ORIGINAL ARTICLE

Anatomy Journal of Africa. 2023. Vol 12 (3): 2504 - 2509

CURCUMA LONGA RENAL HISTORESTORATIVE EFFECTS ON SILDENAFIL INDUCED NEPHROTOXICITY AMONG MALE ALBINO RATS.

Khisa Wanjala Allan[1], Spencer Opiyo Oyugi[1] and Atanas Malik Nyabola[2]

[1]Department of Human Anatomy, School of Medicine, Maseno University, Kisumu, Kenya.

[2]Department of Human Anatomy, School of Medicine, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

Corresponding Author: Dr. Khisa Wanjala Allan. **Email:** Allanwanjala345@gmail.com

ORCID ID: https://orcid.org/0000-0002-7464-4170

ABSTRACT

Background: Sildenafil is a phosphodiesterase type 5 inhibitor mostly used in management of erectile dysfunction and pulmonary hypertension. On the other hand, *Curcuma longa* is herbal plant that is mostly used in diets among the Asian and African population and commonly used in treatment of respiratory, renal and dermatological diseases. **Methods:** A post-test only true experimental study design was utilized with 25 Albino rats grouped as follows: negative control, positive control (sildenafil 1µg/g bwt), low dose *Curcuma longa* (38.75mg/kg), medium dose *Curcuma longa* (77.5mg/kg) and high dose *Curcuma longa* (155mg/kg) each having 5 rats. Induction of nephrotoxicity using sildenafil was done for 15 days with an interim sacrifice for negative and positive control groups done on day 15. Experimental groups were sacrificed on day 22 after receiving *Curcuma longa* at respective doses. Blood samples for renal function tests were obtained on day 1, 15 and 22. Enblock harvesting of the kidneys after euthanizing the rats with concentrated CO_2 and 10% neutral buffered formalin perfusion was done on day 15 and 22 then fixed in 10% neutral buffered formalin for 24hours. The kidneys were then processed for Hematoxylin and Eosin staining and photomicrographs were taken using Olympus light microscope fitted with LABOMED ivu 3100 digital camera. **Results:** In sildenafil induced nephrotoxicity group; glomerulus was distorted, dilated bowman`s space, dilated renal tubules and necrotic epithelial cells. Minimal histological changes were observed in low *Curcuma longa* dose group while in medium and high *Curcuma longa* dose groups; the glomerulus had well defined margins, bowman`s space reduced in size, epithelial cells appeared normal. **Conclusion:** It can be concluded that medium and high dose *Curcuma longa* have kidney historestorative effects in sildenafil induced nephrotoxicity among male albino rats.

Keywords: *Curcuma longa*, Historestorative, Kidney, Nephrotoxicity and Sildenafil.

DOI: https://dx.doi.org/10.4314/aja.v12i3.7

INTRODUCTION

Nephrotoxicity is kidney rapid deterioration function due to toxic effect of medicines, chemicals, environmental and industrial toxins (Lv & Zhang, 2019) . Drug induced nephrotoxicity is the third leading cause of acute kidney injury as this type of nephrotoxicity has a wide range of damage on the nephron (Sales & Foresto, 2020). Sildenafil has wide variant methods of nephrotoxicity as it affects different parts of kidney namely; glomerulus, bow man capsule, medulla, cortex, medullary tubule, cortical tubules, proximal convoluted tubule, renal vessels and glomerular capillaries. It releases oxidative chemicals that can cause stress thereby damaging cell membrane (Cadirci et al., 2011; Ebrahimi et al., 2009) . It causes accumulation of lactate in kidney tubules causing damage to cytoplasm leading to elevation in osmotic pressure that cause water intracellular influx (Medeiros et al., 2017) . The accumulation of calcium

