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Research Article

Anticonvulsant and toxicity effects of ethanolic extract of *Thevetia Peruviana (Pers.)* leaves

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Epilepsy is a neurologic condition due to disordered firing of brain neurons characterised by seizures. Most currently available antiepileptic drugs are synthetic and do not offer a complete cure yet with devastating side effects. Studies have shown that extracts from certain plants can produce anticonvulsant effects and may, therefore be useful against epileptic seizures. To investigate anticonvulsant effect of ethanolic extract of the leaves of *Thevetia peruviana* on chemically induced seizures in Wister rats. Leaves of *T. peruviana* were pulverised and extracted with ethanol. Graded doses of the ethanolic extract were used to test for the anticonvulsant effect of the extract using pentylenetetrazole model of seizures in rats. Acute toxicity testing and phytochemical analysis were done using Lorke's method. Graded doses of *T. peruviana* leaf extract significantly delayed onset of seizures. They protected animals from death due to pentylenetetrazole-induced tonic seizures. There was no death up to 3000mg/kg. The extract was found to be rich in essential oils, flavonoids, alkaloid, phenols, proteins and resins. The ethanolic extract of the leaves of *T. peruviana* contains compounds with anticonvulsant effects since it protected the animals from death and delayed the onset of seizures produced by pentylenetetrazole and that is relatively safe.

Keywords: *Thevetia peruviana*, Antiepileptic activity, pentylenetetrazole, Seizures, rats.

INTRODUCTION

Epilepsy is a neurological disorder charaterised by seizures or convulsions. Seizures refer to transient alterations of behavior due to disordered, synchronous and rhythmic firing of a population of brain neurons (James OM, 2001). Seizures also predispose the epileptics to risks like falling on sharp objects or fire, which result in serious and sometimes fatal accidents. The resulting deformities make them unfit for employment and sometimes lead to discrimination during recruitment. Consequently they are stigmatised and have a lower quality of life than people with other chronic illnesses (Scott RA et al., 2001).

Epilepsy affects approximately 50 million people worldwide with about 12 million in subsaharan Africa (Fisher R et al., 2005) and up to 5% of the world population develops epilepsy in their lifetime. About 90% of people with epilepsy (PWE) live in developing countries where there is limited access to health care facilities and this tends to worsen their plight since such patients do not receive adequate medical treatment (Winkler et al.,2010).

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Pharmacological management of seizures involves use of drugs called anticonvulsants or anti epileptic drugs (AEDs). The current regiment of antiepileptic drugs is associated with a number of dose-related side effects, acute and chronic toxicity, as well as teratogenic effects. An estimated 30% of the patients treated with these drugs are reported to continue to have seizures inspite of therapy (Smith and Bleck, 1991, Mattson, 1995, Samren EB, et al, 1997).

This, therefore, calls for development of better drugs in terms of effectiveness and safety profile. Compounds derived from natural products can provide one of the possible sources.
Several plants used for the treatment of epilepsy in different systems of traditional medicine have also been reported to have shown activity when tested in modern bioassays for the detection of anticonvulsant activity (Raza et al., 1999). Many such plants are yet to be scientifically investigated. Among the plants reported as being used by traditional medicine practitioners in the management of seizures is *Thevetia peruviana* (Pers.). *T. peruviana* is a tree belonging to the family Apocynaceae. The plant is native and common in America, from Mexico to Argentina, France and Africa (Mazza G, 2003). In traditional system of medicine, the plant is used in sorcery. Earlier studies revealed that the extract from the plant possesses HIV-1 reverse transcriptase and integrase inhibitory effects, antipyretic, antifungal and antimicrobial effects. In Kigezi, in south western Uganda the extract of the leaves of this plant are used as remedies in the management and/or control of convulsions and epilepsy. They mix it with fresh cow urine and administer the mixture by oral route (Buhiri, Personal communication). Prior to this study, no scientific study to validate these claims had been undertaken. This, therefore, necessitated a scientific study to validate the ethno botanical claims for its use and to undertake toxicity studies to determine the safety profile. The aim of this study was, therefore, to evaluate the anticonvulsant potential of the ethanol extract of the leaves of *T. peruviana in* experimental animal models. This was with a view to providing a pharmacological justification (or otherwise) for the ethno medical use of the plant in the management of convulsions and epilepsy.

