

Full Length Research Paper

Neuroprotective effects of methanol extract of *Terminalia macroptera* leaf in mice

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The plant *Terminalia macroptera* has been reported to possess many pharmacological activities. The aim of the present study was to screen the effect of the methanol extract of *T. macroptera* against ketamine-induced mice model of psychosis and the apomorphine climbing test. The behavioural studies entailed an evaluation of locomotor activity, stereotypic behaviours in the open field and stereotypic climbing behaviour, immobility duration in the forced swim test, memory retention using the Y- maze and descent latency effects on catalepsy in the woodblock of methanol extract of *T. macroptera* (100-400 mg/kg) administered orally. The acute toxicity study as well as the phytochemical study was also carried out. Animals treated with the methanol extract of *T. macroptera* demonstrated significant reduction in locomotor activity, stereotypic behaviours, immobility duration, and increase in memory retention and decreased descent latency. The LD₅₀ was found to be greater than 5000 mg/kg indicating that the extract is safe for consumption and phytochemical studies revealed the presence of flavonoids, tannins, saponins, cardiac glycosides and alkaloids which might be responsible for its pharmacological activity. This study concluded that methanol extract of *T. macroptera* could ameliorate ketamine-induced behavioural abnormalities in mice indicating its promising effect as a neuroprotective agent in the management of psychotic symptoms.

Key words: Behaviours, ketamine, neuroprotection, psychosis, stereotype, *Terminalia macroptera*.

INTRODUCTION

Psychosis, is a debilitating disorder affecting about 1% of the population worldwide and it is exhibited as positive (delusions, bizarre behaviours, hallucinations) and negative (apathy, anhedonia, alogia) symptoms along with disturbance in cognition (Faludi et al., 2011). Imbalance in neurotransmitters, oxidative stress, dysfunctional mitochondria, neuroinflammation and some enzymatic variations are the prominent causes of

psychosis (Davis et al., 2014; Kumar et al., 2017). Furthermore, hypo functioning of NMDA receptor can modify neurotransmitter release or function in diverse portions of the brain, mainly the dopaminergic, glutamatergic, cholinergic, GABAergic, and serotonergic, leading to the pathogenesis of psychosis. A number of theories have been proposed to better comprehend the relationship between dysfunctional brain and psychosis,

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however, the cellular and molecular pathology of psychosis is yet to be sufficiently understood (Coyle, 2006; Stahl, 2007; Chatterjee et al., 2012). Typical antipsychotics are basically useful in the management of positive symptoms of psychosis with concomitant extrapyramidal side effects (Jankelowitz, 2013), while atypical antipsychotics are helpful in the management of positive, negative and cognitive symptoms of schizophrenia with fewer extrapyramidal effects, but may result in metabolic adverse effects such as diabetes mellitus, cardiovascular disorders and agranulocytosis (Chatterjee et al., 2012). While, antipsychotics have a long history of clinical use, the efficacy of most is not completely ascertained besides being associated with numerous adverse effects coupled with the tendency for psychotic relapse. Therefore, plants and other natural compounds were preferred because of their reputed safety as well as nutritional and therapeutic activities (Chatterjee et al., 2012), coupled with the claim for the efficacy of *Terminalia macroptera* in the treatment of psychotic disorders by traditional healers (Ior et al., 2017). *T. macroptera* Guill. & Perr. (Combretaceae) is a tree up to 20 m in height (Arbonnier, 2004). Ethnomedicinal report from Mali mentions the decoction of leaves of *T. macroptera* in treatment of epilepsy (Pham et al., 2011), and anxiolytic effects of *T. macroptera* has also been reported by Bum et al. (2012). Therefore, the aim of the present study was to screen the effect of the methanol extract of *T. macroptera* against ketamine-induced mice model of psychosis and the apomorphine climbing test.

