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PAUSINYSTALIA YOHIMBE ETHANOLIC EXTRACT RESTORE ERECTILE AND CARDIAC FUNCTIONS IN PAROXETINE-INDUCED ERECTILE DYSFUNCTIONAL RATS

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ABSTRACT
Erectile dysfunction (ED) is a continuous inability to achieve or maintain an erection, often linked to hormonal, vascular and neurological imbalances. Selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, can exacerbate ED by reducing nitric oxide (NO) availability and increasing phosphodiesterase 5 (PDE5) and arginase activities. This study investigated the effects of *Pausinystalia yohimbe* ethanolic extract (PYE) on paroxetine-induced ED in male Wistar rats. Thirty-six rats were divided into six groups: control, paroxetine untreated, sildenafil citrate, and three PYE-treated groups (10, 15, and 20 mg/kg). ED was induced with 10 mg/kg paroxetine, and treatments were administered for four weeks. Results showed a significantly lower ($p < 0.05$) penis-body ratio in the untreated group (0.380 ± 0.005) compared to the 20 mg/kg PYE group (0.790 ± 0.005). PDE5 and arginase activities were significantly elevated in the untreated group, while NO levels were lower. The 20 mg/kg PYE group showed the highest NO concentration and significantly reduced PDE5 and arginase activities. Lipid profile analysis revealed that the untreated group had elevated total cholesterol (27.384 ± 2.815 mmol/L) and triglycerides (10.434 ± 7.120 mmol/L), which were lowered by PYE treatment. PYE effectively reversed paroxetine-induced ED, with the 20 mg/kg dose demonstrating the strongest pro-erectile and cardioprotective effects. These findings suggest *P. yohimbe* as a promising natural alternative for managing SSRI-induced ED, worthy of further biochemical investigations.

Keywords: Paroxetine; *P. yohimbe*; Arginase, Phosphodiesterase 5; Penile; Cardiac.

1. INTRODUCTION

Erectile dysfunction (ED) is a complex disorder associated with persistent inability to sustain or maintain an erection, hindering optimal sexual function and satisfaction (Mazzilli, 2022). There are some cultural, ethical, social, and religious challenges in accurately estimating the prevalence of ED (Sangiorgi *et al.,* 2021). However, Al-Madhagi (2024) reported that approximately 152 million men worldwide were affected by ED in 1995. The prevalence of ED increases as age increases, and it depends on the assessment tool and the study setting used (Muhammad *et al.,* 2023). For example, the consensus questionnaire of National Institute of Health (NIH) gives higher prevalence compared to the International Index of Erectile Function (IIEF-5) Questionnaire (McKinlay & Krane 1999). An increase in prevalence from 152 million men to about 322 million in 2025 has been projected, representing an increase of about 170 million men, and the increase is mostly observed in the developing world, specifically Asia, South America and Africa (Al-Madhagi, 2024). In Nigeria, ED is predominantly prevalent in the three Southern regions of the country, while the condition has also been reported to affect the North-Central and Northwest regions (Muhammad *et al.,* 2023). The symptoms of ED range from reduced libido to decreased erectile rigidity, anxiety and difficulty in maintaining erection.

ED pathophysiology involves a complex interaction of neurological, hormonal and vascular factors. Normal erectile function is mediated by the release of nitric oxide (NO) from epithelial cells, leading to relaxation of smooth muscle cells and increased blood flow to the penile organ (Sangiorgi *et al.,* 2021). However, in ED, this process is interrupted, leading to disrupted blood flow, reduced NO production, and decreased erectile function (Kaltsas *et al.,* 2024). Vascular diseases and neurological disorders can all contribute to the development of ED. Selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, are common antidepressants that can induce or aggravate ED in men (Edinoff *et al.,* 2021). This drug reduces dopamine levels, a neurotransmitter involved in sexual arousal and pleasure. It can also elevate prolactin levels, which can suppress gonadotropin-releasing hormone (GnRH), leading to reduced testosterone production and erectile challenges (Speranza *et al.,* 2021).
Phosphodiesterase 5 (PDE 5) catalyzes the degradation of cGMP, and PDE5 inhibitors, such as sildenafil (Viagra) are commonly used to treat ED (Ahmed *et al.,* 2021). Via inhibition of PDE5, they increase the levels of cyclic guanosine monophosphate (cGMP), a signaling molecule which stimulates the relaxation of smooth muscle cells in the corpus cavernosum, allowing increased blood flow and erection (Paronetto *et al.,* 2021). By preventing the degradation of cGMP, PDE 5 inhibitors enhance the effects of NO, a potent vasodilator that stimulates NO production. Long term use of these drugs has been linked to side effects like headache, dyspepsia, nasal congestion, dizziness and back pain (Soulaidopoulos *et al.,* 2024). This encourages investigation on natural therapies for development of medication for ED with minimal or no side effects.

