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(RESEARCH ARTICLE)

A scientific compendium of the effects of sildenafil citrate on the liver, kidney and heart of male albino rats at Nnewi, South East Nigeria

Okpalakunne SE [1], Unekwe PC [1], Chukwu LC [2,*] and Okwara JE [3] and Mansur Aliyu Ramalan [4]

[1] *Department of Pharmacology and Therapeutics, Faculty of Medicine, College of Health Sciences, Nnamdi Azikiwe University Awka, Nnewi- Campus, Nnewi.*
[2] *College of Medicine, Chukwuemeka Odumegwu Ojukwu University, Amaku Awka Campus Nigeria.*
[3] *Department of Chemical Pathology, Faculty of Medicine, Nnamdi Azikiwe University Awka, Nnewi- Campus, Nnewi.*
[4] *Department of Internal Medicine, Aminu Kano Teaching Hospital / Bayero University Kano.*

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Abstract

This study investigated the various effects of Sildenafil citrate on the liver, kidney and heart of male *albino rats*. Twenty eight male rats randomly divided into 4 groups and weighing 131-214g were used. While the animals in group 1 (control) received food and water only, those in the study groups 2,3&4 respectively received 25mg/kg, 50mg/kg and 100mg/kg of Sildenafil citrate orally, daily for 4 weeks. All animals were sacrificed and blood samples collected by cardiac puncture for analysis of biochemical parameters. The rats Liver, kidneys and hearts were subjected to histopathological tests. Study results showed no changes in food consumption, fluid intake, body weight and relative organ weight of the animals. The animals in group 4 showed significant increase in mean Lactate dehydrogenase and Aspartate aminotransferase ($^{*}P<0.05$) compared to control. Mean levels of creatinine was significantly higher among group 4 animals ($^{*}p<0.05$) but not significantly high among the animals in other groups. Mean Na+ and Cl- level were significantly high among the animals in group 4 ($^{*}p<0.05$). Although no histopathological changes were observed in the heart of the rats in groups 2,3 and 4, there were significant increase in serum levels of Na+, K and Cl- of animals in group 4 which could have affected their heart owing to fatigue. Sildenafil citrate (100mg/kg) caused distortion in cyto-architecture of the liver and mild distortion of cortical structures in the kidneys of *albino rats*. Sildenafil citrate has potential toxic effects on the liver, kidney and heart of studied rats with higher doses. Conclusion: Sildenafil citrate has potential toxic effects on the liver, kidney and heart of male *albino rats* especially with higher doses.

Keywords: Male albino rats; Sildenafil; Biochemical parameters; Histopathological changes

1. Introduction

Erectile Dysfunction (ED) is clinically defined as the inability to achieve and or maintain a penile erection sufficient for sexual intercourse. The problem may be seen in 1 in 5 men but may be larger with increasing ages. In patients without trauma or surgery, a duration of 3-months of this symptom is usually accepted as the basis for making a diagnosis of ED [1,2,3].

Another school of thought defined erectile dysfunction as the persistent inability to achieve or maintain penile erection sufficient for a desired satisfactory sexual activity [4].

Erectile Dysfunction is the most common disorder of sexual function in men after premature ejaculation. It is said to affect nearly 30 million individuals in the United States of America [5].

* Corresponding author: Chukwu, Leo Clinton Chukwu
College of Medicine, Chukwuemeka Odumegwu Ojukwu University, Amaku Awka Campus Nigeria.

In terms of causation, ED has a complicated interaction between the contributions from vascular, neurogenic, hormonal, psychogenic, iatrogenic, and anatomic causes. All these causative factors are seen to play important roles in the propagation of ED [6]. There is a high prevalence and incidence of ED worldwide as demonstrated by many large epidemiological studies. In the Men's Attitude to Life Events and Sexuality Study, which included 20 to 75-year-old men from 8 countries (United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil), the ED prevalence, assessed by International Index of Erectile Function (IIEF), ranged from 22% in the United States to 10% in Spain [7]. Sildenafil Citrate otherwise called Viagra is an orally active drug for the treatment of erectile dysfunction. It is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Chemically, Sildenafil citrate is designated as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate [8].

2. Mechanism of Action of Sildenafil citrate

To have an erect penis during sexual stimulation, there has to be an adequate release of nitric oxide (NO) in the corpus cavernosum. The released nitric oxide will activate the enzyme, guanylate cyclase which results in an increased level of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood [9].

Sildenafil citrate (Viagra) enhances the actions of NO by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. It is worthy of note that Sildenafil citrate has no direct relaxant effect on isolated human corpus cavernosum. When sexual stimulation causes local release of NO via parasympathetic stimulation, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum. This will now result in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation [9,10].

After sexual stimulation, NO concentration is significantly increased and contributes to the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP). Downstream, cGMP decreases intracellular Ca^{2+} (calcium ions) in the cavernosal smooth muscles, leading to smooth-muscle relaxation. Once relaxed, the smooth muscles collapse the veins, which causes reduced drainage of arterial blood, thus sustaining an erection. The homeostatic role of phosphodiesterses (PDEs) as related to the intracellular levels of cAMP and cGMP was first described by Sutherland who, because of this, was awarded the Noble Prize for Physiology and Medicine in 1971 [11]. These enzymes hydrolyse the phospodiester bond of cAMP and cGMP to form the inactive 5-AMP and 5-GMP. In optimizing the intracellular levels of cAMP and cGMP, breakdown is predominant over synthesis.

The importance of PDEs as regulators of signaling is evident going by their development as drug targets in various diseases. Cardiovascular disease such as heart failure and atherosclerotic peripheral disease, neurological disorders, erectile dysfunction. Various phosphodiesterases that regulate cAMP catabolism include PDE_5A, PDE_6, PDE_9A, $PDE_{10}A$, $PDE_{11}A$ and their expression is often selective to tissues [12].

Among the PDE's, PDE_5 which is influenced by sildenafil and other inhibitors of clinical use, has been investigated widely. It should be noted that PDE_5 inhibition is a primary target for the treatment of erectile dysfunction and pulmonary hypertension [11,12].

Scientifically described also are the three PDE_5 isoforms. These have been identified as PDE_5A1, A2, and A3. PDE_5A1 and A2 isoforms are expressed in several tissues, including brain, lung, heart, kidney, bladder, prostate, urethra, penis, uterus and skeletal muscle. The A3 isoform is located in tissues having a cardiac or smooth muscle constituent, like heart, bladder, prostate, urethra, penis, uterus and skeletal muscle [11,13].

2.1. The Effect of Sex Enhancing Drugs on Different Organs of Male Albino Rats

Sildenafil citrate, a drug for Erectile dysfunction is commonly known, in public as Viagra or Revatio. It causes serious histopathological side effects when used at overdosed levels or misused leading to an increased risk for male reproductive function, which can be disrupted by exposure to sex enhancing drugs that can exogenously mimic and increase or disturb the testis, at overdoses of erectile drugs [14].

A good knowledge of the entire list of side effects of performance enhancing medications are very necessary for impotent men before seeking treatment for same. Associated adverse effects of most impotence medications like Sildenafil citrate (Viagra), Vardenafil (Levitra) and Tadanafil (Cialis) may include minor side effects like headaches (occasioned by the opening up arteries in the brain's lining and causes excess pressure) while major side effects may

include heart attacks. Co-administration of drugs like nitroglycerin for angina may pose another major problem. Nitroglycerin acts by increasing nitric oxide, and it can help angina cases by opening up the arteries that supply the heart with oxygen. By taking nitroglycerin and sildenafil citrate together, the increased nitric oxide plus the blockade of PDE5 can aggravate problems. This combination could result in a severe drop in blood pressure (hypotension) and lead to extreme dizziness, fainting or even a heart attack. These may further lead to a condition called Priapism (persistent often painful penile erection without sexual interest). These medications may cause dizziness and may affect the ability to drive or operate machinery safely [9,14].

