RESEARCH ARTICLE

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Acute Antidepressant Activity Investigation of Selected African Medicinal Plants in Mice: A Preliminary Study

Ajibola Monisola Umarudeen, Mohammed Garba Magaji, Ferhat Khan, and Abdulhakim Abubakar

ABSTRACT

The therapeutic gap arising from high global incidence of depressive disorders and the efficacy and toxicity shortcomings of existing antidepressant drugs indicate a need to further search the plant kingdom with the goal of discovering novel antidepressant pharmacotherapeutic agents. Crude 50% ethanol *Terminalia catappa* (CETC), *Tapinanthus dodoneifolius* (CETD) and *Bryophyllum pinnatum* (CEBP) leaf extracts were investigated for their acute antidepressant activity on the forced swim (FST) and tail suspension (TST) tests. Groups of mice (n = 6) were each exposed to the tests 1 hour following oral administration of distilled water (10 ml/kg), extracts (125, 250 and 500 mg/kg body weight) and fluoxetine (20 mg/kg), using the mean immobility time as endpoint. Qualitative phytochemical analysis of these crude extracts indicated the presence of alkaloids, cardiac glycosides, saponins, phenolic compounds, tannins, steroids, carbohydrates, flavonoids, terpenoids and anthraquinones. Compared to distilled water treatments (FST, 84.16 ±3.92; TST, 82.85 ±5.84), CETC (FST, 84.17 ±4.44, 71.67 ±1.89, & 44.31 ±8.23*; TST, 79.03 ±2.62, 74.10 ±3.11, & 52.57 ±6.00*) and CEBP (FST, 77.02 ±2.70, 66.11 ±4.42 & 49.99 ±4.20*; TST, 69.51 ±7.24, 49.73 ±11.85* & 46.39 ±5.68) treatments caused dose-dependent and significant (P < 0.05) reductions in the mean immobility times on both paradigms while CETD caused dose-dependent and significant (P < 0.05) reductions of this parameter only on the TST. Overall, acute antidepressant activities at the highest dose level (500 mg/kg) of all extracts approximated that of the standard antidepressant fluoxetine (20 mg/kg). The findings of this study are a justification for the widespread ethnomedicinal uses of extracts of these plants. There is a need to further characterize their antidepressant and other neuropharmacological effects. 1.**

Keywords: *Bryophyllum pinnatum*, Crude ethanol, forced swim test, tail suspension test, *Tapinanthus dodoneifolius*, *Terminalia catappa*.

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I. Introduction

Depression (major depression, major depressive disorder, MDD) is a clinical disorder dominated by moodiness, anhedonia, demotivation, low self-esteem, and emotional instability. Reports indicate this psychological disorder has high global severity and prevalence (up to 20% in some populations) – asserting heavy socioeconomic burdens in virtually all world communities [1]–[5].

Despite the huge and increasing prevalence/severity of MDD, so far, only two therapeutic options - pharmacotherapy and/or psychotherapy - are commonly deployed in its management [6]–[8]. Psychological treatment as a mono-therapeutic approach to alleviating depressive symptoms is reportedly encumbered with cumbersome, expensive treatment requirements and slow, unpredictable, sub-optimal, and relapse-prone effectiveness [8]–[10]. Meanwhile, the pharmacotherapeutic approach to these disorders has its own challenges – including the fact the antidepressant drugs currently available in clinical practice belong to few chemical and mechanistic (majorly monoamine-related) classes, thus limiting pharmacotherapeutic choices. In addition, some of the most frequently used antidepressants - the tricyclics – have reports of intolerable toxicities and therapy discontinuations associated with their use, and the current first-choice drugs for MDD - the selective serotonin reuptake inhibitors (SSRIs) are frequently associated with the occurrence of delayed and failed efficacies [11]–[16]. In view of the high prevalence and socioeconomic burden of MDD, the limitations of psychotherapy coupled with the paucity, toxicity, and efficacy liabilities of the current antidepressant drugs, there is a need to discover new antidepressant pharmacotherapy agents to bridge the therapeutic gap.

Medical historical antecedents indicate the plant kingdom is an attractive direction to look in the search for new generations of therapeutic agents for different disease classes, including antidepressants. Medicinal plants and their products have been found effective for traditional treatments

of diverse disease spectra – cancers, diabetes mellitus, snake bites, hypertension, infection, neuropsychiatric disorders, and so on [17]–[23]. Plant pharmacopeia has also been the direct sources of several modern-day drugs and bioactive compounds – antineoplastics (paclitaxel, vincristine, and vinblastine) [24], antimalarials (quinine, artemisinins, Andrographis Paniculata tablets) [25], [26], cardiotonics (digoxin, digitoxin) [26], [27], analgesics (codeine, aspirin, dronabinol, capsaicin, cannabidiol) [26], [27], anti-infectives (the penicillin, papaverine, schumannificine, isoquinolines, quinolines) [27], [28], antidiabetics (rutin, egallic acid, quercetin, mangiferin) [29] and antipsychotics (reserpine) [5], [30]. Studies have previously shown significant anxiolytic activity of extracts obtained from *P. methysticum* and *H. maculatum* [31], [32], and significant antidepressant activity for extracts of *R. officinalis, C. longa, M. charantia*, *A. paniculate* and *W. somnifera*. It is worth noting that the antidepressant activity demonstrated by *H, perforatum* L. extracts is comparable to, but better tolerated than, the standard antidepressants – albeit it is only effective for mild and moderate depression [33]–[35].

