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Research Article

Effect of Tomato Extract (*Lycopersicon esculentum*) on Gentamycin-Induced Acute Kidney Injury in Albino Wistar Rat

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Abstract

One of the causes of acute kidney disease is the excessive use of drugs, which has left some patients hospitalized. The aim of this study was to evaluate the effect of tomato extract on gentamycin-induced acute kidney injury in male albino wistar rats. The tomato fruits were properly processed and the phytochemicals determined. A total of twenty five (25) albino wistar rats were used and they were randomly allocated to five groups (A-E) with five (5) rats per group. Group A received no treatment and served as the normal group. Group B received gentamycin alone (100 mg/kg, I.p) daily for 6 days and served as the negative control. Groups C, D and E were pre-administered, post-administered and co-administered with tomato extract (30 mg/kg; oral) for 3 weeks following administration of gentamycin respectively, and served as the test groups. Biochemical results revealed: Creatinine, Urea, Na^+ and K^+ levels of: (1.40 ± 0.21 mmol/l, 49.00 ± 9.54 mmol/l, 126.30 ± 1.86 mmol/l and 6.90 ± 0.87 mmol/l) respectively. However, pre administration, post-administration and coadministration of tomato showed: Creatinine, urea, Na^+ and K^+ levels of: (0.50 ± 0.06 mmol/l, 24.00 ± 4.36 mmol/l, 130.00 ± 0.58 mmol/l, and 4.90 ± 0.06 mmol/l); (0.67 ± 0.09 mmol/l, 20.00 ± 1.16 mmol/l, 133.30 ± 2.40 mmol/l and 5.27 ± .41 mmol/l); (0.60 ± 0.10 mmol/l, 23.00 ± 3.51 mmol/l, 135.00 ± 1.53 mmol/l, and 4.53 ± 0.09 mmol/l), respectively. Histopathological results showed slight or no significant alterations in the test groups (C, D and E) when compared to the normal control. This shows that tomato possesses renal protective effect against gentamycin induced acute kidney injury.

Keywords: Ethnopharmacology; Renal-Protection; Renototoxicity; Lycopersicon esculentum; Gentamycin

Introduction

Acute kidney injury remains a common complication in hospitalized patients and is usually associated with high morbidity, mortality and significant healthcare resource and costs [1]. It is a rapid decline in renal excretory function resulting in the inability of the kidney to regulate fluid and electrolyte homeostasis; usually it is characterized by increase in serum creatinine level, nitrogenous wastes and a decrease in urine output [2]. Despite their limitations, high serum creatinine, blood urea nitrogen and low urine output are currently used in diagnosis of acute renal injury [3]. The causes of acute kidney injury are as a result of; inadequate renal perfusion, obstructive uropathy and direct infection on the kidney parenchyma [4]. Furthermore, it has been shown that, by increasing the generation of superoxide anion, hydroxyl radicals, hydrogen peroxide and reactive nitrogen species in kidney, drugs such as gentamycin induces renal injury [5].

Gentamycin is a naturally occurring substance produced by the environmental gram positive bacteria, Micromonospora [6]. It belongs to the aminoglycoside class of drugs that are particularly potent against gram negative bacteria, but are known to be toxic to

some patients [7]. Aminoglycosides are known to cause ototoxic damage, vestibule-toxic impairment, encephalopathy and nephrotoxicity [7]. In spite of these undesirable toxic effects, they still constitute the only effective therapeutic alternative against germs insensitive to other antibiotics [8]. Thus, some plants or plant product have been proposed to possess strong potential to reduce the risk of oxidative stress on the kidney, and tomato fruit is possibly one of such.

Tomatoes (*Lycopersicon esculentum* is a highly perishable fruit vegetable of the family Solanaceae, and is consumed in every home [9]. It is considered a protective food because of its nutritive value, as it provides important nutrients such as lycopene, beta-carotene, flavonoids, vitamin C and hydroxycinnamic acid derivatives [10]. In recent years, this crop has achieved tremendous popularity with the discovery of lycopene's antioxidative activities [10]. Previous studies have shown that intake of tomato or tomato products strengthen the antioxidant system and prevent renal diseases [11].

