



Antidepressant Activity of Methanol Stem Bark Extract of *Ficus platyphylla* Del (Moraceae) in Mice

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ABSTRACT

Background & Aim: Depression is a heterogeneous mood disorder affecting both people in developing and developed countries. The drugs used in its management are associated with adverse effects and delayed response which compromises their therapeutic benefits. This makes it worthwhile to look for antidepressant plants with proven advantage and favourable benefit-to-risk ratio. *Ficus platyphylla* is used traditionally in West Africa for the management of mental illnesses. The aim of this study was to evaluate the antidepressant potential of the methanol stem bark extract of *F. platyphylla*.

Experimental: Thin layer chromatographic finger prints of the extract were established. The oral median lethal dose of the extract was estimated using OECD 420 guidelines. Antidepressant activity of the extract at doses of 125-500 mg/kg was evaluated using tail suspension test (TST) and forced swim test (FST). The Effects of the extract on motor co-ordination deficit and locomotion were evaluated using beam walking assay (BWA) and open field test (OFT) respectively.

Results: The chromatographic profile suggested the presence of steroids, tannins, flavonoids, alkaloids and saponins. The LD50 was found to be ≥ 2000 mg/kg orally. The extract significantly ($p < 0.01$) and dose dependently (125, 250 and 500 mg/kg) decrease the duration immobility in the TST and FST. There is no significant increase in the number of lines crossed and on the number of foot slips in the OFT and BWA respectively.

Recommended applications/industries: The methanol stem bark extract of *F. platyphylla* possesses antidepressant activity. The phytoconstituents found present in the plant assumed to be responsible for the activity can be characterized and isolated to serve as lead compounds in the treatment of depression.

1. Introduction

Depression is a severe disorder affecting millions of people which is the fourth leading cause of disability

worldwide (WHO, 2001) with approximately over half of depressed patients experiencing suicidal thoughts and suicidal attempts (Vikran and Swati, 2011). Antidepressant drugs used in the management of

depression have been proven to be effective. However, they are associated with some disadvantages including various unwanted side effects, severe interactions and delayed response (Ronald, 2014). Additionally, reports have shown that some patients do not show response to any given treatment better than placebo.

However, naturally originated drugs were found to be effective with lower suicidal risk and minimal side effects profile (Dhingra and Sharma, 2006). This made search for new treatment modalities from medicinal plants in management of psychiatric disorders to progress tremendously. Therefore, medicinal plants such as *F. platyphylla* with folkloric claims used in psychiatric abnormalities are useful alternatives in the search for novel antidepressant from plant origin. The plant *F. platyphylla* (FP) Del.-Holl belongs to the family Moraceae. It is a tall tree of about 18 metres height and 6 meters in diameter popularly known as flake rubber tree, red Kano rubber tree and gutta-percha tree in English, "Ogbagba" in Nupe and "Gamji" in Hausa. *Ficus platyphylla* is an epiphyte, widely available in crown of open and wooded savannah, believed to have evolved from Senegal to Northern and Southern Nigeria (Nnabuk *et al.*, 2012). It was reported to be used in northern Nigeria for the management of epilepsy and other psychiatric disorders (Chindo *et al.*, 2009).

A scientific evidence proposed the plant *F. platyphylla* to contain phytoconstituents with anticonvulsant activities (Chindo *et al.*, 2014). The analgesic, anti-inflammatory (Amos *et al.*, 2008) and fertility enhancing (Ugwah-Oguejiofor *et al.*, 2011) effects of the plant have also been scientifically validated. Additionally, an ethnobotanical survey among Hausa tribes of Kaduna State reported the use of *F. platyphylla* in the management of depression (Shehu *et al.*, 2017). Thus, this suggested the screening of the methanol stem bark extract of *F. platyphylla* for antidepressant potentials.

2. Materials and Methods

2.1. Plant Collection and Extraction

The stem barks, leaves and fruits of plant *F. platyphylla* (SBFP) were collected. The plants were taken to Herbarium Site of Department of Biological Sciences, Ahmadu Bello University Zaria where it was identified and authenticated. A specimen voucher number 900106 was assigned there in the Department.