To address the therapeutic gap arising from the high depression disease burden and the failings of the existing antidepressant agents and availing the rich deposits of bio-active compounds in the African flora, this study selected three African medicinal plants – *Terminalia catappa* (*T. catappa*), *Tapinanthus dodoneifolius* (*T. dodoneifolius*) and *Bryophyllum pinnatum* (*B. pinnatum*) on ethnopharmacological grounds to be screened for their acute antidepressant potential.

T. catappa (Tropical almond tree) Combretaceae is a medium to large-sized Tropical tree whose leaves, stem bark, fruits, and roots are said to possess rich nutritional and potent medicinal benefits. Decoctions from different parts of the plant have been traditionally used to treat diverse diseases, including abdominal colic, leprosy, stomach ulcer, reduced/lost libido, fever, skin infections, urinary tract infections, headache, and cardiac decompensation [36]–[40], and extracts obtained from its different components have reported to exhibit significant hypoglycemic, anti-inflammatory, anti-cancerous, antibacterial, lipid-lowering, hepatoprotective and age-retarding activities [41]–[47]. However, there is a paucity of scientific reports on its antidepressant activity, and the aim of the study is to investigate the acute antidepressant activity of freshly fallen *T. catappa* brown leaves in mice.

T. dodoneifolius (Loranthaceae) selected for this study is an epiphyte to *T. catappa* host tree. *T. dodoneifolius*, like other epiphytic Loranthus species, is a common leafy shrub parasitic on several host trees (Cocoa, Kolanut, Neem, Tamarind, *Parkia biglobosa*, *T. catappa* etc.) [48] - [50]. Reports indicate decoctions from *T. dodoneifolius* and its synonyms have efficacy in traditional management of malarial fever, hyperglycemia, raised blood pressure, dysentery, nervous disorders, abdominal colic, neoplasms, diarrhea, and gonorrhea [51]–[56], and their extracts have been associated with a wide spectrum of pharmacological activities including antimalarial, hypotensive, anti-neoplastic, anti-dyspeptic, and antimicrobial [53]–[57] effects. Aqueous *T. dodoneifolius* bark extract had exhibited significant anxiolytic and antidepressant activities in mice, [58] but the leaf extract of this plant has not been screened for its antidepressant activity, and this study aims to assess its acute antidepressant activity in mice.

The third plant selected for the current study, *B. pinnatum* (Lam.) Pers. (syn: *K. pinnata*), is an invasive herb reputed for diverse ethnomedicinal efficacies and ethnopharmacological activities. Some of the traditional indications for this plant, commonly called Miracle or air plant in Nigeria, include rheumatoid arthritis, gastrointestinal and ear infections, palpitation, renal calculi, smallpox, hyperglycemia, chicken pox, cardiac failure, menstrual disorders, migraine headache, tumours, hypertension, retained placenta, hypertension, and conjunctivitis [59]–[63]. Reported pharmacological activities for extracts of this plant and its synonym K. pinnata include anti-inflammatory, antidiabetic, antibacterial, hepatoprotective, immunosuppressive, antineoplastic, hypotensive, nephroprotective, hypnotic, anxiolytic, myorelaxant and analgesic [62]–[70]. However, the extracts of this plant are yet to be examined for their antidepressant potential, and the aim of this study is to determine their acute antidepressant activity in mice. Acute antidepressant activities of the selected plant extracts will be determined using the tail suspension (TST) and forced swim (FST) tests. TST and FST – with proven predictive and construct validity for the detection of antidepressant activity in putative and known compounds and for the characterization of depressive behavioural patterns in mice – are well suited for primary antidepressant activity screening of the selected medicinal plant extracts.

II. Materials and Methods

A. Drugs and Plant Materials

Fluoxetine capsules (Flutex, 20 mg) were purchased from a pharmacy around Ahmadu Bello University campus, Zaria. *B. pinnatum* fresh leaves were harvested in Gwagwalada area of Abuja, while freshly fallen leaves of *T. catappa* and fresh leaves of *T. dodoneifolius* epiphyte on *T. catappa* were obtained from the premises of Ahmadu Bello University main campus, Zaria, Nigeria, in December 2022. Botanical authentication of *B. pinnatum* and *T. catappa* leaves was done by Dr Idrisu Mohammed of the Faculty of Agriculture and Rural Development, University of Abuja, and that of *T. dodoneifolius* was done by Malam Muazu K. of the Department of Botany, Ahmadu Bello University, Zaria. *T. dodoneifolius* and *T. catappa* leaves were each air-dried to dryness. Owing to the difficulty of air-drying *B. pinnatum* leaves due to their succulent nature, they were first blended with an electrical blender to fine paste, after which it was thinly spread on a clean, flat, inert white surface and air-dried by electric fanning to dryness. The dry leaves were pulverized to fine powders and stored in plastic containers. 21 g of dry *B. pinnatum* leaves, 40 g each of dry *T. dodoneifolius* and *T. catappa* leaves were each soaked in 0.5 L of equal volumes of distilled water and ethanol for 24 hours, following which the macerates were separately Whatman paper filtered. The filtrates were separately air dried aided by electric fanning until their weights remained constant.

