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Antidepressant activity of the n-Butanol fraction of *Terminalia macroptera* (Guill & Perr.) leaves in Mice

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Abstract: Depression is a disease that affects a high proportion of the world's population and people of different ages, preventing them from a good performance at work and in social relationships and causing emotional disorders in millions of families. *Terminalia macroptera* belongs to the family Combretaceae. It's a medicinal plant with numerous therapeutic benefits and is used to treat depression. The present study aimed to evaluate the antidepressant activity of the n-butanol fraction obtained from methanol leaves extract of *Terminalia macroptera*. Phytochemical screening and acute toxicity (LD_{50}) studies were done using standard procedures. The antidepressant activity was evaluated using a tail suspension test (TST) and forced swim test (FST) in mice. The phytochemical screening of the n-butanol fraction showed the presence of flavonoids, alkaloids, steroids, tannins and saponins. The intraperitoneal LD50 was found to be 1130 mg/kg in mice. The n-butanol at doses of 25, 50 and 100 mg/kg body weight significant, $P < 0.01$ and dose dependent decreased in the duration of immobility in both FST and TST. No significant changes were observed in the number of lines crossed in the Open Field Test. The results demonstrated that the fraction obtained from methanol leaves extract of *Terminalia macroptera* possesses antidepressant activity.

Keywords: n-Butanol fraction, *Terminalia macroptera*, Antidepressant activity, Depression, Medicinal plant

Introduction

Terminalia macroptera is native to Africa and can be found in Benin, Burkina Faso, Ghana, Senegal, Sudan, Uganda, Guinea-Bissau and Nigeria (Burkill, 1985). The plants are widespread gregarious savanna trees that may be readily recognised by the prominent tuft of nearly stalkless pale green leaves and fruits (Silva *et al.* 2012). Pharmacological screening is the first step and most effective method of identifying medicinal plants today in Ethno-pharmacological. Research into psychoactive plants that may affect the central nervous system (CNS) has succeeded, apart from remarkable psychoactive constituents isolated from plants (usually containing alkaloids, flavonoids, saponins and tannins) such as cocaine from Erythroxylon coca (coca), morphine from Papaver somniferum (opium poppy) and other plants, such as Hypericum perforatum (St John's wort), have developed evidence of beneficial therapeutic activity over the last several decades (Sarris *et al*. 2011).

Depression is a complex recurring illness with an important global public health problem. The symptoms of depression has been attributed to the hypo-functioning of monoamine neurotransmitters in the brain. The major neurotransmitters implicated in depressive episodes are noradrenaline, serotonin and dopamine (Fred-Jaiyesimi and Oredipe, 2013). Depression significantly contributes the diseases burden and also a life-threatening disorder that affects hundreds of millions of people worldwide (WHO, 2012). It often starts at a young age, reduces people's functioning, and often is recurring. It is the leading cause of disability and morbidity worldwide in terms of total years lost due to disability and morbidity (Kessler *et al*. 2009). Studies have shown a relationship between depression and comorbidity, especially due to cardiovascular diseases, epilepsy, stroke, pain syndromes, Parkinsonparkinson's disease, cancer and diabetes mellitus (Åkerblad *et al*. 2006). There are a lot of synthesised drugs utilised in treating the disorder. Still, most are associated with unwanted side effects and delayed onset of action and are effective in only 50 % of patients (Shehu *et al*., 2021).

Animal models served as an essential tool for studying the aetiology of depression and the development of effective therapeutic targets for an antidepressant agent (Porsolt *et al*., 1977; Steru *et al.*, 1985; Willner, 1997). These models significantly help in the understanding of psychiatric illnesses. However, some symptoms of depression are difficult to observe in animal models and these symptoms mainly limited to humans, which include: feelings of sadness, guilt, or suicidal thoughts (Nestler and Hyman, 2010).

