



ETHANOL EXTRACT OF *LEPIDIUM MEYENII* INHIBITS PHOSPHODIESTERASE-5 ACTIVITY AND AMELIORATES BIOCHEMICAL ALTERATIONS IN PAROXETINE-INDUCED ERECTILE DYSFUNCTION IN RATS

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ABSTRACT

Phosphodiesterase-5 (PDE-5) plays a crucial role in erectile function by regulating the degradation of cyclic guanosine monophosphate, and its overactivity is associated with erectile dysfunction (ED). ED, dyslipidemia, and cardiovascular diseases are interrelated conditions that frequently coexist in affected individuals. One plant that has been traditionally linked to ED management is *Lepidium meyenii*. Despite numerous claims of its efficacy, its inhibitory potential against PDE-5 and capacity to manage dyslipidemia—often present in ED and a precursor to cardiovascular diseases—remain unclear. In this study, the effect of ethanol extract of *Lepidium meyenii* roots on penile and cardiac PDE-5 activities, nitric oxide levels, testosterone concentration, and lipid profile was evaluated. ED was induced in rats by oral administration of paroxetine (10 mg/kg body weight) for 21 days prior to treatment with the plant extract. Forty-eight adult male rats were randomly assigned to six experimental groups: normal control; paroxetine (10 mg/kg); paroxetine + sildenafil (4 mg/kg); and paroxetine + *Lepidium meyenii* (25, 50, and 100 mg/kg). Treatment lasted for seven days following confirmation of ED, and relevant biochemical assays were conducted. The ethanol extract of *Lepidium meyenii* roots significantly inhibited penile and cardiac PDE-5 activities, elevated nitric oxide and testosterone concentrations, reduced cholesterol and triacylglycerol levels, and increased high-density lipoprotein concentrations. These results suggest that the ethanol extract of *Lepidium meyenii* roots may be effective in managing ED through PDE-5 inhibition and improvement of dyslipidemia, a key contributor to cardiovascular risk.

Keywords: Erectile dysfunction, *Lepidium meyenii*, phosphodiesterase-5 inhibition, lipid profile

INTRODUCTION

Erectile dysfunction (ED) and dyslipidemia frequently coexist and are both significant risk factors for cardiovascular diseases (Nehra, 2009), sharing endothelial dysfunction as a common underlying mechanism (Wang and He,

2024). Endothelial dysfunction arises due to the disruption of endothelium-dependent relaxation in the smooth muscle cells of the corpus cavernosum, primarily caused by hypercholesterolemia, which serves as a crucial link between dyslipidemia and erectile

dysfunction (Mei, 2024). This impairment reduces penile relaxation during erection and decreases nitric oxide (NO) production, further complicating erectile function (Borges, 2024; Wang and He, 2024). Atherosclerotic lesions, which impair vasodilation, can block cavernosal arteries, leading to structural vascular ED (Borges, 2024).

Two primary strategies for managing ED and associated cardiovascular conditions include inhibiting phosphodiesterase type 5 (PDE5) activity and enhancing nitric oxide bioavailability. PDE5 inhibition promotes the cyclic guanosine monophosphate (cGMP)-signaling pathway, which is essential for smooth muscle relaxation in the corpus cavernosum, resulting in increased blood flow and penile erection (Paronetto and Crescioli, 2023). Similarly, in vascular smooth muscle cells, cGMP-signaling reduces muscle contraction, leading to vessel relaxation and decreased blood pressure (Soulaïdopoulos *et al.*, 2023). Nitric oxide is essential for activating guanylyl cyclase, which catalyzes the conversion of GTP to cGMP, thereby maintaining the cGMP-signaling pathway, promoting penile erection, and lowering blood pressure (Bhadar and Shah, 2024).

Medicinal plants have long served as a valuable source of bioactive compounds used in the management of various diseases, including erectile dysfunction (ED), due to their therapeutic efficacy, cultural acceptance, and minimal side effects compared to synthetic drugs (Masuku *et al.*, 2020). One promising plant for the management of ED is *Lepidium meyenii* (maca),

which has been traditionally and experimentally recognized for treating male impotence and hormonal imbalances (Zhang *et al.*, 2019; Ergun, 2024). However, its potential to inhibit enzymes like PDE5 or to address biochemical changes linked to cardiovascular diseases in ED remains unexplored (Kyarimpa *et al.*, 2023). Consequently, this study aims to investigate the inhibitory potential of ethanol extract of *L. meyenii* root on PDE5 activity and evaluate its ability to correct biochemical alterations associated with ED, using paroxetine-induced erectile dysfunction in rats as a model.

