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Original Article

Adansonia digitata L. Stem Bark Attenuates Epileptic Seizure, Depression, and Neurodegeneration by Mediating GABA and Glutamate in Pentylenetetrazol-Kindled Rats

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Objectives: Epilepsy is a neurological condition characterized by repeated seizures attributable to synchronous neuronal activity in the brain. The study evaluated the effect of acetone extract of *Adansonia digitata* stem bark (ASBE) on seizure score, cognition, depression, and neurodegeneration as well as the level of Gamma-Aminobutyrate acid (GABA) and glutamate in Pentylenetetrazol-kindled rats.
Methods: Thirty-five rats were assigned into five groups (n = 7). Groups 1-2 received normal saline and 35 mg/kg PTZ every other day. Groups 3-4 received 125 mg/kg and 250 mg/kg ASBE orally while group 5 received 5 mg/kg diazepam daily for twenty-six days. Group 3-5 received PTZ every other day, 30 mins after ASBE and diazepam.
Results: The results showed that Pentylenetetrazol (PTZ) induces seizure, reduces mobility time in force swim test and decreases the normal cell number in the brain. It also significantly decreases ($p < 0.05$) catalase, superoxide dismutase and reduced glutathione activities compared to the ASBE pre-treated rats. Pre-treatment with ASBE reportedly decreases seizure activities significantly ($p < 0.05$) and increases mobility time in the force swim test. ASBE also significantly elevate ($p < 0.05$) the normal cell number in the hippocampus, temporal lobe, and dentate gyrus.
Conclusion: ASBE reduced seizure activity and prevented depression in PTZ-treated rats. It also prevented neurodegeneration by regulating glutamate and GABA levels in the brain as well as preventing lipid peroxidation.

Keywords: *Adansonia digitata*, catalase, cell count, glutamate, GABA, seizure

INTRODUCTION

Epilepsy is a nervous disorder characterized by recurring epileptic seizures that occur due to unexpected synchronous neuronal activity in the brain [1]. An epileptic seizure is characterized by varying degrees of uncontrolled, shaky movement that may be experienced throughout the body with loss of consciousness (tonic–clonic) or in some parts of the body with variable levels of consciousness and absence of seizures (focal) [2]. Epilepsy can result from numerous factors, such as genetic disarray, traumatic brain injury, drugs and/or chemicals, and electrical impulses, while the effects of recurrent seizures include behavioral and emotional imbalance, depression, anxiety, and cognitive impairment [3-5]. Kindling is an animal model of epilepsy produced by either electrical impulses or chemicals that alter brain functions, resulting in repeated focal stimulation and the development of a predisposition to epileptiform convulsions [6]. As a model of epilepsy, kindling provides a source

of clinical hypotheses, particularly concerning the progression of epileptic symptomatology [7]. The World Health Organization (WHO) estimated that about 50 million people live with epilepsy globally. People with epilepsy are more likely to be unemployed with a lower annual income [8]. The most common challenge in the treatment of epilepsy is the lack of clinical evidence to support a particular drug for a given patient. Hence, achieving seizure control is a big problem [9]. Glutamate is the most common free amino acid in the brain and an excitatory neurotransmitter that plays a key role in the formation and spread of seizure activity [10]. Gamma-aminobutyrate acid (GABA) is a non-proteinogenic amino acid, an inhibitory neurotransmitter in the cerebral cortex, and maintains the quality of inhibition that counterbalances neuronal excitation [11]. Epilepsy occurs due to an imbalance between the excitatory (glutamate) and inhibitory (GABA) neurotransmitters [5].

Adansonia digitata L. (Baobab) is the most abundant plant species in its genus. The name *Adansonia* is in honor of Michel Adanson (1727-1806), who brought the seed to Paris and contributed to describing and presenting a picture of the plant, while baobab is derived from the Arabic word "buhibab," meaning fruit with many seeds [12]. Baobab is used as a traditional medicine for the treatment of malaria, diarrhea, anemia, and inflammation [13, 14]. In India, the leaves and fruit pulp of baobab are combined with buttermilk for external use in the treatment of dysentery and diarrhea [15]. In South and East Africa, the seed and seed oil are used for oral hydration, to neutralize toxins, and as an antipyretic agent, while the leaf is used to treat toothache and gingivitis and to induce perspiration [15, 16]. In West Africa and Asia, fruit pulp is used as an anti-inflammatory, anti-diabetic, analgesic, and immunostimulatory agent [17-19]. In Africa, the leaves and fruit pulp contribute to the nutritional status of many households because they constitute the main ingredients of local foods and drinks [20]. Previous studies reported the use of different parts of *A. digitata* in the prevention and treatment of brain-related disorders ranging from convulsions to neurodegeneration. The stem bark is reported to prevent convulsions in pentylenetetrazole (PTZ)-treated rats [21]. The fruit shell ameliorates aluminum chloride-induced depression and cognitive impairment in rats, while the leaves were reported to attenuate cortical histoarchitectural changes and oxidative stress in them [22, 23]. Due to various traditional uses of *A. digitata*, the current study evaluated the effect of an acetone extract of the plant's stem bark on seizure score, cognition, depression, and neurodegeneration, as well as the level of some neurotransmitters (GABA and glutamate) in PTZ-treated rats.

MATERIALS AND METHODS

1. Chemicals

Pentylenetetrazol (Sigma-Aldrich, USA) was used to induce seizures; acetone was used to extract *A. digitata* stem bark (Poole England); and ketamine and diazepam (Swiss Pharma, India) were used as an anesthetic and a standard drug, respectively.

