Evaluation of Antipsychotic Properties of Aqueous Extract of *Lophira alata* (Ochnaceae) and *Afzelia africana* (Leguminosae) Stem Barks in Rats

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ABSTRACT

Stem barks of *Lophira alata* (family: Ochnaceae) and *Afzelia africana* (family: Leguminosae) are used in ethnomedicine for the management of psychosis. Since no existing data was found on their anti-psychotic properties, this study was carried out to evaluate their ability to reduce amphetamine induced stereotypy in rats. The oral mean lethal dose (LD_{50}) of both extracts was estimated and preliminary phytochemical screening was conducted. *Lophira alata* and *Afzelia africana* extract (6.25, 12.5 and 25 mg/kg *po*) was investigated for antipsychotic potential on amphetamine induced stereotypy model in rats. The LD_{50} of each of the plants was estimated to be greater than 5000 mg/kg. Oral administration of *Lophira alata* and *Afzelia africana* extract produced a significant reduction ($p<0.05$) in locomotive activity and in episodes of rearing and sniffing typical of stereotypy in rats. The results obtained suggest that the aqueous stem bark extract of *Lophira alata and Afzelia africana* possess antipsychotic properties which may account for their use in ethnomedicine.

Key words: *Lophira alata, Afzelia africana*, amphetamine, locomotion.

INTRODUCTION

Traditional medicine is defined as the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illness. It forms the mainstay of treatment for majority of the inhabitants of Africa. In industrialized countries, adaptations of traditional medicine are termed complementary or alternative medicine (WHO, 2003).

Schizophrenia, a form of mental disorder characterized by psychotic symptoms affects about 1% of the population and ranks among the top five causes of disability in adults (Hodgins, 1992; Murray and Lopez, 1996). Drugs currently used for clinical management of psychotic illnesses are dopamine receptor antagonists, some of which also antagonize serotonergic, muscarinic and alpha adrenoceptors. They can be divided into two groups viz :
(i) typical or first generation anti-psychotics such as chlorpromazine, haloperidol, fluphenazine, flupentixol and clopentixol which produce unwanted motor side effects including acute dystonias and tardive dyskinesia (extra-pyramidal side effects) .
(ii) atypical or second generation anti-psychotic drugs such as clozapine, risperidone, sertindole, quatiapine, aripiprazole, olazapine and zotepine which are associated with lower incidence of extra-pyramidal side effects (Rang *et al.,* 2007; Meltzer, 2009).

Herbal medicines form the cornerstone of therapy for management of psychiatric disorders including psychotic symptoms and schizophrenia in some parts of the world where leaves, stem barks, roots, flowers and fruits of various plants are often used in combination with different rituals for treatment of mental disorders (Ibrahim *et al.,* 2007; Magaji *et al.,* 2008; Romeiras *et al.,* 2012; Ahmed and Azam, 2014). Different parts of *Afzelia africana, Annona senegalensis, Datura metel, Euphorbia hirta, Ficus hirta, Ginkgo biloba, Hypericum perforatum, Lophira alata, Milicia excels, Morinda citrifolia, Ocimum americanum, Panax ginseng, Piper retrofractum, Rauwolfia vomitoria, Thevetia peruvian, Valeriana officinalis, Ximenia americana* are used in folkloric and in alternative and compl ementary Medicine for management of psychiatric illness. They are used in form of decoctions, juice extracts, taken as food or made into pills for oral consumption (Gill, 1992; Iwu, 1993; Iwu and Wootton, 2002; Ibrahim *et al.,* 2007; Pieme *et al*., 2008; Sofowora, 2008; Sonibare *et al.,* 2008; Sonibare *et al.,* 2011; Romeiras *et al.,* 2012; Ahmed and Azam, 2014)

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Lophira alata locally known in many parts of Nigeria as red iron wood, *Namijin kadai* (Hausa), *Ekki* (Yoruba), *Aba, Akufo or ugiri nwautobo* (Igbo), is used for its analgesic, anti-inflammatory, anxiolytic, anti-malarial, sedative and antiepileptic effects (Bolza and Keating, 1972; Burkill, 1985; Tih *et al.,* 1994, Ibrahim *et al.,* 2007; Musa *et al.,* 2013; Ajiboye *et al.,* 2014; Falade *et al.,* 2014, Balde *et al*., 2015). *Afzelia africana* locally known as *Lucky bean tree* or *Kawo* (Hausa), *Apa* (Yoruba) *Akpalata* (Igbo) is credited with antiepileptic, antipyretic, analgesic, antidiabetic, antimicrobial, antipsychotic and wound healing properties (Burkill, 1985; Adjanohoun *et al.,* 1986; Onweluzo *et al.,* 1995; Balde *et al.,* 2006; Akah *et al.,* 2007; Magassouba *et al.,* 2007; Akinpelu *et al.,* 2008). A decoction of the stem bark of *Lophira alata* and *Afzelia africana* are used together in traditional medicine for the management of psychosis and as a sedative agent (Ibrahim *et al.,* 2007).