The SBFP were transported to Department of Pharmacognosy and Drug Development where they were dried under shade with occasional weighing until fixed weight obtained. The plant materials were grounded using mortar and pestle. About 1000 grams of powdered SBFP was extracted with 2.5 liters of methanol via soxhlet extraction. The solution was concentrated under temperature 45° C which resulted in a brownish mass identified as methanol stem bark extract of *F. platyphylla* (MEFP). The extract was stored in desiccator until needed for the work. Aqueous solution was freshly prepared for each study using distilled water.

2.2. Animals

Albino mice (Swiss type weighing 18-22 grams) of both sexes were bought from the Animal House Facility of Pharmacology and Therapeutics Department, Ahmadu Bello University Nigeria. They were kept in improvised propylene cages under natural day and light cycle. The animals were given laboratory animal feeds and water freely available. All tests protocols carried out were as approved by the University Animal ethical committee and conducted within 7.00 to 5.00 hours.

2.3. Drugs and Chemicals

Some of the chemicals used for the experiment were Imipramine (Tofranil GSK brand), Diazepam (Roche, France), Methanol (Fluka-Aldrich)

2.4. Phytochemistry

Phytochemical tests were done on the methanol extract of the *Ficus platyphylla* (MEFP) using thin layer chromatographic finger printing technique (Marston and Hostettmann, 1991).

2.5. Acute Toxicity Studies

Acute toxic dose (LD₅₀) was determined using Organization for Economic Co-operation and Development (OECD 420) guidelines in mice. In this method, two groups each of three mice were fasted 3 hours before administration, then fasted body weight was used to calculate doses administered. Food was further withheld for 1-2 hours after the MEFP has been administered. The extract was administered in one oral dose using canula. A start dose of 5000 mg/kg (limit test) was used for one mouse in the first phase and observed for 48 hours. The mouse died and the main test was conducted where another mouse was

dose at 2000 mg/kg then observed as above. The mouse survived, and an additional four mice were dosed and all five mice were each observed within 30 minutes post treatment, then occasionally within 24 hours with observation most at first 4 hours and then every day for 14 days. Changes in skin and fur, eyes and mucosa, behaviour pattern and central nervous systems activities were observed. Animals were further observed for shaking, seizures, salivation, diarrhoea, wilting, sedation and coma. Time of onset of toxic symptoms and disappearance were also noted. Individual weights of animals was determined weekly for two weeks.

2.6. Antidepressant Screening

2.6.1. Tail suspension test in mice

Mice were kept in propylene cages for 10 days under natural day and night cycle prior to test, with food and water *ad libitum*. They were taken to test area and adapted for 1 hour. Forty animals divided into five groups each of eight mice were used. Groups 1, 2 and 3 received graded doses of MEFP (125, 250 and 500 mg/kg) orally 1 hour prior to test. Group 4 and 5 were administered distilled water (10 ml/kg) and imipramine (15 mg/kg) respectively. For the test, each mouse was hung on the edge of a shelf 58 cm high above a table surface with a masking tape placed about 1 cm from the tip of the tail. Immobility time was recorded over 6 minutes period (Steru *et al.*, 1985).

2.6.2. Forced swim test

Forty mice were taken to laboratory one day before the test and kept individually in cages with food and water freely available. On the day of test, mice were grouped into five each of eight animals. Groups 1, 2 and 3 received 125, 250 and 500 mg/kg of MEFP orally. Groups 4 and 5 were treated with distilled water (10 ml/kg) and imipramine (15 mg/kg) respectively. One hour after treatment, each mouse was forced to swim inside a vertical Plexiglass cylinder of 24 cm height, 12 cm in diameter containing about 12 cm level of water at temperature of 25 degrees. The immobility time was measured over 5 minutes period. An animal was considered immobile when it floated passively in the water in a hunched but upright position (Alpermann *et al.*, 1992).

