

- ethnopharmacology*. 243: 112085
- Ponte-Sucre, A. (2016). An overview of *Trypanosoma brucei* infections: An intense host-parasite interaction. *Front. Microbiol.* 7, 2126.
- Ross JA, Kasum CM. (2002). Dietary flavonoids: bioavailability, metabolic effects, and safety. *Annu Rev Nutr.* 22:19-34.
- Warren CA, Paulhill KJ, and Davidson LA. (2009). Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. *J Nutr.* 139:101-105.
- WHO. The World Health Report, 2003. Geneva: World Health Organization, 2003.
- Woznicka, E., Pieniazek E., Zapala, L., Byczynski, L., Trojnar, I., Kopacz, M. (2015). New sulfonic derivatives of quercetin as complexing reagents: synthesis, spectral, and thermal characterization, *Journal of Thermal Analysis and Calorimetry*. 120:351–361.

CHAPTER NINE

BCH UIL Festschrift MAA 009

EFFECTS OF ETHANOLIC EXTRACT OF *FICUS CAPENSIS* LEAVES ON SOME BIOCHEMICAL PARAMETERS OF PAROXETINE-INDUCED ERECTILE DYSFUNCTION IN MALE WISTAR RATS

Muritala, H.F., Raji, T.A., Kolawole, M.M., Ligali, F.O., Sadiq, A.A., Qasim, A.O and Bewaji, C.O.

Department of Biochemistry, University of Ilorin, Ilorin

Corresponding email: muritala_hf@unilorin.edu.ng

ABSTRACT

This study investigates the efficacy and dose-response of an ethanolic extract of Ficus capensis (fig plant) on various biochemical parameters related to cardiovascular disease and erectile dysfunction. Using Gas Chromatography-Flame ionization detector (GC-FID), active phenolic compounds in the extract were identified. Male Wistar rats were divided into groups, with some induced with erectile dysfunction using paroxetine hydrochloride. After induction, groups were treated with either distilled water, sildenafil citrate, or different doses of Ficus capensis extract for seven days. Results showed that Ficus capensis

extract significantly reversed the adverse effects induced by paroxetine, including alterations in enzyme activity, lipid profile, nitric oxide levels, and hormone concentrations. The study suggests Ficus capensis extract as a potential co-management option for erectile dysfunction and cardiovascular disease, with the 150 mg/kg dose showing the most effectiveness. Keywords include Ficus capensis, GC-FID, Paroxetine, and Erectile dysfunction.

Keywords: *Ficus capensis*, GC-FID, Paroxetine, Erectile dysfunction

INTRODUCTION

Several theoretical claims have been drawn to establish that there exists a relationship between the embryological and physiological nature of both the penis and the heart. As such, any observed malfunction seen in the penile vascular system is more likely to occur in the heart (Tuiten *et al.*, 2014). Cardiovascular disease has been identified as a very significant risk factor for Erectile dysfunction (inability to achieve and/or maintain penile erection for satisfactory sexual performance). Almost 50% of men with known coronary artery disease proven by cardiac catheterization have significant erectile dysfunction (Soriyamoorthy and leslie, 2020). Another report claimed that hypertension is a known contributing risk factor of ED with a record as high as 71% of hypertensive patients have been found to have ED (Cordero *et al.*, 2010).

Paradoxically, Erectile dysfunction has also been identified as a significant risk factor of cardiovascular disease. About 40% of men with ED will have hypertension while 35% of all hypertensive men will also have ED (Seftel *et al.*, 2004; Manolis and Doumas, 2008).

However, the quest of man to find

remedy to restore, improve and/or maintain normal sexual function in patients with erectile dysfunction and/or cardiovascular disease-related Erectile dysfunction has been perturbing since ancient times. Several proclaimed non-traditional remedies such as oral administration of phosphodiesterase 5 inhibitors (e.g., Sildenafil, tadalafil) have been found to have accompanying complications which include headaches, dyspepsia, nasal congestion, flushing, syncope etc. (Anand *et al.*, 2021). Other therapeutic mechanisms with no or less side effects such as Intracavernosal injection, Intraurethral prostaglandin E1 suppository, Vacuum erectile device, Penile prosthesis, Maxi-K channel activator, Guanylate cyclase activator, nitric oxide donors, stem cell regeneration therapy, nutraceuticals (e.g L- arginine, vitamin B complexes, zinc, trace minerals, aspartate and dehydroepiandrosterone) have also been found to improve erectile function (Kushakulla *et al.*, 2021; Kim *et al.*, 2021). Aside from the fact that these treatments only deal with the symptoms of ED and do not address any underlying pathogenesis (Chung, 2019), most of them are quite expensive and unaffordable for low-income earners.

Due to the claimed side effects associated with the therapeutic

mechanisms of treating ED, the use of herbal/ medicinal plants has gained more attention globally and has been considered a revolutionary breakthrough in the co-management of erectile dysfunction and cardiovascular disease related ED, and up to about 718 plant species have been used as an aphrodisiac to treat ED (Malviya *et al.*, 2011; Sin *et al.*, 2020). One of such medicinal plants is *Ficus capensis*.

Ficus capensis, locally referred to as “Opoto” (Yoruba, Western Nigeria), “Uwaryara” (Hausa, Northern Nigeria), “Akokoro” (Igbo, Eastern Nigeria) belongs to the family of Moraceae. In Nigeria, the plant is cultivated in all parts of the country but more abundant in the Middle-Belt (North-Central) of Nigeria. It usually grows to about 5- 12 meters (16-39 ft) in height, but may attain a height of 35-40 meters (115-131 ft). The large, alternate and spirally-arranged leaves are ovate to elliptic with irregularly serrated margins. Fresh foliage is conspicuous red color and papery. The bark of young trees is smooth and pale greyish-white in color, with increasing age, the bark becomes darker and rough. The figs are carried on short or long drooping spurs (or fascicles) which may emerge from surface roots, the trunk or especially from lower main branches. The figs are 2 to 4 cm in diameter and acquire a rosy, speckled exterior when ripe (Otitoju *et al.*, 2014). Aside from being aphrodisiac, other benefits of *Ficus capensis* leaves have been reported which include; remedy for ulcer, chest problems, tonsillitis, tuberculosis, abscesses, sores and as a lactogenic and

purgative agent (Esiebo *et al.*, 2018). Also, the antioxidant, antibacterial and antibacterial activity of the plant extract have also been scientifically validated (Muandal *et al.*, 2010).

A lot of botanical extracts including *Ficus capensis*, used by traditional medicine practitioners in Nigeria as decoctions for the treatment of various sexual abnormalities have been investigated, established, and shown to enhance sexual function. However, extract of *Ficus capensis* leaves have been identified in an In vitro study to simultaneously treat both ED and cardiovascular disease (hypertension) (Akomolafe *et al.*, 2016; Ajeigbe *et al.*, 2021) but there is dearth of information about the in vivo studies and the mechanism of action of the plant extract. Hence this research was designed to identify the probable mechanism of action of the ethanolic extracts of the plant by investing their effects on some biochemical parameters of male Wistar rats exposed to Paroxetine hydrochloride.

MATERIALS AND METHODS

Collection and Authentication of the Plant Samples

Fresh leaves of *Ficus capensis* were obtained from Ile Apa village, Unilorin, kwara state Nigeria and identified at the herbarium unit of the department of plant biology, Faculty of life sciences, university of Ilorin, where a voucher number UILH/501/1471/2022 was obtained.

Experimental Animals

Forty-eight healthy and sexually mature male albino rats (*Rattus norvegicus*) of an average weight of 170 ± 20 g were obtained from the animal holding unit, department of biochemistry, University of Ilorin. All the animals were housed in clean cages placed in well ventilated house. The animals were allowed to acclimatize for two weeks, where they were fed pelletized growers mash (vital feed) and clean water.

Reagents and Materials used

Ethanol, sucrose, Paroxetine, sildenafil citrate, Trizma base were products of G-tech, Golden penny sugar, GlaxoSmithKline, Pfizer, sigma Aldrich chemicals respectively.

Other reagents used include (NaHCO_3) (pH 9.5), arginine, $(\text{MnCl})_2$, $(\text{HClO})_4$, Ehrlich's reagent, HCl, NaOH, cGMP, $(\text{MgSO})_4$, Crotalus atrox, trichloroacetic acid, reagent C, vanadium chloride, Griess reagent, sulfanilamide, N-(1-N-naphthyl ethylendiamine dihydrochloride, sodium citrate, testosterone-HRP reagent, biotin reagent, TMB substrate reagent, phosphotungstic acid, MgCl_2 , sodium acetate, p-nitrophenyl phosphate, 4-aminoantipyrine, phenol, peroxide, cholesterol oxidase, cholesterol esterase.