2.0 MATERIALS AND METHODS

2.1 Materials

2.1.1 Plant Material and Reagent

Lepidium meyenii root was purchased from an herb seller at Oje market, Ibadan, Oyo state, Nigeria. It was identified at the Herbarium unit of the Department of Plant Biology, Faculty of Life Sciences, University of Ilorin, where an identification number UILH/001/1352 was given. Analytically graded chemicals and reagents were used without further purification. Sildenafil citrate was product of Pfizer, New York., Trizma base, *Crotalux atrox* venom and cyclic guanosine monophosphate (cGMP) were product of Sigma Aldrich Chemicals, St. Louis, United State of America., and paroxetine hydrochloride was a product of Glaxo Smith Klein (GSK), Brasov, Romania.

2.1.2 Experimental Animals

Forty-eight (48) healthy and sexually matured male Wistar rats (*Rattus norvegicus*) with an average weight of 145g were obtained from the Animal holding unit, Department of Biochemistry, University of Ilorin, Ilorin, Nigeria.

2.2 Methods

2.2.1 Sample Preparation

Roots of *Lepidium meyenii* were peeled, washed and cut into small pieces. The sliced *Lepidium meyenii* was oven dried at 40 °C to remove moisture and then pulverized using mechanical blender. Three hundred grams (300 g) of powder *Lepidium meyenii* was extracted in 500 ml of ethanol for 48 hours at 25 °C with intermittent stirring. The extract was sieved and filtered using Whatman filter paper. The filtrate obtained was then concentrated in water bath at 40 °C which yielded a yellowish sticky residue and the residue was weighed to be 42 g extract corresponding to a percentage yield of 2.33 %.

2.2.2 Induction of Erectile and Endothelial Dysfunction

Forty male rats were induced with erectile dysfunction by oral administration of 10 mg/kg of paroxetine suspension which was prepared daily in Tween-80, suspended in 9 g/L saline solution for twenty-one days using an oropharyngeal cannula (Chan *et al.*, 2010; Malviya *et al.*, 2011; Yakubu and Nurudeen, 2012). Erectile dysfunction was confirmed with nitric oxide depletion and elevated levels of

phosphodiesterases-5 in the tissues after twenty-one days.

2.2.3 Animal Grouping and Extract Administration

Forty erectile dysfunction rats were completely randomized into five groups (B-F) of eight rats in each group. The rats in group A (Normal Control) were given daily 0.75 ml physiological saline solution for seven days. Group B (Negative Control) were erectile dysfunction-induced and received 0.75 ml physiological saline solution for seven days; group C (Positive Control) were erectile dysfunction-induced and received 4 mg/kg body weight of sildenafil citrate for seven days; group D (Treatment Group) were erectile dysfunction-induced and received 25 mg/kg body weight of ethanol extract of *Lepidium meyenii* roots for seven days; group E (Treatment Group) were erectile dysfunction-induced and received 50 mg/kg body weight of ethanol extract of *Lepidium meyenii* roots for seven days and group F (Treatment Group) were erectile dysfunction-induced and received 100 mg/kg body weight of ethanol extract of *Lepidium meyenii* roots for seven days.

2.2.4 Blood and Tissue Preparation

After seven days of treatment, the rats were weighed and sacrificed under diethyl ether anesthesia, and the blood samples were collected into dry plain sample bottles using jugular veins puncture on both sides of the neck (Akanji and Ngaha, 1989). After blood collection, the rats were dissected and the organ of interest (cardiac

and penile) were excised, cleaned of superficial fatty layer, weighed and then transferred into 0.25 M sucrose solution. These were later blotted with tissue paper, cut very thinly with sterile razor blade and homogenized in ice-cold 0.25 M sucrose solution (1:5 w/v). The homogenates were further centrifuged to obtain the supernatant, which was then carefully collected into sample bottle and stored in a freezer (-4°C) until later used for the desired biochemical assays.

2.2.5 Determination of Organ-body Weight Ratio

Prior to sacrifice, each rat was individually weighed. Under light ether anesthesia, the animals were quickly dissected, and the target organs—the penis and heart—were excised. These organs were carefully cleared of any superficial fat, reweighed, and then placed in a 0.25 M sucrose solution. The organ-to-body weight ratio was calculated by dividing the weight of each organ by the corresponding body weight of the rat.

