International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 5 (1): 22-29, 2009
ISSN 1811-7775

Antidepressant-Like Effects of an Ethanolic Extract of *Sphenocentrum jollyanum* Pierre Roots in Mice

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Abstract: In the present study, the effect of an ethanolic extract of the roots of the plant in two animal models of depression the Forced Swimming Test (FST) and Tail Suspension Test (TST) has been reported. The extract (100-1000 mg kg^{-1}; p.o.), dose-dependently reduced the duration of immobility in both the FST (ED_{50}: 296.20±53.97 mg kg^{-1}) and TST (203.90±39.01 mg kg^{-1}).The effect of the extract was 20-50 times less potent than imipramime and fluoxetine which were used as standards. Pretreatment with α-methydopa (400 mg kg^{-1}; 3 h; p.o.) attenuated the anti-immobility effects of imipramime but not SJE and fluoxetine. Similarly, pretreatment with reserpine (1 mg kg^{-1}; 24 h; s.c.) abolished the effect of imipramime and partially the effects of SJE but not fluoxetine. A concomitant treatment with α-methyldopa and reserpine attenuated the effects of all but fluoxetine. The extract, imipramime and fluoxetine did not modify motor performance on the rotarod test at all doses tested. Putting all together, present results suggest that SJE has antidepressant-like effects in the model employed and may possibly exert its effects by modifying monoamine transport and/or metabolism.

Key words: *Sphenocentrum*, forced swimming, tail suspension, reserpine, α-methyldopa

INTRODUCTION

Sphenocentrum jollyanum Pierre belongs to the family Menispermaceae and is known locally in Ghana as *aduro kokoo* (red medicine) or *okramankote* (dog's penis). It is a small erect sparsely branched shrub, growing up to 1.5 m in height with very few branches. The roots which are bright yellow with a sour taste (Neuwinger, 1996) are used as chew-sticks, relief for constipation, as a stomachic, as a cough medicine, for sickle cell disease, rheumatism and other inflammatory conditions (Burkill, 1985; Iwu, 1993; Moody *et al*., 2006).

The root of *S. jollyanum* is chewed or taken in alcoholic bitters for its stimulant effect on the Central Nervous System (CNS) and as an aphrodisiac in Ghana (Irvine, 1961; Abbiw, 1990). Earlier studies have showed that the ethanolic extract of *S. jollyanum* increased libido and enhanced sexual behavior in male mice. Furthermore, daily administration of the extract to rats for three weeks increased levels of testosterone and FSH (Owiredu *et al*., 2007). This study confirmed earlier reports of (Yinusa *et al*., 2006) who indicated that 50 and 100 mg kg^{-1} of a methanolic extract of the plant increased significantly the serum levels of testosterone. Preliminary study has also established an anxiogenic property of the extract in murine models (Woode *et al*., 2006). As part of the study of the neuropharmacological properties of *S. jollyanum*, the present study evaluates the effect of the root extract on two well-established murine models of depression the forced swimming and tail suspension (Porsolt *et al*., 1977; Steru *et al*., 1985; Dalvi and Lucki, 1999; Cryan *et al*., 2005) by tests. The study also attempts to evaluate the involvement or otherwise the role of adrenergic mechanisms in the antidepressant effects of the plant. Comparable data for known antidepressants imipramine, a tricyclic antidepressant and fluoxetine, a selective serotonin re-uptake inhibitor, obtained under the same experimental conditions have also been provided.

MATERIALS AND METHODS

Plant material: Sun-dried roots of *Sphenocentrum jollyanum* Pierre (family Menispermaceae) were bought from the Central Market, Kumasi in August, 2006. They were identified by Dr. T.C. Fleischer, Department of Pharmacognosy, KNUST, Kumasi, Ghana. A voucher sample was deposited at the Department.

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Preparation of the extract: The roots were pulverized with a hammer-mill to obtain a coarse powder and 5 kg of the powder was extracted with 70% (v/v) ethanol in a Soxhlet apparatus for 24 h. Using a vacuum rotary evaporator, the hydro-alcoholic filtrate was concentrated under reduced pressure to obtain a yellowish-brown syrupy mass which was then air-dried at room temperature (28°C). This yielded 478 g (9.56%) of a yellowish brown extract which was kept in a desiccator and is subsequently referred to as extract or SJE.

