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Psychopharmacological Potentials of Methanol Leaf Extract of *Securinega virosa* Roxb (Ex Willd) Baill. in Mice

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Abstract: Schizophrenia is a highly disabling chronic psychiatric illness. The existing antipsychotic agents are associated with untoward effects and drug interactions leading to the intensification of search for newer agents with better efficacy and safety profile. *Securinega virosa* is a commonly used medicinal plant in African traditional medicine. The decoction of the leaves of the plant in combination with other plants is used in the management of mental illness. In this study, we evaluate the antipsychotic potential of the methanol leaf extract (25, 50 and 100 mg kg^{-1}) of the plant using apomorphine-induced stereotypic climbing behavior and swim-induced grooming tests, all in mice. The CNS depressant effect was also evaluated using ketamine-induced sleep test mice. The extract at the highest dose tested (100 mg kg^{-1}) significantly reduced the apomorphine (1 mg kg^{-1})-induced stereotypic climbing behavior after 30 min. Similarly, haloperidol (2 mg kg^{-1}), the standard agent significantly ($p<0.001$) decreased the mean climbing behavior. In the swim-induced grooming test, the extract significantly ($p<0.01$) and dose-dependently decreased the total grooming time. Similarly, haloperidol (2 mg kg^{-1}) significantly ($p<0.001$) decreased the mean grooming activity. The extract significantly increased the total ketamine-induced sleep duration at doses of 50 and 100 mg kg^{-1}. These findings suggest that the extract possesses antipsychotic and sedative potentials and lend credence to the ethnomedical use of the leaves of the plant in the management of mental illness.

Key words: Schizophrenia, pyschosis, *Securinega virosa*, apomorphine, grooming, ketamine, medicinal

INTRODUCTION

Schizophrenia, the most persistent and disabling mental illnesses presented as abnormal mental functions and perturbation of behavior (Lewis and Lieberman, 2000). It has a mean lifetime morbidity risk of approximately 1:100 (McGrath and Susser, 2009). The existing antipsychotic agents used in its management are associated with untoward effects and drug interactions. This has led to intensification of research into newer agents with superior efficacy and safety profile.

The plants kingdom constitutes the corner stone of traditional medicine. It is the source of some of the existing drugs in use today and will continue to serve as source of "lead" compounds in the drug development process. A number of medicinal plants have enjoyed patronage among traditional practitioners in the management of mental illnesses. One of such medicinal plant is *Securinega virosa* which has been described as a "cure all" in African traditional medicine (Neuwinger, 1996). It is a dense, low branching, many branched shrub, sometimes a small spreading tree up to about 6 meters high of the family Euphorbiaceae. It is widely distributed throughout tropical Africa, also in India, Malaya, China and Australia (Dalziel, 1936). In Nigeria, it is found in virtually all parts of Nigeria where it is commonly referred to "tsuwaawun karee, gussu, gwiiwar karee" (Hausa), "iranje" (Yoruba), "njisinta" (Ibo), "shim shim" (Kanuri) and "kartfi-kartfi" (Shuwa Arabs). In many parts of Africa including the north Eastern Nigeria, the root and leafy twig decoctions are used for the treatment of epilepsy. The decoction of the leaf of *Securinega virosa* with some other plants is used in northern Nigeria for the treatment of mental illness (Neuwinger, 1996). The present study is designed to evaluate the neuromodulatory effect of the methanol leaf

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extract of *Securinega virosa* on dopaminergic system using apomorphine-induced stereophytic climbing and swim-induced grooming and general central depressant effect using ketamine-induced sleep test in mice.

MATERIALS AND METHODS

Plant material: The whole plant was collected in Basawa town, Sabon Gari Local Government Area of Kaduna State, Nigeria in December, 2008. The plant was authenticated by Messrs Umar Gallah and Musa Muhammad of the Herbarium Section, Department of Biological Sciences, Ahmadu Bello University (ABU), Zaria, Kaduna State, Nigeria, by comparing it with existing specimen (Voucher specimen number 918). A specimen was deposited for future reference.