2.6.3. Test for locomotor behaviour (Open field test)

Forty animals were shared into five groups each of eight animals. The first, second and third groups received 125, 250 and 500 mg/kg of MEFP orally 1 hour prior to test. Group 4 and 5 received distilled water (10 ml/kg) and imipramine (15 mg/kg) respectively. Each mouse was placed in white wooden open field apparatus (70×70×35 cm, length × breadth × height) of which one wall is made up of transparent plexiglass and also a plexiglass floor divided into 16 visible squares (15×15 cm) with a central square. Peripheral and central square crossing behavior of each mouse was recorded for 5 minutes with the aid of a camera suspended at the top of the apparatus. The open field inner surface area was cleaned with 10% alcohol between tests (Rex *et al.*, 1996, 1998).

2.6.4. Test for motor co-ordination deficit (Beam walking assay)

Mice were forced to walk from one point on a ruler of length 80 cm, width 3 cm placed 30 cm above a table by a wooden support to a targeted goal box (Magaji *et al.*, 2008). Each mouse was tested thrice and made to be aware that there was a goal box that could be reached. A ruler was used because the mouse easily crosses it with minimum anxiety. About forty mice that successfully attempted the walk were randomly grouped into five groups. The first, second and third groups received 125, 250 and 500 mg/kg of MEFP orally one hour prior to test. The fourth and fifth groups received distilled water (10 ml/kg) and diazepam (0.25 mg/kg) respectively via the oral route. An hour post-treatment, each mouse was placed at one end of the beam which was 60 cm long, 8 mm in diameter and elevated 30 cm above a table and allowed to walk to the targeted goal box. Fallen mice were returned to the point of fall, a maximum of one minute was allowed on beam. The number of foot slips (one or both hind limbs slipped from the beam) was counted (Stanley *et al.*, 2005).

2.6.5. Novel object recognition task (NORT)

It involved the use of open field arenas (44 × 44 × 17 cm²) kept in a sound attenuated cubicle with reduced light. The NORT was divided into familiarization, training and retention sessions carried out over three days. On day one, each mouse was exposed (habituated) to open field apparatus for 30 minutes. On day two (training session), mice were exposed to a 10 minutes' trial in the presence of two identical objects

made up of cylindrical glassware of diameter 3 cm and height 8 cm packed with white cotton placed oppositely 12 cm from the walls. Exploration time for the objects by each mouse was hand-scored using stopwatches. Mice with exploration time less than 3 seconds were not used for the test. On day three (test session), mice were subjected to a trial choice where familiar object F and a novel object N were placed oppositely by the corner for 10 minutes. The exploration time of the two objects F and N was scored for 5 minutes. After each test, apparatus and objects were cleaned with 70% ethanol solution. Each mouse was placed in the centre of the apparatus facing the wall and allowed to freely explore it and the objects (Sahay *et al.*, 2011).

Exploration of object is taken as the animal moving its nose close to the object at a distance of about 2 cm. In addition, if animal placed the fore paws on the objects but not climbing it is considered exploration. Data from this test were expressed as (1) exploration time (in seconds) of each object which was calculated as time spent exploring familiar or novel object by total exploration time of both objects and (2) a discrimination index (DI) between objects, calculated as the exploration time difference between the novel object (N) and the familiar object (F) divided by the total exploration time of both objects ($DI = [N - F] / (N + F)$). A high significant discrimination index reflects good recognition memory.

2.7. Statistical analysis

Values were expressed as mean \pm SEM. The differences in the mean duration of immobility, climbing and swimming from FST, mean duration of immobility from TST, mean exploration time and mean discrimination index from NORT, mean number of foot slips from BWA and mean count of line crossed from OFT among different treated groups were analysed using one-way ANOVA followed by Bonferroni post hoc test using SPSS version 23.0. A value of $p < 0.05$ was considered significant.

3. Results and discussion

The present study attempted to provide some scientific rationale on ethnomedicinal use of methanol stem bark extract of *F.platyphylla* in the treatment of depressive illnesses using the TST and FST. The methanol stem bark extract of *F.platyphylla* decreased the duration immobility in both TST (Figure 1) and

FST (Figure 2) in the treated mice. Significant response was obtained at 125 mg/kg ($p < 0.05$), and at doses of 500 and 1000 mg/kg ($p < 0.01$) in the TST. Significant response ($P < 0.05$) was also obtained at doses of 250, 500 and 1000 mg/kg tested in the FST followed by increased climbing activity with no swimming modifications (Figure 3).