2. Plant material and extraction

A. digitata stem bark was collected from the University of Maiduguri campus and submitted, together with the fruit and leaf, to a botanist at the University of Maiduguri, Nigeria, for authentication. The stem bark was ground and soaked in acetone (1.5 kg in 5 liters) for 48 hours. The mixture was filtered and evaporated in an oven at 40℃.

3. Experimental animals and ethical approval

Thirty-five male Wistar rats, 9-12 weeks old (175-198 g), were used for the study. They were kept at the Department of Biochemistry Animal House, University of Maiduguri, and given food and water ad libitum. The study was approved by the postgraduate board of studies, faculty of basic medical sciences, University of Maiduguri, and was piloted according to the ARRIVE guidelines.

4. Experiment design

The rats were allotted into five groups (n = 7). Groups 1 and 2 received normal saline at 1 mL/kg (control) and 35 mg/kg of PTZ dissolved in normal saline (negative control) every other day via intraperitoneal injection, respectively, for 26 days. Groups 3 and 4 received 125 mg/kg *A. digitata* stem bark extract (ASBE) and 250 mg/kg ASBE orally daily, while group 5 received 5 mg/kg diazepam via intra-peritoneal injection, respectively, for 26 days. Groups 3 to 5 received 35 mg/kg of PTZ every other day, 30 minutes after ASBE and diazepam. The rats were observed for seizure activity 30 minutes after PTZ injections, and the seizure activity was estimated using the Racine scale as shown in Table 1. The rats were considered fully

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Table 1. Summary of the Racine scale for seizure activity [5]

Seizure stage	Activity
Zero	No response.
One	Vibrissae twitching, hyperactivity.
Two	Head nodding and clonus, myoclonic jerks.
Three	Unilateral and bilateral limb clonus.
Four	Rearing with forelimb clonic seizures.
Five	Generalized tonic-clonic seizure with loss of postural control and consciousness.

kindled once stages 4 and/or 5 appeared repetitively after three consecutive PTZ injections. The seizure score of any group is the mean seizure score of each rat in that group.

5. Elevated plus maze

The elevated plus maze (EPM) test with little modification was used to assess the anxiety-related behavior of rats 24 hours after treatment. A plus-shaped device 50 cm from the ground with two open and closed arms opposite to each other and linked by a central square was used. The parameters are as follows: open arm (50 cm long and 10 cm wide), closed arm (50 cm long, 10 cm wide, and 40 cm high), and the central square (10 × 10 cm). Acquisition phase (first day): rats were put at one end of the open arm, and the initial transfer latency (ITL) was noted (time to enter the closed arm). Rats were left for 20 seconds, but those that couldn't locate the arm after 60 seconds were led in. Retention phase (second day): the procedure was repeated, and the first transfer latency (FTL) was noted (time to enter the closed arm). Rats that couldn't locate the closed arm within 120 seconds were removed. To prevent the olfactory queue, the maze was washed with 70% ethanol after each process.

6. Force swim test

The force swim test was used to evaluate the antidepressant-like activity of rats following the procedure of Slattery and Cryan [24]. The process comprises a 15-minute pretest followed by a 5-minute swim test after 24 hours. Pretest: rats were allowed to swim for 15 minutes in a cylinder (18 cm deep and 20 cm wide) filled with water at about 25℃. Swim test: the initial procedure was repeated after 24 hours, and the immobility time was recorded. The rats were euthanized after 24 hours, and the brains of each rat were dissected and separated into two halves.

7. Neurotransmitters and oxidative stress

One-half of the brain was homogenized in normal saline and centrifuged at 5,000 rpm. The supernatant was used to evaluate glutamate and GABA levels with an enzyme-linked immunesorbent assay (ELISA) kit according to the manufacturer's instructions. Catalase, glutathione (GSH), superoxide dismutase (SOD), and malondialdehyde (MDA) activities were also evaluated from the supernatant, as described in our previous study [25].

8. Histological study and cell count

The other half of the brain was fixed in Bouin's fluid, processed for light microscopy, and stained with hematoxylin and eosin (H&E). Tissues were observed using a microscope (Los Angeles, USA), interpreted, and micrographs of the dentate gyrus, hippocampal cornu ammonis (CA), and temporal lobe were obtained (10 slides per group) with a digital camera at 200× magnification. Degenerating and normal cells were counted in five different areas of each slide. Cells with a dense crescent or round-shaped nucleus and cells detached from surrounding tissues were considered degenerating cells.

9. Statistical analysis

A one-way ANOVA followed by a Sidak post-hoc test was performed using GraphPad Prism 9.0 (San Diego, USA). Statistical significance was considered at $p < 0.05$ and the results were displayed as the mean ± SE (standard error).

RESULTS

1. Seizure score

The seizure score of control rats remain zero throughout the experiment. In diazepam-pretreated rats, the seizure score increased to 0.3 after the 11th PTZ injection. Rats receiving PTZ injections displayed a gradual increase in seizure activities from the third injection; the seizure score reached its maximum (4.2) after the 11th PTZ injection, resulting in kindling through 13 injections (Fig. 1). Conversely, pretreatment with ASBE decreased seizure activities compared to PTZ-treated rats. The maximum seizure scores of rats pretreated with ASBE at 125 mg/kg and 250 mg/kg were 2 and 3, respectively (Fig. 1).