Animals: Male ICR mice were purchased from Noguchi Memorial Institute for Medical Research, University of Ghana, Accra and housed at the animal facility of the Department of Pharmacology, KNUST, Kumasi, Ghana. The animals were housed in groups of 6 in stainless steel cages (34×47×18 cm) with soft wood shavings as bedding, fed with normal commercial pellet diet (GAFCO, Tema) and given water *ad libitum*. All behavioral experiments were carried out under dim light and therefore to acclimatize the animals to the test conditions, they were brought to the laboratory and exposed to dim light at the stipulated time of testing daily for 6 days before the experiment. All animals used in these studies were treated in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals (NIH, Department of Health and Human Services publication No. 85-23, revised 1985). The research protocol was approved by the College Ethics Committee.

Drugs and chemicals: Fluoxetine hydrochloride (Prozac®), imipramime hydrochloride, α-methyldopa (Aldomet®) and reserpine were purchased from Eli Lilly and Co., Basingstoke, England, Phyto-Riker Pharmaceuticals, Accra, Ghana, Merck Sharp Dohme, Herts., England and BDH, Poole, England, respectively.

Forced Swimming Test (FST): The FST was based on that described by Porsolt *et al.* (1977, 1978). Mice were divided into ten groups of six animals each. Test groups received extract (100, 300 or 1000 mg kg^{-1}, p.o.). The positive control groups received standard reference drugs imipramine (3, 10 or 30 mg kg^{-1}, p.o.) or fluoxetine (3, 10 or 30 mg kg^{-1}, p.o.). The negative control group received only vehicle. Thirty minutes after i.p. and 1 h after oral administration of drugs, mice were gently dropped individually into transparent cylindrical polyethylene tanks (25 cm high, 10 cm internal diameter) containing water (25 to 28°C) up to a level of 20 cm and left there for 6 min. Four identical polyethylene cylinders were prepared and four animals, separated by opaque screens, were exposed simultaneously and videotaped. Each session was recorded by a video camera suspended approximately 100 cm above the cylinders. After each session, animals were removed from the cylinders, dried with absorbent towels and then returned to their home cages. Water was changed for each mouse and tanks were cleaned in between studies. An observer scored the duration of immobility (when it floated upright in the water and made only small movements to keep its head above water), during the last 4 min of the 6 min test, from the videotapes with the aid of the public domain software JWatcher™ Version 1.0 (University of California, Los Angeles, USA and Macquarie University, Sydney, Australia. Available at http://www.jwatcher.ucla.edu/).

ED_{50} (dose responsible for 50% of the maximal effect) for each drug was determined by using an iterative computer least squares method, with the following nonlinear regression (three-parameter logistic) Equation:

$$Y = \frac{a + (b - a)}{\left(1 + 10^{(\text{Log}ED_{50} - X)}\right)}$$

where, X is the logarithm of dose and Y is the response. Y starts at a (the bottom) and goes to b (the top) with a sigmoid shape.

Tail Suspension Test (TST): The TST was carried out as previously described by (Steru *et al.*, 1985). Mice were allowed to acclimatize to the room for 3.5-4 h before the test. Groups of six mice were treated with SJE (100, 300 or 1000 mg kg^{-1}, p.o.), imipramine (3, 10 or 30 mg kg^{-1}, p.o.), fluoxetine (3, 10 or 30 mg kg^{-1}, p.o.) or vehicle. Thirty minutes after i.p. and 1 h after oral administration of the test compounds, mice were individually suspended by the tail from a horizontal bar (distance from floor = 30 cm) using adhesive tape (distance from tip of tail = 1 cm). Duration of immobility, defined as the absence of all movement except for those required for respiration, was recorded by an observer for 6 min from video recordings of the test as described above for forced swimming test. Mice that climbed up on their tails during the test session were gently pulled down and testing continued. Mice that continued to climb their tails were excluded from the study.