Preparation of Ethanolic Extract of *Ficus capensis* Leaves

Fresh leaves of *Ficus capensis* were washed, oven-dried at 40°C , pulverized using a mechanical blender (Mikachi Blender Model MK-1830, China) and stored into an airtight material prior to

extraction, after which 900 g of the resulting powder was extracted in 3600 ml of ethanol (ratio 1:4) for 48 hours in a tight glass bottle at room temperature with intermittent shaking. The extract was then filtered with a white muslin cloth and Whatman No. 1 filter paper.

The resulting filtrate was concentrated at 40°C in a water bath and it was kept in a universal bottle, which was afterwards kept in a refrigerator maintained at 4°C .

Induction of Erectile Dysfunction

After the period of acclimatization, the rats (with the exception of the control group) were induced to have erectile dysfunction after oral administration of paroxetine at a dosage concentration of 10 mg /kg body weight on a daily basis for 21 days (time taken for spermatogenesis).

Grouping and Treatments of Animals

After 21 days, the animals were completely randomized into six groups which include; control group which received only water, untreated, 4 mg/kg body weight sildenafil citrate which received 4 mg/kg of Viagra, while 50 mg/kg body weight *Ficus capensis*, 100 mg/kg body weight *Ficus capensis* and 150 mg/kg body weight *Ficus capensis* groups received 50, 100, 150 mg/kg body weight of *Ficus capensis* respectively.

Collection and Preparation of Tissue Samples

The animals were made unconscious

using diethyl ether as anesthesia, after which they were sacrificed via the jugular vein puncturing method. Blood samples were collected in a sterile sample bottle, and the rats' penis, hearts, epididymis and testes were cut and cleared of connective tissues. All the organs (except the epididymis used for sperm morphological parameters) were washed in a sucrose buffer, cut into strips and homogenized in 0.25M sucrose solution (ratio 1:5) in a cold environment. The homogenates were kept in the refrigerator.

The blood in the plain bottles was left to coagulate properly after which it was spun in a centrifuge. The sera (supernatant) were thereafter aspirated using Pasteur pipette into dry, sterile sample bottles and kept in the refrigerator.

Determination of Biochemical Parameters

Determination of PDE V Activity in Paroxetine-Induced Penile Homogenate

0.5 mL of Tris buffer was pipetted into test tubes, and 0.1 mL of distilled water was added to each test tube. 0.1 mL of the enzyme was added, and 0.1 mL MgSO₄ was added to each tube. This was incubated at 37 °C for 20 minutes, after which 1.0 mL cGMP was added to all test tubes, after which 0.1mL of crotalus atrox was added to each test tube and also incubated at 37 °C for 10 minutes. 0.1 mL of Trichloroacetic acid was added to each test tube.

The solution was centrifuged immediately at 4000 g for 10 minutes using HELMRAESINN centrifuge 80-2, 0.5 mL of the supernatant was pipetted into another test tube each and 1.0 mL of distilled water was added to a separate test tube to serve as a blank and 2.0 mL of reagent C was added to all test tubes. It was left for 20 minutes for the color to develop and absorbance was taken at 820 nm using UV-VIS Spectrophotometer 752D.

Determination of Nitric oxide in Paroxetine-Induced Penile and Cardiac Homogenates

The NO levels were determined according to the procedure reported by Miranda *et al.*, 2001.

In brief, 100 µL of supernatant was applied to a micro titer plate well, 100 µL vanadium (III) chloride (8 mg/ml) was added to each well (for reduction of nitrate to nitrite) and this was followed by addition of Griess reagents, 50 µL sulfanilamide (2%) and 50 µL N-(1-Naphthyl) ethylenediamine dihydrochloride (0.1%). After incubating for 30 minutes at 37 °C, absorbance was read at 540 nm using ELISA reader (Sunrise, Tecan, Austria). Concentration of nitric oxide in serum samples was determined from linear standard curve established by 0-150 µmol/l sodium nitrate.

Determination of PDE V Activity in Paroxetine-induced Cardiac Homogenate

0.5 mL of Tris buffer was pipetted into

test tubes and 0.2 mL of distilled water was added to each tube. 0.2 mL of the enzyme was added and 0.2mL MgSO₄ was added to each test tube. This was incubated at 37°C for 20 minutes after which 2.0 mL cGMP was added to all test tubes. The tubes' content was incubated at 37°C for 20 minutes after which 0.1mL of crotales atrox was added to each test tube and also incubated at 37°C for 10 minutes. 0.1mL of Trichloroacetic acid was added to each test tube. 1.0 mL of distilled water was added to a separate test tube to serve as a blank and 2.0 mL of reagent C was added to all the test tubes. It was left for 20 minutes for the color to develop and absorbance was taken at 820 nm using UV-VIS Spectrophotometer 752D.

Determination of serum testosterone

The serum testosterone concentration was quantitatively determined using the direct human testosterone enzyme immunoassay (EIA) kit as described by Tietz (1995).

Procedure:

A 50 µl of the standard specimens and controls were dispensed into appropriate wells. Then, 100 µl of Testosterone-HRP conjugate reagent was dispensed into each well and mixed thoroughly for 30 seconds. Then, 50 µl biotin reagent was added into each well, the microplate was swirled for 30 seconds to mix the reagents. The plate was covered and incubated for 60 minutes at 25 °C. The liquid was removed from all the wells and the well was washed three times

with 300µl of 1X wash buffer. Then, 100µl of TMB substrate reagent was added into each well. The plate was covered and incubated at 25 °C for thirty (30) minutes. Then, 50 µl of stop solution was added to each well, mixed gently for 20 seconds. The absorbance was read on ELISA reader for each well at 450 nm within 15 minutes after the stop solution was added.

Determination of Serum Lipid Determination of Serum Total Cholesterol Concentration

The total cholesterol in the serum was assayed by the method of Fredrickson *et al.* (1967).

Procedure:

Using a micropipette, 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. 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°C for 5 min. The absorbance of sample and standard were read against the blank at 546 nm.

Determination of Serum Triacylglycerides concentration

The method describes by alblin *et al.* (1980) was used for the determination

of serum triglyceride concentration.

Using a micropipette, 10 μ l of appropriately diluted sample, standard and distilled water were pipetted into clean test tubes labelled sample, standard and blank respectively. 100 μ l 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°C). The absorbance of sample and standard was measured against the blank within 60 min at 500 nm.

Determination of Serum High Density Lipoprotein-Cholesterol

Concentration

HDL-cholesterol concentration in plasma was determined by adopting the procedure described by Albers *et al.* (1978).

Using a micropipette, 200 μ l of appropriate diluted sample, standard and distilled water were pipetted into clean test tubes labelled sample, standard and blank respectively. 500 μ l 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 minutes 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.

Determination of Serum Low Density Lipoprotein-Cholesterol

Concentration

Serum low density lipoprotein-cholesterol concentration was calculated using the formula described by Friedwald *et al.* (1972). The equation is expressed as:

$$\text{LDL Cholesterol (mmol/l)} = \text{Total Cholesterol} - \text{VLDL-C} - \text{HDL-C}$$
$$\text{VLDL-C} = \text{TAG}/2.2$$

Determination of Acid Phosphatase Activity

Acid phosphatase activity

The method described by Wright *et al* (1972a) was employed in this assay.

Procedure:

2.2 ml of sodium acetate (0.1 M) and 0.1 ml of $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ (0.1 M) were added in series to the test tubes. Then 0.2 ml of the enzyme source (appropriately diluted) was added and incubated at 37 °C for 10 minutes. 0.5 ml of 10 mM p-nitrophenyl phosphate (substrate) was added and the assay mixture incubated again for 30 minutes at 37 °C. The reaction was terminated immediately by adding 2.0 ml of 1 N sodium hydroxide. The blank was constituted by replacing the enzyme source with 0.2 ml of distilled water. The absorbance was read spectrophotometrically at 400 nm.

Arginase Inhibition Assay Procedure in Penile Homogenate

Penile homogenates are prepared by homogenizing 10 g (w/v) of penile tissue in 3 volumes of homogenizing cold buffer (phosphate buffer with a pH of 7.2). The homogenate was centrifuged for 20 min at 400 rpm and the supernatant was used as the source of the enzyme. Arginase activity was determined by the measurement of urea produced by the reaction of Ehrlich's reagent.

Ehrlich reagent:

The reaction mixture contained in final concentration 1.0 mM Tris HCl buffer pH 9.5 containing 1.0 mM $MnCl_2$, 0.1 M arginine solution and 50 mM of the enzyme preparation in a final volume of 1.0 ml. The mixture was incubated for 10 minutes at 37°C. The reaction was terminated by the addition of urea assay kit.