MATERIALS AND METHODS

Obtaining Crude extract

Collection, drying and pulverising

The leaves of *Thevetia peruviana* were collected in the rainy season between 8am and 9am**,** from Kabale District in South-Western Uganda. They were packed in a plastic bag and transported immediately to the laboratory. A sample of the plant (fresh and dry) was taken to Mbarara University of Science and Technology Herbarium for identification by a qualified Botanical Taxonomist Dr. Eunice Apio Olet and voucher number Ninsiima 2011 was given. They were air dried under shade for approximately ten days and then ground using a motor and pestle. The fine powder was weighed (980g) and poured in a dry clean plastic bag in a cool dry place in one of the laboratory cabins.The bag was closed on top and kept in a plastic container in the laboratory cabin not to lose any powder or to contaminate it.

Extractions

The powder, 5 g was weighed in a thimble and it was placed in a Soxhlet apparatus. Ethanol was taken in the round bottom flask and hot extraction was carried out. The temperature was kept at eighty degrees until the color of the powder changed from green to brown and no liquid was seen flowing into the flask. The ethanol was recovered by collection into a conical flask and later put in its container for future use. The extract in the round bottom flask was concentrated by distillation and the dry extract was weighed to get the ethanol soluble fraction (Trease and Evans, 2005).

Separation of crude extract

The ethanol extract was evaporated using a Rotary evaporator maintained at 40 degrees Celsius to concentrate it. The relatively concentrated extract was further evaporated to dryness, weighed to determine the yield and and then stored in refrigerator at 4 degrees Celsius for subsequent use.

Determination of anticonvulant activity of crude ethanolic leaf extract of *Thevetia peruvian*

Animals used

Male Albino Wistar rats (167.35g) (*Rattus norvegicus*), were obtained from the animal facility at Kampala International University in the Pharmacology Department. They were fed on standard NUVITA animal feeds (Nuvita Ind. Ltd, Kampala) and provided with tap water *ad libitum*. The animals were maintained at room temperature throughout the study period, 12 hours alternative day and night, and ambient humidity. They were handled according to the NIH guidelines for care and use of laboratory animals in teaching and research (Guide for the care and use of laboratory animals 2011).

Effect of extract on Pentylenetetrazole (PTZ)-induced convulsion in rats

Before administration, the extract was reconstituted in dimethylsulfoxide to make solutions of various concentrations used in the test. Five groups, each of six (average weight 167.35g) male Wistar rats (*Rattus norvegicus*) were used to test for the effect of the extract on PTZ-induced seizures. They were treated as follows: Group I (control): dimethylsulfuroxide (0.5 ml p.o.); Group II: phenobarbital (phenobarbitone) (30

Table 1. Effect of ethanolic leaf extract of *T. peruviana* and phenobarbital (phenobarbitone) on PTZ- induced seizures in rats

Group	Dose mg/kg	Time before onset of convulsion (seconds)
I	Vehicle (DMSO)	0 ± 6
II	500	19.8 ± 2.5
III	750	45.4 ± 0.8
IV	1000	40.8 ± 0.6
V	Phenobarbital (phenobarbitone) (30mg/kg)	28.7 ± 0.3

