ABUAD INTERNATIONAL JOURNAL OF NATURAL AND APPLIED SCIENCES
ISSN: 2955-1021
AIJNAS Volume 5, Issue 2, 2025 pp 115-122
https://doi.org/10.53982/aijnas.2025.0502.05-j

https://journals.abuad.edu.ng/index.php/aijnas

EVALUATION OF THE LEAF EXTRACT OF *BLIGHIA SAPIDA* K.D. KOENIG FOR SEDATIVE, ANTICONVULSANT AND ANTIDEPRESSANT-LIKE PROPERTIES IN MICE

Juliet N. **Olayinka**[1,2]*, Emma E. **Okpakpor**[3], Raymond I. **Ozolua**[1]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Benin, Benin City, Edo State, Nigeria
[2]Neuropharmacology Unit, Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, Afe-Babalola University, P.M.B. 5454, Ado-Ekiti, Ekiti State, Nigeria
[3]Department of Science Laboratory Technology, Faculty of Life Sciences, University of Benin, Edo State, Nigeria.

*Corresponding author. Juliet Nnenda Olayinka,
E-mail address: julietolayinka@abuad.edu.ng or julietolayinka19@gmail.com

Abstract

Background/Aim: *Blighia sapida (BS) is a widely used medicinal plant in West Africa. Its leaf has been reported in folkloric medicine to be used in the management of migraines, epilepsy, pains, and several other diseases. However, there is limited knowledge about the scientific basis for its folkloric use in the management of epilepsy and other central nervous system (CNS)-related disorders. The study was aimed at evaluating the sedative, anticonvulsant, and antidepressant-like properties of the aqueous leaf extract of BS in mice.* ***Methods:*** *The extraction process was by cold maceration for three days. Twenty-five mice (n = 5) of both sexes were used for each of the evaluations (diazepam-induced sleep time, anticonvulsant and antidepressant tests) at oral doses of 125, 250, and 500 mg/kg p.o. of BS.* ***Results:*** *Doses of BS shortened diazepam-induced sleep time in mice, and did not protect the mice against pentylenetetrazole (PTZ) and maximum electroshock (MES)-induced convulsion. BS increased duration of immobility in both the tail suspension test (TST) and forced swimming test (FST) in mice.* ***Conclusion:*** *These finding show that BS lacks sedative-hypnotic effect and has no anticonvulsant and antidepressant activities. The results from this study do not justify its use in the treatment of epilepsy and some CNS-related disorders such as depression.*

Keywords: *Blighia sapida*; Central nervous system, Sleep; Seizures; Depression

Introduction

Disorders of the brain are most frequently referred to as 'mental disorders', 'neuropsychiatric disorders', or 'neurological disorders' (Collins *et al.,* 2011). While depression, panic disorders, schizophrenia, insomnia and drug dependence are examples of mental disorders; epilepsy, multiple sclerosis and dementia are examples of neurologic defects (Collins *et al.,* 2011). Many people are still unaware of the burden of brain disorders. It was reported by the World Health Organization (World Health Organization, 2006) of the rise in brain disorder which is now a worldwide problem in the 21st century. Some reports have shown that one-third of the worlds' population is affected by these brain disorders (Organization, 2002; World Health Organization, 2006; Direk and Tiemeier, 2010). Since there are no improved care and treatment for the disorder; and only a few persons with the health issue have access to treatment (Wittchen *et al.,* 2011), identifying strategies for improved prevention and treatment of brain disorders through elucidating the activities of plant-based products for their effects in the brain becomes necessary.

Blighia sapida (BS) K.D Koenig, is called 'Ackee' in Jamaica and regarded as one of their top fruits (Mitchell *et al.*, 2008). Different names are ascribed to the plant in West Africa. The Yorubas in Nigeria call it 'Isin' (Onuekwusi *et al.,* 2014). In Ghana, the Twi speaking tribe call it 'Akyefufo/Akye' (Osei *et al.*, 2014). The Foulama speaking tribe in the Republic of Benin, call it 'Natema' (Dansi *et al.,* 2012). Herbal doctors use the leaves including the pulp to treat conjunctivitis (Abolaji *et al.*, 2007; Etukudo, 2003). Trachoma and iritis have been treated with the leaf's juice (Etukudo, 2003). The pulp of the twiggy leaf, as well as the leaf itself have been reported in ethnomedicine to manage migraines and epilepsy (Sinmisola *et al.,* 2019; Orwa *et al.,* 2009). Diabetes mellitus, hypertension, constipation, hemorrhage and vomiting have been reported to be managed by the leaf extract traditionally (Marles, 1995; Ekué *et al.* 2010). Okogun (1996) has reported the use of the bark pulp of the plant as an ointment for edema and in managing intestinal pains.

