ORIGINAL RESEARCH article

Pharmacological evaluation of the effects of aqueous nut extract of *Cyperus esculentus* (Tiger nut) on convulsive episodes and anxiety-like behaviors in mice

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Abstract: Patients with convulsive disease exhibit disorders as anxiety, which further impairs their quality of life and productivity. Despite the availability of anticonvulsant drugs, most patients in Africa for several reasons, still depend largely on herbal medicines as alternative forms of therapy for epilepsy. This study investigates the effect of the aqueous extract of *Cyperus esculentus* (tiger nut) on convulsive episodes and anxiety-like behaviors in mice. Male mice were pretreated orally with the extract (50, 100, and 200 mg/kg), diazepam (1.0 mg/kg), 30 min before induction of convulsions with pentylenetetrazole (100 mg/kg) or isoniazid (300 mg/kg). The mice were then observed for the onset of convulsions for 30 min for pentylenetetrazole, and two hours for isoniazid. A new set of mice was divided into five groups and was given diazepam and the extract (50-200 mg/kg). Thirty minutes later, the mice were evaluated for anxiety-like behaviors. The extract exhibited protective effect against convulsions induced by pentylenetetrazole at doses of 50 and 100 mg/kg, and against isoniazid at 50 mg/kg as evidenced by increased latency to sezuires and reduced number of mice that had convulsions. The extract also demonstrated anxiolytic-like activity in the light/dark box and elevated plus maze tests when compared with the controls. These findings suggest that *C. esculentus* exhibited anticonvulsant and anxiolytic-like activities in mice, and might be relevance in improving the quality of life of persons compromised by epilepsy.

Introduction

Epilepsy is a common neurologic disease, characterized by seizures that take various forms, and is often due to episodic neuronal discharges; the type of seizure depends on the part of the brain regions affected [1]. A seizure is a single event that occurs whenever a strong surge of electrical activity causes abnormal and excessive discharges of a set of neurons in the brain described as a brief electrical storm within the brain [2-3]. The uncontrolled neuronal discharges that cause seizures are thought to occur when the membrane-stabilizing

mechanisms within neurons are disrupted due to abnormal membrane structure or an imbalance between excitatory and inhibitory neurotransmitters [2-3]. The major inhibitory and excitatory neurotransmitters in the brain are gamma-aminobutyric acid (GABA) and glutamate, respectively [4-5]. The major pathological mechanism involved in epilepsy has been linked to overstimulation of the glutamatergic pathway and diminished inhibitory neurotransmission mediated by GABA [5-6].

Epilepsy, a non-communicable disease that can affect people of all ages, may result from brain insults such as chronic infections, injury and tumor as well as gynecological complications [7]. Epidemiological data showed that about 70 million people worldwide suffer from epilepsy and about 80.0% of people with epilepsy are known to live in low- and middle-income countries [8]. In Nigeria, the estimated prevalence of epilepsy is 8 per 1000 people indicating a high burden of the disease in the country [9]. The efficacy of available drugs for the treatment of epilepsy has been compromised by several factors such as poor patients' compliance, adverse effects, failures in certain persons and incidence of anxiety [10-11]. Studies have shown that patients with epilepsy are known to exhibit other psychiatric comorbidities especially anxiety, which further impairs the quality of life of the sufferers [10, 12]. In various countries of the world, people with epilepsy are targets of discrimination and human rights violations. The stigma of epilepsy can discourage people from seeking treatment, leading to an increase in the burden of the disease [13, 14]. Social stigma and the fear of seizures have been reported as the major factors responsible for anxiety in patients with epilepsy [13, 14]. Consequently, management of anxiety is being considered in persons with epilepsy [12, 15].