Effect of catecholamine depletion on the anti-depressant actions of SJE: To investigate the possible role of noradrenergic system in the actions of SJE, a separate experiment in which catecholamines were depleted by treatment with α-methyldopa (αMD) (400 mg kg^{-1}, i.p.) and/or reserpine (1 mg kg^{-1}, s.c.) was carried out. Because the TST presents some advantages over the FST in allowing an objective measure of immobility and does not

induce hypothermia by immersion in water (Ripoll *et al.*, 2003), it was chosen for this study. The doses of αMD and reserpine were chosen on the basis of the study by Van Giersbergen *et al.* (1990) and O'Leary *et al.* (2007). To deplete newly synthesized pools of Noradrenaline (NE) and Dopamine (DA), mice were treated with a single dose of α-MD (400 mg kg^{-1}, i.p.) 3.5 h before behavioral testing. To deplete vesicular pools of NE and DA, mice were treated with a single dose of reserpine (1 mg kg^{-1}, s.c.) 24 h before behavioral testing. In an effort to deplete both the vesicular and cytoplasmic pools of NE and DA, mice were pretreated with a combination of reserpine (1 mg kg^{-1}, s.c., 24 h before behavioral testing) and α-MD (200 mg kg^{-1}, i.p., 3.5 h before behavioral testing), respectively. All control animals received 0.9% saline on the same schedule as the treated groups.

Motor co-ordination - rotarod test: Deficits in motor-coordination and increase in activity could invalidate conclusions drawn from the tail suspension test and the forced swimming test. Therefore, the effect of the various treatments was assessed using the rotarod apparatus. The rotarod apparatus (model 7600, Ugo Basile, Cormerio, Italy) rotated at a speed of 12 rpm. This apparatus consists of a base platform and a rotating rod of 3 cm diameter with a non-skid surface. The rod, 50 cm in length, is divided into five equal sections by six disks. Five mice were tested simultaneously. The mice were placed individually on the rod. Before the start of the experiment, animals were trained to stay on the rotarod for 300 sec. Mice that failed to learn the test or did not reach the criterion (300 sec endurance) were excluded from the study. On the test day, the length of time each mouse remained on the rod (endurance time, maximal score 300 sec) was measured after administration of the test compounds or vehicle.

The animals were acclimatized to the revolving drum and habituated to handling in order to avoid stress during testing. The integrity of motor coordination was assessed as the performance time on the rod, measured from acceleration start until fall from the drum. The mice were acclimatized to acceleration by three training runs.

Statistical analysis: All data are presented as Mean±SEM. To compare differences between groups, one-way ANOVA was performed with Newman-Keuls's test as post hoc. Fitted midpoints (ED_{50}s) of the dose-response curves in the FST and TST were compared statistically using F-test (Motulsky and Christopoulos, 2003; Miller, 2003). GraphPad Prism for Windows version 4.03 (GraphPad Software, San Diego, CA, USA) was used for all statistical analyses and ED_{50} determinations $p<0.05$ was considered statistically significant.

RESULTS

Effects of SJE, fluoxetine and imipramime in the forced swimming and tail suspension tests: Acute administration of SJE (100, 300 and 1000 mg kg^{-1}; p.o.) significantly decreased the duration of immobility of the mice in a dose-dependent manner in both the FST ($F_{3,20}$ = 19.16; $p<0.0001$) and the TST ($F_{3,16}$ = 25.11; $p<0.0001$), indicating an antidepressant activity (Fig. 1). Similarly, the selective 5-HT uptake inhibitor fluoxetine (3, 10 and 30 mg kg^{-1}; p.o.) significantly reduced the immobility periods in the FST ($F_{3,20}$ = 31.51; $p<0.0001$) and the TST ($F_{3,16}$ = 15.94; $p<0.0001$). Also, the tricyclic antidepressant imipramine, (3, 10 and 30 mg kg^{-1}; p.o.) administered for 30 min before the tests decreased the immobility period ($F_{3,20}$ = 26.02; $p<0.0001$ and $F_{3,20}$ = 21.70; $p<0.0001$), respectively for the FST and TST.