leads to glomeruli calcification and reduced renal function (Küçük et al., 2012). *Curcuma longa* has the physiological properties that can counteract, attenuate, improve and protect the kidney from drug induced nephrotoxicity (Manikandan et al., 2011; Tirkey et al., 2005; Trujillo et al., 2013). However, there is less data which shows the restorative effects of *Curcuma longa* on sildenafil induced nephrotoxicity. *Curcuma longa* is greatly able to protect the kidney from sildenafil induced nephrotoxicity by counteracting the tubular damages, apoptosis and oxidative stress released (He et al., 2015), activities of heme oxygenase, endothelial nitric oxide synthase and gene expression of tumor necrosis factor alpha (Hassan et al., 2019) and it has Curcumin that has anti-inflammatory and antioxidative effects thus able to counteract the reactive oxygen and nitric oxide radicals released (Ueki et al., 2013). Therefore, the aim of this study was to evaluate *Curcuma longa* renal historestorative effects on sildenafil induced nephrotoxicity among male albino rat.

MATERIALS AND METHODS

Experimental animals

A total of twenty-five male albino of species *Rattus norvegiccus* rats were used. They were simple randomly assigned into five groups as either; control, sildenafil induced nephrotoxicity, low, medium and high dose *Curcuma longa* groups. 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.

Drug administration

The four subgroups received a single dose of 1µgm/gm bwt/day sildenafil(Suriyakumari et al., 2016) for 15 days through gastric gavage. The five animals in group2 were sacrificed four hours post last dosage and renal function test was done to confirm toxicity while group 3, 4 and 5 were subjected to *Curcuma longa* at 38.75mg/kg, 77.5mg/kg and 155mg/kg respectively for seven days to try and restore the damage that had been caused(Fança-Berthon et al., 2021; Nair & Jacob, 2016). Thereafter, renal function test was done to confirm if restoration had been effective.

Sacrificing and histological preparation

CO_2 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 kidneys. The kidneys were identified and excised. The fibrous capsule and adipose tissue were removed. They were then preserved in 10% formalin. Later, they were stained using hematoxylin and eosin stains and observed under a light microscope. Photomicrographs were then taken and key histological changes were noted and described as below. 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

Histological findings in negative control group and sildenafil induced nephrotoxicity group.

In negative control group (feeds + water ad libitum), the glomerulus was surrounded by a narrow bowman`s space. The epithelial cells were normal along the proximal tubule with well-defined margins and lumen had normal brush borders. In sildenafil induced nephrotoxicity group, the glomerulus was distorted with a dilated bowman`s space, dilated cortical tubule with deranged

borders, vacuolations, necrotic epithelial cells and lumen had distorted brush borders (Figure 1). Kidney histo-morphological findings among low, medium and high Curcuma longa groups.

In low *Curcuma longa* dose*(*38.75mg/kg/day*)*, the glomerulus had poor defined margins and was surrounded by a bowman`s space. The epithelial cells appeared cuboidal in shape around the cortical tubule while the lumen had defined borders. In medium *Curcuma longa* dose(77.5mg/kg/day), glomerulus had poor defined margins, narrow bowman`s space, the lumen was well defined (Figure 2).

In high *Curcuma longa* dose(155mg/kg/day), the glomerulus had well defined margins and a narrow bowman`s space, the epithelial cells appeared cuboidal and the lumen had well defined brush borders (Figure 3).

