ORIGINAL ARTICLE

Attenuating effects of Mucuna pruriens on paroxetine-induced male sexual dysfunction in Wistar rats: behavioural, hormonal, antioxidant, and histological evaluation

[1] Onoja, B.A.,[2] Oyewopo, A.O., [2] Yunusa, M.M.,[3] Adesoye, D.S., [4] Ajayi, A.J., [5] Oyewopo, C., [6] Adepoju, A.E

[1] Department of Anatomy, Federal University of Health Sciences, Otukpo, Benue State, Nigeria

[2] Department of Anatomy, University of Ilorin, Ilorin, Kwara State, Nigeria

[3] Department of Environmental Health Sciences, Thomas Adewumi University, Oko-irese, Nigeria

[4] Department of Physiology, Thomas Adewumi University, Oko-Irese, Nigeria

[5] Department of Anesthesia, University of Ilorin Teaching Hospital

[6] Department of Clinical Pharmacy, North South College of Health Technology, Kwara State, Nigeria

ABSTRACT

Background: Male sexual dysfunction is a common adverse effect of selective serotonin reuptake inhibitors such as paroxetine, mediated through oxidative stress, nitric oxide dysregulation, and androgen deficiency. This study investigated the attenuating effects of Mucuna pruriens 70% ethanolic seed extract on paroxetine-induced male sexual dysfunction in Wistar rats. Methods: Thirty adult male Wistar rats (10-12 weeks old) were randomly allocated to five groups (n = 6): control (distilled water), paroxetine only (10 mg/kg/day), paroxetine plus sildenafil (5 mg/kg/day), and paroxetine plus M. pruriens extract at low (200 mg/kg/day) and high (400 mg/kg/day) doses, administered concurrently for 21 days. Sexual behavior indices, hormonal profiles, oxidative stress biomarkers in testicular and penile tissues, and histological changes were evaluated. Results: Paroxetine impaired sexual behaviour, reduced testosterone, and disrupted antioxidant balance. Co-treatment with M. pruriens dose-dependently attenuated paroxetine-induced changes in sexual performance, increased testosterone, enhanced antioxidant enzyme activity, and ameliorated testicular cytoarchitecture, with the high-dose extract showing the most pronounced improvement. Conclusion: These findings provide preclinical evidence supporting the ethnomedicinal use of M. pruriens and suggest potential for further investigation as an adjunct in managing SSRI-associated male sexual dysfunction.

Keywords: Paroxetine, Mucuna pruriens, Male sexual dysfunction, Testosterone, Oxidative stress

Stephen David Adesoye, Department of Environmental Health Science, Thomas Adewumi University, Oko-irese, Kwara state.
Email:david.stephen@tau.edu.ng.TEL:+234810728144

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INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to attain or maintain penile erection sufficient for satisfactory sexual activity. It is a global health problem with significant psychosocial impact, affecting over 150 million men worldwide, with projections reaching 322 million by 2025 (1). Its prevalence is rising in aging populations and in men with comorbidities such as diabetes, hypertension, obesity, and cardiovascular disease (2,3). Beyond physical health, ED has profound psychosocial consequences, impairing quality of life, relationships, and mental health (4).

The disorder has a multifactorial aetiology, involving neurogenic, psychogenic, endocrine, and vascular components. At the molecular level, impaired nitric oxide (NO) signaling, oxidative stress, endothelial dysfunction, and reduced androgen activity play central roles in its pathophysiology (5,6). NO released from endothelial and neuronal nitric oxide synthases activates guanylate cyclase, increasing cyclic GMP, which mediates smooth muscle relaxation and penile erection (7). Dysregulation of this pathway, coupled with reduced testosterone and impaired steroidogenesis, contributes to ED pathogenesis (8).

Phosphodiesterase 5 inhibitors (PDE5i), such as sildenafil, revolutionized ED management by enhancing cyclic GMP signaling. However, adverse effects including headache, flushing, visual disturbances, and contraindications in cardiovascular disease limit their use (9,10). Moreover, not all patients respond adequately, and cost remains a barrier in resource-limited settings (11). These limitations highlight the need for alternative or adjunct therapies that are safe, effective, and affordable.

Selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine, are widely prescribed for depression and anxiety but are associated with sexual dysfunction. Mechanistically, paroxetine disrupts hypothalamic--pituitary-- gonadal signaling, reduces testosterone, impairs spermatogenesis, and alters NO pathways (12,13). Clinical and preclinical studies confirm its negative impact on sperm quality, testicular architecture, and persistent sexual dysfunction even after discontinuation (14,15).

Mucuna pruriens (velvet bean) is a tropical legume traditionally employed for its neuroprotective, aphrodisiac, and fertility-enhancing properties. Its seeds contain bioactive compounds such as L-DOPA, flavonoids, tannins, alkaloids, saponins, and phenolics, conferring neuroprotective, antioxidant, and androgenic properties (16,17). Evidence indicates that M. pruriens improves semen quality, testosterone levels, and spermatogenesis in both animal models and infertile men (18,19). Its antioxidant activity protects against oxidative stress-induced testicular damage, while modulation of dopaminergic and steroidogenic pathways enhances sexual behaviour (20,21). Comparative studies of aphrodisiac herbal extracts highlight M. pruriens as a potent modulator of NF-kappaB/Nrf2 pathways, enhancing sexual function and reducing oxidative stress (22).

This study investigated the attenuating effects of Mucuna pruriens 70% ethanolic seed extract in paroxetine-induced male sexual dysfunction in Wistar rats, focusing on hormonal profiles, oxidative stress biomarkers, and histological changes in reproductive tissues.