Some bioactive secondary metabolites identified in the leaf of BS are chlorogenic acid, saponin, tannin and quercetin (Olayinka *et al.*, 2021). Studies have demonstrated that the plant possesses antioxidant (Ojo *et al.,* 2017; Adekola *et al.*, 2023), analgesic (Olayinka *et al.,* 2021), antidiabetic (Oloyede *et al.,* 2014; Ojo *et al.,* 2017), antimicrobial

(John-Dewole and Popoola, 2013), hypoglycaemic (Saidu, 2012), antihyperlipidemic (Oloyede *et al.,* 2014) and anti-diarhoeal (Antwi *et al.*, 2009) properties. The leaf extract of *Blighia sapida* has been reported to attenuate oxidative stress in *Drosophilia melanogaster* fly (Ibraheem *et al.*, 2020; Ibraheem *et al.*, 2022). A study on the stem bark of BS has shown that it possesses antipsychotic effects in mice (Fehintola, 2019). Other studies have also revealed that the stem bark has the potential of inhibiting cholinergic enzymes associated with Alzheimer's disease, and has demonstrated its use in pest control (Ojo *et al.,* 2017; Adekola *et al.,* 2023).

Although the leaf of BS has been reported in ethnomedicine to possess anti-migraine and antiepileptic actions (Orwa *et al.,* 2009; Sinmisola *et al.,* 2019), there seems to be no detailed neuropharmacological evaluations to lend scientific basis to these claims. Therefore, this study investigated the neuropharmacological properties of the leaf extract of BS in mice.

Materials and Methods

Plant material

The collection of the leaf of the plant was done in Ureje village in Ado-Ekiti with Latitude: 7.607463; longitude: 5.255823; accuracy: 2400 m. The name of the plant was verified using http://www.theplantlist.org. The voucher specimen was deposited at the herbarium unit of the Department of Botany in Ekiti State University, Ado-Ekiti, Nigeria with voucher number UHAE 2020092 and compared with the reference plant.

Procedure for crude drug extraction

Dried and ground leaves (150 g) of BS were subjected to aqueous (1 L) extraction by cold maceration for 72 h. After the extraction time, the crude filtrate was concentrated with a water bath at 45 ˚C before drying in an oven for three days. The percentage yield of the crude extract obtained was 10% w/w, and packed into amber-colored bottle and stored in a refrigerator at 4 ˚C until when needed.

Drugs and reagents

The drugs used include phenobarbitone (May and Baker, USA), diazepam (Roche Pharmaceuticals, Germany), pentylenetetrazole (Sigma Aldrich, USA), acetic acid (May and Baker Ltd., Dagenham, England), imipramine (Sigma Aldrich, St. Louis, MO, USA), and haloperidol (May and Baker, USA).

Fingerprint of BS using HPLC/DAD

The fingerprint of aqueous leaf extract of BS using high performance liquid chromatography/photodiode array detector (HPLC/DAD) has been performed in a previous study (Olayinka *et al.,* 2021).

Experimental animals

Male and female mice weighing 20 - 25 g were procured for each experiment from the Animal House of the Department of Pharmacology and Toxicology, University of Benin, Benin City, Nigeria, where they were kept in metabolic cages in groups (males separated from females) under normal environmental conditions. The mice were fed with mice pellets and water, and hygienic conditions were maintained. The experimental process was carried out during the day (between 09.00 a.m. and 17.00 p.m. daily).

Ethical considerations

Experimental procedures and protocols employed in this study conformed to the “Guide to the Care and Use of Animals in Research and Teaching” (NIH publications number 85-93 revised in 1985). Ethical approval certificate (reference number EC/FP/020/13) was obtained from the Animal Research and Ethics Committee of the Faculty of Pharmacy, University of Benin.

Acute toxicity test

Acute toxicity test of BS has been conducted in a previous study (Olayinka *et al.,* 2021) using the method of Lorke (1983).

Neuropharmacological Evaluation of BS extract

Diazepam-induced sleeping time

The method described by Beretz *et al.* (1978) and modified by Rakotonirina *et al.* (2001), were adopted. Mice were allowed to fast for 12 h before the start of the experimental process. They were randomly allotted to five groups (n=5). Group I served as control which received 0.1 ml (10 ml/kg of distilled water, orally). Groups II-IV (extract-treated groups) were administered 125, 250, and 500 mg/kg doses of BS orally and Group V was treated with haloperidol (1 mg/kg) intraperitoneally (i.p). After 30 min of extract administration, diazepam (20 mg/kg) was administered i.p. to all the groups (Groups I – V)). Loss of righting reflex was the criterion for onset of sleep (Ajibade *et al.*, 2022). The latency to sleep was determined as the difference in time between administering the drug and losing righting reflex.

Test for anticonvulsant activity of BS extract

Pentylenetetrazole-induced convulsion

Mice were randomly grouped into five (n = 5 each). Group I served as control (administered 10 ml/kg of distilled water orally). Groups II, III and IV (extract-treated groups), were administered 125, 250, and 500 mg/kg doses of BS orally. Group V received diazepam (2 mg/kg, i.p.). After 30 min of treatments, pentylenetetrazole (PTZ) (70 mg/kg), was administered i.p. to all the animals. The latency to convulsion, number of animals that convulsed and the degree of protection were observed (Swinyard, 1982; Ajibade *et al.*, 2022).

Maximum electroshock-induced convulsion

Mice were randomly grouped into five (n = 5 each). Group I was the control and was given 10 ml/kg of distilled water orally. Groups II, III and IV (extract-treated groups) received BS (125, 250, and 500 mg/kg) orally. Group V received phenobarbitone (30 mg/kg, orally), the standard drug. Convulsion was induced 1 h after, by applying electrical stimulus of 100 mA, at a frequency of 50 Hz for

0.2 s through auricular electrodes (Ugo Basile ECT unit, Model 57800). Abolition or reduced duration of tonic hindlimb extension indicated inhibition of maximum electroshock (MES)-induced convulsion (Toman *et al.,* 1946; Ajibade *et al.*, 2022).