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B. Experimental Animals

Healthy adult white albino Swiss mice of equal number of sexes were obtained and kept in clean plastic battery cages for at least 14 days under room temperature under a 12-hour light/dark cycle with access to feeds and water ad libitum in the animal house of the Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna State, North-west Nigeria. Good and ethical laboratory practices were adopted before and throughout this study. Ethical clearance for this study was sought and obtained from the Ethical Committee of Ahmadu Bello University, Zaria.

C. Qualitative Phytochemical Analysis of Plant Extracts

Extracts were tested for the presence/absence of bioactive compounds by the following standard methods: Dragendorff test for alkaloids, Keller-Kiliani test for cardiac glycosides, frothing test for saponin, Lead acetate test for phenolic compounds, Ferric Chloride test for tannins, Salkowiski test for steroids, Molisch test for carbohydrates, Shinoda test for flavonoids, Liebermann Burchard test for terpenoids, and Bontragers test for anthraquinones [73], [74].

D. Antidepressant Screening: Forced Swim Test (FST)

All mice were brought into the experimental room at least 1hour before commencing the behavioural studies. Oral distilled water (10 ml/kg; negative control), extracts (125, 250, & 500 mg/kg), and fluoxetine (20 mg/kg) treatments were administered to experimental groups 1 hour before testing. Behavioural studies were carried out between 10. 00 and 18.00 h. Briefly, FST for the determination of acute antidepressant activity was carried out in randomized groups of treated mice (n=6; equal number of sexes) weighing 22.60 ± 0.67 g by gently dropping them in transparent plexiglass (13 cm diameter, 24 cm height) cylinders. They were observed to freely swim in the cylinders for a total of 6 minutes – with the period of immobility of the last 4 minutes recorded against each mouse.

E. Antidepressant Screening: Tail Suspension Test (TST)

All mice were brought into the experimental room at least 1hour before commencing the behavioural studies. Oral distilled water (10 ml/kg; negative control), extracts (125, 250, & 500 mg/kg), and fluoxetine (20 mg/kg) treatments were administered to experimental groups 1 hour before testing. Behavioural studies were carried out between 10. 00 and 18.00 h. Briefly, TST for the determination of acute antidepressant activity was carried out in randomized groups of treated mice (n=6; equal number of sexes) weighing 20.90 ± 0.45 g by suspending each mouse by the tail at about 50-cm height of a cubicle and allowed to float freely for 6 minutes. The period of immobility of the last 4 minutes was recorded against each mouse.

F. Data Analysis

Data was presented as mean ± standard error of the mean (mean ±SEM); analyzed using one way ANOVA. All graphs were drawn using Microsoft Excel. *P*-values less than 0.05 ($P < 0.05$) was taken to be statistically significant.

III. Results

A. Extract Yields

Forty (40) g of T. catappa, 40 g of T. dodoneifolius, and 21 g of B. pinnatum dry leaf powders soaked in 0.5 L of fifty percent ethanol yielded 13.40 g (31.50%) rich brown crude ETC, 4.40 g (20.10%) bright green crude ETD, and 7.80 g (19.50%) deep green crude EBP extracts, respectively.

B. Qualitative Phytochemical Analysis Results

Phytoconstituents present in crude 50% ethanol T. catappa (CETC), T. dodoneifolius (CETD), and B. pinnatum (CEBP) extracts are shown in Table I.

TABLE I: Phytoconstituents in CETC, CETD, and CEBP

Phytoconstituents	CETC	CETD	CEBP
Alkaloids	+	+	+
Cardiac Glycosides	+	+	+
Saponins	+	+	+
Phenolic compounds	+	+	+
Tannins	+	+	+
Steroids	+	+	+
Carbohydrates	+	+	+
Flavonoids	+	+	+
Terpenoids	+	+	+
Anthraquinones	+	-	+

Note. + = present; - = absent.

C. Forced Swim Test (FST) Result

Compared to distilled water (negative control) treatment (Table II), single acute CETC and CEPD administrations caused dose-dependent reductions in mean percent immobility period in mice that were significant ($P < 0.05$) at their highest doses. CETD treatment exhibited an insignificant ($P > 0.05$) non-dose dependent inverted U-shape reduction in this parameter while fluoxetine (20 mg/kg) treatment caused a very significant ($P > 0.001$) reduction in the mean percent immobility in the experimental animals.

TABLE II: Effect of Plant Extracts on Mean Immobility of Mice on FST

Exp. groups	Mean % immobility reduction		
Extract doses	125	250	500
Distil. water	84.16 ±3.92	84.16 ±3.92	84.16 ±3.92
CETC	84.17 ±4.44	71.67 ±1.89	44.31 ±8.23*
CETD	53.00 ±5.73	64.86 ±4.58	62.50 ±8.41
CEBP	77.02 ±2.70	66.11 ±4.42	49.99 ±4.20*
Fluoxetine	34.10 ±7.74**	34.10 ±7.74**	34.10 ±7.74**

All results were expressed as mean ± S.E.M of mice (n=6). Analysis was done using the one-way ANOVA with significance set at *P*-values ≤ 0.05.