MATERIALS AND METHODS

The fresh leaves of *T. macroptera* were collected in September 2017, from its natural habitat at Jengre, Bassa Local Government Area of Plateau State, Nigeria. The plants were first identified on the field using keys and description given in the Flora of West Tropical Africa (Hutchinson and Dalziel, 1954). They were further authenticated by Mr. J. J. Azila, a taxonomist in herbarium section of the Federal College of Forestry, Jos. A voucher specimen (FHJ 259) was deposited at the herbarium for future reference. The dried and powdered leaves of *T. macroptera* was extracted by cold maceration for 72 h using 70% methanol as a solvent, the filtrate was dried using rotary evaporator and water bath. The dried extract was stored in the refrigerator for this study.

Experimental animals

Male and female Swiss albino mice weighing between 25 and 30 g were used. They were kept in a well-ventilated room in clean plastic cages with wood shavings as bedding in the animal facility of the Department of Pharmacology, Faculty of Pharmaceutical Sciences, University of Jos. The animals were kept under standard conditions; temperature of 25°C and a 12 h day/night cycle. They were given free access to food (standard animal feed) produced by the Animal house, University of Jos and clean water *ad libitum* under hygienic conditions. The animals were allowed to acclimatize in the laboratory environment prior to any experiment. Experimental animal groups used in the present study consisted of six mice in

each group. The investigation conformed to the Guide for the Care and Use of Laboratory Animal Published by the US National Institute of Health (NIH No. 85 - 23, revised 1996). All protocols were also approved by the University of Jos Animal Care and Use in collaboration with the office of Laboratory Animal Welfare (OLAW). With Reference: Assurance Approval-UJ/FPS/F17 -00379.

Drugs and chemicals

All drugs and extract were freshly prepared on the days of the experiment; they were dissolved in normal saline. Vehicle (normal saline) was administered in a volume of 10 mL/kg/body weight. Drugs used include haloperidol hydrochloride, apomorphine hydrochloride, risperidone and ketamine (Sigma Aldrich).

Acute oral toxicity study

The LD₅₀ was evaluated in Swiss albino mice (Lorke, 1983), to determine the acute toxicity of the methanol leaf extract of *T. macroptera*. The study involved two phases; the first phase was conducted as follows. Nine mice were grouped into three groups of three mice each. The crude extracts were suspended in normal saline. Each group received 10, 100 and 1000 mg/kg per oral (p.o.) body weight of the methanol extract, respectively. The animals were observed keenly for about 60 min for any signs of toxicity or mortality, and further observations were made every 8 h for 24 h after administration of the extracts. The absence of death of any animals in this phase necessitated the conduct of the second phase. In the second phase, three mice were grouped into three groups of one mouse each. The groups received 1,500, 2,900 and 5,000 mg/kg p.o. body weight of the extract respectively. The mice were observed for any signs of toxicity or mortality within 24 h.

Apomorphine climbing test in mice

The method previously described by Costall et al. (1978) was adopted. This determines the neuroleptic (anti-dopaminergic) potentials of the extracts. Thirty mice were allotted into 5 groups of 6 mice each. Animals were administered 10 mL/kg normal saline and 1.5 mg/kg apomorphine intraperitoneally (i.p.). The typical antipsychotic risperidone was used as positive control in this experiment. Risperidone was orally administered at 0.5 mg/kg dose 1 hour before apomorphine 1.5 mg/kg i.p. the extract was prepared to administer 100, 200, and 400 mg/kg (p.o.) 1 h before the injection of apomorphine. After apomorphine injection, mice were placed in a cylindrical mesh cage. The duration and frequency of climbing were observed for 30 min and the results were reported for the time point 10, 20, and 30 min after apomorphine injection.

Phytochemical screening

The phytochemical analysis of the crude extract was carried out according to standard methods described by (Sofowora, 2008).

Spontaneous motor activity

The open field test was employed to screen the effect of the methanol extract of *T. macroptera* on spontaneous motor activity (SMA) in mice. Mice 6 per group (n = 6) were administered (p.o.) 100, 200 and 400 mg/kg, respectively. The atypical antipsychotic drug risperidone, used as positive control, was administered at 0.5 mg/kg (as the salt) p.o. 1 h after the injection, each animal was placed in the center of an open field chamber; a wooden box (72

cm × 72 cm × 36 cm). Each mouse was individually placed at the centre of the open field and the number of lines crossed and duration of ambulation(s) for 5 min was recorded (Brown et al., 1999).