The acute animal models for assessing new antidepressant agents include Tail suspension and Forced swim tests. These are all easy to use, have very good reproducibility and are used to select new antidepressant drugs. The classes of antidepressants decrease the immobility period during TST and FST by increasing the mobility of animals and improving or eliminating behavioural despair of animals (Abelaira *et al*., 2013).

The OFT is considered one of the most popular procedures used to measure behaviours in experimental animal models. It is a fast and provides various behavioural information ranging from locomotor activity to emotionality in rodents (Seibenhener and Wooten 2015). Locomotor activity due to psychostimulants (e.g. Amphetamine, Caffeine and Cocaine) results in a significant increase in mean squares crossed in OFT. An earlier study by Sani *et al*. (2021) has demonstrated the in-vivo antidepressant effect of methanol leaves extract *Terminalia macroptera.* However, this study aimed to evaluate the antidepressant activity of the butanol fraction obtained from methanol leaves extract of *Terminalia macroptera* in mice.

Materials and Methods

Drugs

Drugs and chemicals were obtained from reputable scientific suppliers such as Imipramine (Tofranil® GSK, Britain), methanol, n-hexane, ethyl acetate, and n-butanol (Sigma Chemical Co. St Louis USA) and distilled water.

Experimental Animals

Swiss albino mice (18 - 22 g) were obtained from the Animal House of the Department of Pharmacology, Bayero University Kano. Mice were housed and allowed to acclimatise with free access to food and water and maintained under standard laboratory conditions according to the National Academy of

Science guidelines for care and use of laboratory animals. All experimental protocols were approved by the College of Health Sciences, Ethics Committee BUK, with reference number BUK/CHS/REC/VII/53.

Preparation of Plant Extract and Fractionation

The plant leaves were collected from Kiru LGA., Kano State, Nigeria. It was identified and authenticated by a Taxonomist of the Department of Plant Biology, BUK, with specimen voucher number (BUKHAN 0511). The plant was in the Department of Pharmacology and Therapeutics laboratory, where it was air-dried and crushed using a mortar and pestle. About 1000 g of the pounded leaves materials was extracted with 3.5 L of methanol via Soxhlet extraction. The resultant extract was dried in a water bath at 45 °C. A blue-black solid mass of the methanol leaves extract obtained.

Fractionation

T. macroptera extract (100 g) was subjected to liquid-liquid partitioning to separate it into different fractions. The extract was reconstituted with 300 ml of distilled water. The reconstituted extract was placed in a separating funnel, and 300 ml of chloroform was added sequentially as a 1:1 (v/v) solution and shaken (Yaro *et al.*, 2015). The sample was left to stand for 30 minutes in the separating funnel until a fine separation line appeared, clearly indicating the sediment's supernatant before desorption. The process was repeated thrice until the chloroform fraction was exhaustively collected in a container and concentrated in a water bath maintained at 45ºC. The same process was sequentially repeated using ethyl acetate, n-butanol and the residual aqueous fractions.

The concentrated fractions were kept in sealed containers for further use, and the fractionation is diagrammatically represented as follows:

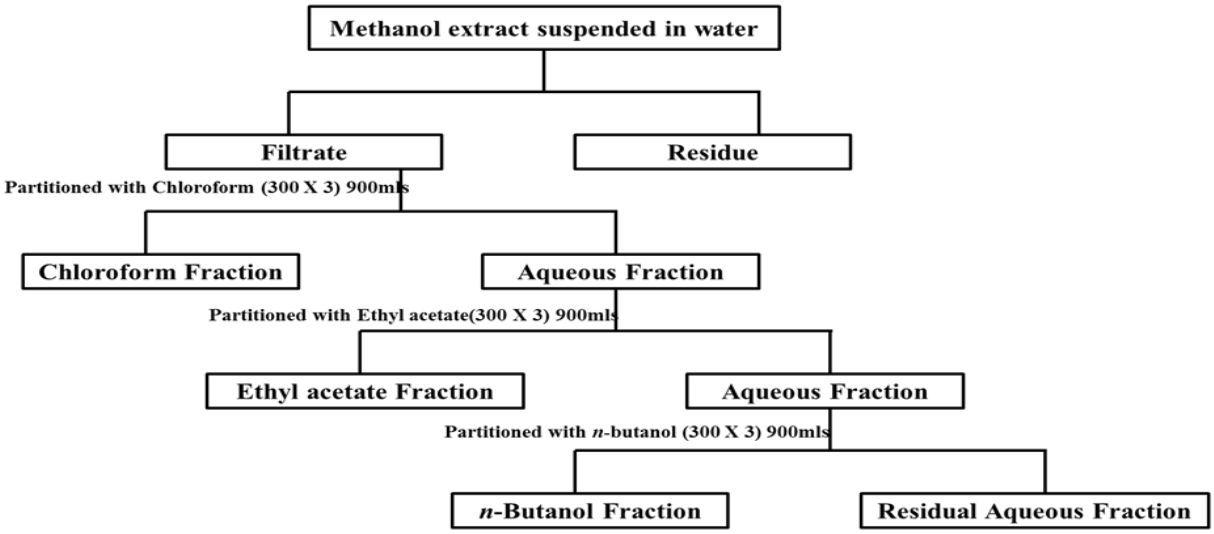

Plate I: Fractionation of the Methanol leaves Extract of *T. macroptera*.

Phytochemical screening

A freshly prepared n-Butanol fraction of methanol extract of *Terminalia macroptera* (NETM) was subjected to phytochemical tests to detect various chemical constituents using standard protocols (Trease and Evans, 1989).

Acute Toxicity Studies

Lorke's method was adopted to determine LD_{50} of n-Butanol fraction (Lorke, 1983). The method consists of two phases, and 13 mice of both sexes were used. Three groups of three mice each were administered with the NETM intraperitoneally at doses of 10, 100 and 1000 mg/kg body weight and observed for signs and symptoms of toxicity and death within 24 hours. In the second phase, which was determined by the first phase results, three groups of one mouse each were treated with the extracts or fractions at more specific doses of 1600, 2900 and 5000 mg/kg. Mice were observed for signs and symptoms of toxicity, including death for 24 hours. The LD_{50} was determined by calculating the geometric mean of the lowest dose that caused death and the highest dose for which the animal survived.

$LD_{50} = \sqrt{Lowest\ dose\ that\ causes\ death\ x\ highest\ dose\ in\ which\ the\ animal\ survived}$

Tail suspension test (TST)

The TST was performed according to the method described by Steru *et al.* (1985). Animals were randomly divided into five groups of six mice each. Group I was treated (*i.p*) with 10 ml/kg distilled water, group II with 10 mg/kg imipramine, while the three experimental groups were treated (*i.p*) with three graded doses (25, 50 and 100 mg/kg) of NETM. Thirty minutes later, mice were suspended on the edge of the shelf 58 cm above a table top by adhesive tape placed approximately 1cm from the tip of the tail. The duration of immobility was then recorded for 6 minutes after discarding activity in the first 2 minutes, during which the mouse tried to escape. The mouse was considered immobile when hung passively and remained motionless.

Forced swim test (FST)

The FST was performed according to the method described by Alpermann *et al.* (1992). Animals were randomly divided into five groups of six mice each. Group I was treated (*i.p*) with 10 ml/kg distilled water, group II with 10 mg/kg imipramine, while the three experimental groups were treated (*i.p*) with three graded doses (25, 50, and100 mg/kg) of NETM. Thirty minutes later, each was mouse placed in a Plexiglas cylinder tank of 40 cm in height and 18 cm in width filled with 15 cm of water at 25℃. A mouse was considered immobile

whenever it remained floating passively in the water in a slightly hunched but upright position with its nose just above the surface.

