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RESEARCH ARTICLE

Anticonvulsant and Anxiolytic Property of Tanin on the Cerebellum of Adult Wistar Rat following Administration of Pentylenetetrazol

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Abstract

The plant used in traditional medicine, *Phyllanthus amarus*, has demonstrated possible anticonvulsant and anxiolytic effects. This study investigated the anti-convulsion and anxiolytic properties of tannin fractions of *Phyllanthus amarus* leaf on the cerebellum of adult wistar rats following pentylenetetrazol (PTZ) administration. Forty-two adult male wistar rats (150-200g) were assigned into seven groups (1-7; n=6). Group 1 (normal control) received no treatment. Group 2 (negative control) received 33mg/kg of PTZ only. Group 3, 4 and 5 were given 33mg/kg/ of PTZ and treated with 100, 200 and 400mg/kg tannin of *Phyllanthus amarus* respectively for 16 days. Group 6 received 400mg/kg of tannin only while group 7 (positive control) received 6.4mg/kg of carbamazepine and 41.2mg/kg of PTZ. At the end of the experiment, the rats were test for neurobehavior using elevated plus maze and Y-maze test, toxicity was evaluated histopathologically by light microscopy and threshold and latency response were measured using stop clock at the interval between administration of PTZ to commencement of convulsion. The data collected were statistically analyzed using SPSS package version 23. The group 2 had high threshold and latency response. The treatment groups showed a reduced activity and stability following tannin administration compared to group 2 and 7. The group 2 had mild traumatic tissue encephalopathy in neuronal cell compared to the group 1 with normal histoarchitecture. The treatment groups showed normal cyto-architecture. Tannin fraction of *Phyllanthus amarus* alleviates impairment and neuroinflammation, and prevents convulsion; thus it is useful in convulsion management.

Keywords: Tannin Fraction, *Phyllanthus amarus*, Anticonvulsant, Anxiolytic Effects.

1. Introduction

Epilepsy is one of the most common neurological diseases, affecting approximately 0.5–1% of the general population. It presents a serious health burden, and it has a mortality rate of 2–3% in patients admitted to emergency services (French and Pedley, 2008). Epilepsy also commonly causes psychological, behavioral, and cognitive impairments; thus,

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impairment in functionality will be increased. Besides its high prevalence and effects on functionality, it can be said that effective control of seizures is not sufficient with the currently available antiepileptic drugs (Chen *et al.,* 2019). In fact, 20 new agents are currently being marketed for epilepsy treatment, but the seizure rate has not changed. As a result, it is clear that work is still needed for the development of more sophisticated drugs to treat epilepsy (Gibson and Patel, 2008).

The Genus Phyllanthus (family: *Phyllantheae*) consists of approximately 1000 species, spread over the American, African, Australian and Asian Continents (Tasheen and Mishra, 2013). All the major habits are trees, shrubs and herbs are seen amongst the Phyllanthus species. Most of the herbs, belonging to the Phyllanthus, afford various secondary metabolites with important medicinal properties. Bioactives such as alkaloids, flavonoids, lignins, phenols, tannins and terpenes have been isolated from these plants (Bahar *et al.,* 2011). Phyllanthus amarus is one of the most pharmacologically important species of the Phyllanthus family. It is a medicinally important plant, otherwise known as "stone breaker", "carry me seed" etc. In Nigeria, the plant is called "geron tsuntsaye" (Hausa), "eyinolobe" (Yoruba) and "ngwu" (Igbo). The decoctions of various parts of the herbs are used traditionally for the treatment of hepatic, urinary and sexually transmitted diseases, diabetes, hypertension and cancer (Khartoon *et al.,* 2004). In folk medicine, P. amarus herb has found applications in the management of several health problems such as diarrhea, dysentery, dropsy, jaundice, intermittent fevers, urinogenital disorders, scabies and wounds. Literature indicated the application of the plant in the treatment and management of kidney problems, appendix inflammation, prostate problems, pain, gonorrhea, diabetes and chronic dysentery (Sen and Batra, 2013). Topically, it is used for several skin-related problems ranging from skin ulcers, sores, swelling, itchiness, wounds, bruises, scabies, ulcers, sores, edematous swellings, tubercular ulcers, ringworm, scabby and crusty lesions (Ushie *et al.,* 2013). Other reported pharmacological activities of the plant include anticancer, antioxidant, antileptospiral, antimicrobial, anti-diabetic, antiinflammatory and anti-convulsant activities (Chandan *et al.,* 2012; Saranraj and Sivasakthivelan, 2012; Adeolu and Sunday, 2013).

