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Antipsychotic effects of ethanol extract of *Blighia sapida* (Sapindaecea) stem bark on pharmacological models of psychosis in Swiss mice

Y Usman, AO Aderibigbe, BA Benneth and FA Fehintola
Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, ,Nigeria

Abstract

Background: *Blighia sapida* is a common plant consumed as vegetable in southern part of Nigeria. The ackee plant has a long history of use as a medicinal plant by several ethnic groups to treat a wide variety of Central Nervous System (CNS) disorders. The present study was designed to evaluate the antipsychotic effect of ethanol extract of *Blighia sapida* (*Sapindaecea*) stem bark in ameliorating psychotic features in mice.

Materials and methods: Graded doses of ethanol extract of *Blighia sapida* (EEBS) (10, 20, 40, 80 mg/kg, i.p) were administered 30 minutes prior to apormorphine (1 mg/kg, i.p) or ketamine (10 mg/kg, i.p). The animals were subsequently subjected to forced swim test to determine the effect of EEBS on ketamine enhanced immobility. Catalepsy and ptosis in the experimental mouse model were also assessed for probable side effects associated with antipsychotics. Doses of EEBS being tested and haloperidol (1 mg/kg) were administered intraperitoneally to animals (i.p) 30 minutes prior to the catalepsy and ptosis observation. Catalepsy was measured using the bar test, ptosis for each animal was evaluated in a transparent observation chamber at 30, 60, and 90 minutes post-treatment with EEBS or haloperidol.

Results: Ethanol extract of *Blighia sapida* stem bark (20, 40, 80 mg/kg, i.p) significantly decreased stereotyped behaviours induced by apomorphine (1mg/kg, i.p) and ketamine (10mg/kg, i.p) in a dose-dependent manner, as 10 mg/kg EEBS failed to significantly inhibit ketamine induced stereotyped behaviours. EEBS showed differential effects against the ketamine induced hyperactivity compared to negative control. EEBS significantly ($p < 0.05$) reduced the ketamine enhanced immobility in the forced swim test and did not show extra-pyramidal side effects in the bar test of catalepsy. EEBS at higher doses induced ptosis that is commonly observed with most antipsychotics.

Conclusion: Ethanol extract of *Blighia sapida* stem bark reduced apomorphine and ketamne induced stereotypy and hyperactivity in mice model suggesting its potential antipsychotic activity.

Keywords: *Blighia sapida, Psychosis, Apormorphine, Ketamine, and Stereotypy*

Abstrait

Contexte : Blighia sapida est une plante commune consommée comme légume dans la partie sud du Nigéria. La plante 'ackee' est utilisée depuis longtemps comme plante médicinale par plusieurs groupes ethniques pour traiter une grande variété de troubles du système nerveux central (SNC). La présente étude a été conçue pour évaluer l'effet antipsychotique de l'extrait à l'éthanol de l'écorce de la tige de *Blighia sapida (Sapindaecea)* dans l'amélioration des caractéristiques psychotiques chez les souris.

Matériaux et méthodes : Doses graduées d'extrait à l'éthanol de *Blighia sapida* (EEBS) (10, 20, 40, 80 mg / kg, ip) ont été administrés 30 minutes avant l'apomorphine (1 mg / kg, ip) ou la kétamine (10 mg / kg, ip). Les animaux ont ensuite été soumis à un test de nage forcée pour déterminer l'effet de l'EEBS sur l'immobilité accrue par la kétamine. La catalepsie et le ptosis dans le modèle expérimental chez la souris ont également été évalués pour déterminer les effets secondaires probables associés aux antipsychotiques. Des doses d'EEBS à l'essai et d'halopéridol (1 mg / kg) ont été administrées par voie intrapéritonéale aux animaux (ip) 30 minutes avant l'observation de la catalepsie et du ptosis. La catalepsie a été mesurée à l'aide du test de barre, le ptosis de chaque animal a été évalué dans une chambre d'observation transparente 30, 60 et 90 minutes après le traitement avec l'EEBS ou l'halopéridol.

Résultats : L'extrait d'éthanol de l'écorce de la tige de *Blighia sapida* (20, 40, 80 mg / kg, ip) diminuait significativement les comportements stéréotypés induits par l'apomorphine (1 mg / kg, ip) et la kétamine (10 mg / kg, ip) en fonction de la dose, comme 10 mg/kg d'EEBS n'a pas réussi à inhiber de manière significative les comportements stéréotypés induits par la kétamine . EEBS a montré des effets différentiels contre l'hyperactivité induite par la kétamine par rapport au control négatif. Les EEBS ont significativement ($p < 0,05$) réduit

Correspondence: Prof. F.A. Fehintola, Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria. E-mail: fentolamine@gmail.com

l'immobilité accrue par la kétamine dans le test de nage forcée et n'ont pas montré d'effets secondaires extra-pyramidaux dans le test de barre de catalepsie. EEBS à des doses plus élevées a induit un ptosis qui est couramment observé avec la plupart des antipsychotiques.
Conclusion : L'extrait d'éthanol de l'écorce de la tige de *Blighia sapida* a réduit la stéréotypie et l'hyperactivité induite par l'apomorphine et la kétamine avec des modèles de souris suggérant son activité antipsychotique potentiel.