A search through existing Literature did not reveal any studies on the antipsychotic properties of these plants; this study was therefore carried out to evaluate their activity in animal models of psychosis.

MATERIALS AND METHODS

Plant materials

Leaves and stem barks of *Lophira alata* obtained from Idi Mongoro forest, Ore Ondo State-Nigeria in November 2012 were identified by authenticated by Mr. K. A. Adeniji and Mr. O. A. Ugboga of the Forest Research Institute of Ibadan, Oyo State-Nigeria where a voucher specimen (FHI 109820) was deposited for future reference. Leaves and stem bark of *Afzelia africana* obtained from Okuomu forest in Benin City, Edo State in October 2011 were identified by Mr. S. Nweke of the Department of Pharmacognosy, Faculty of Pharmacy, University of Benin, Benin City, Edo State and authenticated by Mr. K. A. Adeniji and Mr. O. A. Ugboga of the Forest Research Institute of Ibadan, Oyo State-Nigeria where a voucher specimen (FHI 110362) was deposited for future reference The stem barks were cleaned, dried and reduced to powdered form by milling. Three hundred (300) grams of each plant powder was macerated with 2 liters of distilled water for 24 hours, with occasional shaking at room temperature. The extracts were decanted, filtered and concentrated over a water bath at 40^{o}C. Fresh solutions of both extracts in distilled water were prepared for use each day and a mixture of equal amounts of *Lophira alata* and *Afzelia africana* was made just before drug administration.

Phytochemical Screening

Phytochemical screening was carried out in accordance with the standard protocol as described by Trease and Evans (1983). The extracts were screened for the presence of alkaloids, tannins, saponins, flavonoids, glycosides, phytosterols and triterpenoids.

Animals

Male Wistar rats weighing 180-230 grams procured from the Department of Pharmacology and Toxicology, University of Benin, Benin-City, Edo State, Nigeria were used for the study. They were kept in polypropylene cages at the Animal House Facility of the Department of Pharmacology and Toxicology, University of Benin, Benin City, Edo State, Nigeria. The animals were maintained under standard laboratory conditions with access to animal feed and clean water *ad libitum*. Adequate hygiene was maintained through daily cleaning of cages. Handling of the animals was done according to standard protocols for the use of laboratory animals of the National institute of Health (NIH, 2002).

Drugs/Chemicals

Amphetamine (Tocris Bioscience McKinley, Minneapolis USA) and haloperidol (Janssen Pharmaceuticals, Lagos Nigeria) were used in this study.

Acute toxicity study in mice

The acute toxicity and lethality of *Lophira alata* and *Afzelia africana* was determined in rats using the method described by Lorke (1983). Briefly, nine rats randomly distributed into three groups (n=3) were orally administered 10, 100 and 1000 mg/kg of *Lophira alata* respectively and observed for signs of toxicity and death for 24 hours. Based on the outcome of the first phase, 1600, 2900 and 5000 mg/kg *Lophira alata* were administered to a fresh batch of animals (n=1) and observed for number of deaths for 24 hours. The same procedure was conducted for *Afzelia africana* extract. The median lethal (LD_{50}) dose was estimated as the geometric mean of the lowest lethal dose at which the animal died and the highest non-lethal dose at the animal survived.

Behavioural Studies

Anti-psychotic potential of *Lophira alata* and *Afzelia africana* was evaluated using the amphetamine induced model of stereotypy in rats (Ayoka *et al.,* 2006). Male Wistar rats were brought to the test room one hour before the test in order to acclimatize. Each animal was further introduced into the test box for 30 minutes prior to drug administration. Rats were randomly assigned into groups of 5 each and treated with distilled water orally (group I), 3 dose levels of