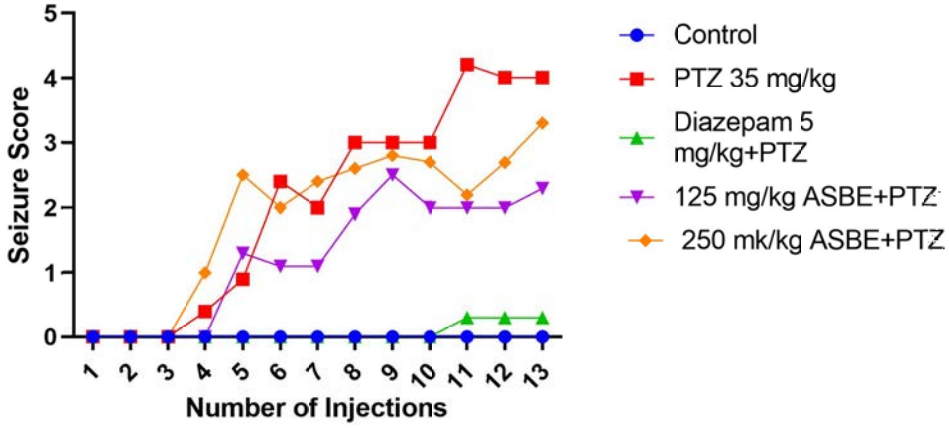

Figure 1. Effect of ASBE on average seizure score of PTZ-treated rats. ASBE, acetone extract *Adansonia digitata* stem bark; PTZ, pentylenetetrazol.

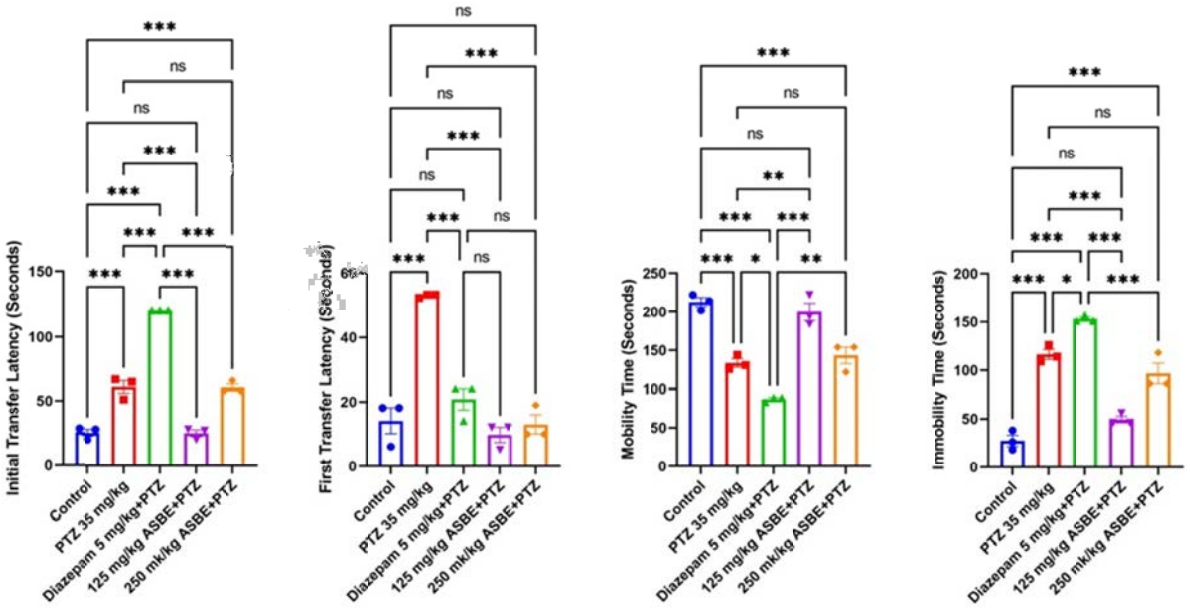

Figure 2. Effect of ASBE on the transfer latency, mobility, and immobility time in PTZ-treated rats. Values are presented as Mean ± SE. *, **, and *** indicates significant difference at $p < 0.05$. ASBE, acetone extract *Adansonia digitata* stem bark; SE, standard error of mean; ns, non-significant difference. n = 5.

2. Anxiety-related behavior

The results of the anxiety-related behavior as evaluated by the EPM test revealed that the ITL of PTZ-treated and ASBE (250 mg/kg)-pretreated rats was significantly higher ($p < 0.05$) relative to the control. No significant change ($p > 0.05$) exists between the ITL of PTZ-treated and ASBE-pretreated rats. A significantly higher ($p < 0.05$) ITL was observed in diazepam-treated rats compared to the control, PTZ-treated rats, and ASBE-pretreated rats (Fig. 2). The FTL of PTZ-treated rats was significantly higher ($p < 0.05$) compared to the control. The FTL of diazepam- and ASBE-pretreated rats was significantly lower ($p < 0.05$) compared to PTZ-treated rats. The FTL of the ASBE-treated rats was comparable to the control (Fig. 2).

