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Anticonvulsant Activity of *Tapinanthus dodoneifolius* (DC.) Danser in Chicks and Mice: A Potential Source of Novel Anticonvulsant Agent

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Abstract

Background and Aim: *Tapinanthus dodoneifolius* is a mistletoe growing on numerous host plants. It's a popular plant among traditional medicine practitioners in Nigeria and is claimed to have anticonvulsant properties. The purpose of this research is to provide scientific validation for the traditional use of *Tapinanthus dodoneifolius* as an anticonvulsant herb.

Experimental Method: The leaves of the plant were collected from the wild, air-dried, size-reduced and extracted using methanol (70%$^{w}/_{v}$). Acute toxic effect of *T. dodoneifolius* in mice and chicks was evaluated using OECD 425 guideline and the anticonvulsant activity was assessed using various seizure tests.

Results: Methanol extract of *T. dodoneifolius* had LD_{50} value >5000 mg/kg in both chicks and mice. Higher doses of the extract significantly ($p<0.05$) shortened duration of tonic-hind limb extension (360.0 ± 24.7) compared to the negative control (394.9 ± 42.8). Extract at 1500 mg/kg significantly ($p<0.05$) delayed onset of pentylenetetrazole-induced clonic spasm (5.61± 0.94) compared to the negative control group (3.52 ± 0.14). Higher doses of the extract also significantly ($p<0.05$) protected mice against picrotoxin, bicuculline, and 4-aminopyridine-induced seizure.

Conclusion:

These findings justify the use of *Tapinanthus dodoneifolius* as an anticonvulsant herb and may serve as a valuable source of novel anticonvulsant agents.

Introduction

Epilepsy, a chronic neurological condition characterized by abnormal electrical discharges in CNS neurons affects about 70 million people worldwide (WHO, 2019). The treatment of epilepsy is largely based on the use of conventional anticonvulsant agents, vagus nerve stimulation and diet (Bordey, 2021). Treatment of epilepsy in low- and middle-income countries is however, mainly achieved with traditional medicine. This preference for traditional herbal medicine by indigenous people may not be unconnected to certain cultural and psychological beliefs. For instance, in Africa, the majority of people still believe that epilepsy is caused by evil spirits, and hence, cannot be effectively treated with modern medicine (Mugumbate and Zimba, 2018). Other reasons for this preference and non-adherence to orthodox medication include the high frequency and occurrence of side-effects associated with the former (Elsayed *et al.*, 2019), polypharmacy and therapeutic failure (Ejeliogu and Courage, 2020; Ahmed *et al.*, 2019; Egenasi *et al.*, 2015).

Mistletoes in the Loranthaceae family, including *T. dodoneifolius* (DC) and other species are widely distributed in Nigeria and other parts of Africa. The plant is found on many host trees such as *Mangifera indica, Phyllanthus niruri, Parkia biglobosa, Ziziphus spina-christi* and *Azadirachta indica* trees (Deeni and Sadiq, 2003). Traditionally, the plant is claimed to be beneficial in the management of several medical conditions including cancer (Deeni and Sadiq, 2003) dysentery, gastralgia and diarrhea (Baso and Mudi, 2018) in Northern Nigeria; respiratory and cardiovascular conditions in Burkina Faso (Boly *et al.*, 2016); and epilepsy in almost every continent, prepared as infusion or macerated (Adesina *et al.*, 2013).

phytochemicals constituents and ultimately the pharmacological activities of mistletoes may be influenced by or dependent on their host plant (Moghadamtousi *et al*., 2013). As such, even though Garba and colleagues (2015) reported the presence of anthraquinone in, and evaluated the anticonvulsant activity of *Tapinanthus dodoneifolius* growing on *Azadirachta indica* tree, in pentylenetetrazole (PTZ)-induced seizure. This work will nonetheless assess the anticonvulsant potential of *T. dodoneifolius* growing on *Parkia biglobosa* tree using PTZ-induced seizure and other seizure models. The phytochemical screening of the extract revealed the presence of flavonoids, tannins, alkaloids, and steroid/triterpenoids but not anthraquinone. This finding is not included in this article since it has been published in a separate article. See Bello *et al.*, 2021.