The control experiment was performed without the test sample and the arginase inhibitory activity was expressed as percentage inhibition.

Arginase Inhibition Assay in Heart Homogenate

The method of Campbell (2003) was employed in this assay procedure.

Principle: In the assay reaction mixture contained in 1ml include 50 μmol of $NaHCO_3$ buffer with a pH of 9.5, 20 μmol arginine, 0.5 μmol $NaCl_2$, 0.2 ml crude extracts and 0.79 ml of 10% rat

heart homogenate. The reaction mixture was incubated at 37 °C for an hour. The reaction was stopped with 1 ml of 0.5 mol/L $HClO_4$ and centrifuged to attain clear supernatant and the urea formed was determined using urea kits.

Determination of organ/body weight percentage

Organ/body weight can be expressed mathematically as:

$$\text{Organ/body weight} = \frac{\text{weight of the organ}}{\text{weight of the animal}}$$

Also, the percentage organ/body weight can be expressed mathematically as:

$$\text{Percentage organ/body weight} = \frac{\text{weight of the organ}}{\text{weight of the animal}} \times 100$$

Methodology of GC-FID

The method described by Wang (1997) was employed in this analysis.

Principle: The sample solution injected into the instrument enters a gas stream which transports the sample into a separation tube known as the "column" (Helium or nitrogen is used as the so-called carrier gas). The various components are separated inside the column. The detector measures the quantity of the components that exit the column. To measure a sample with an unknown concentration, a standard sample with known concentration is injected into the instrument. The standard sample peak retention time (appearance time) and area are compared with the test sample to calculate the concentration.

Methodology of Semen Analysis

Epididymis from a mature male wistar rat was macerated into 2 ml of 0.9% normal saline, 9 ml of sodium bicarbonate solution was distributed into 24 test tubes (4 samples each from each 6 groups). Tissue was left for about 30-60 seconds to allow sperm leak out of the epididymis and the epididymis and the resulting fluid was handled as semen

Sperm Motility

A drop of semen mixture was placed on a glass slide using 2ml syringe and covered with a coverslip. Glass slide was placed on a microscope stage and sperm motility was assessed as described by (Sonmez *et al.*, 2007).

The motility of epididymal sperm was evaluated microscopically within 2 min of their isolation from the caudal epididymis and data were expressed as % of fast motile, sluggish and dead sperm spermatozoa. The percentage of motility was evaluated visually at $\times 40$ magnifications (Sonmez *et al.*, 2007).

Sperm cell count

Dilution factor of 1:10 of the seminal fluid in normal saline was prepared for cell concentration using the semen dilution fluid. The glass slide was then placed on the Neubauer chamber and viewed under a microscope. A grid system divides the counting chamber into 5 major squares and each square containing 16 smaller boxes. The count includes all the sperm cells within the

five major squares using the top and right or left and bottom system of counting as described by Verma *et al.*, (2002).

Statistical Analysis

All data were presented as the mean of five 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 $P < 0.05$.

Results

Following the screening of the plant extract using a gas chromatography flame ionization detector (GC-FID), it was observed that the extract contained a wide range of phenolic compounds, which include Alpha-Caryophyllin, Geranyl Acetone, Orientin, Catechin, Epigallocatechin, Luteolin, Cetyl Behenate, Quercetin, Kaempferol, Rutin, Linalool, Lupeol, and Mycrene (Table 1).

Table 1: Components of *Ficus capensis* from Gas Chromatography Flame Ionization Detection

Components	Retention (S)	Area (M ²)	Height (M)
Solvent			
	0.500	87975.3305	5662.833
Alpha-Caryophyllene	6.916	71.7730	6.956
Geranyl Acetone	10.216	213.9490	20.999

Orientin	11.683	294.5310	29.788
Catechin	12.583	226.3155	14.660
Epigallocatechin	13.050	416.1520	34.352
Luteolin	13.750	194.0370	9.844
Cetyl Behenate	14.350	386.8800	35.273
Quercetin	15.016	195.2660	14.279
Kaempferol	15.600	538.7130	33.927
Rutin	16.750	437.7365	29.151
Linalool	17.833	300.1810	26.784
Lupeol	18.883	298.5815	21.720
Mycrene	20.850	135.0950	11.499

Quantitatively, kaempferol, the component with the highest peak and area, is the most abundant (15%), followed by rutin (12%) (Figure 1).

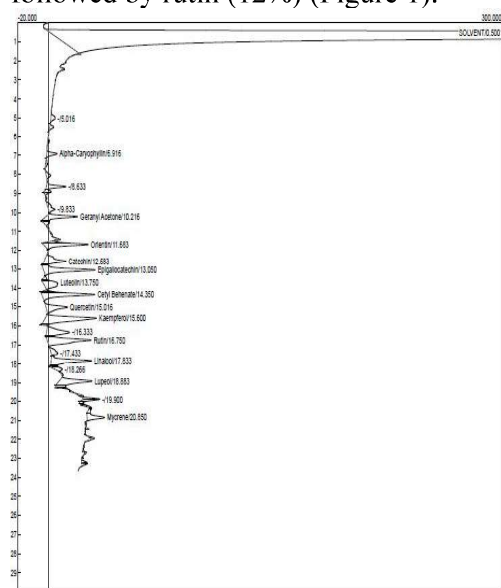


Figure 1: Components of *Ficus capensis* from Gas Chromatography Flame

Ionization Detection (GC-FID).

Whereas, alpha-caryophyllene represented the component with the lowest concentration (2%) (Table 1) (Figure 1).

Paroxetine treatment generally altered both the reproductive and cardiovascular biomarkers of the Wister rats when compared to the control group. In specific terms, paroxetine significantly raised ($p<0.05$) the specific activity of serum creatinine kinase myocardia band (CK-MB), specific activity of serum acid phosphatase (ACP), concentration of cholesterol, triacylglycerol (TAG), low density lipoprotein (LDL), very low-density lipoprotein (VLDL), atherogenic index, specific activity of both penile and heart Phosphodiesterase 5 (PDE5), concentration of heart nitric oxide (NO), and specific activity of both penile and heart Arginase.

On the other hand, paroxetine significantly lowered ($p<0.05$) the specific activity of the heart CK-MB, the concentration of penile nitric oxide (NO), serum high density lipoprotein (HDL), the specific activity of testicular acid phosphatase (ACP), and testosterone concentration.

Furthermore, the semen analysis upon administration of paroxetine revealed that paroxetine significantly raised ($p<0.05$) the number of dead cells, sluggish cells, cells with curved tails, detached head and tangled tails. Concurrently, paroxetine lowered ($p<0.05$) the number of motile and live

cells.

Virtually all the paroxetine-related changes in the biochemical parameters of the rats were significantly ($p<0.05$) reversed or improved by the *Ficus capensis* extract. Explicitly, in the heart, the plant extract significantly increased ($p<0.05$) the specific activity of CK-MB in a dose-dependent manner when compared to the untreated group (Figure 2).

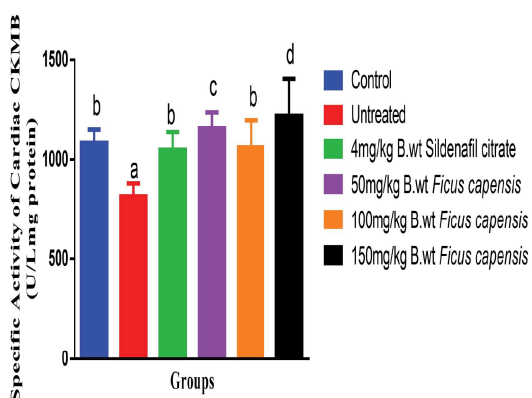
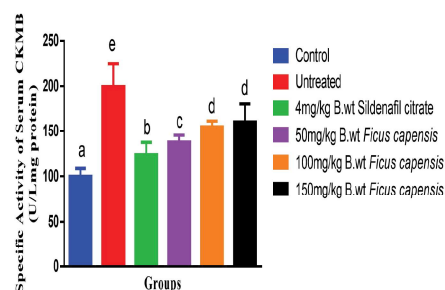


Figure 2: Specific activity of cardiac CK-MB in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.

However, a more pronounced increment was observed in the 150 mg/kg body weight of the *Ficus capensis* group when compared with the group that received 4 mg/kg body weight of sildenafil citrate (standard drug) and the control group (Figure 2). Also, the specific activity of heart CK-MB in the animal group administered with 50 mg/kg body weight was not significantly different ($p<0.05$) from the animal group that received the standard drug (Figure 2).

On the other hand, a significant increase ($p<0.05$) was observed in the specific activity of serum CK-MB in the untreated group (Figure 3).

Figure 3: Specific activity of serum CK-MB in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.



