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Anti-epileptic Role of *Tetrapleura tetraptera* Methanol Extract on Pentylenetetrazol (PTZ)-Induced Epilepsy in Mice

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Abstract

Pentylenetetrazole (PTZ) is a chemical convulsant that can generate seizure in humans and rodents which mirror the effects of naturally occurring pathological seizure disorders. This study aimed to investigate the role of methanolic extract of *Tetrapleura tetraptera* (METT) on neurological behavior and motor coordination in PTZ-induced epilepsy in male mice. A total of 50 mice were randomly assigned to 5 groups (n=10) as: Control (0.2ml saline orally); PTZ (single dose 35kg/mg s.c); Diazepam (1ml/100g-i.p) used as reference control; Low dose (LD: 400mg/kg) and High dose (HD: 800mg/kg) of METT was administered orally for 14 days after which PTZ (single dose, 35kg/mg s.c) was induced on the 22nd day. Seizure was confirmed using the Racine scale. Neurological test include; open field test (OFT) and social behavior test (recognition memory) and fine motor coordination using beam balance. These behavioral studies were performed 24 hours after the completion of the PTZ dose. OFT results showed that METT extract and diazepam significantly reduced locomotor activity (line crossing and rearing), but HD of METT suppresses line crossing better than diazepam. Centre square duration did not differ significantly, but METT extract and diazepam significantly reverse exploratory behavior (stretch attend posture and freezing duration). METT extracts was more potent than diazepam in ameliorating the abnormal social behavior posed by PTZ. Mice treated with diazepam and METT extract showed fine motor coordination which reduced the beam crossing time. METT may have anti-epileptic effect against PTZ-induced epilepsy in mice, and could be a better remedy than diazepam against epileptic seizures.

Keywords: Epilepsy, Pentylenetetrazole, Diazepam, Tetrapleura tetraptera, Remedy.

INTRODUCTION

Epilepsy is a chronic and heterogeneous neurological disorder characterized by recurrent seizures affecting about 0.5–1% of the global populace [1,2]. These seizures can manifest in various forms, affecting motor, sensory, cognitive, and emotional functions [3]. Induced models of epilepsy in rodents have been instrumental in identifying and developing treatments for epilepsy [4]. PTZ is a chemical convulsant that can generate seizure in humans and rodents. It has varied dosage-dependent effects on behavior [5]. Induced seizures with PTZ consistently mirror the effects of naturally occurring pathological seizure disorders [6]. PTZ at higher dosage cause acute seizures in rodents, but at sub-convulsive dosage, produce a chronic epileptic state [7]. Studies have demonstrated that the injection of PTZ leads to the death of neurons and cognitive impairments resulting from seizures [8-10]. Alrashdi *et al*., [2] revealed bidirectional relationships between epilepsy and depression, suicidal ideation, and attention deficit disorders. Mahmoudi *et al*., [11] reported that several antiepileptic drugs have been discovered, but these drugs have to be used for a long time, sometimes for a lifetime. While, Herrera-Calderon *et al*., [12] showed that antiepileptic medication pose serious side effects such as ischemia, hepatotoxicity, depression, cognitive disorders, motor disability and Salem [13] showed that antiepileptic medication leads to behavioral anomalies. As a result, there is increasing interest in natural products as alternative therapies [14]. WHO reported that 80% of the global populace is reliant on herbal medicine for the treatment of several diseases [15] because of the many adverse effect posed by conventional medications. Herbal medications provide promising and valuable reservoirs of medicinal compounds [8].

