

Acute anxiolytic activity of aqueous *Ampelocissus africana* whole-plant, *Ficus sycomorus* stem bark and *Tapinanthus globiferus* leaf extracts in Swiss Albino mice

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ABSTRACT

Anxiety disorders are among the most prevalent mental disorders in all age groups world-wide. The attendant socio-economic burden is huge and on the increase. The currently used anxiolytic drugs are few and their usefulness are limited on account of toxicity, delay in, or lack of efficacy. This scenario calls for discovery of additional anti-anxiety therapeutic agents. This study investigated the acute anxiolytic effects of 50, 150 and 500 mg/kg aqueous *A. africana* whole-plant, *F. sycomorus* stem bark and *T. globiferus* leaf extracts, 10 ml/kg distilled water and 0.5 mg/kg diazepam in Swiss Albino mice in a battery of open-field and elevated zero-maze tests using key rodent anxiety parameters, one hour post extract/drug administration. Compared with distilled water treatment, aqueous *T. globiferus* leaf extract caused dose-dependent and significant ($p < 0.05$) increase in mean % centre zone and open segment times and reduction in mean rears and stretch-attend postures. *A. africana* whole-plant and *F. sycomorus* stem bark extracts, when compared with water, caused dose-independent and insignificant ($p > 0.05$) anxiolytic activity on most of these anxiety parameters. The findings of this study indicate that aqueous *T. globiferus* leaf extract has an anxiolytic activity that is superior to that of *A. africana* whole-plant and *F. sycomorus* stem bark extracts and comparable to that of 0.5 mg/kg diazepam. There is a need for further investigation of different extracts and fractions of *T. globiferus* leaves for their potential anxiolytic activity.

Keywords: Anxiolytic activity, selected medicinal plants, test battery, mice

INTRODUCTION

Anxiety is a universal emotion dominated by the arousal of physical, psychological, and physiological functions in response to stressful or potentially stressful situations. Anxiety disorders are characterized by autonomic hyperactivity and dysregulated expression of anxiety.¹ Anxiety disorders are highly prevalent mental disorders globally, with an ever-increasing social and economic burden.²⁻⁴ In Nigeria, anxiety disorders have also been reported as the commonest childhood mental disease and a highly prevalent class of mental disorders with a lifetime prevalence of 5.7% and a 12-month prevalence of 4.1% in the general population.⁵ Pharmacotherapy is a key treatment modality for anxiety disorders but the anti-anxiety drugs presently in clinical use are few and have

individual class liabilities that are related to intolerable adverse effects (e.g. the benzodiazepines, the tricyclic antidepressants, and anticonvulsant anxiolytics), delayed onset of anxiolytic effects (e.g. the selective serotonin reuptake inhibitors, the serotonin-noradrenaline reuptake inhibitors) or weak and unpredictable anxiolytic efficacy (e.g. the azapirones).⁶ The paucity and the inherent limitations of the currently available anxiolytic drugs in the face of the huge prevalence and socio-economic toll of anxiety disorders calls for concerted efforts at discovering additional novel anxiolytic agents. Hence, the present study was conducted to investigate the acute anxiolytic activity of extracts of *Ampelocissus africana* whole-plant, *Ficus sycomorus* stem bark, and

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Received: 04-10-2019

Revised: 26-11-2019

Published: 28-11-2019

Tapinanthus globiferus leaves (being the medicinal plants that were selected on ethnobotanical grounds) in Swiss Albino mice with a view to discover new potential anxiolytic agents.

Ethno-pharmacopeia and Ethno-medicine hold great promise for the discovery of diverse new therapeutic agents generally and anti-anxiety compounds cannot be an exception.⁷ The plant kingdom has always proven to be an enormous reservoir for new pharmacological agents as demonstrated in the discovery of a novel plant-based antimalarial⁸ in addition to earlier discoveries of chloroquine, quinine, artemisinin derivatives, digitalis, penicillin and aspirin.⁹ Already, it has been estimated that between 60% and 80% of the global population still depend on ethno-medical resources for their primary health care on account of cultural acceptability.⁹ Previously, leaf extracts from *Azadirachta indica* (Neem) tree -the host tree for the parasitic plant *Tapinanthus globiferus* have been credited with an anxiolytic activity.