Open field test (OFT)

The OFT was performed according to the method described by Prut and Belzung (2003). Animals were randomly divided into five groups of six mice each. Group I was treated (*i.p*) with 10 ml/kg distilled water, group II with 10 mg/kg imipramine, while the three experimental groups were treated (*i.p*) with three graded doses (25, 50 and 100 mg/kg) of NETM. After thirty minutes of administration, each mouse was placed in white wooden open field apparatus (70×70×35 cm, length × breadth × height). The exploratory behaviour of each mouse in the apparatus was recorded for 5 minutes. The apparatus was cleaned with 10% ethanol before and after subjecting each mouse to the test.

Statistical analysis

All values were expressed as Mean ± SEM. Data were analysed by one-way analysis of variance (ANOVA) followed by Bonferroni as *post-hoc* tests using the International Business Machines Corporation's statistical package for social sciences (IBM SPSS statistics) version 23 (IBM SPSS, Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant.

Results

Preliminary Phytochemical Constituents of n-Butanol fraction of the T. macroptera

Phytochemical constituents of NETM revealed the presence of alkaloids, flavonoids, tannins, glycosides, saponins, steroids and anthraquinones (Table 1).

Table 1: Preliminary phytochemical constituent of the n-Butanol Fraction of NETM

Phytoconstituents	Inference
Alkaloids	+
Flavonoids	+
Tannins	+
Saponin	+
Glycoside	+
Steroids	+
Anthraquinones	-

Key: += Present, - =absent

Acute toxicity (LD_{50}) of n-Butanol fraction of the NETM

The intraperitoneal median lethal dose (LD_{50}) of n-Butanol fraction of the methanol leaves extract of *Terminalia macroptera* in mice was estimated to be 1,130 mg/kg *i.p.* body weight.

Effect of NETM on the Tail Suspension Test

The NETM decreased the duration of immobility in treated mice. A significant response was obtained at all the tested doses ($p < 0.01$) as compared to the distilled water (10 ml/kg) group. Similarly, the standard drug, imipramine (10 mg/kg), also decreased significantly ($p<0.01$) the duration immobility time (**Fig. 1**).

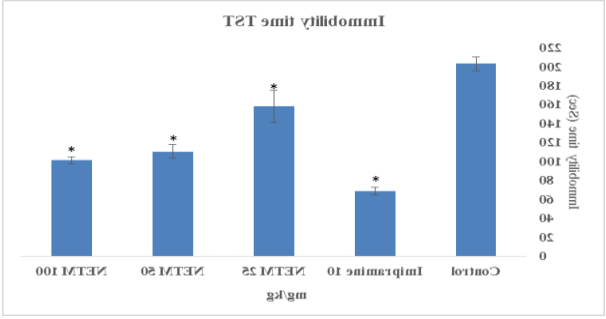

Figure 1: Effect of n-Butanol fraction on immobility time in tail suspension test. * $p < 0.01$, compared to control group using One-way ANOVA followed by Bonferroni's *post-hoc* test. n= 6, data = Means ± SEM, NETM = n-Butanol fraction of *Terminalia macroptera* methanol extract and control = distilled water 10 ml/kg.

Effect of NETM on the Forced Swim Test

The NETM treated mice. A significant response was obtained at all tested doses ($p < 0.01$) as compared to the distilled water (10 ml/kg) group. Similarly, the standard drug, imipramine (10 mg/kg), also decreased significantly ($p<0.01$) the duration immobility time (**Fig. 2**).

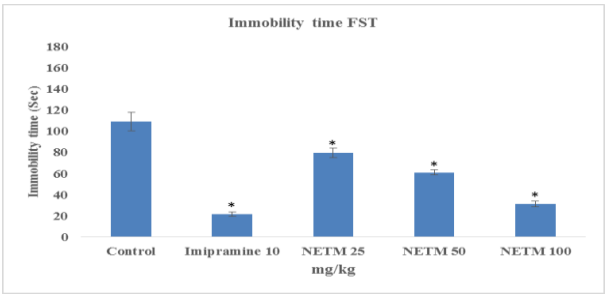

Figure 2: Effect of n-Butanol fraction on immobility time in Forced swim test. * $p < 0.01$ compared to control group using One-way ANOVA followed by Bonferroni 's *post-hoc* test. n= 6, data = Means ± SEM, NETM = n-Butanol fraction of *Terminalia macroptera* methanol extract and control = distilled water 10ml/kg.