Tetrapleura tetraptera (TT) is a deciduous plant native to West Africa that belongs to the family Mimosaceae [16]. The fruit are commonly found in Ghana and Nigeria where it is highly valued for its use in traditional medicine and its nutritional properties. In English it is known as Aidan fruit [15], locally it is known as Aridan in Yoruba, Uyayak in Ibibio; Edeminang in Efik; Osakirisa or Oshosho in Igbo; Dawo in Hausa; and Prekese in Twi language of Ghana [17]. The fruits, made up of a fleshy pulp with small, brownish-black seeds, are green when tender and dark brown when fully ripe [16]. When dry, they have a pleasant aroma, and are used as spice [16], that translate into its nutritive value. TT is a source of calcium, phosphorous, potassium, zinc and iron [18], rich in ash, fiber, proteins, carbohydrates, vitamins, and fats, while phytochemical constituents found are polyphenols (tannins, flavonoids), alkaloids, steroids, saponins, coumarinic (scopoletin), triterpenoids, phenolic (caffeic acid, cinnamic acids) compounds, a triterpene glycoside (aridanin) and phytate [15,19,20] which could be responsible for its varied biological and pharmacological properties. It spicy property makes them valuable for preparing soup for nursing mothers from the first day of birth to prevent postpartum contraction [16]. The fruit has been found to possess anticancer, anticonvulsant [17], antioxidant and anti-inflammatory properties [15]. As such, it is germane to assess the neuro-protective benefit of TT in PTZ-induced epilepsy in mice.

METHODS

Collection and preparation of materials

The dried adian fruit was bought from a local market in Okuku, Yala Local Government Area of Cross River State, Nigeria. Samples of the dried fruit were identified and authenticated by Dr. Ijioma James of the department of Botany Cross River State University, Nigeria. Sample of the plant voucher deposited for reference purpose (voucher number-Bot/Herb/CSU/018).

The dried fruits was washed and blended into coarse particles. The milled particles (300 g) was macerated in 80% of methanol and 20% of water for 48 hours at room temperature and filtered through cheese cloth, followed by Whatman #1 filter paper. The filtrate was dried in an oven at 40^{o}C. The drying was monitored until it turned into a paste form. The yield of the dried extract was 75.03 g. From the prepared TT fruit extract, 1g was weighed using electrical sensitive weighing balance and diluted in 10ml of normal saline using syringe and allowed to dissolved. Method used as described by [21].

Acute toxicity study (LD50)

The method of Nofal *et al*., [22] was adopted for acute toxicity testing using albino mice. Five groups of six (6) mice each weighing (20-25g) body weight received via intra-peritoneal route different gradual doses (10-10,000mg/kg) of the extract. The animals were observed for physical signs of toxicity and death for 24 hours. There was no toxicity and mortality recorded even at the highest dose of 10,000mg/kg. Therefore, in this study for the low and high extract dosage, 400mg/kg and 800mg/kg was orally administered.

Experimental animal ethics

Fifty male albino mice (25-39g) obtained from Physiology Department, University of Cross River State, Nigeria were used. The animals were kept under standard laboratory conditions and housed in well ventilated plastic cages at room temperature and relative humidity with light and dark cycles (12hr/12hr). The animals were acclimatized for one week and were provided standard rat pellet (Pfizer feed PLC, Lagos, Nigeria) and water ad libitum. The animals were kept in line with laid - down ethics for animal care approved by the National Committee for Research Ethics in Science and Technology, 2018. Before the commencement of this research, ethical approval was obtained from the Faculty of Basic Medical Science Ethical Committee. The study was permitted with ethical clearance with approval number(UNICROSS/FBMS/NIG/REC/2025/Vol. 2/03).

Induction of epilepsy

Convulsions were induced by subcutaneous injection of single dose of PTZ (35 mg/kg body weight) dissolved in saline. Administration of a single dose of PTZ 35 mg/kg elicited convulsion in all the mice in accordance with the report of Goto *et al*., [23]. Seizure was confirmed using the Racine scale.

Diazepam preparation

Diazepam was dissolved with 1N HCl solution and then neutralized with 1N NaoH solution, followed by dilution with saline to make the desired concentration of 1ml/100g body weight.

Experimental design

After one week of acclimatization, 50 mice were divided into five groups (n=10) as follows:

Group 1: Normal control received 0.2ml/kg of distilled water (orally)

Group 2: PTZ received single dose (35mg/kg subcutaneously)

Group 3: Diazepam (reference control) received 1ml/100g (i.p)

Group 4: TT extract low dose (400mg/kg orally) + PTZ single dose (35mg/kg s.c)

Group 5: TT extract high dose (800mg/kg orally) + PTZ single dose (35mg/kg s.c)

Adian fruit extract was administered for 14 days in group 4 and 5 after which PTZ was induced s.c on the 22nd day.

