RENAL GROSS MORPHOLOGICAL RESTORATIVE EFFECTS OF *CURCUMA LONGA* ON SILDENAFIL INDUCED NEPHROTOXICITY AMONG MALE ALBINO RATS.

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ABSTRACT

Background: Sildenafil is a phosphodiesterase inhibitor used in the management of erectile dysfunction and management of pulmonary hypertension. *Curcuma longa* is a traditional herbal plant that is commonly used as a diet in Africa and Asian countries. It has a variety of benefits including; antioxidant, anti-cancerous, management of diabetes and respiratory diseases. The objective of this study was to evaluate the renal gross morphological changes in restorative effects of *Curcuma longa* on sildenafil induced nephrotoxicity among male albino rats. **Methodology:** A total of 25 male albino rats were used and classified control or experimental group. Simple random sampling method was used to allocate them into each group. Animals in group1 were only fed on feeds and water ad libitum, group 2 to 5 received Sildenafil 1mg/gm bwt for 15 days. Animals in group 3,4 and 5 were further subjected to *Curcuma longa* at calculated dose of low, medium and high respectively. Animals in group 2 were sacrificed 4 hours post last dose and the remaining animals were sacrificed 7 days later. On sacrificing gross morphometrics were done. **Results:** It was observed that mean weight of rat, weight and volume of kidney increased significantly (p=0.0001) in medium and high dose *Curcuma longa* as compared to Sildenafil induced nephrotoxicity group. The mean length and thickness in medium and high dose *Curcuma longa* increased significantly (p=0.0001) as compared to Sildenafil induced nephrotoxicity group. **Conclusion:** Medium and high dose *Curcuma longa* have renal gross morphological effects on sildenafil induced nephrotoxicity among male albino rats.

Keywords: Antioxidant, Anti-cancerous, Diabetes, Kidney and pulmonary hypertension.

INTRODUCTION

The economic burden and care of patients with acute kidney injury and chronic renal injury cannot be overlooked. Nephrotoxicity still remains the leading cause of acute kidney injury accounting for 18%-27% of most case hospitalized. The cost particularly may increase especially if the patient might need renal transplant or dialysis. Most of the population affected are from African countries due to increased industrialization, poor hygiene, sedentary lifestyle and poor access to health care systems. Sildenafil is a phosphodiesterase inhibitor majorly used in management of erectile dysfunction and pulmonary hypertension(Hsu et al., 2015; Nichols et al., 2002). Overtime there is increased report of cases of individuals developing acute kidney injury secondary to overdose or prolonged use. A case of 39-year-old man who developed signs and symptoms of AKI secondary to a two-day consecutive intake of 100mg Sildenafil was admitted with deranged renal biochemical markers of blood urea and nitrogen levels and creatinine levels(Liu et al., 2018). On the other hand, *Curcuma longa* is a traditional herbal plant with wide range of benefits; antioxidant, anti-cancerous, used in management of dermatological conditions, respiratory conditions, and renal diseases(Witkin & Li, 2013). Sildenafil has been postulated to cause nephrotoxicity by

releasing radical elements like oxygen, nitrogen oxide and enzymatic activities due to presence of hemeoxygenase enzymes. These radicals destroy the glomerulus structure, increase bowman`s space, dilate kidney tubules and cause epithelial cell destruction and necrosis(Suriyakumari et al., 2016). It also causes damage to cellular permeability and vacuolations. *Curcuma longa* on the other hand might have antioxidant and anti-inflammatory benefits. It has widely been used in renal attenuation and amelioration however, there is paucity of data on the restoration capacities of *Curcuma longa*. Therefore, this study sought to evaluate the renal gross morphological changes in restorative effects of *Curcuma longa* on sildenafil induced nephrotoxicity among male albino rats.

MATERIALS AND METHODS

The present study used twenty-five male albino rats(150-250gm) of species *Rattus Norvegicus* which was calculated using modified human resource formula (Arifin & Zahiruddin, 2017). The animals were selected using systematic random sampling method having attained desired weight at commencement of study. Here every second rat was picked from a pool of 100 which the animal house could hold for a single study. The animals were put in polycarbonate cages for a period of ten days to allow acclimatization take place. The standard experimental conditions like humidity, temperature and light/dark cycle of 12 hours were maintained. Feeds and water were given under strict hygiene conditions with researcher upholding occupational animal handling procedures.