Other problems besides headache may include body aches, digestive problems, flushes, dizziness, vision changes, congestion and severe or major adverse effects [15].

2.2. Effects of Sildenafil citrate on some major organs of the *Albino rat*

In an experimental study on the effect of sildenafil Citrate on the liver structure and function in obstructive jaundice, there was no difference between the sildenafil-treated and control groups with regard to the aspartate aminotransferase and alanine aminotransferase levels ($p=0.423$, $p=0.661$). The alkaline phosphatase and total bilirubin levels among the groups were statistically different ($p<0.001$). At the 28th day, liver function tests except alanine aminotransferase showed statistical significant differences among the groups ($p<0.001$). Liver function tests did not show statistical significant changes between the 10th and 28th day in sildenafil-treated rats ($p>0.05$)[16].

In that same study, there was statistical significant differences among the groups as regards cholestasis, fibrosis, inflammation, and necrosis ($p<0.001$). Also edema increased in the sildenafil-treated group ($p<0.001$). On the 28th day, the severity of structural changes in the liver after obstructive jaundice, except edema, reduced significantly ($p<0.001$). The sildenafil-treated groups at different time points didn't show any statistical difference in histopathological changes ($p>0.05$) [16].

As the largest glandular organ of the body, the liver which approximately weighs between 1.4-1.6 kg, performs major roles in body metabolism besides its numerous functions including protein synthesis, glycogen storage, bile production and detoxification of most substances [17].

Another important organ in the body, the Kidneys functions in the removal of waste products from the blood as well as regulate the amount of fluid and electrolytes balance in the body. A combination of hepatic metabolism and renal excretion in humans functions to eliminate the majority of administered drugs [18].

In studying the hepatocellular attenuating effects of Sildenafil by a group of authors, it was found that Sildenafil when used as pretreatment for hepatic injuries has a hepato-protective effect in a rat model of partial liver ischemia-reperfusion injury. This was evidenced by suppression of the increase in AST and ALT, decreased scores of necrosis, attenuation of morphological liver injury, and antiapoptotic activity. There was a decrease in the expression of ICAM-1 mRNA and reduction of leukocyte-endothelial interaction, as evidenced by attenuated MPO staining in the sildenafil treated rats, were also observed [19].

Sildenafil is said to be a highly selective inhibitor of cyclic guanine monophosphate (cGMP)-specific phosphodiesterase type 5. There have been reports that sildenafil citrate may increase cardiovascular risk, particularly fatal arrhythmias, in patients with cardiovascular disease [20]. 34.8% of men aged 40 to 70 years have moderate to complete ED, and 15% of men aged 70 have complete ED as reported by the Massachusetts Male Aging Study. The risk of ED has been shown to markedly increase with age, with a high prevalence of ED found in patients with cardiovascular disease. Since PDE-5 (Sildenafil) inhibitors promote vasodilatation, they are said to have the potential to cause hypotension. This medical concern has been greatest for elderly patients with pre-existing cardiovascular disease. [20,5].

Sudden cardiac death is a major cause of death in many industrialized countries. Aetiologically, a lethal cardiac arrhythmia known as ventricular fibrillation (VF) may be responsible. Post-marketing surveillance data following the Food and Drug Administration (FDA) approval of Sildenafil citrate by the US FDA DID reveal some significant cardiovascular problems, including sudden cardiac death. These problems are related to the use of sildenafil citrate [21].

In justifying the need for this study, one can recall that in the past the US Food and Drug Administration (FDA) reported 130 confirmed deaths among men (mean age, 64 years) who received prescriptions for sildenafil citrate. During that period, more than 6 million out patient prescriptions totaling about 50 million tablets were dispensed, March-November 1998 [20]. Such deaths may equally occur in Nigeria but are either under reported or totally unreported. The US FDA

reported recently that significant cardiovascular events, including sudden cardiac death, have occurred in men with erectile dysfunction using sildenafil citrate. Such reports raises the concern that sildenafil citrate may increase the risk of cardiovascular events, particularly fatal arrhythmias in patients with cardiovascular disease. Also there have been deaths of many prominent Nigerians suspected to arise from Sildenafil usage but such deaths were histopatologically unreported owing to the black man's aversion for post mortem histological analysis of the dead. Also this research study prefers to take an indebt study of the 3 major body organs (liver, kidneys and heart) together. This aims at imparting a comprehensive knowledge since most other earlier studies concentrate on only one or two organs at a time. Also a comprehensive literature search will reveal a paucity of such studies in Nnewi, South East Nigeria in the past necessitating the need for this very one. This very study aims at filling the above stated knowledge/research gaps already existing in the academic world.

From the knowledge gaps above stated, we set out to achieve the following objective which included: to investigate the effects of sildenafil citrate on food consumption and water intake of albino rats, as well as investigate the effects of sildenafil citrate on the average body weight and relative organ weight of the animals. Others included investigating the effects of sildenafil citrate on some biochemical parameters of the test animals and also studying the effects of sildenafil citrate on the histological features of these vital organs (heart, liver, kidney) of male albino rats

3. Material and methods

3.1. Materials

3.1.1. Animals

Twenty-eight (28) healthy male *albino rats* were used for this study**.**

3.1.2. Drugs and Reagents

The Drugs and reagents employed for the study were Sildenafil citrate 100mg tablets, Potassium bicarbonate 2g, Magnesium sulphate 20g, Distilled water (1000ml), Xylene, Ethanol, Normal saline

3.1.3. Equipment and Sources

Orogastric tube, kerro electronic scale, Weighing balance, Centrifuge, Biochemistry analyzer (accurex)^{RX}, Water bath, Microtome, RANDOX commercial kits and Microscope.

3.2. Methods

This study was carried out at the animal laboratory of the Nnamdi Azikiwe University Nnewi Campus, Nigeria after the ethics committee of the institution had given the due approval to for the study to commence. This research was designed as a prospective cross sectional descriptive and experimental study involving 28 adult male *albino rats* (twenty eight) weighing between 131-214g. The rats were also obtained from the animal care unit of the Department of Pharmacology and Therapeutics, College of Health Sciences, Nnamdi Azikiwe University Nnewi campus. The animals were randomly kept in their individual cages for one week to enable them acclimatize before the study proper. They were maintained in a well-ventilated house at temperature of about 25± 30^{o}C on a 12-hours light-dark cycle. They had access to the recommended animal feed (produced by Bendel Feed Mill Ltd Benin city, Nigeria) and tap water. Daily observations and daily body weight were taken. Feed and water were measured before giving it to the animals. The animals were thereafter randomly divided into four (4) groups of seven (7) animals each and kept in separate cages. Group 1 served as control while those in 2 to 4 served as the study (test) groups.

The control received only food and water daily. The average feed and water consumption as well as the animal's average weight were measured and recorded weekly. The animals in the different study groups were administered with different doses of sildenafil citrate. Study group 2 received 25mg/kg; study group 3 received 50mg/kg while study group 4 received 100mg/kg of Sildenafil citrate orally every day for 4 weeks. They were dosed accordingly from first week to fourth week of the study.