3. Antidepressant-like activity

The one-way ANOVA result showed a significant reduction ($p < 0.05$) in the mobility time of the force swim test for rats treated with PTZ and diazepam relative to the control. No significant change ($p > 0.05$) was observed in the mobility time of ASBE (125 mg/kg)-pretreated rats compared to the control (Fig. 2). The immobility time of control rats was significantly lower ($p < 0.05$) relative to PTZ-treated rats and rats pretreated with di-

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azepam and ASBE at 250 mg/kg. However, the immobility time of rats pretreated with 125 mg/kg ASBE was not significantly changed ($p > 0.05$) compared to the control (Fig. 2).

4. Neurotransmitters

Rats treated with PTZ had a higher ($p < 0.05$) glutamate level and glutamate/GABA ratio compared to the control. However, pretreatment with ASBE was found to significantly decrease ($p < 0.05$) the previously elevated glutamate level and glutamate/GABA ratio as a result of PTZ treatment (Fig. 3). No significant change ($p > 0.05$) was observed in the GABA level of PTZ-treated rats relative to the control. Furthermore, pretreatment with ASBE significantly elevated ($p < 0.05$) the GABA level compared to PTZ-treated rats (Fig. 3).

5. Oxidative stress markers

One-way ANOVA results revealed a non-significant decrease ($p > 0.05$) in catalase, GSH, and SOD activities in PTZ-treated rats relative to the control and diazepam-pretreated rats. Furthermore, pretreatment with ASBE significantly increased ($p < 0.05$) the activities of catalase, GSH, and SOD relative to the control and PTZ-treated rats (Fig. 4). The enzymes' activities of rats pretreated with ASBE at 125 mg/kg were significantly higher ($p < 0.05$) compared to diazepam-pretreated rats. A non-significant increase ($p > 0.05$) in MDA activities was observed

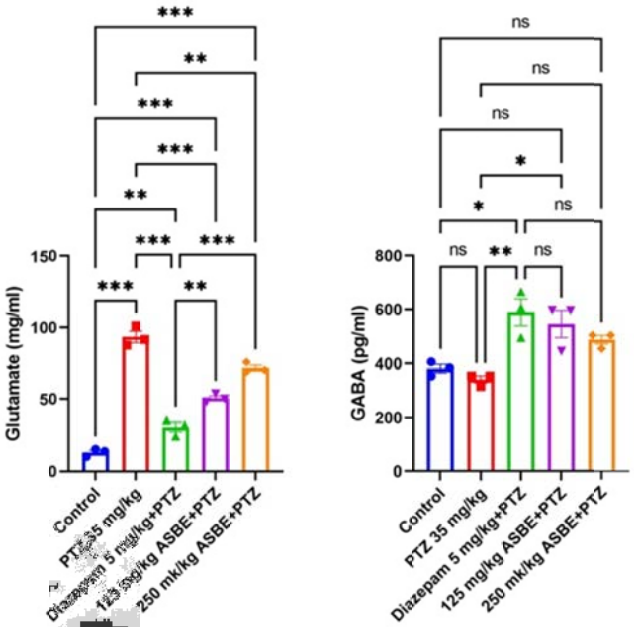

Figure 3. Effect of ASBE on glutamate and GABA in PTZ-treated rats. Values are presented as Mean ± SE. *, **, and *** indicates significant difference at $p < 0.05$. ASBE, acetone extract *Adansonia digitata* stem bark; SE, standard error of mean; ns, non-significant difference. n = 5.

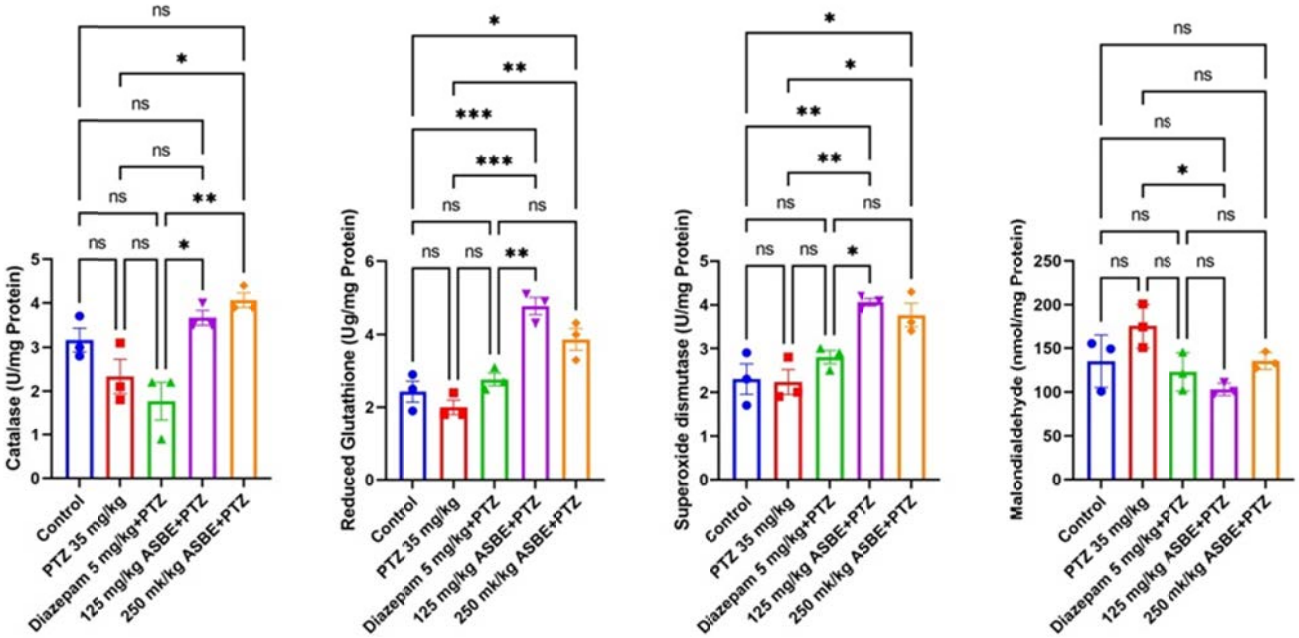

Figure 4. Effect of ASBE on oxidative stress markers in PTZ-treated rats. Values are presented as Mean ± SE. *, **, and *** indicates significant difference at $p < 0.05$. ASBE, acetone extract *Adansonia digitata* stem bark; SE, standard error of mean; ns, non-significant difference. n = 5.