MATERIALS AND METHODS

Plant material and extract preparation

Mucuna pruriens (L.) DC. seeds were collected from a certified herbal farm in Nigeria. The species identity was confirmed using morphological characteristics and standard taxonomic keys by a qualified taxonomist in the Department of Plant Biology, Faculty of Life Sciences, University of Ilorin, Nigeria. The nomenclature was verified against the World Flora Online database (World Flora Online, 2026: Mucuna pruriens (L.) DC. Available at: http://www.worldfloraonline.org/taxon/wfo-0000182545. Accessed 30 July 2026)

The seeds were cleaned, air-dried at room temperature, and pulverized into a fine powder using an electric grinder. The powdered material was extracted with 70% ethanol by cold maceration for 72 h with intermittent stirring. The extract was filtered through Whatman No. 1 filter paper and concentrated under reduced pressure using a rotary evaporator at 40°C to obtain a crude hydroethanolic extract. A voucher specimen was not deposited, and extraction yield was not recorded. The crude extract was transferred into airtight amber bottles and stored at 4°C until use. Before administration, the extract was

reconstituted in distilled water to the required concentrations for oral gavage.

Preliminary qualitative phytochemical screening confirmed the presence of alkaloids, flavonoids, tannins, saponins, phenolics, and L-DOPA using standard colorimetric methods (22). Although quantitative phytochemical standardization and L-DOPA content determination were not performed in the current study, the phytochemical profile of M. pruriens seeds is well-documented in the literature, with L-DOPA, flavonoids, and phenolics being the principal bioactive constituents (22). It has been reported to contain 1.79–7% L-DOPA by dry weight; thus, the administered doses of 200 and 400 mg/kg correspond to approximately 3.6–28 mg/kg L-DOPA, which is within the biologically active range in rodent models (23-24).

Experimental animals

Thirty adult male Wistar rats (10–12 weeks old, 200–250 g) were procured from the Animal House of the Faculty of Basic Medical Sciences, University of Ilorin. Animals were housed in standard polypropylene cages (2–3 rats per cage) under standard laboratory conditions (12 h light/dark cycle, temperature 22 ± 2°C, relative humidity 50–60%) with free access to standard rat chow and water ad libitum**.** Cage position was rotated weekly to minimize potential cage-specific environmental effects. They were acclimatized for 14 days prior to experimentation.

Sample size was determined based on prior rodent studies employing *Mucuna pruriens* and antidepressant treatment protocols, which demonstrated significant effects with 6–8 animals per group (27-30). A total of 30 rats **(**n = 6 per group**)** was used.

Experimental design

Rats were randomly allocated to five groups (n = 6) using a computer-generated random number sequence. Exclusion criteria included: (i) body weight loss >15% during acclimatization, (ii) signs of illness or abnormal behavior, and (iii) failure to display sexual behavior during the training sessions. No animals met the exclusion criteria, and there was no attrition during the study.

Group I (control) received distilled water by oral gavage. Group II received paroxetine hydrochloride (10 mg/kg/day, orally for 21 days; Sigma-Aldrich, St. Louis, MO, USA). Group III received paroxetine (10 mg/kg/day) plus sildenafil citrate (5 mg/kg/day, orally for 21 days; Pfizer Inc., New York, USA). Group IV received paroxetine (10 mg/kg/day) plus *M. pruriens* extract (200 mg/kg/day, orally for 21 days). Group V received paroxetine (10 mg/kg/day) plus *M. pruriens* extract (400 mg/kg/day, orally for 21 days). Blinding was not formally implemented in this study due to resource limitations. Investigators were aware of group allocation during behavioral assessments, histological evaluation, and data collection. This is acknowledged as a methodological limitation.

Assessment of sexual behavior

Male rats were trained once weekly in a 30-minute test with receptive females for 3 sessions to ensure sexual experience. Sexually active rats were selected for the experiment. Female rats were hormonally primed with estradiol benzoate (10 µg/100 g body weight, subcutaneously) 48 h and progesterone (0.5 mg/100 g body weight, subcutaneously) 4 h prior to testing to induce behavioral estrus. Receptivity was confirmed by the presence of lordosis upon gentle manual stimulation of the back and flanks.

Testing was conducted under dim light during the dark phase of the light cycle (19:00–22:00 h) in a plastic cage with fresh beddings. Female Rats were introduced to the cages of the males and their behaviours towards them therein observed.

This was video-recorded and stored offline by an investigator. Only mount latency (ML) and intromission frequency (IF) were assessed and reported in this study**.** Mount latency was defined as the time interval (seconds) from the introduction of the female into the cage until the first mount. Intromission frequency was defined as the total number of intromissions recorded during the 30-minute observation period. Sexual behavior was assessed on day 21 under controlled conditions (25). *T*he experimental timeline was as follows: Day 0 (baseline) body weight recording; Days 1–21 daily drug and extract administration; Day 21 final sexual behaviour assessment (30-minute observation period); Day 22 sacrifice and tissue collection for biochemical and histological analyses.

Sacrifice of Animals and tissue homogenization

Twenty-four hours after the last treatment, animals were weighed and anaesthetized with ketamine (80

mg/kg body weight, intraperitoneal). Blood was collected via cardiac puncture under deep anaesthesia. Animals were then euthanized by cervical dislocation. Testes and penis were immediately excised, weighed, and processed for biochemical analysis analyses.

Hormonal and oxidative stress biomarkers

Blood samples were collected via cardiac puncture under anaesthesia for hormonal analysis. Serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were quantified using ELISA kits (Cusabio Rat Testosterone ELISA Kit, Cat. No. CSB-E05100r; Elabscience Rat LH ELISA Kit, Cat. No. E-EL-R0392; Invitrogen Rat FSH ELISA Kit, Cat. No. EEL125).

