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.

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

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], antimarialars (quinine, artemisinins, Andrographis Paniculata tablets) [25], [26], cardiotonics (digoxin, digitoxin) [26], [27], analgesics (codeine, aspirin, dornabinol, capsaicin, cannabidiol) [26], [27], anti-infectives (the penicillins, papaverine, schumannifince, isoquinolines, quinolines) [27], [28], antiadibiotics (rutin, eagallic acid, quercetin, mangifirin) [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 bioactive 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 deccotions 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 ethnomedical 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, antiadibiotic, 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.
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 during 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, Salkowski test for steroids, Molisch test for carbohydrides, Shindoa test for flavonoids, Liebermann Burchard test for terpenoids, a Dragendorff test for alkaloids, and Keller Kiliani test for cardiac glycosides. Phytoconstituents present in crude 50% ethanol T. catappa (CETC), T. dodoneifolius (CETD), and B. pinnatum (CEBP) extracts are shown in Table I.

D. Antidepressant Screening: Forced Swim Test (FST)

All mice were brought into the experimental room at least 1 hour 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 cylinders (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 1 hour 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 22.60 ± 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

Fifty (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>
<thead>
<tr>
<th>Phytoconstituents</th>
<th>CETC</th>
<th>CETD</th>
<th>CEBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac Glycosides</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Saponins</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phenolic compounds</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tannins</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Steroids</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Flavonoids</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antraquinones</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Exp. groups</th>
<th>Mean % immobility reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distil. water</td>
<td>84.16 ±3.92</td>
</tr>
<tr>
<td>CETC</td>
<td>84.17±4.44</td>
</tr>
<tr>
<td>CETD</td>
<td>73.00±5.73</td>
</tr>
<tr>
<td>CEBP</td>
<td>77.02±2.70</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>34.10±7.74**</td>
</tr>
</tbody>
</table>

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.
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 depressive 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 depressive 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.
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