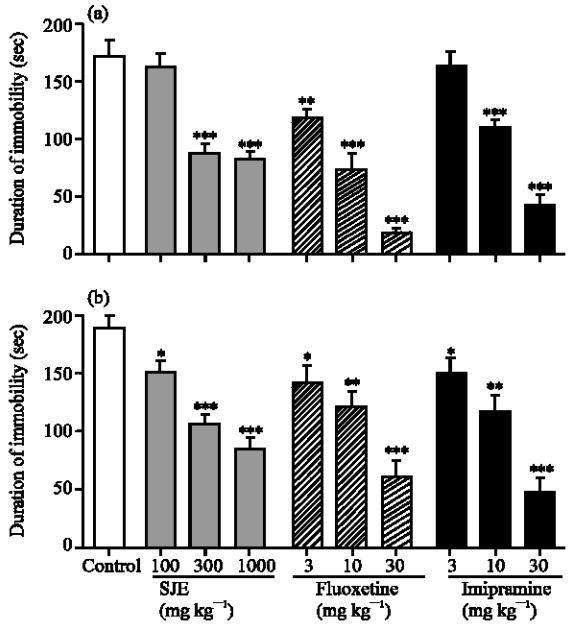

Fig. 1: Effects of SJE (100, 300 and 1000 mg kg^{-1}; p.o.); fluoxetine (3, 10 and 30 mg kg^{-1}; p.o.) and imipramine (3, 10 and 30 mg kg^{-1}; p.o.) on duration on immobility in the forced swim test (panel a) and tail suspension test (panel b) in mice. Data are shown as Mean±SEM (n = 6). ***$p<0.001$; **$p<0.01$; *$p<0.05$ compared to control group (vehicle-treated) by one-way ANOVA followed by Newman-Keul's post hoc test, (a) Forced swimming test and (b) Tail suspension test

Table 1: ED_{50}s for the effect of SJE, fluoxetine and imipramine in the forced swimming and tail suspension tests in mice

	ED_{50} (mg kg^{-1} body weight)	
Drug	Forced swimming test	Tail suspension test
SJE	296.20±53.97	203.90±39.01
Fluoxetine	6.33±1.190	14.52±3.450
Imipramine	15.52±1.190	12.96±2.900

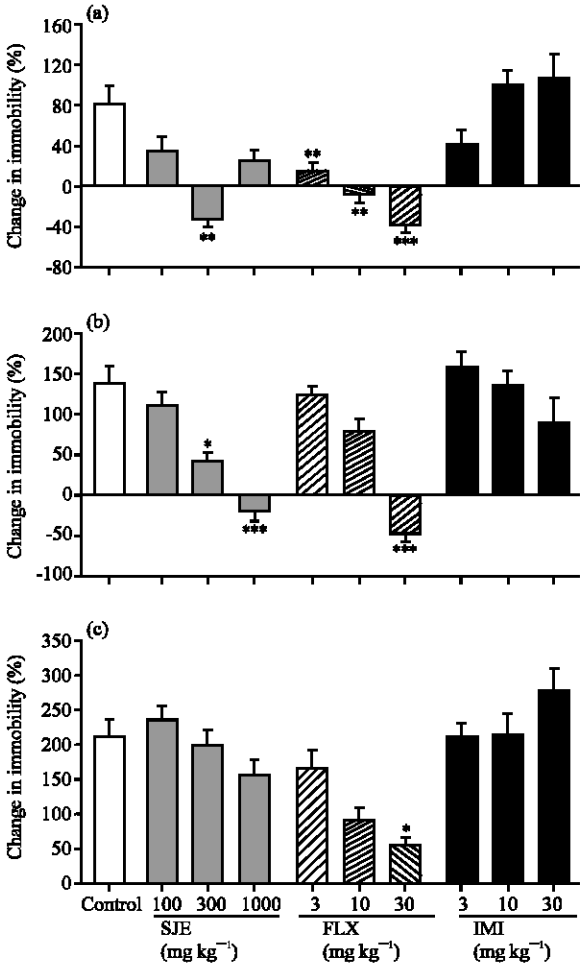

Fig. 2: Effects of pretreatment of mice with α-methyldopa (400 mg kg^{-1}; 3.5 h; panel a); reserpine (1 mg kg^{-1}; 24 h, panel b) and co-administration of reserpine (24 h) and a-methyldopa (3.5 h), panel c, on changes in immobility induced by SJE (100, 300 and 1000 mg kg^{-1}; p.o.); fluoxetine (3, 10 and 30 mg kg^{-1}; p.o.) and imipramine (3, 10 and 30 mg kg^{-1}; p.o.) in the tail suspension test in mice. Data are shown as Mean±SEM (n = 6). ***p<0.001; **p<0.01; *p<0.05 compared to control group (vehicle-treated) by one-way ANOVA followed by Newman-Keul's post hoc test, (a) αMD, (b) Reserpine and (c) αMd+reserpine

