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Psychopharmacological properties of the saponin fraction of *Ficus platyphylla* stem bark

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ABSTRACT

The psychopharmacological effects of a saponin-rich fraction (SFG) obtained from crude methanolic extract of *Ficus platyphylla* stem bark were studied on spontaneous motor activity (SMA), pentobarbital-induced sleep, motor coordination, amphetamine-induced hyperactivity and stereotyped behaviour, catalepsy, forced swim and tail suspension tests in rodents. SFG reduced SMA dose dependently, suggesting that it may contain psychoactive principles with sedative effects. The fraction shortened the onset and prolonged the duration of pentobarbital-induced sleep, which confirmed its sedative properties. The fraction diminished immobility time in forced swim and tail suspension tests, which is indicative of antidepressant properties. It attenuated amphetamine-induced hyperactivity and stereotyped behaviour, induced catalepsy and exacerbated haloperidol-induced catalepsy in rodents, but had no effect on motor coordination in the treadmill experiment at the doses tested. These effects were similar to those of classical neuroleptics and antidepressants. Our study provides scientific evidence of psychopharmacological effects of the saponin fraction of *Ficus platyphylla* stem bark and therefore supports further development of its psychoactive components as antipsychotics and antidepressants.

Keywords: *Ficus platyphylla,* depression, psychosis, sedation, spontaneous motor activity, stereotyped behaviour.

INTRODUCTION

Preparations of the stem bark of *Ficus platyphylla Del.-Holl (*Family: Morace*ae)* have been used in Nigerian traditional medicine to treat psychoses, depression, epilepsy, pain and inflammation for many years, and their efficacies are widely acclaimed among the Hausa communities of Northern Nigeria (Audu, 1989). The cold water extract, decoction or powder of the stem or root bark are usually taken orally, while the powder is often mixed with food and eaten, or placed in burning charcoal and inhaled (Audu, 1989).

The therapeutic benefits of traditional remedies are often attributed to the presence of active secondary metabolites. In our previous studies, we investigated the biological activities of the crude methanolic extract of the stem bark of *Ficus platyphylla*.

The results revealed the presence of sedative principles with profound central nervous system effects (Chindo et al., 2003). Since saponins were the major components of the crude extract and are believed widely to have profound central nervous system activities (Attele et al., 1999; Pal and Nandi, 2005; Einat 2007; Ojewole 2008), we suggested that saponins could be responsible for, or could have contributed to the observed effects. It is on this basis that we evaluated some of the psychopharmacological properties of the saponin-rich fraction obtained from the crude methanolic extract of *Ficus platypyhlla* stem bark, as a step towards the isolation of its psychoactive components. This study was also designed to provide scientific evidence supporting further development of psychoactive principles from saponin-rich fraction of the stem bark of this medicinal plant as antipsychotics and antidepressants.

MATERIALS AND METHODS
Animals
Swiss albino mice (18 - 25 g), Wistar rats (180 – 250 g) of either sex maintained at the Animal Facility Centre (AFC) of the National Institute for Pharmaceutical Research and Development, Abuja were used. All animals were housed under standard conditions of temperature ($25 \pm 2\ ^oC$), and light approximately (12/12 h light/dark cycle) and fed on standard diet (Ladokun Feeds, Plc, Ibadan, Nigeria) and water *ad libitum*. These animals were approved for use by the AFC committee after reviewing the protocol for good laboratory practice and animal handling, which is in compliance with the National Institutes of Health *Guide for the Care and use for Laboratory animals* (Publication No. 85-23, revised 1985).

Plant material
The plant material was collected from Zaria in Kaduna State, Nigeria. The plant 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. A voucher specimen (no. 4035) was deposited at NIPRD Herbarium for future reference.

Extraction of saponin components of *Ficus platyphylla* stem bark
The method described by Ebata et al. (1996) was used with modifications. Briefly, One hundred grammes (100 g) of the coarse powder were sequentially extracted with solvents of increasing polarities (hexane, ethylacetate, dichloromethane, and methanol) each for 6 h using a soxhlet apparatus. The resulting extracts were concentrated to dryness *in vacuo* at 40 ^oC using a rotary evaporator, yielding Fraction A (2.92%), Fraction B (1.23%), Fraction C (Traces), and Fraction D (29.79%) w/w respectively. Fraction D was partitioned between water and butanol (1:3) to give Fractions E and F. Fraction E was then dissolved in methanol and added dropwise to diethylether. A precipitate was formed, which was separated from the solution by filtration to give the saponin-rich fraction designated Fraction G (SFG). The filtrate was concentrated. The saponin-rich fraction (SFG) was used for this study.