For oxidative stress analyses, testicular and penile tissues were separately processed. Tissues were rinsed in ice-cold phosphate-buffered saline (PBS, pH 7.4), blotted dry, and weighed. Homogenization was performed in ice-cold PBS (1:10 w/v) using a mortar and pestle at 4°C. Homogenates were centrifuged at 10,000 × g for 15 min at 4°C, and the supernatants were collected for analysis. Protein concentration was determined using the Bradford protein assay (Bio-Rad) with bovine serum albumin as standard. All oxidative stress markers were assayed in duplicate according to the manufacturers' protocols.

Oxidative stress markers were assayed spectrophotometrically assayed in duplicates using commercial kits: superoxide dismutase (SOD; Abcam, ab65354), catalase (CAT; Elabscience, E-BC-K022), reduced glutathione (GSH; Sigma-Aldrich, CS0260), and malondialdehyde (MDA; Elabscience, E-BC-K025).

Determination of superoxide dismutase (SOD)

Superoxide dismutase (SOD) activity in tissue homogenates was assessed using a modified protocol based on the method of Christine and Joseph, 2009 (30).

Determination of catalase (CAT)

Catalase activity in tissue was assessed following the procedure of Hadwan et al., 2024 (31).

Determination of reduced glutathione (GSH)

The concentration of reduced glutathione (GSH) in tissue homogenates was quantified in accordance with the method utilized by Tipple and Rogers, 2012 (32).

Determination of MDA concentration

Lipid peroxidation in tissue homogenates was evaluated by quantifying thiobarbituric acid reactive substances (TBARS), following the method of Aguilar and Borges, 2020 with modifications (33).

Histological examination

Testicular and penile tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 micrometres, and stained with haematoxylin and eosin (H&E) following standard protocols (34). Morphometric analysis was not performed; therefore, only qualitative histological descriptions are presented.

Ethics approval

All animal experiments were approved by the Institutional Animal Care and Use Committee of the Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin (Ethical Approval No. DRERC/ANA/2026/193). The study was conducted in accordance with the ARRIVE guidelines 2.0 (35).

Statistical analysis

Data were analyzed using GraphPad Prism software (version 10.0.2; GraphPad Software Inc., San Diego, CA, USA). Normality was assessed using the Shapiro-Wilk test, and homogeneity of variance was evaluated using Brown-Forsythe and Bartlett's tests. All data met parametric assumptions. Data were analyzed by one-way ANOVA followed by Tukey's multiple comparison test. For count data (intromission frequency), parametric ANOVA was deemed appropriate as counts were sufficiently large and variance was homogeneous across groups. ANOVA statistics are reported as F(df_between, df_within) = F-value, p-value. Effect sizes are reported as partial eta-squared (ηp^2). Post-hoc p-values are adjusted for multiple comparisons. Data are presented as mean ± standard error of the mean (SEM) with individual data points overlaid on bar graphs. A p-value < 0.05 was considered statistically significant and is denoted as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ns = not significant.

RESULTS

Reproductive endocrine function

Testosterone.

Serum testosterone (Figure 1A) levels differed significantly across groups ($F(4,25) = 1401$, $p < 0.0001$, $\eta p^2 = 0.996$). Paroxetine significantly reduced testosterone compared to control (mean difference = 4.21 ng/mL lower, 95% CI: 4.02 to 4.40, $p < 0.0001$). Co-administration of low-dose *M. pruriens* significantly increased testosterone compared to paroxetine (mean difference = 2.60 ng/mL higher, 95% CI: 2.41 to 2.79, $p < 0.0001$), and high-dose *M. pruriens* produced an even greater increase (mean difference = 4.00 ng/mL higher, 95% CI: 3.81 to 4.19, $p < 0.0001$). Sildenafil also significantly improved testosterone compared to paroxetine (mean difference = 3.40 ng/mL higher, 95% CI: 3.21 to 3.59, $p < 0.0001$). Testosterone in the high-dose *M. pruriens* group remained slightly but significantly lower than control (mean difference = 0.21 ng/mL, 95% CI: 0.02 to 0.40, $p = 0.0242$). High-dose *M. pruriens* was significantly more effective than both sildenafil (mean difference = 0.60 ng/mL higher, 95% CI: 0.41 to 0.79, $p < 0.0001$) and low-dose *M. pruriens* (mean difference = 1.40 ng/mL higher, 95% CI: 1.21 to 1.59, $p < 0.0001$).

Luteinizing hormone (LH).

LH levels (Figure 1B) differed significantly across groups ($F(4,25) = 463.4$, $p < 0.0001$, $\eta p^2 = 0.987$). Paroxetine significantly reduced LH compared to control (mean difference = 2.40 IU/L, 95% CI: 2.21 to 2.59, $p < 0.0001$). Sildenafil significantly increased LH compared to paroxetine (mean difference = 1.90 IU/L, 95% CI: 1.71 to 2.09, $p < 0.0001$) but remained significantly lower than control (mean difference = 0.50 IU/L, 95% CI: 0.31 to 0.69, $p < 0.0001$). Low-dose *M. pruriens* also increased LH compared to paroxetine (mean difference = 1.70 IU/L, 95% CI: 1.51 to 1.89, $p < 0.0001$) and remained significantly lower than control (mean difference = 0.70 IU/L, 95% CI: 0.51 to 0.89, $p < 0.0001$). High-dose *M. pruriens* restored LH to levels comparable to control (mean difference = 0.10 IU/L, 95% CI: −0.09 to 0.29, $p = 0.5302$). High-dose *M. pruriens* was significantly more effective than both sildenafil (mean difference = 0.40 IU/L higher, 95% CI: 0.21 to 0.59, $p < 0.0001$) and low-dose *M. pruriens* (mean difference = 0.60 IU/L higher, 95% CI: 0.41 to 0.79, $p < 0.0001$).