The ED_{50} (dose responsible for 50% of the maximal effect) for the test compounds are shown in Table 1. In the FST, fluoxetine was found to be approximately 45 times more potent than SJE ($F_{1,34}$ = 246.6; p<0.0001) and 2.5 times more potent than imipramime ($F_{1,34}$ = 13.68; p<0.0001). However, in the TST, fluoxetine was equipotent to imipramime ($F_{1,28}$ = 0.7023; p = 0.1491) but 14 times more potent than SJE ($F_{1,28}$ = 116.10; p<0.0001). Also, the results show the effects of fluoxetine to be significantly greater ($F_{1,31}$ = 16.04; p = 0.0004) in the FST than in the TST. The effect of SJE and imipramime were similar in both tests.

Effect of α-methyldopa and reserpine-pretreatment on the effects of SJE, fluoxetine and imipramime in the tail suspension test: All the pretreatments increased the basal (control) level of immobility by more than 80%. SJE (100-1000 mg kg^{-1}) decreased significantly the increased basal levels of immobility in the αMD-pretreated ($F_{3,16}$ = 6.98; p = 0.0032) and reserpine-pretreated ($F_{3,16}$ = 11.12; p = 0.0003) mice (Fig. 2a). However, SJE did not have any significant effect ($F_{3,16}$ = 1.2298; p = 0.34) on the increased immobility caused by the combination, though there seemed to be a slight decrease. The effect of SJE in the αMD-treated mice displayed a U-shaped dose-response curve whilst the effect in the reserpine-treated mice was dose-dependent. Similarly, the SSRI, fluoxetine (3-30 mg kg^{-1}) decreased significantly the effect of αMD-pretreated ($F_{3,16}$ = 12.61; p = 0.0002) and reserpine pretreated ($F_{3,16}$ = 18.18; p<0.0001) mice (Fig. 2b). In addition, fluoxetine also decreased significantly ($F_{3,16}$ = 5.06; p = 0.0118), the raised level of immobility due to pretreatment with a combination of αMD and reserpine. However, in contrast to SJE all the effects of fluoxetine were dose-dependent. Imipramine, a tricyclic antidepressant, on the other hand, did not have any significant effect in all the pretreated mice.

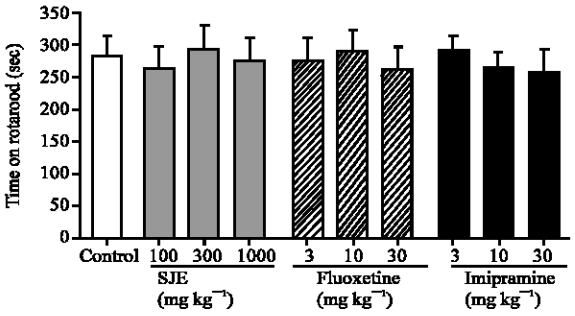

Fig. 3: Effects of SJE (100, 300 and 1000 mg kg^{-1}; p.o.); fluoxetine (3, 10 and 30 mg kg^{-1}; p.o.) and imipramine (3, 10 and 30 mg kg^{-1}; p.o.) on motor co-ordination of mice on the rotarod

Motor co-ordination - rotarod test: The effect of the test drugs on motor co-ordination is shown in Fig. 3. None of the treatment showed significant impaired motor co-ordination compared to the control group.