High morbidity and mortality is constantly being observed in clinical settings due to high cost of medication and harmful effect of orthodox medicine. Investigation on the effect of tomato on renal function has not been adequately studied; but none induced renal damage using gentamycin, and only few studies have shown the benefits of tomato constituents. Therefore, base on hypothesis, we assert that high intake of tomato or its product could ameliorate the risk of renal injury following gentamycin administration. The aim of this research was to evaluate the effect of tomato extract on Gentamycin-induced acute renal injury in albino rats.

Materials and Methods

Collection and authentication of Tomato fruits

Fresh samples of tomato (*Lycopersicon esculentum*) fruits were purchased from Akwata, Ogbete main market in Enugu, Nigeria.

Processing of tomato fruits extract

The tomato fruits were processed by washing thoroughly in clean water. After washing they were put in an electric blender (Saisho, China) and blended at maximum speed for five minutes. The extracts obtained were passed through a 52 mm pore size sieve, and were subsequently preserved in the refrigerator at a temperature between 4 - 6°C for 24 hours.

Phytochemistry of tomato fruit

Preliminary phytochemical screening for the presence of glycosides, flavonoids, saponins, steroids, tannins, carbohydrates, proteins and terpenoids was carried out at Department of Pharmacognosy, Faculty of Pharmaceutical Science, University of Nigeria Nsukka. Procedures outlined by Trease and Evans [12] were employed for the analyses.

Induction of Nephrotoxicity

Each experimental rat was administered with gentamycin at the dose of 100 mg/kg intraperitoneally, daily for six (6) days.

Experimental animals

Twenty-five (25) adult male albino wistar rats, with an average weight of (120 - 140g) were used in this study. They were obtained from the Animal House of the University of Nigeria Teaching Hospital (UNTH) Old Site, Enugu state, Nigeria. The animals were housed in metallic cage in the animal house under ambient temperature (25 ± 3°C) and 12-hour light and dark periodicity. They were adequately fed with commercial rat pellets (Neimeth Livestock Feeds Ltd., Ikeja) and water *ad libitum* and allowed to acclimatize for 2 weeks. All the animals were handled in this study according to Institutional guidelines describing the use of rats and in accordance with the American Physiological Society guiding principles for research involving animals and human beings [13]. In addition, proper care was taken as per the ethical rule and regulation of the concerned committee of the University of Nigeria, Nsukka, Enugu State, Nigeria.

Ethical approval

An ethical approval for the use of animals for experimental research was applied for and obtained from the Institutional Ethics Committee at Department of Animal Science, University of Nigeria, Nsukka, Enugu State, Nigeria.

Experimental design and conduct

A total of 25 male albino wistar rats were used. The rats were randomly allocated to five (5) groups (A-E) of five (5) rats per group in well ventilated cages. The experimental animals received the following treatments for at most three weeks period together with stipulated feed and water.

- **Group A:** (Normal Control): No treatment was administered to this group.
- **Group B:** (Negative Control): Received gentamycin alone (100mg/kg, i.p) daily for six (6) successive days.
- **Group C:** Received gentamycin for 6 days following 14 days of oral tomato extract (30mg/kg, daily) pre-treatment.
- **Group D:** Received orally tomato extract for 14 days following pre-treatment with gentamycin for 6 days.
- **Group E:** Received 6-days of simultaneous tomato extract and gentamycin.

Sacrificing of animal and sample collection

Blood samples for biochemical analysis were taken by cardiac puncture of the left ventricle of heart under chloroform anesthesia and subsequently the kidneys were excised for histopathological studies. The kidneys were isolated immediately after sacrificing the animal and washed with saline and then processed.

