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Research report

Standardized extract of *Ficus platyphylla* reverses apomorphine-induced changes in prepulse inhibition and locomotor activity in rats

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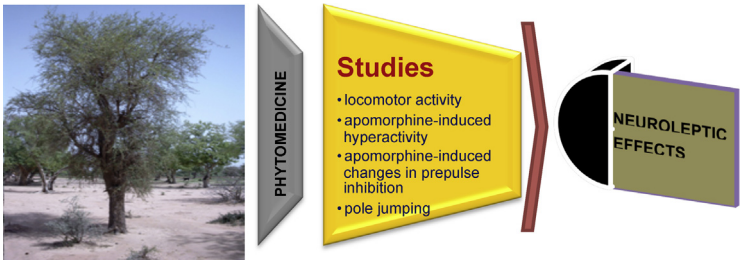
HIGHLIGHTS

- *Ficus platyphylla* stem bark extract (FP) is used in traditional African medicine.
- We tested FP on apomorphine-induced behavioral changes in rats.
- FP reversed apomorphine-induced deficits in prepulse inhibition.
- FP reduced locomotor activity and apomorphine-induced hyperactivity.
- FP inhibited the retrieval of a conditioned avoidance reaction.
- Thus, FP contains psychoactive principles with potential antipsychotic properties.

GRAPHICAL ABSTRACT

The effects of the standardized extract of *Ficus platyphylla* (FP) were studied on apomorphine-induced changes in prepulse inhibition and locomotor activity in rats, and retrieval of a conditioned avoidance response in mice to complement our existing knowledge on the antipsychotic potential of FP. Our data indicate that FP contain psychoactive principles with neuroleptic-like properties.



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ABSTRACT

Preparations of *Ficus platyphylla* are used in Nigeria's folk medicine to manage a plethora of diseases including, insomnia, psychoses, depression, epilepsy, pain and inflammation. In this study, we examined the effects of the standardized methanol extract of *F. platyphylla* stem bark (FP) on apomorphine-induced changes in prepulse inhibition and locomotor activity in rats, as well as on the retrieval of a conditioned reaction in one-way active avoidance in mice. FP did not affect basal prepulse inhibition, but significantly reduced locomotor activity. The apomorphine-induced prepulse inhibition deficit and hyperactivity were significantly reversed by co-administration of clozapine or FP. Furthermore, FP inhibited the retrieval of a conditioned avoidance reaction. Our results revealed that FP contains psychoactive ingredients with neuroleptic-like properties, thus supporting the isolation and development of the biologically active components of this medicinal plant as antipsychotic agents.

Abbreviations: CAR, conditioned avoidance reaction; CS, conditioned stimulus; FP, standardized extract of *Ficus platyphylla* stem bark; PPI, prepulse inhibition; UCS, unconditioned stimulus.

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1. Introduction

Ficus platyphylla Del. Holl. (Moraceae) is a deciduous plant locally known as "gamji" and is widely distributed throughout the savannah region of the West African coast. In Northern Nigeria, preparations of this medicinal plant are used in traditional medicine to manage a plethora of diseases including insomnia, psychosis, depression, epilepsy, pain and inflammation [1]. The cold water extract or decoctions of the stem or root bark are usually taken orally. The powder is often mixed with food and eaten, or placed in burning charcoal and inhaled [1]. Our previous studies revealed that the methanol extract of *F. platyphylla* stem bark (FP) is safe in rodents [2] with potential central nervous system activity, including analgesic and anti-inflammatory properties [3,4]. We have also reported the psychopharmacological and anticonvulsant effects of the saponin-rich fraction from this medicinal plant [5,6] to justify, in part, for its use in Nigeria's folk medicine for the management of CNS disorders. Recent studies examined and reported the intraperitoneal LD_{50} and HPLC fingerprint characteristic of *F. platyphylla* [5,6]. The behavioral and anticonvulsant properties of FP were also evaluated following acute and repeated intraperitoneal administration of the standardized and relatively safer methanol extract to scientifically describe the potential values of this important medicinal plant in the management of epilepsy [7,8].

We have shown in our previous studies that FP reversed amphetamine-induced hyperactivity and stereotypy in mice [5] which suggested its neuroleptic-like effects. However, FP also dose-dependently reduced locomotor activity [5,7] indicating sedative effects. Prepulse inhibition of the acoustic startle response is an animal paradigm to investigate neuroleptic-like effects that have no critical interference with sedative compound effects [9–12]. Prepulse inhibition (PPI) refers to the phenomenon that presentation of a weak stimulus before a startling stimulus (around 50–500 ms) inhibits the magnitude of the startle response. PPI can be observed across species and it is impaired in several human diseases [13]. For example, schizophrenic patients are deficient in PPI [14]. It is believed that this deficit reflects impaired sensorimotor gating mechanisms in the brain which then contributes to several symptoms of schizophrenia such as sensory flooding or cognitive fragmentations [15]. In laboratory rodents, a PPI deficit can be induced by application of dopamine agonists and this deficit can be reversed by application of clinically-validated neuroleptic drugs [15].