3.3. Drug preparation and administration

Sildenafil citrate procured from Signature Pharmaceutical Mumbai, India was used for this study. The stock solution was prepared by dissolving 100mg by weight of sildenafil tablet in 10mls of distilled water. This means that 1ml of stock

solution was equivalent to 10mg of Sildenafil, therefore animals in various treatment groups were dosed based on their daily body weight. The solution was constituted just before use and left over was discarded.

Group 1 of the animals served as control and was given only feed and 10mls of water only.

The other three (3) groups 2, 3, 4 were given varying daily doses of the test substance (Sildenafil citrate).

Group 2 served as the low dose group and was given sildenafil citrate at a dose of 25mg/kg.

Group 3 received the medium dose of Sildenafil citrate at the dose of 50mg/kg.

Group 4 were served high dose of Sildenafil citrate dosages at dosages of 100mg/kg.

All the animals were sacrificed after 4 weeks of study with chloroform anesthesia. The animals were weighed just before the sacrifice. Blood samples were collected by cardiac puncture with 5ml syringes and same analyzed for some biochemical parameters.

3.4. Histopathological analysis

The experimental animals were sacrificed after 4 weeks of the study period and the following organs of the studied animals (liver, kidney and heart) harvested. The recorded weights of the harvested organs were then used in calculating their relative weights in relation to the total animal body weights. Thereafter, the organs were fixed in 10% normal saline and processed for histopathologic analysis [22].

3.5. Tissue processing

Tissue processing was done as follows: 70% ethanol was allowed to stay for 2 hours, while 90% ethanol stayed for 16hrs (overnight), Absolute ethanol I stayed for 1hr, Absolute ethanol II 1hr, Chloroform/xylene mixture (1:1) 16hrs (overnight), Paraffin wax I 1hr, Paraffin wax II, 1hr, and Paraffin wax III for 1hr. The tissues were embedded in molten paraffin wax. Sections 5µm thick were obtained by collecting three sections, omission of the next ten (10), then collection of the next three sections. Sectioning was with a rotary microtome. The cut sections were stained with Ehlirich's haematoxylin and eosin (H & E) [22].

3.6. Staining procedure

Paraffin wax was removed from sections by immersing in 2 changes of xylene (5mins each) Sections were washed in absolute ethanol, two changes of 1min each. Treatment with 90% and 70% ethanol, washed thoroughly in several changes of water. Differential in acid (1% conc. HCL in 70% ethanol) controlled microscopically until only nuclei remain blue. Thoroughly washed in water. "Blued" in Scott's tap water substitute (potassium bicarbonate 2g, Magnesium sulphate 20g, distilled water to make up 1000mls) for 5mins was rinsed briefly in water, Sections were counterstained in 1% aqueous eosin for 3mins, washed in running water for 1 min dehydrated by washing in 70%, 90% and three change of absolute ethanol. Sections were cleared in xylene 2 changes. Section mounted in DPC mountant. The tissue is now ready to be viewed under a microscope [22].

3.7. Preparation of stains

Staining of tissues were done using the method as described by Avwiro in his 2010 publication, Histochemistry and Tissue Pathology, [23].

3.8. Biochemical parameters determination

3.8.1. Determination of serum alkaline phosphate (ALP)

Serum alkaline determination was done using method as described in [24].

3.8.2. Determination of transaminases

Asparatate amino transferase (ast) and Alanine amino transferase (alt) activities. The determination of Asparatate amino transferase (ast) and Alanine amino transferase (alt**)** was done by using the method as describe in [25].

3.8.3. Determination of serum bilirubin

By the odification of Jendrassik-Grof method of bilirubin determination in serum method was adopted [26].

3.8.4. Determination of serum total protein

Total protein determination was done using the biuret 2 method. Absorbance reading was taken after 30 minutes at 546nm against reagent blank [27].

3.8.5. Determination of serum albumin

This was done using bromocresol green method (BCG) [28].

3.8.6. Determination of serum urea

Weatherburn's enzymatic method of urea estimation as modified by [29] was adopted

3.8.7. Determination of serumm creatinine

This was done using the modified Jaffe's method [16].

3.8.8. Determination of serum sodium, potassium and chloride

The electrolytes sodium, potassium and chloride determination were done using an ion selective electrode (ISE) device [30].

3.9. Statistical analysis

The results gotten were expressed as means ±SD. Comparative analyses among variables were done using one way analysis of variance (ANOVA) test. A post Hoc comparison (Bonferonni) test was performed to ascertain significant differences between means. Statistical significance was set a p value <0.05. All statistics were done using SPSS for windows (version 16.0).

4. Results and discussion

1. Effect of sildenafil on average weekly food intake (mean + sd) of treated animals and control in (g)

Week 1: Animals in control group that received food and water had a value of (203.76±0.05) grams of food and water while food intake of animals administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had following values (203.66±0.05; 203.43± 0.46; 203.7±0.09) g respectively. Analysis of variance (ANOVA) showed no significant differences in food consumption among the study groups Table 1.

Table 1. Effect of Sildenafil Citrate on the Average Weekly Food Consumption of the Animals

	Food intake (g)			
Dose (mg/kg)	Week (1)	Week (2)	Week (3)	Week (4)
Control	203.76±0.05	203.75±0.05	203.70±0.09	203.70±0.09
25	203.66±0.05	203.68±0.07	203.65±0.08	203.68±0.07
50	203.43±0.46	203.68±0.12	203.61±0.04	203.63±0.05
100	203.70±0.09	203.68±0.09	203.68±0.07	203.70±0.09
F-STATISTIC	2.21	0.83	1.47	0.98
P-VALUE	0.12	0.49	0.25	0.42

Values represent mean±SEM; Significance relative to control: p<0.05, (n = 7); SEM = Standard Error of Mean; (n = 7): each group had 7 animals.

Week 2: Animals in control group had a value of (203.75 ± 0.05) g, while food intake of animals administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had following values (203.68 + 0.07; 203.68 + 0.12; 203.68 +

0.09) g respectively. ANOVA showed no statistical significant differences in food consumption among the studied groups. Table 1.

Week 3: Animals in control group had a value of (203.70 ± 0.09)g, while food intake of animals administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had following values (203.65±0.08; 203.61± 0.04; 203.68±0.07)g respectively. ANOVA showed no significant differences in food consumption among the study groups Table 1.

Week 4: Animals in the control group had a value of (203.70±0.09)g, while food intake of animals treated with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had following values (203.68±0.07; 203.63±0.05; 203.70+0.09)g respectively. ANOVA showed no significant differences in food consumption among the study groups. Table 1.

2. The effect of sildenafil citrate on the average weekly fluid intake (mean ± sd) of treated and untreated animals in (ml)

Week 1: The control animals had a value of (279.0±1.09) ml, while fluid intake of animals treated with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had the following values (278.83±2.04; 279.33±2.42; 279.0±1.26) ml respectively. Analysis of variance (ANOVA) showed no statistical significant differences in fluid consumption among the study groups. Table 2.

Week 2: The control animals had a value of (278.83±2.04) ml, while fluid intake of animals treated with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had the following values (278.83±2.04; 276.83±2.13; 277.33±1.96) ml respectively. Analysis of variance (ANOVA) showed no statistical significant differences in fluid consumption among the study groups compared to the control group. Table 2.

Week 3: The control group had a value of (279.50±0.83) ml while fluid intake of animals treated with 25mg/kg,50mg/kg and 100mg/kg of sildenafil citrate had the following values (278.83±2.04; 278.83± 2.04; 277.83±2.48) ml respectively. Analysis of variance (ANOVA) showed no significant differences in fluid consumption among the study groups. Table 2.

