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Anti-psychotic-like effects of *Blighia unijugata*: pharmacological validation of traditional uses in mental health management

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Abstract

Background: *Blighia unijugata*, is a tropical African plant used by traditional healers in Ghana for the management of mental disorders.

Objective: This study sought to explore the neuropharmacological effects of an ethanolic extract from the leaves of this plant to provide corroborating evidence for its use in mental health disorders.

Methods: Mice were subjected to Irwin test to ascertain the general effects of oral *Blighia unijugata* extract (BUE;100, 300 and 1000 mg/kg, p.o) on the physiology of mice and to determine the onset of neuro-activity. The effects of BUE (100, 300, and 1000 mg/kg, p.o) in novelty- and apomorphine-induced locomotor effects were assessed using the open-field paradigm. Further, apomorphine-induced cage climbing assay was used to assess for any anti-psychotic-like potential of BUE. The potential of BUE to cause extrapyramidal motor effects was also tested.

Results: BUE-treated mice demonstrated excitation at 15 and 30 minutes post-treatment with lower doses at 100 and 300 mg/kg and also showed sedation at 1000 mg/kg at 60,120 and 180 minutes post-BUE administration. There was no significant difference between BUE and the vehicle-treated group regarding the frequency and entry into the centre, corners, or peripheral regions of the open field. BUE, however, significantly decreased the frequency of cage climbing in the apomorphine-induced cage climbing test. BUE also significantly increased haloperidol-induced cataleptic activity 60 minutes post-administration.

Conclusion: The ethanolic extract of the whole plant of *Blighia unijugata* possesses antipsychotic-like activity. This finding lends corroborating pharmacological evidence for the traditional use of BUE in the management of mental health disorders.

Keywords: apomorphine, Irwin Test, *Blighia unijugata*, antipsychotic agent

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INTRODUCTION

Schizophrenia is a psychotic condition involving some shared but variable presentation of mood and substance use disorders. It is a relatively common feature of many developmental, acquired, and degenerative neurologic and medical conditions [1,2]. Schizophrenia contributes significantly to disabilities and is a huge barrier to productive living in the affected individuals [2]. The World Health Organization estimates that 21 million people worldwide have psychosis [3]. Despite the significant impact that the numerous antipsychotic drugs have on the

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care of patients with psychotic disorders, there are still challenges when aiming at therapeutic goals such as remission, recovery, and improvement in health-related quality of life and functioning [4].

The use of conventional antipsychotic drugs has been associated with a lack of efficacy and effectiveness in 30 - 60% of patients, and most present with extrapyramidal motor side effects, malignant and fatal neuroleptic syndrome, agranulocytosis and weight gain, among others [5]. Given these limitations of antipsychotic medications, drug discovery research for newer antipsychotics, with potentially fewer side effects, is warranted. In developing countries where access to primary health care is limited, patients resort to traditional alternatives and complementary therapeutic agents, the majority of which are herbal medicines. Antipsychotic drug discovery from plants used traditionally in the management of psychosis may, therefore, be a viable option. Thus, providing pharmacological evidence in support of traditional folkloric uses of plants is important in lending legitimacy and rationalising the use of such plants. An example of a plant-derived compound with antipsychotic properties is reserpine, which was isolated from the plant Rauwolfia serpentina [6].

Blighia unijugata (family; Sapindaceae), a tropical African plant, is a medium to large evergreen tree with pleasantly scented flowers and pink to red, pear-shaped fruit that burst open to reveal quick-growing, shiny black seeds nestled on a yellow base. In Ghana, the roots are used in palm nut soup to control haemorrhage during childbirth. The bark pulp is steeped in water, consumed for fever-related illnesses, or given as an enema. A decoction of an infusion of the pounded seeds is utilized in Ghana for nausea and vomiting [7]. The plant's macerated twigs, leaves, flowers and fruits are used to produce fish poisoning [8]. In a previous survey we conducted to determine plants used for the management of psychosis in Ghana, it was recorded that the dried bark or roots of *Blighia unijugata* are boiled and ingested as required and the extract smeared on the body for the treatment of mental problems [9]. There is, however, no published scientific work validating this claim by the traditional healers in Ghana [9]. Unpublished data from our laboratory indicates that the phytochemical analysis of the root and stem barks did not differ significantly from those of the leaves, and as a means of conservation of the plant, we focused on the leaves for the current study. Thus, this study sought to investigate the neuropharmacological activity of *Blighia unijugata* leaf extract and to further explore its potential anti-psychotic effects.

