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Renal Biochemical Marker Changes in Restorative Activities of *Curcuma longa* on Sildenafil Induced Nephrotoxicity Among Male Albino Rats

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ABSTRACT

Background: Nephrotoxicity is the rapid deterioration of kidney function due to altered histoarchitecture and drug clearance characterized by increased levels of renal biochemical markers. Sildenafil is among the drugs postulated to cause nephrotoxicity if taken over a long period of time or as an overdose as it interferes with the kidney histoarchitecture. *Curcuma longa* is a traditional herbal plant which is used in diet, treatment of diabetes, dermatological conditions and renal diseases.

Objective: The aim of this study was to evaluate renal biochemical marker changes in restorative activities of *Curcuma longa* on sildenafil induced nephrotoxicity.

Methodology: A total of 25 male albino rats of species rattus norvegiccus were used in this experiment. 5 rats received water and feeds, 20 received 1µg/gmbwt Sildenafil for 15 days from these 5 rats were sacrificed four hours post last dose. The remaining 15 rats were treated with *Curcuma longa* at calculated doses. Animals were sacrificed in humane end points, blood collected through cardiac puncture stored in sample bottle and centrifuged to harvest serum.

Results: It was observed that blood urea and creatinine levels in Sildenafil-induced nephrotoxicity group significantly increased as compared to negative control group and reduced significantly in medium and high dose *Curcuma longa* groups.

Conclusion: Based on this study it can be concluded that medium and high dose *Curcuma longa* reduces blood urea and nitrogen and creatinine levels when used in the assessment of restorative effects of *Curcuma longa* on Sildenafil induced nephrotoxicity among male albino rats.

Keywords: Biomarkers; Histoarchitecture; Kidney; Nephrotoxicity; Restoration.

Introduction

Kidney biomarkers are the chemicals used to determine any decrease in kidney function and estimate both severity and nature of kidney injury. These biomarkers include lipids, proteins, genes, metabolites and cells present on urinalysis. Drug induced nephrotoxicity remains the leading cause of acute kidney injury. Majority of the population affected being from industrialized countries and this is attributed to the excess environmental pollution witnessed, lifestyle changes that has led to the development of hypertension and diabetes mellitus.

Therefore, there is a high need of increase sensitivity and specificity of different tools, need to combine different biomarkers so as to increase the diagnostic accuracy (Wasung et al., 2015) used to detect drug induced nephrotoxicity as a cause of acute kidney injury at early stages. The emerging new biochemical markers include: kidney injury molecule 1 and 2, Cystatin C and FGF-23 (Wasung et al., 2015).

Serum creatine remains the major kidney biomarker however, it is associated with challenges like patients with low muscle bulky and fluid overload it may be hard for you to use Serum creatinine as biomarker therefore, there is Sildenafil has been associated with nephrotoxicity because of increase in rate of reports of patients developing acute kidney injury upon its intake. It has cytotoxic effects as it's known to damage cell membrane. It also increases levels of lactate, calcium thus causing calcification and necrosis of tubules. In human beings' sildenafil causes increased blood urea nitrogen and serum creatinine levels. This is based on the management of 67-year-old

man who developed acute kidney injury upon taking 400mg of sildenafil within four hours and who on laboratory analysis on admission was serum creatinine of 1.94 mg/dl and blood urea and nitrogen of 16mg/dl. On days 4 and 6 the patient had a serum creatine level of 5.07mg/dl and blood urea and nitrogen of 71 mg/dl respectively (Liu et al., 2018).

Curcuma longa contains high concentration of Curcumin that have antioxidant benefits. In a study to evaluate effects of *Curcuma longa* on renal function test, rats were co-treatment with 12.5mg and 25mg/Kg respectively of Curcumin. It was observed that there was a significant reduction in serum creatinine and urea levels with prevention on serum electrolyte derangements like potassium, sodium, chloride and hydrogen carbon (Akinyemi & Adeniyi, 2018).

Curcuma longa causes a significant decrease of blood urea and nitrogen(BUN), serum creatinine and creatinine kinase levels that indicates Curcuma has Reno-protective benefits based on study to evaluate the effect of curcumin on glycerol-induced acute kidney injury(AKI) (Wu et al., 2017). This study is in agreement with (Venkatesan et al., 2000) in which rats were subjected to doxorubicin and treated with curcumin, on evaluation of biochemical markers there was a significant reduction in urine levels of N-Acetyl-B-glycosaminidase (NAG) which is normally a marker of tubular damage. In a study on reno-protective effects of Curcumin on cyclosporin A induced nephrotoxicity, the researcher establishes that curcumin attenuates renal morphology, antioxidant enzymes and renal function that was altered by treatment of cyclosporin A was normalized (Tirkey et al., 2005). Therefore, this study sought to evaluate the renal biochemical marker changes of restorative activities of *Curcuma longa* in Sildenafil-induced nephrotoxicity among male albino rats.