Materials and Methods:

Equipment and Chemicals:

Ugobasil electroshock machine, pentylenetetrazole (*Sigma Aldrich, UK*), Phenytoin sodium (*Pfizer Global Pharmaceuticals, USA*), Phenobarbitone sodium (*Sterop laboratories, Belgium*), diazepam (*Juhel Pharmaceuticals, Nigeria*), 4-aminopyridine, strychnine, carbamazepine (*Novartis, Switzerland*), bicuculline (*Adooq bioscience, USA*) and picrotoxin (*Adooq bioscience, USA*).

2.1 Animals:

Day-old chicks and P70 mice weighing between 19 – 23g were obtained from the Animal house facility of the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria. Ethical approval for the use of laboratory animals was obtained from the Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC) and an approval number of ABUCAUC/2020/10 was given. The animals were kept inside polypropylene cages and maintained under normal environmental conditions of ventilation, hygiene, fed with laboratory rodent pellet and water *ad libitum*. The experimental protocols adopted in this study were in accordance with NIH guideline 2005

2.2. Plant Description:

2.2.1. Plant Collection and Identification:

The whole plant was collected together with parts of the host plant from a secondary forest area (Latitude: 11° 06' 60.00"N and Longitude: 7° 43' 59.99" E) of Sabon-Gari Local Government, Kaduna State in March, 2019 and was taken to the Department of Botany, Faculty of Life Sciences, Ahmadu Bello University, Zaria for identification. A voucher specimen number of 0350 was assigned to the plant and 02846 for the host plant by comparing with an existing herbarium specimen. The plant name has been checked and confirmed on the website, http://www.theplantlist.org/tpl1.1/record/kew-2441938 using the search term 'Tapinanthus dodoneifolius'.

2.2.2. Plant Preparation and Extraction:

The whole plant was air-dried for 2 weeks to a constant weight of 1000g. The dried plant was size-reduced and subjected to cold maceration using 70% methanol. The extract was concentrated to dryness and the resultant weight was noted to enable the calculation of percentage yield.

2.3. Acute Toxicity Study:

The oral acute toxic effect of the extract was determined using the OECD 425 guideline. 5000mg/kg limit dose of the extract was administered to a mouse and observed for sign of toxicity and death within a 24 hours period. Subsequently, two more mice were dosed with the same 5000mg/kg of the extract and were observed for another 24 hours for death and other signs of toxicity. The same procedure was adopted to determine the LD_{50} in chicks.

2.4. Maximum Electroshock-induced Seizure:

The protocol described by Swinyard and Kupferbag (1985) was adopted. Thirty-five (35) day-old chicks weighing between 29 and 33g were used for this experiment. There were kept in the experimental laboratory several hours prior to the commencement of the study to enable acclimatization. The chicks were divided into 5 groups of 7 chicks each. Chicks in group I received distilled water (10ml/kg, *p.o*); group II chicks received phenytoin (20mg/kg. *i.p*); group III, IV and V chicks received 1500mg/kg, 750mg/kg and 375mg/kg of the extract respectively via oral route. The electroshock machine was set and maintained at the following parameters- current (80mA), pulse width (0.6ms), frequency pulse (150/sec) and shock duration (0.8sec). All chicks were pretreated appropriately and 60 minutes after pretreatment, electric shock was administered to the chicks via cornea electrode. Tonic hindlimb extension (THLE) was considered as seizure and lack of it was considered quantal protection. The time taken for chicks display THLE was noted and recorded