Pausinystalia yohimbe, a plant species traditionally used in West African folk medicine, has been reported to exhibit vasodilatory properties. The bark of the plant contains an indole alkaloid known as yohimbine (Drevin *et al.,* 2020), which has been observed to possess aphrodisiac properties (Nowacka *et al.,* 2024). Therefore, using a range of biochemical assays, including serum, cardiac and penile total proteins, as well as PDE5, NO and arginase, this study investigated the modulatory effects of *P. yohimbe* bark extract on erectile dysfunction induced by paroxetine administration.

2.0 MATERIALS AND METHODS

2.1 Materials

2.1.1 Plant Materials

Pausinystalia yohimbe stem bark was purchased from a local herbs dealer in Oja Tuntun, Ilorin, Kwara State. It was then processed at the laboratory of Biochemistry department, University of Ilorin, by cutting it into smaller pieces and shade-dried for 14 days. The dried material was then pulverized into a fine powder using a locally fabricated grinding mill and kept for extraction.

2.1.2 Experimental Animals

Thirty-six (36) male Wistar rats (180-200 g) were obtained from the lab of Biochemistry Department, University of Ilorin. The animals were housed in standard laboratory cages under controlled conditions of 25 ± 2°C temperature, 50 ± 10% humidity, and a 12 hour light/dark cycle. They were acclimatized for one week before the experiment and had free access to standard rat chow and water *ad libitum*.

2.1.3 Chemicals and Reagents

Tween-80 (BDH Chemicals, UK), normal saline (Sigma-Aldrich, USA), diethyl ether (Merck KGaA, Germany), lithium heparin (Randox Laboratories Ltd., UK), Griess reagent (Sigma-Aldrich, USA), biuret reagent (Sigma-Aldrich, USA), polyvinyl sulfate (PVS) (Randox, UK), and lipid profile assay kits (Randox Laboratories Ltd., UK) were used. Paroxetine tablets (20 mg/tablet) manufactured by GlaxoSmithKline (GSK, UK), and Sildenafil citrate tablets (Viagra, 50 mg/tablet) produced by Pfizer Inc., USA were purchased. Ethanol (99%) manufactured by Sigma-Aldrich (USA) was purchased from Integrated SUNAF Nigeria Limited, Ilorin, Kwara State.

2.2 Methods

2.2.1 Preparation of *Pausinystalia yohimbe* Stem Bark Ethanolic Extract

Pausinystalia yohimbe stem bark ethanolic extract was prepared using the method described by Okwakpam *et al.* (2023) with slight modification. *Pausinystalia* yohimbe bark was properly washed with distilled water, and then cut into pieces and allowed to air dry for 3days. It was then blended into fine powder, after which 60 g of the fine powder was soaked in 300 mL of ethanol for 3days. The mixture was sieved using a mash cloth and then a filter paper thereafter. The extract was concentrated in water bath at about 40°C for 24 hours and then stored in a refrigerator for further use.

2.2.2 Experimental Design

Thirty-six male Wistar rats were randomly assigned to six groups, each consisting of six rats. Group A (control) received 2 mL of 0.9% normal saline, while group B (Paroxetine untreated) was administered only 10 mg/kg of paroxetine orally. Group C (standard drug) received 10 mg/kg of paroxetine along with 50 mg of sildenafil citrate (Viagra) dissolved in 9.375 mL of distilled water (0.6 mL solution). Groups D, E, and F were treated with 10 mg/kg of paroxetine combined with 10 mg/kg, 15 mg/kg, and 20 mg/kg of *Pausinystalia yohimbe* extract (PYE), respectively. These treatments were administered orally to evaluate the potential protective effects of *Pausinystalia yohimbe* against paroxetine-induced erectile dysfunction. At the end of the experiment, the rats were humanely sacrificed using diethyl ether anaesthetization. Blood samples were collected via cardiac puncture into plain bottles. The bottles were labelled according to the groups of the rats. Creatinine kinase and lipid profile analysis were done using the serum.

2.2.3 Induction of Erectile Dysfunction

Erectile dysfunction was induced using the method described by Muritala and Bewaji (2021). This involved oral administration of 10 mg/kg of paroxetine suspension which was prepared using Tween-80 (BDH Chemicals, Ltd.; Poole, England) suspended in 9 g/L saline solution as the vehicle.

2.2.4 Determination of Body-Organ Weight Ratio

For assessment of possible changes in the organ sizes after induction of erectile dysfunction and administration of the extract, the animals were weighed before sacrifice. After sacrifice, their hearts and penises were excised, blotted in tissue paper to remove blood and water, and weighed for determination of hearts-body and penises-body weight ratios (Yakubu, 2006).

2.2.5 Determination of Total Protein

The total protein concentrations in 10% tissue heart and penis homogenates, as well as in serum were determined using the Biuret method (Gornall et al., 1949). Briefly, 0.5 mL of each of the samples was diluted with 1.0 mL of distilled water, bringing the total volume to 1.5 mL. A blank was prepared using 1.5 mL of distilled water. For solubility enhancement, 0.2 mL of 5% sodium deoxycholate (DOC) in 0.01 N KOH was added, followed by 1.5 mL of Biuret reagent (1.50 g $CuSO_4 \cdot 5H_2O$, 6.0 g sodium potassium tartrate, and 300 mL of 10% NaOH per liter). The mixture was then vortexed and incubated at 37°C for 15 minutes, and absorbance was measured at 540 nm using a spectrophotometer, with the blank serving as the reference.