Pharmacological evaluation
Spontaneous motor activity (SMA) in mice
This study was done in adult mice of both sexes (ratio 1:1). The mice were randomly divided into 4 groups of 6 mice each. Group I, which served as control received normal saline, while mice in groups II, III and IV received graded doses (25, 50, 100 mg/kg, i.p.) of SFG. Thirty minutes post drug administration, the animals were transferred individually into Letica Activity Cages (LE 886) connected to a multicount (LE 3806) and after one minute latency period, activity counts were recorded for 6 min (Wambebe et al., 1997), at 30 min intervals for a period of 120 min (Amos et al., 2004).

In another set of experiments adult mice (males and females) were divided randomly into 5 groups of 6 mice each. Group I which served as a control received normal saline, while animals in groups II, III and IV received SFG at doses of 25, 50 and 100 mg/kg *i.p.* respectively and group V received chlorpromazine (2 mg/kg, i.p.). Thirty minutes post drug administration, d-amphetamine (2 mg/kg, i.p.) was administered to all the mice. They were then transferred individually into Letica Activity Cages (LE 886) connected to a multicount (LE 3806) and after one-minute

latency period, hyperactivity counts were recorded for 6 min at 30 min intervals for the period of 120 min.

Pentobarbital-induced sleep in mice

This test was performed in 5 groups of 6 mice each which were treated as follows: one group received normal saline; three groups received SFG at the doses of 25, 50 and 100 mg/kg i.p. Animals in the fifth group received diazepam (1 mg/kg, i.p.). Thirty minutes post drug administration; pentobarbital sodium (30 mg/kg, i.p.) was administered to all the mice. Each mouse was observed for the onset and duration of sleep, with the criterion for sleep being loss of righting reflex (Wambebe, 1985), indicated by the animals inability to resume or return to its upright position on all four limbs after being gently rolled sideways (Roland et al, 1991). The interval between loss and recovery of righting reflex was used as the index of hypnotic effect (Soulimani et al., 2001).

Test for motor coordination (Rota-rod test) in mice

The method used for the assessment of locomotor (force motor) activity in mice was used as described previously (Perez et al., 1998). A treadmill device (Ugo Basile Rota-Rod, Model 7650, Jones and Roberts, Italy) was used in this experiment. Mice were trained to remain on slowly moving (16 revolutions/minute) rods of 5 cm diameter for 180 sec by walking. Those mice that were able to remain on the rod 180 seconds or longer were selected and divided into 4 groups of 6 mice each. Group I served as control and received normal saline, while groups II, III and IV received graded doses of SFG (25, 50 and 100 mg/kg, i.p., respectively). Thirty minutes after treatment, the animals were singly placed on the rod at intervals of 30 min, up to 120 min. If an animal failed more than once to remain on the rod for 3 min, the test was considered positive, meaning there was a lack of motor coordination (Adzu, et al., 2002).

Amphetamine-induced stereotyped behaviour in mice

The method of Randrup and Munkvad (1967) as modified by Amos et al. (2004) were followed for the stereotyped behavioural studies. Briefly, adult mice of both sexes (ratio 1:1) were randomly divided into five groups of six mice each. Three groups were administered graded doses (25, 50 and 100 mg/kg, i.p.) of SFG. Animals in the control groups received normal saline and the remaining fifth group received chlorpromazine (2 mg/k, i.p.). Thirty minutes later, amphetamine (2mg/kg, i.p.) was administered to each mouse. Signs of stereotyped behaviour, which include mainly sniffing, jumping/climbing and reciprocal forelimb trading/licking, were observed and counted using hand tally counters for 2 h.