Mots clés : *Blighia sapida, psychose, apomorphine, kétamine et stéréotypie*

Introduction

Psychosis is among the most severe and incapacitating medical diseases [1] and has been ranked the most disabling condition after quadriplegia and dementia in a WHO multi-country study [2]. Psychosis covers a range of psychiatric disorders and may present as: hypoactivity, hyperactivity, agitation, aggressiveness, hostility, and combativeness [3]. Affected individuals may exhibit: social withdrawal paying less-than-normal attention to the environment and other people; deterioration in self-care and interpersonal skills; hallucinations and paranoid delusions [4, 5]. Psychosis may be acute or chronic. Acute psychosis or acute confusional state or delirium usually develop suddenly within hours or days and may be secondary to organic diseases such as brain injury related to cerebrovascular disease or head trauma, metabolic disorders and infections. In addition, drug intoxication with adrenergic, antidepressants, illicit drugs such as amphetamines and cocaine, and drug withdrawal after chronic use (e.g., alcohol; benzodiazepine anti-anxiety or sedative-hypnotic agents) may also cause acute psychosis [6]. An acute psychotic episode may be superimposed on chronic dementias and psychoses, such as schizophrenia. Psychosis has been linked with abnormality in the brain structure and brain chemistry specifically imbalances and abnormal integration among several neural pathways and neurotransmission [7]. Three of the most prominent theories propounded to explain the basis of psychosis are linked to neurotransmission, namely: the dopamine hypothesis, serotonin (or serotonin–dopamine) hypothesis, and glutamate hypothesis [8]. The dopamine theory has been more extensively studied [8] and psychotic disorders have long been attributed to increased dopamine activity in the brain. Stimulation of dopaminergic pathway can initiate psychotic symptoms or exacerbate an existing psychotic disorder. The behavioural effects of dopamine (D_2) receptor agonists (apomorphine) in rodents, either locomotor hyperactivity or stereotypy, have a high degree of pharmacologic isomorphism as models for testing the efficacy of dopamine- antagonist treatments for psychosis [9, 10]. Mesolimbic dopaminergic neuron hyperactivity is linked to the positive symptoms [11]. Whereas, a decrease in the dopamine levels in fronto-cortical part of mesocortical dopamine neurons is linked to the negative symptoms [12].

Dysfunctional glutamate neurotransmission has been implicated in psychotic disorders. Antagonists of the N-Methyl-D-Aspartate (NMDA) subtype of glutamate receptors, phencyclidine (PCP) and ketamine produce a behavioural syndrome in healthy humans that closely resembles psychotic symptoms [13].

Ketamine, a PCP analog still used in human anesthesia, has been reported to cause reactions similar to but not as severe as those caused by PCP, including brief, reversible "positive" and "negative" schizophrenia-like symptoms [14, 15]. Both PCP and ketamine can exacerbate psychosis in schizophrenia [16, 17]. PCP-induced psychosis, unlike amphetamine or apormophine-induced psychosis, incorporates both positive and negative symptoms of schizophrenia [14, 15]. In addition, the fact that high doses of NMDA antagonists produce neurodegenerative changes in corticolimbic regions [18] has been cited as evidence that alterations in the glutamatergic system, particularly NMDA receptor function, might contribute to the negative symptoms of schizophrenia.

Antipsychotics may be broadly categorized as "typical," (also known as conventional or first-generation agents Phenothiazines and older nonphenothiazines) such as haloperidol [19] and "atypical" or second-generation agents, which can also be called newer nonphenothiazines (clozapine and risperidone). Newer (atypical) antipsychotic drugs offer not only a better therapeutic effect but, because of their stratified effect on the finer dimensions of psychotic symptoms, they also provide deeper insight into the pathophysiology of psychosis itself [20, 21]. Current antipsychotic drugs may be limited, sometimes by questionable effectiveness or poor tolerability [22, 23].

Blighia sapida is a "herbaceous tree" commonly found in the forests of most West African countries where it is mainly used for medicinal purposes. In Nigeria, various parts of *B. sapida* plant are said to be used for the treatment of psychosis, cancer, gonorrhea, stomach ache, hernia, backache, diarrhoea and constipation [24, 25]. *Blighia sapida*

leaves, stem bark and fruits are rich in phytochemicals including; saponins, anthraquinones, cardiac glycosides, flavonoids, alkaloids, tannins, phlobatannins and terpenes [26]. *Blighia sapida* has antimicrobial, antioxidant, anti-inflammatory activities and also a useful herb for the treatment of epilepsy [27, 28]. Few reports have suggested that *B. sapida* stem bark may be useful in treating psychotic disorders given its "dopaminergic or glutaminergic-inhibitory activity [27, 29].This study evaluated the effect of EEBS stem bark on psychosis in mice.