Follicle-stimulating hormone (FSH).

FSH levels (Figure 1C) differed significantly across groups ($F(4,25) = 230.8$, $p < 0.0001$, $\eta p^2 = 0.974$). Paroxetine significantly reduced FSH compared to control (mean difference = 1.70 IU/L, 95% CI: 1.51 to 1.89, $p < 0.0001$). Sildenafil significantly increased FSH compared to paroxetine (mean difference = 1.40 IU/L, 95% CI: 1.21 to 1.59, $p < 0.0001$) but remained significantly lower than control (mean difference = 0.30 IU/L, 95% CI: 0.11 to 0.49, $p = 0.0007$). Low-dose *M. pruriens* also increased FSH compared to paroxetine (mean difference = 1.20 IU/L, 95% CI: 1.01 to 1.39, $p < 0.0001$) and remained significantly lower than control (mean difference = 0.50 IU/L, 95% CI: 0.31 to 0.69, $p < 0.0001$). High-dose *M. pruriens* restored FSH to levels comparable to control (mean difference = 0.10 IU/L, 95% CI: −0.09 to 0.29, $p = 0.5330$). High-dose *M. pruriens* was significantly more effective than both sildenafil (mean difference = 0.20 IU/L higher, 95% CI: 0.01 to 0.39, $p = 0.0326$) and low-dose *M. pruriens* (mean difference = 0.40 IU/L higher, 95% CI: 0.21 to 0.59, $p < 0.0001$).

Oxidative stress biomarkers

Superoxide dismutase (SOD).

SOD activity (Figure 2A) differed significantly across groups ($F(4,25) = 758.8$, $p < 0.0001$, $\eta p^2 = 0.992$). Paroxetine significantly reduced SOD compared to control (mean difference = 6.90 U/mg protein, 95% CI: 6.47 to 7.33, $p < 0.0001$). Sildenafil significantly increased SOD compared to paroxetine (mean difference = 5.60 U/mg protein, 95% CI: 5.18 to 6.03, $p < 0.0001$) but remained significantly lower than control (mean difference = 1.30 U/mg protein, 95% CI: 0.87 to 1.72, $p < 0.0001$). Low-dose *M. pruriens* also increased SOD compared to paroxetine (mean difference = 4.41 U/mg protein, 95% CI: 3.98 to 4.83, $p < 0.0001$) and remained significantly lower than control (mean difference = 2.50 U/mg protein, 95% CI: 2.07 to 2.92, $p < 0.0001$). High-dose *M. pruriens* restored SOD to levels statistically indistinguishable from control (mean difference = 0.19 U/mg protein, 95% CI: −0.23 to 0.62, $p = 0.6738$).

Malondialdehyde (MDA).
MDA levels (Figure 2B) differed significantly across groups ($F(4,25) = 1769$, $p < 0.0001$, $\eta p^2 = 0.997$). Paroxetine significantly increased MDA compared to control (mean difference = 3.52 nmol/mg protein, 95% CI: 3.38 to 3.66, $p < 0.0001$). Sildenafil significantly reduced MDA compared to paroxetine (mean difference = 3.03 nmol/mg protein, 95% CI: 2.89 to 3.17, $p < 0.0001$) but remained significantly elevated compared to control (mean difference = 0.49 nmol/mg protein, 95% CI: 0.35 to 0.63, $p < 0.0001$). Low-dose *M. pruriens* also reduced MDA compared to paroxetine (mean difference = 2.47 nmol/mg protein, 95% CI: 2.32 to 2.61, $p < 0.0001$) but remained significantly elevated compared to control (mean difference = 1.06 nmol/mg protein, 95% CI: 0.92 to 1.20, $p < 0.0001$). High-dose *M. pruriens* significantly reduced MDA compared to paroxetine (mean difference = 3.30 nmol/mg protein, 95% CI: 3.16 to 3.44, $p < 0.0001$); however, MDA levels remained significantly elevated compared to control (mean difference = 0.22 nmol/mg protein, 95% CI: 0.08 to 0.36, $p = 0.0009$).

Reduced glutathione (GSH).
GSH levels (Figure 2C) differed significantly across groups ($F(4,25) = 297.9$, $p < 0.0001$, $\eta p^2 = 0.979$). Paroxetine significantly reduced GSH compared to control (mean difference = 4.31 µmol/g tissue, 95% CI: 3.89 to 4.72, $p < 0.0001$). Sildenafil significantly increased GSH compared to paroxetine (mean difference = 3.40 µmol/g tissue, 95% CI: 2.99 to 3.82, $p < 0.0001$) but remained significantly lower than control (mean difference = 0.91 µmol/g tissue, 95% CI: 0.49 to 1.32, $p < 0.0001$). Low-dose *M. pruriens* also increased GSH compared to paroxetine (mean difference = 2.80 µmol/g tissue, 95% CI: 2.39 to 3.21, $p < 0.0001$) and remained significantly lower than control (mean difference = 1.51 µmol/g tissue, 95% CI: 1.09 to 1.92, $p < 0.0001$). High-dose *M. pruriens* restored GSH to levels comparable to control (mean difference = 0.31 µmol/g tissue, 95% CI: −0.11 to 0.72, $p = 0.2185$).