Week 4: The control group had a value of (278.66 ±1.96) ml, while fluid take of animals treated with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (278.0±2.45; 278.0±2.45; 277.66±2.16) ml respectively. Analysis of variance (ANOVA) showed no significant differences in fluid consumption among the study groups. Table 2.

Table 2 the effect of sildenafil citrate on the average weekly fluid intake (mean ± sd) of treated and untreated animals in (ml).

		Fluid intake (ml)		
Dose (mg/kg)	Week (1)	Week (2)	Week (3)	Week (4)
Control	279.0±1.09	278.83±2.04	279.50±0.83	278.66±1.96
25	278.83±2.04	278.83±2.04	278.83±2.04	278.0±2.45
50	279.33±2.42	278.83±2.13	278.83±2.04	278.0±2.45
100	278.0±1.26	277.33±1.96	277.83±2.48	277.66±2.16
F-STATISTICS	0.08	1.52	0.76	0.21
P-VALUE	0.96	0.24	0.54	0.89

Values represent mean±SEM; Significance relative to control: $p<0.05$.

3. The effect of sildenafil citrate on average body weight of the animals (g).

Week(1): The control animals group had a value of (176.23±25.41) g, while body weight of the animals administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had the following values (189.75±26.96, 187.60±26.85;174.41±18.10) g respectively. Analysis of variance (ANOVA) showed no statistical significant differences in body weight among the study groups. Table 3.

Week (2): The control animals group had a value of (185.53±23.35) g, while body weight of animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (194.55±22.83; 193.58±23.05; 172.45±17.38) g respectively. Analysis of variance (ANOVA) showed no statistical significant differences in body weight among the study groups. Table 3.

Week (3): The control animals group had a value of (210.85±12.85) g, while animals administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (186.68±37.47; 186.68±37.37; 183.71±19.17) g respectively. Analysis of variance (ANOVA) showed no statistical significant differences in body weight among the study groups. See Table 3.

Week (4): The control animals group had a value of (223.48±14.61) g, while animals administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (223.20±26.19; 221.66±24.87; 197.63±21.55) g respectively. Analysis of variance (ANOVA) showed no statistical significant differences in body weight among the study groups. Table 3.

Table 3 The effect of sildenafil citrate on average body weight of the animals (g).

		Body Weight (g)		
Dose (mg/kg)	Week (1)	Week (2)	Week (3)	Week (4)
Control	176.23±25.41	185.53±23.35	210.85±12.85	223.48±14.61
25	189.75±25.96	194.55±22.83	186.68±37.47	223.20±26.19
50	187.60±26.85	193.58±23.05	186.68±37.37	221.66±24.87
100	174.41±18.10	172.45±17.38	183.71±19.17	197.63±21.55
F-STATISTIC	0.62	1.32	1.16	1.92
P-VALUE	0.61	0.29	0.3	0.16

Values represent mean ± SEM; Significance relative to control: $p<0.05$.

4. The effect of sildenafil citrate on the average relative weight of the organs of the animals.

Liver: The average relative weight of liver of the animals that received food and water, (control) was (0.0398±0.0058), while animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (0.0389±0.0080; 0.0389±0.0080; 0.0364±0.0098) respectively. Analysis of variance (ANOVA) showed no statistical significant differences in relative weight of organs of the animals among the study groups. Table 4.

Table 4 the effect of sildenafil citrate on the average relative weight of the organs of the animals**.**

	Organ Weight (g)		
Dose (mg/kg)	Liver	kidney	Heart
Control	0.0398±0.0058	0.0036±0.0007	0.039±0.0106
25	0.0389±0.0080	0.0040±0.0007	0.0035±0.0008
50	0.0389±0.0080	0.0040±0.0007	0.0034±0.0009
100	0.0364±0.0098	0.0037±0.0010	0.0037±0.0007
F-STATISTICS	0.22	0.52	0.46
P-VALUE	0.88	0.68	0.72

Values represent mean ± SEM; Significance relative to control: $p<0.05$.

Kidney: The average relative weight of kidney of the control group was (0.0036±0.0007), while animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (0.0040±0.0007; 0.0040±0.0007; 0.0037±0.0010) respectively. Analysis of variance (ANOVA) showed no statistical significant differences in relative weight of organs of the animals among the study groups. Table 4.

Heart: The average relative organ weight of the control group was (0.0039±0.00106), while animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (0.0035±0.0008; 0.0034±0.0009; 0.0037±0.0007) respectively. Analysis of variance (ANOVA) showed no statistical significant differences in relative weight of organs of the animals among the study groups. Table 4.

4.1. Biochemical parameters

4.1.1. Enzymes activities

The results obtained from the enzyme activities of lactate dehydrogenase LDH showed that the control had a mean value of (518.64±587.5) IU/L, while animals that administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these mean values (993.1±412.3; 1003.5±416.3; 1685.7±329.9) IU/L respectively. Lactate dehydrogenase (LDH) in the control was statistically significantly lower than that in 100mg/kg group ($p<0.05$), but did not differ significantly with the 25mg/kg and 50mg/kg groups respectively. Table 5.

The mean Aspartate amino transaminase (AST) level among the control group was (30.57±1.81) UI/L, while animals that received 25mg/kg 50mg/kg and 100mg/kg of sildenafil citrate had these mean values of (34.57±1.81; 37.14±8.78; 52.14±8.78) IU/L respectively. AST in the control group was significantly lower in the control than 100mg/kg group ($p<0.05$), but did not differ significantly with 25mg/kg group and 50mg/kg group respectively. Table 5.

The mean Alanine aminotransaminase (ALT) in control group was (17.85±2.79) IU/L, while animals administered with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these mean values (20.57±2.93; 21.85±3.28; 24.00±4.31) UI/L respectively. ALT was significantly lower in the control group than in the 100mg/kg group ($p<0.05$), but did differ significantly with 25mg/kg group and 50mg/kg group respectively. Table 5.

The mean Alkaline phosphatase (ALP) in control group was (500.4±132.9) IU/L, while animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these mean values (578.6±133.5; 606.4±176.8; 618.9±190.2) IU/L respectively. There were no statistical significant differences in alkaline phosphatase (ALP) level among the study groups. Table 5.

Table 5 liver and kidney functions test of animals exposed to sildenafil citrate

		Dose (mg/kg)		
Parameters Control	**25**	**50**	**100 F-STA**	**p**
LDH (IU/L)	0.50±0.00 1686.64±329.00	993.11±413.94 **8.09**	1003.54±416.3	0.001*
AST (IU/L)	30.57±1.81 52.00±8.80	34.57±1.81 **15.44**	37.14±8.78	0.000*
ALT (IU/L)	17.86±2.79 24.00±4.31	20.57±2.94 **3.54**	21.86±3.29	0.03*
ALP (IU/L)	500.43±132.84	578.61±133.53	606.41±176.80	
Conjugate	618.09±190.20	**0.77**	**0.52**	
Bilirubin (mmol/L)	1.28±0.83 1.42±0.55	1.51±0.63 2.28±1.60	0.84±0.48	
Total Bilirubin (mmol/L)	2.14±0.75 2.48±0.78	3.17±0.87 3.27±1.87	**1.56**	**0.22**
Urea (mmol/L)	5.53±0.69 5.69±0.54	5.80±1.11 5.90±0.50	**0.37**	**0,77**
Creatinine (mmol/L)	0.47±0.05 0.50±0.00	0.51±0.04 0.57±0.05	**8.0**	0.001*

Values represent mean ± SEM. Significance relative to control: $p<0.05$, (n=7)

4.1.2. Conjugated and total bilirubin

The mean conjugated bilirubin for control animals administered with food and water was (1.28±0.83) mMol/L, while animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these mean values (1.42±0.55; 1.51±0.63; 2.05±1.55) mMol/L respectively. ANOVA showed no statistical significant differences in conjugated bilirubin level among the study groups. Table 5.