Also, apart from the anecdotal reports of anti-anxiety usage of different parts of the three medicinal plants that were selected for this study, extracts from *Ficus sycomorus* have been reported to have aphrodisiac, anaesthetic, muscle-relaxing, sedative, anticonvulsant and anti-plasmodial effects,¹⁰⁻¹³ those of *Ampelocissus africana* to have anti-trypanosomal, anti-bacterial and antineoplastic activities¹⁴⁻¹⁶; and those from *Tapinanthus globiferus* to have demonstrated efficacy in hypertension, cancer, epilepsy, and diabetes mellitus.¹⁷ However, there has not been any scientific investigation of the anxiolytic property of extracts of *Ampelocissus africana* whole-plant, *Ficus sycomorus* stem bark, and *Tapinanthus globiferus* leaf extracts. This study therefore set to evaluate the preliminary anxiolytic activity of aqueous extracts of these plant parts in mice using standard rodent behavioural test battery comprising the open-field and elevated zero-maze tests.

MATERIALS AND METHODS

Tapinanthus globiferus leaves on a Neem tree sited at Shuni road, Mabera, Sokoto, Nigeria; whole plant of *Ampelocissus africana* and *Ficus sycomorus* stem bark from the forests of Rabah, Rabah Local Government Area, Sokoto State, Nigeria, were collected in the month of January 2018.

They were subsequently briskly washed, air-dried, pulverized and stored dry in opaque plastic containers till use. Plant parts were identified and specimen vouchers deposited at the Herbarium of the Department of Botany, Usmanu Danfodiyo University, Sokoto, Sokoto state, Nigeria. The plant extraction and drying took place in the laboratory of the Pharmacognosy Drug development Department, and the behavioural experiments took place in the behavioural room of the Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna state, Nigeria. Two hundred and fifty grams (250g) of the fine powders of each plant part was cold-macerated for 24 hours in 1L of distilled water, filtered using Whatman's paper (150 mm) and evaporated in rotatory water bath at 45-50 degree Celsius to obtain dry crude aqueous extracts of *Tapinanthus globiferus* leaves (12.21%), *Ampelocissus africana* whole-plant (13.44%) and *Ficus sycomorus* stem bark (15.90%).

The behavioural anxiolytic efficacy screening of the selected plants' extracts was carried out in a fashion that is similar to the method previously used by Schmitt and Hiemke,¹⁸ but with a modification of eliminating inter-test latency. One hour following administration of 50, 150 or 500 mg/kg of plant extracts, 0.5 mg/kg diazepam or 10 ml/kg distilled water, orally by gavage, to randomized groups (n=10; 5 per sex) of mice (21.00±0.15 g) under good laboratory practices, each mouse was exposed to a test battery consisting of an open-field an elevated zero-maze in an opaque cubicle with 100-lux illumination (Figure 1).

The behavioural assay was initiated by placing each mouse in the centre of the open field and allowing it to move freely and explore the field for 5 minutes. At the end of this period, each mouse was again transferred to the mid-point area of an open segment of the zero-maze with the mouse facing one of the closed segments. The animal was allowed to freely explore its new environment for 5 minutes. Animals that jumped off the open segment of the zero maze during the procedure were gently returned immediately to the test. Tests sessions were videotaped and visually monitored and subsequently interpreted. Data were analyzed using analysis of variance (ANOVA) followed by Turkey post hoc test; and p values ≤ 0.05 were considered as significant.