2.2.6 Determination of Phosphodiesterase 5 Activity

Phosphodiesterase 5 (PDE5) activity was measured using the Butcher and Sutherland (1962) method. Concisely, the samples (heart and penis homogenates) were incubated with cGMP, which served as the substrate, followed by spectrophotometric detection of the reaction product. The enzymatic activity was then estimated using the following equation:

$$EA = \frac{V\Delta C}{V3} \text{ (units/mL)}$$

Where:
EA is enzyme activity
V is total volume of reaction
ΔC is reaction velocity (Pi/ incubation time of 20 minutes)
V_3 is volume of enzyme source
Pi is amount of inorganic phosphate released

2.2.7 Determination of Cardiac and Penile Nitric Oxide Concentrations

The cardiac and penile nitric oxide concentrations were determined following the method of Green et al. (1982). This assay involved the reaction of nitrate and nitrite with Griess reagent to form a colored complex, which was quantified spectrophotometrically. The nitric oxide concentration was determined based on standard calibration curve.

2.2.8 Arginase Activity

Arginase activity assay in both cardiac and penile was carried out using the method of Stickings *et al.* (2002). In this method, 50 µl of the homogenate of each of the organs was measured into an eppenduff tube, and 200 µl of arginase buffer was added to it. The mixture was incubated for 1 hr. at 37 ^{o}C, after which 100 µl of 0.5 M hypochloride was added to it. The mixture was then centrifuged at 8000 rpm for 3 minutes. The mixture was thereafter quantified using urea i.e. 100 µl of urea reagent was added to 20 µl of the supernatant. The absorbance value was taken at 380 nm and the concentration of urea is estimated using the following equation:

$$\text{Concentration of urea (mg/dl)} = \frac{\text{Asample x Concentration of standard}}{\text{Astandard}}$$

Concentration of standard = 13.1 mg/dl

2.2.9 Creatine Kinase (CK) Activity Assay

Serum creatine kinase (CK) activity was quantified using the Witt and Trendelenburg (1982) method. The assay measured CK activity based on the enzymatic conversion of creatine phosphate, with absorbance recorded spectrophotometrically. The enzyme activity was calculated using the following equation:

Creatine kinase (U/l) = 4127 x (ΔAbsorbance/minute x dilution factor)

Where 4127 is the standard factor used in preparation of the enzyme kit.

2.2.10 Lipid Profile

2.2.10.1 Serum Total Cholesterol Concentration

The assay for total cholesterol in the serum was carried out using the method of Fredrickson *et al.* (1967). Micropipette was used to measure 20 µL each of appropriately diluted sample, standard and distilled water were pipetted into different test tubes and were labeled sample, standard and blank respectively. Thereafter, 2000 µL of working reagent composing of 4-aminoantipyrine, phenol, peroxide, cholesterol esterase, cholesterol oxidase and buffer (pH 6.8) were added to each test tube. The reaction constituents were thoroughly mixed and incubated at 37 ^{o}C for 5 min. The absorbance of sample and standard were read against the blank at 546 nm. The cholesterol concentration was then calculated using the following equation:

$$\text{Concentration of cholesterol (mmol/L)} = \frac{A_{sample} \times \text{Concentration of standard}}{A_{standard}}$$

Concentration of standard = 5.10 mmol/L

2.2.10.2 Triglycerides concentration

The concentration of serum triglyceride was determined using the method describe by Warnick *et al.* (2008). Using a micropipette, 10 µL of appropriately diluted sample, standard and distilled water were pipetted into clean test tubes labelled sample, standard and blank respectively. Then 100 µL of working reagent comprising of 4-aminophenazone, ATP, lipases, glycerokinase, glyceryl-3-phosphate oxidase and peroxidase were added to each test tube. The solution was mixed, left undisturbed for 10min at room temperature (20-25 ^{o}C). The absorbance of sample and standard was measured against the blank within 60 min at 500 nm. The triglycerides were then estimated using the equation below:

Calculation:

$$\text{Concentration of TG (mmol/L)} = \frac{A_{sample} \times \text{Concentration of standard}}{A_{standard}}$$

Concentration of standard = 2.21 mmol/L

2.2.10.3 Serum High Density Lipoprotein-Cholesterol Concentration

By adopting the procedure described by Albers *et al.* (1978), HDL-cholesterol concentration in serum was determined. Using a micropipette, 200 µL of appropriate diluted sample, standard and distilled water were pipetted into clean test tubes labelled sample, standard and blank respectively. Then 500 µL of working reagent comprising of phosphotungstic acid and magnesium chloride were added to each test tube. The solution was mixed and left undisturbed for 10 min at room temperature. This was then centrifuged at 4000 rpm for 10 minutes. The clear supernatant was separated off within two hours and the cholesterol content determined by the CHOD-PAP method earlier described.

$$\text{Concentration of HDL cholesterol (mmol/L)} = \frac{A_{sample} \times \text{Concentration of standard}}{A_{standard}}$$

Concentration of standard = 5.10 mmol/L

2.2.10.4 Serum Low Density Lipoprotein-Cholesterol Concentration

The assay for serum low-density lipoprotein cholesterol concentration was carried out using the polyvinyl sulphate (PVS) reaction as described by Demacker *et al.* (1984).