Furthermore, we investigated whether FP affects the retrieval of conditioned avoidance reaction (CAR). Inhibition of retrieval of CAR is considered to be a specific paradigm to screen for potential neuroleptic-like effects of drugs [16]. Drugs with neuroleptic-like activity inhibit CAR in doses with no effect on unconditioned avoidance or the induction of catalepsy [17]. This paradigm is sensitive to classical and atypical neuroleptics [17–19].

The aim of the present study was to evaluate potential neuroleptic-like effects of FP in three different behavioral paradigms, namely apomorphine-induced PPI deficits in rats, apomorphine-induced hyperactivity in rats, and the retrieval of CAR in mice. In all three paradigms, clozapine was used a positive control.

2. Material and methods

2.1. Animals

A total of 90 male Wistar rats (RjHan:WI, Janvier Labs, St. Berthevin, France) weighing 240–300 g at the start of the experiments were used. Rats were bred and reared at the local animal facility. The rats were housed in groups of 4–6 animals in Macrolon IV cages under a 12 h light/dark cycle (light on at 6 am), room temperature 18 ± 2 °C, and with food (ssniff R/M-H, ssniff Spezialdiäten GmbH, Soest, Germany) and drinking water available ad libitum. The experiments were carried out in accordance with the ethical guidelines of European Community for the care and use of laboratory animals for experiments (2010/63/EU), and were approved by the local authorities (Landesverwaltungsamt Sachsen-Anhalt, Az. 42505-2-1172 UniMD, 42502-2-1189 UniMD).

In the conditioned avoidance reaction (CAR) experiment, we used male C57Bl/6JRj mice (Janvier, Le Genest-Saint-Isle, France) which are known for a quick acquisition of the one-way active avoidance task. At the beginning of the experiments, the mice were aged 8 weeks. The experiments were carried out between 08:00 am and 02:00 pm.

2.2. Preparation of the F. platyphylla stem bark extract

The plant material was collected from Zaria in Kaduna State, Nigeria. It was identified and authenticated by Mallam I. Muazzam of the Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria. A voucher specimen (No. 4035) was deposited at the NIPRD Herbarium for future reference.

The bark was chopped, cleaned, air dried for 10 days and milled into a coarse powder using a pestle and mortar. 100 g of the coarse powder was extracted to exhaustion with 500 ml of methanol using a Soxhlet extractor for 12 h. The solvent was removed under reduced pressure using a rotary evaporator and it gave a yield of 34.8% (w/w) of the crude methanol extract that was used for the study.

2.3. Behavioral procedures

2.3.1. Test protocols

2.3.1.1. Experiment 1 (12 animals). Animals were intraperitoneally injected with either saline, 5 mg/kg clozapine (C6305, Sigma–Aldrich, Taufkirchen, Germany), 12.5, 50, or 200 mg/kg FP. FP was dissolved in saline and clozapine was dissolved by adding a drip of acetic acid and the final volume was made up with saline. Injection volume was 10 ml/kg. Fifteen minutes later, the animals were submitted to the PPI test (see below). After a washout period of two days, the animals were treated and tested again. This was repeated until every animal was tested with every treatment. Both treatment and the order of treatment were pseudo randomized (latin-square design).

2.3.1.2. Experiment 2. First, animals got subcutaneous injections of saline or 2 mg/kg apomorphine (injection volume 1 ml/kg). Immediately after this injection, saline, 5 mg/kg clozapine, 12.5, 50, or 200 mg/kg FP were intraperitoneally administered individually. Fifteen minutes later, the animals were submitted to the PPI test. In this experiment, animals were only tested once. Treatment group sizes was $n = 12–13$.

2.3.2. Test on prepulse inhibition of the startle response

A startle system with four boxes (San Diego Instruments, San Diego, USA) was used for the present experiments. Each ventilated wooden box (35 cm × 35 cm × 38 cm) was equipped with a high-frequency loudspeaker for delivering acoustic stimuli. During the startle experiments, the animals were put into acrylic (Plexiglas) cylinders with 9 cm diameter and a length of 16 cm. The cylinders were fixed onto a horizontal plate with a transducer. Animal movements (i.e., startle responses) were detected with the transducer. The output signal of the transducers was digitized for data acquisition (sampling rate 24 bit, 1 kHz) and stored on a computer. The peak-to-peak amplitude of the transducer output within the 100 ms