Neurological behavior assessment

These behavioral studies were performed 24 hours after the completion of the PTZ dose. Only one animal was tested at a time for the neurological study.

Open field test

The OFT apparatus is a white painted plywood (72 X 72 cm) with blue lines drawn on the floor to divide it into 18 x 18 cm squares. A central square (18 x 18 cm) is drawn in the middle of the open field. Each mice was placed in the center of the apparatus and allowed to explore the area for 5 min. Behaviours Scored include line crossing, rearing, center square duration (CSD), stretch attend postures (SAP), and freezing duration. Each mouse was then given a score for total locomotor activity and emotionality that was calculated as the sum of line crosses and number of rears [24]. The apparatus was cleaned with 70 % ethanol after each trial.

Social Behavior Test

The goal of this test was to study social interaction in mice and memory. The Novel object recognition test (NORT) assesses rodent's ability to recognize a familiar object over a variable length of time; this ability has been coined recognition memory [24]. The test was conducted in the open field apparatus. There is an initial habituation to the apparatus prior to the social recognition test for 5 min, and then two sessions, familiarization session where the animal explore two identical objects for 5 min and test session where one of the objects is replaced by a novel object. These two sessions are separated by an inter-trial interval of 15 min. The apparatus was cleaned with 70 % ethanol after each trial. The ability to recognize a familiar object is the foundation for social relationships [25]. As such, animals would tend to investigate the novel object over one which they were already acquainted with [26]. Preference for social novelty was determined by the amount of time the subject spent exploring the novel object relative the familiar one [27].

Beam walking

The beam walking assesses fine motor coordination and balance [28]. This test examines the ability of the mice to remain upright and to walk on an elevated and relatively narrow beam [28]. The beam has a length of 120 cm, a width of 0.6 cm and is suspended about 60 cm above some foam pads. The beam is marked at 5 cm and 1 cm intervals. It is composed of wood and is coated with black paint. The mouse was placed on one end of the beam. The trial was started after the mouse has secured its grip on the beam and lasted for approximately five minutes. The tests were videotaped for scoring. The parameter scored was the duration to beam ending. The apparatus was cleaned with 70 % ethanol after each trial.

Statistical Analysis

The results obtained were expressed as mean ± SEM. The statistical analysis was done using one way analysis of variance. A difference between means was considered significant at $p < 0.05$. The statistical software used includes SPSS version 20 and graphpad prism version 8.

RESULTS

Neurological behavior observation

Frequency of line crossing in the OFT

The mean frequency of line crossing for control, PTZ, Diazepam, LD and HD were 41.50 ± 0.60, 63.25 ± 0.48, 57.00 ± 0.41, 62.50 ± 0.50 and 53.75 ± 0.63 respectively. There was a significant increase in PTZ, Diazepam, LD and HD ($p<0.001$) against control. Diazepam reduced significantly ($p<0.001$) against PTZ. HD decreased ($p<0.01$), while LD increased ($p<0.001$) significantly against diazepam. HD decreased ($p<0.001$) significantly against LD (Figure 1).

Frequency of rearing in open field maze

The mean rearing frequency for control, PTZ, Diazepam, LD and HD were 12.5±0.29, 34.50±0.29, 11.50±0.50, 17.50±0.50, and 12.50±0.50 respectively. From the result, PTZ and LD increase significantly ($p<0.001$) against control. Diazepam, LD and HD decrease significantly ($p<0.001$) against PTZ. HD decreased ($p<0.001$) significantly against LD (Figure 2).

Center square duration

The mean CSD for control, PTZ, Diazepam, LD and HD were 0.00±0.00, 0.00±0.00, 0.00±0.00, 4.50±4.50, and 3.00±3.00 respectively. The result shows that there was no significant difference in all groups (Figure 3).