2.2.6 Determination of Phosphodiesterases-5 Activity

The method of Butcher and Sutherland (1962) was used for the determination of phosphodiesterase-5 activity. Briefly, the supernatant, prepared from the tissue homogenates (cardiac and penile), containing the enzyme was suspended in a reaction mixture containing 0.36 μ mole of cGMP, 1.8 μ moles of $MgSO_4$, and 36 μ moles of Tris buffer, pH 7.5. This mixture was then incubated at 37 °C for 30 minutes. After the first 20 minutes of the incubation, 0.1 ml of a *Crotalux atrox* venom

solution was added containing 0.1 mg of venom in 1×10^{-2} M Tris, pH 7.5. The entire reaction was terminated by the addition of 0.1 ml of ice-cold 55% trichloroacetic acid. After addition of trichloroacetic acid, the solution was centrifuged at 2000 g for 10 minutes, the precipitate was removed, and 500 μ l of the supernatant fluids were analyzed for inorganic phosphate.

2.2.6.1 Determination of Inorganic Phosphate Release

Inorganic phosphate was determined using the method of Fiske and Subarrow (1925) as modified by Butcher and Sutherland (1962). Exactly 0.5 ml of the supernatant solution was taken and 0.5 ml of distilled water was added in a cuvette. The colour was developed by the addition of 1 ml of reagent containing 9% ascorbic acid and ammonium molybdate solution in ratio 4:1 which was prepared just before use and read at 820 nm on a spectrophotometer. The amount of inorganic phosphate released per unit time was extrapolated from the calibration curve for inorganic phosphate.

2.2.7 Measurement of Nitric Oxide Concentration

The nitric oxide concentration in penile tissue was determined using the Griess reagent following the method of Green *et al.* (1982). Briefly, penile tissue homogenate was deproteinised by treating 500 μ l of appropriately diluted homogenate with 100 μ l of 5% $ZnSO_4$ and 100 μ l of 0.3 M NaOH. The reaction mixture was then centrifuged at 4000 g for 20 minutes. Thereafter, 100 μ l of the supernatant was treated

with 1000 µl of Griess reagent and the absorbance was read at 540 nm. Griess reagent was used as the blank. The nitrite concentration was determined using calibration curve for sodium nitrite.

2.2.8 Measurement of Testosterone Concentration

The serum testosterone concentration was quantitatively determined using the direct human testosterone enzyme immunoassay (EIA) kit described by Tietz (1995). Briefly, 10.0 µl each of standards, samples and controls were dispensed into appropriate wells. 50 µl of testosterone-HRP conjugate reagent and 50 µl of rabbit anti-testosterone were dispensed into all the wells. This was then mixed for 30 seconds after which it was incubated at 37 °C for 1 hour. The microwells were rinsed and flicked 5 times with distilled water. 350 µl of 3, 3', 5, 5' tetramethylbenzidine (TMB) reagent (a surfactant) was dispensed into each well, gently mixed for 5 seconds and incubated at room temperature for 15 minutes. The reaction was stopped by adding 50 µl of 1N HCl to each well and then gently mixed for 20 seconds. The resultant yellow colour solution formed from blue colour was read at 405 nm with a microtitre plate reader within 15 minutes.

2.2.9 Measurement of Triglyceride Concentration

Triglyceride concentration in the serum were determined as described by Searcy (1969). Exactly 1.0 ml of the reconstituted reagents was pipetted into three test tubes labelled blank, standard and sample. Then 0.01ml each of the

standard solution and appropriately diluted serum sample was pipetted into test tubes labelled standard and sample respectively. The contents of the tubes were mixed and incubated at 25 °C for 10 minutes. The absorbance of the standard and sample was determined at 500 nm against the reagent blank. The concentration of triacylglycerol in the sample was determined by multiplying the absorbance of the sample by the concentration of the standard (192 mg/dL), and then dividing the result by the absorbance of the standard.

2.2.10 Measurement of Cholesterol Concentration

The total cholesterol concentration was determined by colorimetric method as described by Fredrickson *et al.* (1967). Three test tubes were set and labelled blank, sample and standard. Then, 1.0 ml of the working reagent was pipetted into the three test tubes after which 0.01ml of distilled water, appropriately diluted plasma and standard solution was respectively added into the blank, sample and standard test tubes. The resulting solution in each test tube was properly mixed and incubated at 37 °C for 5 minutes. The absorbance of the sample was read against the reagent blank at 500 nm. The concentration of cholesterol in the sample was calculated by multiplying the absorbance of the sample by the concentration of the standard (208 mg/dL), and then dividing by the absorbance of the standard.

