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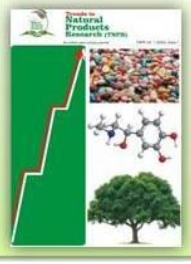

Evaluation of the Neuropharmacological Potential of *Zapoteca portoricensis* (Jacq) HM. Hernández in Experimental Murine Models.

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Abstract: *Zapoteca portoricensis* (Jacq) HM Hernández is a medicinal plant of the Fabaceae family. It is traditionally used in Southern Nigeria as anticonvulsant, antispasmodic and in the treatment of gastrointestinal disorders with acclaimed success. The anti-depressant and sedative potential of the methanol root extract and fractions of *Z. portoricensis* was investigated using murine models. In each test (open field test, forced swimming test and elevated plus maze), mice were allotted into five groups (n = 5) and administered distilled water (control), *Z. portoricensis* root extract and fractions (100, 200, 400 mg/kg, p.o), as well as diazepam (0.5 mg/kg).In the open field test, *Z. portoricensis* extract (ZPE) decreased the number of line crossing, centre square duration, rearing and grooming non-dose dependently while increasing freezing time. N-hexane fraction (HF) and methanol fraction (MF) exhibited similar results. In the forced swimming test, ZPE (100 mg/kg) significantly decreased the duration of immobility and increased swimming duration. The fractions significantly ($p < 0.05$) decreased the duration of immobility and increased duration of swimming with HF producing the highest effects. In the elevated plus maze, ZPE exhibited a dose-dependent increase in the number of entries in the open arms, while the fractions caused a decrease in open arm entries. EF (400 mg/kg) exhibited significant ($p < 0.05$) decrease compared with the control. Results obtained from this study revealed that *Z. portoricensis* root extract and fractions may serve as a useful sedative and anti-depressant agent.

Introduction

Insomnia, defined as persistent difficulty in falling or staying asleep that affects daytime function, can be triggered by psychological (anxiety and depression) events, as well as environmental, dietary and drug-related causes (Harvey, 2001). Depression is an affective disorder, which results in a state of low mood and aversion to activities that can negatively affect a person's thought behaviour, worldview and physical well-being (APA, 2003). The prevalence of depressive disorder is about 13-20 % (Licinio and Wong, 1999). Anxiety, a common form of mental disorder, affects about 40 % of the adult population worldwide (Rhebergen *et al.*, 2011; Gustavson *et al.,* 2018). It is intimately linked with depression and usually appears as comorbid medical conditions (Outhoff, 2010). Approximately two-thirds of those suffering anxiety attack and severe depression has suicidal thoughts and 10-15 % of whom attempt suicide before the age of 40 (Moallem *et al*., 2007). While there are many potential precipitating factors, it is currently believed that depression is primarily the result of biochemical alterations in the brain (Post, 1992; England and Sim, 2009). Pharmaceutical treatments including selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI) and long-term use of benzodiazepine analogues cause alterations in brain chemistry through neurotransmitter amplification and regulation. They are reported to be effective in the treatment of depression (Dwyer *et al*., 2011). However, these drugs have limited benefits with obvious side effects including impaired cognitive function, anticholinergic effects, gastrointestinal disturbances, orthostatic hypotension, arrhythmias, weight gain, and sexual dysfunction etc. (Thomas and Christopher, 2004). Thus, there is a need to search for new compounds and treatment strategies that could improve conventional therapies. Numerous herbal medicines are recognized as active in the central nervous system (CNS), and they have at least a hypothetical potential to affect chronic conditions such as anxiety, depression, headaches or epilepsy, that do not respond well to conventional treatments (Phillipson, 2001; Carlini, 2003). *Zapoteca portoricensis* (Jacq) HM Hernández (Fabaceae) is a medicinal plant widely distributed in Southeast Asia, West Indies, Atlantic Coast of America, and West Tropical Africa. Decoctions of the aqueous and alcohol extracts of different parts of the plant are used traditionally in Southern Nigeria as an anticonvulsant, antispasmodic, and in the treatment of tonsillitis and gastrointestinal disorders (Nwodo and Uzochukwu, 2008).