Materials and methods

Plant materials

The bark of the stem of *Blighia sapida (Sapindaecae)* was collected from Iloora farm settlement in Afijio, Oyo state, Nigeria and identified at the Forestry Research Institute of Nigeria (FRIN), Ibadan with voucher number 110254.

Preparations of Blighia sapida stem bark extract

The ethanol extract of *Blighia sapida* (EEBS) was prepared using cold extraction. The stem bark was air – dried for 4 weeks, and was pulverized with an electric crusher. Two hundred grams (200g) of the pulverized stem bark was soaked in 70% ethanol and left for 48 hours, after which, it was filtered using absorbent cotton and What man paper. The filtrate was concentrated using Rotary evaporator at 40^{0}C and the dark brown paste obtained was dried to a constant weight and kept in a desiccator.

Animal

Male and female Swiss mice (*Mus musculus)* weighing between 18-24g were used for the experiment. The animals were obtained from the central animal house, University of Ibadan. The male and female mice were housed separately in plastic cages and had unrestricted access to standard pellet feed and water. They were acclimatized for 1 week before use. All procedures in this study were performed in compliance with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving the care and use of laboratory Animal (American Physiological Society, 2002).

Drugs and chemicals

Apomorphine, Haloperidol (Sigma-Aldrich, St. Louis, MO, USA), Ketamine hydrochloride injection (SwissPharma) Risperidone (Ranbaxy). All drug solutions were prepared fresh in distilled water and administered intraperitoneally (i.p).

Experimental design

Acute toxicity studies

Male and female Swiss mice (18-24 g) were used. The study was carried out as described by Lorke [30] to determine the LD_{50}, which is the index of acute toxicity. The animals were divided into three groups of three animals in each group. Doses of 10, 100, and 1000 mg/kg of the ethanolic extract of *Blighia sapida* (*sapindaecae*) were administered intraperitoneally (i.p.). The treated animals were monitored for 24 hours for mortality and general behaviour. Number of death was recorded after 24 hours. From the results that were obtained from the initial procedure, three different doses ranging (2000, 3000 and 4000 mg/kg) were chosen, and administered intraperitoneally to three groups of one mouse per group respectively. The treated animals were monitored for 24 hours. Number of deaths after 24 hours was recorded. The LD_{50} was calculated as the geometric mean of the lowest dose showing death and the highest dose that caused no death.

Apomorphine-induced stereotypy

The antipsychotic effect of the ethanol extract of *Blighia sapida* was assessed using the Apomorphine-induced stereotyped behavioural paradigm in male mice [31]. The animals were divided into 7 treatment groups (n = 5). Groups 1 and 2 received vehicle (distilled water 10 mL/kg i.p), groups 3, 4, 5 and 6 were pretreated respectively with doses of EEBS (10, 20, 40, 80 mg/kg, i.p.), while group 7 was pretreated with haloperidol (HLP) (1 mg/kg, i.p.). Thirty minutes later, each animal received apomorphine (APO) 1 mg/kg intraperitoneally, except group 1.The animals were subsequently placed in a transparent observation chamber measuring: 20 cm × 20 cm × 23 cm. Thereafter, stereotype behaviours were observed for a period of 2 minutes at 10, 15, 30, 45, and 60 minutes after APO injection. Stereotype behaviours were scored as: 0 = absence of stereotype behaviour; 1 = presence of stereotype movements of the head; 2 = intermittent sniffing; 3 = chewing; 4 = intense licking [31].

Ketamine-induced stereotypy and hyperactivity

The male mice were divided into 7 treatment groups (n = 5). The animals in groups 1 and 2 received vehicle (distilled water 10 mL/kg i.p), while those in, groups 3,4,5 and 6 were pretreated with 10, 20, 40 and 80 mg/kg, i.p of EEBS respectively, and the group 7 mice were pretreated with risperidone (RISP) (0.5 mg/kg, i.p). Thirty minutes later, each animal was treated with sub anaesthetic dose of ketamine (KET) (10 mg/kg i.p) [31], except group 1.

Stereotype behaviours were assessed by Bourin *et al.* [31]. The hyperactivity was evaluated as described by placing each mouse individually at the center of an open field chamber measuring: 35 cm x 30 cm x 23 cm. The duration of ambulation and number of lines crossed were recorded for 5 min.