Effects of NETM on the Locomotor Activity in the OFT

The ambulatory activity of mice was assessed in an open-field arena. Treatment of mice with NETM at doses of 25, 50 and 100 mg/kg and imipramine at 10 mg/kg had no significant effect on the number of lines crossed in mice OFT (**Fig. 3**).

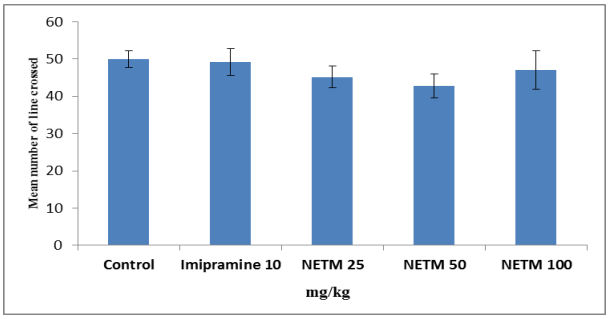

Figure 3: Effect of the n-Butanol fraction on locomotor activity in mice open field test. No significant difference was observed in the control and treated groups, using One-way ANOVA followed by Bonferroni's *post-hoc* test, data = Means ± SEM, NETM = n-Butanol fraction of *Terminalia macroptera* methanol extract and control = distilled water 10 ml/kg.

Discussion

Phytochemical constituents from medicinal plants are responsible for the observed pharmacological activities, and their therapeutic benefits depend upon one or a combination of the phytochemical constituents of the medicinal plants. Polyphenols are naturally occurring secondary metabolites of plants. The most studied classes are flavonoids, alkaloids, saponins, steroids, tannins, etc. Numerous studies have shown that polyphenols have neuroprotective effects (Letenneur *et al.*, 2007; Yadav *et al.*, 2016), anti-ageing (Pandey and Rizvi, 2009) and anti-diabetic effects (Rizvi and Zaid, 2005) among others. These medicinal benefits of the plants are due to bioactive compounds that produce characteristic biological action in humans (Akinmoladunm *et al*., 2007).

Moreover, studies have shown that some phytochemical constituents like alkaloids, flavonoids, tannins and saponins were linked to antidepressant activities (Gutierrez-Merino *et al*., 2011; Mroczek *et al.*, 2012; Yadav *et al.*, 2016; Hussain *et al.*, 2019; Luduvico *et al.* 2020). These phytochemical constituents were present in the plants reported in this study. The results showed that NETM has the highest contents of flavonoids and saponins relative to other constituents. Hamid *et al.* (2017) reported the antidepressant effect of some secondary metabolites such as flavonoids, alkaloids, saponins and tannins. Thus, these bioactive components present in the NETM may be responsible for the observed antidepressant activity. The medicinal plants derived flavonoids have been reported to possess multiple biological effects, including antidepressant activity (Shi and Wang, 2006; Chao *et al.*, 2009; Hritcu *et al.*, 2017). Furthermore, the flavonoids of Hypericum perforatum (St. John's wort) have been reported to possess antidepressant activity (Shi and Wang, 2006). Also, another study reported antidepressant activity of Rutin (flavonoids) exhibited the same efficacy as imipramine (Nöldner and Schötz, 2002). Han *et al*. (2007) showed that various flavonoids possess antidepressant activities such as quercetin (flavonol), luteolin (flavone), and apigenin that could regulate the activity of Monoamine oxidase inhibitor enzymes.