Lophira alata and *Afzelia africana* orally (6.25, 12.5 and 25 mg/kg, groups II-IV respectively) and haloperidol 2 mg/kg *i.p* (group V) followed thirty minutes later by 2 mg/kg amphetamine administered subcutaneously (s.c). One hour post administration of amphetamine, animals were placed individually in the open field box measuring 40×20×18 cm and several indices were scored according to the method described by Costall and Naylor with some modifications (Costall and Naylor, 1973). Locomotive activity indicated by number of lines crossed, stereotypy measured by episodes and frequency of rearing and sniffing were scored by observers blinded to treatment in blocks of 5 minutes for one hour (Costall and Naylor, 1973). The open field box was cleaned with 70% alcohol after each animal was removed. In order to simulate psychosis which is often associated with hyperdoparminergic activity in the nigrostriatal and mesolimbic pathways (Burt *et al.,* 1977; Abi-Dargham *et al.,* 2005), a separate set of animals (5 per group) were pretreated with amphetamine 2 mg/kg s.c followed thirty minutes later by distilled water orally (group I), 6.25, 12.5 and 25 mg/kg, of *Lophira alata* and *Afzelia africana* orally (groups II-IV respectively) and haloperidol 2 mg/kg *i.p* (group V). One hour later indices of locomotive activity and stereotypy were scored by unbiased observers as previously described (Costall and Naylor, 1973).

Statistical Analysis

Data are expressed as mean ± SEM and statistically analyzed by one-way ANOVA followed by the Tukey test. A probability value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Sigma Plot version 11.0 for Windows.

RESULTS

Percentage yield post extraction for *Lophira alata* and *Afzelia africana* was 10% and 4% respectively.

The preliminary phytochemical screening of aqueous extract of *Lophira alata* and *Afzelia africana* stem barks revealed the presence of alkaloids, tannins, saponins, flavonoids, triterpenoids, phytosterols and glycosides (Table 1).

The oral LD_{50} of *Lophira alata* and *Afzelia africana* in rats was estimated to be greater than 5000 mg/kg (for each plant).

Pretreatment with *Lophira alata* and *Afzelia africana* decreased locomotive activity at all 3 dose levels in the first 20 minutes of observation; there was a significant difference ($p<0.05$) between test groups and amphetamine treated groups within this time frame. Locomotive activity increased in the last forty minutes of observation in the *Lophira alata and Afzelia africana* treated groups, locomotion here was not significantly different from amphetamine treated groups (Figure 1).

Post treatment with *Lophira alata* and *Afzelia africana* resulted in reduced locomotive activity with 12.5 mg dose level for the entire 1 hour of observation, this was significantly different ($p<0.05$) from the amphetamine treated group. The lowest dose 6.25 mg also significantly ($p<0.05$) reduced this index within 15-20 minutes of test time (figure 2).

Lophira alata and *Afzelia africana* significantly reduced sniffing and rearing in both models at some of the doses used for this study. Pretreatment with *Lophira alata* and *Afzelia africana* at doses of 6.25, 12.5 and 25 mg/kg showed a reduction in episodes of rearing while 12.5 and 25 mg/kg dose level significantly reduced constant rearing compared to amphetamine treated animals (Table 2).

Post treatment with *Lophira alata* and *Afzelia africana* significantly reduced episodes of rearing at all 3 dose levels used (Table 3).

Table 1: Result of phytochemical screening of the aqueous extract of *Lophira alata* and *Afzelia africana* stem barks.

Phytoconstituents	*Lophira alata*	*Afzelia africana*
Alkaloids	+	+
Reducing sugar	-	-
Saponins	+	+
Glycosides	+	+
Phytosterols	+	+
Tannis	+	+
Flavonoids	+	+
Triterpenoids	+	+