All the treated groups (4 mg/kg Sildenafil Citrate, 50 mg/kg, 100 mg/kg, and 150 mg/kg body weight) of *Ficus capensis* showed a significant difference ($p<0.05$) when compared with the control group (Figure 3). However, the 50 mg/kg ethanolic extract of *Ficus capensis* was more able to reverse the paroxetine effect and caused a significant decrease ($p<0.05$) in serum CK-MB when compared with both the 100 mg/kg and 150 mg/kg *Ficus capensis*-treated groups. Nevertheless, the rats treated with the standard drug showed a significant decrease ($p<0.05$) when compared with those in the *Ficus capensis*-treated groups (Figure 3).

In contrast to the significant increase ($p<0.05$) in the specific activity of cardiac PDE5 caused by paroxetine as

observed in the untreated group, the 50, 100, and 150 mg/kg body weight of the plant extract dose-dependently reduced ($p<0.05$) cardiac PDE5 specific activity (Figure 4).

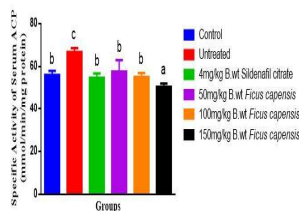


Figure 4: Specific activity of cardiac phosphodiesterase V (PDE V) in paroxetine-treated rats administered with three doses of ethanolic extract of *Ficus capensis* leaves during the period of treatment.

This reduction was more pronounced in the 150 mg/kg body weight group compared with all other test groups and the control. Also, there was no significant difference ($p<0.05$) in the group treated with the standard drug and 50 mg/kg body weight of *Ficus capensis* when compared with the control group (Figure 4).

In similar terms, the increased penile PDE5-specific activity was also restored significantly ($p<0.05$) in a dose-dependent manner, with the 150 mg/kg body weight group being the most pronounced (Figure 5).

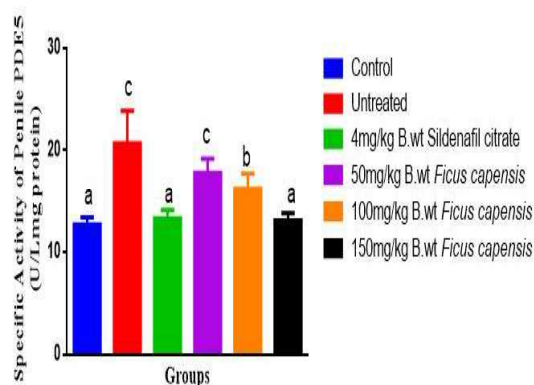


Figure 5: Specific activity of penile phosphodiesterase V (PDE V) in paroxetine-treated rats administered with three doses of ethanolic extract of *Ficus capensis* leaves during the period of treatment.

However, there was no significant difference ($p<0.05$) between the animal group treated with 150 mg/kg body weight of *Ficus capensis* and the standard drug when compared with the control group. Also, the animal group treated with 50 mg/kg body weight of *Ficus capensis* tends to show no significant difference ($p<0.05$) when compared to the untreated group (Figure 5).

In Figure 6, the penile arginase activity was significantly increased ($p<0.05$) (as

observed in the untreated group) after the administration of paroxetine when compared to the control group. The 50, 100, and 150 mg/kg doses of the plant extract were able to dose-dependently reverse this increment to normalcy when compared to the control.

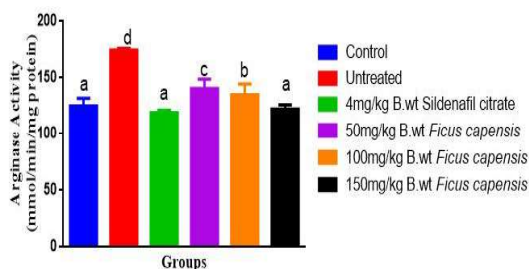


Figure 6: Activity of penile arginase enzyme in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves during the period of treatment.

However, the 150 mg/kg body weight of the plant extract tends to have the same effect as the standard drug (Figure 6). Furthermore, a similar paroxetine-effected increase in arginase activity was observed in the heart. The group of animals treated with 100 mg/kg and 150 mg/kg body weight of *Ficus capensis* showed no significant difference ($p < 0.05$) when compared with the group treated with the standard drug (Figure 7).

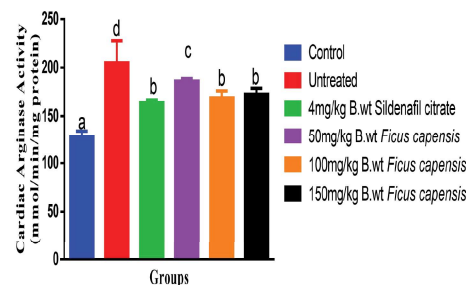


Figure 7: Activity of cardiac arginase enzyme in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves during the period of treatment.

In Figure 8, the paroxetine-effected decrease in penile nitrogen oxide concentration was significantly increased ($p < 0.05$) by the plant extract.

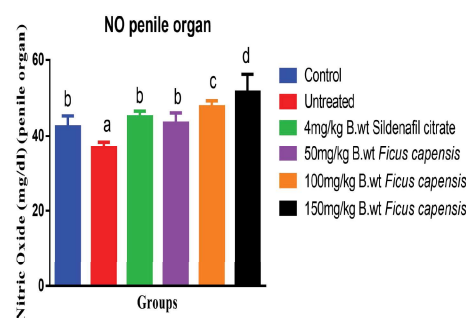


Figure 8: Concentration of penile nitric oxide in paroxetine-induced rats administered with three different doses of ethanolic extracts of *Ficus capensis* leaves during the period of treatment.

In specific terms, the group of animals administered 50 mg/kg, 100 mg/kg, and 150 mg/kg body weight of *Ficus capensis* significantly raised ($p < 0.05$) the concentration of NO in a dose-dependent manner when compared with the control. It was also observed that the 150 mg/kg *Ficus capensis* extract was able to increase nitric oxide

concentration more significantly ($p < 0.05$) than the standard drug (Figure 8). The animal groups treated with 4 mg/kg body weight of Sildenafil and 50 mg/kg body weight of *Ficus capensis* showed no significant difference ($p < 0.05$) when compared with the control group.

In Figure 9, the significant increase ($P < 0.05$) in the concentration of cardiac nitric oxide in the animals induced with paroxetine when compared with the control group was reversed during the period of treatment with the plant extract.

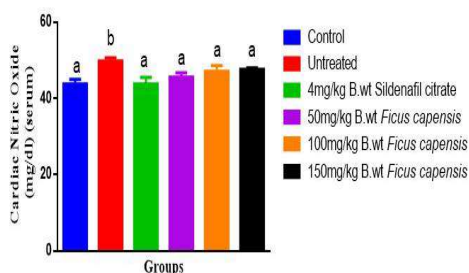


Figure 9: Concentration of cardiac nitric oxide in paroxetine-induced rats administered with three different doses of ethanolic extracts of *Ficus capensis* leaves during the period of treatment.

However, there was no significant difference ($P < 0.05$) among the animal groups treated with 4 mg/kg body weight of Sildenafil citrate, 50 mg/kg, 100 mg/kg, and 150 mg/kg body weight of *Ficus capensis* when compared with those in the control group (Figure 9).

Conversely, there was no significant difference in the concentration of serum nitric oxide in all of the groups, which include the control group, the

paroxetine-induced untreated group, the Sildenafil citrate group, and the *Ficus capensis*-treated group (Figure 10).

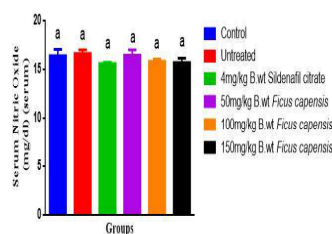


Figure 10: Concentration of serum nitric oxide in paroxetine-induced rats administered with three different doses of ethanolic extracts of *Ficus capensis* leaves during the period of treatment

In Figure 11, the specific activity of serum acid phosphatase (ACP) increased significantly ($P < 0.05$) in paroxetine-induced erectile dysfunctional rats when compared with the control and other treated groups.

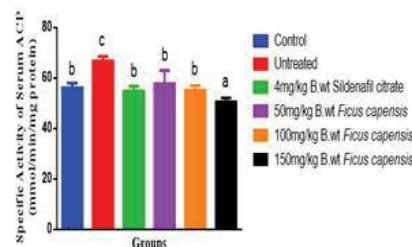


Figure 11: Specific activity of serum acid phosphatase in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves during the period of treatment.