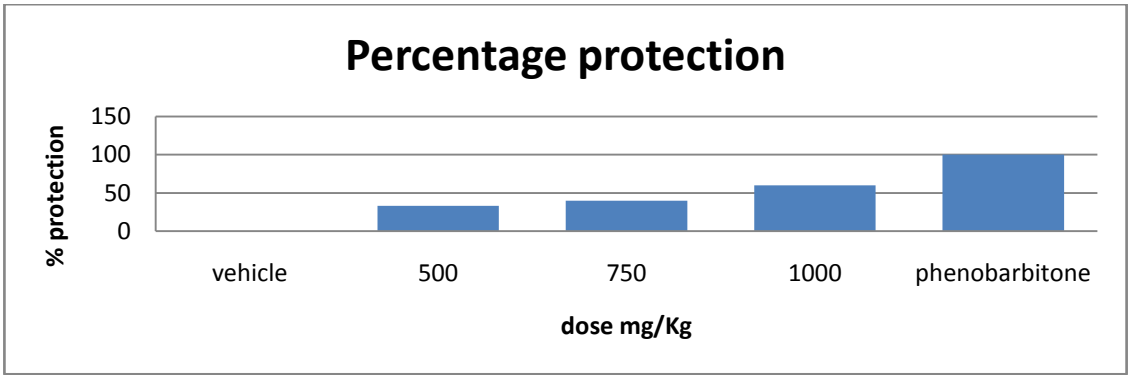

Figure 1. Percentage Protective effect of *Thevetia peruviana* crude ethanol extract and phenobarbital (phenobarbitone) (30mg/kg) against PTZ induced seizures in rats

mg/kg i.p.) and for Groups III-VI: graded doses of ethanolic extract (500, 750, and 1000 mg/kg p.o.) were administered. After a pretreatment time of 60 minutes, PTZ (40 mg/kg i.p.) was administered to the six groups of animals. The onset of convulsion, number of animals that convulsed and number of animals that were protected were recorded (Kliouéva et al., 2001).

Acute toxicity effects of Thevetia peruviana in Wistar rats

Extract dosage calculation

The dosage of the extract to be administered to the experimental animals (rats) was chosen arbitrarily but the exact dose(s) that were given to each of the animals was calculated using the standard formula:

$$\text{Injectable volume} = \frac{\text{dose (mg/kg) x animal weight (grams)}}{\text{Concentration (mg/ml) x 1000.}}$$

Method of acute toxicity test used

Two methods are commonly used; Lorke's method and the Classical method. The Lorke's method (1983) was used for this experiment because it uses minimal animals and provides reliable results. The method proceeded in two phases:

Phase 1: Three groups of three rats per group each were given increasing dose levels of the extract orally. The treated rats were observed for four (4) hours after administration of the extract for signs of toxicity and after 24 hours they were scored for mortality and general behavior.
Phase 2: After 24 hours, 3 groups of each containing one rat were given geometrically increasing doses (1000 mg/kg, 1500 mg/kg, 2000 mg/kg and 2500 mg/kg) based on the findings of phase 1 again using the oral route. The observations were done as in phase 1 (Lorke D, 1983).

Preliminary Phytochemical Analysis

The phytochemical analysis was carried out to determine the classes of phytochemical compounds present in the crude extracts. Glycosides (carbohydrates), reducing sugars, proteins, amino acid (arginine in particular), alkaloids, steroids (sterols), saponins, tannins, flavonoids, terpenoids, phenols and essential oils were tested for.

Table 2. Signs observed during acute oxicity testing

Effect	Observed (+)/Not observed (-)
Hypersalivation	+
Vomiting	+
Diarrhoea	+
Diuresis	+
Reduced activity	+
Arching of the back	+
Curdling in one corner	+
Piroerection	+
Flaccid paralysis	+
Death	-

Table 3. Results of Phytochemical analysis

S/ No.	Test For	Tests	Result
1.	Glycosides	Molisch's test	+ve
		Barfoed's test	+ve
2	Alkaloids	Meyer's reagent test	+ve
		Picric acid test	+ve
3	Saponins	Honey-comb test	-ve
4	Resins		+ve
5	Tanins		-ve
6	Phenols		+ve
7	Essential Oils	Sudan III Test	+ve
8	Proteins	Ninhydrin test	+ve
		Millon's test	+ve
9	Amino Acids	Ninhydrin test	+ve
10	Flavonoids	Ferric chloride test	+ve
11	Terpenoids		-ve

Data analysis and presentation

Data on the anticonvulsant studies and toxicity findings are presented in tables for easy interpretation. Mean and standard error of mean were calculated. Quantitative data were analyzed using the ANOVA to compare the anticonvulsant effects of the standard drug and the crude extract and the F- tables were used to determine the correlations. Results of $p< 0.05$ were taken to be significant.