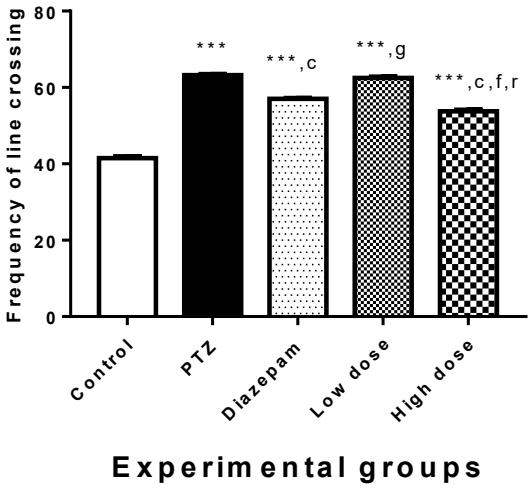

Figure 1: Comparison of frequency of line crossing between experimental groups
Values are mean ± SEM; n=10
***p<0.001 vs control; c=p<0.001 vs PTZ, f=p<0.01, g=p<0.001 vs diazepam; r=p<0.001 vs low dose

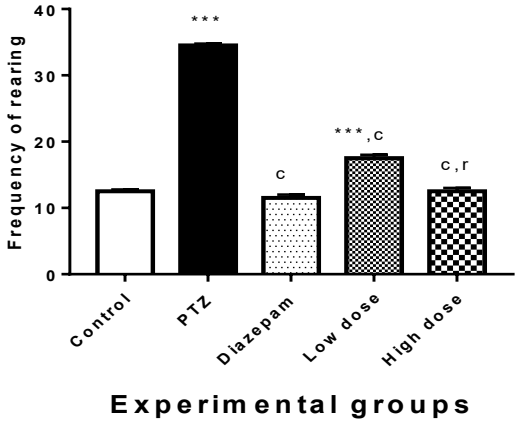

Figure 2: Comparison of frequency of rearing between experimental groups
Values are mean ± SEM; n=10
***p<0.001 vs control; c=p<0.001 vs PTZ, r=p<0.001 vs low dose

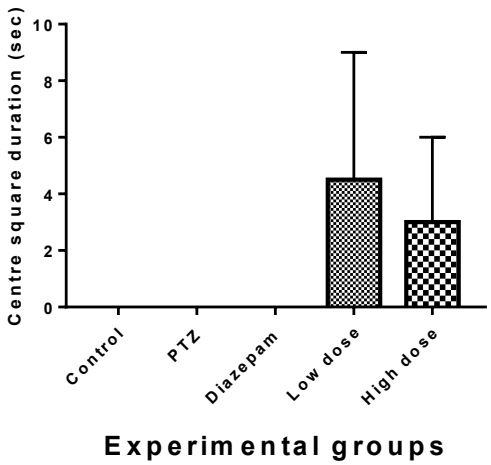

Figure 3: Comparison of centre square duration between experimental groups
Values are mean ± SEM; n=10

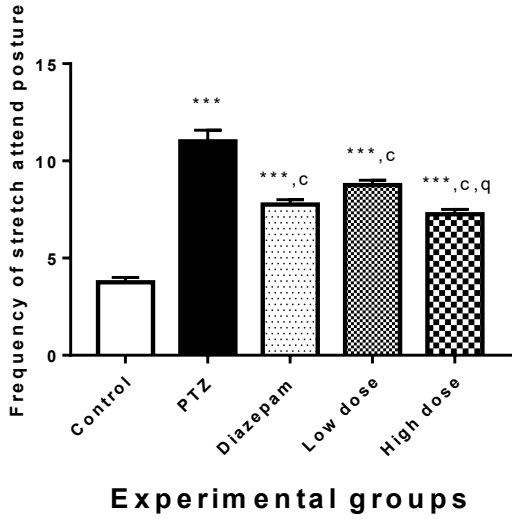

Figure 4: Comparison of frequency of stretch attend posture between experimental groups
Values are mean ± SEM; n=10
***p<0.001 vs control; c=p<0.001 vs PTZ; q=p<0.01 vs low dose

Frequency of stretch attend posture

The mean SAP frequency for control, PTZ, Diazepam, LD and HD were 3.75±0.25, 11.00±0.58, 7.75±0.25, 8.75±0.25 and 7.25±0.25 respectively. The result shows that there was a significant increase in PTZ, Diazepam, LD and HD (p<0.001) compared to control There was a significant decrease in diazepam, LD and HD (p<0.001) compared to PTZ. Also HD decreased (p<0.01) significantly compared to LD (Figure 4).