Calculation:

LDL-C (mg/dl) = Total cholesterol (mg/dl) – 1.5 x Supernatant cholesterol (mg/dl).

2.2.10.5 Atherogenic Index

The atherogenic index of each animal was estimated using the method of Dobiášová (2006). It is expressed as the logarithmic transformation of the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C):

$$AI = \log\left(\frac{TG}{HDL}\right)$$

2.2.11 Statistical Analysis

Data obtained were expressed as mean ± standard error of mean (S.E.M.) of three replicates. Using Graphpad prism version 8.0, one-way analysis of variance (ANOVA) was used for statistical evaluation, followed by Duncan's posthoc test for multiple comparisons. Values analyzed were considered statistically significant at $p<0.05$.

3.0 RESULTS

3.1 Organ-body Ratio and Protein Concentrations of Serum, Hearts and Penile Organs

The penis-body ratio showed variation across the groups. The paroxetine untreated group had the significantly lower ratio ($p < 0.05$) than all other groups (Table 1). There was no significant difference ($p < 0.05$) between the control group (0.450 ± 0.005) and sildenafil citrate group (0.470 ± 0.005). The 10 mg/kg P. yohimbine

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group (0.530 ± 0.020) had a significantly higher ratio than the control and sildenafil citrate groups ($p < 0.05$). The 15 mg/kg P. yohimbine group (0.470 ± 0.150) showed no significant difference compared to the control and sildenafil citrate groups. The 20 mg/kg *P. yohimbine* group had a significantly higher ($p < 0.05$) penis-body ratio (0.790 ± 0.005) than all other groups.

The heart-body ratio also showed significant differences across groups. The paroxetine untreated group (0.430 ± 0.010) had the lowest value, which was significantly lower ($p < 0.05$) than all other groups. The 10 mg/kg P. yohimbine group (0.460 ± 0.005) was significantly higher ($p < 0.05$) than the paroxetine untreated group but lower ($p < 0.05$) than the control (0.540 ± 0.010) and sildenafil citrate (0.530 ± 0.005) groups. The 15 mg/kg P. yohimbine group (0.540 ± 0.015) had a heart-body ratio comparable to the control group, with no significant difference. The 20 mg/kg P. yohimbine group (0.650 ± 0.005) had the highest heart-body ratio, which was significantly higher ($p < 0.05$) than all other groups.

Table 1: Effect of ethanol extract of *Pausinystalia yohimbe* on organ-body weight ratio

Groups	Penis-body ratio	Heart-body ratio
Control	0.450 ± 0.005^{b}	0.540 ± 0.010^{c}
Paroxetine Untreated	0.380 ± 0.005^{a}	0.430 ± 0.010^{a}
Sildenafil Citrate	0.470 ± 0.005^{b}	0.530 ± 0.005^{c}
10 mg/kg *P. yohimbine*	0.530 ± 0.020^{c}	0.460 ± 0.005^{b}
15 mg/kg *P. yohimbine*	0.470 ± 0.150^{b}	0.540 ± 0.015^{c}
20 mg/kg *P. yohimbine*	0.790 ± 0.005^{d}	0.650 ± 0.005^{d}

There was no significant difference ($p < 0.05$) in the serum total protein concentrations of the normal control, sildenafil citrate and 20 mg/kg bw PYE groups, and their total protein concentrations were significantly lower ($p < 0.05$) than that of the 10 and 15 mg/kg bw PYE groups (Figure 1). There was no significant difference in the total protein of the 10 and 15 mg/kg bw PYE groups. The paroxetine untreated group had higher ($p < 0.05$) total protein level compared to all other groups.

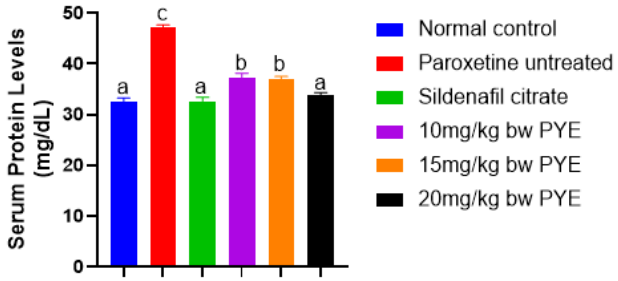

Figure 1: Serum Total Protein Concentration of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($P < 0.05$). SEM = standard error of the mean

There was no significant difference ($p < 0.05$) in the cardiac total protein concentrations of the normal control, sildenafil citrate 15 and 20 mg/kg bw PYE groups, and their total protein concentrations were significantly lower ($p < 0.05$) than that of the 10 mg/kg bw PYE group (Figure 2). The paroxetine untreated group had higher ($p < 0.05$) total protein level compared to all other groups.

