]. The Tukey's post hoc test showed a significant increase in the seizure scores for PTZ (3.38±0.29, P<0.0001) as compared to the rats treated with the BC extracts. They showed a decline in the seizure score dose-dependently at 250 mg/kg (2.72±0.25, P=0.0001) and 500 mg/kg (2.55±0.28, P=0.0007). Diazepam resulted similarly in reduced scores compared to those of the extract (0.95±0.13; P<0.0001). The group that received normal saline recorded zero seizure scores.

Effects on depressive behaviors: The groups treated with the BC extracts manifested a statistically significant different immobility time (sec) during the FST [$F_{(4, 18)}$=6.91, P=0.0015]. Tukey's post hoc test further revealed a significant dose-dependent decrease in the immobility time at the BC extract 250 mg/kg (125.0±5.59, P=0.01) and 500 mg/kg (138.8±6.58, P=0.01). The model group, treated with PTZ manifested increased immobility time (163.8±12.03) compared to the rats treated with the extracts. Diazepam was used as an anxiolytic reference drug, producing the same properties as the BC extracts (Figure 1). The normal control group had a significant decreased immobility time (110.3±6.76, P=0.0009) in contrast to that noted in the model group, demonstrating increased immobility time.

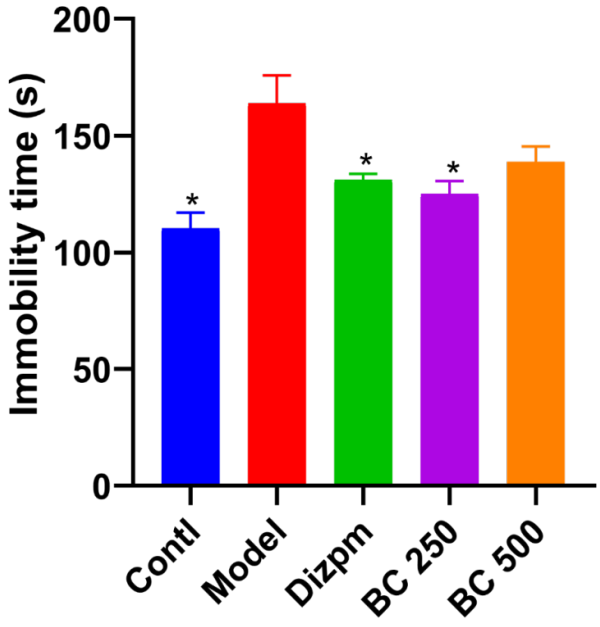

Figure 1. Forced swimming test: Effect of *B. costatum* on depression in PTZ kindled wistar albino rats

Data are expressed as Mean±SEM, n=4-5. *P < 0.05, control, diazepam and BC 250 group vs. Model group. Normal saline (Contl), PTZ 35 mg/kg/2 days (Model), PTZ 35 mg/kg/2days+Diazepam 5 mg/kg/2days (Dzpm), PTZ 35 mg/kg/2 days+BC 250 mg/kg/2 days and PTZ 35 mg/kg/2 days+BC 500 mg/kg/2 days.

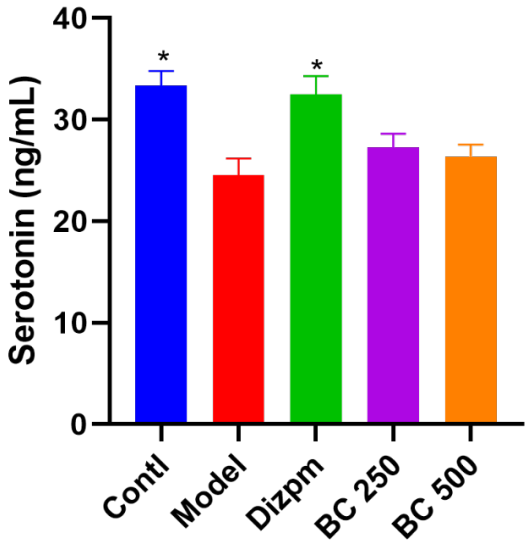

Figure 2. Effect of *B. costatum* on concentration of serotonin in brain homogenate of PTZ kindled Wistar rats.

Data are expressed as Mean±SEM, n=3-4. *P<0.05, control, diazepam BC 250 and BC 500 group vs. model group. Normal saline (Contl), PTZ 35 mg/kg/2days (Model), PTZ 35 mg/kg/2 days+Diazepam 5 mg/kg/2 days (Dizpm), PTZ 35 mg/kg/2 days+BC 250 mg/kg/2 days and PTZ 35 mg/kg/2 days+BC 500 mg/kg/2 days.