Cyperus esculentus lativum widely known as tiger nut [16, 17] has been cultivated for many centuries for its nutritional and medicinal qualities. *C. esculentus* is a perennial monocotyledonous plant that consists of an erect stem, covered with many sheaths of leaves and a tough fibrous root, which develops the tubers [17]. Tiger nut has been reported to contain high-energy nutrients such as starch and proteins [18]. It is known to have large amounts of amino acids such as aspartic acid, glutamic acid, leucine, alanine and arginine [16]. It is also rich in minerals such as phosphorous, potassium, calcium, magnesium and iron, and vitamins B, C, D, and E [16]. Phytochemical analysis revealed that tiger nut contains oils alkaloids, tannins, saponins, glycosides, steroids, phlobatanin and flavonoids [16-18]. Moreover, studies using Liquid Chromatography coupled with tandem mass spectrometry (LC-MS/MS) have identified the presence of quercetinin *C. esculentus* [19]. In ethno-medicine, tiger nut tonic commonly known as 'kunnu' is use in the management of gastrointestinal, anemic and diabetic diseases [18, 20]. Rural folkloric surveys reveal that tiger nuts are used for the management of various neurological conditions including migraine headaches, insomnia, mood disorders and amnesia [18, 21]. Previous studies have documented the anti-atherosclerotic, anti-inflammatory, hepatoprotective antioxidant, anti-amnesic and sexual stimulating effects in rodents [17, 19, 22-26]. It was reported to be beneficial to sickle cell disease patients and the possibility of its use in the nutritional management of the disease has been suggested in literature [27]. Although the methanol extract of tiger nut was reported to protect mice against PTZ-induced convulsion [28], no studies have been carried out to evaluate the effects of its aqueous extract on convulsions and anxiety-like activity in rodents. This study aimed to evaluate the effects of the aqueous leaf extract of tiger nut, which represents its usage in ethnomedicine.

Materials and methods

Experimental animals: Male Swiss mice (body weight of 21-24 g) were used in the study and were procured from the Central Animal House, University of Ibadan, Ibadan and housed in plastic cages at room temperature. Mice were fed with a standard rodent pellet diet and allowed to free access to water. They were left for two weeks for acclimatization before the commencement of experiments. The experimental procedures were performed in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals.

Preparation of plant extract: Tiger nuts were purchased from Ojoo market, Ibadan, Oyo State, Nigeria. The nuts were washed, dried and pulverized into fine powder using electric blender. Three hundred grams of the powdered nut was soaked in 1000 mL of distilled water, stirred and left for 72 hrs in a refrigerator at 4°C. The mixture was sieved and then filtered using Whatman No.1 filter paper. The resultant filtrate was dried in a water bath at 40°C and the concentrate, which was stored at 4°C, was later diluted to appropriate concentrations used for this study. The doses of 50, 100, and 200 mg/kg of the extract were selected based on the results obtained from preliminary investigations.

Pentylenetetrazole convulsion test: The effect of *C. esculentus* extract on pentylenetetrazole-induced convulsions was evaluated according to the method described by Löscher et al. [29]. Six mice were pretreated with oral administration of the extract for each dose (50, 100, and 200 mg/kg), diazepam (1.0 mg/kg, DZP, p.o) or vehicle (10.0 mL/Kg of water) 30 min prior to induction of convulsions with intraperitoneal injection of 100 mg/kg pentylenetetrazole. Mice were then observed individually in a transparent chamber for the first appearance of convulsions for a period of 30 min after administration of pentylenetetrazole.

Isoniazid convulsion test: The effect of the aqueous extract of *C. esculentus* on isoniazid-induced convulsion was evaluated using the procedure previously described [30]. 30 mice were distributed into five different groups (each of 6 mice) and were given water, *C. esculentus* (50, 100, and 200 mg/kg, p.o) and DPZ (1.0 mg/kg). 30 min later, mice were given 300 mg/kg isoniazid and were then observed for the onset of convulsion for a period of two hrs.