The mean total bilirubin in control group was (2.14±0.76) mMol/L, while animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate has these mean values (2.48±0.77, 3.17±0.87; 3.27±1.85) mMol/L respectively. ANOVA showed no significant differences in Total bilirubin among the study groups. Table 5.

4.1.3. Urea and creatinine

The mean urea result in control animals administered with food and water was (5.53±0.69) mMol/L, while animals treated with 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these mean values (5.69±0.54; 5.77±1.11; 5.94±0.49) mMol/L respectively. Serum urea level showed no significant differences among the study groups. Table 5.

The mean creatinine result in control group was (0.47±0.05)mg/dl, while animals that received 25mg/kg, 50mg/kg and 100mg/kg of sildenafil citrate had these values (0.50±0.00; 0.51±0.04; 0.57±0.05) mg/dl respectively. Mean creatinine in the control group was significantly lower than that in the 100mg/kg group ($p<0.05$), but did not differ significantly with the 25mg/kg group and 50mg/kg group respectively. Table 5**.**

4.2. Total protein and albumin (g/l)

There was a statistical significant increase in total protein in all the treatment groups (of varying doses) compared to the control p value = $^{*}<0.05$. The mean Albumin level showed no statistical significant increase in albumin levels in the study groups that received 25mg/kg and 50mg/kg of Sildenafil citrate compared to the control group. However, there was a recorded statistical significant increase in albumin levels among animals that received 100 mg/kg sildenafil compared to the control p value = $^{*}<0.05$. Table 6.

Table 6 effect of sildenafil citrate on total protein and albumin levels in albino rats in (g/l)

	Parameters	
Dose (mg/kg)	Total Protein (g/l)	Albumin (g/l)
Control	67.60±3.93	32.86±4.88
25	77.14±7.63	35.14±4.88
50	80.71±9.84	36.57±7.02
100	96.00±31.80	43.00±5.58
F-STATISTIC	3.11	4.17
P-VALUE	0.04*	0.02*

Values represent mean ± SEM; Significance relative to control: $p<0.05$.

4.3. Serum electrolytes (Na^+, K^+ and Cl^-) mmol/l

The Na^+ level in the control group was significantly lower than as recorded for the 100mg/kg study group ($p<0.05$). The mean Potassium (K^+) showed no significant differences among the study groups. Meanwhile the mean Chloride (CL^-) level in the control group was significantly lower than 100mg/kg group ($p<0.05$), but did not differ significantly with other doses. Table 7.

Table 7 Effect of sildenafil citrate on electrolytes (Na^+, K^+, Cl^-).

		Dosage (mg/kg)				
Parameters	**Control**	**25**	**50**	**100**	**F-STAT**	**p**
Na^+(mMol/L)	134.71±13.57	144.86±6.47	146.57±5.94	147.86±5.90	3.38	0.03*
K^+ (mMol/L)	4.81±0.66	4.93±0.32	4.94±0.31	5.06±0.55	0.29	0.83
CL^- (mMol/L)	116.43±8.85	120.00±8.43	139.00±22.47	139.00±22.47	4.24	0.02*

Values represent mean + SEM
Significance relative to control: $p<0.05$.

4.4. Demonstration of photomicrograhs of the organs of albino rats

4.4.1. Heart

The heart photomicrographs of the animals Figures 1,2,3 and 4 showed normal cardiac myocytes. No histopathological changes were observed between the control (Figure 1) that received food and water only compared to those treated with different doses sildenafil citrate. See figure 1 to figure 4

4.4.2. Liver

The photomicrographs of the animals Figures 5,6,7 and 8 were histological sections of the liver. The Figure 5 showed liver of the control group with normal histological features like irregular hexagonal boundaries with central vein. However, the treatment groups that received 25mg/kg and 50mg/kg of sildenafil citrate showed mild to moderate cyto-architectural distortions of hepatocytes respectively. The group that received 100mg/kg sildenafil citrate showed evidence of dilatation of the central veins and marked distoritions of the hepatocytes. See figure 5 to figure 8.

4.4.3. Kidney

The photomicrograph of the animals Figures 9,10,11 and 12 were histological sections of the kidney. The Figure 9 showed kidney of the control group which received foof and water only. This Figure 9 showed sections of parenchyma and the renal corpuscles appeared as dense rounded structures with the glomerulus surrounded by a narrow Bowman's spaces. Figure 10 from the group that received 25 mg/kg of sildenafil citrate, showed mild distortion of the cortical structures when compared with control. Figure 11 from the group that recevied 50 mg/kg of sildenafil citrate showed scanty tissue stroma, glomeruli shrunken with mild celluarity within the tuft. Figure 12 from the group that received 100 mg/kg of sildenafil citrate, showed vacuolations in the stroma and loss of renal corpuscles which were less identified and Bowman's spaces were sparsely distributed. See figure 9 to figure 12.

Effect of sildenafil on the histological sections of the heart of *albino rats*

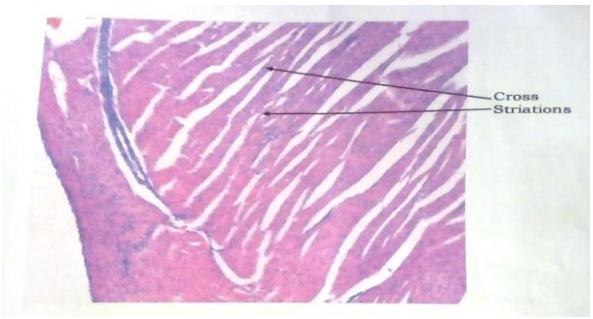

Figure 1 Photomicrograph of h & e- stained heart histology**.**

Figure 1: H&E- Stained photomicrograph of the heart for the control group administered with food and water. The Figure showed normal cardiac myocytes arranged in interlacing and parallel arrays.

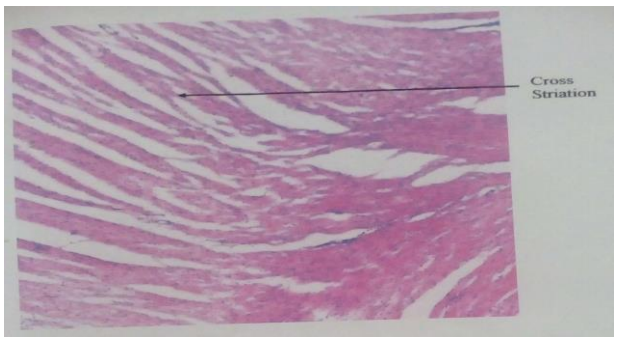

Figure 2 photomicrograph of h & e- stained heart histology.

Figure 2: H&E- stained photomicrograph of the heart from treatment group that received 25 mg/kg body weight of sildenafil citrate. Normal cardiac myocytes arranged in interlacing and parallel arrays.