When compared with the control group, there was no significant difference ($p < 0.05$) in the specific activity of serum ACP in the group of animals treated with 4 mg/kg body weight of Sildenafil citrate (a standard drug), 50 mg/kg, and 100 mg/kg body weight of *Ficus capensis*. Also, the group treated with 150 mg/kg body weight of *Ficus*

capensis showed a more significant decrease ($p<0.05$) in serum ACP than the ones treated with the standard drug and those in the control group (Figure 11).

In contrast, the untreated group showed a significant decrease ($p<0.05$) in the specific activity of testicular ACP when compared with the control and other treated groups. The group of animals treated with the standard drugs 50 mg/kg and 100 mg/kg showed no significant difference ($p<0.05$) when compared with the control (Figure 12).

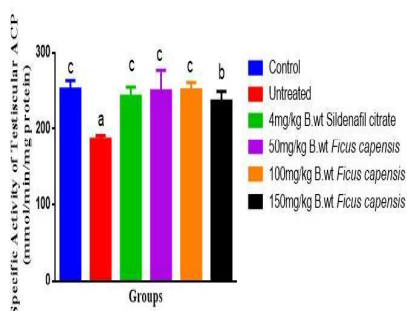


Figure 12: Specific activity of testicular acid phosphatase in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves during the period of treatment.

In Figure 13, cholesterol concentration significantly increased ($p<0.05$) in the paroxetine-induced untreated group for the period of the experiment when compared with the control.

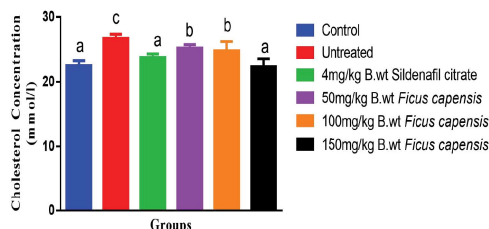


Figure 13: Concentration of cholesterol in paroxetine-induced rats administered with ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.

Significantly, sildenafil citrate and 150 mg/kg body weight of ethanoic extract of *Ficus capensis* reversed this back to normalcy when compared to the control group. Also, both the sildenafil citrate and 150 mg/kg body weight of the ethanoic extract of *Ficus capensis* have the same effect on cholesterol concentration.

In Figure 14, the increase in triacylglycerol caused by paroxetine was significantly reversed ($p<0.05$) to normalcy by the plant extract.

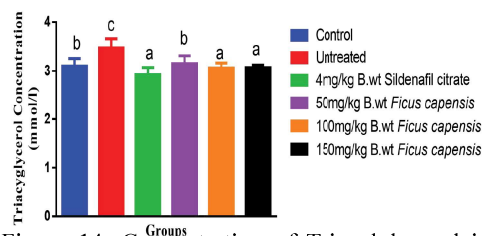


Figure 14: Concentration of Triacylglycerol in paroxetine-induced rats administered with ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.

In specific terms, the animals administered 50 mg/kg body weight of *Ficus capensis* were found to have no significant difference ($p<0.05$) when compared with the control. Also, there was no significant difference ($P<0.05$) in the serum triacylglycerol concentration of the group of animals treated with 100 mg/kg and 150 mg/kg body weight of *Ficus capensis* when compared with the ones treated with 4

mg/kg body weight of Sildenafil citrate (the standard drug).

In Figure 15, there was a significant ($p<0.05$) difference in the serum HDL concentration of the paroxetine-untreated group when compared with the control and all other test groups.

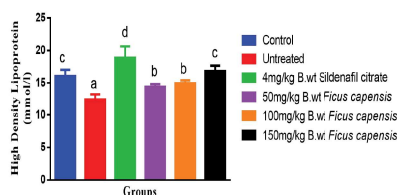


Figure 15: Concentration of High density lipoprotein (HDL) in paroxetine-induced rats administered with ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.

The animal group administered 150 mg/kg body weight of *Ficus capensis* had no significant ($p<0.05$) difference when compared with the control group, while both the 50 mg/kg and 100 mg/kg body weight *Ficus capensis* groups showed a significant decrease ($p<0.05$) when compared with the control and the Sildenafil-treated groups.

In Figure 16, there was a significant increase ($p<0.05$) in serum LDL concentration was observed in the paroxetine-induced erectile dysfunctional rats when compared with the control and other test groups.

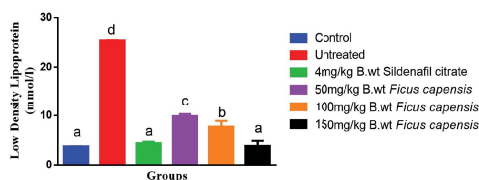


Figure 16: Concentration of Low density lipoprotein (LDL) in paroxetine-induced rats administered with

ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.

Upon treatment, the Sildenafil citrate (standard drug) and the *Ficus capensis* extracts were able to reverse the abnormal increase to normalcy, during which the group of animals in the SC-treated group and 150 mg/kg body weight *Ficus capensis* showed no significant difference ($p<0.05$) when compared with the control group. All the *Ficus capensis*-treated groups showed a significant difference ($p<0.05$) when compared with the control in a dose-dependent manner. The 150 mg/kg *Ficus capensis*-treated group showed a more significant decrease ($p<0.05$) than the 50 mg/kg and 100 mg/kg *Ficus capensis*-treated groups.

In Figure 17, VLDL concentration significantly increased ($p<0.05$) in the paroxetine-untreated group during the period of the experiment when compared with the control.

Figure 17: Concentration of Very Low density lipoprotein (VLDL) in paroxetine-induced rats administered with ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.

Significantly, the 50 mg/kg body weight *Ficus capensis*-treated group reversed this back to normalcy when compared

to the control group. Animals were administered 100, 150 mg/kg body weight of an ethanolic extract of *Ficus capensis*, and the Sildenafil citrate-treated group significantly decreased ($p < 0.05$) the VLDL concentration during the period of administration with respect to the control group.

In Figure 18, the atherogenic index significantly increased ($p > 0.05$) in the paroxetine-untreated group during the period of the experiment when compared with the control.

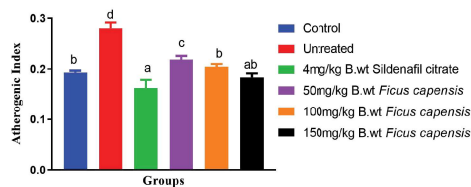


Figure 18: Atherogenic index in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment

There was a significant difference ($p < 0.05$) in the group of animals treated with 50 mg/kg and 150 mg/kg body weight of *Ficus capensis* when compared with the control group. However, the animals treated with 100 mg/kg body weight of *Ficus capensis* showed no significant difference ($p < 0.05$) when compared to the control group.

In figure 19, a significant reduction ($p < 0.05$) in testosterone concentration was observed in the untreated group.

This reduction (caused by paroxetine) was reversed on treatment with the

standard drug and doses of *Ficus capensis*. There was no significant difference ($p < 0.05$) between the group treated with the standard drug and those treated with 50 mg/kg body weight of *Ficus*. However, none of the treated groups was able to raise testosterone to its initial state when compared with the normal control group.

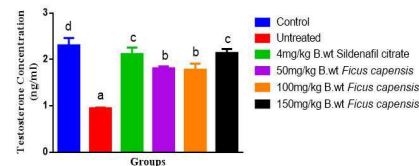


Figure 19: Testosterone concentration in paroxetine-induced rats administered with three doses of ethanolic extracts of *Ficus capensis* leaves in comparison with Sildenafil citrate during the period of treatment.

Table 2:	Organ/Body	Weight
	Percentage	
Animal Groups	PenileOrgans	Heart
Control	0.175 ± 0.041	1.154 ± 0.089
PXT	0.256 ± 0.053	1.236 ± 0.043
SFC	0.282 ± 0.039	1.274 ± 0.045
50 mg/kg B.wt	0.319 ± 0.028	1.387 ± 0.042
100 mg/kg B.wt	0.269 ± 0.019	1.351 ± 0.079
150 mg/kg B.wt	0.320 ± 0.035	1.356 ± 0.060

Table 2 indicates the organ/body weight percentage. With respect to the Paroxetine untreated group, the percentage of organ-body weight of the penile organ has no significant differences ($P < 0.05$) following the administration of 100 mg/kg body weight doses of *Ficus capensis* extract to the experimental animals. While the animals administered with 50, 150 mg/kg body weight of *Ficus capensis* extracts and 4 mg/kg body weight of Sildenafil citrate significantly increased ($P < 0.05$) the organ-body weight percentage of the penile organ when compared with the control group, The administration of 50 mg/kg, 100 mg/kg, and 150 mg/kg of the extract did not have a significant difference ($P < 0.05$) on the organ-body weight percentage of the heart when compared with the control and Paroxetine untreated groups (Table 2). The animals administered with 4 mg/kg of Sildenafil citrate showed a significant decrease ($P < 0.05$) in the organ-body weight percentage of the heart. However, there was no significant difference ($p < 0.05$) in the percentage organ-body weight of the testes across all the test groups (Table 2)

For the sluggish cells, there was a significant increase ($p < 0.05$) in the percentage of sluggish cells observed in all the animal groups: paroxetine untreated, Sildenafil treated, 50 mg/kg, 100 mg/kg, and 150 mg/kg body weight *Ficus capensis* extract groups when compared with the control group. The 100 mg/kg and 150 mg/kg *Ficus*-treated groups showed no significant difference ($p < 0.05$) when compared with the

Sildenafil-treated group (Table 3).