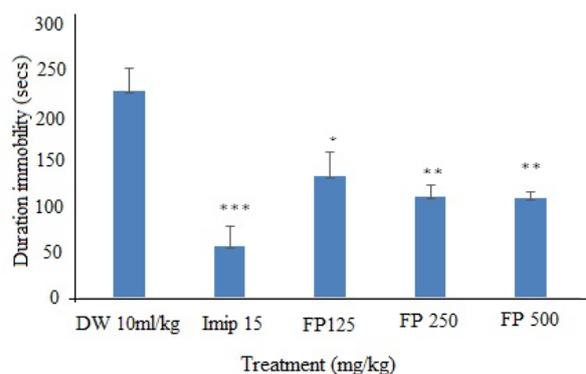


Figure 1. Effects of methanol stem bark extract of *Ficus platyphylla* (FP) and Imipramine (Imip) on the TST in mice. Animals were acutely treated with FP (125, 250 or 500 mg/kg, *po*), distilled water (10 ml/kg), or imipramine (15 mg/kg, *po*). Each column represents the mean \pm S.E.M. of 8 animals. Data was analysed using one-way ANOVA followed by Bonferroni post hoc test, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ significantly different from distilled water treated group.

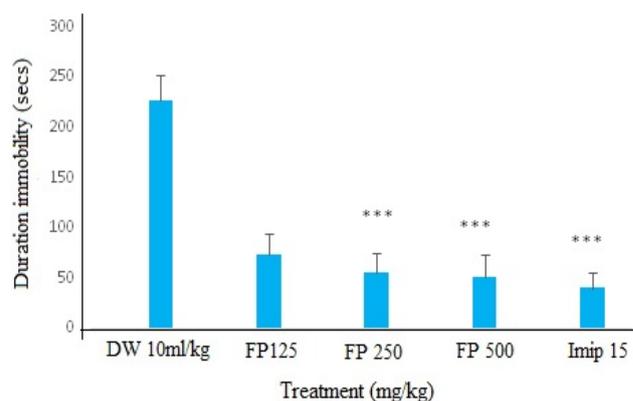


Figure 2. Effects of methanol stem bark extract of *Ficus platyphylla* (FP) and imipramine (Imip) on the FST in mice. Each column represents the mean \pm S.E.M. of 8 animals. Data was analysed using one-way ANOVA followed by Bonferroni post hoc test, *** $P < 0.001$ significantly different from distilled water treated group.

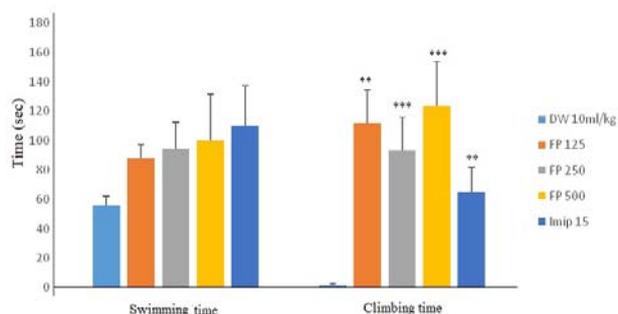


Figure 3. Effect of methanol stem bark extract of *Ficus platyphylla* (FP) and Imipramine (Imip) on swimming and climbing time on FST in mice. Animals were acutely treated with FP (125, 250 or 500 mg/kg, *po*), distilled water (10 ml/kg), or imipramine (15 mg/kg, *po*). Each column represents the mean \pm S.E.M. of 8 animals. Data was analysed using one-way ANOVA followed by Bonferoni post hoc test, ** $P < 0.01$, *** $P < 0.001$ significantly different from distilled water treated group.

Both behavioural models are widely accepted for assessing pharmacological antidepressant activity (Bourin, 1990; Porsolt *et al.*, 1977). The FST is the most utilized pharmacological model for screening novel antidepressants in rodents with acute or immediate treatment (Cryan *et al.*, 2002).