Antidepressant screening test

Forced swimming test

Different set of mice were distributed into five groups (n = 5) in a random manner. Group I was the control group and was given distilled water (10 ml/kg, orally). Groups II, III, and IV, respectively received BS (125, 250, and 500 mg/kg) orally, and group V received imipramine (25 mg/kg, orally). An hour after pre-treatment, animals were placed one after the other into a plexiglas cylinder (height = 25 cm, diameter = 10 cm) with water at 23-25 ˚C to a height of 10 cm and observed for 6 min. A mouse stationary in the water vertically and making slight movements to prevent drowning was considered immobile. The total duration of immobility was recorded during the last 4 min of the 6 min test (Porsolt, 1981; Olayinka *et al.*, 2023).

Tail suspension test

Mice were allotted randomly into five groups (n=5). Group I was given distilled water (10 ml/kg, orally). Groups II, III, and IV received BS (125, 250, and 500 mg/kg) orally, respectively, while group V was given imipramine (25 mg/kg, orally). An hour after treatment, the mice were hung on the edge of a table using an adhesive tape that was to the tip of the tail, on the edge of a table, that was 50 cm above the floor. Immobility state was taken in 6 min a mouse from each group. If a mouse does not show any sign of movement, that mouse is considered as being immobile (Porsolt *et al.,*1978; Olayinka *et al.,* 2023).

Statistical analysis

Results were represented as mean ± standard error of mean (SEM) and 'n' stands for the number of mice, which were examined in a group. One-way Analysis of Variance (ANOVA) with Tukey's multiple comparison tests was adopted for inferential statistics. Graphpad prism version 8.00 was the statistical software used to run the analysis. Differences were considered significant at $p < 0.05$.

Results

Effect of BS on diazepam-induced sleep time

Figure 1A shows that BS at all the treatment doses increased the latency to sleep as compared with the control. This result shows no statistically significant difference in latency to sleep time compared with the control. Haloperidol decreased the latency to sleep, but was not statistically significant in comparison with the control group (Figure 1A). Figure 1B revealed that BS, at all the doses (125, 250, and 500 mg/kg), did not increase the duration of sleep induced by diazepam (30 mg/kg). However, haloperidol (1 mg/kg) significantly ($p < 0.01$) increased duration of sleep relative to the control group.

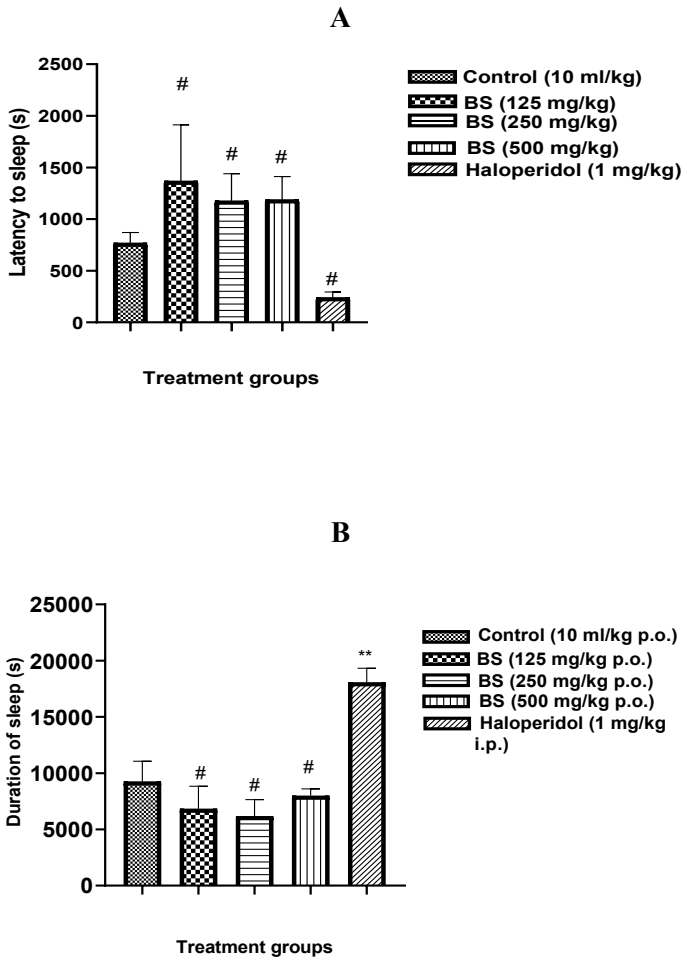


Figure 1: Effect of BS in diazepam-induced sleep time in mice. (A) Latency to sleep time, (B) Duration of sleep time. Data expressed as mean ± SEM, n=5. # indicates no significant difference relative to the control. **p < 0.01 *vs* control. BS, *Blighia sapida.*

Effect of BS extract on convulsion in mice

Figure 2A shows that PTZ (70 mg/kg) produced hindlimb tonic seizures in all the BS-administered doses (125, 250 and 500 mg/kg). There was no statistically significant difference between the BS-treated groups and the control. Diazepam significantly ($p < 0.0001$) protected the mice against hindlimb tonic seizures compared to the control as shown in Figure 2A. In Figure 2B, there was no statistically significant difference in the duration of hindlimb extension between the control group and BS-treated groups in the MES-induced convulsion. There was no protection against hindlimb extension seizure (HLES) at all the doses. Phenobarbitone (30 mg/kg, orally) significantly ($p < 0.0001$) raised latency to convulsion as seen in Figure 2B.