For the curved tails, there was a significant difference ($p < 0.05$) in the percentage of cells with a curved tail in all the animal groups: paroxetine untreated, sildenafil citrate, 50 mg/kg, 100 mg/kg, and 150 mg/kg treated groups when compared with the control. All the *Ficus capensis*-treated groups showed a significant difference ($p < 0.05$) in the percentage of curved cells in a dose-dependent manner (Table 3).

For the detached head cell, it was observed that animals treated with 150 mg/kg *Ficus capensis* extract showed no significant difference ($p < 0.05$) in the percentage of cells with detached heads when compared with the control. All the *Ficus capensis*-treated groups showed a significant difference ($p < 0.05$) in the percentage of detached head cells in a dose-dependent manner. It was also observed that animals that received 150 mg/kg body weight of *Ficus* extract significantly reduced the percentage of cells with detached heads compared to the standard drug (Table 3).

For the tangled cells, it was observed that the group of animals that received the extract of *Ficus capensis* (50 mg/kg, 100 mg/kg, and 150 mg/kg) showed no significant difference ($p < 0.05$) in the percentage of tangled cells when compared with the control group. The group treated with the standard drug proved to have the lowest percentage of tangled cells, followed by the 150 mg/kg *Ficus*-treated group (Table 3).

For the total number of cells, the

Animals treated with the standard drug showed a significant difference ($p < 0.05$) in the total number of cells when compared with the control group. It was also observed that the animals administered 100 mg/kg body weight *Ficus capensis* extract significantly increased ($p < 0.05$) the total number of cells when compared with the standard drug, 50 mg/kg, and 150 mg/kg Ficus-treated groups (Table 3).

SC= Paroxetine-induced and treated with Sildenafil citrate

FC 50 mg/kg= Paroxetine-induced and treated with 50 mg/kg dose of ethanolic extract of *Ficus capensis*

FC 100 mg/kg= Paroxetine-induced and treated with 100 mg/kg dose of ethanolic extract of *Ficus capensis*

FC 150 mg/kg= Paroxetine-induced and treated with 150 mg/kg dose of ethanolic extract of *Ficus capensis*

Table 3: Semen analysis of paroxetine-induced male wistar rats administered with ethanolic extract of *Ficus capensis* and Sildenafil citrate during the post treatment treated.

PARAMETERS	PC	NC	SC	FC 50 mg/kg	FC 100 mg/kg	FC 150 mg/kg
Motility (%)	62.5± 6.29 ^a	40.0± 10.00 ^a	47.5± 6.29 ^b	40.0± 10.00 ^a	55.0± 2.89 ^b	62.5± 2.50 ^b
Live cell (%)	62.5± 8.54 ^a	50.0± 12.25 ^a	57.5± 9.47 ^a	55.0± 6.50 ^a	65.0± 2.89 ^b	60.0± 4.08 ^b
Dead cells (%)	23.8± 7.47 ^a	42.5± 13.15 ^a	20.0± 4.08 ^a	35.0± 11.90 ^a	27.5± 4.79 ^b	22.5± 2.50 ^b
Sluggish cells (%)	10.0± 0.00 ^a	20.0± 4.08 ^{ab}	27.5± 11.81 ^{ab}	32.5± 6.29 ^b	25.0± 2.89 ^b	15.0± 2.89 ^b
Morphology (%)	57.5± 2.50 ^a	57.5 ± 2.50 ^a	57.5± 6.29 ^a	62.5± 2.50 ^a	60.0± 0.00 ^b	57.5± 4.79 ^b
Curved tail	2.5± 0.29 ^a	7.0± 0.58 ^a	3.5± 0.28 ^b	6.3± 1.44 ^a	4.8± 0.75 ^{abc}	5.5± 0.86 ^{bc}
Detached head	3.0± 0.00 ^a	7.5± 1.26 ^a	4.0± 0.00 ^b	6.3± 1.03 ^{bc}	3.3± 0.25 ^a	5.5± 1.04 ^{abc}
Tangled tail	4.3± 1.93 ^b	7.8± 2.93 ^b	0.8± 0.75 ^a	7.0± 3.14 ^b	1.5± 0.65 ^b	3.3± 0.75 ^b
Bent neck	4.3± 0.25 ^a	5.5± 0.29 ^a	5.8± 2.53 ^a	4.5± 0.65 ^a	4.8± 0.75 ^a	2.8± 0.48 ^a
Total cells (×106)	57.5± 14.08 ^b	45.0± 10.41 ^a	72.8± 9.20 ^b	51.3± 6.57 ^b	92.5± 4.79 ^b	62.5± 22.87 ^{ab}

KEY PC= Positive control; NC= Paroxetine-induced but not treated

DISCUSSION

Ficus capensis is a widely known medicinal plant employed in treatment of a number of diseases, such as dysentery, oedema, epilepsy, respiratory disorders, erectile dysfunction, etc., and has gained much interest in research owing to its pharmacological properties such as antioxidant, anti-inflammatory, antimicrobial, etc.

In this study, the ethanolic extract of *Ficus capensis* was analyzed, and different components of the extract were obtained by the Gas Chromatography-Flame Ionization Detector (GC-FID).

According to Israa *et al.* (2017), GC-FID identifies bioactive compounds based on peak area, retention time and molecular weight. From Table 1, myrcene has the highest retention time while alpha caryophyllene has the lowest retention time. A component with high retention time signifies that the component is more polar and as such has a higher boiling temperature with strong adherence to the separating column. Kaempferol has the highest peak area, while alpha caryophyllene has the lowest peak area; components with the highest peak area are in high concentrations, and vice versa. Other components with high peak areas include Epigallocatechin and cetyl Behenate. It is safe to say that the

concentration of bioactive compounds in *Ficus capensis* is closely related to health effects of fig and fig extract potential in treating erectile dysfunction.

The increase in serum CK-MB specific activity of the rats after 21 days administration of paroxetine (Figure 2) may be due to the fact that paroxetine, like other antidepressant, disrupts or alters the integrity and permeability of the myocardial membrane, which, when damaged, will release its constituents (cytosolic enzymes) such as CK-MB, LDH, AST, etc. into the extracellular fluids (Khalil *et al.*, 2015).

Conversely, the reduction in CK-MB specific activity after seven days administration of different doses of ethanolic extract of *Ficus capensis*, (Figure 2) indicates that *Ficus* may help in maintaining the membrane integrity, thereby restricting the leakage of the enzyme. This is in tandem with Mahmood *et al.* (2016) who measured the effect of Sildenafil citrate (standard drug) against cardiotoxicity induced by isoproterenol in male rats.

The biochemistry underlying the cardioprotective effect of Sildenafil can be traced to NO-cGMP signaling pathway since it has been observed that in the presence of cNOs inhibitors, Sildenafil was deprived of its cytoprotective effect (Hassan *et al.*, 2005). In addition, the cardioprotective effect of *Ficus* can be accounted for due to the presence of orientin and rutin in the plant extract (Lam *et al.*, 2016; patel and patel, 2019).

Also, the decrease in PDE5 activity observed after seven days of administration of different doses of the extract of *Ficus capensis* indicates that the extract possesses PDE5 inhibitory properties, which its mechanism may be

somewhat similar to that of Sildenafil citrate, which has been found to potentiate an endogenous increase in cGMP by inhibiting its breakdown at PDE5 catalytic site, thereby causing its accumulation and ultimately mediating a negative feedback regulation of the cGMP pathway (Corbin, 2004). In addition, the decrease caused by the extract of *Ficus* may somewhat be attributed to some of its polyphenolic constituents, quercetin and rutin which are found to possess erectogenic properties (Adefegba *et al.*, 2018).

An increased level of arginase activity is common among patients with ED and CVD such as hypertension, atherosclerosis, heart failure, etc., which could be a consequence reducing the biosynthesis of nitric oxide (NO) via the NO–cGMP pathway (Kim *et al.*, 2004; Li *et al.*, 2022). Thus, the decrease in both penile and heart Arginase activity observed in this study after seven days of administration shows that extracts of *Ficus capensis* possess an inhibitory effect on Arginase activity and could be of great importance in the management of ED as they could increase the genital blood flow during sexual arousal and in CVD as they could prevent endothelial dysfunction. The inhibitory properties of the extract can be attributed to some of its phenolic components, such as catechin, quercetin which have shown to be a strong inhibitor of arginase activity, and its biochemistry could be linked to the formation of hydrogen bond and hydrophobic interactions with the hydrophobic active site of the enzyme (Obboh *et al.*, 2015). This is in agreement with previous findings of de

Mello Cruz *et al.* (2013).