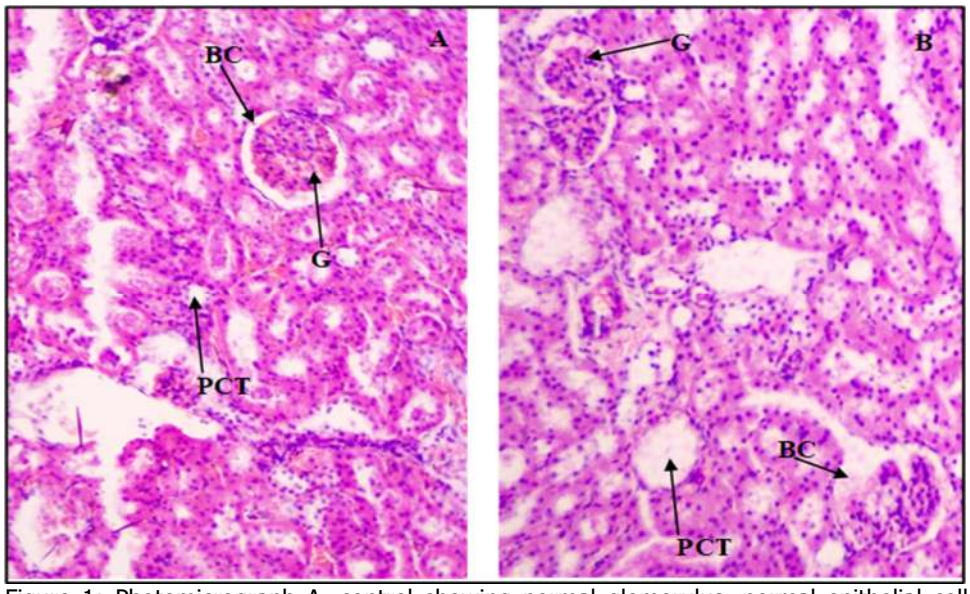

Figure 1: Photomicrograph A, control showing normal glomerulus, normal epithelial cells, bowman`s capsule and proximal convoluted tubule. B, in Sildenafil induced nephrotoxicity showing distorted glomerulus, dilated bowman`s capsule and cortical tubule with necrosis. At x10 using hematoxylin and eosin stain. G=glomerulus, PCT=proximal convoluted tubule, BC=bowman`s capsule, A=control group and B= sildenafil induced nephrotoxicity group.

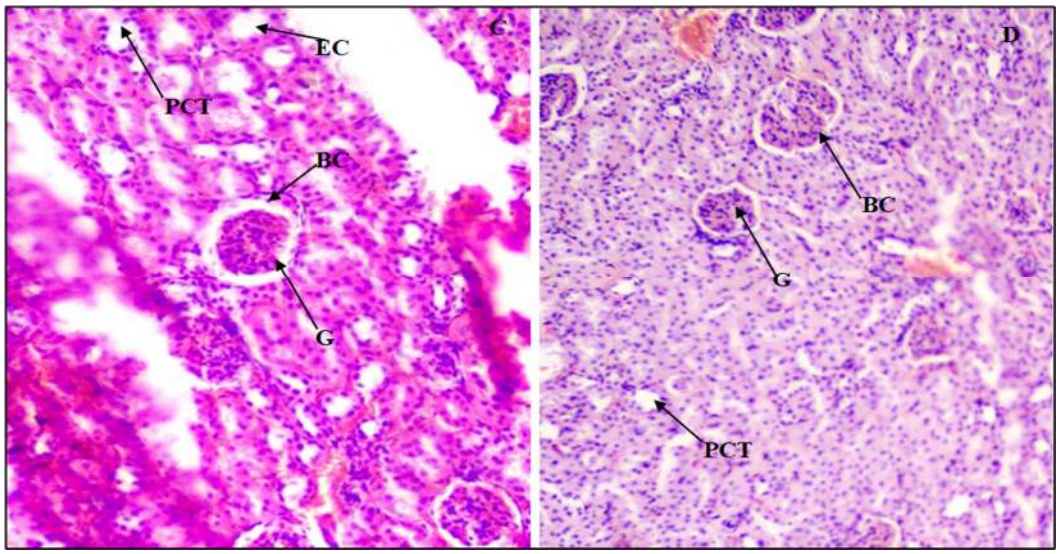

Figure 2: Photomicrograph C, low *Curcuma longa* dose showing glomerulus with defined margins, cuboidal epithelial cells, bowman`s capsule and proximal convoluted tubule with defined edges. D, in medium *Curcuma longa* dose

showing normal glomerulus with well-defined. At x10 using hematoxylin and eosin stain. G=glomerulus, PCT=proximal convoluted tubule, BC=bowman`s capsule, EC= epithelial cells, C=low *Curcuma longa* dose group and D= medium *Curcuma longa* dose group.