These animals were grouped as either control or experimental. The experimental group was further grouped into four subgroups as Sildenafil induced nephrotoxicity group, low dose *Curcuma longa* group, medium dose *Curcuma longa* group and high dose *Curcuma longa* group. Each group had five animals that were simple randomly selected. The four subgroups received a single dose of 1µgm/gm bwt/day Sildenafil for 15 days through gastric gavage (Suriyakumari et al., 2016). This was adopted because sildenafil has shown to be nephrotoxic when used as high dose or used for a prolonged period of time. The five animals in group2 were sacrificed four hours post last dose of sildenafil and renal function test was done to confirm toxicity while group 3, 4 and 5 were subjected to *Curcuma longa* at different doses for further studies at 38.75mg/Kg/day low dose *Curcuma longa*, 77.5mg/Kg/day medium dose *Curcuma longa* and 155mg/kg/day high dose *Curcuma longa* (Fança-Berthon et al., 2021; Nair & Jacob, 2016).

The renal biochemical parameters for low, medium and high dose *Curcuma longa* were determined at the end of experiment and results were analyzed using one way ANOVA and post hoc Bonferroni was adopted to determine inter group significance in assessment of restorative effects. Chloroform was used as anesthesia after which a vertical incision was made from pubic symphysis to xiphoid process so as to expose the viscera and collect the kidney samples. The kidneys were identified and excised. The fibrous capsule and adipose tissue were removed before weighing was done.

Gross morphological studies were then carried out whereby volume of the organs was determined using Archimedes principle, weight by use of electronic weighing machine whereas length, width and thickness were determined by use of a digital Vanier caliper. The following dimensions of right and left kidney were taken; Width: Measured from the medial to lateral border. Length: Measured from the upper to lower pole. Thickness: Measured from the visceral to parietal surface. The ethical approval to

carry out the study was sought from Baraton University of Eastern Africa (UEAB/ISERC/08/01/2023) and NACOSTI (NACOSTI/P/2023/23374).

RESULTS

A total of 25 adult male albino rats of between the weights of 150g and 250g were randomly selected for study. Each rat was allocated to the 5 groups as either pretreatment group or treatment group. Every group received a total of 5 rats (20%). They were treated with Sildenafil 1µg/gmbwt/day for 15 days to induce nephrotoxicity then *Curcuma longa* was introduced at varying doses for 7 days to try and restore the damage caused. The following results were observed from the study.

Behavioral changes and mortality report.

Rats in all the 5 selected groups did not show any behavior changes during routine inspection. There were no observable signs of nephrotoxicity during and after administration of drugs. No mortality was recorded during the entire process of the experiment.

Body weight

The average body weight of the 25 rats used at the commencement of the study was 183.75g with a standard error of ±3.14g.

Mean terminal body weight, mean weight of right and left kidney and mean volume right and left kidney between positive control group and experimental groups

The mean terminal body weight group four (MCL77.5mg/gm/bwt/day) and five (HCL155mg/gm/bwt/day) was statistically significantly different (P=0.0001) and (P=0.0001) respectively as compared to the positive control (Sildenafil 1µg/gmbwt/day) group. The mean weight of right kidney in group four and five was statistically significantly different (P=0.0001, P=0.0001) as compared to the positive control (Sildenafil 1µg/gmbwt/day) group whereas the mean weight of left kidney in group four and five was statistically significantly different (P=0.0001, P=0.0001) as compared to the positive control (sildenafil 1µg/gmbwt/day) group. The mean volume of right kidney in the group four and five was statistically significantly different (P=0.0001, P=0.0001) as compared to the positive control (Sildenafil 1µg/gmbwt/day) group. The mean volume of left kidney in the group four and five was statistically significantly different (P=0.0001, P=0.0001) as compared to the positive control (Sildenafil 1µg/gmbwt/day) group respectively (Table 1).