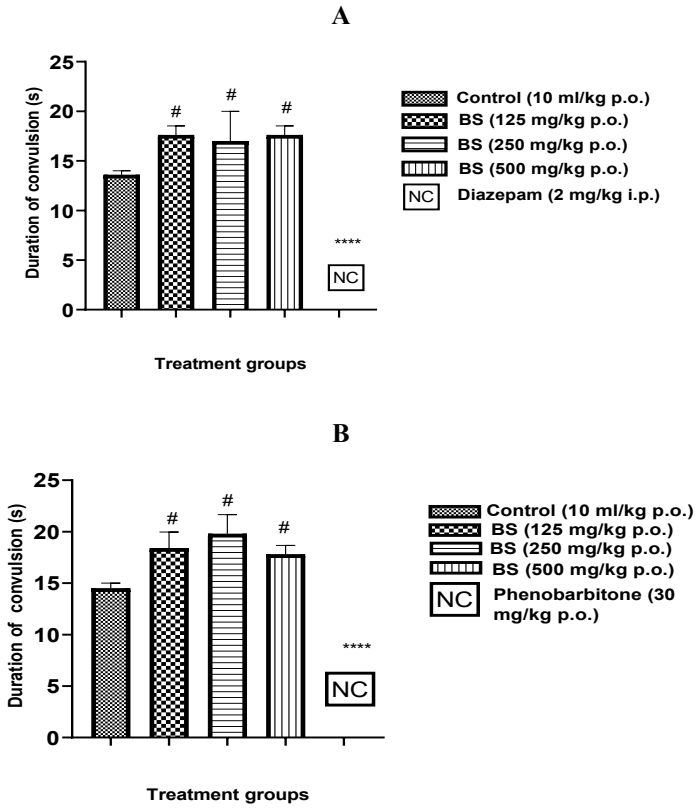
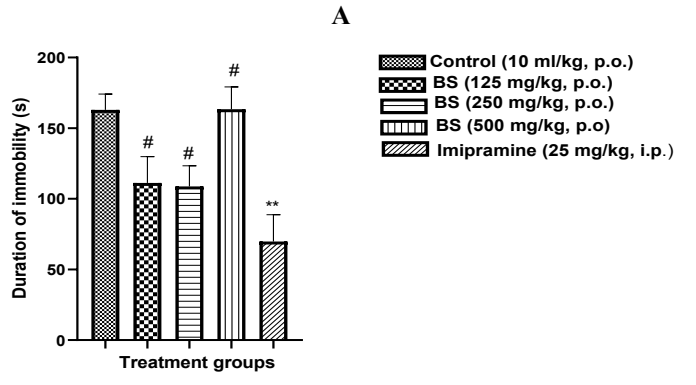


Figure 2: Effect of BS extract on seizures in mice. **(A)** PTZ-induced convulsion in mice, **(B)** MES-induced convulsion in mice. Data were expressed as mean ± SEM, n=5. # indicates no significant difference in comparison to the control; ****p < 0.0001 vs control, NC: Indicates no convulsion. PTZ, pentylenetetrazole; MES, maximum electro shock, BS, *Blighia sapida*.

Effect of BS extract on depressive-like behaviour in mice

Figure 3A shows that immobility time in the FST at every given dose of BS (125, 250, and 500 mg/kg) was not significantly different from the control. However, the duration of immobility in the imipramine group was significantly different ($p < 0.01$) in compared with the control group. Figure 3B shows that there was no statistically significant difference in the duration of immobility in the BS-treated groups compared to the control in the TST. The duration of immobility in the imipramine group was statistically significant ($p < 0.001$) in compared to the control group.



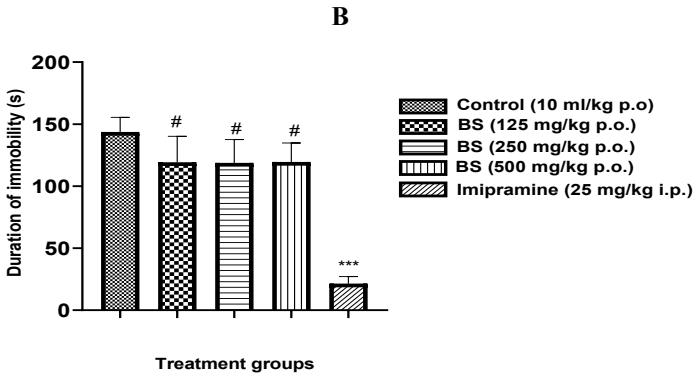


Figure 3: Effect of BS extract on duration of immobility in mice. (A) FST in mice, (B) TST in mice. Data expressed as mean ± SEM, n=5. # indicates no significant difference relative to the contr; ***p < 0.001 vs control, **p < 0.01 vs control. FST, Forced swimming test; TST, Tail suspension test; BS, *Blighia sapida.*

Discussion

The leaf of BS is endowed with a lot of therapeutic benefits in ethnomedicine. However, this study demonstrated that the leaf extract lacks the sedative-hypnotic, anticonvulsant, and antidepressant-like activity in mice.