Freezing duration

The mean freezing frequency for control, PTZ, Diazepam, LD and HD were 145.00±0.58, 105.00±1.22, 127.25±0.48, 126.75±0.48, and 122.00±1.08 respectively. The results shows that there was a significant decrease in PTZ, Diazepam, LD and HD (p<0.001) compared to control. There was a significant increase in diazepam, LD and HD (p<0.001) compared to PTZ. Also HD decreased (p<0.01) significantly compared to LD (Figure 5).

Motor coordination

Beam ending balance duration

The mean beam ending duration for control, PTZ, diazepam, LD and HD were; 6.93 ± 0.02, 11.89 ± 0.03, 3.13 ± 0.01, 4.19 ± 0.02, 5.74 ± 0.04 respectively. PTZ increase (p<0.001), while diazepam, LD and HD decreased significantly (p<0.001) compared to control. Diazepam, LD and HD decreased significantly (p<0.001) against PTZ. LD and HD increased significantly (P<0.001) against diazepam. HD significantly increase (p<0.001) against LD (Figure 6).

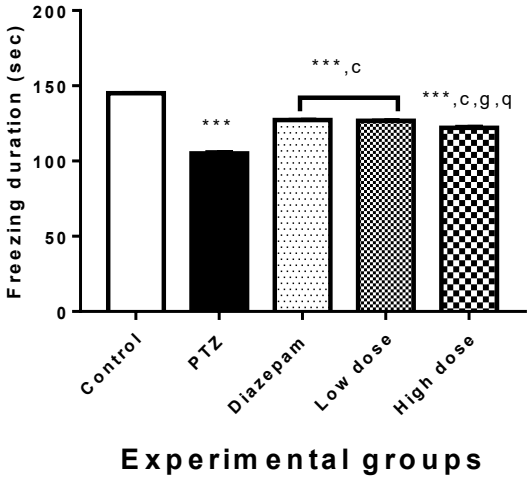

Figure 5: Comparison of frequency of freezing duration between experimental groups
Values are mean ± SEM; n=10
***p<0.001 vs control; c=p<0.001 vs PTZ, g=p<0.001 vs diazepam; q=p<0.01 vs low dose

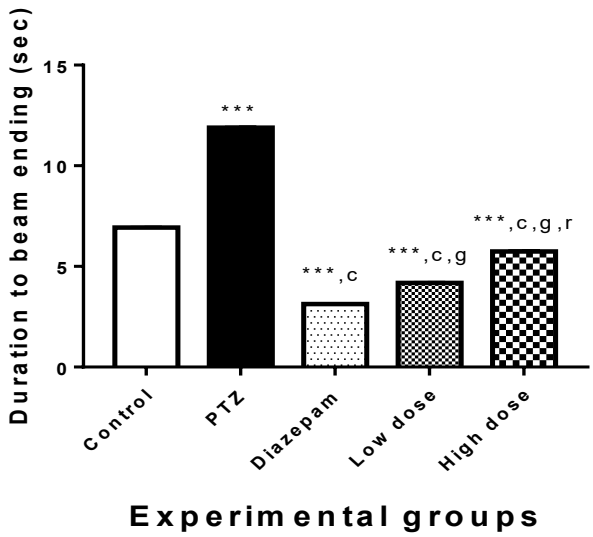

Figure 6: Comparison of duration to beam balance between experimental groups

Values are mean ± SEM; n=10

***p<0.001 vs control; c=p<0.001 vs PTZ, g=p<0.001 vs diazepam; r=p<0.001 vs low dose

SOCIAL BEHAVIOR

Duration with familiar object

The mean duration with familiar object for control, PTZ, Diazepam, LD and HD were 115.00±0.41, 241.00±5.24, 191.75±063, 99.00±13.03, 61.00±0.41 respectively. PTZ and diazepam showed increase frequency (p<0.001) against control, but HD reduced significantly (p<0.001) against control, while LD differed not significantly against control. Diazepam, LD and HD decreased significantly (p<0.001) against PTZ. LD and HD reduced significantly (P<0.001) versus diazepam. HD reduced significantly (p<0.01) against LD (Figure 7).