Methods

This was a post-test only true experiment in which a total of 25 male albino rats were used. The 25 male albino rats were simple randomly assigned into two groups as either control or experimental. The experimental group was further divided into four groups as either Sildenafil induced nephrotoxicity, low *Curcuma longa* dose, medium *Curcuma longa* dose and high *Curcuma longa* dose. All the four experimental groups received a constant dose of 1µg/gmbwt sildenafil for 15 days then *Curcuma longa* at calculated dose of 38.75mg/kgbwt,77.5mg/kg bwt and 155mg/kg bwt for seven days. All 5 rats in Sildenafil-induced nephrotoxicity group were sacrificed four hours post-last dosage administration. The remaining 20 animals, from negative control group and the four experimental groups were sacrificed after seven days through humane endpoints. All procedures on feeding, cleaning, drug administration and weighing were carried out as per the animal use and care laboratory procedures. Blood was harvested via cardiac puncture, put in labeled specimen bottles and immediately centrifuged. Serum was harvested and blood urea and nitrogen levels and creatinine were determined.

Renal biochemical parameters assay before and after administration of Sildenafil

The renal biochemical marker assays were determined before administration of sildenafil in order to ascertain that albino rats have a normal kidney function. Sildenafil was administered then biochemical marker assays were done before administration of *Curcuma longa*. Here, BUN and Creatinine were used to assist in early diagnosis of acute kidney injury.

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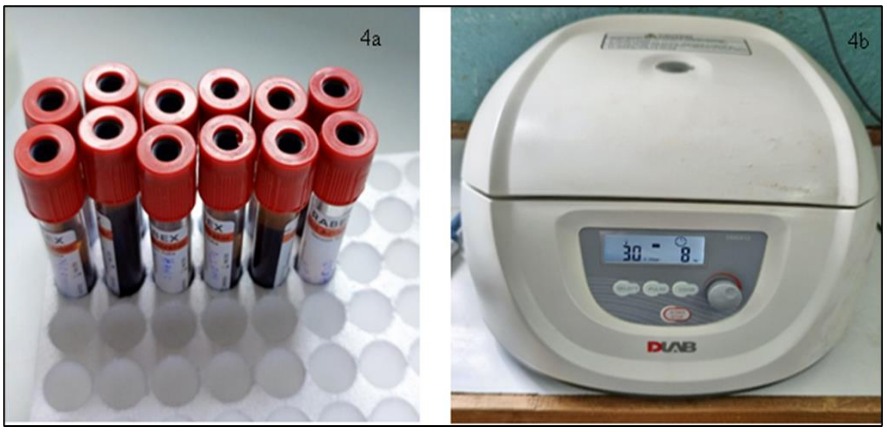

Figure 1. A collected sample of blood for renal parameters and a centrifuging machine

Sample collection of blood for renal biochemical parameters analysis

Collection of blood samples from rodents is important for in-vitro and in-vivo studies. The sites varies but they may include; jugular veins, maxillary vein, saphenous vein and the heart. In order to collect large amounts of blood, Cardiac puncture may be used as an average of 10ml blood can be collected from a rat weighing 150g (Beeton et al., 2007).

The procedure includes: Prepared a 5 ml syringe with a gauge 23 needle, deeply anesthetized the rat, checked for anesthesia by lack of spontaneous movements or response to stimuli, placed the rat on its back facing away from you, placed the left index finger at the level of lowest ribs, without applying pressure. (Heart was located 1 cm above this point and slightly to the right), held the syringe at 45-degree angle inserted the needle between two ribs and watched for a drop of blood to come into the needle, a total of 3- 5 ml of blood was collected and immediately euthanized the rat.

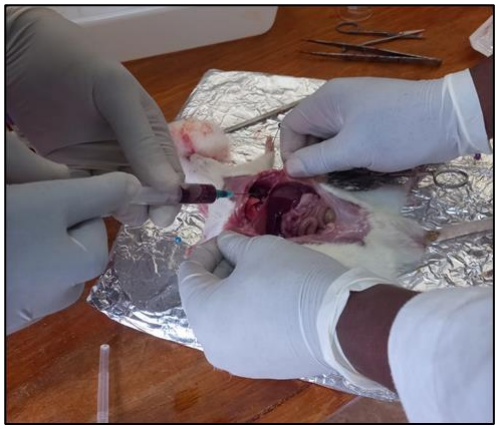

Figure 2. Cardiac puncture conducted after the rat had been anaesthetized

Results

Comparative renal biochemical marker findings between control groups and experimental groups

Renal parameters were compared between the control groups (negative control and positive control) and experimental groups (restorative groups) using a One Way ANOVA and an inter-group significance test done using post hoc Bonferroni. The mean blood urea and nitrogen in positive control (sildenafil1µg/gmbwt/day)

increased significantly (*P*=0.0001) as compared to negative control group (feeds+ water). The mean creatinine levels in positive control group (sildenafil1µg/gmbwt/day) increased significantly (*P*=0.0001) as compared to negative control group (feeds+ water) respectively (Table 2).