2.2.11 Measurement of High-density Lipoprotein Cholesterol Concentration

High-density lipoprotein (HDL)-Cholesterol was determined by a colorimetric

method described by Burstein and Mortin (1969). 1.0 ml of phosphotungstic acid in the presence of magnesium ions (precipitating agent) was added to 0.5ml of serum in a test tube, mixed and left for 10 minutes at room temperature. The mixture was then centrifuged at 4000 rpm for 10 minutes to obtain the supernatant. After, 0.1 ml each of distilled water, supernatant and standard solutions were added to test tubes labelled blank, sample and standard, respectively. 1.0 ml of the cholesterol reagent was added into the three tubes. The contents were thoroughly mixed and incubated for 5 minutes at 37 °C. The absorbance of the sample and standard was read at 500 nm against the reagent blank. The concentration of HDL-cholesterol in the sample was calculated by multiplying the absorbance of the sample by the concentration of the standard (0.433 mg/dL), and then dividing by the absorbance of the standard.

Statistical Analysis

All data were presented as the mean of six determinations $\pm$ standard error of mean (S.E.M.). Statistical evaluation was done by one-way analysis of variance (ANOVA), followed by Duncan's posthoc test for multiple comparisons using Graphpad prism 5. Values were considered statistically significant at $p < 0.05$.

3.0 RESULTS

3.1 Effect of the Ethanol Extract of *Lepidium meyenii* on Organ/Tissue-body Weight Ratio of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *lepidium meyenii* root on the organ/tissue-body weight ratio

of paroxetine-induced erectile dysfunction rats is shown in Table 1. The separate administration of the extract at all the doses considered and the standard drug sildenafil did not significantly alter ($p > 0.05$) the penile and cardiac organ/tissue-body weight ratio of erectile dysfunction rats. Also, paroxetine-induced erectile dysfunction in rats did not significantly alter the penile and cardiac organ/tissue-body weight ratio within the experimental period considered.

Table 1: Effect of ethanol extract of *Lepidium meyenii* roots on organ/tissue-body ratio of paroxetine-induced erectile dysfunction rats

Groups	Organ-body weight ratio	
	Penile	Heart
Control	0.238 $\pm$ 0.01 ^a	0.292 $\pm$ 0.01 ^a
Paroxetine	0.252 $\pm$ 0.02 ^a	0.274 $\pm$ 0.01 ^a
Paroxetine + Sildenafil Citrate	0.219 $\pm$ 0.01 ^a	0.297 $\pm$ 0.01 ^a
Paroxetine + 25 mg/kg body weight of <i>L. meyenii</i>	0.258 $\pm$ 0.01 ^a	0.291 $\pm$ 0.01 ^a
Paroxetine + 50 mg/kg body weight of <i>L. meyenii</i>	0.277 $\pm$ 0.02 ^a	0.289 $\pm$ 0.01 ^a
Paroxetine + 100 mg/kg body weight of <i>L. meyenii</i>	0.239 $\pm$ 0.01 ^a	0.310 $\pm$ 0.03 ^a

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Values on the same column followed by the same letters do not differ significantly ($p < 0.05$)

3.2 Effect of the Ethanol Extract of *Lepidium meyenii* on the specific activity of penile Phosphodiesterase-5 of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *Lepidium meyenii* roots on the specific activity of penile PDE-5 of paroxetine-induced erectile dysfunction rats is shown in Figure 1. The separate administration of the extract at all the doses considered and the standard drug sildenafil

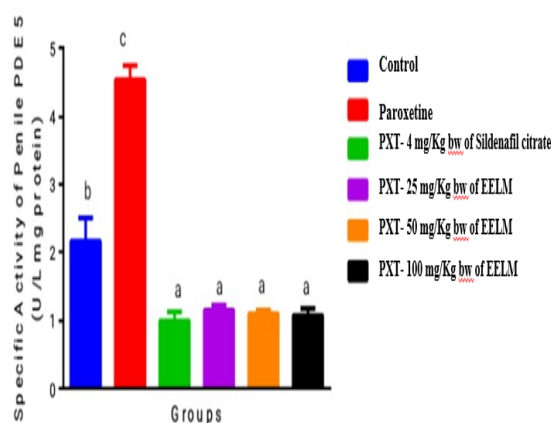


Figure 1: Effect of ethanol extract of *Lepidium meyenii* roots on specific activity of penile Phosphodiesterase-5 on paroxetine-induced erectile dysfunction rats

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Bars at the different groups with different letters are significantly different at $p < 0.05$.