The scientific studies conducted by Qiao *et al.* (2011) and Martínez-Vázquez *et al.* (2012) have shown that alkaloid extract from the aerial parts of *Annona cherimola* and *Zizyphi sponosae* produces an antidepressant effect by an increasing monoaminergic turnover, with a significant reduction of immobility time observed using TST and FST behavioural test models.

Scientific evidence revealed that saponins possess neuroprotective and antidepressant effects (Xiang *et al.*, 2011). Numerous works have reported preclinical results supporting the role of saponins in the treatment of depression and justified their inclusion in drug discovery programs of antidepressants (Haixia *et al.*, 2009; Abbas *et al.*, 2015). Also, saponins and some antidepressant drugs were reported to have a synergistic effect with a resultant reduction of oxidative stress (Xu *et al.* 2010). Tannins are biological molecules with various pharmacological properties, such as neuroprotection and antidepressant effect due to their activity in reducing neurodegeneration and inhibiting monoamine oxidase (Hussain *et al.*, 2019; Luduvico *et al.* 2020).

The results from the present study indicated that the presence of flavonoids, alkaloids, saponins, and tannins might be linked to possessing the antidepressant effect, as indicated by numerous researchers (Nöldner and Schötz, 2002; Shi and Wang, 2006; Wang *et al.*, 2007; Mroczek *et al.* 2012; Zhen *et al.* 2012; Gong *et al.* 2014; Yadav *et al.* 2016; Hussain *et al.* 2019; Luduvico *et al.* 2020).

The duration of immobility is considered the core index in using FST and TST to evaluate the antidepressant activity. These tests are the most widely utilised models for screening potential antidepressant drugs. The time spent in an immobile state by the animal during the 6 minutes is a measure of escape related behaviour (Abelaira *et al.*, 2013). The decrease in immobility time is used as the main index for the antidepressant effects of the test agents in TST and FST models (Cryan *et al*., 2010). These tests are quite sensitive to major antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), tricyclics and monoamine oxidase inhibitors (MAOIs), which can effectively reduce the immobility time and increase activity (Porsolt *et al.* 1977; Steru *et al.* 1985). Thus, the ability of NETM at the tested doses to significantly reduce the duration of immobility is an indication of their antidepressant properties.

These models have some defects, although their predictive validity has been confirmed (Abelaira *et al*., 2013). Some psychostimulant drugs, such as caffeine, amphetamine, and methylphenidate that stimulate the CNS, also increase locomotor activity, but they are devoid of antidepressant properties (Kang *et al*. 2010). Hence, to avoid the possibility of false-positive results, the effect of NETM on locomotor activity was assessed in an open-field arena. This study showed that NETM did not produce any significant changes in the number of lines crossed, suggesting that the decreased immobility time of mice in the TST and FST models are specific since they do not increase spontaneous locomotor activity. Therefore, NETM decreases behavioural despair and thus possesses antidepressant activity.

Flavonoids, saponins and alkaloids were reported to show antidepressant activity. Thus, the antidepressant activity shown by NETM extract may be due to the presence of these phytoconstituents.

Hence, this study substantiates the previous report that phytochemical constituents improve the synthesis and storage of brain monoamines with a subsequent increase in noradrenaline, serotonin and or dopamine (Nöldner and Schötz, 2002; Shi and Wang, 2006; Wang *et al.*, 2007; Mroczek *et al.* 2012; Zhen *et al.* 2012; Gong *et al.* 2014; Yadav *et al.* 2016; Hussain *et al*. 2019; Luduvico *et al.* 2020).

Conclusion

The results demonstrated that the n-Butanol fraction obtained from methanol leaves extract *T. macroptera* possesses biologically active constituents that have antidepressant activity and may have potential therapeutic value in managing depression. The secondary metabolites with antidepressant properties (e.g. Flavonoids, Alkaloids, Saponins and Tannins) were present in *T. macroptera.*

Conflict of interest

The authors declare no conflict of interest.

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