Pentylenetetrazol (PTZ) is a selective blocker of the GABA-A receptor. It is used as a chemical kindling and has properties leading to dose-dependent sub-convulsions and generalized tonic–clonic seizures (Erbas *et al.,* 2013). Anxiety has been conceptualized as a frequent and serious disorder affecting the world's population, independent of ethnicity, and is considered a cardinal symptom of many psychiatric disorders (Cassano *et al*., 1999). Epilepsy (convulsion) is one of the most common neurological disorders that severely affect the life quality of many people worldwide. Excitatory-inhibitory mechanisms, oxidative stress, and also inflammation systems have been implicated in the pathogenesis of epilepsy (Ahmet *et al.,* 2020).

The extract of Phyllanthus amarus retains multiple pharmacological activities such as anticarcinogenic, antiproliferative, gastroprotective, cardioprotective, antileptospiral, antibacterial, antidiabetic, antiviral, antivenom, anti-inflammatory etc (Mansi and Vaghela, 2019). Therefore, this study assesses the anti-convulsant and anti-anxiolytic properties of tannin extract of Phyllanthus amarus on cerebellum of adult wistar rat following the induction of PTZ. The aim of this study is to investigate the anti-convulsion and anti-anxiolytic propertoes of tannin fractions of phyllantus amarus leaf on the cerebellum of adult wistar rats following pentylenetetrazol administration.

2. Materials and Method

2.1 Purchase and Preparation of *phyllanthus amarus*

About 4500 g of fresh leaves of P. amarus were collected in UZAIRUE, Etsako west LGA, Edo State, Nigeria. It was authenticated at the Forestry Research Institute of Nigeria (FRIN), Ibadan and a voucher specimen (no SH 107623) has been deposited at the Forestry Herbarium Ibadan. The leaves were then blended using a manual blender and were further taken in for fractionation of tannin using column chromatography technique. 9.3g of Tannin was gotten as final fractionate and kept in a refrigerator. To get stock solution for administration, Ig (1000mg) of Tannin fractionate was dissolved in 3% tween 80 solution.

2.2 Purchase and Preparation of PTZ

5g of Pentelenetetrazol (PTZ) was purchased from the Sogladen Pharmaceutical Store Jattu- Uzairue, Etsako-west, Edo State and kept in a refrigerator. Prior to use, 2.4g (2,400mg) of PTZ was immersed in 232.8mls of distilled water to get the stock solution.

2.3 Animal Purchase and management

Wistar rats used for this study were purchased from

the animal house of the Mr Ahmed's Farm, Kogi State. There were kept under standard conditions with good ventilation and a clean environment in standard cages. There were fed with animal growers feed and water throughout and were allowed to acclimatize for 14 days prior to commencement of administration.

2.4 Ethical Approval

Ethical approval (SMCCN/CREC/2024/007) was duely obtained and the study followed the guideline of the ethics committee on animal research of Sancta Maria Catholic College of Nursing Sciences, Uzairue, Edo State

2.5 Research Design

Pilot study for dose response trial was carried out to ascertain the appropriate dose of PTZ and for Tannin using Lorke's method (Enegide *et al*, 2017).

Basal parameters were carried out in line with the outcome measures of this study prior to commencement of administration and administration of Tannin was via oral route while PTZ was administered via intraperitoneal route.