Table 1: The mean terminal body weight, mean kidney weight and volume between positive control group and experimental groups.

Mean body weight, kidney weight and volume in gms and mls					
Groups	Mean terminal body weight	Mean weight right kidney	Mean weight left kidney	Mean volume right kidney	Mean volume left kidney
SIN 1µg/gmbwt/day	254.74±.81	0.94±.02	0.82±.04	1.38 ±.04	1.14 ±.02
Low *Curcuma longa* dose (38.75mg/gm/bwt/day)	270.92±2.23	0.98±.06	0.90±.03	1.39 ±.11	1.24 ±1.59
Medium *Curcuma longa* dose (77.5mg/gm/bwt/day)	285.22±1.76	1.02±.02	0.94±.02	1.66±06	1.58 ±1.61
High *Curcuma longa* dose (155mg/gm/bwt/day)	288.98±2.2	1.18±.11	0.96±.02	1.86±.11	1.82 ±.08

All values are expressed as the mean± the standard error of the mean (SEM). The test of significance was performed in rows. Values are expressed as mean ± standard error of mean (n=5), SIN- sildenafil induced nephrotoxicity, LCL- low Curcuma longa dose, MCL- medium Curcuma longa dose and HCL-high Curcuma longa dose.

Mean terminal body weight, mean weight of right and left kidney and mean volume right and left kidney between positive group and restorative group

The mean terminal body weight of rats in restorative group (different doses of *Curcuma longa*) was statistically significantly different (*P*=0.0001) when compared to positive control (Sildenafil 1µg/gmbwt/day) group. The mean weight of right and left kidney in restorative group was statistically significantly different (R; *P*=0.0001, L; *P*=0.0001) as compared to positive control (Sildenafil 1µg/gmbwt/day) group. The mean volume of right and left kidney in restorative group was statistically significantly different (R; *P*=0.0001, L; *P*=0.0001) as compared to positive control (Sildenafil Iµg/gmbwt/day) group respectively (Table 2).

Table 2: The mean terminal body weight, mean kidney weight and volume between positive control group and restorative group.

Kidney gross morphometries in mm.						
Groups	Mean right kidney length	Mean left kidney length	Mean right kidney width	Mean left kidney width	Mean right kidney thickness	Mean left kidney thickness
SIN 1µg/gmbwt/day (5 rats)	14.16±.36	11.97±.58	10.27±.16	9.66±.22	3.03±.07	2.91±.02
Restorative groups (15 rats)	17.37±.17	16.95±.16	10.46±.26	10.14±.14	4.81±.17	4.38±.11
P value	**0.0001**	**0.0001**	1.000	0.264	**0.0001**	**0.0001**

All values are expressed as the mean± the standard error of the mean (SEM). The test of significance was performed in rows. Values are expressed as mean ± standard error of mean (n=5), SIN- sildenafil induced nephrotoxicity.

Comparative mean of total kidney weight, percentage ratios kidney weights to mean body weight in controls against experimental groups.

It was observed that the mean weight percentage ratio of right kidney in positive control group (sildenafil 1µg/gmbwt/day) reduced 0.37% as compared to the negative control group (feeds + water) 0.41% whereas the mean weight percentage ratio of right kidney in high Curcuma longa dose group increased (0.41%) as compared to positive control group (sildenafil 1µg/gmbwt/day) (Table 3).

Table 3: A table indicating the total kidney weight and percentage ratios kidney weights to mean body weight in control against experimental groups.

	Gross measurements				
Groups	Weight of rats	Weight of right kidney	Weight of left kidney	Mean % right kidney weight ratio	Mean % left kidney weight ratio
Control (feeds+ water ab libitum)	284.78±.32	1.16±.08	0.92±.02	0.41%	0.32%
SIN 1µg/gmbwt/day	254.74±.81	0.94±.02	0.82±.04	0.37%	0.32%
Low *curcuma longa* 38.75mg/kg/day	270.92±2.23	0.98±.06	0.90±.03	0.36%	0.33%
Medium *curcuma longa* 77.5mg/kg/day	285.22±1.76	1.02±.02	0.94±.02	0.36%	0.33%
High *curcuma longa* 155mg/kg/day	288.98±2.2	1.18±.11	0.96±.02	0.41%	0.33%

KEY: All values are expressed as the mean, ± is the standard error of the mean (SEM). The test of significance was performed in rows. Values are expressed as mean ± standard error of mean (n=5), SIN- sildenafil induced nephrotoxicity, LCL-Low curcuma Longa, MCL-Medium Curcuma Longa, HCL-High Curcuma Longa

Comparative mean width and thickness between positive control and experimental groups.