Measurement of catalepsy in rats

Adult Wistar rats of both sexes were trained for 3 days prior to cataleptic study. The study was carried out in two phases. In the first phase, four groups of rats were treated with SFG (50 and 100 mg/kg, i.p.) and haloperidol (1 mg/kg, i.p.). Control groups received normal saline. The severity of catalepsy was measured every 30 min thereafter up to a total of 3 h. In the second phase of the study, the effects of fractions G on haloperidol (1 mg/kg, i.p.)-induced catalepsy was also investigated. Four groups of rats (five rats per group) were treated with SFG (25, 50 and 100 mg/kg, i.p.) and normal saline 2 ml/kg. Thirty minutes later, haloperidol (1 mg/kg, i.p.) was administered to each rat and the severity of catalepsy was measured every 30 min for 3 h to determine the effects of the fraction G on haloperidol-induced catalepsy in the rat.

Catalepsy of an individual rat was measured in a stepwise manner by a scoring method described by Khisti et al. (1997) as follows:

Step I: The rat was taken out of the home cage and placed on a table. If the rat failed to move when touched gently on the back or pushed, a score of 0.5 was assigned. Step II: The front paws of the rat were placed alternately on a 3 cm high block. If the rat failed to correct the posture within 15 sec, a score of 0.5 for each paw was added to the score of Step I. Step III: The front paws of the rat were placed alternately on a 9 cm high block. If the rat failed to correct the posture within 15 sec, a score of 1 for each paw was added to the scores of Steps I and II. Thus, for an animal, the highest score was 3.5 (cut off score). SFG and normal saline (control) were administered 30 min before haloperidol (Reavill et al., 1999).

Antidepressant study

Forced swim and tail suspension tests were employed as animal models of depression to assess the antidepressant effects of the fraction.

The forced swim test in rats was carried out according to the method of Porsolt et al. (1978), as described by Kroczka et al. (2001). The rats were placed in Plexiglas cylinders (height 40 cm, diameter 18 cm) containing 17 cm of water at 25 ^{o}C. The rats were removed and allowed to dry in a heated enclosure (32 ^{o}C) before being returned to their home cages after the 15 min pretest swim in water. They were divided into 5 treatment groups of 5 rats each. Three groups received graded doses of SFG (25, 50, 100 mg/kg, i.p.), while the other two groups received normal saline (control group) and imipramine (30 mg/kg, i.p.). SFG and imipramine were administered intra-peritoneally three times: 24, 5 and 1 h before the test. The duration of treatment with the fraction and imipramine was adapted from established methods described by Noda et al. (1995) and Kroczka et al. (2001). The rats were again placed in the cylinders 24 h later, after the last 1 h dose. The duration of immobility in each rat was measured during a 5 min test. A rat was judged to be immobile when it remained floating passively in the water.

The tail suspension test in mice was carried out as described previously by Steru et al. (1985) with modifications. Briefly, adult mice were randomly divided into five groups of five mice each. Three groups were administered graded doses (25, 50 and 100 mg/kg, i.p.) of SFG. Animals in the control groups received normal saline and the remaining fifth group received imipramine (30 mg/kg, i.p.). Thirty minutes later, each mouse was suspended by the tail on the edge of a shelf 58 cm above a table top and the length of their immobility recorded during a 4 min period as described previously (Steru et al., 1985), after discarding activity in the first 2 min, during which an animal tries to escape (Jain et al., 2003). A mouse was considered immobile only when it hung passively and remained motionless.

Statistical analysis

All results were expressed as mean $\pm$ S.E.M., and differences in mean were estimated by means of ANOVA followed by Dunnet's post hoc test for multiple comparison. Results were considered significant at $p<0.05$.

RESULTS

Spontaneous motor activity (SMA) in mice

This study was carried out to evaluate the gross behaviour and measure the degree of excitability of animals. Our results showed that SFG (25, 50, 100 mg/kg) produced a significant ($p<0.05$) decrease in spontaneous motor activity in mice (Figure 1). The effect was dose and time dependent. The decrease in activity was pronounced at 30 min and continued to decline with increase in time. Thus, suggesting that SFG decreased central nervous system excitability in laboratory animals.

SFG was also found to attenuate amphetamine-induced hyperactivity dose-dependently. The decrease in hyperactivity became significantly pronounced at 30 min and continued until 2 h (Figure 2).

Pentobarbital-induced sleep in mice

SFG (25, 50, 100 mg/kg) significantly and dose dependently shortened the onset and prolonged the duration of pentobarbital-induced sleep in mice (Figure 3). Diazepam (1 mg/kg) also produced a significant prolongation of the duration of pentobarbital-induced sleep, with no significant effect on the onset of sleep.