Light/dark box test for anxiolytic activity: The anxiolytic activity of *C. esculentus* extract was evaluated using the light/dark transition test [31]. The apparatus consisted of a rectangular box (45×27×27 cm), partitioned into two compartments connected by a 7.5×7.5 cm opening in the wall between the two compartments. Six mice per group were given the extract of *C. esculentus* (50, 100, and 200 mg/kg), DZP (1.0 mg/kg), or vehicle (water) orally. 30 min later, each mouse was placed in the illuminated compartment of the box, and the number of entries and time spent on light and dark compartments of the box were recorded for a period of five minutes.

Elevated plus maze test for anxiolytic activity: The anxiolytic effect of the plant extract of *C. esculentus* was further tested using the elevated plus maze model of anxiety [32, 33]. The apparatus consisted of a central square platform (5x5 cm) from which emanated two opposite open arms (30x5x0.25 cm) and two opposite closed arms (30x5x15 cm), respectively. The entire apparatus is elevated to a height of 50 cm above floor level to induce fear. Mice were divided into five different treatment groups (n=6). Mice in group 1 received vehicle (water), groups 2 to 4 were pretreated with extract of the extract of *C. esculentus* (50, 100, and 200 mg/kg) while group 5 received DZP (1.0 mg/kg) as the standard drug. 30 min later, each mouse was placed at the edge of an open arm, with its head facing the center and allowed to explore the maze for five minutes and the number of arm entries and time spent on open and closed arms were recorded. An entry with all feet put into one arm is defined as an arm entry. The index of open arm avoidance was then calculated (IOAA). The results were expressed as time spent on arms.

Statistical analysis: After normality and homogeneity data checks, all data were expressed as mean±S.E of the mean, and analyzed using Graph Pad Prism software version 9.00 (San Diego, CA, USA). Data analysis was carried out by using one-way ANOVA, followed by aBonferroni post-hoc test. $P<0.05$ was considered significant.

Results

On pentylenetetrazol convulsion: The effect of *C. esculentus* on pentylenetetrazole-induced convulsion in mice is shown in **Table 1**. Pentylenetetrazole (100 mg/kg, i.p.) induced convulsive-like features of tonic-clonic limb extensions that terminated in death. However, the extract at oral doses of 50 and 100 mg/kg or DZP (1.0 mg/kg) increased the latency to convulsion and reduced the number of mice that exhibited seizure episodes.

Table 1: Effect of aqueous extract of *Cyperus esculentus* on pentylenetetrazole-induced convulsion in mice

Group	Dose (mg/kg)	Latency to convulsion(s)	Convulsion (%)
Vehicle	10 mL/kg	81.67± 8.93	100
Tiger nut	50.0	141.5±9.81*	50*
	100	140.7±17.05*	50*
	200	101.5±8.32	100
Diazepam	1.0	249.8±18.49*	17*

Values are mean±S.E.M, *P< 0.05 by One-way ANOVA followed by Bonferroni *post-hoc* test

On isoniazid convulsion: **Table 2** showed that the injection of isoniazid to mice at a dose of 300 mg/kg produced intense convulsive episodes with 100% death. However, the plant aqueous extract at a dose of 50 mg/kg was able to increased the latency to convulsion and reduced the number of mice with convulsion induced by isoniazid. Thus, 100 mg/kg and 200 mg/kg of the extract did not attenuate isoniazid-induced convulsion.

Table 2: Effect of aqueous nut extract of *Cyperus esculentus* on isoniazid-induced convulsion in mice

Group	Dose (mg/kg)	Latency to convulsion(s)	Convulsion (%)
Vehicle	10 mL/kg	29.74±2.51	100
Tiger nut	50.0	54.80±3.62*	50
	100	44.83 ±3.77*	83
	200	42.25±1.89	100
Diazepam	1.0	50.64±4.84*	50

Data are mean±S.E.M, *P< 0.05 by One-way ANOVA followed by Bonferroni *post-hoc* test