D. Tail Suspension Test (TST) Result

Compared to negative control (distilled water) treatment (Table III), single acute CETC treatments caused dose-dependent reductions in mean % immobility that was significant ($P < 0.05$) at the highest dose level of 500 mg/Kg; CETD caused a similar dose-dependency and significant reduction in this parameter; and CEBP demonstrated dose-dependent and significant ($P < 0.05$) and very significant ($P < 0.001$) reductions in the mean values of this parameter in the animals treated with it. Mean percent immobility reductions caused by the three extracts at their highest levels were comparable to that caused by fluoxetine 20 mg/kg treatment.

TABLE III: EFFECT OF PLANT EXTRACTS ON MEAN IMMOBILITY OF MICE ON THE TST

Exp. groups	Percent immobility reduction		
Extract doses	125	250	500
Distil. water	82.85 ±5.84	82.85 ±5.84	82.85 ±5.84
CETC	79.03 ±2.62	74.10 ±3.11	52.57 ±6.00*
CETD	63.96 ±8.21	64.08 ±5.90	49.72 ±4.48*
CEBP	69.51 ±7.24	49.73 ±11.85*	46.39 ±5.68**
Fluoxetine	51.31 ±3.21*	51.31 ±3.21*	51.31 ±3.21*

Note. All results were expressed as mean ±S.E.M of mice (n = 6). Analysis was done using the One-way ANOVA. Significance set at *P*-values ≤ 0.05.

IV. DISCUSSION

The rising global incidence of depressive disorders in the face of the therapeutic shortcomings of existing antidepressant drugs makes the need to continue to search the plant kingdom for the discovery of new antidepressant compounds – preferably with novel mechanistic persuasions different from the monoaminergic pathways - using cost-effective and predictive experimental paradigms is imperative. Both the FST and TST adopted for antidepressant activity testing of the crude ethanol extracts (CETC, CETD, and CEBP) of the medicinal plants investigated in this study are ethologically well validated not only for the primary screening of antidepressant activity of putative and known compounds but also for the characterization of experimental animal inter-strain phenotypes and the deciphering of the neurobiological underpinnings of different depressive disease states [75], [76]. The endpoint of interest on both tests is the percent (%) immobility, i.e., the proportion of test duration for which the experimental rodent remains immobile or inactive. Immobility, in this context, is the natural tendency of rodents to assume immobile/inactive/quiet mode (despair mode) after an initial brief phase of active efforts to exit a confinement/restraint from which escape is foreclosed. Immobility in these experimental setups is a measure of the level of despair in mice, and this rodent behaviour is thought to correlate with depressed mood/hopelessness in human depressive disorders. Rodent percent immobility has been shown to be sensitive to effects of diverse classes of antidepressant agents – with experimental animals exposed to antidepressants on these tests exhibiting less percent immobility [77].

The finding of consistent dose-dependent and significant acute depressant activity on both FST and TST (Tables II and III) represents one of the few reports of antidepressant activity on extracts obtained from *T. catappa*. This report is only second (as far as our literature search) to and in agreement with an earlier finding of antidepressant effects of hydrolysable tannins of hydro-alcoholic *T. catappa* leaf extract in a mouse chronic mild stress model [78].

T. dodoneifolius leaf extract, CETD, exerted antidepressant depressant activity on both paradigms in this study, albeit insignificantly on the FST (Tables II and III). This finding, again, is one of the few reports on the antidepressant activity of *T. dodoneifolius* extracts generally and probably the first report ever, of antidepressant activity screening of *T. dodoneifolius* epiphytic on *T. catappa*. The demonstrated antidepressant activity is in tandem with a previous finding of a stem bark extract of this epiphyte exhibiting antidepressant activity in mice [58]. The inconsistent findings on CETD's demonstration of non-dose dependent and insignificant (P > 0.05) mean percent immobility reductions on the FST, on the one hand, and of dose-dependent and significant reductions in the same parameter on the TST, on the other hand, is unexpected. This is because *T. dodoneifolius* from which CETD leaf extract was obtained in this study, is an epiphyte on *T. catappa* host tree, which leaf extract has demonstrated consistent significant acute antidepressant activity on both tests in this same study. Since the phytochemistry and biological activities of epiphytes are expected to reflect those of their host trees [79], the variation of CETD antidepressant activity from that of CETC needs further scrutiny. The lack of significant antidepressant activity by CETD on FST as opposed to TST may also be due to differences in the neurotransmitter sensitivity of the two tests – with the mouse TST reportedly more sensitive to a wider spectrum of antidepressant compounds than FST [80].

B. pinnatum leaf extract (CEBP) treatments caused impressive acute antidepressant activity on both assays (Tables II and III). Again, this finding is one of the few, if not the first and only, reports on the antidepressant activity of *B. pinnatum* leaf extracts. The observed antidepressant activity of CEBP in this study may be related to a previous report of acute anxiolytic activity in young zebra fish [81]. *T. catappa*, *T. dodoneifolius* and *B. pinnatum* whose crude ethanol leaf extracts are investigated in this study, are widely used medicinal plants with efficacy in the traditional treatments of diverse disease spectrums. The observed acute antidepressant activity in this study and other previously reported ethnomedicinal/ethnopharmacological/biological activities of these plant extracts may be related to the rich presence of phytochemical constituents in them (Table I) [82]–[84].