"+" represent class of phytochemicals present

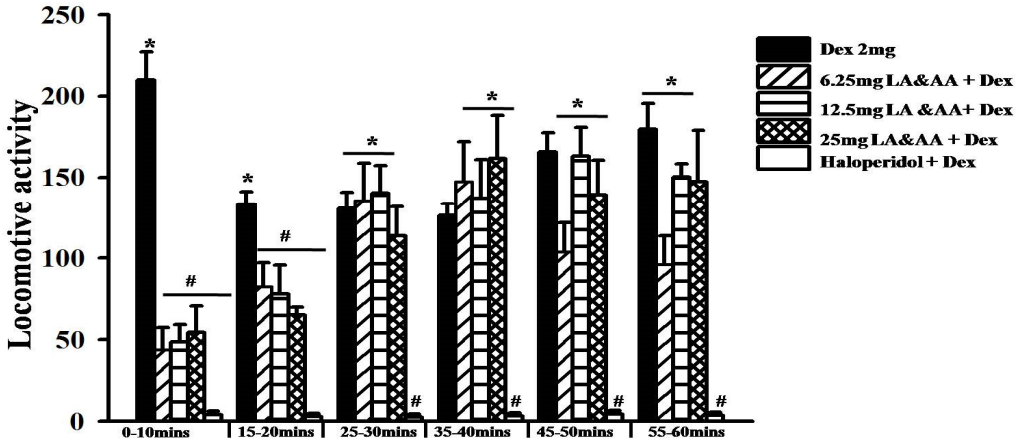

Figure 1: Effect of pretreatment with *Lophira alata* and *Afzelia africana* on amphetamine induced locomotive activity
Data are expressed as mean ± SEM. *p<0.05 compared to haloperidol, #p<0.05 compared to dextroamphetamine, n=5 per group.
Dex indicates dextroamphetamine; AA , *Afzelia africana*; LA, *Lophira alata*

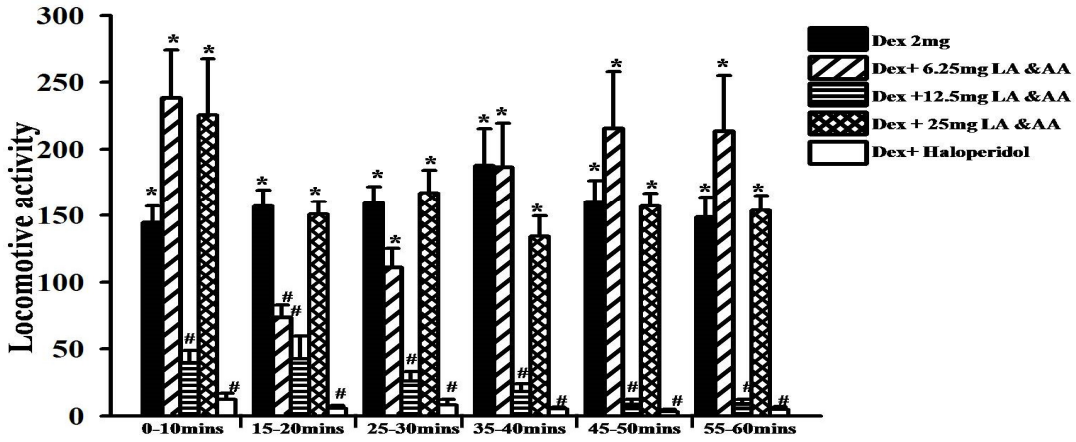

Figure 2: Effect of post treatment with *Lophira alata* and *Afzelia africana* on Amphetamine induced locomotive activity
Data are expressed as mean ± SEM. *p<0.05 compared to haloperidol, #p<0.05 compared to dextroamphetamine, n=5 per group
Dex indicates dextroamphetamine; AA, *Afzelia africana*; LA, *Lophira alata*.

Table 2: Effect of pretreatment with *Lophira alata* and *Afzelia africana* on Amphetamine induced stereotypy

	Dex	6.25mg LA&AA + Dex	12.5mg LA&AA + Dex	25mg LA&AA + Dex	Haloperidol 1mg + Dex
IS	0.28 ± 0.13	0.52 ± 0.12	0.53 ± 0.13	0.65 ± 0.13*	0.00 ± 0.00
CS	1.84 ± 0.28*	1.27 ± 0.23*	1.40 ± 0.23*	1.26 ± 0.23	0.00 ± 0.00#
OR	0.44 ± 0.15	0.67 ± 0.12	0.67 ± 0.12	0.67 ± 0.11	0.00 ± 0.00
RM	1.06 ± 0.29*	0.57 ± 0.19#	0.86 ± 0.21*	0.70 ± 0.20#	0.00 ± 0.00#
RA	0.82 ± 0.37*	0.92 ± 0.28*	0.10 ± 0.11#	0.45 ± 0.21*#	0.00 ± 0.00#

Data are expressed as mean ± SEM. *p<0.05 compared to haloperidol, #p<0.05 compared to dextroamphetamine, n=5 per group
Dex indicates dextroamphetamine; AA, *Afzelia africana*; LA, *Lophira alata*; IS, intermittent sniffing; CS constant sniffing; OR occasional rearing; RM rearing most of the time; RA rearing all the time.