Frequency of unfamiliar object

The mean duration with unfamiliar object for control, PTZ, Diazepam, LD and HD were 32.25±025, 23.00±0.58, 92.75±1.38, 155.25±1.89 and 132.75±1.11 respectively. PTZ decreased significantly (p<0.001), while diazepam, LD and HD increased significantly (p<0.001) against control. Diazepam, LD and HD increased significantly (p<0.001) against PTZ. LD and HD increased significantly (P<0.001) against diazepam. HD significantly decrease (p<0.001) against LD (Figure 8).

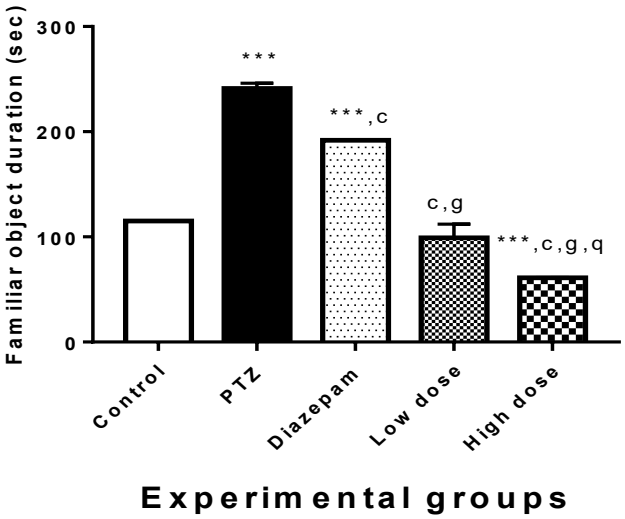

Figure 7: Comparison of familiar object duration between experimental groups

Values are mean ± SEM; n=10

***p<0.001 vs control; c=p<0.001 vs PTZ, g=p<0.001 vs diazepam; q=p<0.01 vs low dose

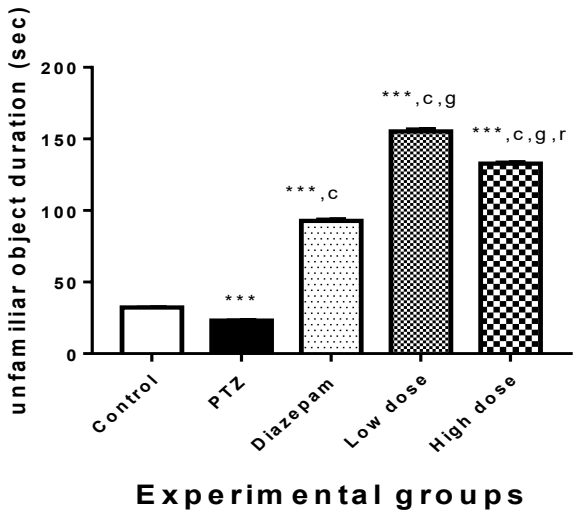

Figure 8: Comparison of unfamiliar object duration between experimental groups
Values are mean ± SEM; n=10
***p<0.001 vs control; c=p<0.001 vs PTZ, g=p<0.001 vs diazepam; r=p<0.001 vs low dose