V. CONCLUSION

Taken together, crude ethanol *T. catappa, T. dodoneifolius* and *B. pinnatum* leaf extracts have demonstrated significant acute antidepressant activity in mouse FST and TST. This and other several biological activities of these medicinal plants may be due to their possession of rich phytoconstituents. The findings in this study are a justification for their widespread ethnomedicinal uses. Further investigations of antidepressant and other neuropharmacological activities of these plant extracts are recommended.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

REFERENCES

[1] Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of depression in the community from 30 countries between 1994 and 2014. *Sci Rep*. 2018. 8 (1): 2861.

[2] Edwards N, Walker S, Paddick S-M, Prina AM, Chinnasamy M, Reddy N, Mboya LB, Mtei M, Varghese M, Nakkasuja N, Guerra M, Sapkota N, Dotchin C. Prevalence of depression and anxiety in older people in low- and middle- income countries in Africa, Asia and South America: A systematic review and meta-analysis. *Journal of Affective Disorders*. 2023; 325:656-674.

[3] Kessler RC, Bromet EJ, de Jonge P, Shahly V, Wilcox M. The burden of depressive illness. In Cohen NL (Ed.). *Public health perspectives on depressive disorders.* Johns Hopkins Uni. Press; 2017, pp. 40–66.

[4] Lépine JP, Briley M. The increasing burden of depression. *Neuropsychiatric disease and treatment*, 2011;7(sup1):3–7.

[5] Farahani M. S., Bahramsoltani R., Farzaei M. H., Abdollahi M., Rahimi R. (2015). Plant-derived natural medicines for the management of depression: an overview of mech. of action. *Rev Neurosci*. 2015;26 (3):305–321.

[6] Patel K, Abdool PS, Rajji TK, Mulsant BH. Pharmacotherapy of major depression in late life: what is the role of new agents? *Expert Opinion on Pharmacotherapy*. 2017; 18 (6):599–609.

[7] Keefe RS, McClintock SM, Roth RM, Doraiswamy PM, Tiger S, Madhoo M. Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. *The Journal of clinical psychiatry*. 2014;75(8):3169.

[8] Barber JP, Barrett MS, Gallop R, Rynn MA, Rickels K. Short-term dynamic psychotherapy versus pharmacotherapy for major depressive disorder: a randomized, placebo-controlled trial. *The Journal of Clinical Psychiatry*. 2011;72 (1):19513.

[9] Fonagy P. Psychotherapy research: do we know what works for whom? *The British Journal of Psychiatry*. 2010;197(2):83–85.

[10] Minelli A, Zampieri E, Sacco C, Bazzanella R, Mezzetti N, Tessari E, Barlati S, Bortolomasi M. Clinical efficacy of trauma-focused psychotherapies in treatment-resistant depression (TRD) in-patients: A randomized, controlled pilot-study. *Psychiatry Research.* 2019;273:567–574.

[11] De Maat S, Dekker J, Schoevers R, De Jonghe F. Relative efficacy of psychotherapy and pharmacotherapy in the treatment of depression: A meta-analysis. *Psychotherapy Research*. 2006;16 (5):566–578.

[12] Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds III CF. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. *World psychiatry*. 2013;12(2):137–148.

[13] Thomas KL, Ellingrod VL. Pharmacogenetics of selective serotonin reuptake inhibitors and associated adverse drug reactions. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2009;29(7):822–831.

[14] Marshe VS, Islam F, Maciukiewicz M, Bousman C, Eyre HA, Lavretsky H, Mulsant BH, Reynolds CF 3rd, Lenze EJ, Müller DJ. Pharmacogenetic implications for antidepressant pharmacotherapy in late-life depression: a systematic review of the literature for response, pharmacokinetics and adverse drug reactions. *The American Journal of Geriatric Psychiatry*. 2020;28(6): 609–629.

[15] Outhoff K. Switching antidepressants. *South African Family Practice.* 2015;57(2):32–34.

[16] Lader M. Limitations of current medical treatments for depression: disturbed circadian rhythms as a possible therapeutic target. *European neuropsychopharmacology*. 2007;1 (12):743–755.

[17] Efferth T, Li PCH, Konkimalla VSB, Kaina B. From traditional Chinese medicine to rational cancer therapy. *Trends in Molecular Medicine*. 2007;13(8):353–361.

[18] Ezuruike U., Prieto JM. The use of plants in the traditional management of diabetes in Nigeria: Pharmacological and toxicological considerations. *Journal of Ethnopharmacology*. 2014.155(2):857-924.

[19] Tahraoui A, El-Hilaly J, Israili ZH, Lyoussi B. Ethnopharmacological survey of plants used in the traditional treatment of hypertension and diabetes in south-eastern Morocco (Errachidia province). *Journal of Ethnopharmacology*. 2007. 110 (1):105-17.

[20] Shim SY, Aziana I, Khoo BY. Perspective and insight on Clinacanthus nutans Lindau in traditional medicine. *International Journal of Integrative Biology*. 2013;4 (1):7.09738363.

[21] Hosseinzadeh S, Jafarikukhdan A, Hosseini A, Armand R. The Application of Medicinal Plants in Traditional and Modern Medicine: A Review of Thymus vulgaris. *International Journal of Clinical Medicine*, 2015;6(9):635–642.