RESULTS

After extraction and drying, a greenish semisolid substance was achieved. The extraction yield was 14% of the powder.

ANOVA was used to compute the significance difference between activity of the extract, the negative and positive control groups. F-critical value (3.89) was less than the obtained F-value (28.94) giving a p-value < 0.05.

Pentylenetetrazole (40 mg/kg i.p.) induced generalized tonic-clonic seizures in all the groups. The convulsions occurred immediately in the negative control group (vehicle). *Thevetia peruviana* ethanolic leaf extract at doses of 500 mg/kg, 750 mg/kg and 1000mg/kg significantly ($p < 0.05$) delayed the onset of Pentylenetetrazole induced seizures in rats.

The crude ethanolic extract of *Thevetia peruviana* at doses of 500, 750 and 1000 mg/kg provided protection against death due to PTZ induced seizures by 33%, 40%, and 60% respectively.

While phenobarbital (phenobarbitone) (30mg/kg) had 100% protection against death due to PTZ induced seizures but even at more than 30 concentration, phenobarbital still had superior efficacy than the extraction.

The following signs of acute toxicity were noted in the first four hours of extract administration orally: diuresis, diarrhea, hypersalivation, vomiting, piloerection and sedation, shown by reduced activity at a dose of 500 mg/kg. At the dose of 1500 mg/kg, there was flaccid paralysis evidenced by stretching of the hind and fore limbs, signs of hypothermia (curdling). These signs appeared within 10-20 minutes of extract administration and lasted for only three hours on average. There was no death recorded within 24 hours of extract administration at a maximum dose of 3000 mg/kg orally. Another study using the seeds of the same plant

showed death after twenty four hours at a dose of 447mg/kg (Elena et al., 2002).

The phytochemical screening tests on the ethanolic leaf extract revealed the presence of essential oils, flavonoids, alkaloid, phenols, proteins and resins. Results were negative for tanins, saponins and terpenoids. Alkaloids and flavonoids have already been shown to possess anticonvulsant effects.

DISCUSSION

The ethanolic leaf extract at doses of 500, 750 and 1000 mg/kg significantly ($p < 0.05$) delayed onset of PTZ-induced seizures. There was a dose dependent (500, 750, and 1000 mg/kg) protection against mortality from PTZ-induced seizures of 33, 40 and 60%, respectively compared to 100% protection in the standard drug, phenobarbital (phenobarbitone) as shown in table one. This is probably because phenobarbital (phenobarbitone) is in a more purified form compared to the crude extract of *T.peruviana* leaves. Generally, compounds with anticonvulsant activity in the petit mal epilepsy are effective in pentelenetetrazole-induced seizure model (Loscher and schmidt 1988). According to De Sarro *et al*, (1999). pentelenetetrazole may be exerting its convulsive effect by inhibiting the activity of gamma amino butyric acid (GABA) at $GABA_A$ receptors (De Sarro et al,1999). The major inhibitory neurotransmitter which is implicated in epilepsy.

The enhancement and inhibition of the neurotransmission of GABA would attenuate and enhance convulsion respectively (Meldrum 1981, Gale, 1992, Westmoreland et al., 1994). Phenobarbital (phenobarbitone) and diazepam have been shown to exert their antiepileptic effects by enhancing the GABA-mediated inhibition in the brain (Porter and Meldrum 2001). Since *Thevetia peruvian* delayed the onset of PTZ- induced seizures and provided protection against mortality, it is probable that its action is through enhancing GABA-ergic mechanisms to exert its anticonvulsive effects. However, it not possible to attribute the observed antiepileptic action to a single phytochemical compound because the available data are insufficient.