Results obtained from the impact of BS on sleep time induced by diazepam in mice demonstrated that the extract did not potentiate sedative-hypnotic effect in mice. Sedative-hypnotic agents act by increasing gamma amino butyric acid (GABA)-mediated synaptic inhibition by either directly activating GABA receptors or by potentiating the action of GABA on $GABA_A$ receptors. Benzodiazepines and barbiturates are examples of agents that act as $GABA_A$ receptor modulators (Johnston, 2005; Sieghart and Savić, 2018). The ability of a drug to potentiate the sedative actions of diazepam shows that it may be acting by interacting with GABA-mediated synaptic transmission. In this study, the extract lacks the ability to potentiate hypnotic effect induced by diazepam, which is indicative of its non-sedative property. Findings from a previous HPLC screening of the leaf extract identified the presence of caffeine in the leaf extract (Olayinka *et al.,* 2021), which may lend an explanation for the inability of the extract to potentiate sleep time in the experimental animals as caffeine has been well reported in studies to delay sleep time (Goldstein *et al.,* 1965; Dews, 1982; Snel and Lorist, 2011; Vital-Lopez *et al.*, 2018). Experiment in humans has shown that caffeine delayed sleep time through the inhibition of A1 and A2A adenosine receptors, and to some extent, the A2B and A3 adenosine receptors located in the brain (Snel and Lorist, 2011). In rats, caffeine has been shown to block markers of electroencephalogram of non-rapid eye movement sleep homeostasis during sleep and wakefulness (Landolt, 2008).

Electroshock and chemically induced models are conventionally used primarily to screen agents with antiepileptic property. These models induce seizures via different mechanisms. The PTZ-induced convulsion identifies agents that increase seizure threshold and drugs,

which block seizures induced by this model are potential therapies for absence seizures (Kehne *et al.,* 2017). Responses to these seizures include myoclonic jerks, clonic jerks and hindlimb clonic extensor amongst others. An investigational drug increases seizure threshold if there is an absence of the clonic phase (Kehne *et al.,* 2017). Convulsive effect of PTZ is exerted via inhibiting the activity of GABA at $GABA_A$ receptors (De Sarro *et al.*, 1999). Potentiating and inhibiting GABAergic neurotransmission attenuates and enhances convulsion, respectively (Gale, 1992; Ajibade *et al.,* 2022). Benzodiazepines (e.g., diazepam), are anticonvulsant agents that increase the frequency of the chloride channel openings through their ability to enhance the affinity of $GABA_A$ receptors for the neurotransmitter (Kostowski, 1995; Lüddens and Korpi, 2007). The extract, in the present study, increased seizure threshold, although not statistically significant. Similarly, MES-induced convulsion is a valid model for acute seizures and shows a behavioural pattern similar to humans (Swinyard, 1989). The MES is well utilized in identifying compounds that prevent seizure spread (Kehne *et al.,* 2017). This model is a predictive model that is effective against generalized tonic–clonic seizures (Krall, 1978; Toman *et al.,* 1946; Lazarini-Lopes *et al.,* 2020) and the endpoint in this test is tonic hindlimb extension (Krall *et al.,* 1978). Convulsive effect of MES is exerted via enhancement of neuronal firing throughout the neuroaxis, thus increasing the probability of seizures (Rastogi and Ticku, 1985). The present study has shown that the extract did not protect the mice against MES-induced convulsion. This suggests that BS may not possess anticonvulsant activity.

Depression is seen as a form of mental illness which may affect the overall thinking process, behaviour and feelings (Khushboo and Sharma, 2017). Behavioural studies are useful in the evaluation and development of antidepressant drugs (Xu *et al.,* 2008). The FST and TST are very important models that have been utilized widely for screening new antidepressant agents (Cryan *et al.,* 2005; Berrocoso *et al.*, 2013). Studies have hypothesized that the immobility demonstrated by animals subjected to these stress models reflect behavioural despair which in turn may reflect a state of depression in humans. Immobility demonstrated by these animals is often reversed by a number of antidepressants such as tricyclics, monoamine oxidase inhibitors, and some new antidepressants (Cryan *et al.*, 2002; Cryan and Lucki, 2000). The ability of an extract to reduce the duration of immobility indicates that it may possess antidepressant property. However, in this present study, both the FST and TST at all the BS doses prolonged the duration of immobility in mice suggesting that the crude drug (BS) may not be possessing antidepressant activity.

Although, it has been reported that the stem bark of BS demonstrated antipsychotic effects in mice (Fehintola, 2019), and other studies have revealed that the stem bark has the potential of inhibiting cholinergic enzymes associated with Alzheimer's disease (Ojo *et al.,* 2017; Adekola *et al.,* 2023). However, the current investigation was conducted on the aqueous leaf extract of the plant, and did not demonstrate any form of anticonvulsant, sedative-hypnotic, and antidepressant effects, which are core CNS-related activities. The findings in this study are in accordance with the findings from a previous study on the leaf extract of BS that demonstrated that the leaf extract of BS possesses peripheral analgesic property which reduced pain reflex in the inflammatory phase of the formalin induced paw licking test but did not show any central analgesic effects as it did not inhibit pain in the neurogenic phase of the formalin paw licking test (Olayinka *et al.,* 2021), suggesting that the leaf extract of BS may not possess neuropharmacological properties.