Control = received normal saline for 21 days and distilled water for the next 7 days
 Paroxetine = received paroxetine for 21 days and distilled water for the next 7 days
 PXT- 4 mg/Kg bw of Sildenafil Citrate = received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days
 PXT- 25 mg/Kg bw EELM = received paroxetine for 21 days and 25 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 50 mg/Kg bw of EELM = received paroxetine for 21 days and 50 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 100 mg/Kg bw of EELM = received paroxetine for 21 days and 100 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

Significantly inhibited ($p > 0.05$) the specific activity of penile PDE-5 when compared to the control. In contrast, paroxetine significantly increased ($p > 0.05$) the specific activity of penile PDE-5 when compared to the control.

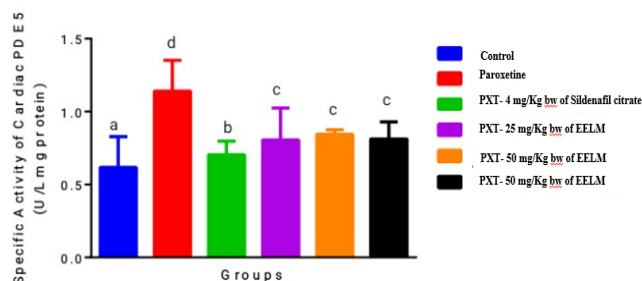


Figure 2: Effect of ethanol extract of *Lepidium meyenii* roots on specific activity of cardiac Phosphodiesterase-5 on paroxetine-induced erectile dysfunction rats

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Bars at the different groups with different letters are significantly different at $p < 0.05$

Control = received normal saline for 21 days and distilled water for the next 7 days
 Paroxetine = received paroxetine for 21 days and distilled water for the next 7 days
 PXT- 4 mg/Kg bw of Sildenafil Citrate = received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days
 PXT- 25 mg/Kg bw EELM = received paroxetine for 21 days and 25 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 50 mg/Kg bw of EELM = received paroxetine for 21 days and 50 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 100 mg/Kg bw of EELM = received paroxetine for 21 days and 100 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

3.3 Effect of the Ethanol Extract of *Lepidium meyenii* on the Specific Activity of Cardiac Phosphodiesterase-5 of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *Lepidium meyenii* roots on the specific activity of cardiac PDE-5 of paroxetine-induced erectile dysfunction

rats is shown in Figure 2. The separate administration of the standard drug sildenafil and the extract at all the doses considered significantly reduced ($p > 0.05$) the specific activity of cardiac PDE-5 when compared to the control. However, the ability of sildenafil to inhibit the specific activity of cardiac PDE-5 surpassed that of the extract at all the doses considered. In contrast, paroxetine significantly increased ($p > 0.05$) the specific activity of cardiac PDE-5 when compared to the control.

3.4 Effect of the Ethanol Extract of *Lepidium meyenii* on the Penile Nitric Oxide Concentration of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *Lepidium meyenii* roots on the penile nitric oxide concentration of paroxetine-induced erectile dysfunction rats is shown in Figure 3. The separate administration of 50 and 100 mg/kg body weight of the extract significantly increased ($p > 0.05$) the penile nitric oxide concentration than 25 mg/kg body weight of the extract.

3.5 Effect of the Ethanol Extract of *Lepidium meyenii* on the Serum Testosterone Concentration of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *Lepidium meyenii* roots on the serum testosterone concentration of paroxetine-induced erectile dysfunction rats is shown in Figure 4. The separate administration of the extract and the standard drug sildenafil significantly increased ($p > 0.05$) the testosterone concentration. The increment observed with the administration of the extract was concentration dependent (25 – 100

mg/kg body weight); however, the concentrations observed with the administration of the extract and the standard drug were no match to that of the control. In contrast, paroxetine significantly reduced ($p > 0.05$) the serum testosterone concentration when compared to the control.

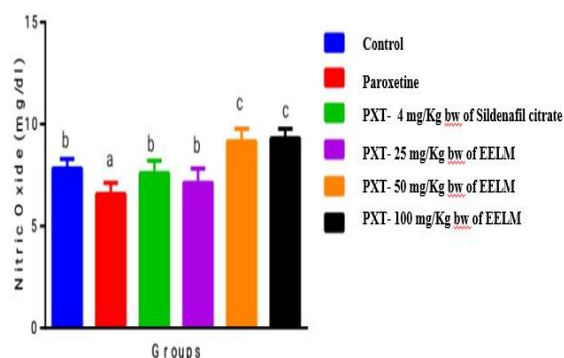


Figure 3: Effect of ethanol extract of *Lepidium meyenii* roots on the penile nitric oxide level of paroxetine-induced erectile dysfunction rats

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Bars at the different groups with different letters are significantly different at $p < 0.05$