Ketamine-enhanced immobility in forced swim test

The male mice were randomly divided into 7 treatment groups (n = 5). Group 1 (vehicle) animals were pretreated with distilled water (10 mL/kg, i.p), groups 2, 3 ,4, 5, 6 and 7 were pretreated with subanaesthetic dose of ketamine (20 mg/kg, i.p.) daily for 5 days. Twenty four hours after the last treatment with distilled water and ketamine respectively, group 2 received nothing, group 3, 4, 5, and 6 received doses of EEBS (10, 20, 40 and 80 mg/kg i.p) respectively, while group 7 received RISP at a dose of 0.5 mg/kg intraperitoneally. Thirty minutes later, each animal was placed in a transparent glass cylinder (Height 46 cm, Diameter 20 cm) containing water at 25°C to a depth of 30 cm; and forced to swim for 6 minutes and the immobility time was recorded for a period of 4 minutes [33] after discarding activity in the first 2 minutes, during which the animal tries to escape [34]. After each session, the mice were removed immediately from the cylinder, dried with a towel and kept in an open space until completely dried before returning the mice to their home cages

Cataleptic behaviour

The male mice were divided into six treatment groups (n = 5). Group 1 was treated with distilled water (10 mL/kg, i.p.), groups 2-5 were treated with increasing doses of EEBS (10, 20, 40 and 80 mg/kg, i.p) respectively, while group 6 was treated with haloperidol (HLP) (1 mg/kg, i.p.), thirty minutes before testing for catalepsy. The test was done by gently placing the fore limbs of each animal on a horizontal plane wood surface (Height 6 cm; Width 4 cm; Length 16 cm) and the duration of akinesia (period of time the animal remained in one position, before initiating any active movement) in seconds was recorded [35].

Ptosis induction

Ptosis as described by Bourin *et al.* [36], was used as a model to screen for the antipsychotic properties of a drug. The male mice were divided into six groups (n = 5). Group 1 was treated with distilled water (10 mL/kg, i.p.), while group 2 - 5 were treated with different doses of the EEBS (10, 20, 40 and 80 mg/kg, i.p) respectively, while group 6 were treated with haloperidol (1mg/kg i.p). The degree of ptosis was evaluated at 30, 60, and 90 minutes post dose with EEBS and haloperidol. Each animal was placed in a transparent observation chamber measuring: 20 cm × 20 cm × 23 cm on a shelf 20cm above the bench top, immediately after EEBS and haloperidol were administered. Ptosis for each animal was recorded by observing the degree of dropping of eyelids through the transparent observation chamber. The degree of ptosis was rated according to the following rating scale: 0=eyes open; 1=eyes one-quarter closed; 2=eyes half closed; 3=eyes three-quarter closed; and 4=completely closed. The results obtained were compared with control group treated with distilled water.

Statistical analysis

Data obtained from this study were expressed as Mean ± S.E.M. The data were analyzed using one-way analysis of variance (ANOVA) and post hoc tests (Student's Newman-Keuls) for the multiple comparisons where appropriate using GraphPad InStat® Biostatistics software. The level of significant for all tests was set at $p< 0.05$.

Results

Acute toxicity

No lethality/mortality was recorded when doses as high as 1000 mg/Kg was given to the animals. The LD_{50} of *Blighia sapida* stem bark ethanol extract was estimated to be 1440 mg/kg intraperitoneally.

Stereotyped behaviours

Effect of EEBS on Apomorphine-induced stereotyped behaviour.

Animals pretreated with EEBS (10, 20, 40 and 80 mg/kg, i.p) showed resistance to apomorphine-induced stereotyped behaviours compared to the negative control group. However, animals pretreated with HLP (1 mg/kg, i.p), showed no stereotype behaviour (stereotype score 0) throughout the observation period suggesting significant ($P < 0.05$) inhibitory effect against the behavioural deficits (stereotype behaviours) induced by APO (1 mg/kg, i.p.), (Fig .1).

Effect of EEBS on Ketamine-induced stereotyped behaviour.

Pretreatment with EEBS (20, 40 and 80 mg/kg, i.p) significantly ($P < 0.05$) inhibited ketamine-induced behavioural deficits compared to the control group. Pretreatment with RISP (0.5 mg/kg, i.p), significantly ($P < 0.05$) demonstrated greater inhibitory effect against the behavioural deficits induced by ketamine (10 mg/kg, i.p.) (Fig .2).