Forty-nine (42) adult wistar rats was used for this study and they were divided into seven (7) groups with seven (6) animals in each (groups 1, 2, 3,4,5,6 and 7). Group 1 was the normal control group, group 2 was given 33mg/kg of PTZ only, group 3 was given 100mg/kg of tannin and 33mg/kg of PTZ, group 4 was given 200mg/kg of tannin and 33mg/kg of PTZ, group 5 was given 400mg/kg of tannin and 33mg/kg of PTZ, group 6 was given 400mg/kg of tannin only while group 7 was given 6.4mg/kg of Carbamazepine (a control drug for convulsion) and 41.2mg/kg of PTZ. Tannin was administered orally to animals in groups 3, 4, 5 and 6 for 20 days. On the 17th day of administration, PTZ administration commenced to the 20th day. At the commencement of administration of PTZ on the 17th day, the thresh-hold for commencement of convulsion was taken with the aid of a stop-watch. This will measure the interval between administrations of PTZ to commencement of convulsion. It was recorded in seconds.

The latency of convulsion was also be taken with the aid of a stopwatch. This will measure the duration of convulsion (from onset to termination) and was also recorded in seconds.

Table 1. *Showing administration duration and doses for tannin and PTZ*

GROUPS	NO OF RATS	DURATION FOR TANNIN	TANNIN DOSAGE (mg/kg)	DURATION OF PTZ ADMINISTRATION	PTZ DOSAGE (mg/kg/bwt)
1 (Normal control)	6	Feed + water	Feed + water	NIL	Feed + water
2(PTZ only)	6	NIL	NIL	4 days	33mg/kg
3(Tannin + PTZ)	6	20 days	100mg/kg	NIL	33mg/kg
4(Tannin + PTZ)	6	20 days	200mg/kg	4 days	33mg/kg
5(Tannin + PTZ)	6	20 days	400mg/kg	4 days	33mg/kg
6(Tannin only)	6	20 days	400mg/kg	4 days	NIL
7Drug + PTZ)	6	20 days (Carbamazepine only)	Nil	4 days	41.2mg/kg

2.6 Sacrifice and Organ Collection

After the 20 days administration period, animals were sacrificed using 0.5mls of ketamine injection as anesthesia and then perfusion was done by injecting Normal saline for three (3) minutes into the heart and then 10% formal saline was used to inject in to the animals for proper fixation. The brain was collected after 5 minutes of perfusion and stored in 10% formal saline.

The cerebellum was isolated from the brain after 24 hours of fixation and processed in the histology laboratory for the following:

A. Hematoxylin and Eosin stain for temporal lobe cyto-architecture
B. Neuronal cell population using Cresyl fast violet stain

Photomicrography was employed using Amscope digital camera (version 3.7) at 200 magnifications.

2.7 Statistical Analysis

Statistical analysis was carried out using IBM SPSS data analysis software version 23. All values that were generated out of this study were expressed as Mean ± Standard error of Mean (SEM), Statistical Error of Mean (SEM).

Statistical difference in mean between group were analyzed using one way ANOVA (Analysis of variance), followed by t-test comparison of all groups.

P –value less than 0.05 was considered as statistically significant.

3. Results

3.1 Threshold Results

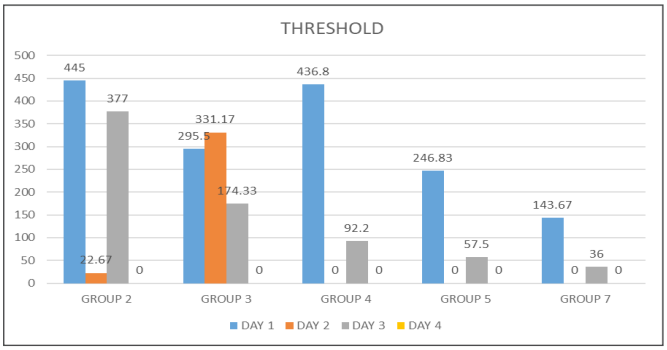


Figure 1. *Showing comparison of thresh-hold response of animals across groups 2, 3, 4, 5 and 7 following pentylenetetrazol induced convulsion. Mean difference is significant at the 0.05 level. p < 0.05 (p=0.020)*