Pharmacologically, different extracts prepared from the leaves and roots of the plant have demonstrated antimicrobial (Nkechukwu *et al.,* 2014), anti-ulcer (Ukwe *et al*., 2010), anti-inflammatory (Agbo *et al,* 2010), hepatoprotective/antioxidant (Agbafor *et al.,* 2014), anti-malarial (Nwodo *et al.,* 2015) and anti-BPH (Joshua *et al.,* 2018) properties. Recently, extract and fractions from *Zapoteca portoricensis* roots exhibited immunomodulatory (Warren *et al.,* 2020) and anticonvulsant (Iyanyi *et al.,* 2020) activities in animal models. There are, however, no published reports regarding the antidepressant and sedative activities of the plant. In this study, a pilot screening of the antidepressant and sedative activities of the extract and fractions of *Zapoteca portoricensis* was carried out using experimental murine models.

Materials and methods

Preparation of plant material

The roots of *Z. portoricensis* were collected from its natural habitat in Nsukka, Enugu State, Nigeria. The plant was identified and authenticated by Mr Alfred Ozioko of the International Centre of Ethnomedicines and Drugs Development, a subsidiary of Bioresources Development and Conservation Program (BCDP), Nsukka, Enugu State (voucher specimen no: InterCEDD/16043). The air-dried and pulverized plant material (4800 g) was macerated with about 10 L of methanol for 48 hours. The resulting filtrate was concentrated using a rotary vacuum evaporator to obtain *Z. portoricensis* extract (ZPE; 300 g). *Z. portoricensis* extract (200 g) was fractionated in a glass column (150 cm x 1.5 cm) packed with 200 g of a slurry silica gel (70-230 mesh) using n-hexane, ethyl acetate and methanol solvents in order of increasing polarity. The fractions were then concentrated to obtain n-hexane (7.54 g), ethyl acetate (12.64 g) and methanol (56.86 g) fractions, respectively. The *Z. portoricensis* extract (ZPE) and fractions (HF, EF, MF) were screened for anti-depressant and sedative activities in mice.

Drugs and Reagents

Diazepam (Valium®) and amitriptyline (Tuton Pharmaceuticals, India). All other reagents used were of analytical grade (Sigma-Aldrich, Germany). They were used as such without further purification.

Animals

Swiss albino mice (20-36 g) of either sex were maintained at room temperature in a 12 h light/dark cycle. Animals were fed with standard pellet (Guinea Feed Plc, Nigeria) and water *ad libitum*. All experiments were conducted per internationally accepted best practices as outlined in the European Community Guidelines (EEC) Directive of 1986 (86/609/EEC) and approved by the Institutional Ethical Committee on Use of Laboratory Animals.

Neuropharmacological tests

Open field test

The Open Field Test (OFT) was carried out in mice according to the method described by Brown *et al.* (1999), with slight modifications. Briefly, the open field apparatus consisted of a wooden arena (72cm x 72cm and 40cm high) with clear Plexiglas walls. Blue lines were drawn on the floor with a marker and were visible through the clear Plexiglas floor. The lines divided the floor into sixteen (18 x18 cm) squares. A central square (18 x 18 cm) was drawn in the middle of the open field The mice were allotted into five groups (n=5). They were treated with the control (distilled water), diazepam (0.5 mg/kg) as a standard agent, and *Z. portoricensis* root extract and fractions (100, 200 and 400 mg/kg, p.o), respectively. Thirty minutes after treatment, each mouse was gently placed in the centre (marked) of the field and allowed to explore the apparatus freely for 5 minutes. A mouse was deemed to cross over from one square to another when all four paws had crossed. The open field maze was cleaned between each trial using 70 % ethanol. Behavioural parameters (number of line crossing, centre square entries and rearing activities, centre square duration, grooming and freezing time) were observed and recorded using a video camcorder positioned above the apparatus.