The test is considered sensitive and relatively specific to all types of antidepressants like tricyclics, serotonin selective reuptake inhibitors and MAO inhibitors (Detke *et al.*, 1995). Although all antidepressant drugs were observed to reduce immobility in the FST, two distinctive behavioural patterns were reported. It has been practically ascertained that swimming is more with serotonergic compounds like fluoxetine, while climbing is linked to compounds like tricyclic antidepressants with selective effects on noradrenergic transmission (Vazquez-Palacios *et al.*, 2004). In this study, treatment with MEFP dose dependently decreased immobility which was accompanied by an increase in climbing activity. Several studies indicated that immobility, swimming and climbing behaviours are displayed by different classes of antidepressant agents. The activity pattern showed by the MEFP and imipramine of increased climbing without swimming modifications is the pattern showed by agents that act via the adrenergic pathways. However, FST has not

been viewed as a consistent model for observing selective serotonin reuptake inhibitory action, but are generally reported as active in the TST with greater pharmacological activity as compared to FST (Cryan *et al.*, 2005). The ability of the MEFP to reduce duration immobility in the TST has further ascertain the antidepressant activity and the utilization of adrenergic pathways.

Control mice when placed in the open field arena exhibited exploratory behaviour marked by the number of lines crossed while the mice treated with methanol stem bark extract of *Ficus platyphylla* unlike diazepam did not alter the number of lines crossed (Figure 4). Similarly, the methanol stem bark extract of *F. platyphylla* did not impair motor coordination at the tested doses (Figure 5).

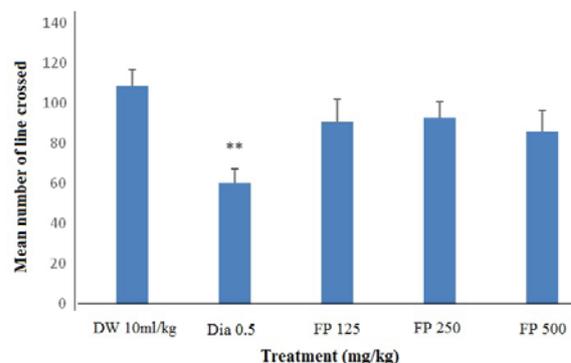


Figure 4. Effects of methanol stem bark extract of *Ficus platyphylla* (FP) and Diazepam (Dia) on the Number of Lines Crossed by mice in the OFT. Animals were acutely treated with the extract (125, 250, or 500 mg/kg, *p.o.*), distilled water (10 ml/kg), or diazepam (10 mg/kg, *p.o.*). Each column represents the mean \pm S.E.M. of 8 animals. Data analysis was performed using One-way ANOVA followed by Bonferoni post hoc test, **= $P \leq 0.01$, significantly different from distilled water-treated animals.

Thus, antidepressant effect of MEFP was further observed not to be associated with any motor and stimulant effects, due to its insignificant change in locomotion of mice in comparison with control in the beam walking assay and open field test. This indicates that the extract neither stimulates nor inhibits the central nervous system (CNS) within the tested dose range. Several studies have also shown its lack of excitatory or inhibitory effects on the CNS (Chindo *et al.*, 2014). The result from the OFT further eliminated the probability of false positive results in FST and TST.

This ensured that the increased active behaviours in the FST and TST were not as a result of CNS stimulatory effect and confirmed the specificity of antidepressant like effect of the extract. It has also further explained the dose dependent effect of the extract on immobility and climbing behaviours resulting in increased response on increasing the dose.

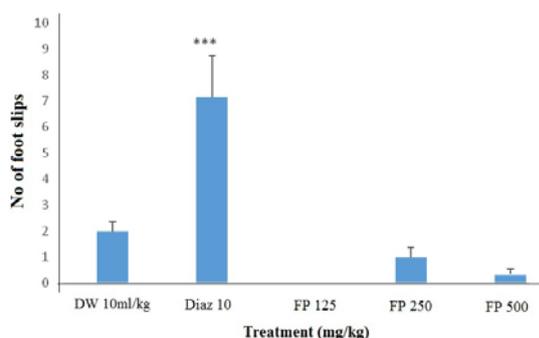


Figure 5. Effects of methanol stem bark extract of *Ficus platyphylla* (FP) and Diazepam on Motor Coordination Deficit in mice. Each column represents the mean ± S.E.M. of 6 animals. Data analysis was performed using One-way ANOVA followed by Bonferroni post hoc test, ***= $P \leq 0.001$, significantly different from distilled water treated animals.