MATERIALS AND METHODS

Plant collection and extraction

Leaves of *Blighia unijugata* were collected from the premises of the School of Pharmacy, University of Ghana. Identification and authentication of the plant material was done at the Department of Plant and Environmental Biology, University of Ghana, where a voucher specimen (PA07/UGSOP/GH17) was deposited. The leaves were dried under shade, pulverized and cold-macerated using 70% ethanol in water. The resultant extract was put in a water bath, and the dried mass obtained was weighed and placed in a desiccator. The percentage yield of the extraction was calculated. The resultant 10% w/w yield was labelled as BUE.

Phytochemical screening

Phytochemical screening was done by modification of a method previously described [10]. The extract was screened for the presence of saponins, tannins, flavonoids, anthraquinones, cardiac glycosides**,** alkaloids and reducing sugars.

Animals

Female Imprint Control Region (ICR) mice (20 - 30 g), 6 - 8 weeks old, were obtained from and maintained at the Department of Animal Experimentation, Noguchi Memorial Institute for Medical Research (NMIMR), University of Ghana, Legon, Accra, where the behavioural experiments were performed. The animals were housed in groups of five in stainless steel cages (dimensions: 34 cm x 47 cm x 18 cm) with soft wood shavings as bedding and maintained under laboratory conditions of temperature: 22 ± 2 °C, relative humidity: 60 - 70%, and 12-hour light-dark cycle. Mice were fed with a normal commercial pellet diet (AGRIMAT, Kumasi) and given water *ad libitum.* All experimental procedures and techniques used in these studies were approved by the Scientific and Technical Committee of the NMIMR [reference number STC - 4 (2) 2013 - 14] and by the Noguchi Institutional Animal Care and Use Committee, College of Health Sciences, University of Ghana, (protocol number NIACUC-2016-01-2Q). Experimental techniques were adhered to per the National Institute of Health Guidelines for the Care and Use of Laboratory Animals (NIH, Department of Health Services publication No. 83-23, revised 1985).

Irwin Test

The Irwin test was done primarily to provide preliminary effects of varying doses of the extract in the experimental animals. While providing a battery of investigations into the onset of neuropharmacological actions of the extract, it also gives an acute toxicity profile [11]. To conduct this investigation, a total of 20 female ICR mice were grouped as follows: 15 animals for the plant extract (five dose levels, n = 5 per dose level) and a vehicle-treated group (n = 5). The animals were treated orally with various doses of the extract (30, 100, 300, 1000, and 3000 mg/kg) or vehicle (10 ml/kg, *p.o.*) and observed at 0, 5, 15, 30, 60 and 120 minutes after drug administration. These doses present low, medium, and highest possible doses with respect to traditional uses. At each observation time, 49 parameters were scored using a rigorous standardized procedure based on that described by Irwin, 1968. The parameters measured were excitation, stereotypy, motor, sedation, pain, and autonomic functions of a test substance in the experimental animals.

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Novelty-induced locomotor behaviour

As previously described, the novelty-induced behaviour was evaluated using a locally manufactured open-field observation box made of transparent plexiglass [11]. The behavioural events were recorded using Everio JVC Camcorders (120 GB HDD, USA). For these experiments, a total of 20 ICR female mice were grouped as follows: three oral doses of the extract (100, 300, or 1000 mg/kg) and vehicle (10 ml/kg, *p.o*). The extract doses were selected based on the findings from the Irwin test described above. The animals were then placed in the open-field observational box, and their behaviour was recorded for 5 minutes. Chlorpromazine (1 mg/kg, i.p.) was used as the standard reference drug for comparison. Using a Behavior Tracker® (Digital Revier GmBH®, Germany), the frequency of entry into and duration spent at the periphery, centre, and corner zones of the open field were tracked for 5 minutes. The total frequency of entry into the zone was calculated as an index of the total locomotor activity.

Apomorphine-induced locomotor behaviours

Locomotor activity was assessed as previously described [11,12]. Standard pretreatments with the extract were administered 30 minutes before apomorphine (1 mg/kg, i.p). Spontaneous locomotor activity was measured immediately after the mice were administered apomorphine and placed in the observation cage, and their behaviour was recorded for 30 minutes, as described above. Chlorpromazine (1 mg/kg, i.p.) was used as the reference drug. The frequency and total duration of zone entries as well as the total frequency of entries, were tracked and calculated as described above.