Conclusion

Although, traditional medicine had reported that the leaf of BS can be used in managing epilepsy and some CNS-related disorders; findings from the anticonvulsant test, diazepam-induced test, and antidepressant assays suggest that the leaf extract of BS may not possess some CNS-related activities and may not be useful in the management of epilepsy. However, further investigations requiring the use of cellular and molecular techniques on the leaf extract of BS, may be recommended to establish these finding.

List of Abbreviations

BS, *Blighia sapida***; PTZ,** pentylenetetrazole**; MES,** Maximum electroshock**; TST,** Tail suspension test**; FST,** Forced swimming test**; HLES,S** Hindlimb extension seizure**; GABA,** Gamma amino butyric acid**.**

Declarations

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them**.**

Consent for publication: Not applicable

Competing interest: Not applicable

Funding: No funding was obtained for this study

Author's Contribution: Juliet N. Olayinka: Conceptualizatuon, Writing- Original draft**,** Methodology, Investigation, Data curation; **Emma E. Okpakpor**: Investigation, Formal analysis; **Raymond I. Ozolua**: Review and Editing, Supervision, Project administration, Formal Analysis, Methodology.

Acknowledgments

The authors thank the entire member of staff of the Department of Pharmacology and Toxicology of the University Benin, Benin City, Nigeria for providing an enabling environment to conduct the experiments. I also thank Dr Olusegun Adeoluwa of Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria who assisted me during the experimental process.

References

Abolaji, A.O., Adebayo, H.A., Odesanmi, O.S., 2007. Nutritional Qualities of Three Medicinal Plant Parts (Xylopia aethiopica, Blighia sapida and Parinari polyandra) commonly used by Pregnant Women in the Western Part of Nigeria. *Pakistan Journal of Nutrition,* 6(6), pp.665-668..

Adekola, M.B., Taiwo, A.M., Oriyomi, V.O., Ogunleye, O.S., Oyebamiji, A.T., Raheem, A.O., Kasali, S.O., Bello, I.R., 2023. Assessment of Ackee Apple (Blighia Sapida) on Cholinergic and Antioxidant Enzymes; Possible Use of the Plant Stem-Bark Extract as a Biological Pest Controlling Agent. *Journal of Applied Science and Environmental Management.* 27, 2213–2219.

Ajibade, M.A., Akhigbemen, A.M., Okolie, N.P., Ozolua, R.I., 2022. Methanol leaf extract of Paullinia pinnata exerts sleep-enhancing and anticonvulsant effects via a mechanism involving the GABAergic pathway. *Epilepsy Research.* 183, 106943.

Antwi, S., Martey, O.N.K., Donkor, K., Okine, L., 2009. Anti-diarrhoeal activity of Blighia sapida (Sapindaceae) in rats and mice. *Journal of Pharmacology and Toxicology*. 4, 115–117.

Beretz, A., Haag-Berrurier, M., Anton, R., 1978. Choice of pharmacological methods for the study of Hawthorn activities, CHOIX DE METHODES PHARMACOLOGIQUES POUR L'ETUDE DES ACTIVITES DE L'AUBEPINE. *Plantes médicinales et phytothérapie* 12, 305–314.

Berrocoso, E., Ikeda, K., Sora, I., Uhl, G.R., Sánchez-Blázquez, P., Mico, J.A., 2013. Active behaviours produced by antidepressants and opioids in the mouse tail suspension test. *International Journal of Neuropsychopharmacology.* 16, 151–162.

Collins, P.Y., Patel, V., Joestl, S.S., March, D., Insel, T.R., Daar, A.S., Bordin, I.A., Costello, E.J., Durkin, M., Fairburn, C., 2011. Grand challenges in global mental health. *Nature* 475, 27–30.

Cryan, J.F., Lucki, I., 2000. Antidepressant-like behavioral effects mediated by 5-hydroxytryptamine2C receptors. *Journal of Pharmacology and Experimental Therapeutics*. 295, 1120–1126.

Cryan, J.F., Markou, A., Lucki, I., 2002. Assessing antidepressant activity in rodents: recent developments and future needs. *Trends Pharmacological Sciences.* 23, 238–245.

Cryan, J.F., Mombereau, C., Vassout, A., 2005. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. *Neuroscience and Biobehavioral Reviews.* 29, 571–625.

Dansi, A., Vodouhè, R., Azokpota, P., Yedomonhan, H., Assogba, P., Adjatin, A., Loko, Y.L., Dossou-Aminon, I., Akpagana, K., 2012. Diversity of the neglected and underutilized crop species of importance in Benin. *Scientific World Journal*. 2012.

De Sarro, A., Cecchetti, V., Fravolini, V., Naccari, F., Tabarrini, O., De Sarro, G., 1999. Effects of novel 6-desfluoroquinolones and classic quinolones on pentylenetetrazole-induced seizures in mice. *Antimicrobial Agents Chemotherapy.* 43, 1729–1736.