3.2 Latency Response Results

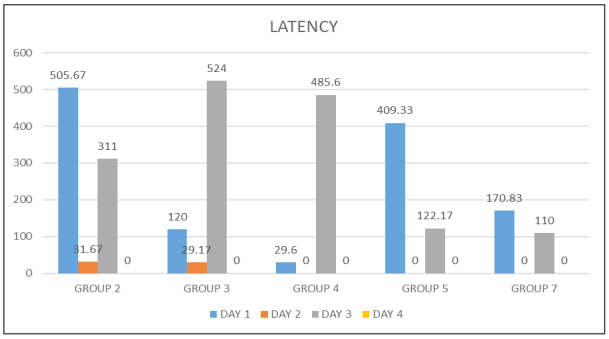


Figure 2. *Showing comparison of latency response of animals across groups 2, 3, 4, 5 and 7 following pentylenetetrazol induced convulsion. Mean difference is significant at the 0.05 level. p = 0.05 (p=0.000)*

Table 2. *One Way Anova*

		Sum of Squares	df	Mean Square	F	Sig.
LATENCY	Between Groups	3946750.958	19	207723.735	3.004	.000
	Within Groups	6431350.900	93	69154.311		
	Total	10378101.858	112			
THRESHOLD	Between Groups	2776288.176	19	146120.430	1.933	.020
	Within Groups	7029550.267	93	75586.562		
	Total	9805838.442	112			

3.3 Result of Weight Comparison across All Groups

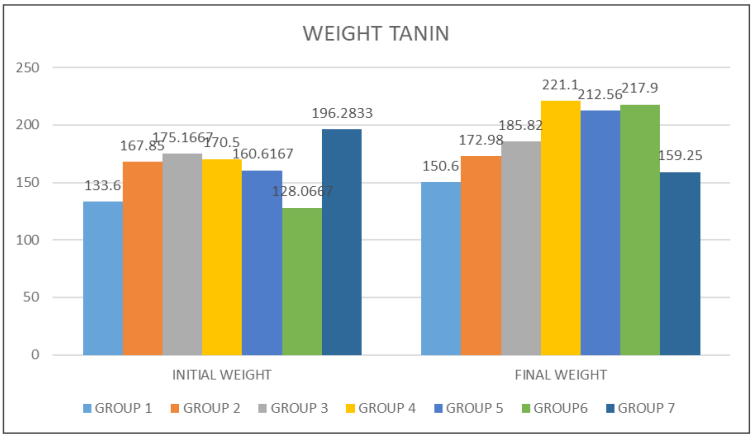


Figure 3. *Showing the mean comparison of weight of animals across all groups. Mean difference is significant at the 0.05 level. p > 0.05 (p=0.237)*

Table 3. *Showing descriptive analytical summary of comparison of weight across all groups. Mean difference is significant at the 0.05 level.*

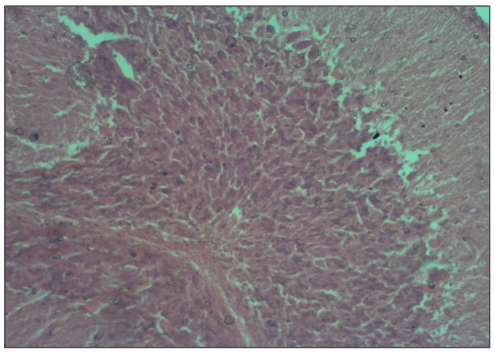
WEIGHT	Sum of square	Df	Mean square	F	Sig.
Between Groups	58086.162	13	4468.166	1.299	.237
Within Groups	216656.641	63	3438.994		
Total	274742.803	76			