Apomorphine-induced cage climbing

The method, as described by Amoateng and colleagues, as well as Davis, Jenner, and Marsden, was adopted [11,13]. The frequency and duration of climbing and swinging were used to assess the climbing activity. Climbing was taken as when a mouse climbed the sides of the cage with all four paws. Swinging was assessed as when a mouse held on to the upper part of the cage with its fore paws. The climbing behaviour assessment ran from 0 to 30 minutes post-apomorphine injection (same dose as extract). Haloperidol (5 mg/kg, i.p.) was used as the standard reference drug. The recorded video was tracked using the Behavior Tracker® (Digital Revier GmBH®, Germany) for the frequency and duration of climbing and swinging. The percentage change in the events scored for the extract-treated mice in comparison to the vehicle-treated ones was calculated and subsequently, the ED_{50} values were determined.

Catalepsy test

Each mouse, after 30 minutes of pretreatment with BUE (100, 300 and 1000 mg/kg, p.o or vehicle, distilled water 10 ml/kg, p.o), was placed in the observation cage with its fore paws over a 3.5 cm bar and observed for the time it took to remove its fore paws from the bar. This procedure was repeated at 30, 60 and 120 minutes post-treatment. The intensity of catalepsy was taken as the duration of time the animal took to remove both forelimbs from the bar to the floor of the observation cage [14].

Data analysis

The ED_{50} (concentration responsible for 50% of the maximal effect) of extract and reference drug were determined using an iterative computer least squares method in Prism 5.0 for Windows version 5.0 (GraphPad Software, San Diego, CA, USA) with the following nonlinear regression (four-parameter logistic equation).

$$Y = \frac{a + (a - b)}{1 + 10^{((LogED_{50} - X) \times Hill\ Slope))}}$$

Where X is the logarithm of concentration, Y is the response, starting at *a* and ending at point b with a sigmoid shape.

The fitted midpoints (ED_{50}s) of the curves were compared statistically using the *F* test.

Statistical analyses (one- or two-way ANOVA followed by an appropriate *post hoc* test) were conducted using Prism 5.0, with $p \leq 0.05$ considered statistically significant. Graphs were plotted using Sigma Plot for Windows version 11.0 (Systat Software Inc., Germany). Unless otherwise stated, all data are presented as mean ± SEM.

RESULTS

Phytochemical analysis of BUE

Phytochemical analysis of the extract revealed the presence of glycosides, saponins, alkaloids, tannins and flavonoids, whereas cyanogenic glycosides and anthracene glycosides were absent.

Irwin test

BUE appeared to exhibit a time-dependent biphasic response in mice. At 15 and 30 minutes post BUE administration, mice

Table 1. Effects of BUE (100, 300, 1000 and 3000 mg/kg, p.o) on pre-treated mice in the Irwin's

BUE (mg/kg)				
30	100	300	1000	3000
Excitation (60 min)	Excitation (15 and 30 min)	Sedation (60, 120 and 180 min)	Sedation (60, 120, 180 min)	Sedation (60, 120 min)
↑Fear	↑Chewing	Excitation (15 and 30 min)	↑ Fear	Excitation (15 and 30 min)
	↑Fear	↑ Chewing		Ptosis
	↑Reactivity to touch	↓ Reactivity to touch		Akinesia
		Piloerection		

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treated with 30 and 100 mg/kg showed some excitation, depicted by increased movement. However, the mice treated with 300, 1000 and 3000 mg/kg became sedated at times of 60, 120, and 180 minutes. The only stereotypical behaviour exhibited was chewing. There was no convulsion, motor incoordination or deaths up to 180 minutes of continuous observation and at 24 hours post-treatment. The autonomic behaviours observed were piloerection and ptosis. Akinesia was present only at the highest dose of 3000 mg/kg (Table 1).