Preparation of extract: The leaves were air dried under shade until constant weights were obtained and then size-reduced into powder with pestle and mortar. One hundred (100 g) of the powdered leaves was macerated with 500 mL methanol for 72 h, with occasional shaking. The extract was concentrated *in vacuo* affording a dark brownish residue (Yield: 13.2% w/w) subsequently referred to as methanol leaf extract of *S. virosa* (MLE) and stored in desiccators before use. Solution of extract was prepared freshly for each study.

Preliminary phytochemical screening: MLE was screened for the presence of alkaloids, tannins, saponins, flavonoids, triterpenes/steroids and cardiac glycosides using standard protocol (Trease and Evans, 1983).

Experimental animals: Swiss Albino mice of either sex (20±2 g), obtained from Animal House Facility of Department of Pharmacology and Therapeutics, ABU Zaria-Nigeria, were used for the studies. The mice were maintained on standard laboratory animal feed and water *ad libitum*. They were housed in standard cages at room temperature with a 12 h light/dark cycle and allowed to acclimatize with the laboratory environment for at least seven days prior to the conduct of the study. All experimental protocols were in accordance with ethic and regulations governing the care and use of experimental animals as contained in "Principles of laboratory animal care" (NIH Publication No. 85-23, revised, 1996). The experiments were conducted in quiet laboratory between hours of 9:00 to 16:00.

Drugs: Apomorphine (Macfarlan Smith Ltd. Edinburgh, U.K), haloperidol (Lab.Renaudin France), diazepam (Roche Product Ltd, Welnyn Garden City) and ketamine (Parke-Davis Medical, Hart). The drugs were freshly prepared to the desired concentration with appropriate solvent just before use.

Acute toxicity study: The intraperitoneal (i.p.) LD_{50} of MLE in mice was estimated according to the method of Lorke (1983). The study was divided into two phases. In the first phase, 3 groups of three mice each were treated with the methanol leaf extract of the plant at dosed of 10,100 and 1000 mg kg^{-1} b.wt. i.p. and observed for signs of toxicity and death for 24 h. In the second phase, 4 groups each containing one mouse was injected with four more specific doses of the extract based on the result of the first phase. The LD_{50} value was determined by calculating the geometric mean of the lowest dose that caused death and the highest dose for which the animal survived (0/1 and 1/1).

Apomorphine-induced stereotypic climbing behavior test in mice: The method previously described by Costall *et al.* (1978) was adopted with some modifications. Mice were grouped into five each consisting six animals. Twenty minutes after treatment with either normal saline (10 mL kg^{-1}), MLE (25, 50 and 100 mg kg^{-1}) or haloperidol (2 mg kg^{-1}), each mouse was placed individually in a cylindrical wire mesh cage with walls of vertical metal bars 2 mm diameter, 1 cm apart, surmounted by a smooth surface. After 10 min habituation, the mice were treated with apomorphine (1 mg kg^{-1}) in 10% sodium metabisulphite. Ten minutes after apomorphine treatment, each mouse was observed every ten minutes for thirty minutes and the climbing behavior was scored as follows; four paws on the floor (0), one paw gasping on the vertical wall (1), fore feet gasping on the vertical wall (2), Four paws gasping on the vertical wall (3). The average climbing score was determined for each group.

Swim-induced grooming test in mice: The method previously described by Chesher and Jackson (1981) was adopted with some modifications. Mice were treated with either normal saline (10 mL kg^{-1}), MLE (25, 50 and 100 mg kg^{-1}) or haloperidol (2 mg kg^{-1}). Thirty minutes post-treatment, each mouse was placed singly in a 1000 mL beaker containing water up to 6 cm mark from the base for 3 min. They were then removed and dried with towel for 30 sec and placed immediately (individually) into rectangular Perspex boxes. The total duration of grooming episodes in seconds were recorded for 5 min.