Control = received normal saline for 21 days and distilled water for the next 7 days
 Paroxetine = received paroxetine for 21 days and distilled water for the next 7 days
 PXT- 4 mg/Kg bw of Sildenafil Citrate = received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days
 PXT- 25 mg/Kg bw EELM = received paroxetine for 21 days and 25 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 50 mg/Kg bw of EELM = received paroxetine for 21 days and 50 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 100 mg/Kg bw of EELM = received paroxetine for 21 days and 100 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

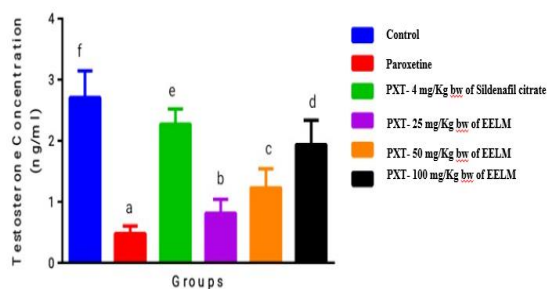


Figure 4: Effect of ethanol extract of *Lepidium meyenii* roots on the serum testosterone concentration of paroxetine-induced erectile dysfunction rats

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Bars at the different groups with different letters are significantly different at $p < 0.05$.

Control = received normal saline for 21 days and distilled water for the next 7 days

Paroxetine = received paroxetine for 21 days and distilled water for the next 7 days

PXT- 4 mg/Kg bw of Sildenafil Citrate = received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days

PXT- 25 mg/Kg bw EELM = received paroxetine for 21 days and 25 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

PXT- 50 mg/Kg bw of EELM = received paroxetine for 21 days and 50 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

PXT- 100 mg/Kg bw of EELM = received paroxetine for 21 days and 100 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

3.6 Effect of the Extract on the Serum Triacylglycerol Concentration of Paroxetine-induced Erectile Dysfunction Rats of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *Lepidium meyenii* roots on the serum triacylglycerol concentration of paroxetine-induced erectile dysfunction rats is shown in Figure 5. The separate administration of the extract and the standard drug sildenafil significantly reduced ($p >$

0.05) the triglyceride concentration. The reduction observed with the administration of the extract was concentration dependent (25 – 100 mg/kg body weight). The separate administration of the standard drug sildenafil and 100 mg/kg body weight of the extract restored the triglyceride concentration to the concentration of the control. In contrast, paroxetine significantly increases ($p > 0.05$) the serum triglyceride concentration when compared to the control.

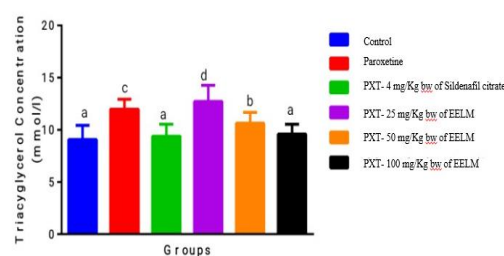


Figure 5: Effect of ethanol extract of *Lepidium meyenii* roots on the serum triacylglycerol concentration of paroxetine-induced erectile dysfunction rats

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Bars at the different groups with different letters are significantly different at $p < 0.05$

Control = received normal saline for 21 days and distilled water for the next 7 days

Paroxetine = received paroxetine for 21 days and distilled water for the next 7 days

PXT- 4 mg/Kg bw of Sildenafil Citrate = received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days

PXT- 25 mg/Kg bw EELM = received paroxetine for 21 days and 25 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

PXT- 50 mg/Kg bw of EELM = received paroxetine for 21 days and 50 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

PXT- 100 mg/Kg bw of EELM = received paroxetine for 21 days and 100 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

3.7 Effect of the Ethanol Extract of *Lepidium meyenii* on the Serum Cholesterol Concentration of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *Lepidium meyenii* roots on the serum cholesterol concentration of paroxetine-induced erectile dysfunction rats in Figure 6. The separate administration of the extract and the standard drug sildenafil significantly reduced ($p > 0.05$) the cholesterol concentration. The reduction observed with the administration of the extract was concentration dependent (25 – 100 mg/kg body weight). The separate administration of the standard drug sildenafil and 100 mg/kg body weight of the extract restored the cholesterol concentration to the concentration of the control. In contrast, paroxetine significantly increases ($p > 0.05$) the serum cholesterol concentration when compared to the control.