[22] Tamuno I. Traditional medicine for HIV infected patients in antiretroviral therapy in a tertiary hospital in Kano, Northwest Nigeria. *Asian Pacific Journal of Tropical Medicine*. 2011;4(2):152–155.

[23] Srivastava JK, Shankar E, Gupta S. Chamomile: A herbal medicine of the past with a bright future (review). *Molecular Medicine Reports.* 2010;3(6):895–901.

[24] Habtemariam S, Lentini G. Plant-derived anticancer agents: Lessons from the pharmacology of Geniposide and its aglycone, Genipin. *Biomedicines*. 2018;6(2):39.

[25] Prakoso N, Zakiyah Z, Liyanita A, Rubiyanto D, Fitriastuti D, Ramadani A, Kamari A, Mow S. Antimalarial Activity of *Andrographis Paniculata Ness's* N-hexane Extract and Its Major Compounds. *Open Chemistry.* 2019;17(1):788–797.

[26] Newman D J, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of Natural Products*. 2020;83(3):770–803.

[27] Veeresham C. Natural products derived from plants as a source of drugs. *J Adv Pharm Technol Res*. 2012;3(4):200-201.

[28] Vlietinck AJ, De Bruyne T, Apers S, Pieters LA. Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection. *Planta Med*. 1998;64(2):97–109.

[29] Rahman MM, Dhar PS, Sumaia, Anika F, Ahmed L, Islam MR, Sultana NA, Cavalu S, Pop O, Rauf A. Exploring the plant-derived bioactive substances as antidiabetic agent: An extensive review. *Biomed Pharmacother*. 2022 Aug;152:113217. doi: 10.1016/j.biopha.2022.113217. Epub 2022 Jun 6. PMID: 35679719.

[30] Monu M, Parle M, Kadian M, Sharma K. A Review on psychosis and anti-psychotic plants. *Asian Journal of Pharmaceutical and Clinical Research.* 2015;8(4):24–28.

[31] Yeung KS, Hernandez M, Mao JJ, Haviland I, Gubili J. Herbal medicine for depression and anxiety: A systematic review with assessment of potential psycho-oncologic relevance. *Phytotherapy Research*. 2018;32(5):865–891.

[32] Bach–Rojecky L, Kalodjera Z, Samarzija I. The antidepressant activity of Hypericum perforatum L. measured by two experimental methods on mice. *Acta Pharm*. 2004;54 (2):157–162.

[33] Farahani MS, Bahramsoltani R, Farzaei MH, Abdollahi M, Rahimi R. Plant-derived natural medicines for the management of depression: an overview of mechanis. of action. *Rev Neurosci*. 2015;26 (3):305–321.

[34] Rahman MR, Ali M, Sharif M, Tajmim A. A review study on the traditional plants has potential antidepressant property. *MOJ Cell Sci Rep*. 2017;4 (5):138–145.

[35] De Vry J, Maurel S, Schreiber R, de Beun R, Jentzsch KR. Comparison of hypericum extracts with imipramine and fluoxetine in animal models of depression and alcoholism. *Eur Neuropsychopharmacol*. 1999 Dec;9(6):461–468. doi: 10.1016/s0924-977x (99) 00005-x. PMID: 10625112.

[36] Lim T.K. Edible medicinal and non-medicinal plants. Vol. 2. New York: Springer; 2012, pp. 143-157.

[37] Ratnasooriya WD and Dharmasiri MG. Effects of Terminalia catappa seeds on sexual behavior and fertility of male rats. *Asian J. Androl.* 2000;2 (3):213–219.

[38] Ahmed SM, Swamy V, Gopkumar P, Dhanapal R. Anti-diabetic activity of Terminalia catappa Linn. leaf extracts in alloxan-induced diabetic rats. *Iranian Journal of pharmacology and therapeutics*. 2005;4(1): 36–40.

[39] Anand AV, Divya N, Kotti PP. An updated review of Terminalia catappa. *Pharmacogn Rev*. 2015; 9(18):93–98.

[40] Chen PS, Li JH, Liu TY, Lin TC. Folk medicine Terminalia catappa and its major tannin component, punicalagin, are effective against bleomycin-induced genotoxicity in Chinese hamster ovary cells. *Cancer letters*, 2000;152(2):115–122.

[41] Akinsanya OB, Ayodele PF, Onifade OF, Salimom MO. extenuating Effects of terminalia catappa leaves and persea americana seed extracts on streptozotocin-induced lipids perturbation and pancreatic damage in diabetic rats. *Open Journal of Bioscience Research* (OJBR). 2021;2(1):01–09.

[42] Fan YM, Xu LZ, Gao J, Wang Y, Tang XH, Zhao XN, Zhang ZX. Phytochemical and antiinflammatory studies on Terminalia catappa. *Fitoterapia*. 2004;75(3–4):253–260.

[43] Gao J, Tang X, Dou H, Fan Y, Zhao X, Xu Q. Hepatoprotective activity of Terminalia catappa L. leaves and its two triterpenoids. *Journal of Pharmacy and Pharmacology*. 2004 Nov;56(11):1449–1455.