Ketamine-induced sleep test in mice: The method previously described by Mimura *et al.* (1990) was adopted. Thirty minutes post-treatment with normal saline, MLE (25, 50 and 100 mg kg^{-1}) or diazepam

(0.5 mg kg^{-1}), animals (n = 6) were administered with ketamine (100 mg kg^{-1}). The time interval between ketamine administration and loss of righting reflex was considered as latency to sleep while the time from the loss to regaining of righting reflex as the duration of sleep (Ramirez *et al.*, 1998; Rabbani *et al.*, 2003).

Statistical analysis: The results were presented as Mean±SEM. The difference between the control and the test groups were analysed for statistical difference using One Way ANOVA followed by Dunnett's post hoc t-test for multiple comparisons. For the apomorphine-induced stereotypic behavior study, where non-continuous data were obtained, Kruskal Wallis test followed by Mann-Whitney U test was used. P-values less than 0.05 were considered significant.

RESULTS

Preliminary phytochemical screening: MLE was found to contain alkaloids, tannins, saponins, flavonoids, cardiac glycolsides, cyanogenic glycosides, resins, steroids/terpenoids and carbohydrates. However, anthraquinones were found to be absent.

Acute toxicity study: The intraperitoneal median lethal dose of MLE in mice was found to be 1265 mg kg^{-1}. The animals exhibited hypolocomotion and respiratory depression before death. However, there was no convulsion.

Apomorphine-induced stereotypic climbing behavior test in mice: MLE did not significantly affect the stereotypic climbing behavior at the lower doses. However, at the highest dose tested, it significantly decreased the mean climbing scores at the end of 30 min. Similarly, haloperidol, the standard agent significantly attenuated the climbing behavior over the 30 min period (Fig. 1).

Swim-induced grooming test in mice: MLE dose-dependently decreased the mean swim-induced grooming time. Similarly, haloperidol significantly decreased the grooming time at the dose of 2 mg kg^{-1} (Fig. 2).

Ketamine-induced sleep in mice: MLE did not significantly reduce the mean onset of sleep induced by ketamine at the dose tested. However, it increased the mean duration by a factor of about 2.5 at the dose of 50 mg kg^{-1}. Diazepam (0.5 mg kg^{-1}), the standard agent used significantly ($p<0.001$) decreased the mean onset of sleep and increased the mean duration of sleep (Fig. 3).

DISCUSSION

The present study showed that the methanol leaf extract of *Securinega virosa* possesses antipsychotic and sedative potentials. The median lethal dose of the extract was found to be 1265 mg kg^{-1}, suggesting that it is relatively toxic, intraperitoneally (Matsumura, 1985). However, it is safe at the doses employed in this study. The phytochemical constituents found to be present in the leaf extract include alkaloids, saponins, flavonoids and tannins and could be responsible of the observed psychopharmacological effect of the leaf extract singly or in combination. Antagonism of apomorphine-induced stereotypic climbing behavior has been correlated with neuroleptic potential (Costall *et al.*, 1978) and is suggestive of dopamine D_1 and D_2 dopaminergic receptor blockade (Moore and Gershon, 1989). It is has been

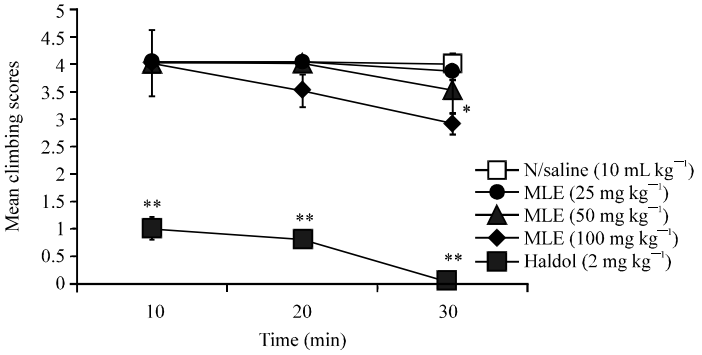

Fig. 1: Effect of methanol leaf extract of *Securinega virosa* on apomorphine-induced stereotypic behavior in mice, Data presented as Mean±SEM, *$p<0.05$, **$p<0.001$ (Compared with control using Man-Whitney, n = 6