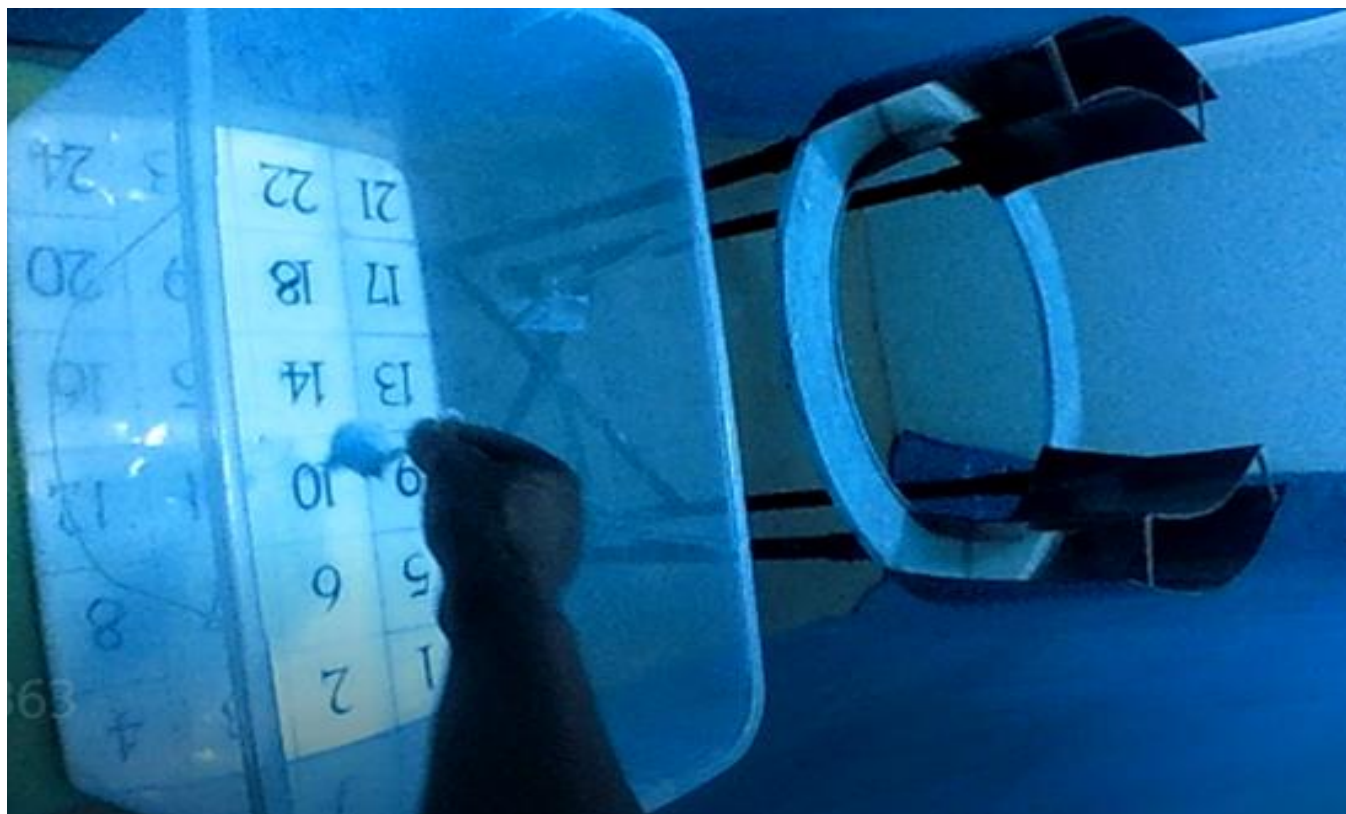


Figure 1: Behavioural test battery of an open field and an elevated zero-maze
(Source: Fabricated by the corresponding author)

RESULTS

Anxiolytic activity of crude aqueous *Ampelocissus africana* whole-plant, *Ficus sycomorus* stem bark and *Tapinanthus globiferus* leaf extracts in mice