Chronic ketamine administration

Chronic ketamine administration induces behavioral deficits in rodents that are thought to recapitulate some cardinal features of schizophrenia including positive symptoms (Chatterjee et al., 2012), negative symptoms (Chindo et al., 2012), and cognitive deficits (Monte et al., 2013). The effect of the extract was studied on hyperlocomotion, immobility in the forced swim test and alternation in the Y-maze test induced by daily injection of ketamine for 7 consecutive days in mice. Ketamine (25 mg/kg) i.p. was administered in the morning. Risperidone, used as positive control, was administered at 0.5 mg/kg as above, 1 h after every dose of ketamine. The extract was prepared in saline to administer p.o. at dose of 100, 200, and 400 mg/kg, respectively, 1 h after every dose of ketamine (Chatterjee et al., 2012).

Effect of *T. macroptera* on hyperlocomotion

Hyperlocomotion induced by chronic injection of ketamine in the open field was used to screen for antipsychotic-like effect of *T. macroptera* and risperidone (Ben Azu et al., 2017). The experiments were done twenty four hours after the last dose of the 7 days administration of ketamine. The mice were each introduced to the center square of the open field chamber. The time of ambulation(s) and the number of lines crossed were then recorded for a period of 5 min.

Effect of *T. macroptera* on memory deficits induced by chronic ketamine injection

The effect of *T. macroptera* on ketamine-induced memory deficit as measured by percentage alternation behaviour using Y-maze test was assessed as described previously by (Casadesus et al., 2006). This test was done immediately after the locomotor activity test, and the mice were individually introduced to the center of the Y-maze. The animals were then allowed to freely explore the three arms of the maze for a period of 5 min. The order and number of arm entries were recorded and the maze was cleaned after each test. The percentage alternation, which is an estimate of the spatial working memory (Monte et al., 2013), was calculated by dividing the total number of alternations by the total number of arm entries, minus one and multiplied by 100. Alternation behaviour was considered as sequential entries into all three arms (that is, ABC, CAB, or BCA but not BAB).

Effect of *T. macroptera* on ketamine-enhanced immobility in forced swim test

The method previously described by Chindo et al. (2012) was used for the ketamine-induced enhancement of immobility test. Each animal was introduced into a standardized transparent glass tube (diameter 20 cm, height 45 cm) filled with water to a depth of 30 cm and at 25°C, and was forced to swim for 5 min (pretest session), 1 h after the last treatment (7th day) with ketamine for habituation. Thereafter, mice received the treatment for 7 days. An hour after the 7th day treatment, each animal was placed in the same transparent glass cylinder under the same conditions and forced to swim for 6 min and the immobility time (the time the mice glide in the water in an erect position with only slight motions to prevent

sinking) was recorded with a stopwatch. After each session, the animals were removed instantly from the glass tube, cleaned with a towel and kept in an aerated space until utterly dried before returning to their home cages.

Effect of *T. macroptera* on catalepsy test

The extrapyramidal symptoms were assessed using the woodblock catalepsy test model, described previously by Costall and Naylor (1974) with slight modifications. The animals were randomly administered one of the following treatments: the typical antipsychotic haloperidol (1 mg/kg, p.o.) *T. macroptera* extract (100, 200, or 400 mg/kg, p.o.), or risperidone (0.5 mg/kg, p.o.). Control animals received saline. An hour later, the animals were tested for cataleptic behaviour. Each mouse was clasped gradually about the shoulders and below the forepaws and rested gently on the upper edge of the wood block surface (L = 18 cm; H = 6 cm; W = 4 cm). This test was repeated at 90 min after drug administration. The descent latency (DL) was recorded as the time it took the animal to descend from the wood block. A mouse was labelled cataleptic if it stayed on the wood block longer than 60 s (Ben-Azu et al., 2017).

Statistical analysis

The data were expressed as mean ± standard error of the mean (SEM). Statistical differences between control and treated were determined by analysis of variance (ANOVA) with Newman-Keuls *post hoc* test. Two way ANOVA was used in the apomorphine climbing tests considering the between factor treatment and the time course. $p < 0.05$ was used as significant level.