DISCUSSION

Data presented here indicate that the ethanolic extract of *S. jollyanum* has an antidepressant-like effect in two widely-used animal models of depression. The forced swimming test has been used in preclinical tests to evaluate; behavioral despair; a measure of failure to seek escape from an aversive stimulus (Crawley *et al*., 1997). When rodents are forced to swim in a narrow space from which there is no escape, they will stop swimming after an initial period of vigorous activity, a characteristic immobile posture, moving only when necessary to keep their heads above the water. Immobility time is considered the measure of depression-like behaviors, in that the animal has stopped swimming and given up; on finding no escape route (Crawley *et al*., 1997). In the FST, an antidepressant response is characterized by a reduction of the duration of immobility. FST has a high degree of predictive validity as shown by its sensitivity to major classes of antidepressants, Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), atypical antidepressants, selective serotonin reuptake inhibitors (SSRIs) and electroconvulsive therapy (Borsini and Meli, 1988; Dalvi and Lucki, 1999). In the tail suspension test, mice immediately engage in several agitation- or escape-like behaviors, followed temporally by increasing bouts of immobility. Like the forced swimming test, immobility is reduced by a broad range of pharmacological and somatic treatments (Steru *et al*., 1985, 1987; Teste *et al*., 1990; Perrault *et al*., 1992; Cryan *et al*., 2004, 2005).

Though statistical analysis did not show any significance, the ED_{50}s for SJE and imipramime were lower in the TST thus confirming the superior sensitivity of the TST. However, fluoxetine was more effective in the FST in contrast to a report indicating that TST shows a greater sensitivity to antidepressant effects of 5-HT uptake inhibitors (Steru *et al*., 1987). Different experimental conditions may explain the difference in observations since factors such as strain and temperature affect such results (Porsolt *et al*., 2001).

To eliminate the involvement of compromised motor activity and coordination, we have shown that SJE at the doses used did not have such effects as determined by the rotarod test.

In this study, an attempt was made to investigate the mechanism of the antidepressant action of SJE. The monoamines dopamine, serotonin (5-HT), noradrenaline and adrenaline in the frontal cortex play crucial roles in processes involved in the control of mood, cognition and motor behaviour functions that are compromised in depression (Millan *et al*., 2000). A perturbation of corticolimbic serotonergic and noradrenergic transmissions is implicated in the etiology of depression and antidepressants act by elevating the monoamine neurotransmission, in particular 5-HT, NE and/or DA in the frontal cortex (Tanda *et al*., 1994; Gobert *et al*., 1997; Brocco *et al*., 2002; Brunello *et al*., 2002; Stone *et al*., 2003). The effect of pretreatment of mice with α-methyldopa and reserpine, both drugs which are known to alter monoaminergic systems.

α-Methyldopa is an L-aromatic amino acid decarboxylase inhibitor and therefore inhibits the biosynthesis of catecholamines and 5-HT (DeMuth and Ackerman, 1983; Schinelli *et al*., 1993). Furthermore, α-methyldopa is a substrate in catecholaminergic pathway leading to production of the false transmitters; α-methyldopamine and α-methylnoradrenaline (DeMuth and Ackerman, 1983). Moreover, these false transmitters are α_2-adrenoceptor agonists (Hey *et al*., 1988) and thus prevent the release of noradrenaline from nerve endings. We therefore, hypothesized that pretreatment with α-methyldopa will have more effect on catecholaminergic than the serotoninergic pathways. This is confirmed by present results which showed that the antidepressant effect of imipramime (a tricyclic antidepressant) was abolished by pretreatment by α-methyldopa whilst the SSRI fluoxetine reversed the effects of α-methyldopa. It must however be pointed out that imipramine is a non-selective inhibitor of monoamine transporters; inhibiting both NET and SERT (Iversen, 2006). In comparison, the extract reversed the effect of pretreatment with α-methyldopa similar to, though not quantitatively, fluoxetine. The effect of methyldopa on responses to imipramime was intriguing. Imipramine is a non-selective inhibitor of monoamines and thus we did not expect α-methyldopa to completely abolish its antidepressant effect. This may possibly be explained by the fact that imipramime is normally metabolized *in vivo* to desipramine, a highly potent and selective NE reuptake inhibitor (Iversen, 2006; O'Leary *et al*., 2007).