Test for motor coordination (Rota-rod test) in mice

The treadmill study was carried out to further investigate whether the effects of SFG were centrally mediated or acting on peripheral neuromuscular system. In this experiment, SFG (25, 50, 100 mg/kg) had no effects on motor coordination as observed in the rota-rod test. Animals in all groups were able to maintain their balance for over 180 sec, which was taken as the cut-off time (Data not shown).

Amphetamine-induced stereotyped behaviour in mice

This study was designed to investigate possible antipsychotic effects of SFG. The SFG (25, 50, 100 mg/kg) and chlorpromazine (2 mg/kg) attenuated the amphetamine-induced stereotyped behaviour, including
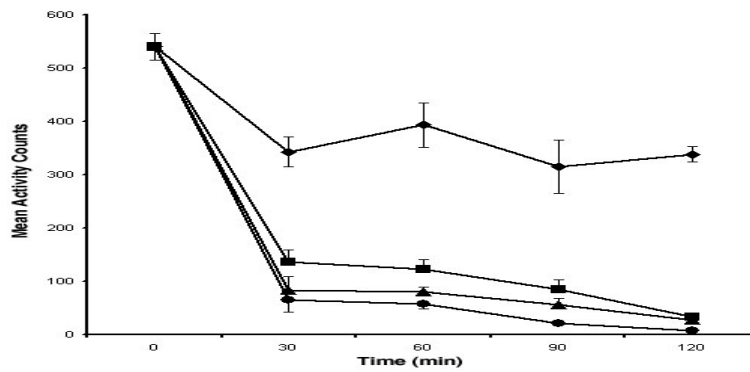
Figure 1: Effects of fraction G on spontaneous motor activity in mice. Saline control 10ml/kg (◆), fraction G 25 mg/kg (■), fraction G 50 mg/kg (▲), fraction G 100 mg/kg (●). * Statistically significance between treated groups and control [F (3, 23) =7.05, p<0.05].
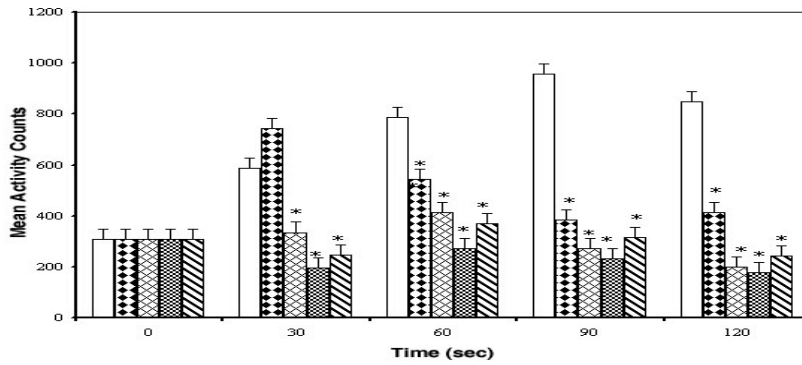

Figure 2: Effects of fraction G on amphetamine-induced hyperactivity in mice. Saline control 10ml/kg (☐), fraction G 25 mg/kg (▨), fraction G 50 mg/kg (▧), fraction G 100 mg/kg (▨) and diazepam 1 mg/kg (◣). * Statistically significance between treated groups and control [F (4, 29) =15.44, p<0.05].
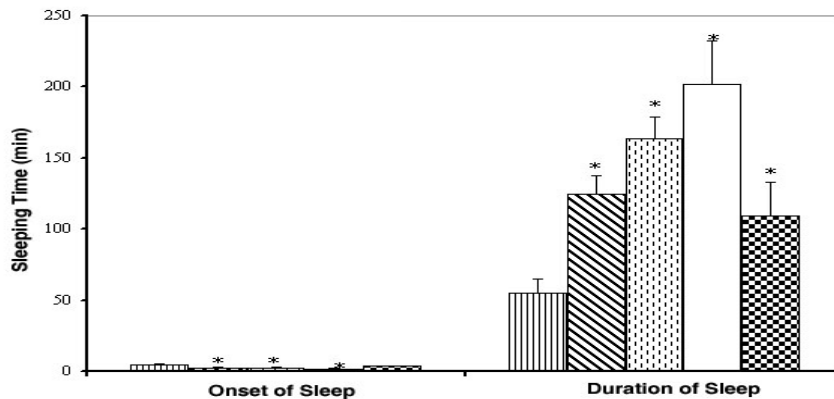

Figure 3: Effects of fraction G on pentobarbital sleep in mice. Saline control 10 ml/kg (▥), fraction G 25 mg/kg (◣), fraction G 50 mg/kg (▤), fraction G 100 mg/kg (☐) and diazepam 1 mg/kg (▩). * Statistically significance between treated groups and control [F (4, 29) =15.94, p<0.05].

sniffing, jumping/climbing and limb licking dose dependently (Figure 4). The reductions in stereotyped activities were more pronounced at doses of 50 and 100 mg/kg than chlorpromazine (2 mg/kg).