RESULTS

Acute toxicity test

The oral LD₅₀ of the methanol extract of *T. macroptera* was found to be >5000 mg/kg.

Phytochemical Screening of *T. macroptera*

The extract was found to possess some useful phytochemical constituents as shown in Table 1.

Effect of *T. macroptera* on apomorphine-induced stereotypic climbing behaviour

The extract inhibited apomorphine-induced stereotypic climbing. As shown in Tables 2 and 3, intraperitoneal injection of apomorphine (1.5 mg/kg,) produced marked stereotypic climbing behavior in mice characterized by initial rearing compared to vehicle control in mice at 10, 20, and 30 min. Pretreatment with the extract at doses of 100, 200 and 400 mg/kg, p.o. significantly reduced the stereotyped climbing behavior ($p < 0.05$) and duration of stereotypic climbing ($p < 0.05$) at different time points ranging from 10 to 30 min. As expected, risperidone (0.5 mg/kg) also significantly inhibited apomorphine-induced stereotyped climbing behavior at 10 and 20 minutes, to reach a total abolishment of the stereotypies at 30 min.

Table 1. Phytochemical screening of *T. macroptera* leaf extract.

Phytochemical constituents	Result
Saponins	+
Tannins	+
Cardiac glycoside	+
Steroid	+
Flavonoid	+
Alkaloid	+
Anthraquinone	+

+ = Present.

Table 2. Effect of methanol extract of *T. macroptera* on the number of apomorphine-induced stereotypic climbing in mice.

Treatment	Dose (mg/kg)	Number of climbs at		
		10 min	20 min	30 min
NS (10 mL/kg)	-	4.60±0.03	4.58±0.01	4.73±0.04
METM	100	2.49±0.03*	2.45±0.03*	2.40±0.06*
METM	200	2.55±0.04*	2.56±0.07*	2.40±0.08*
METM	400	2.03±0.03*	1.93±0.03*	1.93±0.05*
Risperidone	0.5	2.03±0.18*	1.17±0.38*	0.00±0.01*

Value represents the mean ± S.E.M n= 6. * $p < 0.05$ compared to Normal saline group.**Table 3.** Effect of methanol extract of *T. macroptera* on the duration of apomorphine-induced stereotypic climbing behaviour in mice

Treatment	Dose (mg/kg)	Duration of climbs at		
		10 min	20 min	30 min
NS (10 mL/kg)	-	438.33±7.62	411.67±5.16	217.50±3.68
METM	100	290.33±2.91*	251.17±4.05*	155.50±5.38*
METM	200	270.50±3.80*	229.50±2.74*	140.67±1.43*
METM	400	246.83±3.22*	218.00±5.73*	144.00±6.30*
Risperidone	0.5	10.500±1.26*	3.1700±1.28*	0.00±0.01*

Value represents the mean ± S.E.M n= 6. * $p < 0.05$ as compared to normal saline group.

***T. macroptera* decreased spontaneous motor activity (SMA) in open-field test**

The effect of the extract and risperidone on SMA in the open-field test is shown in Figure 1. The extract or risperidone reduced the spontaneous motor activity. The extract at doses of 100, 200 and 400 mg/kg significantly reduced SMA compared to vehicle-treated mice ($p < 0.05$; Newman-Keuls after significant one-way ANOVA); Risperidone (0.5 mg/kg, p.o.) significantly decreased SMA compared to vehicle control group.

The effect of *T. macroptera* on ketamine-induced hyperlocomotion

The effect of the extract and risperidone on ketamine-

induced hyperlocomotion is shown in Figure 2. Chronic treatment with ketamine (25 mg/kg during 7 days) significantly induced hyperlocomotion compared to vehicle-treated control ($p < 0.05$, Newman-Keuls after significant one-way ANOVA). Pretreatment with the extract at 100, 200 and 400 mg/kg, p.o. significantly decreased hyperlocomotion induced by ketamine, similarly, pretreatment with risperidone (0.5 mg/kg, p.o.) significantly ($p < 0.05$) reduced hyperlocomotion in ketamine treated mice.