Anxiolytic-like effect: The performance of the mice treated with different doses of the tiger nut aqueous extract in the light/dark compartment and the elevated-plus maze apparatus of anxiety of mouse is presented in **Table 3** and **Figure 1**. As it is shown in **Figure 2**, the aqueous extract at 100 mg/kg exhibited an anxiolytic-like activity as evidenced by increased time spent on the light compartment of the light/dark test when compared with the control mice. The aqueous extract in the doses of 50 and 100 mg/kg also showed an anxiolytic-like effect as it produced a significant increase in the duration of time spent on the open arms and decreased IOAA when compared with the control group. However, a high dose of 200 mg/kg of the extract did not elicit a significant anxiolytic-like effect.

Table 3: Anxiolytic-like effect of *Cyperus esculentus* extract on the elevated-plus maze test in mice

Group	Dose (mg/kg)	Time (s) spent on open arm	IOAA
Vehicle	-	31.51±5.68	74.35±8.21
Tiger nut	50.0	71.83±11.05$^{\#}$	40.76±0.84$^{\#}$
	100	81.58±4.98$^{\#}$	43.63±0.35$^{\#}$
	200	71.83±11.05$^{\#}$	60.85±4.22
Diazepam	1.0	111.83±11.05$^{\#}$	38.71±0.01$^{\#}$

Values are mean±S.E.M, #P< 0.05 by One-way ANOVA followed by Bonferroni *post-hoc* test

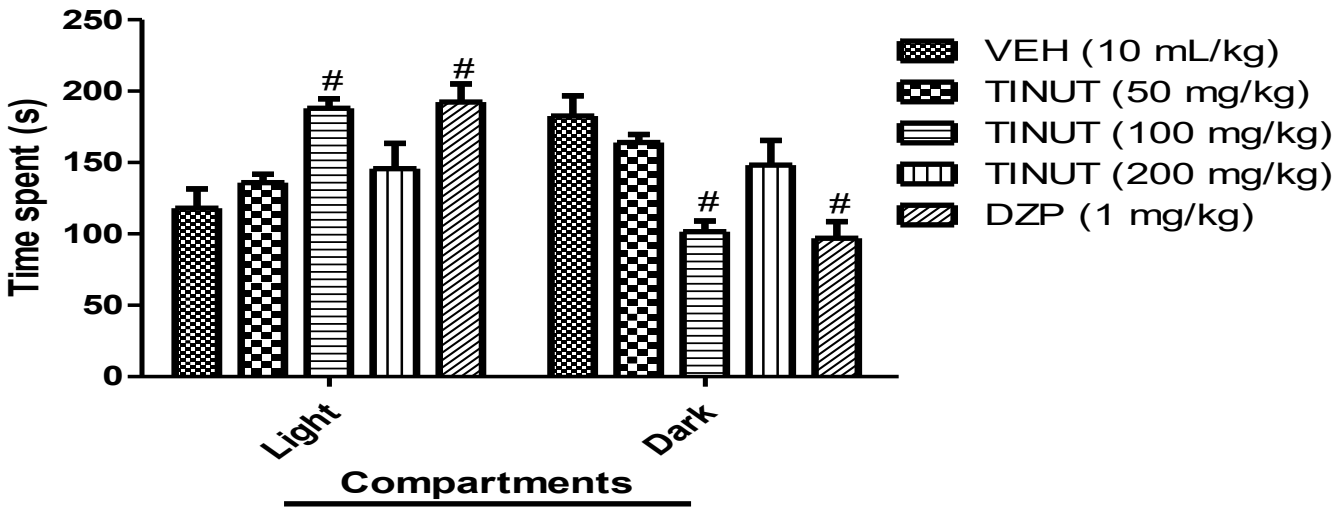


Figure 2: Anxiolytic-like effect of *Cyperus esculentus* extract on the light and dark compartments test in mice
Bar represents the mean±S.E.M, $^{\#}P<0.05$ by ANOVA followed by Bonferroni *post-hoc* test
VEH = water, TINUT = Tiger nut extract, DZP = Diazepam

