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Anticonvulsant Study of *Tapinanthus dodoneifolius* DC Danser Methanol Extract

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Tapinanthus dodoneifolius DC Danser (also called African mistletoe) is a hemi-parasitic plant which belongs to the family *Loranthacea*e. This medicinal plant is found in Nigeria and is used for treatment of leprosy and other diseases. The study was aimed at evaluating the phytochemical constituents and anticonvulsant activity of the methanol leaves extract of the plant. The leaves of the plant were collected on *Vitex doniana* (host) tree. The leaves were air dried and then was size reduced into a coarse powder using wooden pestle and mortar. The powder was extracted by maceration using methanol and the resulting liquid extract was concentrated by open air drying. The acute toxicity was determined using the Lorke's method. (State the LD_{50}). The anticonvulsant activity was investigated by studying the effect of the extract on seizures induced by pentylenetetrazole in albino mice with phenytoin as a standard drug. From the analysis of sample with the mice, the methanol extract given at dose 500 mg/kg provided statistically significant difference ($p<0.05$) and also a prolongation in the mean onset of seizure and a decrease in the mean duration of seizure respectively. The overall data collected suggest that *Tapinanthus dodoneifolius* possesses anticonvulsant activity.

Keywords: *Tapinanthus dodoneifolius,* anticonvulsant, acute toxicity, *Vitex doniana,* phytochemical

1. Introduction

Natural products have been used since ancient times for the treatment and prevention of many diseases. Natural products are the most successful source of potential drug leads (Haefner, 2003; Butler, 2004; Cragg and Newman, 2005 Mishra and Tiwari, 2011; Rey-ladino *et al.,* 2011.).Therefore, natural products continue to provide unique structural diversity in comparison to standard combinatorial chemistry, and present opportunities for discovering mainly novel low molecular weight lead compounds. Since less than 10% of the world's biodiversity have been evaluated for potential biological activity, many more useful natural lead compounds await discovery with the challenge being on how to access this natural chemical diversity (Cragg and Newman, 2005).

Generally, natural products are characterized by the specific functions they perform in plants and animals. Classical natural product chemistry methodologies enabled the discovery of a vast array of bioactive secondary metabolites from various source including terrestrial plants, terrestrial micro-organisms, marine organisms, and terrestrial vertebrates and invertebrates (Tyler *et al.,* 1988). Metabolites are naturally-occurring organic compounds synthesized by plants via their metabolic activities in plants, assisted by enzymes. Primary metabolites are usually found in all living organisms such as plants and animals. They form the fundamental building block of living material e.g. carbohydrates, proteins, fatty acids, glycerol, mevalonic acids, and nucleotides. Primary metabolites have wide distribution in living systems and are usually involved in essential life processes. On the other hand, secondary metabolites such as steroids, alkaloids, triterpenes, tannins, saponins, flavonoids are chemicals synthesized by plants but are not directly used by them. However, these are used indirectly by man as a source of pharmaceutical ingredients (Croteau *et al*,. 2002 and Edreva *et al*. 2008).

However folkloric claims of antiepileptic activity of *Tapinanthus dodoneifolius* was reported by Nwude and Ibrahim (1980. Also African mistletoe that could warrants its prescription in African ethno-medicine for management of epilepsy was reported by Bassy (2012). However it has been proven that herbal extracts have potential to be a rich source for safer and more effective, affordable and culturally acceptable antiepileptic agents especially in resource-poor regions as

compared to orthodox or unnatural medicine (Gupta *et al,.* 2014).

Mistletoe is a common name generally used for woody shoot parasites in various plant families, mostly in the Loranthaceae and Viscaceae families (Parker. and Riches, 1993). In Nigeria; Mistletoe are commonly called '*Kauci'* in Hausa, '*Afomo igba'* in Yoruba, '*Elozie'* in Igbo and *'Etu-lonchi'* in Nupe (Deeni and Sadiq, 2002). The Kamwe (Michika) community of Adamawa State-Nigeria calls it '*Kurle'.* It is a bushy parasitic plant, with stem of up to one meter long that grows on a wide range of trees and bushes of the wooded savannah zone (Abdullahi *et al.,* 2015). African mistletoe (*Tapinanthus dodoneifolius*) (DC), a parasitic plant is used ethno-medicinally for treatment of several human and animal ailments including stomach ache, diarrhoea, dysentery, wound, cancer and hypertension (Ndamitso *et al.,* 2013). The aim of the study is to validate scientifically, the ethno medical claim for the use of *loranthaceae* in the treatment of convulsion.