3.8 Effect of the Ethanol Extract of *Lepidium meyenii* on the Serum High-density Lipoprotein Cholesterol Concentration of Paroxetine-induced Erectile Dysfunction Rats

The effect of ethanol extract of *Lepidium meyenii* roots on the serum high-density lipoprotein cholesterol concentration of paroxetine-induced erectile dysfunction rats in Figure 7. The separate administration of the extract at 50 and 100 mg/kg body weight and the standard drug sildenafil significantly increased ($p > 0.05$) the high-density lipoprotein cholesterol concentration to the concentration of the control. Whereas, the increment observed with the administration of 25 mg/kg body weight of the

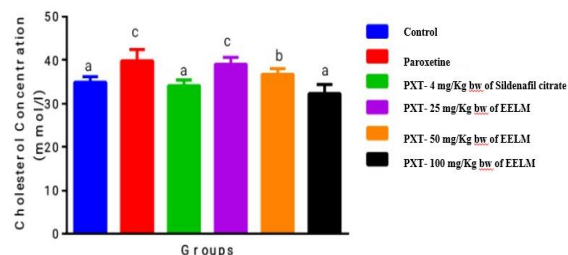


Figure 6: Effect of ethanol extract of *Lepidium meyenii* roots on the serum cholesterol concentration of paroxetine-induced erectile dysfunction rats

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Bars at the different groups with different letters are significantly different at $p < 0.05$

Control = received normal saline for 21 days and distilled water for the next 7 days

Paroxetine = received paroxetine for 21 days and distilled water for the next 7 days

PXT- 4 mg/Kg bw of Sildenafil Citrate = received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days

PXT- 25 mg/Kg bw EELM = received paroxetine for 21 days and 25 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

PXT- 50 mg/Kg bw of EELM = received paroxetine for 21 days and 50 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

PXT- 100 mg/Kg bw of EELM = received paroxetine for 21 days and 100 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

extract was no match to that of the control. In contrast, paroxetine significantly reduced ($p > 0.05$) the serum high-density lipoprotein cholesterol concentration when compared to the control.

4.0 Discussion

The organ-to-body weight ratio serves as a key indicator of cellular constriction and inflammation (Awotunde *et al.*, 2017). In line with this, the absence of significant alterations in tissue size suggests that the ethanol extract of

Lepidium meyenii roots did not induce inflammation or cellular constriction in the penile and cardiac tissues throughout the experimental period (Table 1).

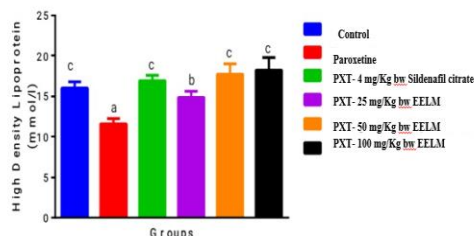


Figure 7: Effect of ethanol extract of *Lepidium meyenii* roots on the serum high-density lipoprotein-cholesterol concentration of paroxetine-induced erectile dysfunction rats

Values represent mean of five determinations $\pm$ standard error of mean (SEM). Bars at the different groups with different letters are significantly different at $p < 0.05$

Control = received normal saline for 21 days and distilled water for the next 7 days
 Paroxetine = received paroxetine for 21 days and distilled water for the next 7 days
 PXT- 4 mg/Kg bw of Sildenafil Citrate = received paroxetine for 21 days and 4 mg/Kg body weight of Sildenafil citrate for the next 7 days
 PXT- 25 mg/Kg bw EELM = received paroxetine for 21 days and 25 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 50 mg/Kg bw of EELM = received paroxetine for 21 days and 50 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days
 PXT- 100 mg/Kg bw of EELM = received paroxetine for 21 days and 100 mg/kg body weight of ethanol extract of *L. meyenii* for the next 7 days

The role of cyclic guanosine monophosphate (cGMP) in smooth muscle relaxation is critical in both penile and cardiac tissues. In the case of the penile vasculature, guanylyl cyclase activation leads to increased

cGMP levels, promoting smooth muscle relaxation and facilitating erection (Friebe *et al.*, 2023). Similarly, in cardiac smooth muscle, cGMP generated in response to nitric oxide or natriuretic peptides inhibits contraction, resulting in vasodilation and reduced blood pressure (Samidurai *et al.*, 2022). PDE-5 is a key enzyme that hydrolyzes cGMP, and its inhibition is a therapeutic strategy for erectile dysfunction and cardiovascular diseases (Hofmann, 2020; Lukowski and Feil, 2022). In this study, ethanol extract of *Lepidium meyenii* roots effectively inhibited penile and cardiac PDE-5 (Figures 1 and 2). In fact, recent studies have shown that natural extracts, such as those from *Lepidium meyenii*, can effectively inhibit PDE-5, highlighting the potential of plant-based therapies in managing these conditions (Fajmut, 2021). Furthermore, previous research has linked the PDE-5 inhibitory potential of plant extracts and food sources to their high phenolic content (Jimoh *et al.*, 2017; Akomolafe *et al.*, 2018). Therefore, it is reasonable to infer that the ethanol extract of *Lepidium meyenii* possesses a high phenolic content, which may account for its PDE-5 inhibitory effects.