Discussion

The results of this study showed that administration of 50 and 100 mg/kg of aqueous extract of *C. esculentus* offers protection against pentylenetetrazole-induced convulsive-like behavior in mice, as evidenced by the increase in latency to convulsion and reduced number of mice with sezuires. Meanwhile, it was the lowest dose of the extract (50 mg/kg) that showed a protective effect against seizures induced by isoniazid. The plant extract of 100 mg/kg exhibited anxiolytic-like activity in the light/dark box and elevated plus maze tests. The reference drug, DZP (1.0 mg/kg), demonstrated anticonvulsive and anxiolytic effects in mice. Pentylenetetrazole has contributed substantially to the understanding of the pathophysiology of epilepsy and screening of anticonvulsant drugs [34]. Pentylenetetrazole is widely used for screening of novel compounds with anticonvulsant activity in rodents [29]. The ability of the test compound to prevent convulsions or to reduce the number of animals with seizures is commonly used to indicate anticonvulsant activity in rodents [35, 36]. Moreover, delay in latency to the first episode of convulsion is used to measure anticonvulsant activity during preclinical investigations [35, 37]. It has been reported that compounds that delay the first appearance of convulsion might effectively reduce the spread of seizures in epileptic brains [34]. Antagonism of the $GABA_A$ receptor complex has been shown to be the mechanism underlying pentylenetetrazole-induced convulsions [29, 38]. The inhibition of the $GABA_A$ receptor leads to increased neuronal discharges that terminate in convulsions and death in laboratory animals [34]. Drugs that enhanced GABAergic activity have been shown to exhibit anticonvulsant activity against pentylenetetrazole [29, 34].

In this study, the extract of *C. esculentus* showed protection against pentylenetetrazole as it delayed the latency to convulsions and reduced the number of animals with seizures. In another study, Yarube [28] reported that the hydro-methanolic extract of *C. esculentus* prolonged the latency to seizures caused by pentylenetetrazole in mice. The anticonvulsant potential of the aqueous extract of *C. esculentus* was further evaluated using the isoniazid model. Convulsion caused by isoniazid has been reported to be mediated via inhibition of pyridoxal-5-phosphate-dependent glutamate decarboxylase enzyme thereby resulting in decreased brain GABA levels [30, 38-40]. The fall in brain GABA concentrations triggers the recurrent seizures that typify isoniazid convulsion [30, 38-40]. Convulsion caused by isoniazid is unique as it serves as a suitable animal model for studying the pathophysiology of status epilepticus [30, 38, 39]. The finding that the extract of *C. esculentus* at an appropriate dose showed

activity against isoniazid-induced convulsions in mice further suggests that it might be effective against certain seizures in clinical settings. However, more studies involving the use of kindling epileptic and maximal electroshock models are necessary before any valid conclusion regarding its anticonvulsant potential can be drawn. Anxiety has been reported as one of the most common symptoms associated with chronic diseases including epilepsy [12-13]. The fears of seizure episodes and stigmatization have been highlighted as the major factors for the increased anxiety in persons suffering from epilepsy [12, 14]. In addition, anxiety might be contributing to the poor quality of life of patients with epilepsy [12, 13]. Therefore, it is important to assess the anxiolytic effect of a potential anticonvulsant agent in the course of drug development for the treatment of epilepsy. The results of this study revealed that the nut extract of *C. esculentus* exhibited anxiolytic activity, which may contribute to its sedative effect in ethnomedicine [41]. Nevertheless, more studies are necessary, especially in elucidating the possible mechanism underlying the anxiolytic effect of the nut extract of *C. esculentus*.

Conclusion: This study suggests that the aqueous extract of the nut of *C. esculentus* exhibited an anticonvulsant effect induced by pentylenetetrazole and isoniazid in mice. The extract demonstrated that anxiety-like behaviors might help in improving the quality of life of patients with epilepsy.

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