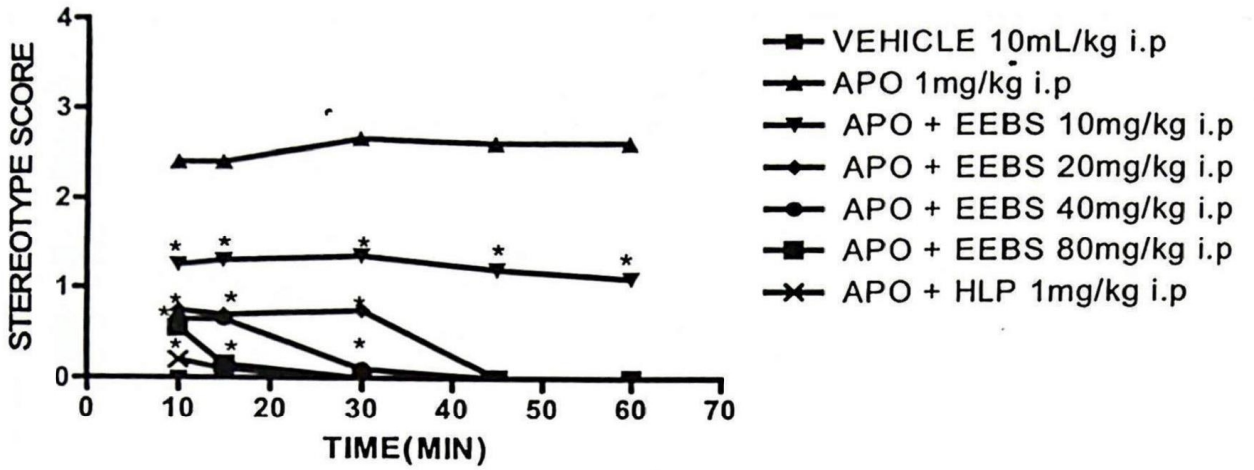

Fig.1: *Effect of EEBS on Apomorphine-induced stereotyped behaviour.*
*Point represent mean value (n=5). One way ANOVA revealed that there is significant [F (6, 28) =81.15, P < 0.001] differences between various treatment groups *Denotes P < 0.05 compared to APO 1 mg/kg i.p.* ***APO*** *= Apomorphine,* ***HLP*** *= Haloperidol,* ***EEBS*** *= Ethanol extract of B. sapida*

Effect of EEBS on acute ketamine-induced hyperactivity

EEBS pretreatment (10, 20, 40 and 80 mg/kg, i.p) significantly ($P< 0.05$) inhibited the hyperactivity induced by ketamine (10 mg/kg i.p). RISP (0.5 mg/kg, i.p), significantly ($P< 0.05$) inhibited the hyperactivity (Table.1.).

Effect of EEBS on ketamine-enhanced immobility in forced swim test in mice.

Ketamine (20 mg/kg, i.p.) significantly enhanced the immobility ($P< 0.05$) compared to the group treated with vehicle (10 mL/kg, i.p) in the forced swim test in mice. EEBS (10, 20, 40 and 80 mg/kg, i.p)