Forced swimming test

The Forced-Swimming Test (FST) was carried out in mice according to the method described by Porsolt (1978), with slight modifications. The experiment was carried out in two phases. In the induction phase, animals were placed in a cylindrical Perspex tank (40 cm height, 15 cm diameter) containing around 30 cm of fresh water at 24 ± 1 ºC. Mice that could stay afloat during 15 minutes of training were subjected to the test phase after a 24-hour resting period. In the test phase of the study, the mice were allotted into five groups (n=5). They were treated with the control (distilled water), amitriptyline (15 mg/kg) as a standard agent, and *Z. portoricensis* root extract and fractions (100, 200 and 400 mg/kg, p.o), respectively. Thirty minutes after administration, each mouse was placed in the water cylinder for 5 minutes and monitored for duration of immobility within the period. The duration of immobility was determined when they remained floating passively in the water without struggling and making movements necessary only to keep their heads above the water surface. The total duration of immobility was recorded using a stopwatch. A decrease in the duration of immobility was an indication of anti-depressant-like effects.

Elevated plus maze (EPM) test

The Elevated Plus-Maze (EPM) test was carried out in mice according to the method described by Leo *et al.* (2014), with slight modifications. Briefly, a custom-made elevated plus-maze (EPM) which is elevated 50 cm above the ground was used. The EPM consists of two opposite closed arms, two opposite open arms and a central square was used. The closed arms measure 30 x 5 cm and a height of 15 cm that enclose the arms. The open arms measure 30 x 5 cm and a height of about 0.3 cm to prevent the animals from falling while exploring the open arms. Glossy painting was avoided to prevent excess glare. Mice were allotted to five (5) groups. Group I received the vehicle (distilled water), groups II, III and IV received *Z. portoricensis* root extract and fractions (100, 200 and 400 mg/kg, p.o), respectively, while group V received diazepam (0.5 mg/kg) as a standard agent. After thirty minutes of treatment, each mouse was gently placed in the central square of the plus maze facing an open arm and was allowed to explore the apparatus freely for 5 minutes. The duration and number of entries into the open and enclosed arms was observed and recorded. An entry was defined as an animal placing all four paws into an arm, and no time was recorded when the animal was in the central area. The maze was cleaned with a solution of 70% ethanol after each trial.

Statistical analysis

Data obtained were analysed using one-way analysis of variance (ANOVA) and expressed as mean $\pm$ SEM. Differences between mean were regarded significant at $p < 0.05$, using Dunnett's post hoc test (Graph Pad Prism version 5.0, USA)

Results

Effect of *Z. portoricensis* extract and fractions on open field test (OFT)

Non-significant ($p > 0.05$) reduced number of line crossing was elicited by ZPE and EF (100 and 400 mg/kg), HF (200 and 400 mg/kg), and MF (200 mg/kg) treated groups compared to the control group (Table 1). The number of line crossing was non-significantly ($p > 0.05$) higher in ZPE and EF (200 mg/kg) and MF (100 and 400 mg/kg) treated groups. In HF (100 mg/kg), number of line crossing was significantly ($p < 0.05$) higher compared with the control group. Centre square duration in groups that received ZPE (200 mg/kg) and HF (100 mg/kg) was significantly ($p < 0.05$) higher compared with the control. However, lower centre square duration occurred in ZPE (100 and 200 mg/kg), HF (200 and 400 mg/kg), EF and MF (at all doses) compared with the control. Non-significantly ($p > 0.05$) lowered rearing time occurred in groups that received ZPE and HF (100 and 400 mg/kg), and MF (100 and 200 mg/kg) compared with the control group. The rearing time was non-significantly ($p > 0.05$) higher in ZPE and HF (200 mg/kg), EF (at all doses), and MF (400 mg/kg) compared with the control.
The grooming time was significantly ($p < 0.05$) reduced in groups that received ZPE and HF (at all doses), EF (200 and 400 mg/kg), and MF (100 and 200 mg/kg) compared with the control. Treatment with EF and MF (100 and 400 mg/kg) showed non-significant ($p > 0.05$) differences in grooming time, respectively, compared with the control.
Freezing time was significantly ($p < 0.05$) higher in groups that received ZPE (100 mg/kg), HF (200 and 400 mg/kg), and MF (at all doses) compared with the control. The freezing time was non-significantly ($p > 0.05$) higher in ZPE (200 and 400 mg/kg), HF (100 mg/kg) and EF (200 mg/kg). EF (100 and 400 mg/kg) non-significantly ($p > 0.05$) reduced the freezing time compared with the control. Conversely, in the group that received diazepam, significant ($p < 0.05$) differences occurred with regards to number of lines crossed, centre square duration, grooming and freezing time with a concomitant reduction ($p > 0.05$) in rearing time compared with the control.