The methanol stem bark extract of *F.platyphylla* had insignificant effect on the exploration time (Figure 6) as well as the discrimination index (Figure 7).

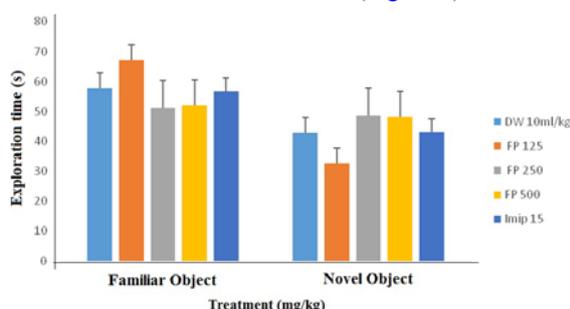


Figure 6. Mean Exploration Time of Identical Objects and Novel Object in the 5-min Acquisition Phase of the Novel Object Recognition Task (NORT) following acute Methanol Stem Bark Extract of *Ficus platyphylla* (125, 250 and 500 mg/kg p.o.), Imipramine 15 mg/kg and Distilled water 10 ml/kg Administration in Mice. Data are expressed as mean ± S.E.M and were analysed by one-way ANOVA followed by Bonferroni *post-hoc* test, ($n=8$).

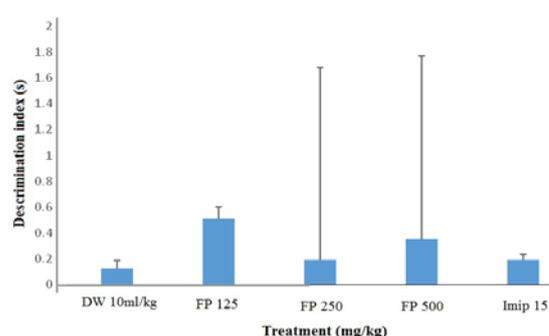


Figure 7. Effects of methanol stem bark extract of *Ficus platyphylla* (FP) (125, 250 and 500 mg/kg p.o.), Imipramine 15 mg/kg and Distilled water 10 ml/kg on the discrimination index (DI). Data were expressed as the mean±S.E.M. and were analysed by one-way ANOVA followed by Bonferroni *post-hoc* test, ($n=8$).

The connections between novelty and behaviour has been considered worthy of attention by many neuropharmacologists. Novelty encompasses distortion from expected likelihood of an event on the basis of both prior information and internal estimated probable circumstances (Antunes and Biala, 2012). Additional interesting aspect about novelty is to know that rodents can be affected by a novel stimulus. The novel tests are utilized to determine effects of various pharmacological therapies as well as brain alterations (Leger *et al.*, 2013). The three tested doses of MEFP did not show any effect on exploratory behaviour as well as on the discrimination index.

Phytochemical tests of methanol stem bark extract of *F.platyphylla* revealed the presence of flavonoids, tannins, saponins, alkaloids and other phenolic compounds (Table 1, Plate I).

Table 1. Phytochemical constituents present in the methanol stem bark extract of *Ficus platyphylla*.

S/No	Phytoconstituents	Inference
1	Alkaloids	+
2	Flavonoids	+
3	Tannins	+
4	Saponin glycoside	+
5	Cardiac glycoside	+
6	Unsaturated Steroids and Triterpenes	+
7	Anthraquinones	+
8	Carbohydrates	+

These secondary metabolites are reported to have wide biological modifications including central nervous system activities (Emamghoreishi and Talebianpour, 2009; Priyanka *et al.*, 2012; Ashok *et al.*, 2013; Mamta *et al.*, 2013). Thus, these phytoconstituents may be responsible for the reported antidepressant effect of *F. platyphylla*.