In the open-field test (OFT), (Table 1), compared to distilled water treatment, while aqueous *Tapinanthus globiferus* leaf extract dose-dependently and significantly ($p < 0.05$) increased mean per cent centre zone time (% CZT) at all graded extracts' doses; aqueous *Ampelocissus africana* whole-plant extract only attained significant ($p < 0.05$) increase in mean % CZT at the 150 mg/kg dose and aqueous *Ficus sycomorus* stem bark only at the highest extracts' dose of 500 mg/kg. On the frequency of rearing events (Table 2), from the lowest mean rearing frequency of 24.60 ± 2.66 in the distilled water-treated mice, aqueous *Tapinanthus globiferus* leaf extract treatment exhibited dose-dependent and significant ($p < 0.05$) reductions in this parameter to 19.00 ± 2.10 and 18.67 ± 1.20 at the 150 and 500 mg/kg dose levels, respectively. Treatments with the other two extracts did not attain any significant ($p > 0.05$) reduction in this parameter at any dose level compared with the distilled water treatment.

On the mean % OST in the elevated zero-maze test (Table 3), compared to the highest mean of 15.10 ± 1.60 recorded in the distilled water-treated mice, aqueous *Tapinanthus globiferus* leaf extract significantly increased ($p < 0.05$) the mean % OST across all dose levels (with the highest mean anxiolytic activity of 34.29 ± 1.43 recorded at the 500 mg/kg). The other medicinal plants' extracts only attained significant ($p < 0.05$) increase in mean % OST at the 500 mg/g dose level. On the stretch-attend postures (Table 4), again, aqueous *Tapinanthus globiferus* leaf extract showed a significant ($p < 0.05$) and dose-dependent reduction in this parameter from the mean value of untreated mice at the 3 extracts' doses; aqueous *Ampelocissus africana* whole-plant extract only attained significant ($p < 0.05$) paradoxical reduction in mean stretch-attend postures (SAPs) only at the lowest dose level, and with aqueous *Ficus sycomorus* stem bark extract displaying no significant ($p > 0.05$) anxiolytic activity on this parameter at any dose level. The anxiolytic activity of aqueous *Tapinanthus globiferus* leaf extract on most of the anxiety parameters evaluated in the two in-vivo efficacy assays was comparable to that of 0.5 mg/kg diazepam (standard anxiolytic) treatment.

Table 1: Per cent centre zone time of mice on open-field test

Treatments groups	Extracts' doses		
	50mg/kg	150mg/kg	500mg/kg
D/water (10ml/kg)	2.57 ± 0.65	3.17 ± 0.81	3.03 ± 0.94
Aq. <i>T. globiferus</i>	7.73 ± 1.80*	9.43 ± 2.45*	9.85 ± 1.17*
Aq. <i>A. africana</i>	3.55 ± 0.54	6.33 ± 2.51*	5.17 ± 0.72
Aq. <i>F. sycomorus</i>	5.67 ± 1.09	4.30 ± 0.59	6.77 ± 1.76*
Diazepam (0.5mg/kg)	9.00 ± 4.00*	9.57 ± 5.16*	9.60 ± 2.06*

Data were entered as mean ± S.E.M. of mice; *Statistically significant ($p \leq 0.05$)

Table 2: Number of rears of mice on open-field test

Treatments groups	Extracts' doses		
	50mg/kg	150mg/kg	500mg/kg
D/water (10ml/kg)	2.60 ± 2.66	27.80 ± 3.93	27.30 ± 7.00
Aq. <i>T. globiferus</i>	19.80 ± 2.37	19.00 ± 2.10*	18.67 ± 1.20*
Aq. <i>A. africana</i>	21.56 ± 4.56	20.10 ± 4.00	30.40 ± 3.47
Aq. <i>F. sycomorus</i>	18.90 ± 4.16	24.56 ± 3.69	28.50 ± 5.17
Diazepam (0.5mg/kg)	16.00 ± 2.24*	14.40 ± 3.43*	15.90 ± 3.98*

Data were entered as mean ± S.E.M. of mice; *Statistically significant ($p \leq 0.05$)