2.5. Chemically induced Seizures:

In each of the chemically induced seizure models, 25 - 30 male mice were divided into five groups of 5-6 mice each. Mice in group I received Distilled water (10ml/kg, *p.o*), those in group II received standard anticonvulsant agents, whereas mice in groups III, IV and V received graded oral doses of the methanol extract of *T. dodoneifolius*. 30 minutes after pretreatment with standard anticonvulsants (and one hour after pretreatment with graded doses of the extract), each mouse in all the five (5) groups was administered the appropriate convulsant agent. These mice were subsequently observed for onset of convulsive behavior for 30 minutes each. The time taken for the commencement of seizure, the duration of seizure, level of protection, and mortality were noted and recorded. Animals that did not convulse within the 30 minutes observation period were considered protected.
The standard drug and convulsant agent for each of the models is shown as follows:

2.5.1. Pentylenetetrazole (PTZ) model: Standard drug is Phenobarbitone (40mg/kg; *i.p*), convulsant agent is PTZ (90mg/kg; *SC*). Swinyard *et al.*, 1989

2.5.2. Bicuculline-induced Seizure: Standard drug is diazepam (5mg/kg, *i.p*), convulsant agent is bicuculline (1.2mg/kg; *SC*).

2.5.3. Picrotoxin-induced Seizure: Standard drug is diazepam (5mg/kg, *i.p*), convulsant agent is picrotoxin (6mg/kg; *i.p*). Paul and Subramanian, 2002.

2.8.3. 4-Aminopyridine (4-AP)-induced Seizure: Standard drug is Carbamazepine (20mg/kg; *i.p*), convulsant agent is 4-AP (15mg/kg; *SC*). Yamaguchi and Ragawski, 1992.

2.8.4. Strychnine-induced Seizure: Standard drug is Diazepam (5mg/kg; *i.p*), convulsant agent is strychnine (1.6mg/kg; *SC*). Porter *et al.*, 1984.

The choice of standard drugs was influenced by the relationship between the mechanism of action of these drugs and the predictive validity of the various seizure tests as reported by Holmes and Zhao (2008).

2.9. Statistical Analysis:

The data obtained for each seizure test were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett post-hoc test in the SPSS version 23 software. *P*-value ≤ 0.05 was considered statistically significant.

Results:

Percentage yield of the extract was calculated to be 20.1% and the median lethal dose (LD_{50}) was greater than 5000 mg/kg in both mice and chicks with no record of death or signs of toxicity.

In the MEST model of seizure, the extract at doses of 1500 and 750mg/kg significantly ($p < 0.05$) hastened recovery from tonic hind-limb extension as shown in figure 1.0. In the PTZ-induced seizure model, only the highest dose of the extract significantly ($p < 0.05$) delayed seizure onset (Fig. 2.0) and only doses of 750 mg/kg and 1500 mg/kg protected the mice against PTZ-induced mortality as shown in table 1.0.

In the bicuculline seizure test, onset (with the exception of extract at 750 mg/kg) and duration of seizure were comparable ($p>0.05$) in all treatment groups (Table 2.0). The extract caused a marked decrease ($p<0.05$) in seizure threshold at 750mg/kg. But at 1500 mg/kg, conferred protection against seizure in few of the mice (Table 2.0). However, in the picrotoxin-induced seizure test, the extract protected against seizure in mice that received 750 and 1500mg/kg doses as shown in Table 3.0.

The extract significantly protected against 4-Aminopyridine-induced seizure in majority of the mice (Table 4.0). Lastly, the extract was unable to protect mice against strychnine-induced clonic spasm and death as shown in figure 3.0.

Treatments	Mean Seizure Onset (Minutes)	Quantal Protection	Percentage Mortality (%)
D/Water (10ml/kg)	3.52 ± 0.14	0/6	66.7
METD375	3.97 ± 0.06	0/6	66.7
METD750	4.69 ± 0.35	0/6	0
METD1500	5.61± 0.94*	0/6	0
Phenobarbitone (40mg/kg)	-	6/6	0

Table 1: Effect of Methanol Leaves Extract of *Tapinanthus dodoneifolius* on Clonic Spasm induced by PTZ in Mice

N=6. Mean seizure onset presented as means ± S.E.M. Data was analyzed using one-way analysis of variance (ANOVA) followed by Dunnett Posthoc multiple comparison. * is *p value* < 0.05 compared to D/Water. All treatments were administered via oral route except phenobarbitone which was administered intraperitoneally. KEY: N= Number of mice in each group; METD = Methanol leaves extract of *Tapinanthus dodoneifolius;* D/Water = distilled water; 375, 750 and 1500 represents the doses of the extract used in mg/kg.