Novelty–induced locomotor activity

BUE administration at all concentrations did not alter the frequency of entry into the centre ($p = 0.0598$, $F_{3,16}$=3.032, Figure 1), periphery ($p = 0.3098$, $F_{3,16} = 1.297$, Figure 1) or corners ($p = 0.2031$, $F_{3,16} = 1.720$, Figure 1) of the open field, neither did it affect the duration of time spent within the centre ($p = 0.3412$, $F_{3,16} = 1.201$, Figure 1), periphery ($p = 0.3851$, $F_{3,16} = 1.153$, Figure 1) or corners ($p = 0.4312$, $F_{3,16} = 0.9699$, Figure 1). Nonetheless, chlorpromazine (CPZ) significantly decreased the frequency of centre entry ($p = 0.0598$, $F_{3,16} = 3.032$, Figure 1) while the duration of time spent in the centre remained unchanged ($p = 0.3412$, $F_{3,16} = 1.201$, Figure 1). However, there was a significant difference ($p = 0.0005$, $F_{4,20} = 8.141$, Figure 3A) between the treatments and vehicle group with regard to the total zone entries,

Apomorphine-induced locomotor activity

The drug treatments (extract and CPZ) significantly decreased the frequency ($p = 0.0175$, $F_{4,20} = 3.685$, Figure 2) and duration ($p < 0.0001$, $F_{4,18} = 44.53$, Figure 2) of centre entries in comparison to the vehicle-treated group of mice. There was also a significant decrease in the frequency of periphery entry between the extract and control group ($p = 0.0008$, F4,20 = 7.374, Figure 2). However, there was no significant difference ($p = 0.1866$, F4,19 = 1.723, Figure 2) in the duration spent in this zone. Furthermore, the extract did not significantly affect the frequency ($p = 0.1108$, F4,20 =

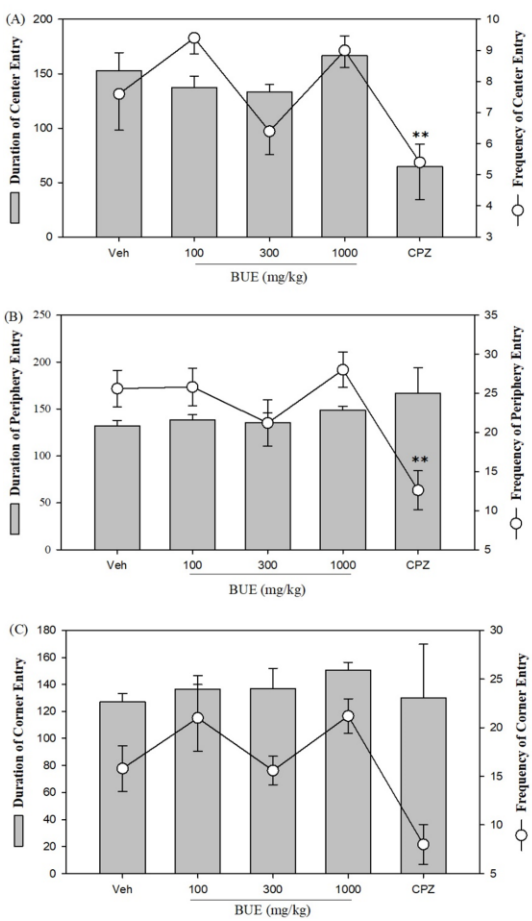

Figure 1: Effects of BUE (100-1000mg/kg) and chlorpromazine (1.0 mg/kg) on the frequency (○) and duration(▄) of novelty-induced locomotor activity. Each column represents the mean ± S.E.M. n = 5. ** p < 0.01 compared to vehicle-treated group (One-way ANOVA followed by Dunnett's post hoc test)