The cells of the vascular endothelium (VE) rely solely on NO (usually synthesized within VE by NO synthase) to carry out a number of physiological processes such as regulation of vessel tone, homeostasis, blood pressure, and vascular remodeling (Naseem, 2005). A large body of evidence supports that the NO system plays a critical role in blood pressure regulation, and any impairment in its production pathway may lead to the onset of essential hypertension (Grandvuillemin *et al.*, 2018). In this study, the recorded abnormal increase in cardiac NO of the untreated group when compared with others can be accounted for by the induction of iNOS (an isoform of nitric oxide synthase) by endotoxins, thereby resulting into abnormal or unregulated synthesis of NO (Naseem, 2005). This disorder is referred to as septic shock, a condition in which overproduction of NO is critical and is characterized by hypotension. This observation is corroborated by Moncada and Higgs (2006), where they attest that while the low concentrations of NO generated by eNOS protect against atherosclerosis by promoting vasodilatation, inhibiting leucocyte and platelet adhesion and/or aggregation, and smooth muscle cell proliferation, higher concentrations of NO generated by iNOS promote atherosclerosis either directly or via the formation of NO adducts, such as peroxynitrite.

Conversely, NO is chiefly needed in penile erection as it is an activator in the catalytic conversion of guanosine triphosphate to cyclic guanosine

monophosphate by soluble guanylyl cyclase. Thus, the significant increase in NO levels observed in both Sildenafil and Ficus-treated groups when compared with the untreated group indicates that the employment of *Ficus capensis* in the management of ED looks promising. A more profound increase observed in NO levels in Ficus extract-treated group may be accounted for by the presence of polyphenolic compounds such as catechin and quercetin, which are found to have inhibitory effects on arginase (Obboh *et al.*, 2015).

Acid phosphatase facilitates the exchange of materials between the germinal cells and Sertoli cells and thus enhances the development of spermatocytes during spermatogenesis (Peruquetti *et al.*, 2010). Therefore, the reduction in acid phosphatase activity observed in the paroxetine-untreated group reflects decreased testicular steroidogenesis due to decreased bioavailability and production of androgens (Yakubu and Jimoh, 2014). In contrast, the reversal and subsequent increase in the activities of the testicular phosphatases in the Ficus extract-treated groups may reflect an increase in functional and metabolic activities of the testis, all of which are androgen-dependent. Thus, it could be inferred that the plant extract possesses some androgenic properties.

In the serum, acid phosphatase is diagnostically useful as a serological and histological marker of diseases (Bull *et al.*, 2002). It is released into the serum from the prostate gland in

increasing amounts as malignant tissue proliferates (xu *et al.*, 2019). Therefore, the significant increase observed in serum acid phosphatase activity in the paroxetine-untreated group compared with the treated ones could be an indicator of prostate cancer. The decrease in serum acid phosphatase in the treated groups reflect the proper functioning of their prostate gland. In addition, alpha caryophyllene, epigallocatechin and rutin may also account for low serum ACP as they are anti-inflammatory, antidepressant, anticarcinogenic, etc.

A lipid profile, or lipid panel, is a panel of blood tests used to find abnormalities in lipids, such as cholesterol and triglycerides. The results of this test can identify certain genetic diseases and determine approximate risks for cardiovascular disease, certain forms of pancreatitis, and other diseases (Brunzell, 2008). The significant increase in cholesterol, triacylglycerol, VLDL, and LDL of the untreated group and a corresponding decrease in HDL observed after the period of 21 days of paroxetine administration indicate that paroxetine has a detrimental effect, probably interfering with membrane receptors or committed enzymes in lipid metabolism, which may result in cardiovascular disorders. The increase in LDL could be accounted for by the impairment of LDL membrane receptors, which are responsible for its uptake, resulting in increased LDL level. High serum HDL are lysosomally degraded by cytosolic enzymes into free cholesterol (Dasgupta and Washed, 2021). This shows a partial justification

for the high cholesterol concentration observed. Also, the increase in VLDL may stem from the observed increase in LDL since VLDL is a known precursor of LDL. Also, the increase in serum triacylglycerol glycerol could result from a genetic factor as well as the observed increase in HDL.

On the other hand, the reversal in cholesterol, triacylglycerol, VLDL, LDL, and HDL after seven days of treatment with different doses of *Ficus capensis* indicates that the plant extract was able to restore any impairment caused by paroxetine. The ability of *Ficus capensis* to reduce serum LDL and cholesterol concentrations could be attributed to catechin, which has been shown to up-regulate the LDL receptor and increase the clearance rate of cholesterol (Somporn *et al.*, 2018). The decrease in triacylglycerol concentration in the serum may be due to the presence of rutin in the plant extract (Manzoni *et al.*, 2019). The decrease in atherogenic index caused by the doses of *Ficus capensis* indicates that it was able to reduce any cardiovascular risk that could have been caused by paroxetine.

Testosterone is a well-known marker of androgenicity. It is the most important androgen secreted by the testes in humans (Walton *et al.*, 1995). The reduction in testicular testosterone content of the rats in the untreated group following the administration of paroxetine could be due to the direct toxic effect of the drug on the gonads or an indirect effect on the pituitary gland that is responsible for the secretion of and release of the androgen (El-

Gaafarawi *et al.*, 2005). This decrease could still imply that paroxetine has probably interfered with some enzymes in the testosterone biosynthetic pathway (Yakubu and Jimoh, 2014).

On the other hand, the reversal in the level of testosterone in the *Ficus capensis* extract-treated group suggests that the plant possesses some androgenic chemicals, which might have stimulated the animals to produce and secrete more testosterone. Also, the increase in testosterone concentration in groups administered various doses of the ethanolic extract of *Ficus capensis* can be attributed to the presence of flavonoids having a 5, 7-dihydroxychromen-4-one backbone, such as luteolin, quercetin, and rutin, in the plant extract, which are critical for the entry of cholesterol into the mitochondria, leading to the increased production of testosterone from testis Leydig cells (Ye *et al.*, 2020).

The decrease in motility and total sperm count observed in the paroxetine untreated-group with respect to the control and other treated groups could be attributed to the fact that paroxetine causes fluency in neurotransmission of serotonin which is paramount in regulation of the function of hypothalamic pituitary adrenal axis and finally affects the gonadotrophins and sperm production mechanisms. Over-released serotonin, which is caused by paroxetine, stimulates the serotonin receptors in different body organs, including the testes and epididymis, and this recessive stimulation might lead to abnormalities in sperm count and

availability (Hashim *et al.*, 2020).

However, the increase in motility and the total sperm count noticed in the groups treated with various doses of ethanolic extract may be due to quercetin, which improved sperm motility, sperm count and sperm viability while causing a reduction in sperm abnormalities such as tangled tails, detached tails and curved tails (Laoung-On *et al.*, 2022).

References

- Ajeigbe, O. F., Oboh, G., & Ademosun, A. O. (2021). Ficus plants in the Co-management of Hypertension and Erectile dysfunction. *Phytomedicine Plus*, 1(3), 100096.
- Akomolafe, S.F., Oboh, G., Oyeleye, S.I., & Boligon, A.A. (2016). Aqueous extract from *Ficus capensis* leaves inhibits key enzymes linked to erectile dysfunction and prevent oxidative stress in rats' penile tissue. *Journal of Nutrition and Food Science*, 4, 15–21.
- Anand, A., & Srivastava, P. K. (2012). A molecular description of acid phosphatase. *Applied biochemistry and biotechnology*, 167(8), 2174–2197.
- Bull, H., Murray, P. G., Thomas, D., Fraser, A. M., & Nelson, P. N. (2002). Acid phosphatases. *Molecular pathology: MP*, 55(2), 65-72.
- Brunzell, J. D., Davidson, M., Furberg, C. D., Goldberg, R. B., Howard, B. V., Stein, J. H., & Witztum, J. L. (2008). Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes
- Corbin, J. D. (2004). Mechanisms of action of PDE5 inhibition in erectile dysfunction. *International journal of impotence research*, 16(1), S4-S7.
- Cordero, A., Bertomeu-Martínez, V., Mazón, P., Fácila, L., Bertomeu-González, V., Conthe, P., & González-Juanatey, J.R. (2010). Erectile dysfunction in high-risk hypertensive patients treated with beta-blockade agents. *Cardiovascular Therapy*, 28, 15–22.
- Dasgupta, A., & Wahed, A. (2021). Clinical Chemistry, Immunology and Laboratory Quality Control: A Comprehensive Review for Board Preparation, Certification and Clinical Practice de Mello Cruz, E., da Silva, E. R., do Carmo Maquiaveli, C., Alves, E. S. S., Lucon Jr, J. F., dos Reis, M. B. G., & Vannier-Santos, M. A. (2013). Leishmanicidal activity of *Cecropia pachystachya* flavonoids: Arginase inhibition and altered mitochondrial DNA arrangement. *Phytochemistry*, 89, 71-77.
- EL-Gaafarawi, I., Hassan, M., Fouad, G., & El-Komey, F. (2005). Toxic effects of paroxetine on sexual and reproductive functions of rats. *The Egyptian Journal of Hospital Medicine*, 21(1), 16-32.
- Esievo, K. B., Anthony, S. O., Fatokun, O. T., & Kunle, O. F. (2018). *Ficus capensis* Thumb (Moraceae): Review of its ethnomedicinal uses,