[44] Taganna JC, Quanico JP, Perono RM, Amor EC, Rivera WL. Tannin-rich fraction from Terminalia catappa inhibits quorum sensing (QS) in Chromobacterium violaceum and the QS-controlled biofilm maturation and LasA staphylolytic activity in Pseudomonas aeruginosa. *J Ethnopharmacol.* 2011 Apr 12;134(3):865–871. doi: 10.1016/j.jep.2011.01.028. *Epub* 2011 Feb 1. PMID: 21291979.

[45] Lin CC, Hsu YF, Lin TC. Antioxidant and free radical scavenging effects of the tannins of Terminalia catappa L. *Anticancer Research*. 2001;21 (1A):237–243. PMID: 11299741.
[46] Pandya NB, Tigari P, Dupadahalli K, Kamurthy H, Nadendla RR. Antitumor and antioxidant status of Terminalia catappa against Ehrlich ascites carcinoma in Swiss albino mice. *Indian journal of pharmacology*. 2013 Sep;45(5):464.
[47] Wen KC, Shih I, Hu JC, Liao ST, Su TW, Chiang HM. Inhibitory effects of Terminalia catappa on UVB-induced photodamage in fibroblast cell line. *Evidence-Based Complementary and Alternative Medicine*. 2010;2011.
[48] WFO. *Tapinanthus dodonaeifolius* (DC.) Danser. Published on the Internet;http: //www.worldfloraonline.org/taxon/wfo-0000413258. 2023.
[49] Ayorinde BT, Akanji MA, Yakubu MT. Alterations in some marker enzymes of liver and kidney damage following chronic administration of aqueous extract of Tapinanthus globiferus leaves to rats. *Pharmacognosy Magazine*, 2008;4(15):S9–S14.
[50] Raji IA, Chaskda, AA, Manu SA, Downs CT. Bird species use of *Tapinanthus dodoneifolius* mistletoes parasitising African locust bean trees Parkia biglobosa in Amurum Forest Reserve, Nigeria. *Journal of Ornithology*. 2021;162 (4):1129–1140.
[51] Abdullahi Z, Anuka JA, Salawu AO, Hussaini IM. In-vivo antiplasmodial activity of methanol whole plant extracts of *Tapinanthus dodoneifolius* (DC) Danser in mice. *African Journal of Pharmacy and Pharmacology*. 2015;9(37):936–942.
[52] Burkill HM. The useful plants of west tropical Africa, Vols. 1-3. The useful plants of west tropical Africa, Vols. 1-3. 1995 (2. ed.).
[53] Mohammed M, Idris A, Gandu I, Tanko UM, Muhammad A, Adeiza A. Phytochemical and Antimicrobial Study on the Leaf Extract of Tapinanthus dodoneifolius (Van Teigh) Loranthaceae. *Journal of Advances in Medicine and Medical Research.* 2019;29(5):1–9.
[54] Deeni YY, Sadiq NM. Antimicrobial properties and phytochemical constituents of the leaves of African mistletoe (Tapinanthus dodoneifolius (DC) Danser) (Loranthaceae): an ethnomedicinal plant of Hausaland, Northern Nigeria. *J Ethnopharmacol*. 2002;83(3):235–40.
[55] Abdullahi Z, Anuka JA, Salawu AO, Hussaini IM. In-vivo antiplasmodial activity of methanol whole plant extracts of *Tapinanthus dodoneifolius* (DC) Danser in mice. *African Journal of Pharmacy and Pharmacology*. 2015;9(37):936–942.
[56] Ofem OE, Eno AE, Imoru J, Nkanu E, Unoh F, Ibu JO. Effect of crude aqueous leaf extract of Viscum album in hypertensive rats. *Indian Journal of Pharmacology*. 2007;39(1):15–19.
[57] Ouédraogo S, Aristide TN, Soméa ML, Pierre IG, Christa S, Bernard B, Ramaroson A. Cardiovascular Properties of Aqueous Extract from Tapinanthus Dodoneifolius DC. Danser. *Afr. J. Traditional, Complementary and Alternative Medicines*. 2005;2(1):25–30.
[58] Harquin Simplice F, David Emery T, Hervé Hervé NA. Enhancing spatial memory: anxiolytic and antidepressant effects of Tapinanthus dodoneifolius (DC) Danser in mice. Neurology Research International. 2014 Feb 5;2014.
[59] Rastogi R, Mehrotra B. Compendium of Indian Medicinal Plants. *Central Drug Research Institute, Lucknow*, 1990;1:388–389.
[60] Al-Snafi AE. The Chemical Constituents and Pharmacological Effects of Bryophyllum calycinum. A review. *International Journal of Pharma Sciences and Research* (IJPSR). 2013;4(12):171–176.
[61] Recknagel RO. Carbon tetrachloride hepatotoxicity. *Pharmacological Reviews*. 1967;19 (2):145–208.
[62] Quazi M, Sayyed N, Sheikh S, Gomase P, Choudhari A. Phytochemical analysis of chloroform extract of roots of *Kalanchoe pinnata* by HPLC and GCMS. *Int J Pharm Sci Res*. 2011;14(4):1693–1699.
[63] Plangger N, Rist L, Zimmermann R, von Mandach U. Intravenous tocolysis with *Bryophyllum pinnatum* is better tolerated than beta-agonist application. *Eur J Obstet Gynecol Reprod Biol*. 2006;124(2):168–172.