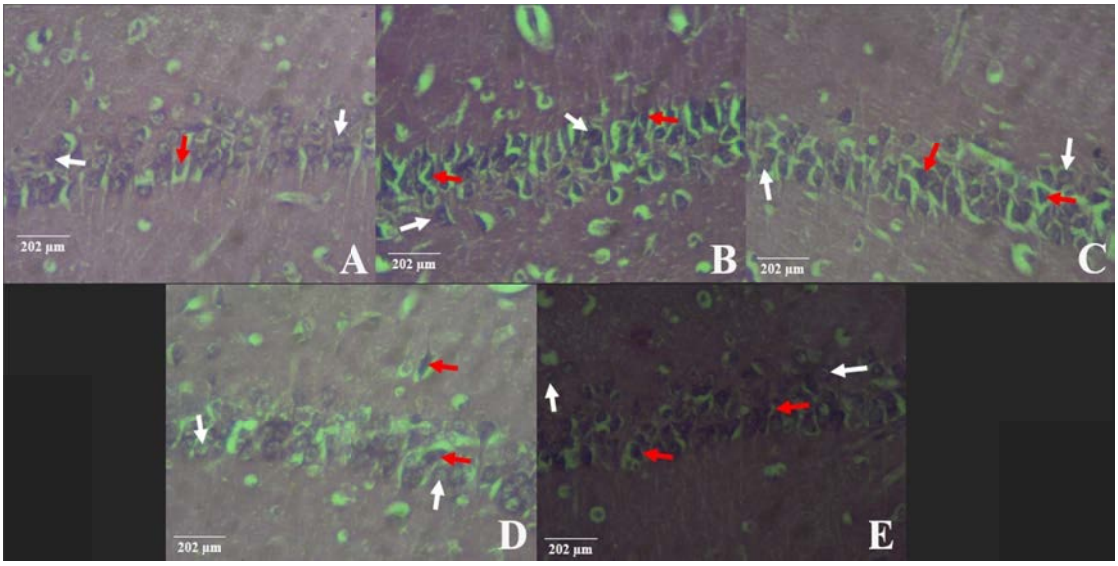

Figure 5. Effect of ASBE on the CA1 region of the hippocampus of PTZ-treated rats showing normal (white arrows) and degenerating neurons (red arrows). (A) control, (B) 35 mg/kg PTZ, (C) 5 mg/kg diazepam + PTZ, (D) 125 mg/kg ASBE + PTZ, (E) 250 mg/kg ASBE + PTZ. ASBE, acetone extract *Adansonia digitata* stem bark. H&E stain, ×200 magnification.

in PTZ-treated rats compared to the control and rats pretreated with diazepam and 250 mg/kg ASBE. Pretreatment with ASBE at 125 mg/kg significantly decreased ($p < 0.05$) MDA activities relative to PTZ-treated rats (Fig. 4).

6. Histological study and cell count

The micrograph of the hippocampus (CA1 region) showed normal cells in diazepam- and ASBE-pretreated rats, as well as the control, while those of PTZ-treated rats revealed intact layers with numerous degenerating cells (Fig. 5). A significant decrease ($p < 0.05$) in the number of normal cells was observed in PTZ-treated rats relative to the control. Pretreatment with diazepam and ASBE was found to significantly increase ($p < 0.05$) the normal cell count compared to PTZ-treated rats (Fig. 6). The degenerating cell count of PTZ-treated rats was significantly higher ($p < 0.05$) compared to the control. Pretreatment with diazepam and ASBE reduced the degenerating cell count significantly ($p < 0.05$) compared to PTZ-treated rats (Fig. 6). The CA3 region of the hippocampus showed normal cells in the control with severe distortion and degeneration in PTZ-treated rats, while that of the diazepam and ASBE-pretreated rats showed mild distortion with a good number of normal cells (Fig. 7). The normal cell count of PTZ-treated rats was significantly reduced ($p < 0.05$) compared to that of the control and ASBE-pretreated rats. The normal cell count of ASBE-pretreated rats