Effects on serotonin: The results of the one way ANOVA showed a statistically significant difference in the brain serotonin levels across the groups [$F_{(4, 13)}$=6.092, P=0.005]. Tukey's post hoc test confirmed a significant increase in the serotonin level in the normal saline group (33.34±1.44; P=0.014) compared to that noted in the model group treated with PTZ (24.54±1.66). The administration of the BC extracts increased the serotonin levels at the BC extract levels of 250 mg/kg (27.28±1.34) and 500 mg/kg (26.38±1.16) as compared to that observed in the model group with decreased serotonin level (Figure 2). Diazepam at 5 mg/kg caused a significant increase in the serotonin level (32.48±1.81, P=0.016), which was comparable to that noted for rats treated with the BC extract only.

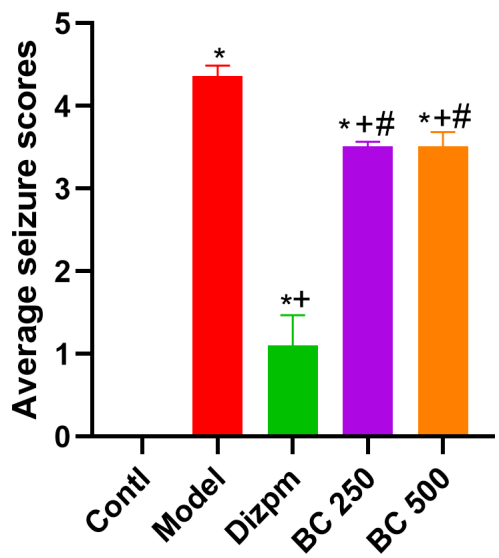

Figure 3. Effect of *B. costatum* on the average seizure scores recorded during the course of kindling in Wistar albino rats

Data are expressed as Mean±SEM, n=4-7. *P<0.05, model, diazepam, BC 250 and BC 500 groups vs control group. +P<0.05, diazepam, BC 250 and BC 500 group vs. model group. #P<0.05, BC 200 and BC 500 mg/kg groups vs diazepam group. Normal saline (Contl), PTZ 35 mg/kg/2 days (Model), PTZ 35 mg/kg/2 days+Diazepam 5 mg/kg/2 days (Dizpm), PTZ 35 mg/kg/2 days+BC 250 mg/kg/2 days and PTZ 35 mg/kg/2 days+BC 500 mg/kg/2 days.

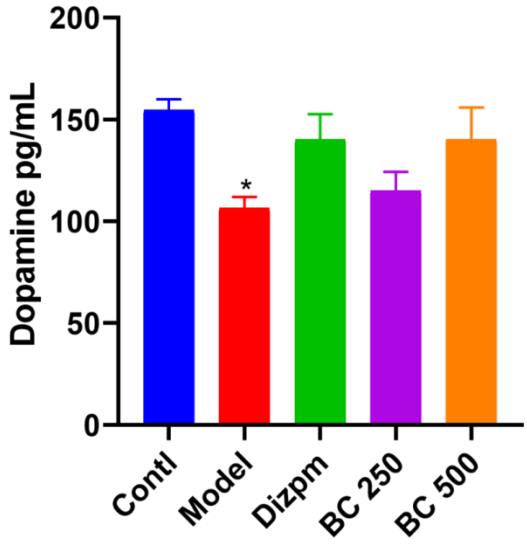

Figure 4. Effect of *B. costatum* on level of dopamine in brain homogenate of PTZ kindled Wistar rats

Data are expressed as Mean±SEM, n=3-4. *P<0.05, model, diazepam BC 250 and BC 500 group vs. control group. Normal saline (Contl), PTZ 35 mg/kg/2 days (Model), PTZ 35 mg/kg/2 days+Diazepam 5 mg/kg/2 days (Dizpm), PTZ 35 mg/kg/2 days+BC 250 mg/kg/2 days and PTZ 35 mg/kg/2 days+BC 500 mg/kg/2 days.

Effects on dopamine: The ANOVA results also demonstrated a significant difference in the brain dopamine levels amongst the treated rats [$F_{(4, 13)}$=3.808, P=0.029]. The extract caused a significant dose-dependent increase in the dopamine levels of the brain homogenates after treatment with the extract either at 250 mg/kg (115±9.2; P=0.01) or 500 mg/kg (140.2±15.6; P=0.01), compared to those in rats treated with diazepam at 5 mg/kg (140.3±12.29; P=0.001). The IP administration of PTZ to the model group induced a significant decrease in the dopamine level (106.4±5.54; P=0.001) in contrast to that noted in the orally treated rats with the BC extracts, which caused an increase in the brain dopamine.