Catalepsy in rats

Fraction G (50 and 100 mg/kg) dose-dependently induced catalepsy in rats. The effects were more pronounced than with the positive control haloperidol (1 mg/kg) (Figure 5). Furthermore, SFG (25, 50, 100 mg/kg) significantly (dose- and time-dependently) exacerbated haloperidol (1 mg/kg)-induced catalepsy. The optimum cataleptic response was evident at 30 min after haloperidol

administration and reached the peak at 150 min for the dose of 50 mg/kg, while at the dose of 100 mg/kg, the effect reached the peak at 120 min (Figure 6).

Antidepressant study

SFG (25, 50, 100 mg/kg) and imipramine (30 mg/kg) significantly ($p < 0.05$) diminished immobility time in rats when they were subjected to forced swim. The results were dose-dependent (Figure 7).

SFG (25, 50, 100 mg/kg) and imipramine (30 mg/kg) significantly ($p < 0.05$) diminished immobility time in mice in the tail suspension test. The results were dose-dependent (Figure 8).
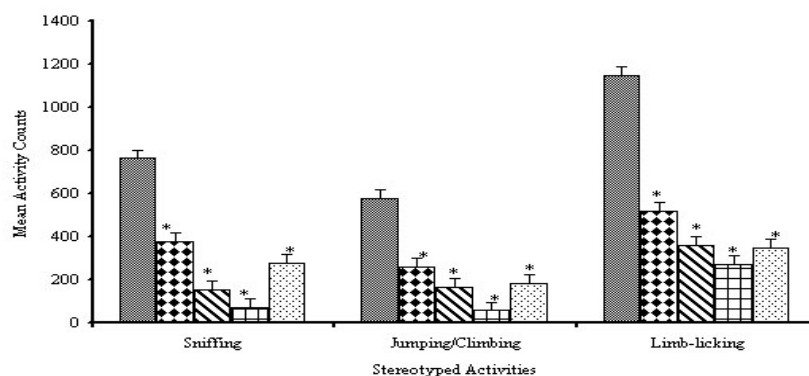

Figure 4: Effects of fraction G on amphetamine-induced stereotyped behavior in mice. Saline control 10ml/kg (▨), fraction G 25 m/kg (⊠), fraction G 50 mg/kg (◪), fraction G 100 mg/kg (☐), chlorpromazine 2 mg/kg (⬚). * Statistically significance between treated groups and control [$F_{(4, 29)} = 17.4$, $p < 0.05$].
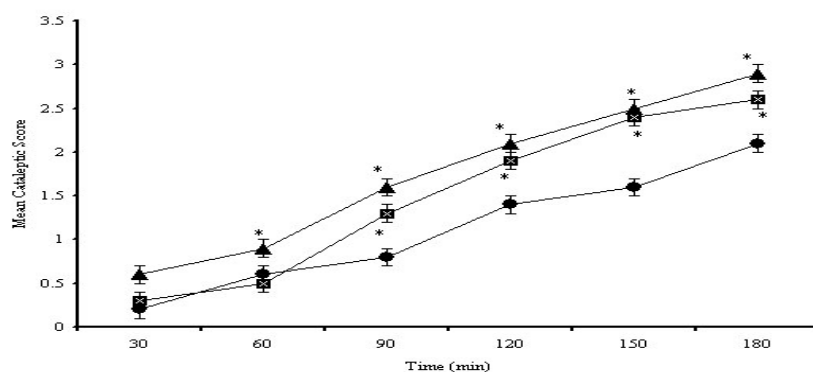