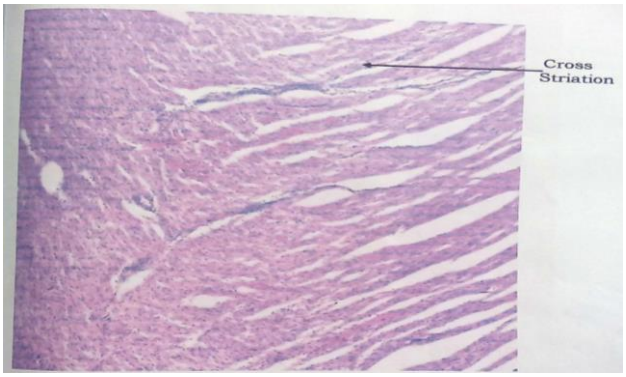

Figure 3 Photoxnicrograph of H & E- Stained heart histology**.**

Figure 3: H&E- Stained photomicrograph of the heart from treatment group that received 50 mg/kg body weight of sildenfil citrate. Normal cardiac myocytes arranged in interlacing and parallel arrays**.**

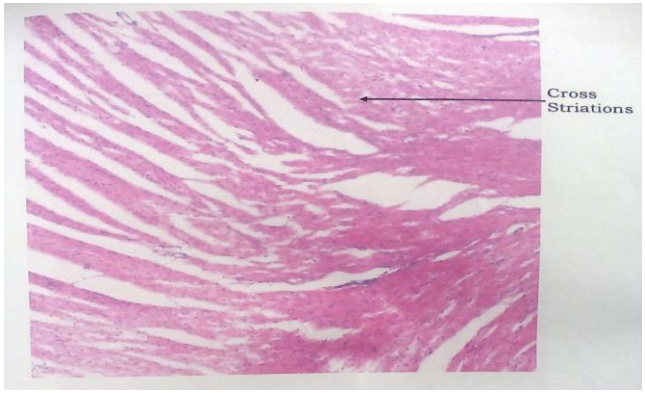

Figure 4 Photomicrograph of H & E- Stained heart histology**.**

Figure 4: H&E- Stained photomicrograph of the heart from treatment group that received 10Q mg/kg body weight of sildenafil citrate. Normal cardiac myocytes arranged in interlacing and parallel arrays.

Effect of sildenafil on the histological sections of the liver of *albino rats*

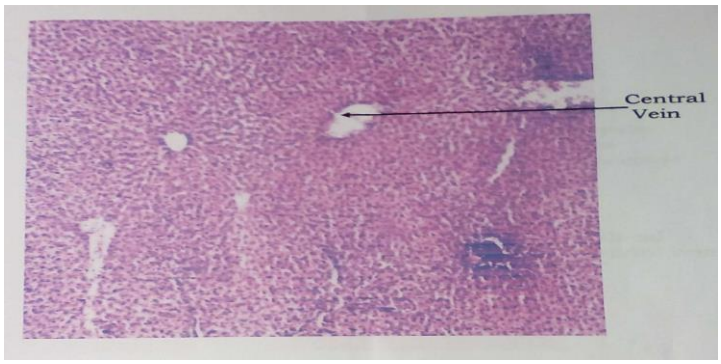

Figure 5 Photomicrograph of H & E- Stained liver histology.

Figure 5: H&E- stained photomicrograph of the liver for the control group administered with food and water (Control). H&E- Stained photomicrograph of the liver showing normal histological features like hexagonal boundaries with solitary central vein.

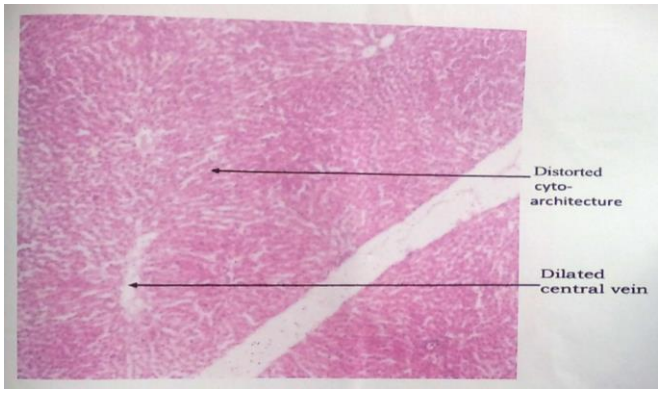

Figure 6 Photomicrograph of H & E- Stained liver histology**.**

Figure 6: H&E- Stained photomicrograph of the liver from the treatment group that received 25 mg/kg body weight of sildenafil citrate. No significant changes seen.

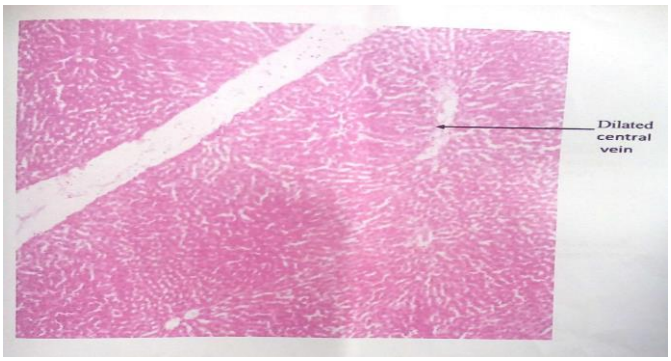

Figure 7 Photomicrograph of H & E- Stained liver histology.

Figure 7: H&E- Stained photomicrograph of the liver from the treatment group that received 50 mg/kg body weight of sildenafil citrate. There is slight change in the hepatocytes.

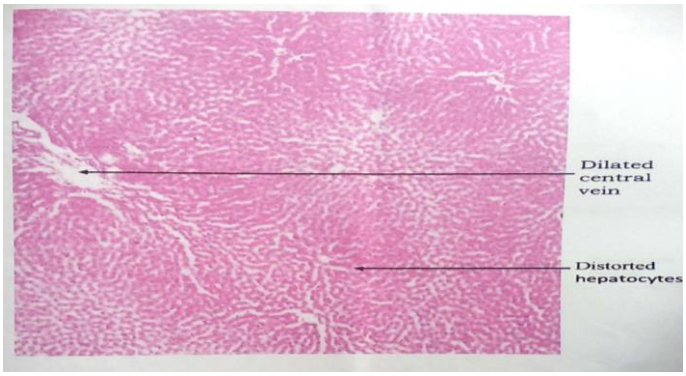

Figure 8 Photomicrograph of H & E- Stained liver histology**.**

Figure 8: H&E- Stained photomicrograph of the liver from the treatment group that received 100 mg/kg body weight of sildenafil citrate. Dilatation of central vein is obvious with changes in liver architecture. This shows toxicity**.**

Effect of sildenafil on the histological sections of the kidney of the *albino rats*

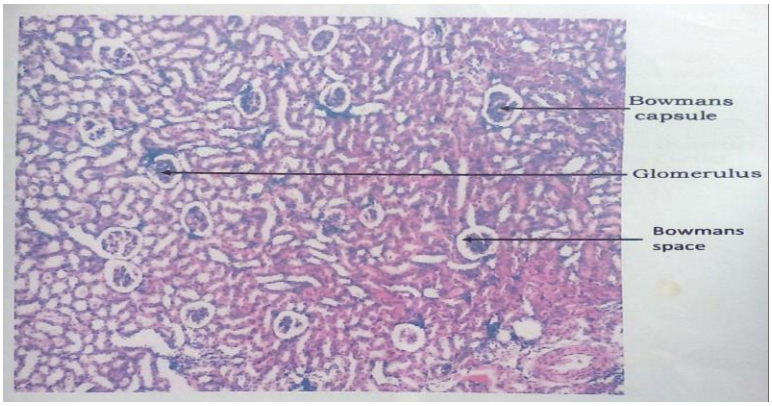

Figure 9 Photomicrograph of H & E- Stained kidney histology**.**

Figure 9: H&E- stained photomicrograph of the kidney for the control group administered with food and water (Control) H&E- Stained photomicrograph of the kidney.