Pretreatment with reserpine increased baseline immobility and attenuated the effects of imipramine in the TST but did not affect that of SJE and flouxetine. The results obtained for imipramime in reserpine-pretreated mice is consistent with the effects of reserpine. Reserpine is an irreversible inhibitor of the vesicular monoamine transporter 2 (VMAT-2) which is located primarily within the CNS and is responsible for transporting monoamines from the cytoplasm into secretory vesicles (Metzger *et al*.,

2002; Ji *et al*., 2007). Treatment with reserpine therefore leads to depletion of vesicular monoamine stores-both serotonin and noradrenaline (Fukui *et al*., 2007). The inability of reserpine pretreatment to affect the actions of fluoxetine seem to suggest that reserpine does not affect vesicular storage of 5-HT to the same extent as that of noradrenaline. At the dose level used in this experiment, O'Leary *et al*. (2007) showed that reserpine depleted tissue in the frontal cortex by 78, 93 and 95%, respectively for 5-HT, noradrenaline and dopamine.

Putting present results together it may be inferred that actions of SJE were similar to the SSRI, fluoxetine. However, the involvement of noradrenergic and dopaminergic systems seems to be greater in SJE as evidenced by the greater decrease in immobility caused by fluoxetine in comparison to SJE. In an earlier study SJE increased plasma levels of testosterone (Owiredu *et al*., 2007) confirming results obtained by Yinusa *et al*. (2006). It has been postulated that testosterone increases DA release in the CNS by upregulating nitric oxide synthase, which produces nitric oxide, which in turn increases DA release (Hull *et al*., 1999; Du and Hull, 1999; Hull and Dominguez, 2007). This may therefore explain in part the stimulant effect of the extract. However, it must be pointed out that SJE contains several secondary metabolites and therefore other mechanisms and neurotransmitters may be involved such as dopaminergic, serotonergic, GABAergic and glutamatergic neurotransmissions. Further experiments, may be necessary therefore to confirm the exact mechanism/s involved in the CNS effects.

Phytochemical analysis of SJE in this study has revealed the presence of flavonoids and terpenoids among others. Recent studies have shown the antidepressant effect of the flavonoid fraction obtained from St. John's Wort (*Hypericum perforatum*) in the FST (Butterweck *et al*., 2000; Noldner and Schotz, 2002; Butterweck, 2003). Also, extracts from *Ginkgo biloba*, which contains flavonoids and terpenoids have also shown antidepressant activities in both the FST and TST (Sakakibara *et al*., 2006).

Chronically administered antidepressant drugs, particularly selective serotonin reuptake inhibitors (SSRIs), are clinically effective in the treatment of anxiety disorders (Borsini *et al*., 2002) and as such with SJE showing antidepressant properties similar to fluoxetine in this study, we anticipated that it will cause anxiety-like behaviors in mice, but on the contrary, an earlier finding by us proved that the extract gives anxiogenic-like effects in mice (Woode *et al*., 2006). This apparent contradiction may be due to the predictive validity of the anxiety models such as the elevated plus, the hole board and the open field, which are use for the anxiolytic effects of antidepressants (Borsini *et al*., 2002).

Affective disorders such as major depression are among the most prevalent and costly disease of the central nervous system with a high morbidity and mortality. It is estimated to affect 10-15% of the population and its prevalence has increased over the last 50 years (Pine *et al*., 1998; Gitanjali *et al*., 2004). Depression is also one of the most costly diseases and in the European Union, it is estimated that costs of affective disorders exceed 105 billion Euros (Andlin-Sobocki and Wittchen, 2005). Thus it may be very useful looking for alternative and cost-effective therapy; especially in developing countries where income is low and majority of the population rely on herbal remedies. Furthermore, we have recently established that the extract has no overt organ specific toxicity but has a potential for drug interactions *via* induction of cytochrome P450 (Amidu *et al*., 2008).

CONCLUSION

Based on present results from this study, it is clear that the ethanolic extract of *S. jollyanum* roots has anti-depressant properties in rodent models of depression and may have actions similar to fluoxetine.

ACKNOWLEDGMENTS

The authors are grateful for the technical support of Messrs Thomas Ansah and George Ofei and also to the Gates Foundation (Grant No.. 97920202379) for partly funding this study. Eric Woode conceived, designed and supervised the experiments. Nafiu Amidu and Eric Boakye-Gyasi are graduate students who worked on different aspects of this study. William K.B.A. Owiredu helped with the design and data analysis with Eric Woode. Charles Ansah and Mahama Duwiejua coordinated the study, read and corrected the galley proofs for the final versions. All authors were involved with the preparation of the manuscripts.

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