Table 4. *Showing mean weight of all groups. $p > 0.05$.*

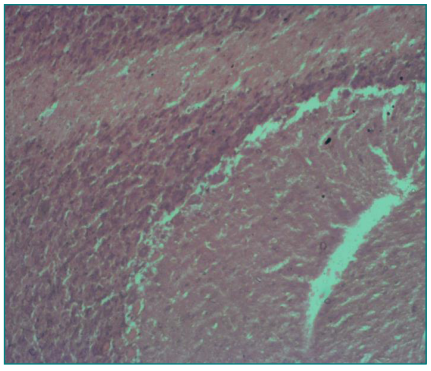
Initial weight	Mean	Std. Deviation	Std. Error	p-value
Group 1	133.6000	3.78153	1.69115	0.340
Group 2	167.8500	17.54010	7.16071	
Group 3	175.1667	18.48120	7.54492	
Group 4	170.5000	85.50967	34.90918	
Group 5	160.6167	79.34684	32.39321	
Group 6	128.0667	66.76246	27.25566	
Group 7	196.2833	87.49079	35.71796	
Final weight				
Group 1	150.6000	3.20936	1.43527	
Group 2	172.9800	18.73478	8.37845	
Group 3	2990.2200	6262.95808	2800.88000	
Group 4	221.1000	24.68390	11.03898	
Group 5	212.5600	9.14237	4.08859	
Group 6	217.9000	27.43110	12.26756	
Group 7	159.2500	123.41711	50.38482	
Total	356.3792	1598.78878	182.19889	

3.5 Result of Histological Studies

Normal Control Group 1

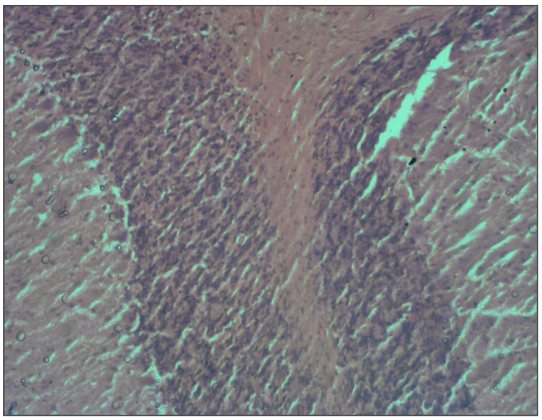


Group 1A. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X250*

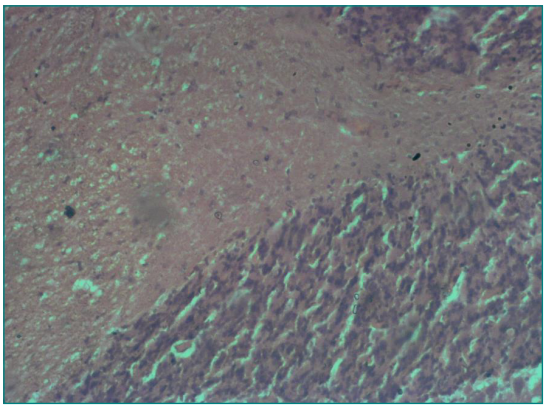


Group 1B. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X250*

Group 2: Pentylenetetrazol Only

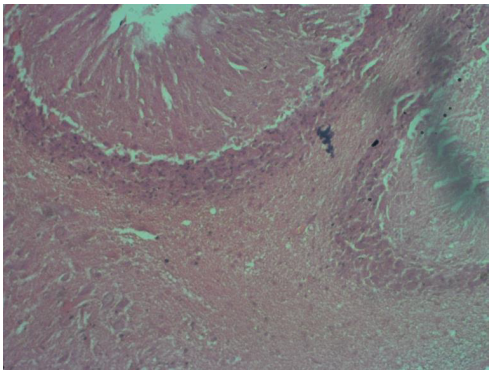


Group 2A. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture shows mild traumatic tissue encephalopathy. H & E. X250*