Catalase (CAT).
CAT activity (Figure 2D) differed significantly across groups ($F(4,25) = 1454$, $p < 0.0001$, $\eta p^2 = 0.996$). Paroxetine significantly reduced CAT compared to control (mean difference = 9.50 U/mg protein, 95% CI: 9.08 to 9.92, $p < 0.0001$). Sildenafil significantly increased CAT compared to paroxetine (mean difference = 7.60 U/mg protein, 95% CI: 7.18 to 8.02, $p < 0.0001$) but remained significantly lower than control (mean difference = 1.90 U/mg protein, 95% CI: 1.48 to 2.32, $p < 0.0001$). Low-dose *M. pruriens* also increased CAT compared to paroxetine (mean difference = 6.51 U/mg protein, 95% CI: 6.09 to 6.93, $p < 0.0001$) and remained significantly lower than control (mean difference = 2.99 U/mg protein, 95% CI: 2.57 to 3.41, $p < 0.0001$). High-dose *M. pruriens* significantly increased CAT compared to paroxetine (mean difference = 8.99 U/mg protein, 95% CI: 8.58 to 9.42, $p < 0.0001$); however, CAT activity remained significantly lower than control (mean difference = 0.50 U/mg protein, 95% CI: 0.08 to 0.92, $p = 0.013$).

Sexual behaviour

Mount latency (ML).
Mount latency (Figure 3A) differed significantly across groups ($F(4,25) = 1751$, $p < 0.0001$, $\eta p^2 = 0.996$). Paroxetine significantly increased ML compared to control (mean difference = 10.41 s, 95% CI: 9.98 to 10.85, $p < 0.0001$). Sildenafil significantly reduced ML compared to paroxetine (mean difference = 7.50 s, 95% CI: 7.07 to 7.93, $p < 0.0001$) but remained significantly elevated compared to control (mean difference = 2.92 s, 95% CI: 2.48 to 3.35, $p < 0.0001$). Low-dose *M. pruriens* also reduced ML compared to paroxetine (mean difference = 2.42 s, 95% CI: 1.98 to 2.85, $p < 0.0001$) but remained significantly elevated compared to control (mean difference = 8.00 s, 95% CI: 7.57 to 8.43, $p < 0.0001$). High-dose *M. pruriens* significantly reduced ML compared to paroxetine (mean difference = 8.42 s, 95% CI: 7.98 to 8.85, $p < 0.0001$); however, ML remained significantly elevated compared to control (mean difference = 2.00 s, 95% CI: 1.57 to 2.43, $p < 0.0001$). High-dose *M. pruriens* was significantly more effective than sildenafil (mean difference = 0.92 s lower, 95% CI: 0.48 to 1.35, $p < 0.0001$) and low-dose *M. pruriens* (mean difference = 6.00 s lower, 95% CI: 5.57 to 6.43, $p < 0.0001$).

Intromission frequency (IF).
Intromission frequency (Figure 3B) differed significantly across groups ($F(4,25) = 2967$, $p < 0.0001$, $\eta p^2 = 0.998$). Paroxetine significantly

reduced IF compared to control (mean difference = 11.80, 95% CI: 11.34 to 12.26, p < 0.0001). Sildenafil significantly increased IF compared to paroxetine (mean difference = 12.90, 95% CI: 12.44 to 13.36, p < 0.0001) and was significantly higher than control (mean difference = 1.10, 95% CI: 0.64 to 1.56, p < 0.0001). Low-dose *M. pruriens* also increased IF compared to paroxetine (mean difference = 12.40, 95% CI: 11.94 to 12.86, p < 0.0001) and was significantly higher than control (mean difference = 0.60, 95% CI: 0.14 to 1.06, p = 0.0063). High-dose *M. pruriens* produced the greatest increase compared to paroxetine (mean difference = 15.40, 95% CI: 14.94 to 15.86, p < 0.0001) and was significantly higher than control (mean difference = 3.60, 95% CI: 3.14 to 4.06, p < 0.0001). High-dose *M. pruriens* was significantly more effective than both sildenafil (mean difference = 2.50 higher, 95% CI: 2.04 to 2.96, p < 0.0001) and low-dose *M. pruriens* (mean difference = 3.00 higher, 95% CI: 2.54 to 3.46, p < 0.0001).

Histological evaluation of testicular cytoarchitecture

Histochemical analysis of the testis (Figure 4) using hematoxylin and eosin (H&E) staining revealed the impact of paroxetine and the protective roles of Mucuna pruriens and sildenafil.

In control animals, seminiferous tubules (ST) appeared well arranged in circular profiles with intact basement membranes (BM) and evident interstitial Leydig cells (LC). Spermatogenesis was clearly visible, with mature sperm cells (MS) populating the luminal spaces (LS) (Figure 5).

In M. pruriens treated groups, seminiferous tubules retained normal morphology, with increased interstitial space (IS) compared to controls (Figure 5). Leydig cells were present, and spermatogenesis showed various cell types. Staining intensity was lighter in the low dose group, while the high dose group exhibited stronger cytoarchitectural preservation, with pronounced basement membranes and clearer Sertoli cells. Tubules appeared finer and more organized, and and more coherent, marked by an increased presence of mature sperm cells in the lumens.

Paroxetine plus M. pruriens groups revealed degenerated seminiferous tubules, sloughing of the germinal epithelium, and reduced staining intensity. However, the high dose group showed significant recovery of tubule architecture, with improved luminal organization and reduced degeneration compared to paroxetine alone (Figure 5). Some lumens contained eosinophilic plaques with deeper staining intensity; however, overall tubule integrity was better preserved.