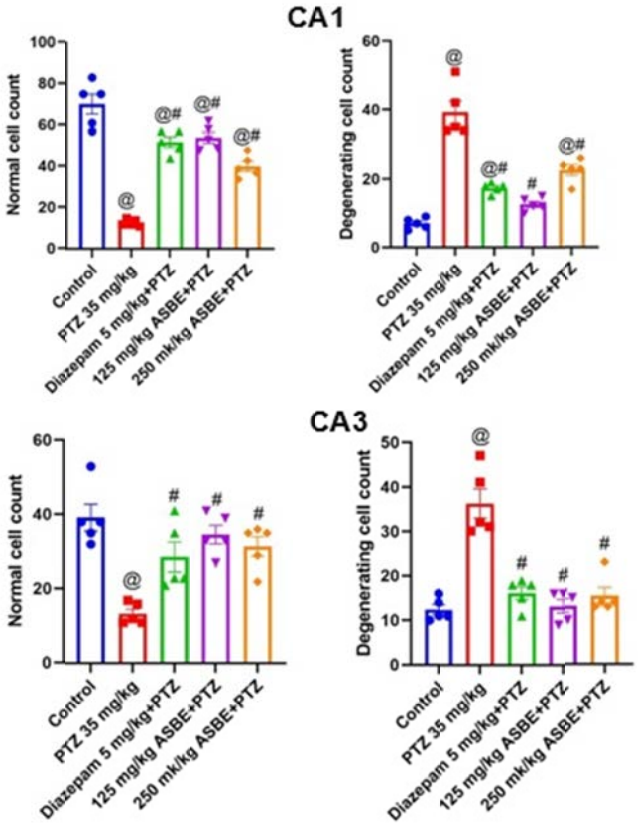

Figure 6. Normal and degenerating cell count in the CA1 and CA3 region of the hippocampus of PTZ-treated rats. Values are presented as Mean ± SE. @ and # indicates significant difference with control and PTZ-treated rats at $p < 0.05$. ASBE, acetone extract *Adansonia digitata* stem bark; SE, standard error of mean. n = 5.

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was comparable to that of the control. The degenerating cells in PTZ-treated rats were significantly higher ($p < 0.05$) relative to the control. Pretreatment with ASBE and diazepam resulted in degenerating cells that were comparable to the control (Fig. 6). Treatment with PTZ did not affect the histoarchitecture of the dentate gyrus. Conversely, it affected the number of degenerating cells, resulting in a significant increase ($p < 0.05$) compared to the control (Figs. 8 and 9). Pretreatment with diazepam and 125 mg/kg ASBE significantly reduced ($p < 0.05$) the number of degeneration cells compared to PTZ treatment. The number of dentate gyrus-degenerating cells in rats pretreated with diazepam and 125 mg/kg ASBE was comparable to the control (Fig. 9). PTZ did not affect the histoarchitecture of the temporal lobe and the number of normal cells. Nevertheless, it significantly

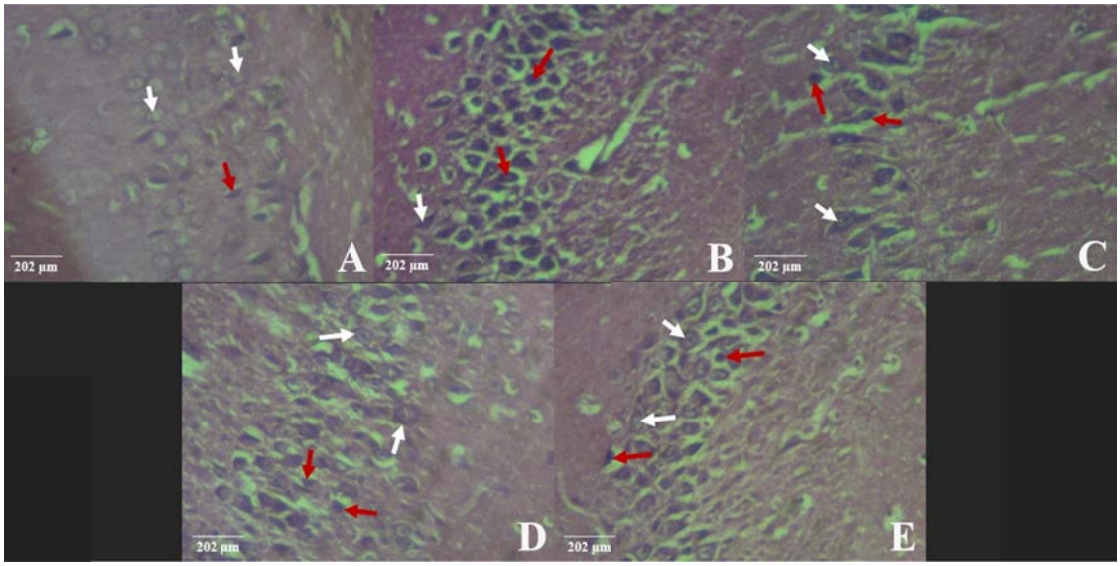

Figure 7. Effect of ASBE on the CA3 region of the hippocampus of PTZ-treated rats showing normal (white arrows) and degenerating neurons (red arrows). (A) control, (B) 35 mg/kg PTZ, (C) 5 mg/kg diazepam + PTZ, (D) 125 mg/kg ASBE + PTZ, (E) 250 mg/kg ASBE + PTZ. ASBE, acetone extract *Adansonia digitata* stem bark. H&E stain, ×200 magnification.