Plate 1. *Mistletoe* ***Source:*** *www.herbal-supplement-resource.com*

2. Materials and Methods

2.1 Collection, Identification and Preparation of Plant Sample

The leaves of *Tapinanthus dodoneifolius* were collected from the forest of Michika Local Government Area, Adamawa State. The sampler was collected in the month of march 2019, the sample plant was then identified in the Department of plant science in Kogi State University Anyingba before further preparation, The leaves were rinsed with distilled water, air dried for 14 days, and then size-reduced into a coarse powder using wooden pestle and mortar.

2.2 Extraction of Plant Sample

The powdered leaves was macerated using a total of 5000 ml of methanol for a period of 9 days. The powdered leaves (412.7g) was macerated initially using methanol (2000 ml) over a period of 3 days, after which the first portion of the filtrate was collected. Another 2000 ml of methanol was poured into the vessel containing fresh powdered leaves ((412.7g) and allowed to macerate for another 3 days after which the second portion of the filtrate was collected. Finally, another 1000 ml of methanol, was poured into vessel containing fresh leaves (412.7g) and allowed to macerate for 3 days, after which the last portion of the filtrate was collected. Using Whatman filter paper. The collected portions of the filtrate were combined and then filtered again using N.041 Whatman filter paper, and air-dried for 21 days. The resulting viscous liquid was then transferred into a ceramic plate and air dried until a constant weight of the extract was then stored in a dry airtight container in a cool dry place.

2.3 Phytochemical Screening

The phytochemical tests were carried out on the methanol extract using standard procedures in order to identify the constituents as described by Trease and Evans (1996).

Test for carbohydrates (Molisch's test)

To a small portion of the aqueous extract in a test tube, 3 drops of Molisch's reagent was added and then followed by addition of few drops concentrated sulphuric acid. The formation of a reddish colored ring at the interface indicates the presence of carbohydrates (Trease and Evans, 1996).

Test for saponins (Frothing test)

To a small portion of the extract in a test tube, 10 ml of distilled water was added and the mixture was shaken continuously for 30 seconds. The solution was allowed to stand for 5 minutes. The formation of a persistent froth indicates the presence of saponins (Trease and Evans, 1996).

Test for flavonoids

I. Shinoda's test

The extract was dissolved in 2 ml of methanol and pieces of metallic magnesium chips were added followed by a few drops of concentrated hydrochloric acid. The formation of pink, or red to purple coloration indicates the presence of flavonoid (Trease and Evans, 1996).

II. Sodium hydroxide test

Two drops of 10% Sodium hydroxide was added to the solution of the extract. A yellow coloration

indicates the presence of flavonoids (Trease and Evans, 1996).

III. Ferric chloride test

Three drops of ferric chloride solution were added to the solution of the methanol extract, a violet coloration was observed. (Trease and Evans, 1996).

Test for tannins

I. Lead sub-acetate test

To a small portion of the extract, 4 drops of lead sub-acetate solution was added. The formation of a cream-colored precipitate indicates presence of tannins (Trease and Evans, 1996).

Test for triterpenoids/steroids

I. Salkowski's test

A small portion of the extract was dissolved in 2 ml of chloroform, before 3 drops of concentrated sulphuric acid were added by the side of the test tube. The formation of red brown coloration at the interface indicates the presence of terpenoids (Edeoga *et al*., 2005).

II. Liebermann-Burchard's test

To the chloroform portion of the extract an equal volume of acetic anhydride was added and mixed gently. 1ml of concentrated sulphuric acid was then added down the test tube. This was observed for colour changes over a period of one hour. Blue to blue-green colour in the upper layer and a reddish, pink or purple colour at the junction of the two layers indicates the presence of triterpenes (Trease and Evans, 1996).

Test for alkaloids

I. Dragendoff's test

The extract (0.2 g) was dissolved in 2 ml of 1% aqueous hydrochloric acid with continuous stirring over water bath. The mixture was filtered and few drops of Dragendoff's reagent were added. The presence of rose red precipitate indicates the presence of alkaloids (Trease and Evans, 1996).

II. Mayer's test

To a 2 ml acidic solution of the extract in a test tube, a few drops of Mayer's reagent were added. A cream precipitate indicates the presence of alkaloids (Trease and Evans, 1996).

Test for Anthraquinones (Bontrager's Test)

A a small portion of the extract was added into 5 ml chloroform, shaken and filtered. To the filtrate, an equal volume of 10% ammonia solution was added with continuous shaking. The formation of a bright pink colour in the aqueous upper layer indicates the presence of anthraquinone (Trease and Evans, 1996).

Test for Cardiac Glycosides (Keller-Kiliani test)

A small portion of the extract was dissolved in 1ml of glacial acetic acid containing traces of ferric chloride solution. The solution was then transferred into a dry test tube to which an equal volume of sulphuric acid was added. A brown ring obtained at the interface indicate the presence of a deoxy sugars (Trease and Evans, 1996).