Furthermore, it is reported that compounds that are generally effective in PTZ induced seizure model (Lorcher et al., 1991) are capable of providing anticonvulsant activity in human generalized myoclonic and absence seizures (petit mal epilepsy). The MES test, on other hand is considered to be a good predictor of likely therapeutic efficacy against generalized tonic-clonic seizures. Other chemoconvulsant models for primary generalized seizures include that involving use of bicuculine ($GABA_A$ receptor competitive antagonist), strychnine (glycine receptor antagonist) and aminophylline (adenosine receptor antagonist) (Duraisami et al., 2009)

PTZ induced seisures in all the study animals. Phenorbarbital at 30mg/kg was able to provide 100% protection against mortality while the crude at 1000mg/kg (more than 33 times the dose for the barbiturate) provided 60% protection as shown in figure one. These results demonstrate that the ethanolic extract obtained from *Thevetia peruviana* leaves possesses reasonable efficacy against PTZ-induced convulsions but much more less than that of phenobarbital. But considering the fact the extract was in a crude form, being compared with the efficacy of pure phenobarbital, this is still reasonable efficacy.

The Phytochemical screening in this study showed that the ethanolic crude extract of *Thevetia peruviana* leaves (table three) contains alkaloids, terpenoids, and one or more of other phytoconstituents such as general glycosides, tannins, polyphenols, carotenois, saponins and flavonoids. Similar phytochemical compounds have been found to be present in other parts of the same plant like stem, seeds and flowers (Trinity 2011, Hammuel 2011, Kumar et al., 2012).
These secondary metabolites are known to possess various pharmacological effects and may be responsible for the observed anti convulsant effect of *Thevetia peruviana*. For example, alkaloids have been shown (herbs200) to actively obstruct the nicotinic acetylcholine receptor spots at the neuromuscular junctions enabling muscles to unwind as well as protect them from paralysis (Herbs 2001). Thus they are effective in relaxing as well as preventing the paralysis of the muscles in the respiratory tract as well as the heart. Significantly, D-tubocurarine, an alkaloid has been extensively used to relax the muscles of the heart during open heart surgeries (Kumar et al.,2012). In addition, this variety of alkaloid has also been used in curing spastic or convulsive paralysis of tetanus toxin that causes unmanageable retrenchment of muscle all over the body (Herbs 2001). Alkaloids have also been shown to possess anticonvulsant activity by delaying the onset of chemically-induced convulsions hence their possible use in epilepsy (Lucindo et al., 2011) Flavonoids have been reported to have numerous physiological activities, for example, soy isoflavones are thought to protect against different cancers, cardiovascular disease, bone loss, and signaling pathways, including but not limited, cell proliferation and differentiation, cell cycle regulation, apoptosis, angiogenesis, cell adhesion and migration, metastasis, and activity of different enzymes to (Valachovicova et al., 2004). Flavonoids have also been shown to possess anticonvulsant activity against chemically- and maximum electric shock (MES) -induced convulsions (Johnston and Beart 2004, Kasture et al., 2002). Triterpenoidalsaponins have also been reported to possess anticonvulsant activity in some experimental seizure models such as MES and PTZ (Kasture et al., 2002, Brester D 1986).