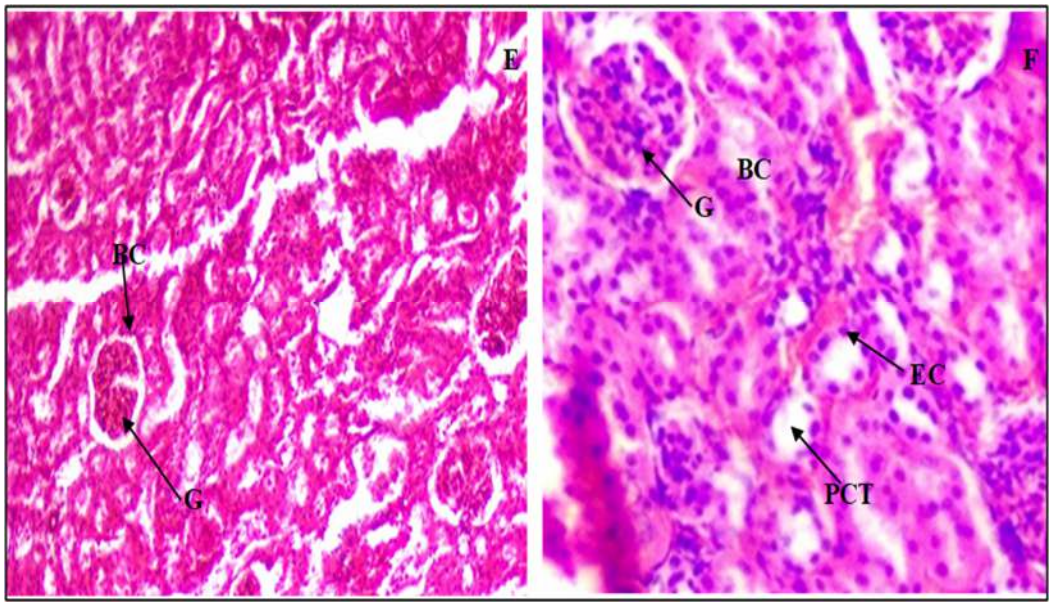

Figure 3: Photomicrograph E and F high *Curcuma longa* dose showing normal glomerulus with well-defined margins, narrow bowman`s capsule and cortical tubule normal epithelial cells. At x10 using hematoxylin and eosin stain. G=glomerulus, PCT=proximal convoluted tubule, BC=bowman`s capsule, EC= epithelial cells, E and F=high *Curcuma longa* dose group.

DISCUSSION

In the current study, it was observed that sildenafil caused gross glomerular damage and widening of bowman`s space which was mediated by cellular degeneration and necrosis (Figure 1 B). This observation is in agreement with the results reported by (Mohammed & Khudair, 2020) who observed similar changes when diclofenac was used in induction of Acute kidney injury. There was obvious distortion, shrinkage of the glomerulus and glomerulosclerosis (Figure1B) on microscopic study in concurrence with the findings of (Ali et al., 2018). This progressive morphological changes in histoarchitecture of kidney may be due to decrease in glomerular filtration of the drug as a result of capillary constriction and increased pro-inflammatory cytokines which lead to a primary renal injury (Suriyakumari et al., 2016).

There were vacuolations seen in the current study (Figure1B) which was mediated by increase in production of lactate that accumulates within the cytoplasm and potentially leading to cellular membrane damage as noted in previous studies (Suriyakumari et al., 2016). There was damage and necrosis of epithelial cells and massive dilatation of proximal tubules and distorted lumen. Previous studies observed that these changes might have been modulated by infiltration of inflammatory cells, intensive swelling of epithelial cells when exposed to oxidant stress which leads to increased production of nitric oxide that reacts with free radicals causing renal damages (Kirbas et al., 2015).

In the current study, there was improvement in the general structure of epithelial cells, the proximal convoluted tubule had defined margins with a narrow lumen as seen (Figure 3 & 4) as compared to positive control group. This general improvement in epithelial cells and proximal convoluted tubules may be due to prevention of renal tubular and epithelial cell degeneration and presence of curcumin in *Curcuma longa* that restores tubular brush borders and anatomical efficiency of renal

tubular basement membrane (Ahmad et al., 2020; Liu et al., 2017).