Biochemical analysis

The levels of Serum Electrolyte, Urea and Creatinine were estimated using the following methods:

Determination of serum electrolytes

Serum electrolytes were determined using Perlong Medical PL1000A Electrolyte Analyser. The electrolyte analyser applies the principle of advanced ion-selective electrode, and measures the ion concentrations of K^+, Na^+, Cl^-, Ca^{++}, and HCO_3- values in the serum sample.

Determination of serum urea

Serum urea concentration was determined using the diacetyl-monoxime method with protein precipitation according to Natelson., *et al* [14].

Determination of serum creatinine concentration

Serum creatinine concentration was determined using the Jaffe Reaction according to Fabing and Ertingshausen [15].

Histopathological analysis

The excised kidneys were fixed in 10% formal saline for 24 hours and further processed using the conventional paraffin wax embedding technique for light microscopic examination. The paraffin-embedded kidney tissues were sectioned at 5 microns and stained using the Haematoxylin and Eosin [H and E] staining procedure by Baker., *et al* [16]. The histological sections were examined using an Olympus™ light microscope.

Statistical analysis

The statistical analysis was done using Graph pad prism 6.0. The results were reported as mean ± SEM (standard error of mean). Statistical significance $\rho < 0.05$ (*), $\rho < 0.01$ (**) or $\rho < 0.001$ (***) was determined by using ANOVA.

Results

Phytochemical results

The result of the preliminary phytochemical analysis is represented in table 1.

Constituent	Indication
Carbohydrate	+
Reducing Sugar	+++
Alkaloids	+++
Glycosides	-
Saponins	-
Tannins	-
Flavonoids	++
Resins	+
Proteins	-
Oils	-
Acidic Compounds	-
Terpenoids	-
Steroids	-

Table 1: Preliminary phytochemical analysis of tomato fruit.

Key: +++ = More intensely present; ++ = Present; + = Present (in trace amount), - = Absent.

Biochemical results

Serum Na, K, creatinine, urea, Ca, HCO_3- and chloride levels in all groups are shown in figures 1 and 2. The levels of K, creatinine and urea were highly elevated significantly in the affected group (gentamycin alone). Pre-administration, post-administration or co-administration of tomato extract (30 mg/kg) with injection of gentamycin (100 mg/kg, i.p) significantly decreased the elevated K ($p < 0.05$), creatinine ($p < 0.01$) and urea ($p < 0.05$) when compared to the affected group. Note-worthy, the levels of Na was significant-

ly decreased in the affected group (gentamycin alone); however the Pre-administration, post-administration or co-administration of tomato extract (30 mg/kg) in the presence of gentamycin (100 mg/kg, i.p) challenge, significantly elevated the decreased Na ($p < 0.05$) when compared to the affected group. Furthermore, there were no significant differences or changes in HCO_3- (renal/acid-base parameter), Ca and chloride levels among the groups ($p > 0.05$).