Figure 5: Cataleptic effects of fraction G and haloperidol in rats. Haloperidol 1 mg/kg (●), Fraction G 50 mg/kg (■), fraction G 100 mg/kg (▲). * Statistically significance between treated groups and control [$F_{(2, 19)} = 16.1$, $p < 0.05$].
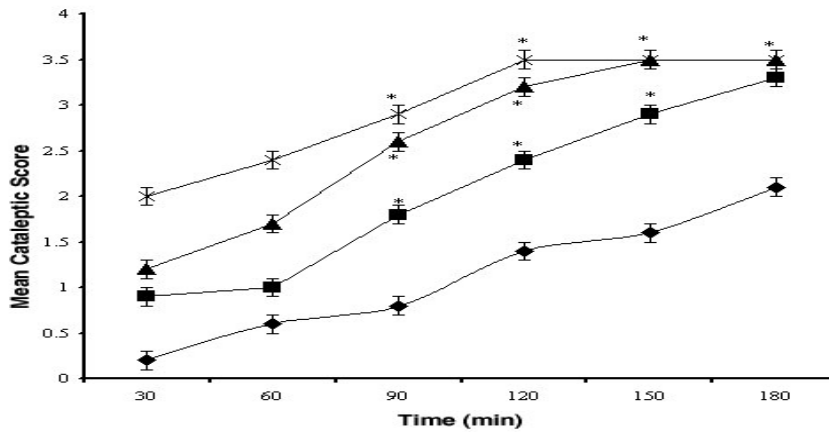
Figure 6: Effects of fraction G on haloperidol-induced catalepsy in rats. Saline control 10ml/kg (◆), Fraction G 25 mg/kg (■), fraction G 50 mg/kg (▲), fraction G 100 mg/kg (X).
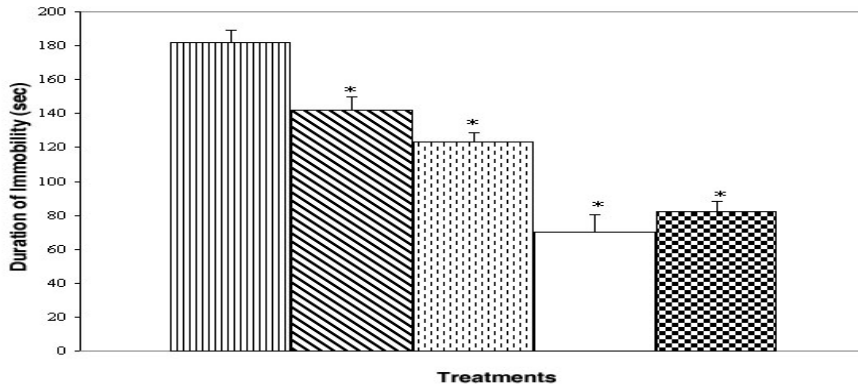* Statistically significance between treated groups and control [F (3, 19) =11.4, p<0.05].

Figure 7: Effects of fraction G on duration of immobility in forced swim test in rats. Saline control 10ml/kg Control (▦), fraction G 25 mg/kg (◩), fraction G 50 mg/kg (▫), fraction G 100 mg/kg (□), imipramine 30 mg/kg (▣). * Statistically significance between treated groups and control [F (4, 24) = 14.16, p<0.05].

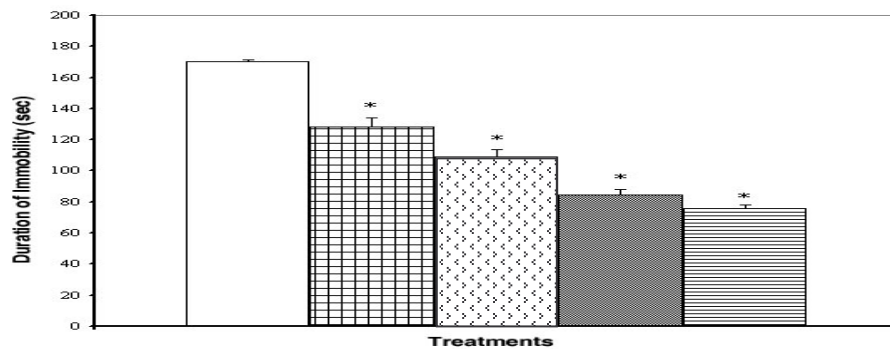**Figure 8:** Effects of fraction G on duration of immobility in tail suspension test in mice. Saline control 10ml/kg (□), fraction G 25 mg/kg (□), fraction G 50 mg/kg (▨), fraction G 100 mg/kg (▨), imipramine 30 mg/kg (⊟). * Statistically significance between treated groups and control [F (4, 24) = 11.31, p<0.05].