The paroxetine plus sildenafil group displayed moderate restoration, with reduced occlusion of lumens, improved Leydig cell presence, and clearer interstitial tissue compared to paroxetine alone.

In contrast, the paroxetine only group exhibited the most severe distortion: irregularly shaped seminiferous tubules, reduced interstitial space, paler staining intensity, blocked lumens, and broken basement membranes. Degeneration spots were observed in both seminiferous tubules and interstitium, along with focal areas of deep staining. Non occluded lumens appeared clear but lacked mature sperm cells, confirming impaired spermatogenesis (Figure 4).

DISCUSSION

The present study demonstrates that Mucuna pruriens 70% ethanolic seed extract effectively ameliorates paroxetine-induced male sexual dysfunction through hormonal, antioxidant, and histological mechanisms. Paroxetine, a selective serotonin reuptake inhibitor, is well documented to impair sexual function by reducing dopaminergic activity, suppressing testosterone synthesis, and disrupting nitric oxide (NO) signaling pathways (12,13).

In this model, these deleterious effects were evident in reduced sexual performance, hormonal imbalance, oxidative stress, and histological damage. Co-administration of M. pruriens attenuated these changes, indicating its potential to protect against paroxetine-associated reproductive dysfunction. The androgenic activity of M. pruriens was evident, as enhanced testosterone synthesis correlated with improved steroidogenesis.

High-dose extracts restored testosterone values close to control, consistent with previous studies showing that M. pruriens improves sperm quality and testosterone levels in infertile men (18,19), and with reports of its androgenic and anabolic potential in experimental models (36). The extract's L-DOPA

content may further contribute by enhancing dopaminergic transmission, stimulating gonadotropin-releasing hormone release, and supporting androgen production. Antioxidant effects were equally pronounced. Reduced malondialdehyde levels and increased superoxide dismutase, catalase, and glutathione activity highlight the extract's potent free radical scavenging properties. These protective effects are attributed to flavonoids and phenolic compounds, consistent with reports that M. pruriens combats oxidative stress in male reproductive tissues and restores spermatogenic function under conditions of reactive oxygen species overload (20,21,26).

Histological recovery corroborated these biochemical findings, with restoration of seminiferous tubule integrity. Similar improvements have been reported in aged rat models and in fluoxetine-treated animals following M. pruriens supplementation (27,28). It should be acknowledged that the behavioural parameters assessed in this study (mount latency and intromission frequency) primarily reflect sexual motivation and copulatory behaviour rather than erectile function per se(35). Direct measurements of erectile haemodynamics, such as intracavernosal pressure or penile tumescence, were not performed. Therefore, this study is more accurately characterized as an investigation of paroxetine-induced male sexual dysfunction, encompassing behavioural, hormonal, antioxidant, and histological dimensions, rather than erectile dysfunction specifically. It is important to note that this study employed a concurrent administration design, wherein paroxetine and M. pruriens were administered simultaneously for 21 days.

Therefore, the observed effects represent attenuation or prevention of paroxetine-induced changes rather than reversal of established dysfunction. Future studies should evaluate the therapeutic potential of M. pruriens in a treatment-of-established-dysfunction paradigm, wherein the extract is administered after a defined period of paroxetine exposure, and should incorporate direct erectile function assessments to substantiate claims regarding erectile performance (37-40).

Taken together, these results confirm that M. pruriens exerts multifaceted effects, integrating hormonal stimulation and oxidative protection. This validates its traditional aphrodisiac use and highlights its potential for further investigation as a safe phytotherapeutic adjunct for SSRI-induced male sexual dysfunction.

Study limitations

This study has several limitations that should be acknowledged. The sample size was small (n = 6 per group), which limits statistical power and generalizability. A crude, non-standardized 70% ethanolic extract was used; the specific contributions of individual bioactive compounds (including L-DOPA) to the observed effects remain unknown. Similarly, the concurrent administration design employed herein represents attenuation or prevention of paroxetine-induced changes rather than reversal of established dysfunction. No toxicity assessment or dose-ranging study was performed to establish the safety margin of the extract and direct measurements of erectile haemodynamics (e.g., intracavernosal pressure, penile tumescence) were not performed; the behavioural parameters assessed (mount latency and intromission frequency) primarily reflect sexual motivation and copulatory behaviour rather than erectile function. The study was limited to a single sex (male) and species (rat), restricting extrapolation to human clinical populations with the 21-day treatment duration being relatively short therefore longer-term effects remain unknown. These findings should therefore be interpreted as preliminary evidence of attenuation of selected behavioural, biochemical, and histological changes in male rats, rather than definitive proof of efficacy against erectile dysfunction. Future studies should isolate active constituents, explore long-term safety, and evaluate efficacy in human trials.

Conclusion

This study demonstrates that co-administration of *Mucuna pruriens* 70% ethanolic seed extract attenuates selected behavioural, biochemical, and histological changes associated with paroxetine-induced male sexual dysfunction in Wistar rats. The observed improvements in sexual behaviour, hormonal profiles, and antioxidant enzyme activity, alongside histological preservation, provide preliminary preclinical evidence supporting the ethnomedicinal use of this plant. However, these findings are limited by the small sample size, crude extract formulation, concurrent treatment design,

absence of toxicity data, and lack of direct erectile haemodynamic measurements. Further studies employing standardized extracts, larger sample sizes, therapeutic treatment paradigms, direct erectile function assessments, and toxicity evaluations are required before any clinical recommendations can be made.

Data availability

The research documents supporting the findings of this study are available from the corresponding author upon reasonable request.