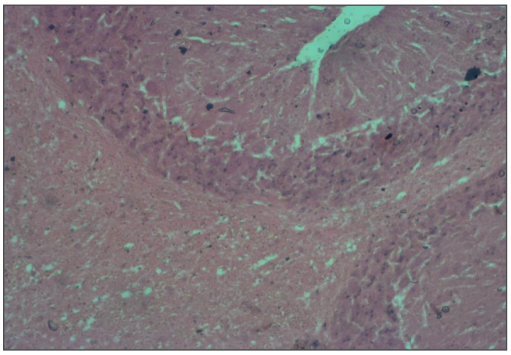


Group 2B. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X25*

Group 3: Experimental Group (Tannin And Pentylenetetrazol Low Dose)

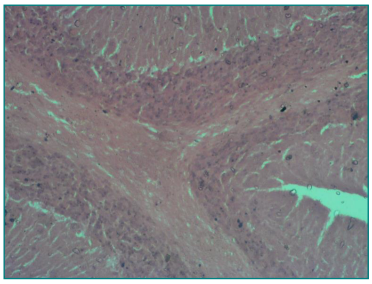


Group 3A. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X250*

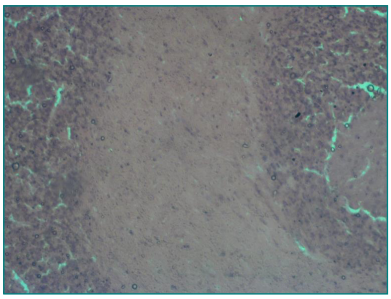


Group 3B. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (m). Cyto-architecture appears normal. H & E. X250*

Group 4: Experimtal Group (Tannin And Pentylenetetrazol Medium Dose)

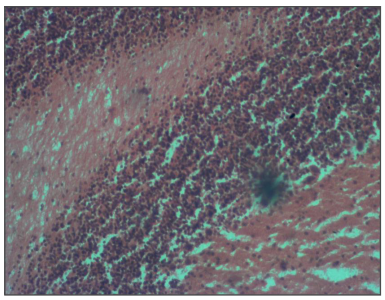


Group 4A. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X250*

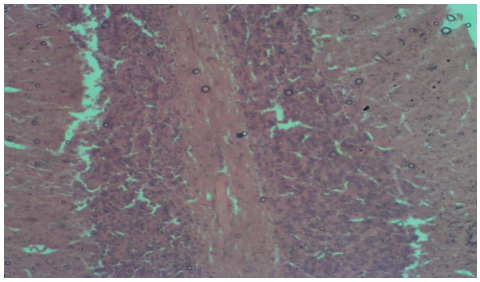


Group 4B. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X250*

Group 5: Experimtal Group (Tannin And Pentylenetetrazol High Dose)

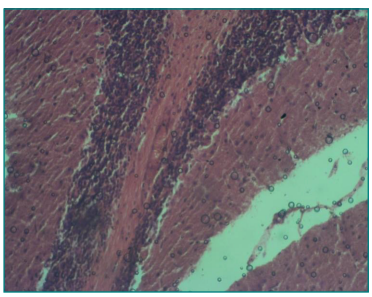


Group 5A. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (m). Cyto-architecture appears normal. H & E. X250*



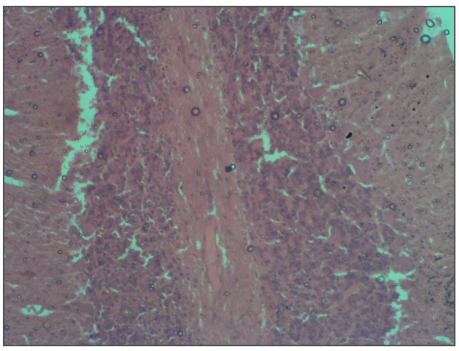
Group 5B. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (m). Cyto-architecture appears normal. H & E. X250*

Group 6: Tannin Only



Group 6. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X250*

Group 7: Standard Drug Group (Carbamazepine And Pentylenetetrazol)



Group 7. *Photomicrograph of the cerebellum showing neuronal cells in the granular layer (g) and molecular layer (M). Cyto-architecture appears normal. H & E. X250.*

4. Discussion

This study was carried out to investigate the Anti-convulsive properties of Tannin fractions of Phyllanthus Amarus leaf on the cerebellum of wistar rats following administration of pentylenetetrazol (PTZ).