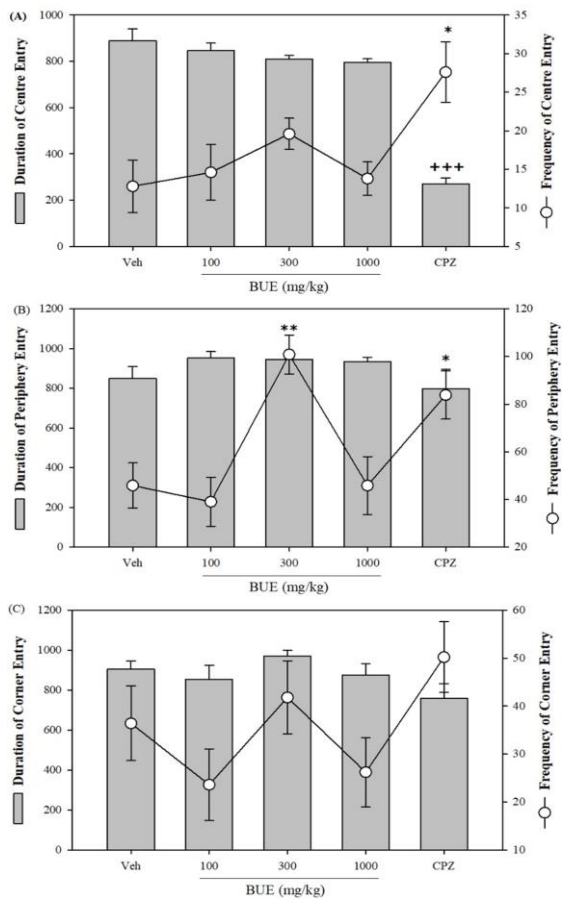

Figure 2: Effects of BUE (100-1000mg/kg) and chlorpromazine (1.0 mg/kg) on the frequency (○) and duration(▄) of apomorphine-induced locomotor activity. Each column represents the mean ± S.E.M. n = 5. *p < 0.05; ** p < 0.01 (line graph); $^{+++}$ p < 0.001 (column graph) compared to vehicle-treated group (One-way ANOVA followed by Dunnett's post hoc test).

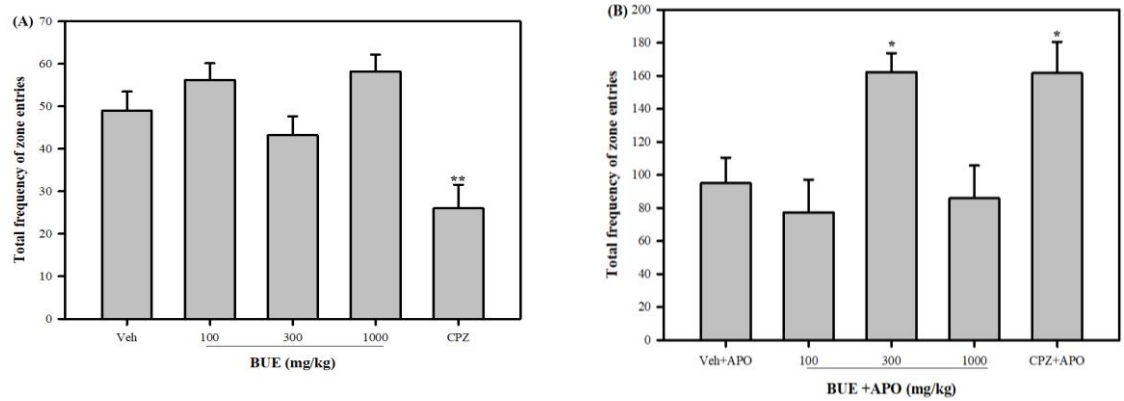

Figure 3. Effects of BUE (100-1000 mg/kg) and chlorpromazine (1.0 mg/kg) on the total frequency of zone entries in (A) novelty-induced and (B) apomorphine-induced locomotor activities. Each column represents the mean ± S.E.M. n = 5. *p < 0.05; ** p < 0.01 compared to vehicle-treated group (One-way ANOVA followed by Dunnett's post hoc test)