Treatments	Mean Seizure Onset (Minutes) *P<0.05*	Mean Seizure duration (minutes) *P>0.05*	Quantal Protection
D/Water (10ml/kg)	9.02 ± 2.52	4.16 ± 1.10	0/6
METD375	8.16 ± 1.92	3.64 ± 1.56	1/6
METD750	2.97 ± 0.21*	4.40 ± 0.91	0/6
METD1500	3.53 ± 0.59	2.27 ± 0.47	2/6
Diazepam (5mg/kg)	-	-	6/6

Table 2: Effect of Methanol Leaves Extract of *T. dodoneifolius* in Bicuculline-induced Seizure in Mice

N=6. Mean seizure onset and mean seizure duration are presented as means ± S.E.M. Data was analyzed using one-way analysis of variance (ANOVA) followed by Dunnett Posthoc multiple comparison. ** is *p value* < 0.01 compared to D/Water; * is *p value* < 0.05 compared to D/Water. All treatments were administered via oral route except diazepam which was administered intraperitoneally. KEY: N= Number of mice in each group; METD = Methanol leaves extract of *Tapinanthus dodoneifolius;* D/Water = distilled water; 375, 750 and 1500 represents the doses of the extract used in mg/kg.

Treatments	Seizure Onset (Minutes) *P<0.05*	Seizure duration (minutes) *P<0.05*	Quantal Protection
D/Water (10ml/kg)	6.76 ± 0.56	5.59 ± 0.82	0/6
METD375	3.65 ± 0.60*	4.38 ± 1.39	0/6
METD750	5.07 ± 0.21	1.40 ± 0.33*	2/6
METD1500	8.11 ± 1.22	3.22 ± 0.47	1/6
Diazepam (5mg/kg)	-	-	5/5

Table 3: Effect of Methanol Leaves Extract of *T. dodoneifolius* Picrotoxin-induced Seizure in Mice

N=5 - 6. Mean seizure onset and mean seizure duration are presented as means ± S.E.M. Data was analyzed using one-way analysis of variance (ANOVA) followed by Dunnett Posthoc multiple comparison. * is *p value* < 0.05 compared to D/Water. All treatments were administered via oral route except diazepam which was administered intraperitoneally. KEY: N= Number of mice in each group; METD = Methanol leaves extract of *Tapinanthus dodoneifolius;* D/Water = distilled water; 375, 750 and 1500 represents the doses of the extract used in mg/kg.

Treatments	Seizure Onset (Minutes)	Seizure duration (minutes)	Quantal Protection
D/Water (10ml/kg)	10.11 ± 0.56	10.13 ± 0.56	0/6
METD375	10.53 ± 0.54	2.70 ± 0.17*	2/6
METD750	5.96 ± 3.10	2.20 ± 0.68*	3/5
METD1500	10.39 ± 0.26	0.95 ± 0.40*	3/5
Carbamazepine (20mg/kg)	15.37 ± 0.81*	2.09 ± 0.85*	3/6

Table 4: Effect of Methanol Leaves Extract of *T. dodoneifolius* 4-AP-induced Seizure in Mice

N=5 - 6. Mean seizure onset and mean seizure duration are presented as means ± S.E.M. Data was analyzed using one-way analysis of variance (ANOVA) followed by Dunnett Posthoc multiple comparison. * is *p value* < 0.05 compared to D/Water. All treatments were administered via oral route except carbamazepine which was administered intraperitoneally. KEY: N= Number of mice in each group; METD = Methanol leaves extract of *Tapinanthus dodoneifolius;* D/Water = distilled water; 375, 750 and 1500 represents the doses of the extract used in mg/kg.