On observation, the current study noted that the glomerulus was histomorphologically restored with well-defined margins after administration of *Curcuma longa* (Figure 3 & 4) as compared to positive control group (Figure 3 & 4). (Ahmed et al., 2015) reported a similar result on kidney histomorphology after assessing the effects of Curcumin and garlic on methotrexate and carbon tetrachloride induced nephrotoxicity, they noted a complete histomorphological restoration of glomeruli and its surrounding margins. This markable improvement in restructuring of the glomerulus may have been due to reduced infiltration of inflammatory cells and release of inflammatory markers that prevent necrosis from taking place. Curcumin being an active component in *Curcuma longa* has the ability to restore the glomerular capillaries to normal size thus improving glomerular filtration rate of glomerulus (Russo et al., 2018).

CONCLUSION

Based on this study, it can be concluded that medium and high dose *Curcuma longa* have historestorative benefits on sildenafil induced nephrotoxicity among male albino rats. Therefore, *Curcuma longa* can be used in the management or can be considered as a component in formulating drugs that can be used in treatment of sildenafil induced nephrotoxicity.

ACKNOWLEDGEMENT

I wish to acknowledge the staffs at the department of human anatomy for their tireless and continuous effort and support to enable me come up with this paper work.

REFERENCES

1. Ahmad, R. S., Hussain, M. B., Sultan, M. T., Arshad, M. S., Waheed, M., Shariati, M. A., Plygun, S., & Hashempur, M. H. (2020). Biochemistry, safety, pharmacological activities, and clinical applications of turmeric: a mechanistic review. *Evidence-based complementary and alternative medicine*, *2020*.
2. Ahmed, W., Zaki, A., & Nabil, T. (2015). Prevention of methotrexate-induced nephrotoxicity by concomitantadministration of garlic aqueous extract in rat. *Turkish journal of medical sciences*, *45*(3), 507-516.
3. Ali, B. H., Al Za'abi, M., Adham, S. A., Al Suleimani, Y., Karaca, T., Manoj, P., Al Kalbani, J., Yasin, J., & Nemmar, A. (2018). The effect of sildenafil on rats with adenine—Induced chronic kidney disease. *Biomedicine & pharmacotherapy*, *108*, 391-402.
4. Cadirci, E., Halici, Z., Odabasoglu, F., Albayrak, A., Karakus, E., Unal, D., Atalay, F., Ferah, I., & Unal, B. (2011). Sildenafil treatment attenuates lung and kidney injury due to overproduction of oxidant activity in a rat model of sepsis: a biochemical and histopathological study. *Clinical & Experimental Immunology*, *166*(3), 374-384.
5. Ebrahimi, F., Shafaroodi, H., Asadi, S., Nezami, B. G., Ghasemi, M., Rahimpour, S., Hashemi, M., Doostar, Y., & Dehpour, A. R. (2009). Sildenafil decreased cardiac cell apoptosis in diabetic mice: reduction of oxidative stress as a possible mechanism. *Canadian journal of physiology and pharmacology*, *87*(7), 556-564.
6. Fança-Berthon, P., Tenon, M., Bouter-Banon, S. L., Manfré, A., Maudet, C., Dion, A., Chevallier, H., Laval, J., & van Breemen, R. B. (2021). Pharmacokinetics of a single dose of turmeric curcuminoids depends on formulation: results of a human crossover study. *The Journal of Nutrition*, *151*(7), 1802-1816.