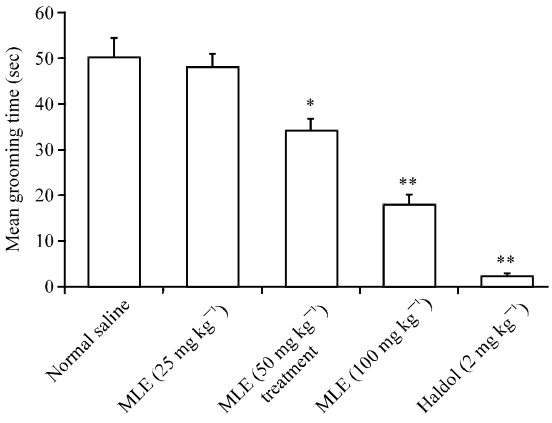

Fig. 2: Effect of methanol leaf extract of *Securinega virosa* on swim-induced grooming in mice. Data presented as Mean±SEM, *p<0.05, **p<0.001 (Compared with control using Dunnet's *post hoc* test for multiple comparison), MLE: Methanol leaf extract, Haldol: Haloperidol, n = 6

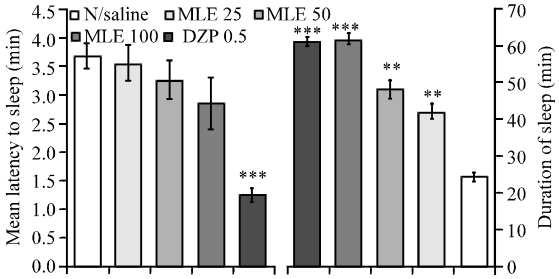

Fig. 3: Effect of methanol leaf extract of *Securinega virosa* on ketamine-induced sleep in mice, Data presented as Mean±SEM, **p<0.05, ***p<0.001 (compared with control using Dunnet's *post hoc* test for multiple comparison), MLE: Methanol leaf extract, DZP: Diazepam, n = 6

previously reported that blockade of apomorphine-evoked climbing behavior is related to the dopamine receptor blockade in the nucleus accumbens (Kedves *et al*., 2008). The ability of the extract to attenuate the apomorphine-induced climbing behavior at the highest dose suggests that it possesses an anti-dopaminergic activity. The swim-induced grooming behavior is one of the models used to predict dopaminergic mechanism of drugs since it is attenuated in a dose dependent manner by dopaminergic antagonists (Ingale and Kasture, 2012). The swim-induced grooming behavior involves mainly dopamine D_1 receptors (Van Wimersma Greidanus *et al*., 1989). SKF 38393, a dopamine agonist has been reported to produce grooming behavior (Molloy and Waddington, 1984). The present results showed that the methanol leaf extract of *Securinega virosa* inhibited the grooming behavior at all the doses tested while it only attenuated the apomorphine induced climbing behavior at the highest dose tested suggesting that its antipsychotic activity may involve more of dopamine D_1 receptors. The methanol leaf extract of *Securinega virosa* increased the total sleep duration induced by ketamine without significantly affecting the mean onset of sleep. Expectedly, diazepam decreased the latency to sleep and increased the sleep duration. This finding suggests that the extract is less sedative when compared with diazepam and it may be beneficial in the maintenance of sleep rather than facilitating sleep induction. Aiyelero *et al*. (2012) reported that the leaf extract of *Securinega virosa* prolonged diazepam-induced sleep in mice.

It may therefore be concluded that the methanol leaf extract of *Securinega virosa* possesses antipsychotic and sedative activities and may lend credence to the ethnomedical use of the plant in the management of psychiatric illness.

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