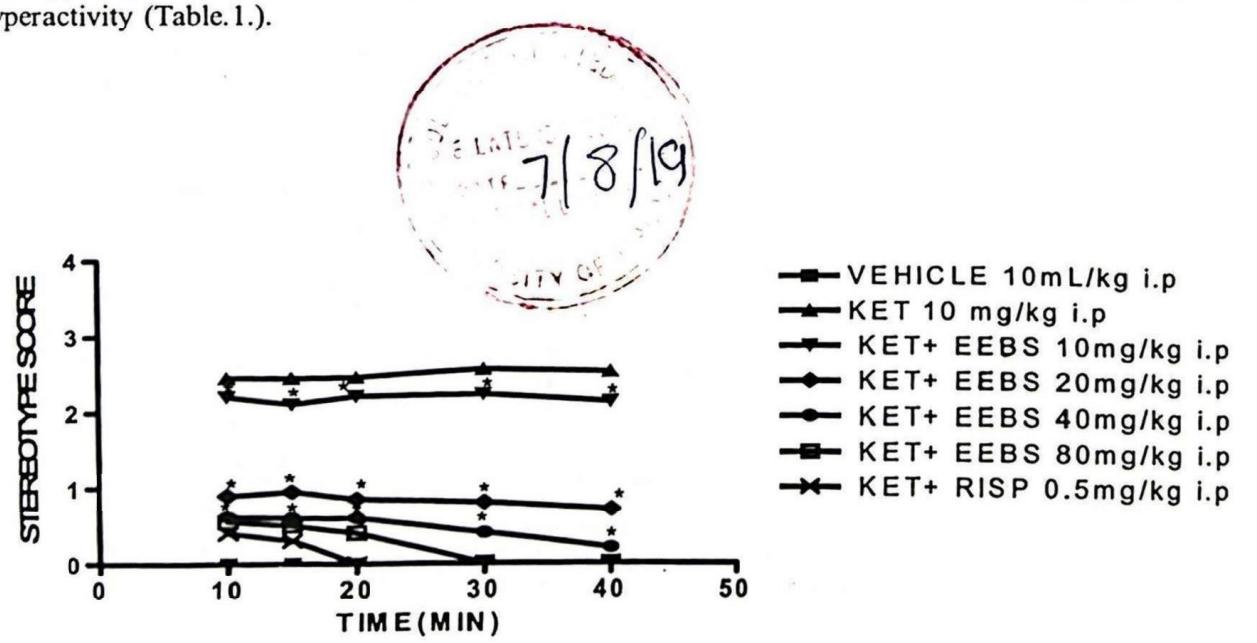

Fig. 2: *Effect of EEBS on Ketamine-induced stereotyped behaviour.*
*Points represent the mean value (n=5). One way ANOVA reveal that there is significant [F (6, 28) =221.3, P < 0.001] differences between various treatment groups. *Denotes P < 0.05 compared to KET 10 mg/kg, i.p..* ***KET*** *= Ketamine,* ***RISP*** *= Risperidone,* ***EEBS*** *= Ethanol extract of B.sapida*

Table 1: Effect of EEBS on acute ketamine-induced hyperactivity.

Treatment and Dose	Number of line crossings	Duration of ambulation (s)
VEH (10 mL/kg)	75.10±3.12	170±2.1 ±2.10
KET (10 mg/kg)	130.4 ± 7.50	22.00 ± 3.11
EEBS (10 mg/kg) + KET	100.0 ± 3.71*	49.40 ± 2.24*
EEBS (20 mg/kg) + KET	63.40 ± 2.04*	100.4 ± 10.78*
EEBS (40 mg/kg) + KET	49.80 ± 5.30*	151.4 ± 7.30*
EEBS (80 mg/kg) + KET	36.60 ± 3.35*	184.8± 7.95*
RISP (0.5 mg/kg) + KET	36.40 ± 4.34*	175.8 ± 16.13*

Value represents mean ± S.E.M (n=5). One way ANOVA revealed that there is significant
[F (5, 24) = 57.41, P< 0.0001] and [F (5, 24) = 54.49, P< 0.0001] differences between various treatment groups for number of line crossing(s) and ambulation(s) time, respectively.
*Denotes P< 0.05 as compared with ketamine group.
KET = Ketamine, **RISP** = Risperidone, **EEBS** = Ethanol extract of *B.sapida*

significantly (P< 0.05) decreased immobility time compared to the group treated with ketamine (20 mg/kg, i.p.) alone (negative control).Similar effect was also observed in the group treated with RISP (0.5 mg/kg, i.p), as it significantly (P< 0.05) decreased immobility time compared to the ketamine treated group (Fig. 3).

Effect of EEBS on cataleptic behaviour.

The EEBS (10, 20 40 and 80 mg/kg, i.p) showed no significant prolongation in the duration of akinesia, compared with the vehicle (10 mL/kg, i.p) treated group. However, HLP (1 mg/kg, i.p) significantly (P< 0.05) prolonged the duration of akinesia in comparison with the group treated with vehicle (Fig .4).

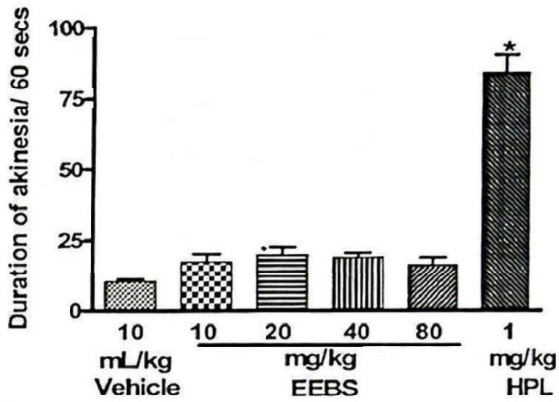

Fig. 4: Effect of EEBS on cataleptic behaviour
Columns represent Mean ± S.E.M (n=5).One way ANOVA revealed that there is significant
[F (5, 26) = 74.56, P< 0.0001] difference between various treatment groups.
* Denotes P< 0.05 compared to vehicle group
VEH = Vehicle, **HLP** = Haloperidol, **EEBS** = Ethanol extract of *B.sapida*