2.4 Biological studies

Experimental animals

The experimental animals used were albino mice of either sex weighing between 19-36 grams. They were obtained from the National Animal Production Research Institute (NAPRI), FCT Abuja Nigeria.

Acute toxicity study

Acute toxicity study of the methanol extract of *Tapinanthus dodoneifolius* was carried out (Lorke's (1983) method. In the first phase, nine mice were randomly divided into three groups of three mice per group. These were then orally given 10, 100 and 1000 mg of the extract per kg body weight (via a cannula), respectively. The mice were observed for signs of adverse effects and death for 24 hrs. and were weighed daily for 14 days. In the second phase of the study, the procedure was repeated using three mice randomly divided into three groups of one mouse each. These were then given 1600, 2900 and 5000 mg of the extract per kg of body weight, respectively. The mice were also observed for signs of toxicity, mortality and weighed for 14 days. The toxicity level was determined using equation 2 below in result section.

Pentylenetetrazole (PTZ) induced convulsion test in mice

The method of Swinyard *et al*., (1989) was employed. Twenty five mice of either sex weighing between 22 and 36 grams were randomly divided into five groups of five mice

each. Mice in group I were treated with normal saline solution of 10 ml per kg *of body weight*. The second, third and fourth groups were treated with 250, 500 and 1000mg doses of the extract *of body weight* respectively. The fifth group was treated with phenytoin as standard. Sixty minutes later, mice in all groups were treated with 90 mg of freshly prepared PTZ administered by I. P injection per kg of body weight. The mice were then observed for the presence or absence of clinic spasm for at least 5 seconds duration or death.

2.5 Statistical analysis

The results obtained were statistically analyzed using one-way analysis of variance (ANOVA) with SPSS version 20.0 statistical package and the results expressed as mean ± standard error of mean (SEM) as well as percentages in the form of tables where appropriate. Dunnett's post hoc test for multiple comparisons was carried out and the alues of $p< 0.05$ were considered significant.

3. Results and Discussion

3.1 Results

3.1.1 Phytochemical Screening

The phytochemical screening of the methanol extract revealed the presence of alkaloids, carbohydrates, cardiac glycosides, saponins, flavonoids, tannins, steroids and triterpenes and the result is presented in Table 1.

3.1.2 Acute toxicity studies

The oral route median lethal dose of the crude extract was found to be greater than 5000 mg/kg in mice. The results are presented in Table 2.

Table 1. Phytochemical constituents of crude methanol leaf extract of *Tapinanthus dodoneifolius*

Constituents	Test	Observation
Anthraquinones	Borntrager's	-
Alkaloids	Dragendoff's	+
Carbohydrates	Molisch's	+
Cardiac Glycosides	Keller-Kiliani's	+
Saponins	Frothing	+
Flavonoids	Sodium Hydroxide	+
Tannins	Lead sub-acetate	+
Triterpenes	Liebermann-Burchard's	+
Terpenoids	Salkowski's	+
		+

+ = Detected, - = Not detected

Table 2. Result of first phase median oral lethal dose (LD_{50})

Doses (mg/kg)	Number of mice	Mortality
10	3	0/3
100	3	0/3
1000	3	0/3

Table 3. Result of Second phase median oral lethal dose LD_{50}

Doses (mg/kg)	Number of mice	Mortality
1600	1	0/1
2900	1	0/1
5000	1	0/1

3.1.3 Anticonvulsant screening

The *Effect of methanol leaf extract of Tapinanthus dodoneifolius on PTZ – induced seizure in mice*

The extract provided statistically significant difference ($P<0.05$) at 500mg/kg and also a prolongation in the mean onset of seizure and a decrease in the mean duration of seizure respectively, as shown Table 4.

Table 4. Effect of PTZ – induced seizure in mice

Treatment (mg/kg)	Mean onset of Seizure (min)	Mean duration of Seizure (min)	Quantal Protection	% Protection	% Mortality
EXT 250	1.4 ± 0.5	1.4 ± 0.50	1/5	20.0	100.00
EXT 500	2.4 ± 0.56*	4.2 ± 2.09	1/5	20.0	100.00
EXT 1000	2.0 ± 0.76	11.0 ± 4.50	0/5	0.00	100.00
PH	1.4 ± 0.36	4.0 ± 1.14	1/5	20.0	100.00
N/S	1.2 ± 0.12	2.0 ± 0.54	1/5	20.0	100.00