Effects of *T. macroptera* on cognitive deficit induced by chronic ketamine administration in mice

The effects of the extract and risperidone on cognitive

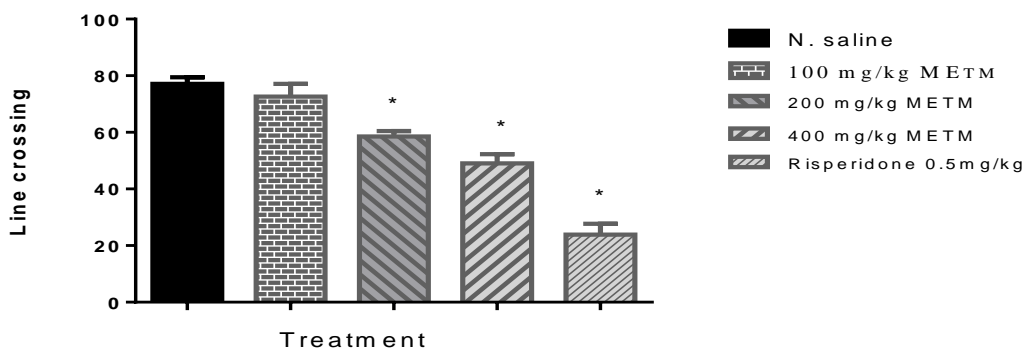


Figure 1. Effect of METM on SMA in open-field test in mice. Value represents the mean \pm S.E.M of 6 animals/group. * $P < 0.05$ as compared to vehicle group (One way ANOVA followed by Newman-Keul post-hoc test). METM= Methanol Extract of *T. macroptera*.

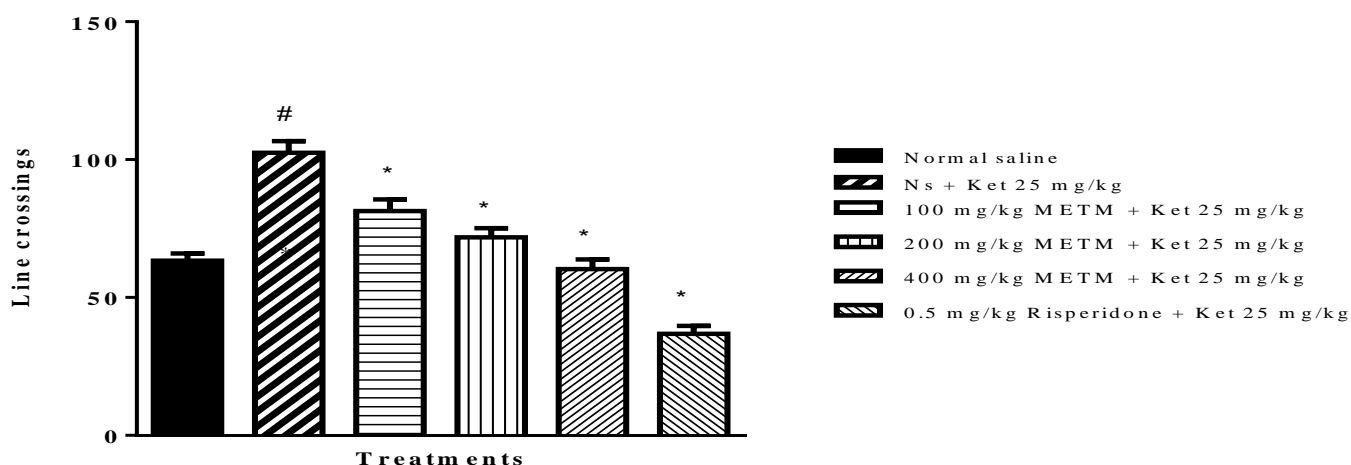


Figure 2. Effect of METM on ket-induced hyperlocomotion in open field test in mice. Value represents the mean \pm S.E.M of 6 animals/group. # $P < 0.05$ as compared to normal saline group; * $P < 0.05$ as compared to Normal saline + ketamine group (One way ANOVA followed by Newman-Keul post-hoc test). Ns=Normal saline, Ket = Ketamine, METM= Methanol extract of *T. macroptera*.

deficits induced by chronic injection of ketamine in mice using Y maze test are reported in Figure 3. Chronic injection of ketamine decreased the percent of alternations performance compared to vehicle-treated mice ($p < 0.05$ after significant one way ANOVA; pretreatment with METM at 100, 200 and 400 mg/kg p.o.) significantly reversed in a dose-dependent manner the deficits induced by ketamine. Similarly, risperidone (0.5 mg/kg, p.o.) significantly alleviated memory deficit ($p < 0.05$).