- pharmacological activities and phytochemical constituents. *Arch. Curr. Res. Int*, 12, 1-7.
- Fredrickson, D. S., Levy, R. I., & Lees, R. S. (1967). Fat transport in lipoproteins—an integrated approach to mechanisms and disorders. *New England Journal of Medicine*, 276(3), 148-156.
- Grandvuillemin, I., Buffat, C., Boubred, F., Lamy, E., Fromonot, J., Charpiot, P., & Yzydorczyk, C. (2018). Arginase upregulation and eNOS uncoupling contribute to impaired endothelium-dependent vasodilation in a rat model of intrauterine growth restriction. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 315(3), R509-R520.
- Hainline Jr, A. (1982). Manual of laboratory operations: lipid and lipoprotein analysis. *HEW Pub. No. (NIH) 75-628 (rev.)*. US Government Printing Office Publication No. 1982-361-132, 678.
- Hassan, M. A., & Ketat, A. F. (2005). Sildenafil citrate increases myocardial cGMP content in rat heart, decreases its hypertrophic response to isoproterenol and decreases myocardial leak of creatine kinase and troponin T. *BMC pharmacology*, 5(1), 1-7.
- Khalil, M., Tanvir, E. M., Afroz, R., Sulaiman, S. A., & Gan, S. H. (2015). Cardioprotective effects of tualang honey: amelioration of cholesterol and cardiac enzymes levels. *BioMed research international*, 2015.
- Kim, S., Cho, M. C., Cho, S. Y., Chung, H., & Rajasekaran, M. R. (2021). Novel emerging therapies for erectile dysfunction. *The World Journal of Men's Health*, 39(1), 48.
- Kuchakulla, M., Narasimman, M., Soni, Y., Leong, J. Y., Patel, P., & Ramasamy, R. (2021). A systematic review and evidence-based analysis of ingredients in popular male testosterone and erectile dysfunction supplements. *International journal of impotence research*, 33(3), 311-317.
- Lam, K. Y., Ling, A. P. K., Koh, R. Y., Wong, Y. P., & Say, Y. H. (2016). A review on medicinal properties of orientin. *Advances in pharmacological sciences*, 2016.
- Laoung-On, J., Jaikang, C., Saenphet, K., & Sudwan, P. (2022). Effect of Nelumbo nucifera Petals Extract on Antioxidant Activity and Sperm Quality in Charolais Cattle Sperm Induced by Mancozeb. *Plants*, 11(5), 637.
- Li, Z., Wang, L., Ren, Y., Huang, Y., Liu, W., Lv, Z., & Xiong, Y. (2022). Arginase: shedding light on the mechanisms and opportunities in cardiovascular diseases. *Cell deathdiscovery*, 8(1), 1-14.
- Mahmood, A. M., Al-Abbassi, M. G., & Al-Obeidy, M. M. (2016). Effect of Sildenafil Citrate against Cardiotoxicity Induced by Isoproterenol in Male Rats. *International journal of pharmaceutical sciences*, 41(1), 27.
- Malviya, N., Jain, S., & Gupta, V.B. (2011). Recent studies on aphrodisiac herbs for the management of male sexual

- dysfunction- a review. *Acta pol Pharm*, 68(1), 3-8.
- Manolis, A., & Doumas, M. (2008). Sexual dysfunction: the 'prima ballerina' of hypertension-related quality-of-life complications. *Journal of Hypertension*, 26(11), 2074-2158.
- Manzoni, A. G., Passos, D. F., da Silva, J. L., Bernardes, V. M., Bremm, J. M., Jantsch, M. H., & Leal, D. B. (2019). Rutin and curcumin reduce inflammatory triglyceride levels and ADA activity in serum and immune cells in a model of hyperlipidemia. *Blood Cells, Molecules, and Diseases*, 76, 13-21.
- Miranda, K. M., Espey, M. G., & Wink, D. A. (2001). A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. *Nitric oxide*, 5(1), 62-71.
- Moncada, S., & Higgs, E. A. (2006). *The discovery of nitric oxide and its role in vascular biology*. *British journal of pharmacology*, 147(S1), S193-S201.
- Naseem, K. M. (2005). The role of nitric oxide in cardiovascular diseases. *Molecular aspects of medicine*, 26(1-2), 33-65.
- Oboh, G., Ademiluyi, A. O., Ademosun, A. O., Olasehinde, T. A., Oyeleye, S. I., Boligon, A. A., & Athayde, M. L. (2015). Phenolic extract from *Moringa oleifera* leaves inhibits key enzymes linked to erectile dysfunction and oxidative stress in rats' penile tissues. *Biochemistry Research International*, 2015.
- Otitoju, G., Nwamarah, J., Otitoju, O., Odoh, E., & Iyeghe, L. (2014). Phytochemical composition of some underutilised green leafy vegetables in nsukka urban Lga of Enugu State. *J Biodiv Env Sci*, 4, 208-17.
- Patel, K., & Patel, D. K. (2019). The beneficial role of rutin, a naturally occurring flavonoid in health promotion and disease prevention: a systematic review and update. *Bioactive food as dietary interventions for arthritis and related inflammatory diseases*, 457-479.
- Peruquetti, R. L., Taboga, S. R., & Oliveira, M. T. V. D. A. (2010). Expression of acid phosphatase in the seminiferous epithelium of vertebrates. *Genetics and molecular research*, 620-628.
- Seftel, AD., Sun, P., & Swindle, R. (2004). The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *Journal of urology*, 6(1).
- Somparn, N., Saenthaweeuk, S., Naowaboot, J., Thaeomor, A., & Kukongviriyapan, V. (2018). Effect of lemongrass water extract supplementation on atherogenic index and antioxidant status in rats. *Acta Pharmaceutica*, 68(2), 185-197.
- Sönmez, M., Yüce, A., & Türk, G. (2007). The protective effects of melatonin and vitamin E on antioxidant enzyme activities and epididymal sperm characteristics of homocysteine treated male rats. *Reproductive Toxicology*, 23(2), 226-231.
- Sooriyamoorthy, T., & Leslie, SW.

- (2020). *StatPearls Publishing*. FL, USA. Tietz, N. W. (1995). Clinical guide to laboratory tests (3rd edition) Philadelphia: *W.B Saunders Company*.
- Tuiten, J.J.A., Bloemers, J.M.M., & De Lange, R.P.J. (2014). Use of testosterone and a 5-HT1A agonist in the treatment of sexual dysfunction. *US Patent*, 8, 648-712.
- Walton, S., Cunliffe, W. J., Keczkes, K., Early, A. S., McGarrigle, H. H. G., Katz, M., & Reese, R. A. (1995). Clinical, ultrasound and hormonal markers of androgenicity in acne vulgaris. *British Journal of Dermatology*, 133(2), 249-253.
- Wang, Y., Zhang, Y., Guan, L., Wang, S., Zhang, J., Tan, L., Kong, L. & Zhang, H. (2021). Lipophilization and amylose inclusion complexation enhance the stability and release of catechin. *Carbohydrate Polymers*, 269, 118251.
- Warnick, G. R., & Albers, J. J. (1978). A comprehensive evaluation of the heparin–manganese precipitation procedure for estimating high density lipoprotein cholesterol. *Journal of lipid research*, 19(1), 65-76.
- Wheatley, D. N., Philip, R., & Campbell, E. (2003). Arginine deprivation and tumour cell death: Arginase and its inhibition. *In Guanidino Compounds in Biology and Medicine* (pp. 177-185). Springer, Boston, MA.
- Wright, P.J., Leatherwood, P.D., Plummer, D.T., 1972. Enzymes in rat urine: alkaline phosphatase.