The study grouped animals used into seven (7) groups with six (6) animals per group. Group 1 were given standard animal feed and water only, group 2 were given 33mg/kg of PTZ only, group 3 were given 100mg/kg of tannin fractions and 33mg/kg of PTZ, group 4 were given 200mg/kg of tannin fractions and 33mg/kg of PTZ, group 5 were given 400mg/kg of tannin fractions 33mg/kg of PTZ, group 6 were given 400mg/kg of tannin fractions while group 7 were given 6.4ml of carbamezepine drug and 41.2mg/kg of PTZ.

All data generated in the course of this study were analyzed using SPSS V.23 analytical software with 0.05 considered as level of significance. Mean levels of all quantitative specific objectives were gotten.

Thresh-hold is the interval between immediate removal of syringe used to administer PTZ from the intraperitoneal region and the onset of convulsion. Normally, a drug that has the ability to either reduce or stop convulsion will have a shorter thresh-hold time. Only animals in group 2, 3, 4, 5 and 7 received PTZ. Animals in group 1 were the normal control while those in group 6 were the negative control which were given 400mg/kg of Tannin only. Pentylenetetrazol (PTZ) was given for four (4) days following 16 days pre-treatment with Tannin fractions.

From findings gotten from this study, animals in group 2 had higher thresh-hold response compared to other groups (groups 3, 4, 5 and 7) in day one. In day two, animals in group 2 had higher thresh-hold response compared to animals in group 4, 5 and 7. Also, animals in group 3 which were treated with 100mg/kg of Tannin had higher thresh-hold response compared to animals in groups 4, 5 and 7 which were treated with 200mg/kg, 400mg/kg of Tannin and 6.4mg/kg bwt of Carbamazepine respectively.

Also in day two of PTZ administration, animals in group 2 given 33mg/kg bwt of PTZ only had lower PTZ thresh-hold response compared to animals in group 3 pre-treated with 100mg/kg of Tannin.

In day three of PTZ administration, animals in group 2 had higher thresh-hold response than animals in groups 3, 4, 5 pre-treated with Tannin and animals in group 7 pre-treated with 6.4mg/kg bwt of carbamazepine.

In day four of PTZ administration, all animals administered with PTZ (groups 2, 3, 4, 5 and 7) did not show any sign of convulsion and thus, had no thresh-hold response consequently.

Latency is the period from when convulsion starts to when it stops after administration of PTZ.

From figure 1 results show in day one of PTZ administration, animals in group 2 (given PTZ only) showed higher latency response compared to animals in pre-treatment groups (3, 4, 5 and 7). Amongst the animals in the treatment groups, animals in group 5 pre-treated with 400mg/kg of Tannin showed more latency response followed by animals in group 7 pre-treated with 6.4mg/kg of carbamazepine.

In day two of PTZ administration, animals in group 2 (given PTZ only) showed the highest latency response when compared to animals in the pre-treatment groups (3, 4, 5 and 7). Also, amongst the pre-treatment groups(3, 4, 5 and 7), animals in group 3 pre-treated with 100mg/kg of Tannin showed the highest latency response compared to animals in groups 4 and 5 treated with Tannin and group 7 pre-treated with 6.4mg/kg of carbamazepine.