Effect of *Z. portoricensis* extract and fractions on forced swimming test (FST)

In mice that received ZPE (100 mg/kg), the duration of immobility was significantly ($p < 0\ .05$) reduced with a concomitant increase in the duration of swimming. The duration of immobility and swimming were non significantly ($p > 0.05$) reduced in ZPE (200 and 400 mg/kg) compared with the control. Among the fractions, HF (100 and 200 mg/kg), significantly ($p < 0.05$) reduced the duration of immobility with increased in the duration of swimming. Ethyl acetate fraction (EF) and methanol fraction (MF), significantly ($p < 0.05$) reduced the duration of immobility and increased the duration of swimming. (Table 2).

Table 1: Effect of *Z. portoricensis* extract and fractions on open field test.

Treatment	Dose (mg/kg)	No of line crossing	Centre square duration (s)	Rearing (s)	Grooming (s)	Freezing
Control	-	51.00±15.63	9.80±2.48	8.00±4.50	69.00±21.97	28.00±4.62
Diazepam	0.5	1.50±0.50*	170.00±2.70*	4.12±0.23	6.24±0.25*	296.80±2.06*
ZPE	100	34.20±4.89	5.20±1.59	4.70±0.48	9.00±2.30*	72.25±17.21*
	200	51.60±13.36	75.00±21.54*	10.50±5.52	18.00±6.88*	57.50±21.26
	400	35.40±8.52	8.80±2.22	3.67±0.82	10.40±2.91*	45.75±5.02
HF	100	70.40±13.22*	133.80±6.55*	6.67±2.60	22.33±3.18*	53.25±18.19
	200	45.00±10.93	6.80±1.66	9.33±3.18	28.00±11.79*	74.80±27.82*
	400	41.80±6.82	7.40±2.25	5.25±1.32	33.50±9.14*	98.20±48.73*
EF	100	38.60±13.20	6.80±1.83	13.67±11.20	40.50±29.50	13.00±6.00
	200	52.80±13.87	8.80±1.24	19.00±7.52	17.50±8.15*	51.33±3.76
	400	39.60±5.50	9.00 ± 2.12	12.20±2.85	35.67±9.96*	26.33±9.06
MF	100	56.60±19.88	5.40±1.21	5.25±2.10	19.67±6.36*	126.80±32.45*
	200	26.20±6.38	5.40 ±1.03	7.75±1.65	21.00±10.15*	82.80±19.06*
	400	51.60±2.21	3.80 ± 0.80	16.40±6.86	69.25±24.97	123.00±42.28*

Values are expressed as mean ± S.E.M; n=5. ZPE= *Zapoteca portoricensis* extract; HF= n-hexane fraction; EF= ethyl acetate fraction; MF= methanol fraction; * significant difference from control ($p < 0.05$).

Table 2: Effect of *Z. portoricensis* extract (ZPE) and fractions on forced swimming test.

Treatment	Dose (mg/kg)	Duration of immobility (sec)	Duration of swimming
Control	-	79.40 ± 6.03	220.60±2.25
Diazepam	0.5	43.40 ± 6.90*	256.60 ± 6.90*
ZPE	100	2.60±1.08*	297.60 ± 1.03*
	200	58.20 ± 22.41	241.80±22.41
	400	69.60±17.98	230.40±17.98
HF	100	6.20 ± 1.99*	293.80±1.99*
	200	10.00 ± 2.92*	290.00 ± 2.92*
	400	58.60 ± 13.93	240.60±14.55
EF	100	17.20 ± 6.15*	282.80±6.15*
	200	37.60 ± 9.70*	260.40 ± 9.78*
	400	44.60 ± 19.71*	255.40 ± 19.71*
MF	100	39.80 ± 16.03*	260.20 ± 16.03*
	200	14.60 ± 5.80*	285.40 ± 5.80*
	400	47.60 ± 17.65*	525.40 ± 17.65*

Values are expressed as mean ± S.E.M; n=5. ZPE= *Zapoteca portoricensis* extract; HF= n-hexane fraction; EF= ethylacetate fraction; MF= methanol fraction; * significant difference from control (p<0.05).