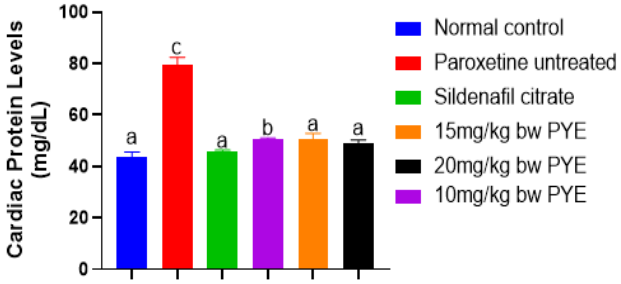

Figure 2: Cardiac Total Protein Concentration of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($P < 0.05$). SEM = standard error of the mean

The penile total protein concentration of normal control was significantly lower ($p < 0.05$) compared to the paroxetine untreated, sildenafil citrate, 10, 15 and 20 mg/kg bw PYE groups (Figure 3). The total protein concentration of the sildenafil citrate group was significantly lower ($p < 0.05$) compared to the 15 mg/kg bw PYE group, which also had a significantly lower ($p < 0.05$) total protein concentration compared to the 10 mg/kg bw PYE. The paroxetine untreated group a significantly higher ($p < 0.05$) total proteins concentrations compare to other groups.

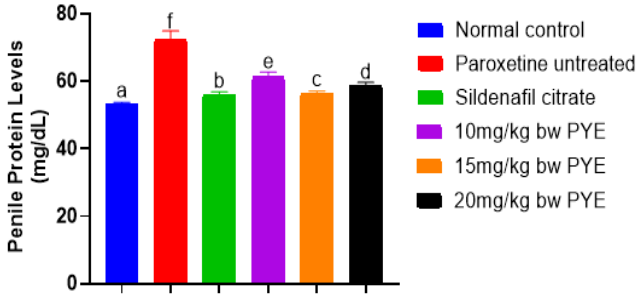

Figure 3: Penile Total Protein Concentration of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($P < 0.05$). SEM = standard error of the mean

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3.2 Erectile Dysfunction Biomarkers

Upon analysis of cardiac phosphodiesterase 5 activity across the animal groups, the enzyme activity in the untreated group was significantly higher ($p < 0.05$) compared to other groups (Figure 4). There was no significant difference in the cardiac PDE 5 activity of normal control, standard, 10, 15 and 20 mg/kg bw PYE groups. Similarly, for penile phosphodiesterase 5 activity, across the untreated group had a significantly higher ($p < 0.05$) PDE 5 activity compared to other groups (Figure 5). There was no significant difference in the cardiac PDE 5 activity of normal control, standard, 10, 15 and 20 mg/kg bw PYE groups.

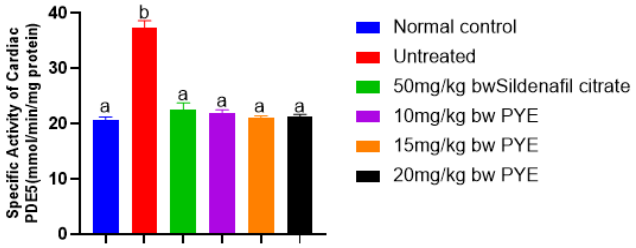

Figure 4: Cardiac Phosphodiesterase 5 Activity of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different (P < 0.05). SEM = standard error of the mean

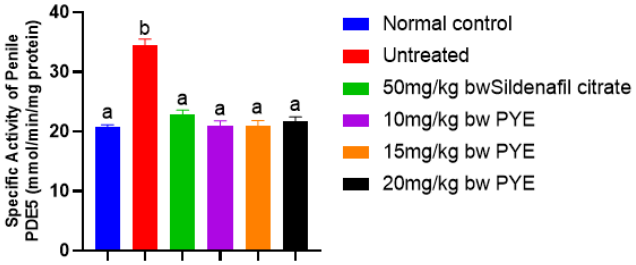

Figure 5: Penile Phosphodiesterase 5 Activity of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different (P < 0.05). SEM = standard error of the mean

The cardiac nitric oxide concentration of the untreated group was significantly lower than that of the normal control, standard, 10, 15 and 20 mg/kg bw PYE groups (Figure 6). There was no significant difference in the cardiac nitric oxide concentration of the normal control, standard, 10, 15 and 20 mg/kg bw PYE groups. Contrarily, the penile nitric oxide level of the 20 mg/kg bw PYE group was significantly higher than that of the normal control, untreated, standard, 10 and 15 mg/kg bw PYE groups (Figure 7). The NO in the untreated group was significantly lower compared to the normal control, standard, 10, 15 and 20 mg/kg bw PYE groups. There was no significant difference in the NO of the normal control, standard, 10 and 15 mg/kg bw PYE groups