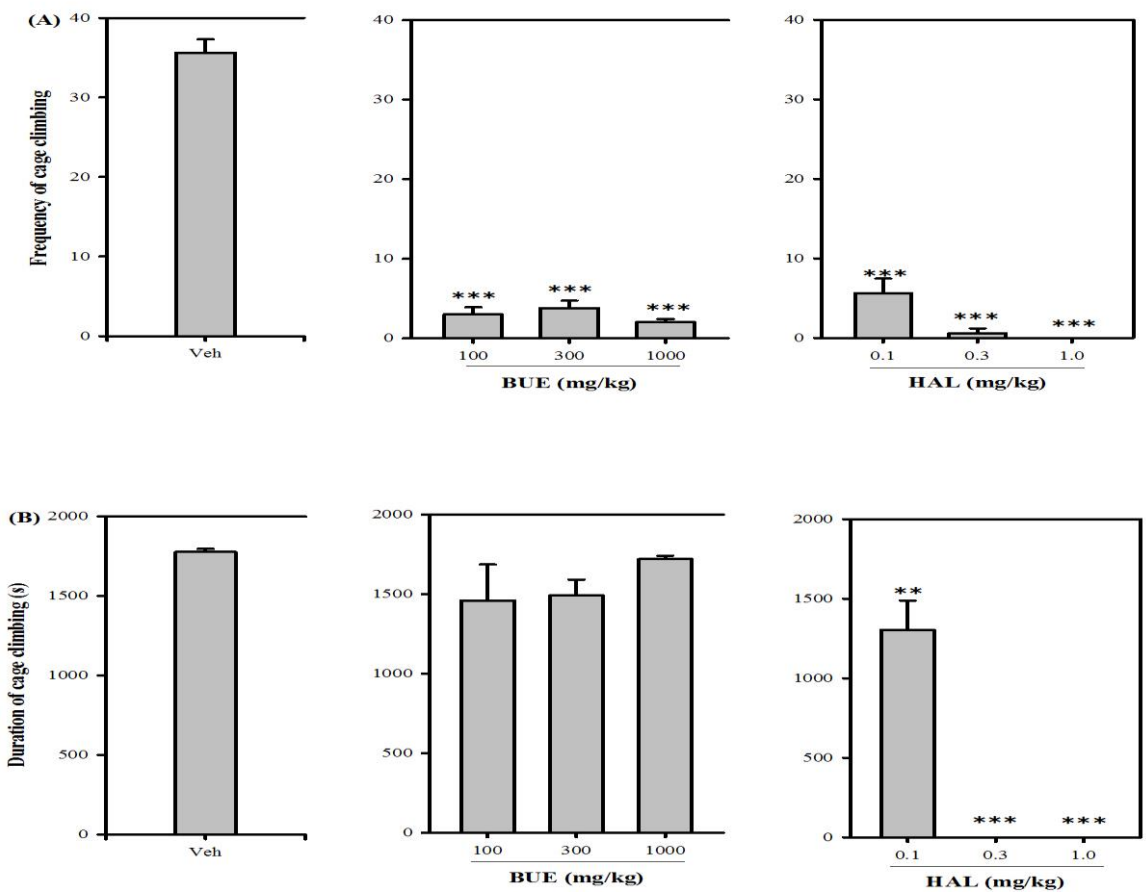

Figure 4. Effects of BUE (100-1000mg/kg) and haloperidol (0.1-1.0 mg/kg) on the frequency and duration of apomorphine-induced cage climbing. Each column represents the mean ± S.E.M. n = 5. *p < 0.05; ** p < 0.01; ***p < 0.001 compared to vehicle-treated group (One-way ANOVA followed by Dunnett's post hoc test)

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2.160, Figure 2) and duration (p = 0.1733, $F_{4,18}$ = 1.786, Figure 2) of entries into the corner zone of the paradigm. When the total entries were calculated, there was a significant difference (p = 0.0028, $F_{4,20}$ = 5.825, Figure 3) between extracts and CPZ when compared to the vehicle-treated group. A *post hoc* test revealed a significant increase for BUE 300 mg/kg and CPZ 1 mg/kg.

Apomorphine-induced cage climbing

BUE significantly reduced the total frequencies (p < 0.001, $F_{3,15}$ = 213.2, Figure 4A) of cage climbing activities in the treated mice. This property was present at all doses of the extract. However, the decrease was not dose-dependent. Like the extract, haloperidol (HAL) showed a significant decrease (p < 0.0001, $F_{3,16}$ = 172.1, Figure 4A) in the frequency of climbing at all doses, but its decrease was dose-dependent (p < 0.0001, $F_{3,15}$ = 146.7, Figure 4B). Haloperidol significantly decreased (p < 0.0001, $F_{3,13}$ = 1.302, Figure 4B) the duration of cage-climbing, unlike the extract, which showed no significant difference (p = 0.3158, $F_{3,12}$ = 3.12, Figure 4B). BUE was less potent than haloperidol (Table 1) in decreasing apomorphine-induced climbing.

Extract-induced catalepsy

There was no significant difference between the extract and the control group (p = 0.0513, F = 3.457, Figure 5) in test substance-induced catalepsy. After a post hoc test, BUE at 300 mg/kg significantly increased catalepsy 30 minutes after administration (p < 0.001). The total effect on catalepsy, calculated as the area under the curve, revealed that the total duration of BUE at a dose of 300mg/kg was significantly increased (p < 0.05). The other doses, however, did not show significant differences (Figure 5B)