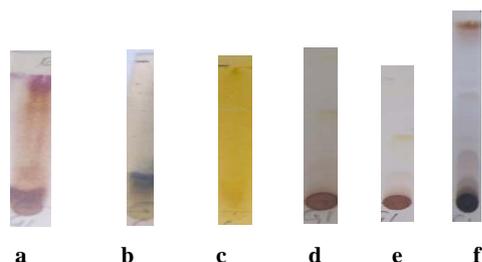


Plate 1. Thin layer chromatogram of the methanol stem bark extract of *Ficus platyphylla* developed in butanol: acetic acid: Water (8:1:1) and sprayed with a) P-anisaldehyde; b) ferric chloride c) dragendorff d) Aluminium chloride e) Borntrager's reagent f) Liebermann's burchard reagent.

The LD₅₀ was found to be ≥ 2000 mg/kg orally in mice with insignificant change in body weights of mice. Symptoms of coma and death were reported when the extract was given at 5000 mg/kg (Table 2). The signs of symptoms observed at the dose of 5000 mg/kg are an indication of its potential toxicity when used at higher doses.

Table 2. Median Lethal (LD50) values for methanol stem bark extract of *Ficus platyphylla*. Data was analyzed using One-way ANOVA followed by Dunnett's test, then presented as mean \pm SEM, n=5.

S / n o	LD ₅₀ Values	Onset of toxicity	Duration of toxicity	Mean body Weight (g)		Signs and symptoms of toxicity
				0 (day)	14(day)	
1	≥ 5000	Immediately	≤ 24 hours	18.6 \pm 2.1	0	Coma, Death
2	≥ 2000	Nil	Nil	19.33 \pm 2.9	17.67 \pm 2.9	Nil

4. Conclusion

This study showed that the methanol stem bark extract of *F. platyphylla* possesses significant antidepressant effects; and provided some scientific basis for the folkloric use of the plant in depressive illnesses. Certainly, further studies are required for

isolation and identification of the bioactive compound(s) responsible for the observed activity.

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6. References

- Alpermann, H.G., Schaut, U., Usinger, P. and Hock, F.J. 1992. Pharmacological effects of Hoc 249: A new potential antidepressant, *Drug Development Research*, 25: 267-282.
- Amos, S., Chindo, B.A., Edmond, I., Akah, P., Wambebe, C. and Gamaniel, K. 2008. Anti-inflammatory and antinociceptive effects of *Ficus platyphylla* Extract in Mice and Rats. *Journal of Herbs, Spices and Medicinal Plants*, 9: 47-53.
- Antunes, M. and Biala, G. 2012. The novel object recognition memory: neurobiology, test procedure and its modifications. *Cognitive Processing*, 13: 93-110.
- Ashok, K.B.S., Lakshman, K., Velmurugan, C., Sridhar, S.M. and Gopisetty, S. 2013. Antidepressant Activity of Methanolic Extract of *Amaranthus spinosus*, *Basic and Clinical Neuroscience*, 5: 11-17.
- Bourin, M. 1990. Is it possible to predict the activity of a new antidepressant in animals with simple psychopharmacological tests? *Fundamentals of Clinical Pharmacology*, vol. 4, pp 49-64.
- Chindo, B.A., Anuka, J.A., McNeil, L., Yaro, A.H., Adamu, S.A., Amos, A., Connelly, W.K., Lees, G., Gamaniel, K.S. 2009. Anticonvulsant properties of Saponins from *Ficus platyphylla* stem bark. *Brain Research Bulletin*, 786: 276-282.
- Chindo, B.A., Yau, J., Danjuma, N.M, Okhale, S.E., Gamaniel, K.S. and Becker, A. 2014. Behavioural and anticonvulsant effects of the standardized extract of *Ficus platyphylla* stem bark. *Journal of Ethnopharmacology*, 154: 351-60.
- Cryan, J.F., Markou, A. and Lucki, I. 2002. Assessing antidepressant activity in rodents: recent development and future need. *Trends in Pharmacological Sciences*, 23: 238-245.
- Cryan, J.F., Mombereau, C. and Vassout, A. 2005. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological