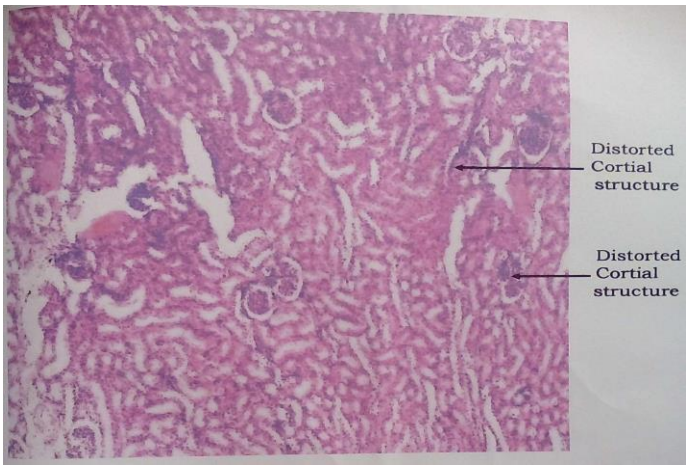

Figure 10 Photomicrograph of H & E- Stained kidney histology.

Figure 10: H&E- Stained photomicrograph of the kidney from the treatment group that received 25 mg/kg body weight of sildenafil citrate. There is no significant change in the cortical when compared with control.

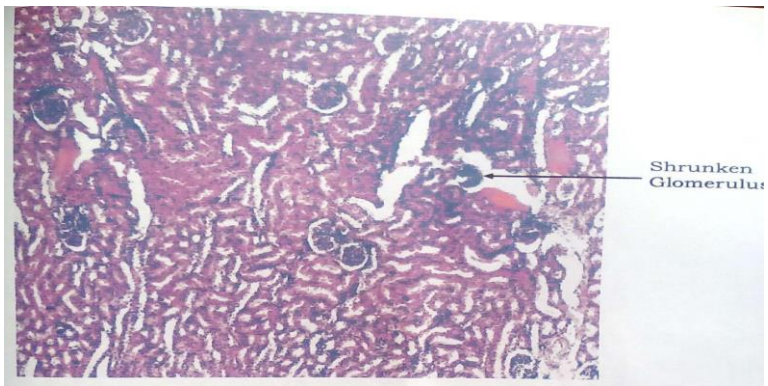

Figure 11 Photomicrograph of H & E- Stained kidney histology**.**

Figure 11: H&E- Stained photomicrograph of the kidney from the treatment group that received SOmg/kg body weight of sildenafil citrate. There is scanty tissue stroma, with shrunken glomeruli and slight cellularity within the tuft.

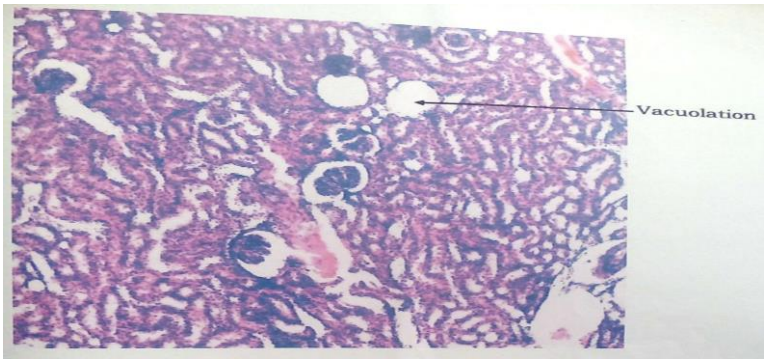

Figure 12 Photomicrograph of H & E- Stained kidney histology.

Figure 12: H&E- Stained photomicrograph of the kidney from the treatment group that received l00mg/kg body weight of sildenafil citrate. Vaculations are obvious in the storm a in addition to disappearance of renal corpuscles. Signs of toxicity obvious.

5. Discussion

The results of the present study showed that there were no statistical significant differences in food consumption among study groups. There was also no significant difference in fluid consumption among the study groups. The study showed that sildenafil citrate had no significant effect on body weight among the study groups respectively. These findings compares with [31], in which it was reported that sildenafil citrate though increased food and water intake but the difference was not statistically significant compared with the control.

In this index study, biochemical parameters like serum levels of lactate dehydrogenase (LDH) in the control was significantly lower than in the 10 mg/kg group ($p<0.05$), but did not differ significantly with 25 mg/kg group and 100 mg/kg respectively. However, this rise in LDH might not be as a result of cardiac insult because histopathological finding did not support it. This showed that the LDH might have been coming from the liver. Liver enzymes were assayed, which included Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and alkaline phosphate (ALP). It was found that the level of AST in the control was significantly lower than in the 100 mg/kg group ($p<0.05$), but did not differ significantly with 25 mg/kg group and 50 mg/kg. ALT was significantly lower in the control group than 100 mg/kg group ($p<0.05$), but did not differ significantly with 25 mg/kg group and 50 mg/kg group. In another study, the 10th day review showed that there was no statistical significant difference between the sildenafil-treated group and the control with regard to the aspartate aminotransferase and alanine aminotransferase levels ($p=0.423$, $p=0.661$). However, the alkaline phosphatase and total bilirubin levels among the groups were statistically different ($p<0.001$). Meanwhile on the 28th day, liver function tests except alanine aminotransferase showed statistical significant differences among the groups ($p<0.001$). Liver function tests did not changed significantly between the 10th and 28th day in sildenafil-treated rats ($p>0.05$). The sildenafil-treated groups at different time points didn't show any statistical difference in histopathological changes ($p>0.05$) [16].

Total protein in the control group was significantly lower than in the 100 mg/kg group ($p<0.05$), but did not differ significantly with the 25 mg/kg group and 50 mg/kg groups respectively. Albumin in the control group was significantly lower than 100 mg/kg group ($p<0.05$), but did not differ significantly with 25 mg/kg group and 50 mg/kg group. The result of this study compared with that of [19]. In the said study, total protein and albumin were said to be increased. The increase in the total protein may be due to the short duration for which the Sildenafil citrate was given. The resultant effect was acute toxicity leading to enhanced hepatocellullar activity and an increase in globulin and albumin components of the protein. However it was also reported that with prolonged usage, hepatic necrosis may likely ensue with a resultant low albumin levels.

Serum urea level showed no statistical significant differences among the study group. However, creatinine in the control group was significantly lower than 100 mg/kg group ($P<0.05$), but did not differ significantly with 25 mg/kg group and 50 mg/kg group. This result may be due to renal impairment from high dose sildenafil citrate since creatinine is more reliable clinical indicator for assessing renal functions than urea. Another study which compared to this index study when considering the results of the 25mg/kg and 50mg/kg group reported that sildenafil ameliorated gentamicin-induced nephrotoxicity as it reduced serum urea and creatinine as well as urinary albumin levels and restored the histological pattern [32].

In another study, Serum creatinine concentration was measured as an indicator of kidney function. At baseline serum creatinine was similar in all treatment groups but its concentrations began to increase between one to two hours after the end of Contrast Media infusion. The increase in serum creatinine was highly dependent on the Contrast Medium (CM) dose. In most animals, maximal serum creatinine concentration was observed at 48 hours; hence this time point was used to compare maximal serum creatinine concentrations. Continuous sildenafil treatment (6.0 mg/kg; q8 h) significantly attenuated the rise in serum creatinine concentration ($p<0.05$), whereas a single dose of sildenafil before CM exposure had no effect. This did not compare with our findings especially with the 100mg/kg group were high dose Sildenafil produced increased creatinine levels [33]. The difference may have resulted from the contrast media that was introduced in the later study. In humans also, Sildenafil treatment has been documented to improve kidney function in patients with Pulmonary Arterial Hypertension (PAH), which was in turn associated with improved exercise capacity and functional class, a reduced risk of clinical worsening, and a trend towards reduced mortality. This action also does not compare with those of higher doses of Sildenafil [34].