Protection against seizure and mortality expressed as percentages; Mean onset of seizures presented as Mean ± SEM, * = $p< 0.05$ compared to normal saline group - One way ANOVA followed by Dunnett's post hoc test of multiple comparison, n=6, NS - Normal Saline, EXT = Extract, PH = Phenytoin

Equation for Percentage yield

$$\%\ Yield = \frac{Weight\ of\ extract}{Weight\ of\ plant\ sample} \times 100 \quad \ldots\ldots\ldots\ldots equation\ 1$$

The percentage yield was calculated to be 1.79%

LD_{50} =

$$\sqrt{minimum\ lethal\ dose \times maximum\ tolerated\ dose} \qquad Equation\ 2$$

3.2 Discussion

The phytochemical screening of the methanol leaf extract of *Tapinanthus dodoneifolius* revealed the presence of tannins, flavonoids, terpenoids, saponnins, carbohydrates, alkaloids, triterpenes and glycosides (Table 1). These phytochemicals have been reported to possess various pharmacological activities (Cowan, 1999), including anti-malarial (Stephen *et al*., 2018) and anti-cancer (Ichino *et al*., 2006), in addition (Musa *et al*., 2014) have reported the anticonvulsant activities of steroids and triterpenes.

The median lethal dose value of plants used by traditional medicine practitioners using acute toxicity studies is of significant importance because it provides information regarding the margin of safety of the plant. The *I. V* (intravenous) median lethal dose (LD_{50}) value of the methanol leaf extract of *Tapinanthus dodoneifolius* was found to be greater than 5000 mg/kg body weight in Swiss albino mice. The results from the LD_{50} imply that the extract from the leaf of *Tapinanthus dodoneifolius* is relatively safe. However, compared to another research, the tested extracts prolonged the time to onset of seizures and decreased their duration. The mode of administration was either intraperitoneal or oral, and where it was recorded, the toxicity was non-lethal up to a dosage of 2000mg/kg. Most importantly, some extracts were able to fully prevent the experimentally induced seizures at non-lethal doses (Singh *et al*., 2012). Doses of less than or equal to 30% of the LD_{50} which have been demonstrated to be relatively safe for ethno-pharmacological research were used through this study to induce the mice.

There are several reports on the phytotherapy in epilepsy, most of them placing emphasis on the crude plant extracts. This may probably arise due to the complexity of extracts. (Zhu *et al*., 2014). Plant secondary metabolites such as triterpenic steroids and triternoidal saponins have been reported to possess potent anticonvulsant activities in some research models such as electroshock and the chemically induced seizures (pentylenetetrazole) (Kasture *et al*., 2002; Chauhan *et al*., 1988).

The PTZ model detect agent that possess the capacity to raise the seizure threshold. Agents that act via the enhancement of the γ-amino butyric acid (GABA) system e.g. benzodiazepine, diminution of glutamatergic system such as felbamate and T-type calcium current have all been shown to be protective against PTZ induced seizure (Sayyah *et al*., 2002). The extract showed some level of activity by the prolongation in the mean onset of seizures and a decrease in the mean duration of seizure which were statistically significant at the extract dose of 500 mg/kg for the mean onset of seizure. Furthermore, at extract concentration of 250 mg/kg a decrease in the duration of seizure was observed, although not statistically significant level when compared to the normal saline treatment. Which suggest that the extract has some degree of activity against the absence seizures.

The anticonvulsant activity arising from PTZ test identifies compounds that can raise the seizure threshold in the brain (White *et al.,* 1998; Raza *et al.,* 2001). PTZ has been shown to interfere with GABA neurotransmitter and the GABA receptor complex (DeDyn *et al.,* 1992). Pentylenetetrazole has been used experimentally to study seizure phenomenon and to identify pharmaceuticals that may control seizure susceptibility. The exact mechanism of the epileptogenic action of PTZ at the cellular neuronal level is still unclear but it has been generally reported to produce seizures by inhibiting gamma-aminobutyric acid (GABA) neurotransmission (De Sarro *et al.*, 2003). Enhancement of GABAergic neurotransmission has been shown to inhibit or attenuate seizures, while inhibition of GABAergic neurotransmission or activity is known to promote and facilitate seizure. Anticonvulsant agents such as diazepam, valproic acid and phenobarbitone inhibit PTZ-induced seizure by enhancing the action of GABA-receptors, thus facilitating the GABA-mediated opening of chloride channels (Gale, 1992; Olsen, 1981).

4. Conclusion

This study validates the antiepileptic property of African mistletoe that could warrants its prescription in African ethno-medicine for management of epilepsy. The data obtained from this study suggests that the methanol leaf extract of *Tapinanthus dodoneifolius* contains pharmacologically active constituents which possess anticonvulsant activity.

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Conflict of interest

The authors declare no conflict of interest.

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