7. Hassan, F.-u., Rehman, M. S.-u., Khan, M. S., Ali, M. A., Javed, A., Nawaz, A., & Yang, C. (2019). Curcumin as an alternative epigenetic modulator: mechanism of action and potential effects. *Frontiers in genetics*, *10*, 514.
8. He, L., Peng, X., Zhu, J., Liu, G., Chen, X., Tang, C., Liu, H., Liu, F., & Peng, Y. (2015). Protective effects of curcumin on acute gentamicin-induced nephrotoxicity in rats. *Canadian journal of physiology and pharmacology*, *93*(4), 275-282.
9. Kirbas, A., Cure, M. C., Kalkan, Y., Cure, E., Tumkaya, L., Sahin, O. Z., Yuce, S., Kizilkaya, B., & Pergel, A. (2015). Effect of infliximab on renal injury due to methotrexate in rat. *Iranian journal of kidney diseases*, *9*(3), 221.
10. Küçük, A., Yucel, M., Erkasap, N., Tosun, M., Koken, T., Ozkurt, M., & Erkasap, S. (2012). The effects of PDE5 inhibitory drugs on renal ischemia/reperfusion injury in rats. *Molecular biology reports*, *39*, 9775-9782.
11. Liu, F., Ni, W., Zhang, J., Wang, G., Li, F., & Ren, W. (2017). Administration of curcumin protects kidney tubules against renal ischemia-reperfusion injury (RIRI) by modulating nitric oxide (NO) signaling pathway. *Cellular Physiology and Biochemistry*, *44*(1), 401-411.
12. Lv, J.-C., & Zhang, L.-X. (2019). Prevalence and disease burden of chronic kidney disease. *Renal fibrosis: mechanisms and therapies*, 3-15.
13. Manikandan, R., Beulaja, M., Thiagarajan, R., Priyadarsini, A., Saravanan, R., & Arumugam, M. (2011). Ameliorative effects of curcumin against renal injuries mediated by inducible nitric oxide synthase and nuclear factor kappa B during gentamicin-induced toxicity in Wistar rats. *European journal of pharmacology*, *670*(2-3), 578-585.
14. Medeiros, V. d. F. L. P., Azevedo, Í. M., Carvalho, M. D. F., Oliveira, C. N., Egito, E. S. T. d., & Medeiros, A. C. (2017). The renoprotective effect of oral Tadalafil pretreatment on ischemia/reperfusion injury in rats1. *Acta Cirurgica Brasileira*, *32*, 90-97.
15. Mohammed, Y. J., & Khudair, Z. W. (2020). Study the Histopathological Effects of Sildenafil Treatment on the Kidney of Adult Male Rats. ttti
16. Nair, A. B., & Jacob, S. (2016). A simple practice guide for dose conversion between animals and human. *Journal of basic and clinical pharmacy*, *7*(2), 27.
17. Russo, E. R., Facincani, I., Nakazato, K. C., Coimbra, T. M., Crevelin, E. J., Pereira, A. M. S., & Carmona, F. (2018). Oral administration of powdered dried rhizomes of Curcuma longa L.(turmeric, Zingiberaceae) is effective in the treatment of doxorubicin-induced kidney injury in rats. *Phytotherapy Research*, *32*(12), 2408-2416.
18. Sales, G. T. M., & Foresto, R. D. (2020). Drug-induced nephrotoxicity. *Revista da Associação Médica Brasileira*, *66*, s82-s90.
19. Suriyakumari, K., Udayakumar, R., & Ruba, T. (2016). Histological investigations on kidney of sildenafil citrate (edegra) treated albino mice. *Int J Anat Res*, *4*(1), 1977-1980.
20. Tirkey, N., Kaur, G., Vij, G., & Chopra, K. (2005). Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys. *BMC pharmacology*, *5*(1), 1-10.
21. Trujillo, J., Chirino, Y. I., Molina-Jijón, E., Andérica-Romero, A. C., Tapia, E., & Pedraza-Chaverrí, J. (2013). Renoprotective effect of the antioxidant curcumin: Recent findings. *Redox biology*, *1*(1), 448-456.
22. Ueki, M., Ueno, M., Morishita, J., & Maekawa, N. (2013). Curcumin ameliorates cisplatin-induced nephrotoxicity by inhibiting renal inflammation in mice. *Journal of bioscience and bioengineering*, *115*(5), 547-551.