The mean length of right kidney in group 4 and 5 was statistically significant (P=0.0001 and P=0.0001) as compared to positive control group (Sildenafil1µg/gmbwt/day) whereas the left kidney of group 4 and 5 was statistically significant (P=0.0001 and P=0.0001) respectively as compared to positive control group (Sildenafil1µg/gmbwt/day) respectively. The mean thickness of right kidney in group 4 and 5 was statistically significant (P=0.0001 and P=0.0001) respectively when it was compared to positive control group (Sildenafil1µg/gmbwt/day) while the thickness of left kidney was statistically significant (P=0.0001 and P=0.0001) when in group 4 and 5 as compared to positive control group (Sildenafil1µg/gmbwt/day) respectively (Table 4).

Table 4: A table indicating mean length, width and thickness between positive controls and experimental groups.

Groups	Kidney gross morphometries in mm.					
	Mean right kidney length	Mean left kidney length	Mean right kidney width	Mean left kidney width	Mean right kidney thickness	Mean left kidney thickness
SIN 1microgram/gmbwt/day (5 rats)	14.16±.36	11.97±.58	10.27±.16	9.66±.22	3.03±.07	2.91±.02
Low curcuma longa dose (38.75mg/gm/bwt/day)	17.15±.34	16.64±.30	10.18±.70	9.99±.18	4.76±.44	4.18±.11
Medium curcuma longa dose (77.5mg/gm/bwt/day)	17.25±.20	16.75±.15	10.48±.36	10.11±.32	4.78±.23	4.36±.19
High curcuma longa dose (155mg/gm/bwt/day)	17.69±.30	17.46±.23	10.74±.24	10.31±.27	4.90±.27	4.59±.24

KEY: All values are expressed as the mean, ± is the standard error of the mean (SEM). The test of significance was performed in rows. Values are expressed as mean ± standard error of mean (n=5), SIN- sildenafil induced nephrotoxicity, LCL-Low curcuma Longa, MCL-Medium Curcuma Longa, HCL-High Curcuma Longa

The mean length, width and thickness between positive control and restorative group.

The mean length of right and left kidney in restorative group was statistically significantly different (R; P=0.0001, L; P=0.0001) as compared to the positive control (sildenafil 1µg/gmbwt/day) group.

The mean thickness of right and left kidney in restorative group was statistically significantly different (R; P=0.0001, L; P=0.0001) as compared to the positive control (sildenafil 1µg/gmbwt/day) group respectively (Table 5).

Table 5: The mean length, width and thickness between positive controls and restorative group.

Kidney gross morphometries in mm.						
Groups	Mean right kidney length	Mean left kidney length	Mean right kidney width	Mean left kidney width	Mean right kidney thickness	Mean left kidney thickness
SIN 1μg/gmbwt/day (5 rats)	14.16±.36	11.97±.58	10.27±.16	9.66±.22	3.03±.07	2.91±.02
Restorative groups (15 rats)	17.37±.17	16.95±.16	10.46±.26	10.14±.14	4.81±.17	4.38±.11
P value	0.0001	0.0001	1.000	0.264	0.0001	0.0001

KEY: All values are expressed as the mean± the standard error of the mean (SEM). The test of significance was performed in rows. Values are expressed as mean ± standard error of mean (n=5), SIN- sildenafil induced nephrotoxicity

DISCUSSION

In this study the control groups were grouped into negative control (feeds+ water ad libitum) and positive control (SIN 1 microgram/gmbwt sildenafil). During gross anatomical observation after dissection, the two kidneys lay on each side of upper lumbar vertebrae within abdominal cavity, this concurred with the normal anatomical relation of Kidneys as observed by other authors (Olukole, 2021) . The superior anterior part of right kidney related to liver while left was associated with pancreas, stomach, spleen, small intestines and descending colon. These findings were similar to those recorded by (Al-Samawy, 2012) in albino rats.

