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Aqueous root extract of *Lecaniodiscus cupanioides* restores nitric oxide/cyclic guanosine monophosphate pathway in sexually impaired male rats

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ABSTRACT

Ethnopharmacological relevance: Aqueous root extract of *Lecaniodiscus cupanioides* is widely used in the management of sexual dysfunction in Nigeria. The effect of aqueous root extract of *L. cupanioides* root on the concentrations of penile cyclic Guanosine Monophosphate (cGMP) and plasma nitric oxide in paroxetine-induced sexually impaired male rats was evaluated.

Methods: Thirty (30) albino rats were assigned into six groups (A, B, C, D, E and F) of five rats each such that animals in Group A (control) received distilled water while those in Groups B, C, D, E and F which were induced into sexual dysfunction (p.o 10 mg/kg of paroxetine hydrochloride suspension in Tween-80) and in addition received distilled water, 7.14 mg/kg body weight of a reference herbal drug (PowmaxM), 25, 50 and 100 mg/kg body weight of the extract respectively, orally, once daily for five days.

Results: Administration of paroxetine significantly reduced the levels of penile cyclic Guanosine Monophosphate (cGMP) and plasma nitric oxide. These decreases were dose dependently reversed by the aqueous extract of *L. cupanioides* root. The reversal by the 25 and 50 mg/kg body weight of the extract compared favorably with the PowmaxM, whereas the 100 mg/kg body weight of the extract compared favorably with the non-sexually impaired distilled water treated control animals.

Conclusion: The results of this study show that aqueous extract of *L. cupanioides* root restored the levels of cGMP and nitric oxide in sexually impaired rats. This study further lends credence to the use of aqueous root extract of *L. cupanioides* in the management of sexual dysfunction in Nigeria.

1. Introduction

The use of plants as medicine to cure or prevent illness and to lubricate the wheels of social interaction at the interpersonal and group level is a behavior that predates civilization, and in today's civilization, it is found in every society, irrespective of its level of development and sophistication (Odugbemi, 2008). It was estimated that over 80% of the people in developing countries rely on traditional remedies for their primary health care and about 855 traditional medicines include crude plant extracts (Biswas and Mukherjee, 2003). In Nigeria, the use of herbal remedies in promoting sperm production and motility, increasing testosterone levels, enhancing normal functioning of the male reproductive organs, and strengthening erection and sex-drive have been validated (Afolayan and Yakubu, 2009; Ajiboye et al., 2014; Nurudeen and Ajiboye, 2012; Yakubu and Nurudeen, 2012; Yakubu et al., 2005).

Lecaniodiscus cupanioides Planch. Ex Bth. (Sapindaceae) is a shrub widely distributed throughout deciduous and non-deciduous rain forests (Gill, 1992). It is known as *aaka* or *akika* (Yoruba), *kaafi-nnamaa-zaaki* (Hausa) and *okpu* (Igbo) in Nigeria. Parts of the plant, such as the root and leaves have various applications in folk medicine for the treatment of boils, burns, wounds, oral hygiene, fever and abdominal swelling caused by liver abscess (Gill, 1992). The decoction of the root of the plant is claimed among the Yoruba people of Nigeria to control epilepsy and to enhance penile erection. The plant has also been reported to possess analgesic (Adeyemi et al., 2005), CNS depressant (Yemitan and Adeyemi, 2005) and testicular enhancing potentials (Nurudeen and Ajiboye, 2012).

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Despite the widespread usage among rural and urban dwellers in Nigeria, its effect on nitric oxide (NO) synthesis and on phosphodiesterase activity via cyclic Guanosine Monophosphate (cGMP) concentration as related to penile erection is scanty in open scientific literature. The present research work investigates the effects of aqueous extract of *L. cupanioides* root on concentrations of cGMP and plasma NO in paroxetine-induced sexually impaired male rats.

2. Materials and methods

2.1 Materials

2.1.1 Authentication of plant material

L. cupanioides root part, bought from herb sellers at a market (Oja tuntun) in Ilorin, Nigeria, was identified and authenticated at the Department of Plant Biology, University of Ilorin, Ilorin, Nigeria. A voucher specimen (UIH/007) was deposited in the departmental herbarium

2.1.2 Animals

Healthy, 4-month old Wistar male rats (30) with an average weight of 156.24 ± 3.22 g were housed in clean aluminum cages contained in well ventilated housing conditions (temperature: 22 ± 3 °C; photoperiod: 12 h; humidity: 45–50%). The cleaning of the cages was done daily. The animals were allowed free access to rat pellets (Bendel Feeds and Flour Mills Ltd., Ewu, Nigeria) and tap water. They were acclimatized for 2 weeks before the commencement of the experiment. The university animal ethics committee gave approval before the commencement of the study. The animals were used according to the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011).