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TABLES AND FIGURES

Tables

Table 1: SUMMARY OF SEX HORMONES PARAMETERS ACROSS GROUPS

Animal Group	Testosterone (ng/mL)	LH (IU/L)	FSH (IU/L)
Control (distilled water)	6.80 ± 0.049	4.50 ± 0.045	3.20 ± 0.045
Paroxetine Only	2.60 ± 0.046 ****	2.10 ± 0.046****	1.50 ± 0.046 ****
Paroxetine + Sildenafil	6.00 ± 0.044 ****	4.00 ± 0.045****	2.90 ± 0.045 ***
Paroxetine + *M. pruriens* Low	5.20 ± 0.044 ****	3.80 ± 0.044****	2.70 ± 0.046 ****
Paroxetine + *M. pruriens* High	6.60 ± 0.044*	4.40 ± 0.045 ns	3.10 ± 0.045 ns

Table 2: SUMMARY OF OXIDATIVE STRESS MARKERS ACROSS GROUPS

Animal Group	SOD (U/mg protein)	MDA (nmol/mg protein)	GSH (µmol/g tissue)	CAT (U/mg protein)
Control	15.10 ± 0.101	2.00 ± 0.026	8.40 ± 0.100	20.10 ± 0.100
Paroxetine Only	8.20 ± 0.101 ****	5.52 ± 0.055****	4.10 ± 0.100****	10.60 ± 0.100****
Paroxetine + Sildenafil	13.80 ± 0.104 ****	2.50 ± 0.027 ***	7.50 ± 0.100****	18.20 ± 0.101****
Paroxetine + *M. pruriens* Low	12.60 ± 0.104 ****	3.06 ± 0.026****	6.90 ± 0.100****	17.11 ± 0.100****
Paroxetine + *M. pruriens* High	14.91 ± 0.104 ns	2.22 ± 0.026 ns	8.10 ± 0.100ns	19.60 ± 0.101 *

Table 3: SUMMARY OF BEHAVIORAL PARAMETERS ACROSS GROUPS

Table 3: Summary of behavioral parameters across groups. Values represent mean ± SEM (n = 6 per group). Only mount latency and intromission frequency were assessed. Statistical significance determined by one-way ANOVA followed by Tukey's post hoc test. * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$.

Animal Group	Mount Latency (s)	Intromission Frequency
Control	12.10 ± 0.10	16.52 ± 0.11
Paroxetine Only	22.52 ± 0.11 ****	4.72 ± 0.11 ****
Paroxetine + Sildenafil	15.02 ± 0.11 ****	17.62 ± 0.11 ****
Paroxetine + *M. pruriens* Low	20.10 ± 0.10 ****	17.12 ± 0.11 **
Paroxetine + *M. pruriens* High	14.10 ± 0.10 ****	20.12 ± 0.11 ****

Figures

Figure 1: Serum hormonal profiles across experimental groups. (A) Testosterone, (B) luteinizing hormone (LH), and (C) follicle-stimulating hormone (FSH). Values represent mean ± SEM (n = 6). Individual data points are displayed as aligned dot plots. Statistical comparisons between groups are indicated by brackets: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

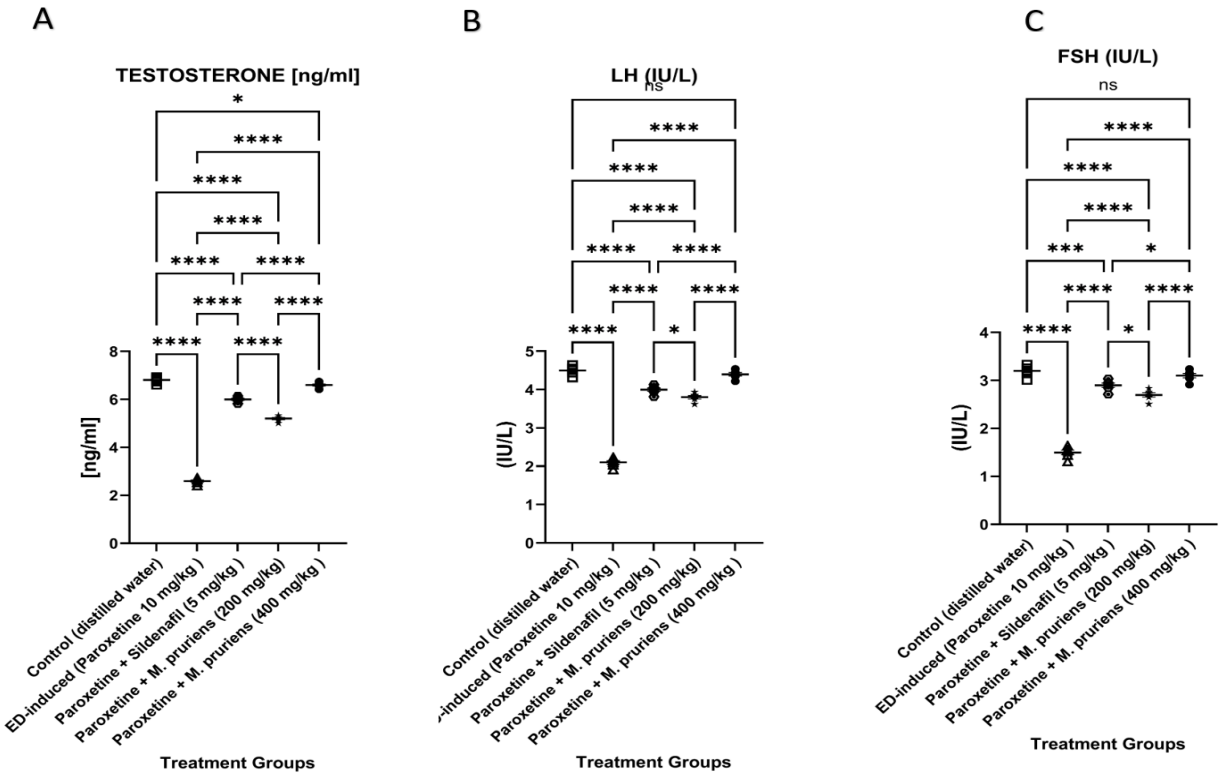

Figure 2: Oxidative stress biomarkers in testicular and penile tissues. (A) SOD, (B) MDA, (C) GSH, (D) CAT. Values represent mean ± SEM (n = 6). Individual data points are displayed as aligned dot plots. Statistical comparisons between groups are indicated by brackets: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