Effect of *T. macroptera* on ketamine-enhanced immobility in forced swim test

The effect of the extract and risperidone on ketamine-enhanced immobility time in forced swim test in mice is as shown in Figure 4. The chronic treatment with ketamine produced a significant increase in the duration

of immobility compared to vehicle-treated mice ($p < 0.05$). The extract at 100, 200 and 400 mg/kg, p.o. significantly reversed ketamine-induced increased duration of immobility. Risperidone similarly counteracted the effect of chronic ketamine ($p < 0.05$).

Effect of *T. macroptera* on catalepsy test in mice

The effect of the extract on cataleptic behaviour was compared to both haloperidol and risperidone and their effects on the descent latency (DL) from the wood block are reported in Figure 5. Haloperidol (1 mg/kg, p.o.)-treated mice showed significant ($p < 0.05$) increase in DL on the woodblock at 60 and 90 min compared to vehicle-treated mice. Administration of the extract at 100, 200 and 400 mg/kg p.o. or risperidone (0.5 mg/kg) failed to increase the DL of the mice following 60 and 90 min post

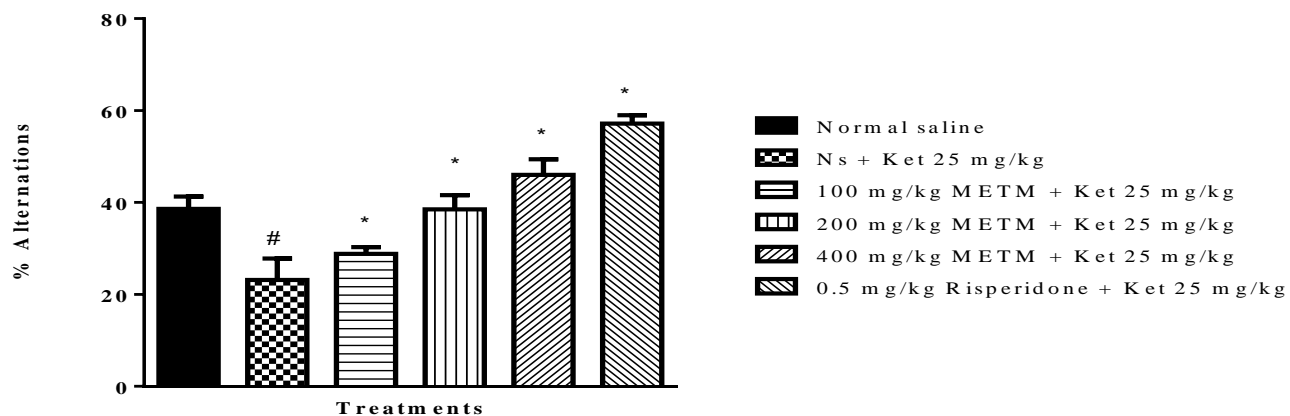


Figure 3. Effect of METM on ket-induced cognitive deficit. Value represents the mean ± S.E.M of 6 animals/group. #P < 0.05 as compared to Normal saline group, *P < 0.05 as compared with ket + Ns group (One way ANOVA followed by Newman-Keul post-hoc test). Ket = Ketamine, Ns= Normal saline, METM = Methanol extract of *T. macroptera*.