- and genetic studies in mice. *Neuroscience and Behavioural Reviews*, 29: 571-625.
- Detke, M.J., Rickels, M. and Lucki, I. 1995. Assessing antidepressant activity in rodents: recent developments and future need. *Trends in Pharmacological Sciences*, 121: 66-72.
- Dhingra, D. and Sharma, A. 2006. A review on antidepressant plants, *Natural Product Radiance*; 5: 144-152.
- Emamghoreishi, M. and Talebianpour, M.S. 2009. Antidepressant effect of *Melissa officinalis* in the forced swim test. *DARU Journal of Pharmaceutical Sciences*, 17: 42-47.
- Leger, M., Quideville, A., Bouet, V., Haelewyn, B., Boulard, M., Schumann-Bard, P. and Freret, T. 2013. Object recognition test in mice. *Nature Protocols*, 8: 2531-2537.
- Mamta, S., Jyoti, S., Rajeev, N., Dharmendra, S. and Abhishek, G. 2013. Phytochemistry of Medicinal Plants. *Journal of Pharmacognosy and Phytochemistry*, 1: 168-182.
- Marston, A. and Hostettmann, K. 1991 Modern separation methods. *Natural Product Representative*; 8: 391-413.
- Nnabuk, O.E., Paul, O.A., Casimir, E.G. and Eno, E.E. 2012. Rheological Modeling and Characterization of *Ficus platyphylla* Gum exudates. *Journal of Chemistry*, 2013: 1-10.
- Porsolt, R.D., Anton, G., Blavet, N. and Jalfre, M. 1978. Behavioural despair in rats: a new model sensitive to antidepressive treatments. *European Journal of Pharmacology*, 47: 379-391.
- Priyanka, B., Sridhar, Y. and Shankaraih, P. 2012. Antidepressant and muscle relaxant activity of *Cardiospermum halicabum* Linn Roots in Mice. *Journal of Advanced Pharmaceutical Sciences*, 2: 193-200.
- Rex, A., Voigt, J.P., Voits, M. and Fink, H. 1998. Pharmacological evaluation of a modified open field test sensitive to anxiolytic drugs. *Pharmacology, Biochemistry and Behaviour*, 59: 677-683.
- Ronald, S.D. 2014. Pathophysiology of depression and innovative treatments: remodeling glutamergic synaptic connections. *State of the Art*, 16: 11-27.
- Sahay, A., Kimberly, N.S., Alexis, S.H., Colin, M.O., Mazen, A.K., Nisha, S.B., Andre, A.F., Alex, D. and Rene, H. 2011. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*, 472: 466-470.
- Shehu, A., Magaji, M.G., Yau, J. and Abubakar, A. 2017. Ethnobotanical survey of medicinal plants used for the management of depression by Hausa tribes of Kaduna state, Nigeria. *Journal of Medicinal Plants Research*, 11: 562-567.
- Stanley, J.L., Lincoln, R.J., Brown, T.A., McDonald, L.M., Dawson, G.R. and Reynolds, D.S. 2005. The mouse beam walking assays offers improved sensitivity over the mouse rotarod in determining motor coordination deficits induced by benzodiazepines. *Journal of Psychopharmacology*, 19: 221-7.
- Steru, L., Chermat, R., Thierry, B. and Simon, P. 1985. Tail Suspension test: a new method for screening antidepressants in mice. *Psychopharmacology*, 85: 367-370.
- Ugwah-Oguejiofor, C.J., Bello, S.O., Okolo, R.U., Etuk, E.U., Ugwah, O.M. and Igbokwe, V.U. 2012. *Ficus platyphylla* promotes fertility in female *Rattus norvegicus* Wistar Strain: a preliminary study. *Reproductive Biology and Endocrinology*, 9: 145.
- Vazquez-Palacios, G., Bonilla-Jaime, H., Velazquez-Moctezuma, J. 2004. Antidepressant like effects of the acute and chronic administration of nicotine in the forced swimming test and its interaction with fluoxetine. *Pharmacology, Biochemistry and Behaviour*, 78: 165-169.
- Vikram, H.P. and Swati, J.K. 2011. Evaluation of antidepressant like effect of *Citrus maxima* leaves in Animal Models of Depression. *Iran Journal of Basic Medical Sciences*, 14: 478-483.
- WHO. The World Health report 2001: Mental health: new understanding, new hope. *Geneva*: 2001.