Effect of *Z. portoricensis* extract and fractions on elevated plus maze test (EPM)

ZPE (400 mg/kg) significantly ($p < 0.05$) increased the number of open arms entries compared with the control (Table 3). Among the fractions, HF exhibited a non-significant ($p > 0.05$) difference in the entry and duration in the open arms, respectively, compared with the control. EF (100 and 200 mg/kg) and MF caused a non-significant ($p > 0.05$) reduction in open arms entry. EF (100 and 200 mg/kg) and MF (100 mg/kg) caused non-significant ($p > 0.05$) reduction in open arms duration contrary to MF (200 and 400 mg/kg) ($p < 0.05$). Open arms duration was significantly ($p < 0.05$) increased in EF (400 mg/kg) compared with the control.

Table 3: Effect of *Z. portoricensis* extract (ZPE) and fractions on elevated plus maze test .

Treatment	Dose (mg/kg)	No of open arms entry	No of close arms entry	Duration on open arms (s)	Duration in close arms (s)
Control	-	7.80±1.16	9.60±1.69	115.40 ± 10.00	100.60±17.37
Diazepam	0.5	1.67 ± 0.33*	1.00±0.00*	51.10 ± 23.63*	143.00±26.66*
ZPE	100	9.40±1.50	8.40 ± 0.81	114.20 ± 2.76	97.00±10.21
	200	10.00 ± 0.84	9.20±1.39	121.80 ± 14.73	88.00±13.97
	400	12.40±1.17*	11.20±1.07	122.20 ± 14.12	60.40±11.42
HF	100	7.40 ± 1.17	8.80±1.88	109.20 ± 2.42	136.80±9.16
	200	7.60 ± 1.81	8.40 ± 1.32	114.60 ± 12.82	113.80 ± 23.47
	400	9.00 ± 1.48	10.40 ± 2.29	123.60 ± 7.40	97.20 ± 15.67
EF	100	6.60 ± 1.47	7.80 ± 0.97	99.80 ± 25.64	105.40 ± 11.69
	200	4.80 ± 0.86	8.40 ± 1.66	89.75 ± 24.24	128.50 ± 25.99
	400	1.60 ± 0.40*	5.20 ± 0.66	170.00 ± 11.29*	83.00 ± 12.72
MF	100	7.60 ± 1.07	9.40 ± 2.16	95.80 ± 15.79	165.80 ± 14.30*
	200	6.00 ± 1.10	9.60 ± 0.93	53.00 ± 16.73*	166.00 ± 21.67*
	400	5.20 ± 1.43	7.00 ± 1.87	68.60 ± 14.40*	190.40 ± 12.27*

Values are expressed as mean ± S.E.M; n=5. ZPE= *Zapoteca portoricensis* extract; HF= n-hexane fraction; EF= ethylacetate fraction; MF= methanol fraction; * significant difference from control ($p < 0.05$).

Discussion

Depression and anxiety are among the most common emotional disorders affecting people in most parts of the world. The side effects and toxicity associated with long-term use of synthetic orthodox agents have necessitated the continuous search for a complementary and alternative strategy for management of mood or behavioural disorders. Natural products have proved to be an important source of lead molecules and many extracts and compounds of plant origin with psychoactive activity have been reported (Foyet *et al.*, 2012; Benneh *et al.*, 2018). The results of the present study demonstrate a pilot investigation of *Z. portoricensis* root extract and fractions for sedative and anti-depressant activities using three experimental murine models: open field test, forced swimming test and elevated plus maze. The open field-test is a screening model for assessing anxiety-related behaviour in rodents (Stanford, 2007). It is generally believed that animals, when removed from their