DISCUSSION

Mouse model of PTZ-induced epilepsy provides an indirect window into human pathology, and has been helpful in the identification and development of treatments for epilepsy [4]. It has been reported that diazepam is an antagonist of PTZ induced seizures [11]. However, many plant extracts have shown the presence of anticonvulsant activity in animal seizure models [10]. The impact of plants or their active components in treatment of diseases can be traced to prehistoric times and are being increasingly studied by medical researchers [29]. Hence, in the present study, the neuro-protective effects of METT of PTZ-induced epilepsy in mice were investigated. Locomotion and exploration behavior was assayed using open field maze. Several studies also reported similar effect of PTZ on locomotor activity [5, 10] and exploratory behaviors [1, 9]. Mahmoudi *et al*., [11], Shimada and Yamagata [30] and Aleshin *et al*., [9] showed that the seizures-associated increases in locomotor activity and exploratory behaviors are as a result of PTZ blocking GABA-A receptors in the central nervous system, leading to increased neuronal activity. PTZ group with 800mg/kg TT extract suppressed locomotor activity by reducing the frequency of line crossing and rearing. However, PTZ group with 400mg/kg TT extract showed no variation in the frequency of line crossing, but reduced the frequency of rearing. Diazepam reduces the frequency of line crossing and rearing. But PTZ group with 800mg/kg TT extract reduction in the frequency of line crossing was more distinct compared to diazepam, while the frequency of rearing did not differ significantly. This shows that TT fruit at 800mg/kg has a stronger effect on seizure suppression than diazepam, probably due to it rich phytochemical constituents. In a 2023 review on TT phytochemicals by Sharanya *et al*., [19] it was reported that TT fruit has anti-convulsant activity due to the presence of Scopoleptin which produced quiecense and reduction of spontaneous locomotor activity in mice.

SAP is a good identifier for exploratory behavior in rodent and can be used to evaluate the effects of medications at reducing this behavior [24]. TT at LD and HD was effective in suppressing this behavior in PTZ-induced mice. Sharanya *et al*., [19] reported that the aqueous extract of TT fruit antagonizes PTZ - induced seizures. Majid *et al*., [31] reported that excessive production of free radicals has been implicated in the pathogenesis of some neurological disorders, including epilepsy and that PTZ-induced seizure raises the levels of secondary products resulting from lipid peroxidation in rats brain. While Adelakun *et al*., [32] and Mensah *et al*., [15] reported that TT extract possess antioxidant properties. The beneficial effect of TT in reducing this behavior posed by PTZ may be due to its antioxidant potential which scavenges free radicals, protect against oxidative stress and prevents the production of lipid peroxides [33, 34].

Antai *et al*., [24] reported that high frequency and duration of center square entry indicates high exploratory behavior. In this study, there was no significant difference in the center square duration. This is consistent with the finding of Kalinina *et al*., [1].

The decrease in freezing time following PTZ injection was consistent with the finding of Shimada and Yamagata [30], which used the contextual fear discrimination test to ascertain the mean percentage of freezing times. In this study diazepam and TT was effective in correcting it. This effect of TT could be attributed to it its antioxidant potential.

The NORT sociality test is based on the spontaneous tendency of rodents to spend more time

exploring a novel object to a familiar one. Such tendency reflects learning and recognition memory [35]. Kalinina *et al*., [1] reported that PTZ can alter emotional behavior in rodents on other behavioral tasks. PTZ-mediated abnormal social behavior observed in this study is consistent with the findings of Shimada and Yamagata [30] and Altyar *et al*., [8]. This could be due to the effect of PTZ to increase production of free radicals [31]. In this study, PTZ groups with TT extract showed preference to the unfamiliar object, and this agrees with the report of Moses *et al*., [36] who concluded that TT extracts protected against PTZ-induced brain oxidative stress. This study showed that TT extracts was more potent compared to diazepam in ameliorating the abnormal social behavior posed by PTZ.

The narrow beam test examines the ability of mice to cross a narrow, elevated beam of wood and it is very sensitive to subtle signs of balance and motor impairment [37]. Balance beam crossing time in mice exposed to PTZ was increased, indicating that PTZ impaired motor coordination. This agrees with the report of Adesua *et al*., [6] who observed poor coordination following post seizure activity which interrupted smooth movement of limbs and Moses *et al*., [36] who also observed reduced beam walk latency in the PTZ group. In this study, mice treated with diazepam and TT extract showed fine motor coordination which reduced the beam crossing time.

CONCLUSION

Our findings show the anticonvulsant effect of TT extract, which is associated with protection against neuronal damage. This neuro-protective effect of TT in suppressing locomotor activity and restoring social behavior in PTZ-induced epileptic mice as shown in this study was better than diazepam. Further studies are required to better understand the mechanism through which TT exert its effects.

Competing Interest: No conflict of interest.

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