Table 3: Per cent open segment time of mice on elevated zero-maze test

Treatments groups	Extracts' doses		
	50mg/kg	150mg/kg	500mg/kg
D/water (10ml/kg)	13.84 ± 2.57	15.77 ± 2.52	15.10 ± 1.60
Aq. <i>T. globiferus</i>	28.00 ± 3.44*	35.10 ± 7.79*	34.29 ± 1.43*
Aq. <i>A. africana</i>	20.23 ± 3.76	27.77 ± 2.66	26.63 ± 2.94*
Aq. <i>F. sycomorus</i>	22.83 ± 6.23	23.13 ± 2.77	26.63 ± 2.41*
Diazepam (0.5mg/kg)	33.37 ± 7.88*	38.63 ± 8.37*	36.67 ± 5.86*

Data were entered as mean ± S.E.M. of mice; *Statistically significant ($p \leq 0.05$)

Table 4: Mean stretch-attend postures of mice on elevated zero-maze test

Treatments groups	Extracts' doses		
	50mg/kg	150mg/kg	500mg/kg
D/water (10ml/kg)	16.80 ± 3.23	12.60 ± 1.67	16.30 ± 2.42
Aq. <i>T. globiferus</i>	7.50 ± 1.89*	5.80 ± 1.35*	5.22 ± 1.28*
Aq. <i>A. africana</i>	10.80 ± 1.60	11.70 ± 2.13	13.10 ± 2.05
Aq. <i>F. sycomorus</i>	8.30 ± 1.86*	11.10 ± 1.00	11.80 ± 2.54
Diazepam (0.5mg/kg)	4.90 ± 1.08*	4.60 ± 1.29*	7.78 ± 1.71*

Data were entered as mean ± S.E.M. of mice; *Statistically significant ($p \leq 0.05$)

DISCUSSION

This report represents findings at a preliminary stage in the investigation of the anxiolytic activity of *Tapinanthus globiferus* leaf, *Ficus sycomorus* stem bark and *Ampelocissus africana* whole-plant extracts in standard mouse anxiety tests as an attempt at discovering potential anxiolytic agents. The important role of rodent anxiety tests in anxiolytic drug discovery has been demonstrated by the deployment of these tests in several previous preclinical screenings of putative anxiolytic agents.^{19,20} This relevance is thought to derive from the ethological advantage of rodent anxiety assays and the close mouse-

human genomic homology,^{21,22} which are, in turn, viewed to confer high predictive validity on these tests for modeling both human anxiety disorders and for pharmacological evaluation of anxiolytic activity of novel putative compounds.^{18,23} The open-field and the elevated zero-maze tests are reputed to be among the most proficient and widely used in-vivo anxiety efficacy paradigms in preclinical drug discovery due to their inherent sensitivity to rodent anxiety-related behaviours.^{24,25}

This study found out that aqueous *Tapinanthus globiferus* leaf extract exhibited an acute anxiolytic activity that was comparable to that of 0.5 mg/kg diazepam and superior to that of aqueous *Ampelocissus africana* whole-plant and *Ficus sycomorus* stem bark extracts on all the four anxiety in the two tests. The four parameters i.e. percentage centre zone time (% CZT), rearing events, percentage open segment time (% OST) and stretch-attend postures (SAPs) used in evaluating rodent anxiety-related behaviours in this study have been adjudged as key rodent anxiety indicators.^{26,27} Per cent CZT represents the proportion of the test duration that is spent by the experimental animals in the portion of the test arena floor that is designated as the central area. A rear or a rearing event describes the posture of rodents whereby the test animals stand erect on their hind limbs with their forelimbs either completely hanging in the air or on the wall of the open field. Increased % CZT and reduced frequency of rearing events have been reported as indices of reduced anxiety levels.²⁸ Percentage OST, defined as the proportion of the total test duration spent on the open segments of the elevated zero-maze, has been shown to be a widely accepted index of anxiety behaviour in rodents,²⁶ and increases in % OST have been thought to indicate reduced anxiety state.²⁹ Stretch-attend postures (SAPs) are also viewed to be an important rodent anxiety parameter.³⁰ SAPs are a risk assessment behaviour of rodents which involves episodic alternating forward stretching and recoil of its entire length while lowering and keeping its trunk to the floor of the test device. Exhibition of reduced SAPs by rodents exposed to zero-maze has also been described to be indicative of reduced anxiety level.³¹