Nitric oxide plays a crucial role in penile erection by facilitating smooth muscle relaxation in the corpus cavernosum. In particular, NO is synthesized by endothelial cells in penile arteries and the corpus cavernosum, primarily through the action of NOS, converting L-arginine to NO and citrulline (Paz *et al.*, 2024). As a result, the increase in NO leads to the activation of guanylyl

cyclase, resulting in elevated cGMP levels, which promote smooth muscle relaxation and erection (Paz *et al.*, 2024; Nicoletti *et al.*, 2020). In this study, ethanol extract of *Lepidium meyenii* roots increased the penile nitric oxide concentration in erectile dysfunction rats (Figure 3). Plant extracts containing alkaloids and flavonoids have been linked to increased NO levels, with alkaloids promoting NO release and flavonoids enhancing NOS expression (Paz *et al.*, 2024). Given the elevated penile nitric oxide levels following the administration of the plant extract, it is likely that the extract contains significant amounts of alkaloids and flavonoids. These compounds may have contributed individually or synergistically to the observed bioactivity.

The relationship between testosterone levels and erectile function is well-documented, with recent studies reinforcing the role of testosterone in enhancing sexual function in experimental models. Increased concentrations of testosterone, dihydrotestosterone, and dehydroepiandrosterone have been linked to improved erectile responses, particularly in animal models of erectile dysfunction (ED) (Latcu *et al.*, 2023; Hu *et al.*, 2023). This hormonal deficiency is associated with reduced arterial inflow, which is critical for achieving penile erection (Nashivochnikova and Krupin, 2024). Indeed, testosterone administration in castrated animals has been shown to restore erectile response and enhance nitric oxide expression in the penis (Latcu *et al.*, 2023). In this study, ethanol extract of *Lepidium meyenii* roots increased the

testosterone concentration in erectile dysfunction rats (Figure 4). The ability of plant extracts to modulate the concentration of testosterone in penile tissue has been attributed to the presence of saponins, and mediated through its metabolic conversion into dehydroepiandrosterone (Nashivochnikova and Krupin, 2024). It is therefore reasonable to presume the plant extract contains considerable amount of saponins, owing to its ability to increase the testosterone concentration of erectile dysfunction rats as observed.

Changes in serum lipid concentrations are critical indicators of cardiovascular health, particularly in assessing risks for conditions like atherosclerosis. Recent studies emphasize the importance of lipid profiles, revealing that elevated levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol correlate with increased cardiovascular disease (CVD) risk, while high-density lipoprotein (HDL) cholesterol remains protective (Kale, 2023; Wazir *et al.*, 2023). The relationship between altered serum lipids and erectile dysfunction (ED) also highlights the profound impact of dyslipidemia on overall cardiovascular health (Agbaje, 2023; Balatskyi *et al.*, 2023). Therefore, a pharmacological agent capable of addressing these interconnected pathological conditions is highly desirable. The plant extract examined in this study not only demonstrated potential in managing ED, as previously discussed, but also showed efficacy in improving serum lipid profiles associated with cardiovascular diseases.

Specifically, it reduced triacylglycerol and cholesterol levels, which were elevated due to paroxetine-induced erectile dysfunction, while simultaneously increasing high-density lipoprotein cholesterol levels, which had been reduced by the same condition (Figures 5–7). This indicates that the plant extract stimulates lipolysis and inhibits cholesterol biosynthesis in erectile dysfunction, contributing to improved cardiovascular health. Furthermore, the elevated high-density lipoprotein cholesterol levels suggest that the extract facilitates reverse cholesterol transport, thereby lowering the risk of atherosclerosis and promoting cardiovascular well-being (Wen *et al.*, 2022).

5.0 Conclusion

The findings of this study indicate that the ethanol extract of *Lepidium meyenii* roots exhibits inhibitory potential against phosphodiesterase-V activity and can mitigate biochemical imbalances associated with cardiovascular diseases in paroxetine-induced erectile dysfunction rats. Thus, the plant extract demonstrates promise in managing both erectile dysfunction and atherosclerosis, a cardiovascular condition linked to erectile dysfunction pathogenesis. Further research is necessary to fractionate the extract, evaluate its specific effects, and identify its bioactive compounds.

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