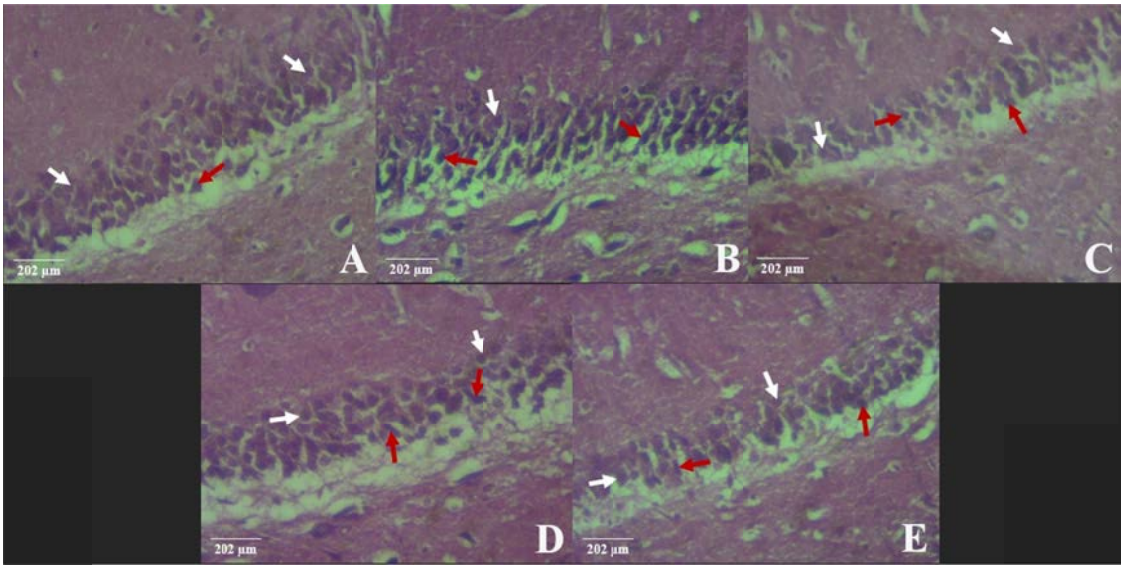

Figure 8. Effect of ASBE on the dentate gyrus of PTZ-treated rats showing normal (white arrows) and degenerating neurons (red arrows). (A) control, (B) 35 mg/kg PTZ, (C) 5 mg/kg diazepam + PTZ, (D) 125 mg/kg ASBE + PTZ, (E) 250 mg/kg ASBE + PTZ. ASBE, acetone extract *Adansonia digitata* stem bark. H&E stain, ×200 magnification.

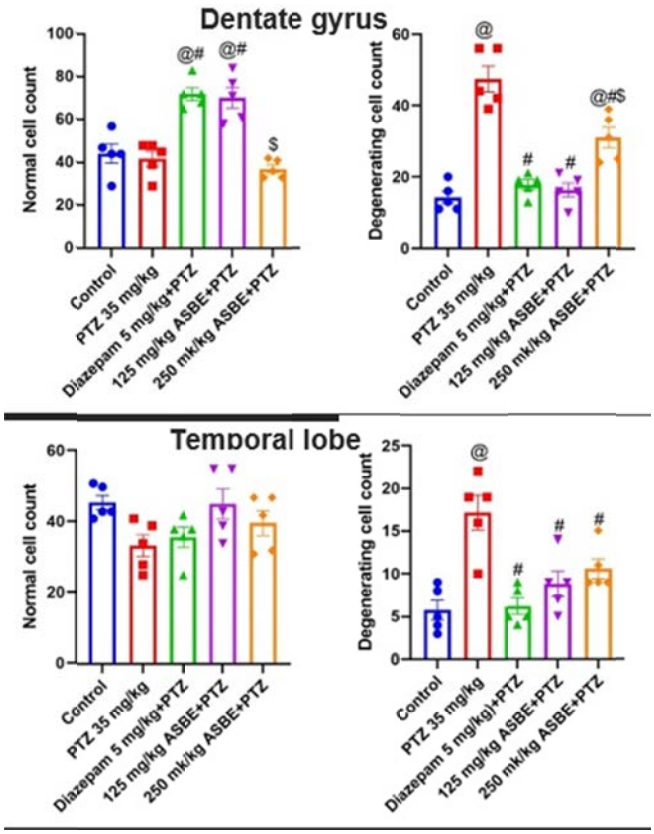

Figure 9. Normal and degenerating cell count in the dentate gyrus and temporal lobe of PTZ-treated rats. Values are presented as Mean ± SE. @ and # indicates significant difference with control and PTZ-treated rats at $p < 0.05$. ASBE, acetone extract *Adansonia digitata* stem bark; SE, standard error of mean. n = 5.

increased the number of degenerating cells compared to the control. Pretreatment with ASBE significantly decreased ($p < 0.05$) the number of degenerating cells compared to PTZ treatment (Figs. 9 and 10).

DISCUSSION

The seizure score and neurotransmitter (glutamate and GABA) study were conducted to determine if ASBE can delay and/or prevent kindling in PTZ-treated rats. The result revealed that ASBE prevented kindling even after 11 PTZ injections. This is an indication that ASBE can attenuate seizure activity in the rat brain. PTZ is a GABA type A receptor agonist that suppresses the inhibitory function of synapses, resulting in higher neuronal activity and leading to seizures [26, 27]. Glutamate is an important neurotransmitter that plays a vital role in memory and neuronal development. Hence, dysregulation of glutamate release is connected to many neurological disorders, such as seizures and memory loss [28]. Thus, we hypothesized that ASBE prevents seizures by regulating glutamate and GABA levels, leading to low neuronal activity and suppressing seizures. This hypothesis is supported by the high brain glutamate level observed in the present study and its regulation by ASBE. Previous studies reported the anticonvulsive and antidepressant effects of *A. digitata* stem bark, suggesting that the plant contains compounds capable of eliciting neuroprotection [21, 29].