Dews, P.B., 1982. Caffeine [Nutritional aspects]. *Annual Review of Nutrition*. 2

Direk, N., Tiemeier, H., 2010. R. C. Kessler, B. Ustun (eds): The WHO world mental health surveys. Global perspectives of mental health surveys. *European Journal of Epidemiology*. 25, 281. https://doi.org/10.1007/s10654-010-9441-9

EA, S., 1989. Experimental selection, quantification, and evaluation of anticonvulsants. *Antiepilepric drugs* 85.

Ekué, M.R.M., Sinsin, B., Eyog-Matig, O., Finkeldey, R., 2010. Uses, traditional management, perception of variation and preferences in ackee (Blighia sapida KD Koenig) fruit traits in Benin: implications for domestication and conservation. *Journal of Ethnobiology and Ethnomedicine*. 6, 1–14.

Etukudo, I., 2003. Ethnobotany. Conventional and Traditional Uses of Plants. Lippincott Williams & Wilkins.

Fehintola, F.A., 2019. Antipsychotic effects of ethanol extract of Blighia sapida (Sapindaecea) stem bark on pharmacological models of psychosis in Swiss mice. *African Journal of Medicine and Medical Sciences*. 48, 151–160.

Gale, K., 1992. Subcortical structures and pathways involved in convulsive seizure generation. *Journal of Clinical Neurophysiology*. 9, 264–277.

Goldstein, A., Warren, R., Kaizer, S., 1965. Psychotropic effects of caffeine in man. I. Individual differences in sensitivity to caffeine-induced wakefulness. *Journal of Pharmacology and Experimental Therapeutics.* 149, 156–159.

Ibraheem, O., Bankole, D., Adedara, A., Abolaji, A.O., Fatoki, T.H., Ajayi, J.M., Eze, C.T., 2020. Methanolic leaves and arils extracts of ackee (Blighia sapida) plant ameliorate mercuric chloride-induced oxidative stress in Drosophila melanogaster. *Biointerface Research in Applied Chemistry*. 11, 7528–7542.

Ibraheem, O., Oyewole, T.A., Adedara, A., Abolaji, A.O., Ogundipe, O.M., Akinyelu, J., Eze, C.T., Albogami, S., Alotaibi, S.S., Adeyemi, O.S., 2022. Ackee (Blighia sapida KD Koenig) Leaves and Arils Methanolic Extracts Ameliorate CdCl 2-Induced Oxidative Stress Biomarkers in Drosophila melanogaster. *Oxidative Medicine and Cellular Longevity.* 2022.

John-Dewole, O.O., Popoola, O.O., 2013. Chemical, phytochemical and antimicrobial screening of extracts of B.sapida for agricultural and medicinal relevances. *Natural Sciences*. 11, 12–17

Johnston, G.A.R., 2005. GABAA receptor channel pharmacology. *Current Pharmaceutical Design.* 11, 1867–1885.

Kehne, J.H., Klein, B.D., Raeissi, S., Sharma, S., 2017. The national institute of neurological disorders and stroke (NINDS) epilepsy therapy screening program (ETSP). *Neurochemical Research.* 42, 1894–1903.

Khushboo, S.B., Sharma, B., 2017. Antidepressants: mechanism of action, toxicity and possible

amelioration. *Journal of Applied Biotechnology and Bioengineering*. 3, 437–448.

Kostowski, W., 1995. Recent advances in the GABA-A-benzodiazepine receptor pharmacology. *Polish Journal of Pharmacology*. 47, 237–246.

Krall, R.L., 1978. Antiepileptic Drug Development. Department of Health, Education, and Welfare, National Institutes of Health.

Landolt, H.-P., 2008. Sleep homeostasis: A role for adenosine in humans? *Biochemcal Pharmacology*. 75, 2070–2079. https://doi.org/https://doi.org/10.1016/j.bcp.2008.02.024

Lazarini-Lopes, W., Do Val-da Silva, R.A., da Silva-Júnior, R.M.P., Leite, J.P., Garcia-Cairasco, N., 2020. The anticonvulsant effects of cannabidiol in experimental models of epileptic seizures: From behavior and mechanisms to clinical insights. *Neuroscience and Biobehavioural Reviews.* 111, 166–182.

Lorke, D., 1983. A new approach to practical acute toxicity testing. *Archives of Toxicology*. 54, 275–287. https://doi.org/10.1007/BF01234480

Lüddens, H., Korpi, E.R., 2007. Benzodiazepines. In: Handbook of Contemporary Neuropharmacology in: Handbook of Contemporary Neuropharmacology. Vol. 2 93-131. https://doi.org/10.1002/9780470101001.hcn025

Marles RJ, F.N., 1995. Antidiabetic plants and their active constituents. *Phytomedicine* 2, 137–189.

Mitchell, S.A., Webster, S.A., Ahmad, M.H., 2008. Ackee (Blighia sapida)-Jamaica's top fruit. *Jamaican Journal of Science and Technology*. 33, 84–89.

Ojo, O.A., Ajiboye, B.O., Ojo, A.B., Olayide, I.I., Akinyemi, A.J., Fadaka, A.O., Adedeji, E.A., Boligon, A.A., de Campos, M.M.A., 2017. HPLC-DAD Fingerprinting Analysis, Antioxidant Activity of Phenolic Extracts from Blighia sapida Bark and Its Inhibition of Cholinergic Enzymes Linked to Alzheimer's Disease. *Jordan Journal of Biological Science*. 10 (4).