Aqueous *Tapinanthus globiferus* leaf extract anxiolytic activity in this study was not only superior to the other two plants' extracts but was also significant on all the four rodent anxiety parameters evaluated. These findings may represent the first report of anxiolytic activity of leaf extracts of *Tapinanthus globiferus* grown on *Azadirachta indica* (Neem) tree and may justify the traditional anti-anxiety use of this medicinal plant in Sokoto metropolis and environs. The anxiolytic effects seen in this study may be due to the presence of certain secondary metabolites in the leaf extract. This finding is in agreement with the finding of a previous study whereby crude aqueous stem bark extract of a related specie, *Tapinanthus dodoneifolius* (DC) Denser has been shown to exhibit anxiolytic and antidepressant effects in mice.³² Other studies have shown crude methanol leaf extract of *Tapinanthus globiferus* to exert antidepressant effect in mice,³³ and aqueous residue fraction of *Tapinanthus*

globiferus has been shown to exert anti-convulsant effects in mice and chicks.³⁴ The anxiolytic activity of *Ampelocissus africana* extract in the study was either insignificant on most anxiety parameters evaluated at the lower extract's doses or significant on few parameters at high doses. This weak anti-anxiety effect exhibited by *Ampelocissus africana* extract may represent the first scientific anxiolytic evaluation on this plant. This plant extract has been under-researched in spite of the anecdotal report of its aphrodisiac property and efficacy in alleviating agitated states in Sokoto and Rabah environs of Sokoto State, Nigeria. The few available academic reports available on the extracts from *Ampelocissus africana* extract include those of anti-diarrhea effect in an ethnobotanical survey in Sokoto State of Nigeria,³⁵ of anti-trypanosomal,¹⁴ anti-bacterial³⁶ and antineoplastic¹⁵ activity.

Ficus sycomorus (FS) stem extract exhibited inconsistent anxiolytic activity in this preliminary anxiolytic activity screening; it significantly increased ($p < 0.05$) the open field mean % CZT and the elevated zero-maze mean % OST only at the highest doses, but it significantly ($p < 0.05$) attenuated the mean SAPs at the lowest extract dose on elevated zero-maze. This study is one of the few (if any) scientific reports on the anxiolytic activity of FS stem bark extracts. The inconsistent anxiolytic profile exhibited by FS in this study is incongruent with anecdotal reports of its usefulness in alleviation of excessive worrying and nervous and depressive afflictions in Sokoto and Rabah districts of Sokoto state, Nigeria. The observed inconsistent anxiolytic activity displayed by aqueous FS stem bark extract in this study might be due to the fact that only acute anxiolytic doses of the extract were used in the anxiolytic activity assays. Perhaps an extended duration dosing regimen may need to be employed in subsequent studies in order to re-assess its anxiolytic property.

CONCLUSION

This study has demonstrated a dose-dependent and significant acute anxiolytic effect of crude aqueous leaf extracts of *Tapinanthus globiferus* grown on Neem tree in mice. This finding may justify the traditional anti-anxiety use of this medicinal plant, and there is a need to carry out comparative anxiolytic activity screening of this aqueous extract, its methanol counterpart, and fractions in subsequent studies.

Source of support

Nil.

Conflict of interest

None declared.

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How to cite this article: Umarudeen AM, Magaji GM, Bello SO, Aminu C, Abdullahi MI. Acute anxiolytic activity of aqueous *Ampelocissus africana* whole-plant, *Ficus sycomorus* stem bark and *Tapinanthus globiferus* leaf extracts in Swiss Albino mice. *Int Arch Med Health Res* 2019; 1(3): 75-81.