2.1.3 Drugs, chemicals and assay kits

Paroxetine hydrochloride was a product of S.C. Europharm, Brasov, Romania, while PowmaxM was from Beijing Kowloon Pharmaceuticals Co., Ltd., Beijing, China. Assay kit for NO was obtained from Biovision Research Products, USA, whereas that for cGMP was obtained from Biomol Research Laboratories Inc., PA, USA. All other reagents used were of analytical grade and were prepared in distilled water and stored in neat and airtight reagent bottles.

2.2 Methods

2.2.1 Preparation of extract

Briefly, dried roots of *L. cupanioides* were pulverized in a blender (Mikachi Blender with Mill, Model MK-1830, China) and the resulting powder weighing 50 g was extracted in 200 mL distilled water for 48 h at room temperature (Nurudeen and Ajiboye, 2012). The extract was filtered with Whatman No. 1 filter paper and the resulting filtrate was concentrated on steam bath to give a yield of 4.98 g of the residue (brownish–black slurry) corresponding to a percentage yield of 9.96%. This was reconstituted in distilled water to give the required doses of 25, 50, and 100 mg/kg bodyweight before administration to experimental animals. Information from ethnobotanical survey was put together to arrive at the most frequently mentioned dose of 50 mg/kg bodyweight while the doses of 25 and 100 mg/kg bodyweight were half and twice the calculated dose of 50 mg/kg bodyweight.

2.2.2 Induction of sexual dysfunction in rats

Twenty-five healthy, sexually experienced male rats were induced with sexual dysfunction by oral administration of 10 mg/kg bodyweight paroxetine hydrochloride (Chan et al., 2010) and paired with healthy female rats (135.76 ± 2.84 g) made receptive by sequential administration of suspension of estradiol benzoate (10 μg/100 g bodyweight) and progesterone (0.5 mg/100 g bodyweight) (Amin et al., 1996). The mating behaviors of mount frequency (MF), intromission frequency (IF), ejaculatory frequency (EF), mount latency (ML), intromission latency (IL), ejaculatory latency (EL) and postejaculatory interval (PEI) were monitored. Male rats that showed a minimum of 25% reduction in MF, IF, and EF as well as minimum increase of 25% in ML, IL, EL, and PEI when compared to the control rats were considered as sexually impaired and subsequently used for this study (Malviya, 2011).

2.2.3 Animal grouping and extract administration

Normal sexually experienced male rats and sexually impaired male rats were employed for this investigation. A total of thirty male rats were completely randomized into six groups (A–F) with each group comprising five animals. Animals in Group A (normal sexually experienced rats) were administered with distilled water only throughout the period of the experiment. Groups B, C, D, E and F were induced with sexual dysfunction by oral administration of 10 mg/kg of the paroxetine hydrochloride (Malviya, 2011). In addition to sexual impairment, groups B, C, D, E and F were treated with distilled water, 7.14 mg/kg of PowmaxM (a reference herbal drug made up of *Panax ginseng*, *Camelia sinensis*, *Cnidium monnier*, *Epimedium brevicornum*, *Songaria cynomorium*, *Gingko biloba*, *Dahurian angelica*, *Salvia miltiorrhiza* root, L-arginine hydrochloride, and gamma aminobutyric acid), 25, 50 and 100 mg/kg bodyweight of aqueous extract of *L. cupanioides* root daily for 5 days, respectively. All administrations were done daily at the same point time of between 08:00 and 08:45 h.

2.2.4 Preparation of plasma and penile supernatants

The rats were euthanized placing them in a jar containing wool soaked in diethyl ether. When they became unconscious, the jugular veins were cut, and 5 mL of the blood was collected into heparin-containing tubes. The plasma was then collected using Pasteur pipette after centrifuging at 33.5*g* for 15 min using Uniscope Laboratory Centrifuge (Model SM800B, Surgifriend Medicals, Essex, UK). The plasma was kept frozen for 12 h before being used for the NO assay. Penile tissues were excised from the rats and were immersed in ice-cold 0.25 mol/L sucrose solution to maintain the integrity. The penile tissue were blotted with tissue paper, cut thinly with sterile scalpel blade and then homogenized in ice-cold 0.25 mol/L sucrose solution at a mass-to-volume ratio of 1:5. The homogenates were centrifuged at 800 r/min for 10 min at 4 °C. The resulting supernatant was frozen at −20 °C before being used for the cGMP analysis.

2.2.5 Determination of penile tissue cGMP

An appropriate dilution of the supernatants was used for the quantitative immunoassay of cGMP concentrations using methods described by Dinnendahl (1974).

2.2.5 Determination of nitric oxide

Estimation of the total nitrate/nitrite in the plasma samples were used for the determination of NO production, since NO is rapidly oxidized to nitrite and nitrate (Wo et al., 2013).

2.2.6 Statistical analysis

Results were expressed as the mean ± SD of five determinations. Data were analyzed using Duncan Multiple Range Test and complemented with Student's *t*-test. Statistical Package for Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Differences were considered statistically significant at $p < 0.05$