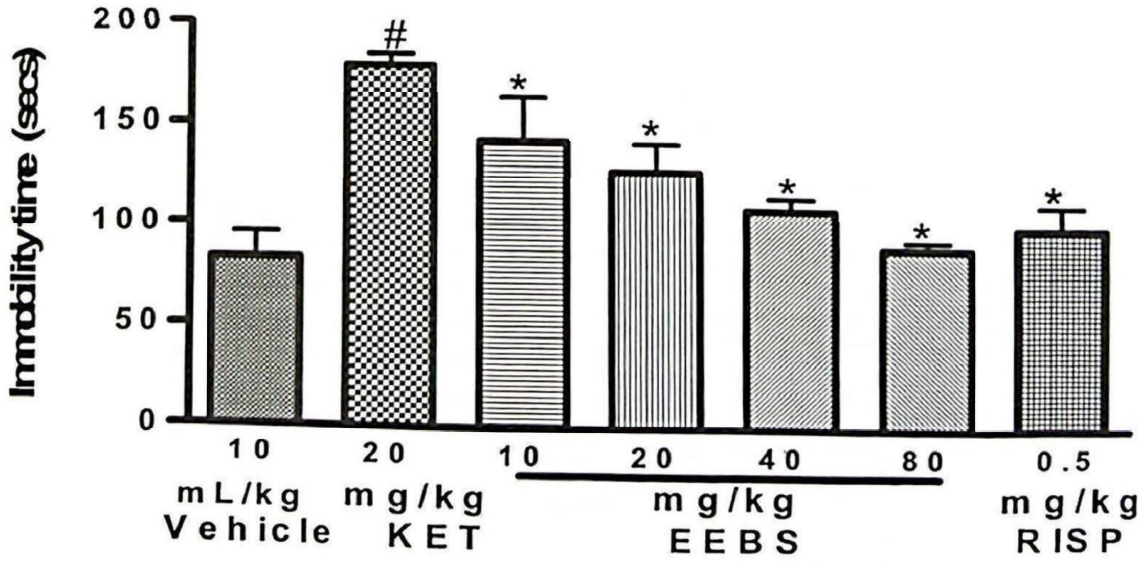

Fig. 3: Effect of EEBS on ketamine-enhanced immobility in forced swim test in mice.
Columns represents mean ± SEM (n=5). One way ANOVA revealed that there is no significant [F (6, 28) = 7.728, P<0.0001] difference between various treatment groups.
*Denotes P< 0.05 as compared with ketamine treated group.
# Denotes P< 0.05 as compared with vehicle treated group
KET = Ketamine, **RISP** = Risperidone, **EEBS** = Ethanol extract of *B.sapida*

Effect of EEBS on Drug-induced Ptosis

Treatment with EEBS (10, 20, 40, and 80 mg/kg, i.p) showed significant induction of ptosis compared to the vehicle (10 mL/kg, i.p). Similarly HLP (1 mg/kg, i.p) was also found to induce ptosis compared to the group treated with vehicle (10 mL/kg, i.p) (Fig 5).

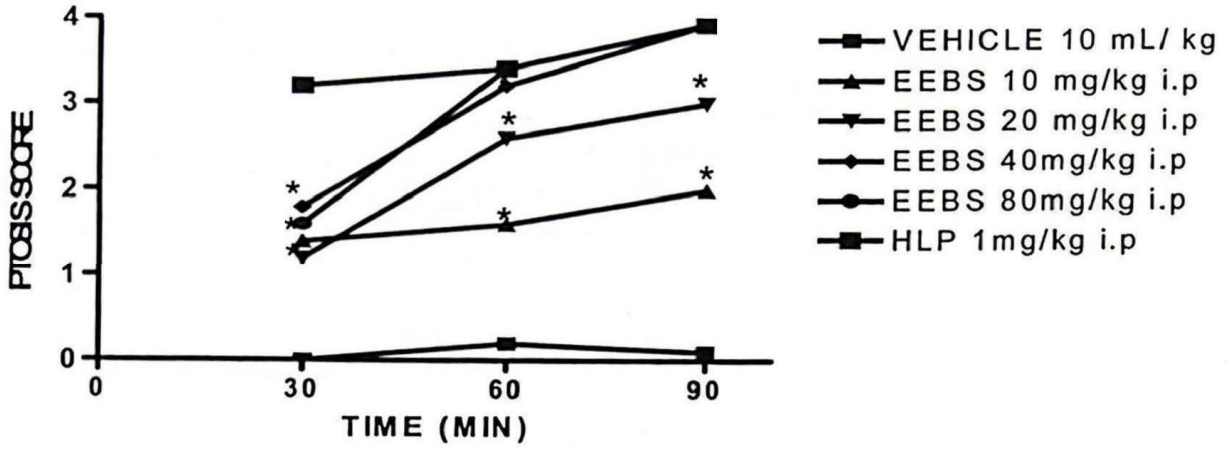

Fig. 5: Effect of EEBS on Drug-induced Ptosis

Points represent the mean (n=5). One way ANOVA shown that there is significant [F (5, 12) =7.283, P < 0.0024] differences between various treatment groups

* Denotes P < 0.05 as compared to vehicle.

APO = Apomorphine, **HLP** = Haloperidol, **EEBS** = Ethanol extract of *B.sapida*

Discussion

B.sapida stem bark attenuated psychotic behavioural manifestations induced by apomorphine and ketamine respectively in mice as compared to risperidone and haloperidol. Mesolimbic and nigrostriatal dopaminergic pathways play key roles in the mediation of locomotor activity and stereotyped behavior [29]. Antagonism of dopamine D_2 receptors may be a common feature of most clinically effective antipsychotic drugs, especially those active against hallucinations and delusions [37]. Activation of dopamine D_2 receptors located striatum induces stereotypes [38] and the nigrostriatal system mediates these stereotypes that predominate at higher doses of apomorphine. Apomorphine is an agonist at the dopamine receptor; it binds to D_2 receptor subtype resulting in inhibition of adenylyl cyclase which reduces potassium ion conductance, and enhances calcium ion channel activity with resulting stereotypes and hyperactivity [39].