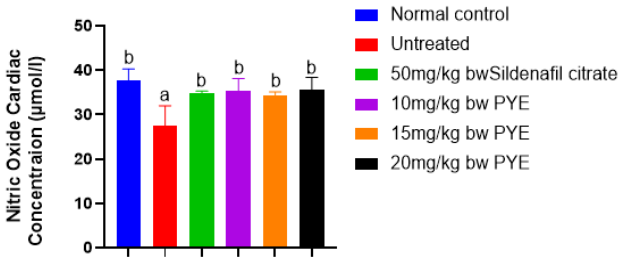

Figure 6: Cardiac Nitric Oxide Concentration of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different (P < 0.05). SEM = standard error of the mean

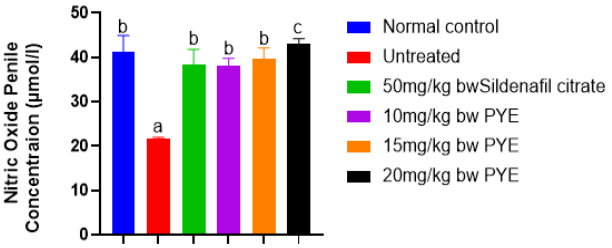

Figure 7: Penile Nitric Oxide Concentration of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different (P < 0.05). SEM = standard error of the mean

The untreated group had a significantly higher ($p < 0.05$) cardiac arginase activity compared to other groups (Figure 8). There was no significant difference in the cardiac arginase activity of normal control, standard, 10, 15 and 20 mg/kg bw PYE groups. However, the normal control showed a significantly lower penile arginase activity compared to other groups. The untreated group had a significantly higher penile arginase activity compared to other groups. There was no significant difference in the penile arginase activity of the standard, 10, 15 and 20 mg/kg bw PYE groups (Figure 9).

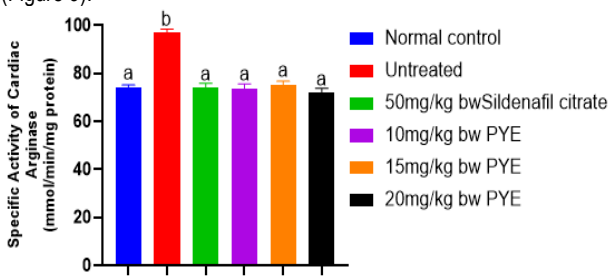

Figure 8: Cardiac Arginase Activity of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

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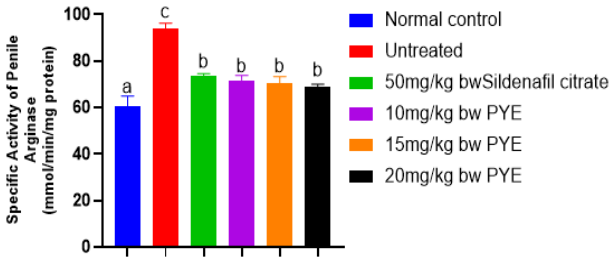

Figure 9: Cardiac Arginase Activity of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different (P < 0.05). SEM = standard error of the mean

The analysis of serum creatinine kinase activity revealed that the untreated group had a significantly higher (p < 0.05) activity compared to other groups (Figure 10). There was no significant difference in the creatinine kinase activity of normal control, standard, 10, 15 and 20 mg/kg bw PYE groups.

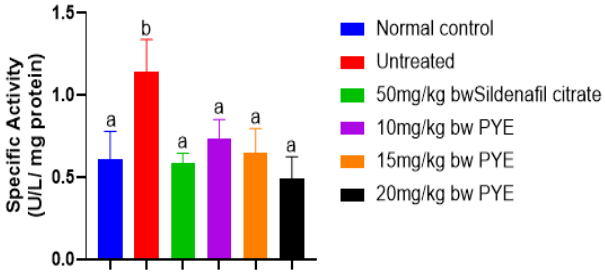

Figure 10: Serum Creatinine Kinase Activity of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

PYE: *Pausinystalia Yohimbe* Ethanolic Extract

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different (P < 0.05). SEM = standard error of the mean

3.2.3 Lipid Profile

Serum cholesterol levels were significantly different among the groups. The untreated group had a significantly higher (p < 0.05) cholesterol level (27.384 ± 2.815) than the sildenafil citrate group (25.616 ± 0.991), 15 (24.086 ± 0.586), and 20 mg/kg PYE groups (25.448 ± 0.818). The control (26.654 ± 0.492) and the 10 mg/kg PYE groups (27.757 ± 3.200) did not show significant differences from the untreated group (Table 2).

The untreated group exhibited a significantly higher (p < 0.05) serum triglyceride level (10.434 ± 7.120) than the control (6.393 ± 1.024), sildenafil citrate (7.250 ± 2.750), and 15 mg/kg PYE (6.863 ± 1.406) groups. The 10 (8.147 ± 5.246) and 20 mg/kg (8.127 ± 5.195) PYE groups did not significantly differ from the untreated group.

Serum HDL levels were significantly lower (p < 0.05) in the untreated (16.207 ± 17.170) and 10 mg/kg PYE groups (15.913 ± 16.370) compared to the control (9.703 ± 3.902), sildenafil citrate (11.297 ± 4.208), and 20 mg/kg PYE (12.454 ± 7.261) groups. No significant differences were observed between the control, sildenafil citrate, 15 (11.540 ± 4.848), and 20 mg/kg PYE groups.