DISCUSSION

The data presented in this study provide evidence that the saponin-rich fraction of the stem bark of *Ficus platyphylla* contains sedative principles with potential neuroleptic and antidepressant properties. SFG significantly reduced the spontaneous motor activity (SMA) in mice in a dose related manner. SMA has been used as an acceptable model for evaluation of the effects of drugs on gross behaviour in laboratory animals (Amos et al., 2004). The model measures the level of excitability of the central nervous system (Morais et al., 1998), which correlates well with drug effects in humans. Many groups of psychotropic agents including antipsychotics, and antidepressants (Baldessarini, 2001) can diminish SMA in all species of animals including humans. The ability of SFG to suppress SMA suggests that it has sedative properties. This suggestion is strengthened by the ability of SFG to shorten the onset and prolong the duration of pentobarbital-induced sleep in mice. The results agree with the reports of our preliminary studies on the crude methanolic extract of this plant (Chindo et al., 2003). The fraction had no observable effects on motor coordination in the treadmill experiment at the doses used, suggesting that the observed sedative effects of the fraction might be elicited via central mechanisms, not by peripheral neuromuscular blockade (Vongtau et al., 2005). The prolongation of pentobarbital–induced sleep could therefore be due to interference with endogenous neurotransmitters in the brain particularly dopamine, norepinephrine, acetylcholine, serotonin, GABA, histamine and neuropeptides, which have been reported to play important roles in sleep mechanisms (Curtis and Jermaine, 2002; Gottesmann, 2002; Parmentier et al., 2002; Dere et al., 2004) or may be interfering with pentobarbital metabolism (Kaul and Kulkarni, 1978).

Furthermore, the saponin fraction attenuated amphetamine-induced hyper-activity and stereotyped behaviour in mice suggesting a possible interference with the central dopaminergic neurotransmission, an effect similar to that of classic neuroleptics. The behavoural effects of amphetamine can be masked by conventional neuroleptics, most of which are believed to be dopamine (D$_2$) receptor antagonists (Ljungberg and

Ungerstedt, 1985; Reynolds, 1992). In this study, the fraction induced catalepsy on its own and exacerbated haloperidol-induced catalepsy in rats in a dose-related manner. The ability of an agent to induce and/or exacerbate neuroleptic-induced catalepsy has been shown to be primarily due to blockade of the nigrostriatal dopamine system (Baldessarini, 2001). A number of other neurotransmitter systems are known to modulate neuroleptic-induced cataleptic effects. Facilitation of noradrenergic neurotransmission for instance, attenuates (Khisti et al., 1997), while that of serotonergic neurotransmission exacerbates (Balsara et al., 1979) neuroleptic-induced catalepsy. Inhibition of the serotonergic neurotransmission attenuates neuroleptic-induced catalepsy (Reavill et al., 1999). The central histaminergic system is also known to interfere indirectly with catalepsy (Zang et al., 2005). Potentiation of haloperidol-induced catalepsy by the fraction examined in this study may well be a simple synergistic effect of the fraction with haloperidol.

In this study, we also evaluated the effects of the fraction against animal models of depression. Our study showed that SFG and imipramine significantly diminished the immobility time in forced swim and tail suspension tests in rats and mice respectively. Forced Swim (Kroczka et al. (2001) and tail suspension tests (Jain et al., 2003) have gained considerable acceptance as reliable screens that predict antidepressant efficacy in human depression. The effects of the fraction on animal models of depression also suggest the presence of psychoactive principles with antidepressant-like effects.

In conclusion, we have presented evidence that the stem bark extract of *Ficus platyphylla* contains sedative principles with neuroleptic and antidepressant properties, which might be attributable to the saponin components of this medicinal plant. The results therefore support further development of psychoactive principles from its saponin-rich fraction as antipsychotics and antidepressants. The multiplicity of putative mechanisms of action reflected by the broad spectrum of activity observed in this study might be attributed to the presence of different psychoactive components in the fraction. Further studies are in progress in our laboratories to isolate and mechanistically

characterize the biologically active components of the saponin fraction from the stem bark of this important medicinal plant.

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