Table 3: Effect of post treatment with *Lophira alata* and *Afzelia africana* on Amphetamine induced stereotypy

	Dex	Dex + 6.25mg LA&AA	Dex + 12.5mg LA&AA	Dex + 25mg LA&AA	Dex + Haloperidol 1mg
IS	0.29 ± 0.13	0.00 ± 0.00	0.09 ± 0.09	0.00 ± 0.00	0.00 ± 0.00$^{\#}$
CS	1.99 ± 0.28*	1.62 ± 0.32*	1.29 ± 0.28*	1.58 ± 0.26*	0.00 ± 0.00$^{\#}$
OR	0.63 ± 0.15*	0.25 ± 0.14	0.26 ± 0.11	0.17 ± 0.09$^{\#}$	0.00 ± 0.00$^{\#}$
RM	1.33 ± 0.29*	0.82 ± 0.29*	0.26 ± 0.15$^{\#}$	0.72 ± 0.22$^{*\#}$	0.00 ± 0.00$^{\#}$
RA	1.02 ± 0.37*	0.96 ±0.37	1.39 ± 0.34*	0.63 ± 0.26$^{\#}$	0.00 ± 0.00$^{\#}$

Data are expressed as mean ± SEM. *p<0.05 compared to haloperidol, #p<0.05 compared to dextroamphetamine, n=5 per group
Dex indicates dextroamphetamine; AA, *Afzelia africana*; LA; *Lophira alata*; IS, intermittent sniffing; CS constant sniffing; OR occasional rearing; RM rearing most of the time; RA rearing all the time.

DISCUSSION

This study was carried out to evaluate the antipsychotic potential of the aqueous extract of *Lophira alata and Afzelia africana* stem barks.

The preliminary phytochemical screening of aqueous extract of *Lophira alata* and *Afzelia africana* stem barks revealed the presence of alkaloids, tannins, saponins, phytosterols, flavonoids, triterpenoids and glycosides. Alkaloids, flavonoids, saponins, triterpenes and tannins have been reported to possess central nervous system modifying activity such as depression, sedation, anxiolysis, psychotropic, analgesic and anti-convulsant activity (Bhatachanya *et al.,* 1997; Verma *et al.,* 2010; Pritam *et al.,* 2011).

The median lethal dose of aqueous extract of *Lophira alata* and *Afzelia africana* was estimated to be greater than 5000 mg/kg using the method described by Lorke (1983). This high median lethal dose (LD_{50}) value suggests they are relatively non-toxic. The highest dose used in the study was less than 30% of the LD_{50} which has been reported to be safe for use in ethnopharmacological assays (Matsumara, 1988; Vongtau *et al.,* 2004)

Amphetamine-induced stereotypy which measures dopamine D_2 receptor reactivity mediated by hyperactivity of dopaminergic mechanisms in the nigrostriatal and mesolimbic pathway is an established animal model for schizophrenia (Valame and Gupata, 1981). Amphetamine, an indirectly acting sympathomimetic agent, releases catecholamines from neuronal storage pools and induces characteristic stereotyped behaviour in rats (Vogel, 2002; Kasture, 2006).

In this study, pre-treatment with a mixture of *Lophira alata* and *Afzelia africana* caused an initial reduction of hyper locomotion but increased locomotive activity which worsened with time. A distinct pattern of sleep was also observed in these animals. This effect could be due to the sedative potential of both extracts and probably displacement by amphetamine. The extracts could also be short-acting.

In order to simulate clinical psychosis, some animals were treated with amphetamine prior to treatment with graded doses of *Lophira alata* and *Afzelia africana*. Treatment with *Lophira alata* and *Afzelia africana* following amphetamine resulted in reduction of locomotion at a dose level of 12.5 mg/kg. At higher doses-50 and 100 mg/kg (data not shown), stereotypy was worsened; hyper locomotion in some animals could not be quantified due to very rapid movements while others exhibited rapid backwards and circular movements. These lasted for about four hours after which animals slept off and could not be roused for another 18 hours. We speculate that higher doses potentiate the effects of amphetamine though more mechanistic studies will be required to substantiate this hypothesis.

Sniffing and rearing are also indices of stereotypy and reduction of these indices are suggestive of sedative and/or antipsychotic activity (Costall and Naylor, 1973; Creese and Iverson, 1973; Costall and Naylor, 1974). In this study, different dose levels of *Lophira alata* and *Afzelia africana* reduced episodes of sniffing and rearing. Reduction in sniffing and rearing taken together with reduction in locomotor activity lends credence to the antipsychotic potential of *Lophira alata* and *Afzelia africana.*

CONCLUSION

Aqueous extract of *Lophira alata* and *Afzelia africana* stem bark extract possess anti psychotic properties which may account for their use as a mixture in ethnomedicine for management of psychosis.

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