The serum LDL levels varied significantly across groups. The 20 mg/kg PYE group exhibited a significantly higher (p < 0.05) LDL level (0.074 ± 0.001) than all other groups. The sildenafil citrate (0.047 ± 0.011) and the 10 mg/kg PYE groups (0.043 ± 0.001) also had significantly higher LDL levels than the control (0.025 ± 0.005) and untreated (0.016 ± 0.012) groups (p < 0.05).

The Atherogenic Index (AI) was significantly higher (p < 0.05) in the 20 mg/kg PYE group (1.280 ± 0.087) compared to all other groups. The sildenafil citrate group (0.566 ± 0.003) and the 10 mg/kg PYE group (0.510 ± 0.020) also had significantly higher AI values than the untreated group (0.205 ± 0.134) (p < 0.05). No significant differences were observed between the control (0.401 ± 0.101), 10 and 15 mg/kg PYE groups (0.4623 ± 0.031).

Table 2: Lipid Profile of Paroxetine-induced Erectile Dysfunctional Rats Administered *Pausinystalia Yohimbe* Ethanolic Extract

GROUP	Cholesterol (mmol/L)	TAG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)	AI
Control	26.654±0.492^{a}	6.393±1.024^{a}	9.703±3.902^{a}	0.025±0.005^{ab}	0.401±0.102^{ab}
Untreated	27.384±2.815^{b}	10.434±7.120^{b}	16.207±17.170^{b}	0.0162±0.011^{a}	0.205±0.134^{a}
Sildenafil citrate	25.616±0.991^{a}	7.250±2.750^{a}	11.297±4.208^{a}	0.0473±0.011^{c}	0.566±0.003^{b}
10 mg of PYE	27.757±3.200^{ab}	8.147±5.246^{ab}	15.913±16.370^{b}	0.0428±0.001^{bc}	0.5100±0.0193^{b}
15 mg of PYE	24.086±0.586^{a}	6.863±1.406^{a}	11.540±4.848^{a}	0.041±0.003^{bc}	0.462±0.031^{ab}
20 mg of PYE	25.448±0.818^{ab}	8.127±5.195^{ab}	12.454±7.261^{a}	0.074±0.001^{d}	1.280±0.087^{ab}

4.0 DISCUSSION

Selective serotonin reuptake inhibitors (SSRIs), such as paroxetine suppress sexual function by modulating serotonergic pathways and reducing nitric oxide (NO) availability, as well as increasing PDE 5 and arginase activities (Olopade *et al*., 2025). In this study, assessment of those markers of sexual dysfunction, cardiac and penile organ-body ratios in paroxetine-induced erectile dysfunctional rats treated with *P. yohimbe* extract revealed notable effects of the extract on the rats. Increased organ body weight ratio has been implicated in inflammation while decreased ratio implies

cell constriction (Yakubu *et al*., 2007). Paroxetine-induced group showed reduced cardiac and penile organs, suggesting higher cell constriction and potentially apoptosis in this group compared to all other groups. The administration of sildenafil citrate and *Pausinystalia yohimbe* extract (PYE) at the tested doses restored the penis-body ratio, with the highest improvement observed in the 20 mg/kg PYE group. This suggests that PYE enhances penile tissue integrity, possibly via α2-adrenergic antagonism and pro-erectile effects on NO-mediated vasodilation (Olutoye and Yakubu, 2025). There were variations in heart-body ratios across the groups, with the lowest observed in the untreated group, supporting previous findings on SSRI-induced disruption in cardiovascular function (Béboy *et al*., 2024). The significant improvements in the 15 mg/kg and 20 mg/kg PYE groups suggest that PYE may confer cardioprotective benefits. This agrees with the findings of Olopade et al. (2025) on the role of yohimbine, an active constituent of *P. yohimbe,* in improving cardiovascular function by enhancing endothelial NO signaling and reducing oxidative stress.

The variations observed in total protein levels across different groups highlight the physiological impact of paroxetine-induced erectile dysfunction (ED) and the therapeutic effects of *P. yohimbe* extract (PYE) and sildenafil citrate. Paroxetine alters metabolic and inflammatory pathways, leading to protein accumulation in tissues (Wu *et al*., 2024). The elevated total protein concentration in the paroxetine-untreated group suggests increased protein synthesis or reduced protein degradation, which may be a compensatory response to oxidative stress and tissue damage induced by chronic SSRI administration. Similarly, the significantly higher cardiac total protein levels than all other groups, including the sildenafil citrate and higher-dose PYE groups exhibited by 10 mg/kg PYE group suggest that lower doses of PYE may exert a more pronounced effect on cardiac protein synthesis, probably through mechanisms involving enhanced NO bioavailability and improved cardiac metabolism (Wu *et al*., 2025). The normalization of cardiac total protein levels in the higher-dose PYE (15 and 20 mg/kg) and sildenafil citrate groups suggests a more balanced regulatory effect at these doses, reinforcing their therapeutic potential for mitigating cardiovascular complications associated with ED.