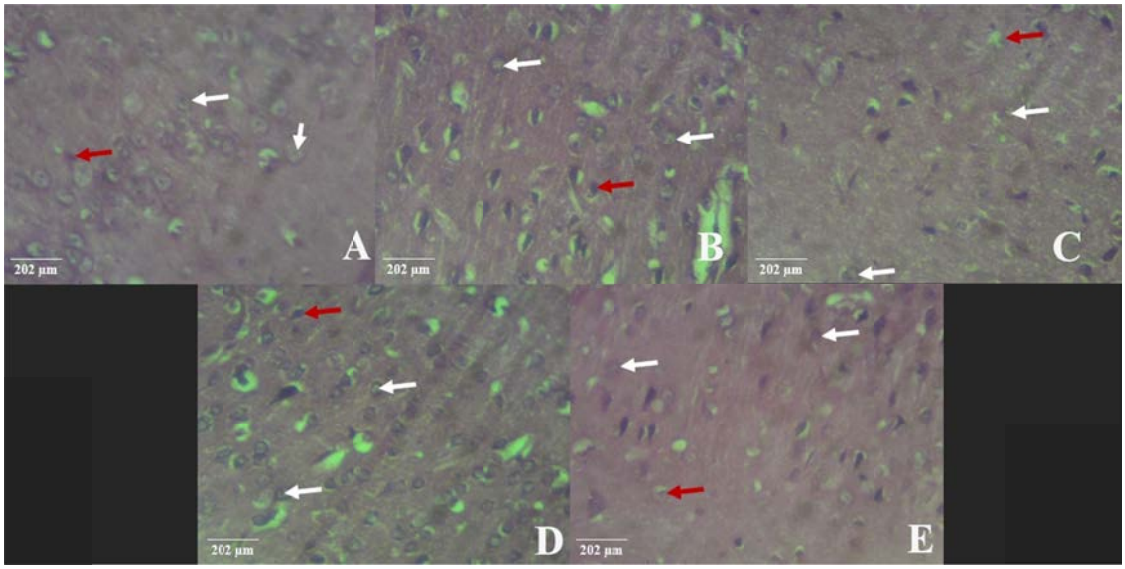

Figure 10. Effect of ASBE on the temporal lobe of PTZ-treated rats showing normal (white arrows) and degenerating neurons (red arrows). (A) control, (B) 35 mg/kg PTZ, (C) 5 mg/kg diazepam + PTZ, (D) 125 mg/kg ASBE + PTZ, (E) 250 mg/kg ASBE + PTZ. ASBE, acetone extract *Adansonia digitata* stem bark. H&E stain, ×200 magnification.

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The EPM and forced swim test studies were performed to assess the role of ASBE on cognition (anxiety-like behavior) and depression. The result showed that ASBE is capable of preventing depression and cognitive impairment by reducing the FTL in the EPM test and increasing mobility time in the force swim test. Several studies demonstrated a link between epilepsy and cognitive impairment/depression with a different hypothesis. While one postulated that epileptic seizure discharge injures the neural network, the other suggested that both seizure and cognitive impairment arise from neural loss [30-32]. Our study hypothesized that PTZ initiates seizures through the dysregulation of glutamate and GABA levels, leading to increased neuronal activity and eventual neural injury and degeneration. This assertion is supported by the increased number of degenerating neurons in the hippocampus, temporal lobe, and dentate gyrus of PTZ-treated rats. However, ASBE pretreatment was found to significantly reduce degenerating neurons, suggesting that ASBE can attenuate neuronal injury in epilepsy and lead to lesser complications such as cognition and depression.

Elevated glutamate levels are usually associated with overexcitation and eventual seizures [33]. Hence, the GABA level has to balance with glutamate in the brain for effective neuron development and function. An elevated brain and plasma glutamate are usually associated with drug-resistant epilepsy [34, 35]. In the present study, PTZ elevated glutamate levels, resulting in increased seizure activity. On the contrary, ASBE pretreatment significantly lowered the glutamate level, resulting in low seizure activity. We postulated that ASBE mediates brain function by lowering glutamate and GABA levels in the brain.

The oxidative stress study evaluated the antioxidant role of ASBE in the progression of neurodegenerative disease. The result revealed that PTZ treatment affects the antioxidant capacity of rats by decreasing catalase and glutathione levels, but ASBE pretreatment was found to elevate catalase, reduce glutathione and superoxide dismutase levels, and decrease lipid peroxidation. Several studies have highlighted the role of antioxidants in preventing the onset and progression of neurodegenerative diseases [36, 37]. The ability of ASBE to enhance antioxidant activity is attributed to the presence of phenolic compounds. We postulated that the antioxidant activity of ASBE might be the reason for the increase in normal cell numbers in the hippocampus, temporal lobe, and dentate gyrus of ASBE-pretreated rats.

Herein, the EPM test was used to evaluate both anxiety-like behavior and cognitive function, while the force swim test was used to evaluate depression. Therefore, these results cannot be used to generalize all aspects of cognition except those related to anxiety-like behaviors.

CONCLUSION

The study revealed that ASBE reduces seizure activity in PTZ-treated rats. The reduced seizure activity prevents kindling, depression, and cognition. It also prevents neurodegeneration by regulating glutamate and GABA levels in the brain, as well as preventing lipid peroxidation. The anti-seizure and neuroprotective effects of ASBE suggest that it can be translated for use in humans for managing epilepsy and depression.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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