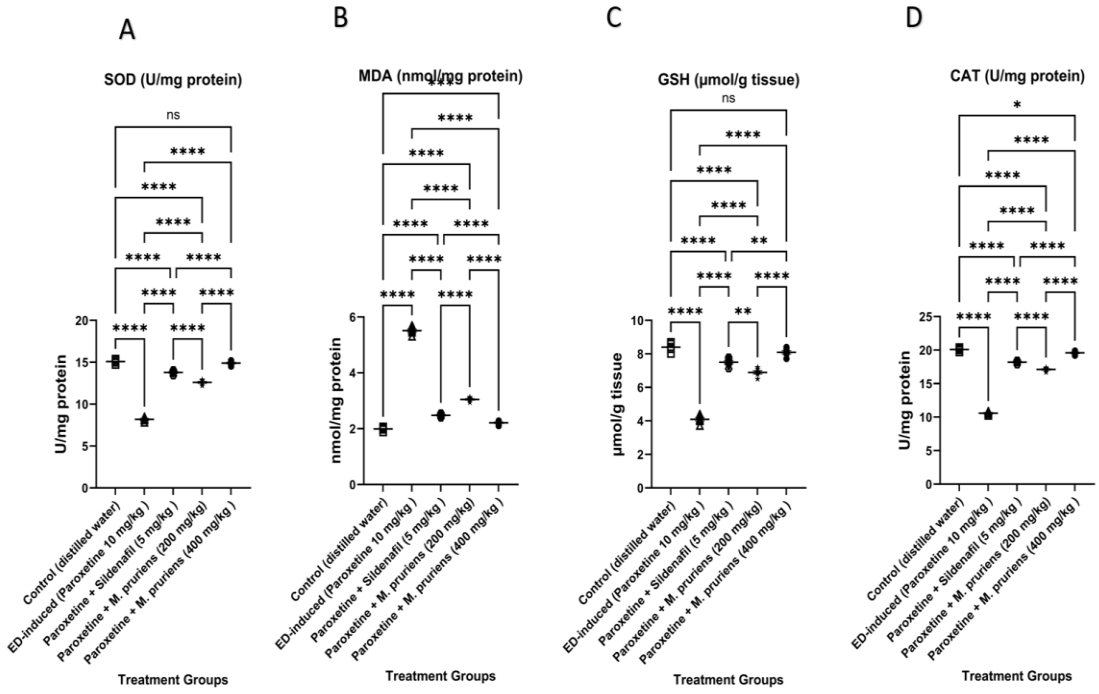

Figure 3: Sexual behaviour parameters on day 21. (A) Mount latency and (B) intromission frequency. Values represent mean ± SEM (n = 6). Individual data points are displayed as aligned dot plots. Statistical comparisons between groups are indicated by brackets: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

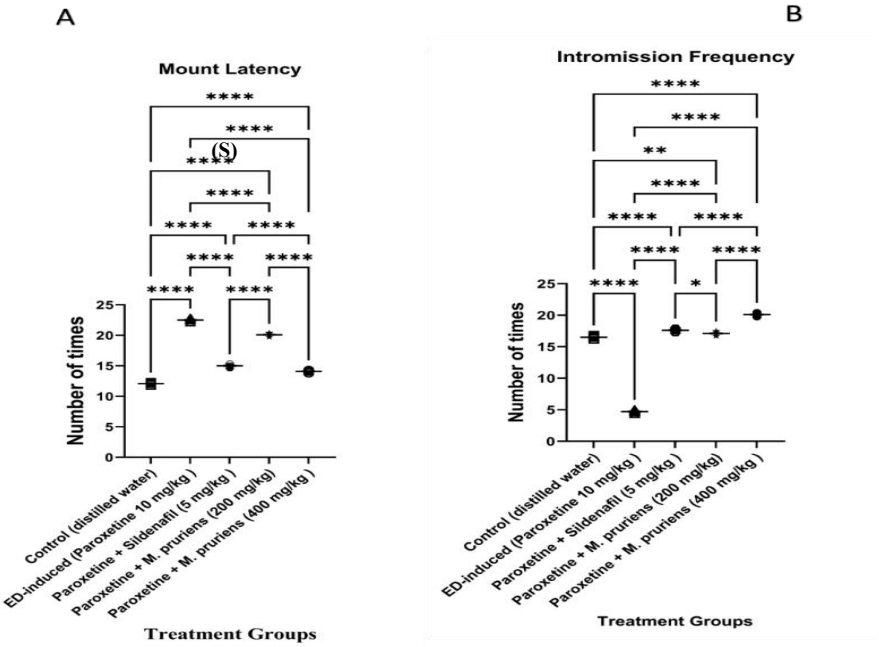

Figure 4: Representative photomicrographs of seminiferous tubules at 400× magnification across experimental groups. Scale bar = 50 µm across all p