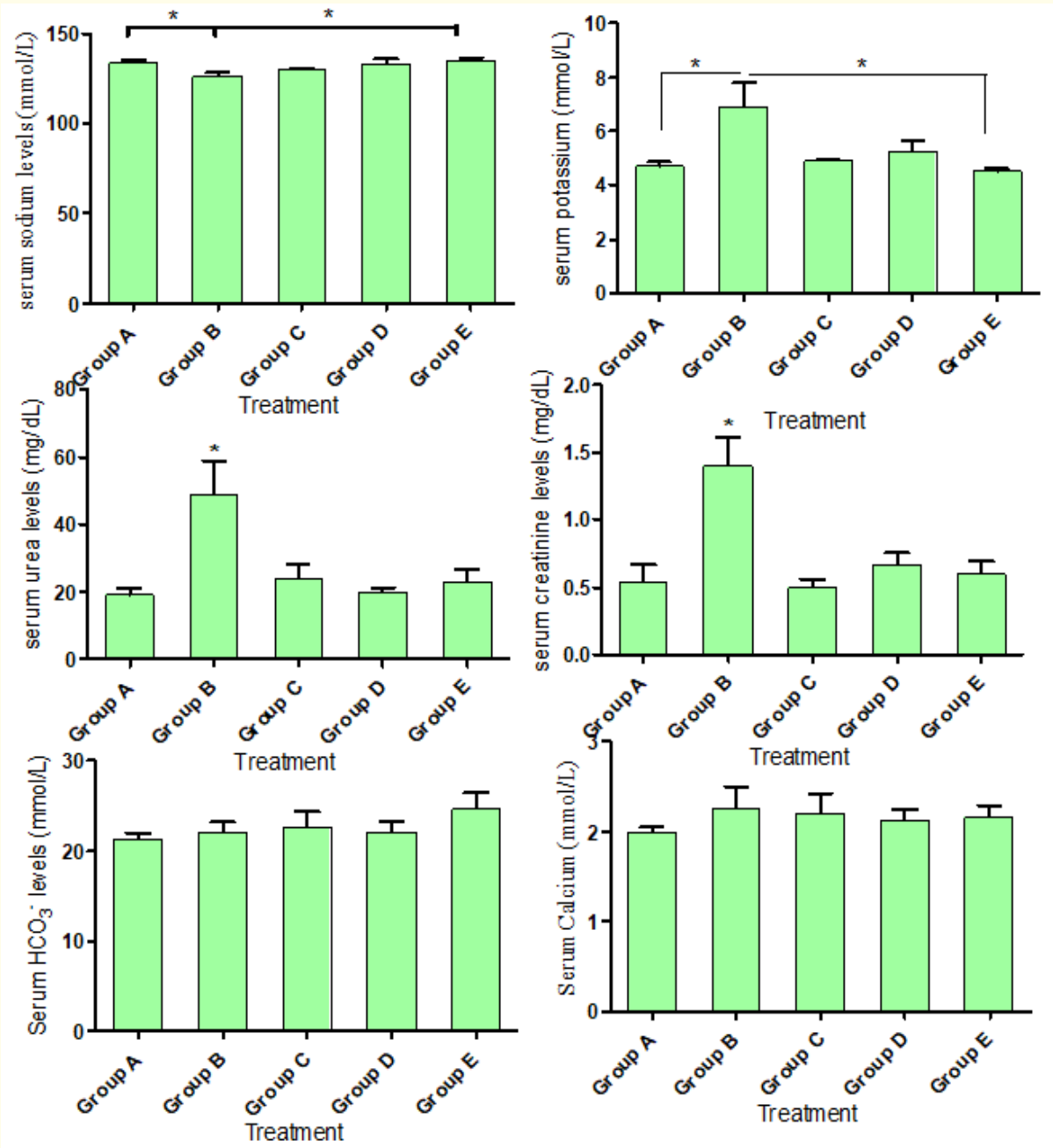


Figure 1: Comparison of renal biochemical concentrations in different experimental groups. The Histograms show serum Na, K, creatinine, urea, Ca, and HCO_3- levels following experimental treatments. The preliminary data shows that tomato extract significantly ameliorated the nephrotoxic effect of gentamycin. The preliminary data shows that there were no significant differences or changes in HCO_3- (renal/acid-base parameter) and Ca levels among the groups. The data are presented as mean ± SEM of Serum Na, K, creatinine, urea, Ca, and HCO_3- levels for individual treatment. Statistical analyses were performed using ANOVA (*$P < 0.05$; **$P < 0.01$).