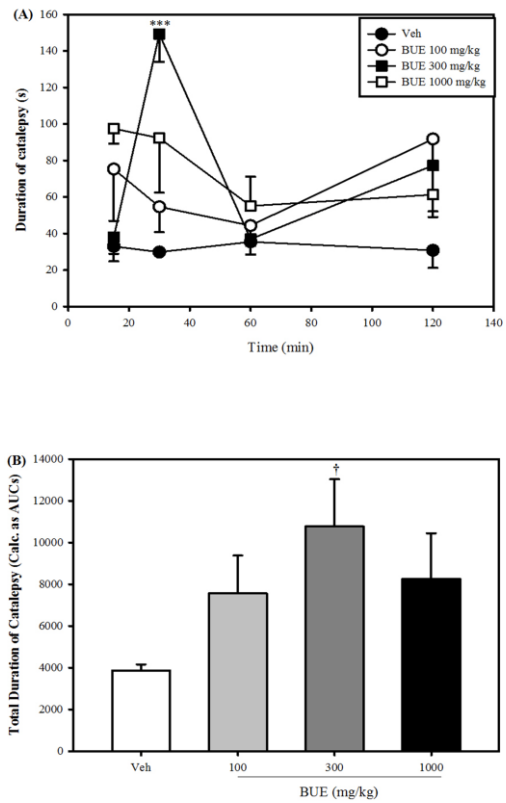

Figure 5. Effects of BUE (100-1000 mg/kg) on the duration of catalepsy. Each column represents the mean ± S.E.M. n = 5. *p < 0.05 compared to the vehicle-treated group (Two-way ANOVA followed by Dunnett's post hoc test); †p < 0.05 compared to the vehicle-treated group (One-way ANOVA followed by Dunnett's post hoc test).

Table 2. ED_{50} (mg/kg ± SEM) of the extract (BUE) and haloperidol (HAL) for the frequency and duration of cage climbing in the apomorphine-induced cage climbing test.

Treatment	Frequency	Duration
BUE	998.70 ± 1.69	473.8 ± 0.07
HAL	0.14 ± 1.59	0.11 ± 2.41

DISCUSSION

The outcome of this study provides initial pharmacological evidence that the hydro-ethanolic extract of *Blighia unijugata* possesses antipsychotic-like activity in the murine models of psychosis used and is worthy of further investigation. The Irwin test, one of the core battery tests, is used to estimate the minimum lethal dose of a test substance, the dose range for CNS responses, and the primary effects on behaviour and physiological functions [15-17]. Taking advantage of the Irwin test, this study revealed that BUE administration induced sedation and motor impairment at higher doses without impairing respiration. The prominence of sedation at high doses of BUE suggests that BUE could possess therapeutic benefits in the treatment of disorders such as anxiety, bipolar disorder, and psychosis [16]. On the other hand, motor impairment at higher doses is indicative of BUE having a cataleptic effect, which is most often mediated through dopaminergic blockade [18,19]. Interestingly, this cataleptic effect is most prominent at 300 mg/kg, with less of an effect observed at 1000 mg/kg, thus suggesting possible opposing effects of BUE at higher concentrations. This phenomenon is common in natural plant-based product research and is likely due to many active metabolites with or without synergistic effects at varying concentrations/ doses.

One of the potential therapeutic benefits of BUE suggested by the results from the Irwin test is that BUE could possess antipsychotic properties. Based on this, the effects of BUE on novelty-induced exploratory locomotor activity in an open field were used to evaluate the potential antipsychotic effect of BUE [20]. Tests were also performed to assess the effect of BUE on exploratory locomotor activity induced by apomorphine, a mixed D_1/D_2 agonist that acts on all the dopaminergic systems in the body [21]. This is because psychosis has been linked with increased dopaminergic and

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serotonergic neurotransmissions, and both preclinical and clinical investigations have confirmed their role in the development of the disease [22,23]. Furthermore, the suppression of exploratory behaviour is due to the suppression of dopaminergic activity in the limbic forebrain in mice [24]. Although BUE did not affect novelty-induced locomotor activity, it ameliorated the effect of apomorphine-induced locomotor activity (like chlorpromazine), as evidenced by the increased frequency of periphery entry. Similarly, BUE increased the total frequency of zone entries during apomorphine-induced locomotion, not novelty-induced locomotion. Exploratory behaviour in an open field is characterized by an increase in the frequency/duration of entry into the central areas and decreased entry or residency in the periphery and corners of the open field. Current available antipsychotic drugs are known to suppress exploratory locomotor activity, suggesting that BUE, causing a similar effect in mice, has antipsychotic properties [25].