4. Discussion:

This research was conducted mainly to validate the ethnomedicinal use of *Tapinanthus dodoneifolius* as an antiseizure herb. The low percentage yield can be attributed to the fact that phytochemicals often exist in minute quantity. The high LD_{50} value indicates that the extract is practically non-toxic when administered via oral route, a finding that confirms the non-toxic nature of similar plant species, *T. bangwensis* and *D. falcata* when administered orally (Jeremiah *et al.*, 2019).

Gold standard animal models– such as MEST, PTZ, picrotoxin, bicuculline, etc. – for screening for potential anticonvulsant agents were employed in this work. The antiseizure activity of the extract in the MES test is an indication that the extract may be acting via the voltage-gated Na-channels since the maximum electroshock test helps to predict anticonvulsants that act primarily via this channel (Meldrum, 1996, 2002). This result also shows that the extract may be effective against grand mal seizure, especially as this model permits evaluation of the ability of a substance to prevent seizure spread through neural tissue (Holmes, 2007).

The blockade of $GABA_A$ receptor in the CNS is the major mechanism by which PTZ exerts its convulsant effects (DeSarro *et al.*, 1999). Enhancement of GABA neurotransmission attenuates seizures while inhibition of this neurotransmission enhances it (Hoang and Phan, 2014). Since the extracts displayed anticonvulsant activity against PTZ-induced seizures, it is probably interfering with GABA transmission through an effect on the GABA-gated chloride channels. The inability of lower dose of the extract to significantly delay seizure onset may be explained by occupancy theory so that, at lower doses, only few receptors are activated, and the activation is not sufficient to elicit noticeable response. To understand the probable mechanism by which the extract potentiates GABA transmission, the activity of the extract was tested in bicuculline and picrotoxin models of seizure. Bicuculline is a competitive $GABA_A$ receptor antagonist that causes tonic-clonic spasm when administered systemically (Borowicz, 2009). Picrotoxin on the other hand is non-competitive allosteric $GABA_A$ receptor antagonist. Upon binding to the GABA receptor, it prevents the opening of chloride channels, and subsequently hinder Cl^- conductance into brain cells (Rang *et al.*, 2003). The activity of the extract in picrotoxin- and bicuculline-induced seizures indicates that the extract probably acts via transient prevention of picrotoxin-mediated GABA receptor blockade. The extract (only at 375 mg/kg) significantly raised seizure threshold without reducing seizure severity (at all doses). The indicates that perhaps low dose of the extract was sufficient to prevent the allosteric binding of picrotoxin, and this inhibition was probably transient and explains why only seizure onset, and not duration was affected.

4-aminopyridine, a potent K^+- channel blocker which is widely used as a convulsant in animals (Schafer *et al.*, 1973), acts to facilitate excitatory neurotransmitter release (Rutecki *et al.*, 1987) predominantly through non-NMDA type glutamate receptors. (Perreault and Avoli, 1991). The ability of the extract to significantly reduce duration and severity 4-AP-induced seizure is an indication of the extract's ability to prevent potassium channel blockade for a long period. The inability of the extract to protect mice against strychnine-induced clonic spasm indicate that the extract may not interfere with the glycine pathway in preventing or reducing seizure.

The medicinal value of plants lies in some chemical substances (phytochemicals) that have a defined physiological action on the human body (Datta *et al.*, 2003; Dubois *et al.*, 1986). The observed anticonvulsant activity in this study can be attributed to phytochemicals such as alkaloids, flavonoids, terpenoids, saponins, and coumarins present in the extract. These phytochemicals have been reported to enhance brain levels of GABA (Paramdeep *et al.*, 2014).

5. Conclusion:

The methanol leaves extract of *Tapinanthus dodoneifolius* is relatively safe and has anticonvulsant activity which justifies its use in the management of seizure-related disorders by traditional healers.

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Data Statement:

The raw data of this research are available in the Mendeley data repository. It can be accessed via the doi: 10.17632/mdxd8wjzz2.1

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