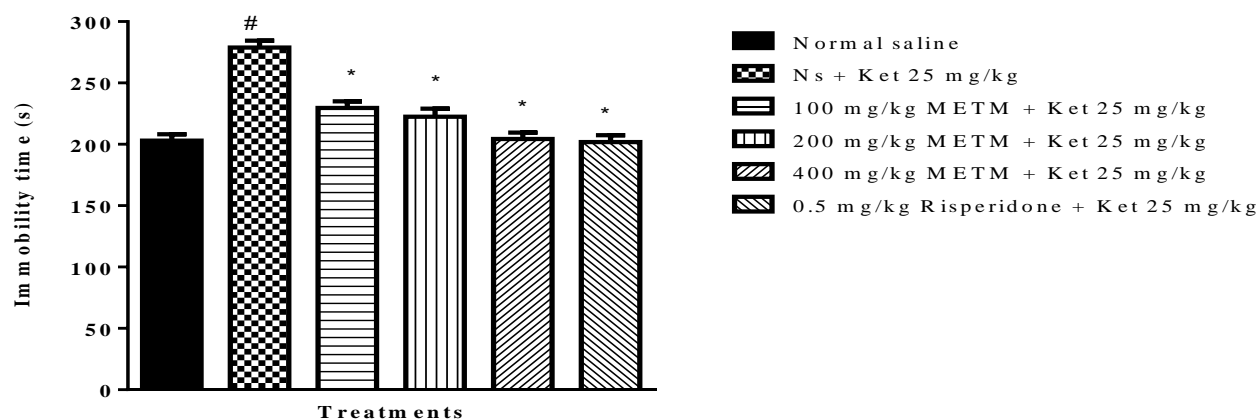


Figure 4. Effect of METM on ketamine-enhanced immobility in forced swim test in mice. Value represents the mean ± S.E.M of 6 animals/group. One way ANOVA Newman-Keul post-hoc test revealed that there is a significant difference between various treatment groups. # P < 0.05 as compared to vehicle group, * P < 0.05 as compared with ket + Ns group. Ket = Ketamine, Ns= Normal saline, METM = Methanol extract of *T. macroptera*.

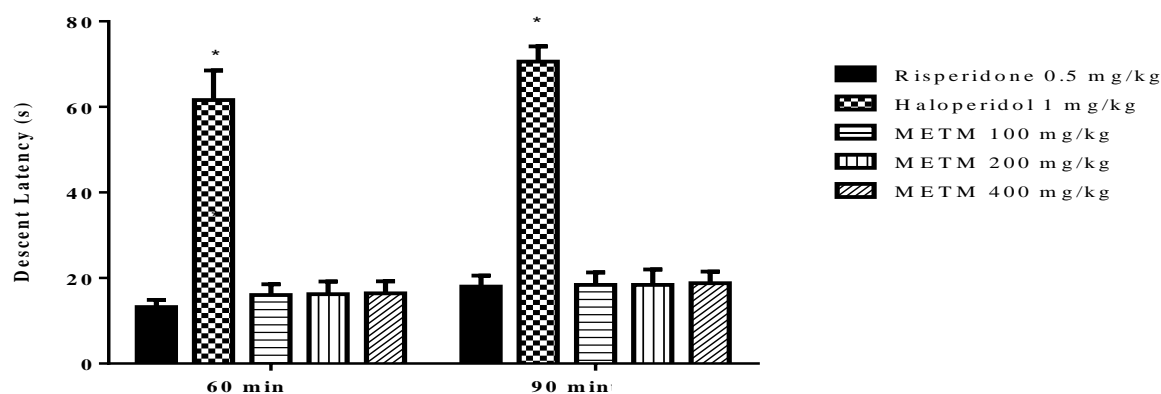


Figure 5. Effect of METM on catalepsy test in mice. Value represents the mean ± S.E.M of 6 animals/group. *P < 0.05 compared to Risperidone group. Data was considered significant above 60 s (two way ANOVA followed by Bonferroni post-hoc test). METM = Methanol extract of *T. macroptera*, RIS= Risperidone, HLP = Haloperidol.

treatments relative to vehicle control group.

DISCUSSION

The study indicated that, the methanol leaf extract of *T. macroptera* is without toxic effects at the doses used for behavioural studies, it reduced spontaneous motor activity, apomorphine stereotypic climbing and ketamine-induced hyperlocomotion, immobility in forced swim test, and cognitive deficit in Y-maze test. The extract did not induce cataleptic effect in contrast to haloperidol, suggesting that *T. macroptera* behaves as atypical antipsychotic.