This study also showed that serum sodium Na+ level in the control was significantly lower than in the 100 mg/kg group ($P<0.05$), but did not differ significantly with 25 mg/kg group and 50 mg/kg group. However, potassium K+ level showed no significant differences among the study groups. Meanwhile, Chloride CL- level which in the control group was significantly lower when compared with the 100 mg/kg group ($P<0.05$), did not differ significantly with 25 mg/kg group and 50 mg/kg group respectively. Another study [33] reported that treatment with sildenafil was associated with lesser degrees of histological injuries, weakening of markers of acute kidney injury (48 hour creatinine 1.54±0.21 versus 4.42±1.31 mg/dl, $p<0.05$). They also reported a reduction in electrolyte derangement (percent change in serum K^+ at 48 hours 2.55±3.80% versus 15.53±4.47%, $p<0.05$; serum Na^+ at 48 hours −0.14±0.26% versus −1.97±1.29%, $p=0.20$). The results further suggested a possible role for PDE5 inhibitors in the treatment of Contrast-induced acute kidney injury (CIAKI) and warrant further evaluation to determine the exact mechanisms of protection. Sildenafil treatment was associated with improved kidney function in patients with PAH (increased eGFR, decreased sCr) with sildenafil and worsened with placebo, which was in turn associated with improved exercise capacity and functional class, a reduced risk of clinical worsening, and a trend towards mortality attenuation [34].

The histological analysis of animal liver in this index study, demonstrated dilatations of the central veins as well as distortions of the cyto-architecture of the hepatocytes noted in the treatment groups. However, these changes were more marked with the group that received 100mg/kg body weight of sildenafil citrate. This showed toxicity from the sildenafil citrate on the liver. The findings compared with those of [17] in which, the liver of rats in the treatment group showed some histological changes that differed with those obtained from the control arm. Noted also were evidence of dilatations of the central veins, which contained lysed red blood cells and cyto-architectural distortions of the hepatocytes and centrilobular haemorrhagic necrosis. There were also atrophic and degenerative changes with the group that received 1.43mg/kg body weight of Sildenafil citrate more. In another study, significant differences were observed among the groups with regard to cholestasis, fibrosis, inflammation, and necrosis ($p<0.001$) while edema increased in the sildenafil-treated group ($p<0.001$). On the 28th day, the severity of structural changes in the liver after obstructive jaundice, except edema, reduced significantly ($p<0.001$). The sildenafil-treated groups at different time points did not show any statistical significant difference in histopathological changes ($p>0.05$). While this very finding compared with the 25mg/kg and 50mg/kg treatment groups, it did not however, compare with the 100mg/kg treatment group of the index study. The difference noted with the 100mg/kg treatment group may be from the higher dose of 100mg/kg body weight of sildenafil citrate and the fact that the male Wister albino rats were induced with obstructive jaundice by legating their common bile ducts which was not the practice in this index study. This cited study concluded that oral administration of 10 mg/kg sildenafil citrate dramatically reversed the biochemical and histopathological liver changes induced by obstructive jaundice in rats [16]. The findings of the index study also compared with those of another research in which it was reported that the use of high doses of sildenafil citrate or its misuse could lead to serious histopathological malformations. In that study, it was reported that oral administration 75 and 100 mg/kg body weight Sildenafil / given on alternate days caused damages to the hepatic cells [16,14,35].

The kidneys of the control group showed normal histological features. However, the kidneys of the animals in low dose group (25mg/kg) of sildenafil citrate showed slight distortion of cortical structures. While medium dose group (50mg/kg) showed scanty tissue stroma, shrunken glomeruli and cellularity within the tuft. High dose group (100mg/kg) showed vaculations in the stroma in addition to disappearance of renal corpuscles. These findings might suggest some forms of nephrotoxicity due to sildenafil citrate ingestion. The findings compared with other researches as reported. In one report, the histological studies revealed that increasing doses of Sildenafil citrate ingestion resulted in varying degree of cyto-architectural distortion and reduction in the number of renal corpuscle in the kidneys of the treated groups compared to the control sections of the kidneys. There were also several diffuse degeneration and necrosis of the tubular epithelial cells of the kidneys of the treated animals. This was seen more on the rats that received the highest dose (1.43mg/kg) of Sildenafil citrate as they showed more degenerative and atrophic changes [17]. From

these results above, it may be inferred that higher doses of Sildenafil citrate may have resulted in the degenerative and atrophic changes seen in the renal corpuscle. The above results can lead to the possible deduction that the secondary metabolites, which are largely responsible for the therapeutic or pharmacological actions of medicinal plants may also account for their toxicity with higher or abused dosage [17, 36]. Another comparable research finding reported several irritation spots on the different portions of the kidneys of adult male mice and this tend to increase with incremental doses of the drug. Because of its effects on the kidneys, the European Public Assessment Report (EPAR) [35] and Muñiz and Holstege [37] postulated that patients with liver problems or severe kidney problems should start treatment with the 25-mg dose [14, 35, 37]. Suffice it to say that, such patients should be on continuous clinical monitoring and evaluation.

The histopathological examinations of the heart of these animals showed no histopathological changes between the control and treatment groups. The stained micrograph of the heart of these animals showed normal cardiac myocytes arranged in interlacing and parallel arrays. It is noteworthy that other studies have reported that animals treated with sildenafil citrate showed a highly statistical significant increase in Nitric Oxide and a decrease in phosphodiesterase type 5 (PDE5) level, but the histological architecture of the cardiomyocytes did not show much changes other than a slightly elongated and swollen nucleus. The cardiomyocytes histologic architectural findings are comparable to the findings of this index study [38]. The study further demonstrated that changes in the levels of total PDE5 were statistically significant at a dosage of 10 mg/kg body weight when compared with the 8-mg/kg body weight and the control groups. This suggests that as the dosage of sildenafil increases, it becomes more potent on PDE in the heart, indicating the presence of PDE5. This is in agreement with the results of a few previous studies, which showed that PDE5 is found in specific compartments within myocytes (specifically at z-bands) [38, 39, 40].

6. Conclusion

In Conclusion, the result of this study shows that liver toxicity was evidenced by increased liver enzyme (ALP, AST and ALT) activity as seen in the serum of the animals. Also albumin and total protein were elevated. Hyperbilirubinaemia was equally present. There were dose dependent increases in urea and creatinine. These were indicators of Renal nephron insult. Histopathological results were in support of the biochemical findings also. Therefore, sildenafil citrate had toxic effects on the liver, kidney and heart. Following these findings of sildenafil citrate toxicity especially with higher doses and the rising cases of erectile dysfunction, there is need for cautious clinical prescriptions and use of the drug, sildenafil citrate. It is hereby recommended that prolonged human exposure to sildenafil citrate should either be discouraged or closely monitored clinically.

Compliance with ethical standards

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Author contributions

Conceived and designed the experiments: UPC, OSE, CLC. Performed the experiments: OSE, OJE. Analyzed the data: OSE,CLC, OJE. Contributed reagents/materials/analysis tools: OSE, UPC, CLC, OJE. Wrote the paper: CLC, MAR.

Disclosure of conflict of interest

All authors declare that they have no conflict of interest.

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