In day three of PTZ administration, animals in group 3 pre-treated with 100mg/kg of Tannin showed the highest latency response compared to animals in groups 2 (given PTZ only), 4 and 5 treated with 200mg/kg and 400mg/kg bwt of Tannin and group 7 pre-treated with 6.4mg/kg bwt of carbamazepine.

In day four of PTZ administration, all animals administered with PTZ (groups 2, 3, 4, 5 and 7) did not show any sign of convulsion and thus, had no thresh-hold response consequently.

All groups of rats treated with the Tannin showed reduced activity and stability after some time of administration of PTZ prior to commencement of convulsion. In a work that checked latency duration of PTZ (80mg/kg) after treatment with Essential oils from eight aromatic plants, it was observed that animals given essential oils from Mentha spicata showed the longest latency (600 ± 31 secs) while animals that received essential oils from Mentha piperita showed no convulsion nor seizure at all and with survival rates (Eleni *et al*, 2013).

In the course of this study, weight of animals used were taken before commencement of administration of Tannin fractions and on day 21 after administration of Tannin fractions and PTZ.

Mean weight of all groups were taken and compared. Table 4.3 showed differences in mean body weight between normal control group and pre-treatment groups and also differences in mean weight between positive control group and pre-treatment groups.

However, observations showed that only animals in groups 7 which received 6.4mg/kg of carbamazepine drug and 41.2mg/kg of PTZ lost weight at the end of administration (fig 4.3). Animals in all other groups reported a normal weight gain. Thus, findings from this study showed that carbamazepine contributed to weight loss of animals used for this study.

Following observations gotten from this findings, animals that were given tannin extracts of Phyllanthus amarus at the doses of 100mg/kg, 200mg/kg and 400mg/kg gained weight. This is in tandem with a work carried out by Karuna *et al.* (2009) which reported that Phyllanthus amarus extract given at a dose of 200mg/kg did not cause any weight loss in animals used for a study on the antioxidant potential of aqueous leaf extract of Phyllanthus amarus in rats. (Karuna et al, 2009). A similar study which explored the protective properties of Phylanthus amarus leaf extracts observed significant increase in final body weight of animals that were pretreated with 200mg/kg and 400mg/kg of Phyllanthus amarus against Mercuric-chloride. (Enogieru and Omoniyi, 2022).

Even though, it has been generally reported that the biochemical constituents of Phyllanthus amarus, does not affect body weight, a work on Effects of Phyllanthus amarus on litter traits in albino rats, has reported that 100mg/kg, 150mg/kg and 200mg/kg of ethanolic extract of phyllanthus amarus reduced the litter size and weight of albino rats.

Histological observations gotten from this study showed that 33mg/kg PTZ caused mild traumatic tissue encephalopathy in neuronal cell in granular and molecular layer of cerebellum (Plate 2). These findings are in line with findings from a related study coined by Yunbo *et al.,* (2018) and Samokhina and Alexander (2018) who found out that pentylenetetrazol induces neuronal damage in the hippocampus.

Photomicrograph of animals in group 3, 4 and 5 which were given 100, 200 and 400mg/kg of tannin extract of *P. amarus* respectively, cyto-architecture were normal and it can be that tannin has curative properties in the histoarchitecture of cerebellum as seen in plate 3,4 and 5 when compared with plate 2. This finding is in line with a related finding coined by Zhang *et al.,* (2020) who reported that administration of phyllanthus amarus at 100 and 200 mg/kg ameliorated histological aberrations induced by PTZ in the brain of a kindled rat.

Also, Enogieru and Omoruyi (2022) from their studies found out that treatment with Phyllanthus amarus demonstrated potent protective activity against the deleterious effects induced by mercury.

5. Conclusion

These findings show that treatment with Phyllanthus amarus for 20 days were comparable to carbamazepine in prevention of convulsion, memory impairment and alleviation of neuroinflammation responses induced by PTZ. Thus, tannin extract from these leaves may be useful in the management of convulsion and other related disorders

Conflict of Interest

The authors declare no conflict of interest.

6. References

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