There was no mortality in both the first and second phase of drug administration, from the result of the acute toxicity study suggesting that LD₅₀ of the leaf extract is higher than 5000 mg/kg body weight orally in mice (Lorke, 1983). There are various studies on LD₅₀ determination of plant extract which reported that substances with LD₅₀ higher than 5000 mg/kg via oral route may be considered practically nontoxic (Lima et al., 2009). Our observations from the acute toxicity studies also indicate that the methanol leaf extract is practically nontoxic up to a dose level of 5,000 mg/kg body weight per day via oral route. The phytochemical analysis of the extract revealed the presence of flavonoids, tannins, and steroids, alkaloids and cardiac glycosides, the antipsychotic properties of flavonoids have been described (Ben-Azu et al., 2017).

The extract at all doses reduced spontaneous motor activity, ketamine induced hyperlocomotion and apomorphine climbing behaviour. These results suggest that *T. macroptera* behaves as an antipsychotic drug. Accordingly, in the same conditions, risperidone had similar effects in the three behavioural tests. These results are consistent with a number of previous studies showing that atypical antipsychotic drugs like risperidone reduce spontaneous motor activity (Ben-Azu et al., 2017), ketamine-induced hyperactivity (Chatterjee et al., 2012) and apomorphine-induced climbing (Costal et al., 1978). The extract have also ameliorated ketamine-induced cognitive deficit in Y-Maze test in a dose dependent manner. Risperidone was also efficacious as expected from previous studies reporting the reversal of cognitive alteration in this test by antipsychotic drugs (Monte et al., 2013). *T. macroptera* also suppressed ketamine induced immobility in forced swim test. According to a recent publication (Ben-Azu et al., 2017), the higher immobility induced by ketamine is sensitive to atypical antipsychotic. Accordingly, we report that risperidone suppressed the time of immobility induced by ketamine in forced swim test. In line with this possibility, we found that *T. macroptera* was not capable of inducing catalepsy in contrast to the typical antipsychotic haloperidol (Ananth et al., 2001). It suggests that long-term administration of the extract would not favour the occurrence of extrapyramidal symptoms including tardive dyskinesia.

One can evoke some possible mechanisms for the efficacy of *T. macroptera*. The finding that it reduces spontaneous locomotor activity or apomorphine-induced climbing suggests a modest anti-dopaminergic effect. These effects can be ascribed to the ability of the extract to potentiate GABA release, as previously found by Chatterjee et al. (2012).

The administration of ketamine increased the immobility period in force swim test; this signifies negative symptoms of psychosis (Chindo et al., 2012). This study found that chronic administration of the extract was effective in reducing the period of immobility in mice. Ketamine promotes oxidative stress by generating free radicals with demolition of the antioxidant defense mechanism of brain and subsequently causes negative as well as cognitive symptoms (de Oliveira et al., 2009; Zugno et al., 2014). The efficacy of the extract in cognition or negative symptoms of the disease could reveal an inhibitory action at D₂/D₃ receptors (Horacek et al., 2006; Di Giovanni et al., 2016), 5-HT₂ receptors including 5-HT_{2A} and 5-HT_{2B} receptor like risperidone (Di Giovanni et al., 2016), or cholinergic mechanisms (Chatterjee et al., 2012). It is thus possible that the efficacy of the extract implies in part changes in the complex balance between serotonergic and dopaminergic systems upon cortico-subcortical glutamatergic systems in the brain (De Deurwaerdère and Di Giovanni, 2017; Heisler et al., 2013). Woodblock test has been used to assess the probable extrapyramidal side effects (e.g., catalepsy) of typical antipsychotics on mice. In our study, no cataleptic effect was observed in the extract treated group as well as the risperidone treated group. These findings indicate that like the atypical antipsychotics *T. macroptera* is devoid of extrapyramidal side effects unlike haloperidol a typical antipsychotic drug.

In conclusion, the methanol extract of *T. macroptera* might be a promising remedy for psychosis, effective in protection against the behavioural effects of apomorphine and ketamine induced psychosis and devoid of extrapyramidal side effects. It is also safe for consumption, therefore, might be beneficial in the treatment of schizophrenic like symptoms.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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