On examination of borders, the lateral border was convex in shape while the medial border was concave and indented at hilus. On examination of the kidneys of rats that were subjected to sildenafil they appeared darker brown in color, shrinked and pale. The obvious shrinkage may have been due to the increased oxidative stress imposed by free reactive and nitrogen oxide radicals released by sildenafil as was observed by (Kirbas et al., 2015) who recorded same in the literature on paracetamol effect on kidney and significant reduction in growth of collagen fibers in kidneys as an effect of sildenafil administration and (Hegazy et al., 2021) on effects of paracetamol on kidney since the two drugs exhibit a similar nephrotoxicity model.

The current study noted a significant (P=0.0001) reduction in weight of the rats on treatment with sildenafil as compared to control group, in addition, the mean terminal or live weight of control group was 284.78±.32gm, this was slightly higher as compared with previous studies carried out in Nigeria (Onyeanusi et al., 2009) of 140.625±3.07gm and similar to(Olukole, 2021) as seen in domesticated African great cane rat. The high weight observed in control group might have been due to the long duration of study and no stress factors that

could interfere with eating habits and weight gain.

The mean weight of rats in SIN group was 254.74±.81gm in the present study, this was also higher as compared to a study done by(Sivasankaran et al., 2007) who noted a mean weight of 183.16±3.76gm after administration of sildenafil. Similar trend in reduction of weight of rats when exposed to sildenafil were also noted by(Mohamed Yousry et al., 2016; Ngulde et al., 2016). The reduction in body weight might suggest that nephrotoxicity process was taking place as a result of administration of sildenafil. Nephrotoxicity leads to accumulation of toxins in the blood associated with reduced metabolism and loss of appetite, the decrease in production of erythropoietin might also lead to anaemia thus causing fatigue, loss of appetite and finally weight loss. The weight of right kidney was higher than left kidney representing 0.41% and 0.32% respectively which was similar to wistar rats and domesticated African great cane rats in the savanna zones of Nigeria (Onyeanusi et al., 2009). However, this was lower than 0.76% results obtained by(Hebel & Stromberg, 1976). This difference could be due to the variations in breed, environmental factors and age.

It was observed that the mean weight of experimental groups increased steadily as compared to sildenafil induced nephrotoxicity group. This increase in weight might have been due to Curcumin which is an active component in *Curcuma longa* that serves as a supplementary diet thus improves growth and weight gain rate. Previous studies in Turkey showed similar trends in weight increase whereby rats that were subjected to Curcumin gained more weight as compared to those that were exposed to aflatoxin(Hatipoglu & Keskin, 2022) . The mean weight of right and left kidney significantly(P=0.0001) increased on high *Curcuma longa* dose as compared to positive control group. The noted increased kidney weight might have been due to reduced destruction of renal collagen fibers, reduced inflammatory process and increased kidney histoarchitecture restructuring due to remodeling nature of *Curcuma longa* in nephrotoxicity.

The mean volume, length and thickness of kidney in experimental groups increased significantly(P=0.0001) as compared to positive control group. The previous studies observed that these changes might have been due to antioxidant and anti-inflammatory effects of *Curcuma longa* as it helps in improving or protecting the kidney(Akinyemi & Adeniyi, 2018). The increase in volume might have also been due to reduced destruction of epithelial cells by nitric oxide, vasodilation of glomerulus and proximal convoluted tubules as a result of reduced infiltration and increased glomerular filtration rate.

CONCLUSION
It can be concluded that medium and high dose *Curcuma longa* has kidney gross morphological restorative benefits in Sildenafil induced nephrotoxicity among male albino rats. Therefore, *Curcuma longa* can be used to mitigate the nephrotoxic effects of Sildenafil in the future or be used as a component in drugs that can be useful in management of Sildenafil induced nephrotoxicity.

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