Okogun, J.I., 1996. The chemistry of Nigerian medicinal plants. *Medicinal Plant Research in Nigeria*. 10, 31–45.

Olayinka, J.N., Akawa, O.B., Ogbu, E.K., Eduviere, A.T., Ozolua, R.I., Soliman, M., 2023. Apigenin attenuates depressive-like behavior via modulating monoamine oxidase A enzyme activity in chronically stressed mice. *Current Research in Pharmacology and Drug Discovery.* 5, 100161.

Olayinka, J.N., Ozolua, R.I., Akhigbemen, A.M., 2021. Phytochemical screening of aqueous leaf extract of Blighia sapida KD Koenig (Sapindaceae) and its analgesic property in mice. *Journal of Ethnopharmacology.* 273, 113977.

Oloyede, O.B., Ajiboye, T.O., Abdussalam, A.F., Adeleye, A.O., 2014. Blighia sapida leaves halt elevated blood glucose, dyslipidemia and oxidative stress in alloxan-induced diabetic rats. *Journal of Ethnopharmacology*. 157, 309–319.

Onuekwusi, E.C., Akanya, H.O., Evans, E.C., 2014. Phytochemical Constituents of Seeds of Ripe and Unripe Blighia Sapida (K. Koenig) and Physicochemical Properties of the Seed Oil, *International Journal of Pharmaceutical Science Invention* 3(9):31-40. ISSN. Online.

Organization, W.H., 2002. The world health report 2002: reducing risks, promoting healthy life. World Health Organization.

Orwa, C., Mutua, A., Kindt, R., Jamnadass, R., Anthony, S., 2009. Blighia sapida Konig Blighia sapida Konig [www document]. Agroforestree Database a tree Ref. Sel. Guid. Version 4. 0(URL ⟨www.worldagroforestry.org/sites/treedbs/treedatabasses.asp⟩

Osei JA, Essuman EK, K. DO, 2014. A survey of ackee fruit utilization in Ghana. Jamaican *Journal of Science and Technology*. 21, 10–17.

Porsolt RD, Anton G, Blavet N, J.M., 1978. Behavioural despair in rats: A new model sensitive to antidepressant treatments. *European Journal of Pharmacology.* 47, 379--91.

Porsolt RD, 1981. Behavioural Despair, in antidepressants: *Neurochemical, behavioural and clinical perspectives*.Pp 121-139.

Rakotonirina, V.S., Bum, E.N., Rakotonirina, A., Bopelet, M., 2001. Sedative properties of the decoction of the rhizome of Cyperus articulatus. *Fitoterapia* 72, 22–29.

Rastogi, S.K., Ticku, M.K., 1985. Involvement of a GABAergic mechanism in the anticonvulsant effect of pentobarbital against maximal electroshock-induced seizures in rats. *Pharmacology, Biochemistry and Behaviour.* 22, 141–146.

Saidu, A., 2012. Phytochemical Screening and Hypoglycemic Effect of Aqueous Blighia sapida Root Bark Extract on Normoglycemic Albino Rats. *British Journal of Pharmaceutical Research*. 2, 89–97. https://doi.org/10.9734/bjpr/2012/1056

Sieghart, W., Savić, M.M., 2018. International Union of Basic and Clinical Pharmacology. CVI: GABAA receptor subtype-and function-selective ligands: key issues in translation to humans. *Pharmacology Review.* 70, 836–878.

Sinmisola, A., Oluwasesan, B.M., Chukwuemeka, A.P., 2019. Blighia sapida K.D. Koenig: A review on its phytochemistry, pharmacological and nutritional properties. *Journal of Ethnopharmacology*. https://doi.org/10.1016/j.jep.2019.01.017

Snel, J., & Lorist, M. M. (2011). Effects of caffeine on sleep and cognition. *Progress in brain research*, *190*, 105-117. https://doi.org/https://doi.org/10.1016/B978-0-444-53817-8.00006-2

Swinyard, E.A., 1982. Experimental detection, quantification, and evaluation of anticonvulsants. *Antiepileptic drugs* 111–126.

Toman, J.E.P., Swinyard, E.A., Goodman, L.S., 1946. Properties of maximal seizures, and their alteration by anticonvulsant drugs and other agents. *Journal of Neurophysiology*. 9, 231–239.

Vital-Lopez, F.G., Ramakrishnan, S., Doty, T.J., Balkin, T.J., Reifman, J., 2018. Caffeine dosing strategies to

optimize alertness during sleep loss. *Journal of Sleep Research*. 27, e12711.

Wittchen, H.-U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. European Neuropsychopharmacology. 21, 655–679.

World Health Organization, 2006. Neurological disorders: Public health challenges. Geneva: World Health Organization. https://www.who.int/publications/i/item/9789241563369

Xu, Q., Yi, L.-T., Pan, Y., Wang, X., Li, Y.-C., Li, J.-M., Wang, C.-P., Kong, L.-D., 2008. Antidepressant-like effects of the mixture of honokiol and magnolol from the barks of Magnolia officinalis in stressed rodents. *Progress in Neuro-Psychopharmacology Biology and Psychiatry* 32, 715–725.