Discussion

This study was planned to investigate the effects of chronic administration of PTZ at a subconvulsive dosage on induced seizures in rats. The treatment resulted in twitching, myoclonic jerks and tonic-clonic seizures in the animals. Also, we recorded manifestations of depressive-like behaviors and variations in the serum levels of serotonin and dopamine in the kindled rats. The PTZ-induced seizure is widely used to screen the clinical effects of anti-epileptic agents in humans [30].

This study revealed that pretreatments with the BC extract at 250 or 500 mg/kg induced a significant decrease in the seizure scores in rats compared to that seen in the control group. This efficacy may be attributed to the increase threshold of the yet unknown mechanisms involved in the onset of seizure in the experimental animals. This finding in turn indicates that the plant extract might have a significant anticonvulsant activity. Further, the BC extracts may contain important compounds that inhibit the myoclonic and tonic-clonic seizures induced by PTZ. The standard drug, i.e. Diazepam at 5 mg/kg, rendered a significant inhibition against the seizures that was comparable to that of the BC extracts dose dependently. See Figure 3 for details. Tentatively, we may conclude that the anticonvulsive effect of the extracts can increase the seizure threshold in the rats' brain, thus effective against seizures.

Epilepsy is associated with a psychiatric comorbidity, such as depression, which may lead to socioeconomic and poor quality of life in patients [31]. The results demonstrated that pretreatment with the BC extract significantly decreased the immobility time, comparable to that induced by diazepam. According to the present study, BC extract is a potential source of neuropharmacological properties and exhibited significant anti-depressive effect. This was in addition to other behaviors observed in the rats, such as suppressed exploratory and social activities, fatigue, and impaired motivation for pleasure, described for depression similar to those seen in humans [32]. This could explain the increased immobility time during the FST sessions, suggesting a mental state consistent with the findings in an earlier study [32]. Further, the immobility time in pentylenetetrazole group in-

creased as compared to that of BC group. This is thought to reflect either a failure of persistence in an escape directed behavior (i.e. behavioral despair) on the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli [33].

The serotonin level is often used as a serum biomarker of depression in humans [33]. In the present study, the administration of the extract to the kindled rats markedly increased their brain's serotonin level dose dependently, suggesting the mitigation of the depressive-like behaviors. In this context, our findings for the BC extract agree with an earlier study [34].

This suggests that the dysfunction of serotonin as one of the major neuromodulators is involved in the pathophysiology of depression in the kindled rats. Further, the decreased brain inhibition reflects the extract ability to reduce the PTZ-induced despair in rats. Thus, the anti-depressive effect of serotonin is likely associated with its anti-biogenic actions. Such property makes the BC extract a potential candidate for the management of major depressive psychiatric disorders [35]. The reduction in the endogenous serotonin level may reflect the compromised neurotransmitter signaling in the brain's serotonergic system [36]. Classic pharmacological studies have clearly shown that serotonin may have potent anti-convulsive and anti-depressive effects, by acting on the brain circuits that control the genesis of epilepsy and depression [37].

The pathophysiological mechanism in the genesis of epilepsy is involved in the dysfunction of brain's dopamine responsible for seizure threshold in animal models of epilepsy [38], as evident by the results observed in the kindled rats. The BC extract significantly increased the endogenous dopamine dose dependently, suggesting its neuro-protective effect against stimuli that trigger PTZ-induced seizures. The rise in the brain's dopamine level may provide antiepileptic and anti-depressive effects. This argument is consistent with the findings reported previously in the literature [39, 40]. It is a known fact that there is a positive working relationship between dopamine and serotonin. They interact to exert similar effects to modulate epilepsy and depression [41]. Therefore, a rise in the brain's dopamine level can also increase the serotonin, improving the depressive behavior and epilepsy in the experimental animals, as shown in the present study.

Conclusions

This study provided experimental evidence on the protective effect of the BC extract against PTZ-induced depressive-like behavior, due to the kindling treatment in rats. The extract clearly increased the seizure threshold and decreased the immobility time initiated by the forced swimming test in rats. This was achieved through the attenuation of the brain's dopamine and serotonin levels. Therefore, the BC bark extract could be a potential candidate as an anti-depressive agent in animal model. Further studies are warranted to investigate the effective of this compound as a therapeutic agent in humans with epilepsy and depression.

Ethical Considerations

Compliance with ethical guidelines

The study protocols were in concordance with the International Guide for the Care and Use of Laboratory Animal as published by National Research Council of Nigeria (2011).

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Authors' contributions

Conceptualization: All authors. Animal handling & data analysis: Abubakar M. Bello, Aishatu A. Ishaku and Nathan I. Dibal; Writing of the initial drafts: Aishatu A. Ishaku. Study supervision, proofreading & editing: Abubakar M. Bello, Musa S. Chiroma and Nathan I. Dibal.

Conflict of interest

The authors declared no conflict of interest.

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