cage and placed in a novel environment, exhibit anxiety, fear and stress, which is manifested as decreased in ambulation and exploration as well as in normal rearing and grooming behaviours (Bikomo *et al.,* 2017). Changes in these measurements that are related to locomotor activities have been used to assess the sedative or stimulant effect of pharmacological agents and extracts from plants (Lalonde and Strazielle, 2008). A high level of locomotor activity indicates mental wakefulness or alertness whereas a decrease in locomotion indicates calmness and sedation, which could be interpreted as reduced CNS excitability (Islam *et al*., 2015). The results in the open field test revealed decreased number of line crossing, centre square duration, rearing, and grooming in a non-dose dependent manner while increasing freezing time compared with the control. This effect indicates of a reduced excitability of the central nervous system (CNS) and sedation (Ozturk *et al.*, 1996; Okoli *et al.*, 2010). The ethyl acetate fraction (EF) also exhibited a decrease in line crossing, centre square duration, and grooming but paradoxically decreasing and increasing freezing time and rearing. This tendency of decreasing freezing time and increasing rearing may be attributed to the complexity and higher concentration of some phytochemical constituents, which may have resulted in the amplification, or inhibition of biochemical processes to produce the observed neurobehavioral activity.

The forced swimming test is a behavioural test that indicates the clinical efficacy of various types of anti-depressant drugs in rodents. In this model, the immobility displayed by rodents when subjected to unavoidable stress such as forced swimming is thought to reflect a state of despair or lowered mood, which is considered as depressive disorders in humans (Foyet *et al*., 2011). It is well-known that low level of monoamines in synapses results in depression, and classical antidepressants such as amitriptyline act by inhibiting reuptake of monoamines (5-HT and noradrenaline), increase levels of these neurotransmitters and show antidepressant activity (Sanchez-Mateo *et al*., 2007; Rojas *et al*., 2011). Treatment with *Z. portoricensis* root extract decreased the duration of immobility accompanied by an increase in swimming duration, which was more prominent at 100 mg/kg. The fractions also exhibited significant decrease in immobility duration and increased swimming duration, likewise with HF producing the highest effects. Interestingly, at the 400 mg/kg dose, the effect of EF was comparable to that of the standard agent, amitriptyline. This suggests an anti-depressant-like activity on the central nervous system (CNS) which may be attributable, like amitriptyline, to the reuptake inhibition mechanism of monoamine neurotransmitters. Elevated plus maze (EPM) is considered a popular and most widely validated tests for assessing anxiolytic related behavioural changes or assaying new benzodiazepine-like anxiolytic agents (Pellow *et al.,* 1985). In the EPM test, the preference shown for the closed arms reflects an aversion to the open arms caused by fear or anxiety induced by open space. *Z. portoricensis* root extract exhibited increased number of entries and duration spent in the open arms while the fractions and diazepam decreased open arms entry and duration. Previous studies had reported the ability of several plants to cause increased exploration in the open arms of the EPM (Helli´on-Ibarrola *et al.,* 2006). However, it is likely, that the various fractions, especially EF, exhibited anxiogenic activity and by extrapolation sedative effect similar to that observed with the reference drug, diazepam, and may have stimulated GABA and/or benzodiazepine receptors.

Furthermore, the neuropharmacological activity of many plants has been attributed to their phenolic contents (Bhatacharya and Satyan, 1997). Previous phytochemical analysis of *Z. portoricensis* extract and fractions revealed the presence of various phenolic constituents (Iyanyi *et al.,* 2020). These constituents may have contributed to the agonistic activities at $GABA_A$ receptor complex in the CNS, indicating that they can act as benzodiazepine-like agents (Protapaditya *et al.,* 2011; Khatoon *et al.,* 2014). Hence, they might partly be responsible for the sedative and CNS-depressant activity.

In conclusion, the findings from this study showed that *Z. portoricensis* root extract and fractions possess sedative and anti-depressant activities, which are likely mediated through GABA inhibitory mechanisms. Further studies are ongoing to identify the phytochemical constituent(s) responsible for the central nervous system anti-depressant effect, elucidate its structure and exact mechanism(s) of action.

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