However, it is not clear why this effect is only present in apomorphine-induced locomotion and not novelty-induced locomotion. BUE likely acts as a dopamine antagonist as previous reports have established that dopamine blockade (e.g. dopamine denervation) decreases exploratory behaviour, while dopamine agonism (e.g. apomorphine) increases novel object-seeking [26]. Other neurotransmitters like serotonin have been identified as mediating novelty-induced locomotion [27]. Therefore, if BUE is indeed mediating its effects via dopamine antagonism, this effect could be reduced under novelty-induced conditions, where other neurotransmitters also play a role. Indeed, our finding that BUE significantly decreased apomorphine-induced climbing in mice lends further support to BUE antagonizing dopamine receptors. Apomorphine-induced climbing is a classical animal model used to screen for the antipsychotic activity of drugs, and it is assumed that the climbing behaviour it induces is mainly due to the stimulation of dopamine D_1/D_2 receptors in the striatum and the mesolimbic system [28]. As elevated extracellular dopamine levels and D_2 receptor expression in the striatum have been observed in highly explorative animals [26], further investigation will seek to correlate the extent of BUE effects with dopamine levels and D_2 receptor expression.

In addition to predicting the antipsychotic effect, open-field exploratory behaviour can also be used to study the effects of drugs on anxiety. It has been suggested that two factors influence exploratory behaviour in the open field. The first is social isolation resulting from the physical separation from cage mates when performing the test. The second is the stress created by the brightly lit, unprotected, novel test environment [29,30]. For these reasons, in experiments involving rodents, investigators do not measure the effects of treatments on exploration, as is sometimes claimed, but the effects on the reaction of the subjects to a stressful event. BUE caused a significant decrease in apomorphine-induced exploratory behaviour in mice, as evidenced by increased entries into the periphery, indicating a possible antipsychotic effect. This is also suggestive of an anxiogenic effect of the extract, but whether this counters the antipsychotic-like effect needs to be further explored with purely anxiogenic models and/or drugs.

Lastly, in support of the proposed dopamine antagonistic-like activity of BUE, it was observed that it significantly induced catalepsy at 300 mg/kg. Catalepsy induced by the typical neuroleptic agent, such as haloperidol in rodents, is used as a model of the extrapyramidal side effects often seen clinically in patients receiving typical antipsychotic drug therapy. There is considerable evidence that blockade of dopamine transmission in the nigrostriatal tract produces catalepsy [18,19]. Evidence indicates that drugs that potentiate or attenuate neuroleptic-induced catalepsy in rodents might aggravate or reduce the extrapyramidal side effects, respectively [31,32]. Furthermore, antipsychotic agents often increase catalepsy, thereby providing a measure of the extrapyramidal side effects observed in humans exposed to prolonged antipsychotic medications. Given that BUE significantly potentiated-induced catalepsy, this may further support the possibility that BUE acts on the dopaminergic system. It also suggests that BUE may cause extrapyramidal side effects.

Conclusion

The research findings suggest that the hydro-ethanolic extract of the leaves of *Blighia unijugata* has antipsychotic-like activity, possibly by having an antagonistic action at dopamine receptors. This study provides pharmacological evidence and lends support to its traditional uses in the management of psychosis. Further studies are required to verify the exact mechanism by which the extract produces the observed antipsychotic-like activity. The investigation into the anti-psychotic-like properties of *Blighia unijugata* offers compelling pharmacological validation for its traditional application in mental health treatment. The data indicates that the hydro-ethanolic extract of *Blighia unijugata* (BUE) demonstrates substantial antipsychotic-like activity in murine models of psychosis. The Irwin test results showed that BUE induces sedation and motor impairment at elevated doses, implying potential therapeutic benefits for conditions such as anxiety, bipolar disorder, and psychosis.

DECLARATIONS

Ethical consideration

Ethical clearance was obtained from the Noguchi Institutional Animal Care and Use Committee, College of Health Sciences, University of Ghana, with protocol number NIACUC-2016-01-2Q. All procedures and techniques used were in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals (NIH, Department of Health Services publication No. 83-23, revised 1985).

Consent to publish

All authors agreed on the content of the final paper.

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Competing Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions
PA participated in the conceptualization, draft and project administration of the study. PA and FABD participated in methodology, analysis, and investigation. PA, FABD, TAT, GAK, SA, KKEK, DOS and SBK participated in writing, reviewing and editing the manuscript.

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Availability of data
Data is available upon request to the corresponding author.

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