Table 1. Normal ranges of biochemical parameters (Blood Urea and Nitrogen and creatinine)

Biochemical parameter	**Normal ranges (mmol/L and mg/dl)**
Blood Urea and Nitrogen	4.2 – 8.97 mmol/L
creatinine	0.2 – 0.8 mg/dl

Table 2. Comparative renal biochemical marker findings between negative and positive control groups

	Renal biochemical parameters			
Groups	**Blood urea and nitrogen (BUN) in mmol/L**	**P values**	**Creatinine Mg/dl**	**P values**
Control (feeds+ water ab libitum)	6.6000±.02983	**0.0001**	0.5160±.01077	**0.0001**
SIN 1microgram/gmbwt/day	11.366±.04622	**0.0001**	1.2640±.00510	**0.0001**

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.*

Comparative renal biochemical marker findings between positive control group and experimental groups

There was a significant reduction in renal biochemical parameters of blood urea and nitrogen (P=0.014 & P=0.009) and creatinine (P=0.0029 & P=0.006) in medium and high dose *Curcuma longa* respectively as compared to Sildenafil induced nephrotoxicity group (Table 3).

Table 3. Comparative renal biochemical marker findings between control groups and experimental groups

Renal biochemical parameters				
Groups	**Blood urea and nitrogen (BUN) in mmol/L**	**P values**	**Creatinine Mg/dl**	**P values**
SIN 1microgram/gmbwt/day	11.366±.04622	**0.0001**	1.2640±.00510	**0.0001**
Low C*urcuma longa* 38.75mg/kg/day	11.248±.01685	0.065	1.2000±.02121	0.069
Medium *Curcuma longa* 77.5mg/kg/day	11.222±.01715	**0.014**	1.1920±.01772	**0.029**
High *Curcuma longa* 155mg/kg/day	11.214±.01327	**0.009**	1.1780±.01497	**0.006**

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.*

Discussions

It was noted that urea increased in positive control group as compared to negative group (Table 2). (Liu et al., 2018) observed a similar trend when assessing the biochemical parameter in rats before and after nephrotoxicity. However, (El-Batsh et al., 2021; Wu et al., 2017) recorded reduced levels of urea in rats when assessing the renal biochemical changes. The slight increase in urea levels might have been due to increased production in inflammatory markers and oxidative stress on the glomerulus, proximal convoluted tubule and epithelial cells that cause nephrotoxicity.

The contrary observations were noted because of the agents used that had effects on both liver and kidney and this could potentially reduce levels of urea as its can also be synthesized in the liver and kidney. The levels of urea in experimental group slightly reduced as compared to positive control group (Table 2). (Ali et al., 2005) study in Brazil demystified similar reports where rats that were exposed to Curcumin or gentamicin + Curcumin (Table 2) showed reduced urea levels signifying positive impact in palliative care. This reduction in urea levels was due to increased anti-inflammatory and antioxidative activities of *Curcuma longa* thus improving the kidney function (Ghosh et al., 2014).

The levels of creatinine in positive control group increased significantly (P=0.001) as compared to negative control group (Table 2). (Kundu et al., 2012) "*Sulvajrini Vatika*" herb. The increase in creatinine levels were due to impaired renal function, aggregation of necrotic cells within the glomerular capillaries thus reduced filtration rate leading to nephrotoxicity. Studies in Iraq (Kata, 2020) while evaluating the short-time effect of Malathion pesticide on functional changes of kidney in female mice reported a similar trend.

The levels of blood urea and creatinine significantly reduced in medium and high dose Curcuma longa as compared to Sildenafil-induced nephrotoxicity group (Table 3). This is in agreement with the findings (Akinyemi & Adeniyi, 2018) on evaluation of *Curcuma longa* effects on renal function test, rats were co-treatment with 12.5mg and 25mg/Kg respectively of curcumin. It was observed that there was a significant reduction in serum creatinine and urea levels with prevention on serum electrolyte derangements like potassium, sodium, chloride and hydrogen carbon.

In a study on reno-protective effects of Curcumin on cyclosporin A induced nephrotoxicity, the researcher establishes that Curcumin attenuates renal morphology, antioxidant enzymes and renal function that was altered by treatment of cyclosporin A was normalized (Tirkey et al., 2005). *Curcuma longa* causes a significant decrease of BUN, serum creatinine and creatinine kinase levels that indicates curcuma has Reno-protective benefits based on study to evaluate the effect of curcumin on glycerol-induced AKI (Wu et al., 2017).This study is in agreement with (Venkatesan et al., 2000) in which rats were subjected to doxorubicin and treated with curcumin, on evaluation of biochemical markers there was a significant reduction in urine levels of N- Acetyl -B-

glycosaminidase (NAG) which is normally a marker of tubular damage. In conclusion, medium and high dose Curcuma longa reduce the levels of BUN and creatinine in Sildenafil induced nephrotoxicity.

Declarations

Source of Funding

This study did not receive any grant from funding agencies in the public or not-for-profit sectors.

Competing Interests Statement

Authors have declared no competing interests.

Consent for Publication

The authors declare that they consented to the publication of this study.

Ethical Approval

Based on institutional guidelines.

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