Similar to Dopamine (DA) agonists, stereotyped behaviours are also induced in rodents by noncompetitive NMDA antagonists acting at the ion channel associated with the NMDA subtype of the glutamate receptor, such as phencyclidine (PCP) and ketamine [40]. Ketamine may present an indirect dopamine agonist activity and induced behavioural stimulation that may be connected with the dopamine system. In the Pre-Pulse Inhibition (PPI) model, reversal of apomorphine- induced disruption does not dissociate between typical and atypical antipsychotic drugs (APDs), but reversal of NMDA antagonist- induced disruption apparently does (although conflicting results have been reported; [41-43], suggesting that behavioral PCP effects in general rather than disrupted PPI in particular are selectively sensitive to atypical APDs. Blockade of apomorphine and ketamine-induced stereotype behavior suggest neuroleptic activity [44]. In the context of this study, it was found that EEBS stem bark significantly produced an inhibitory activity against these stereotyped behaviours induced by both apomorphine and ketamine as a measure of positive symptoms in psychotic patient. Hence, theehanolic extract of *B. sapida* stem bark on the stereotype behaviours suggests the possible interference with central doparminergic neurotransmission and neuroleptic effect.

Acute administration of Ethanol extract of *B.sapida* stem bark prior to ketamine administration significantly antagonized the hyperactivity (hyperlocomotion) induced by ketamine, this also suggests that EEBS stem bark possesses antipsychotic property. It has been shown that dopamine neurotransmission is involved in the motor activating effects of ketamine via the blockade of NMDA receptors. The systemic administration of dopamine antagonist counteracts the motor

activation induced by the systemic administration of NMDA [45]. This shows that the EEBS stem bark may be acting as dopamine antagonist. This effect EEBS stem bark was compared to risperidone thus suggesting an atypical mechanism of action. This work is in agreement with the inhibition of ketamine-induced stereotypy and hyperlocomotion by the root extract of *Panax quinquefolium* [46].

Forced swim-induced immobility in rodent is an acceptable animal model of depression [47] and reduction in the immobility time serves as a specific and sensitive index of antidepressant activity [48, 49]. Consequently, an increase in immobility time in the FST following repeated administration of a subanaesthetic dose of ketamine indicates a depressive state [48]. Ketamine is known to interact with the 5-hydroxytryptaminergic system to decrease the 5-HT_{2A} binding sites in the frontal and parietal cortex associated with reduced $5HT_{2A}$ receptor mRNA abundance [49-51]. Ketamine-induced behavioural changes are inhibited by clozapine and risperidone [52, 53], which are widely believed to be 5-HT_{2A} receptors antagonists [54, 55]. Although, ketamine is known to interact with several other binding sites in the brain, including the PCP binding site within the NMDA receptor channel complex and dopamine-D_2 receptor binding sites at the hippocampus [49], findings suggest that ketamine-enhanced immobility in the FST might be mediated, at least in part, via 5- HT_{2A} receptors. Risperidone is known for its $5HT_{2A}$ receptor blockade, and through which it attenuates the ketamine-enhanced immobility time [56]. The antipsychotic property of EEBS stem bark against negative symptoms induced by ketamine demonstrated significant reduction of ketamine-enhanced immobility in FST compared to ketamine treated group. The EEBS stem bark attenuation of ketamine enhanced immobility in forced swim test may be mediated via the same $5HT_{2A}$ blockade.

Neuroleptics (antipsychotic drugs) which have an inhibitory action on the nigrostriatal dopaminergic system induced catalepsy, while neuroleptics with little or no nigrostriatal blockade produce relatively little or no cataleptic behaviour. The EEBS stem bark produced no extrapyramidal symptoms as compared to haloperidol. This may be as a result of preferential blockade of D2 receptors in the limbic system which confers antipsychotic effects with little or no tendency to produce extrapyramidal symptoms [57].

The phytochemical analysis of the EEBS stem bark has been shown to contain saponins, alkaloid, cardiac glycosides, reducing sugars and carbohydrates [58], hence the antipsychotic properties may be due to the presence of these phytochemicals

Conclusion

Ethanol extract of *Blighia sapida* stem bark inhibited psycho-stimulation induced by apomorpine and ketamine in male Swiss mice. The extract showed no significant prolongation in the duration of akinesia, suggesting that the extract may be devoid of extrapyramidal side effects.

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