[64] Yamagishi T, Haruna M, Yan XZ, Chang JJ, Lee KH. Antitumor agents, 110, Bryophyllin B, A Novel Potent cytotoxic Bufadienolide from Bryophyllum Pinnatum. *J. Nat. Prod.* 1989;52 (5):1071–1079.
[65] Yadav NP, Dixit VK. Hepatoprotective activity of leaves of Kalanchoe Pinnata Pers. *Journal of Ethnopharmacology*. 2003;86(2-3):197–202.
[66] Salahdeen H, Yemitan OK. Neuropharmacological Effects of Aqueous Leaf Extract of Bryophyllum Pinnatum in Mice. *African Journal of Biomedical Research*. 2006. 9 (2): 101-107.
[67] Supratman U, Fujita T, Akiyama K, Hayashi H, Murakami A, Sakai H, Koshimizu K, Ohigashi H. Anti-tumor Promoting Activity of Bufadienolides from Kalanchoe pinnata and K. daigremontiana × butiflora. *Bioscience, biotechnology, and biochemistry*. 2001;65(4): 947–949.
[68] Rossi-Bergmann B, Costa SS, Borges MBS, da Silva SA, Noleto GR, Souza MLM, Moraes VLG. Immunosuppresive effect of the aqueous extract of Kalanchoe Pinnata in mice. *Phytothera*. *Res.* 1994;8(7):399–402.
[69] Siddharta P, Chaudhuri AKN. Further studies on the Anti¬inflammatory profile of the Methanolic Fraction of the fresh leaf extract of Bryophyllum Pinnatum. *Fitoterapia*. 1992;63(5): 451–459.
[70] Supratman U, Fujita T, Akiyama K, Hayashi H. New insecticidal bufadienolide, Bryophyllin C from Kalanchoe pinnata. *Biosci Biotechnol Biochem*. 2000;64 (6):1310–1312.
[71] Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary screening test for antidepressants. *Arch Int Pharmacodyn Ther*.1977;229(2):327–36.
[72] Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology* (*Berl*). 1985;85(3):367–370.
[73] Yadav RN, Agarwala M. Phytochemical analysis of some medicinal plants. *Journal of phytology*. 2011 Dec 14;3(12).
[74] Trease GE, Evans WE. Textbook of pharmacognosy. 13th ed. London: Baillière Tindall; 1989.
[75] Porsolt RD, Brossard G, Hautbois C, Roux S. Rodent models of depression: Forced swimming and tail suspension behavioral despair tests in rats and mice. In: Enna SJ, Williams M, editors. Current Protocols in Neuroscience. Hoboken, NJ: John Wiley & Sons, Inc; 2001. pp. 1–10. Chap 810.
[76] Castagné V, Porsolt R. D. & Moser P. Early behavioural screening for antidepressants and anxiolytics. *Drug Dev Res*. 2006 ;67: 729–742.
[77] Castagné V, Moser P, Porsolt RD. Behavioral Assessment of Antidepressant Activity in Rodents. In: Buccafusco JJ, editor. Methods of Behavior Analysis in Neuroscience. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2009. Chapter 6. PMID: 21204330.
[78] Chandrasekhar Y, Ramya EM, Navya K, Phani Kumar G, Anilakumar KR. Antidepressant like effects of hydrolysable tannins of Terminalia catappa leaf extract via modulation of hippocampal plasticity and regulation of monoamine neurotransmitters subjected to chronic mild stress (CMS). *Biomed Pharmacother*. 2017; 86:414–425.
[79] Majeed M, Pirzadah TB, Mir MA, Hakeem KR, Alharby HF, Alsamadany H, Bamagoos AA, Rehman RU. Comparative study on phytochemical profile and antioxidant activity of an epiphyte, *Viscum album* L. (white berry mistletoe), derived from different host trees. *Plants* (*Basel*). 2021;10(6):1191.
[80] Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. *Neurosci Biobehav Rev*. 2005;29(4–5):571–625.
[81] Martins Fernandes Pereira K, Calheiros de Carvalho A, André Moura Veiga T, Melgoza A, Bonne Hernández R, Dos Santos Grecco S, Uchiyama Nakamura M, Guo S. (2022). The psychoactive effects of Bryophyllum pinnatum (Lam.) Oken leaves in young zebrafish. *PLoS One*. 2022 Mar 9;17(3):e0264987.
[82] Chen PS, Li JH, Liu TY, Lin TC. Folk medicine Terminalia catappa and its major tannin component, punicalagin, are effective against bleomycin-induced genotoxicity in Chinese hamster ovary cells. *Cancer letters*. 2000;152(2):115–122.
[83] Deeni YY, Sadiq NM. Antimicrobial properties and phytochemical constituents of the leaves of African mistletoe (Tapinanthus dodoneifolius (DC) Danser) (Loranthaceae): an ethnomedicinal plant of Hausaland, Northern Nigeria. *J Ethnopharmacol*. 2002;83(3):235–240.
[84] Pattewar SV. Bryphyllum pinnatum: Phytochemical and Pharmacological Profile. *International Journal of Phytopharmacy*. 2012;2(1):1–8.