In penile tissues, the significantly higher total protein levels in the paroxetine-untreated group compared to the control suggest paroxetine-induced alterations in protein metabolism, which may be linked to increased oxidative stress, endothelial dysfunction, or fibrotic changes (Wu *et al*., 2024). The dose-dependent effects of PYE on penile total protein levels indicate that higher doses (15 and 20 mg/kg) contribute to more reduction of penile tissue injury, potentially through mechanisms involving enhanced NO synthesis, improved endothelial function, and increased androgen receptor expression (Kissack, 2023). The significantly lower total protein concentration in the sildenafil citrate group compared to the 15 mg/kg PYE group suggests that PYE may have a stronger anabolic or trophic effect on penile tissues than sildenafil citrate alone.

The significantly higher cardiac and penile phosphodiesterase type 5 (PDE5) activity in the untreated group is in agreement with the findings Muritala and Bewaji (2021) where paroxetine administration negatively disrupted erectile function by dysregulating cyclic guanosine monophosphate (cGMP) metabolism via PDE 5 positive modulation. PDE5 inhibition is critical for sustained erectile function, as it prevents cGMP degradation, thereby promoting smooth muscle relaxation (Olutoye and Yakubu, 2025). The insignificant differences in PDE5 activity among the control, sildenafil citrate, and PYE-treated groups suggests that both PYE and sildenafil citrate effectively normalize PDE5 activity and restore erectile function.

The nitric oxide (NO) concentration results further support the role of NO-cGMP signaling in paroxetine-induced ED. Paroxetine administration lowers both cardiac and penile nitric acid levels, thereby increasing susceptibility to endothelial and erectile dysfunction (Muritala and Bewaji, 2021). The significantly lower penile NO levels in the untreated group provides additional support for previous reports that SSRIs impair endothelial NO synthase (eNOS) activity, leading to erectile dysfunction (Béboy *et al*., 2024). The restoration of penile NO levels in the 20 mg/kg PYE group suggests that PYE enhances NO bioavailability, which is essential for vasodilation and erectile function. Additionally, the significantly lower cardiac NO levels in the paroxetine-administered untreated group suggest an impairment in the hearts of animals in that group, a phenomenon.

Muritala and Bewaji (2021) also reported higher activity of arginase in paroxetine-administered male Wistar rats compared to normal uninduced rats. Arginase reduces nitric oxide (NO) production by competing for L-arginine, leading to poor blood flow and contributing to erectile dysfunction (Caldwell *et al.,* 2018). The significantly higher cardiac arginase activity in the untreated group aligns with research showing that SSRIs upregulate arginase, reducing L-arginine availability for NO synthesis and impairing erectile function (Béboy et al., 2024). The significantly lower penile arginase activity in the untreated group further supports paroxetine-induced NO dysregulation, which was ameliorated in all treatment groups, particularly the 20 mg/kg PYE group, supporting sexual enhancement of PYE.

Serum creatine kinase (CK) activity, a marker of muscle and cardiac stress, was significantly elevated in the untreated group, suggesting SSRI-induced muscle damage and cardiovascular strain. The normalization of CK activity in the sildenafil citrate and PYE-treated groups suggests that PYE, like sildenafil, exerts protective effects against paroxetine-induced oxidative stress and mitochondrial dysfunction (Olutoye and Yakubu, 2025).

Dyslipidemia was evident in the paroxetine-untreated group, characterized by significantly higher cholesterol, triglycerides (TAG), and LDL levels alongside reduced HDL levels. This supports prior findings that SSRIs contribute to metabolic disturbances, oxidative stress, and increased cardiovascular risk (Olopade *et al*., 2025). The significantly higher atherogenic index (AI) in the untreated group suggests an elevated risk of cardiovascular disease, reinforcing the strong link between ED and metabolic dysfunction.

The improvements in lipid parameters observed in the sildenafil citrate and PYE-treated groups suggest that these treatments not only restore erectile function but also mitigate SSRI-induced dyslipidemia. Notably, the 20 mg/kg PYE group exhibited the most favorable lipid profile, which aligns with previous reports of Yohimbine's lipid-lowering effects through enhanced lipid metabolism and endothelial function (Béboy *et al*., 2024). The ability of PYE to reduce AI and LDL levels while increasing HDL suggests that it may offer both pro-erectile and cardioprotective benefits, making it a potential alternative or adjunct to conventional PDE5 inhibitors.

Conclusion

This study has demonstrated the *in vivo* aphrodisiac effects of *Pausinystalia yohimbe* ethanolic extract against paroxetine-induced erectile dysfunction in male Wistar rats. The PYE improved penile and cardiac organ-body ratios, reduced phosphodiesterase 5 (PDE5) and arginase activities, and enhanced nitric oxide (NO) concentration. It also attenuated dyslipidemia as evidenced by the lipid profile results, with the 20 mg/kg dose showing the most significant benefits, suggesting that the effect of the extract may be dose-dependent. These findings suggest PYE as a potential natural alternative for managing SSRI-induced erectile dysfunction, worthy of further investigation.

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