Since the ethanolic extract of T.peruviana was found to contain alkaloids, flavonoids and saponins, one or more of these could be reponsible from the observed

anticonvulsant activity of the crude exrract. It is, however, not possible at this stage to assign the activity to a particular phytochemical group or compound without use of isolated compounds. Also, we cannot rule out the possibility of synergistic effect of various phytochemicals. On administration of the crude ethanaolic leaf extract to the rats orally, the following signs were observed; diuresis, diarrhea, hypersalivation, vomiting, piloerection and sedation, flaccid paralysis, and signs of hypothermia as shown in table two. These are signs of enhanced parasympathetic stimulation. There was no death recorded after twenty four hours at a maximum dose of 3000 mg/kg. The observed signs of toxicity can be attributed to stimulation of cholinegic receptors in the different body organs. The cholinergic effects can be attributed to the alkaloids present in the crude extract. Alkaloids have been shown to possess similar effects in human subjects in cases of mushroom poisoning where they can even result into death31 . The diarrhoea might be due to increased tone, amplitude of contractions, peristaltic activity of the stomach and intestines or enhanced secretion of the gastrointestinal tract. This may be accompanied by belching, nausea, vomiting, intestinal cramps and increased frequency of defeacation. The diuresis could be due to the increased ureteral peristalsis, contraction of the detrusor muscle of the urinary bladder, increased voluntary voiding pressure and the decreased capacity of the bladder. The hypersalivation is due to stimulation of all secretory glands. Most of these effects can be linked to increased cholinergic activity at muscarinic receptors. The observed paralysis could be attributed to overstimulation of nicotinic acetylcholine receptors at neuromuscular junctions while the sedation may be linked to central nervous system (CNS) activity. This extract, therefore may be safe in lower doses but with mild shortlived side effects. Similar signs of acute toxicity have been recorded in rodents 15 using extract from seeds. They also report deaths from convulsions which were recorded after twenty four hours at a median lethal dose of 447 mg/kg (Elena et al., 2002; Loscher 1988).This report shows that the seeds are likely to contain convulsant chemicals and are more toxic, which further suggests that leaves should be the preferred part for use in treatment of convulsions using *T. peruviana*. Chemical and pharmacological studies (Loscher& Schmidt 1988) have also demonstrated that the whole plant, particularly the seeds, contains potentially harmful cardiac glycosides (thevetins A and B, thevetoxin, nerifolin, perevoside and ruvoside) (Elena et al.,2002). Ingestion of the seeds produces a clinical picture very similar to that of digoxin poisoning: vomiting, dizziness, ECG changes, bradycardia, and atrio-ventricular (AV) block. Less common signs and symptoms include diarrhoea, abdominal pain, ectopic beats and palpitations (Elena et al.,2002). In different parts of the world human fatal poisoning with Thevetiaperuviana has been recorded (Brester 1986). Several researchers showed that raw seed cake of Thevetiaperuviana is toxic and lethal and therefore non palatable, even after processing by defatting and autoclaving at 120 degrees celcious33,34,35. (Begum et al.,1993, Space et al., 2003, Taiwo et al., 2004).

CONCLUSIONS

The results of the present study demonstrate that the ethanolic extract obtained from *Thevetia peruviana* leaves possess reasonable efficacy against PTZ-induced convulsions in rats, with mild acute toxicity effects at low doses. Such pharmacological effects tend to valdidate and justify, at least in part, the popular traditional use of this plant to treat convulsions. Considering the limited scope of the work done, however, the results might not exactly guarantee safe use of the extract in human beings, since there are some physiologic differences betweem humans and rats.

The Phytochemical screening in this study showed that the ethanolic crude extract of *Thevetia peruviana* leaves contains alkaloids, flavonoids and some saponins which have been demonstrated to have anticonvulsant activity. The observed activity may be attributed to one of these phytochemicals although it is not possible to pinpoint the exact chemical (s) that is/are responsible for the observed anticonvulsant effect.

The study showed that the ethanolic extract of *T. Peruviana* leaves has mild cholinergic effects that last for a short period of time with no death in twenty four hours at a maximum dose of 3000 mg/kg. This shows that the extract has a relatively safe profile in as far as acute toxicity is concerned. However, this cannot be satisfactory without chronic toxicity tests to rule out long term effects.

Author's contributions

Ninsiima Herbert Izo designed the study and data correction

All authors were involved in analysis and manuscript writing

Competing Interests

We declare no competing interests exist

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