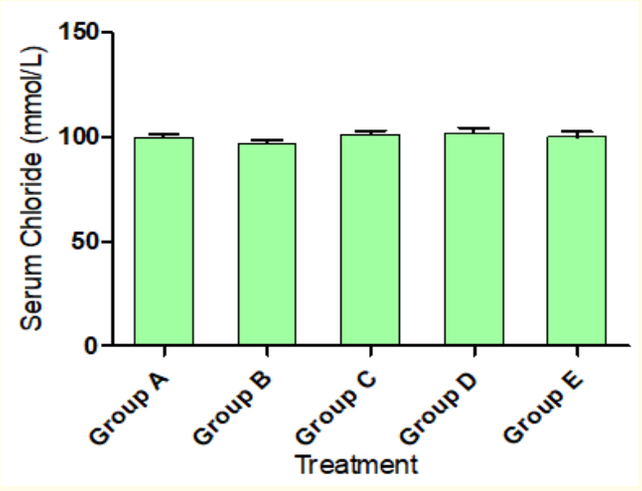
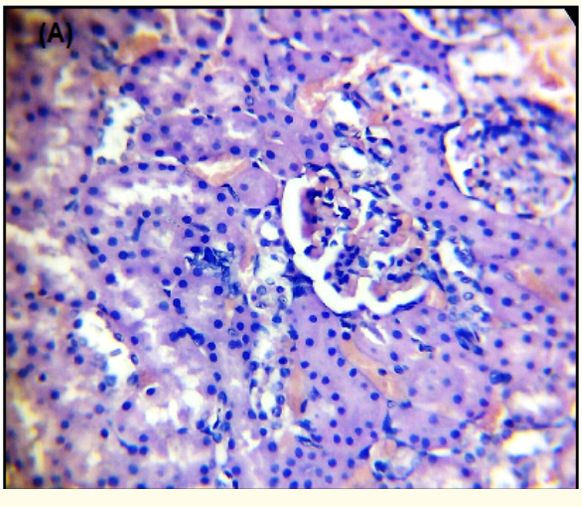
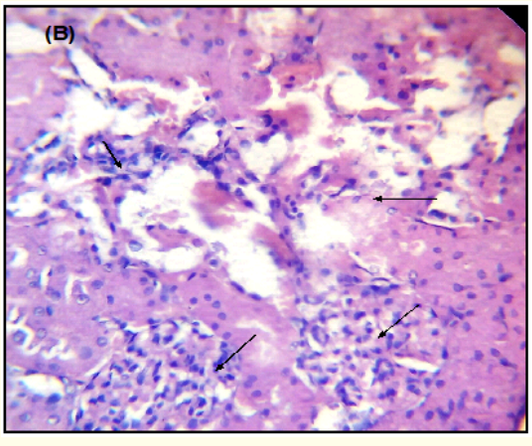


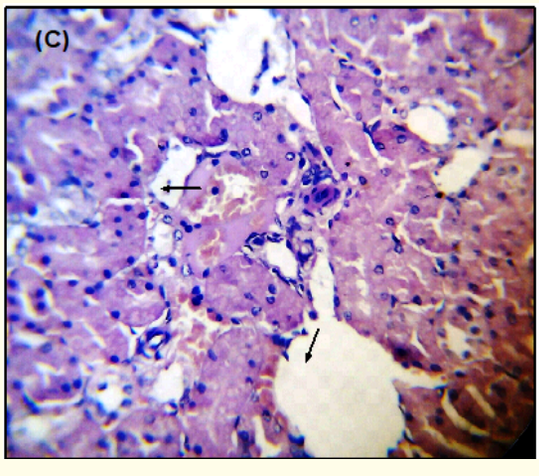
Figure 2: Comparison of chloride levels in different experimental groups. Histogram showing serum chloride levels following experimental treatments. The preliminary data shows that there were no significant differences or change in chloride levels among the groups. The data are presented as mean ± SEM of chloride levels for individual treatment. See Materials and Methods for experimental details. Statistical analyses were performed using the student's t- test (**P < 0.01; *P < 0.05).

Histopathological result

Microscopical examination of the kidney isolated from the rat at sacrifice revealed no histopathological alteration in the control rats. Presence of severe interstitial degeneration and tubular necrosis (arrows indicated) were observed in the kidney of rats treated with intraperitoneal injection of gentamycin (Figure 3B); however non-significant degenerations were observed in rats with pre-administration, post-administration and co-administration of tomato extract separately (Figure 3C-3E, respectively). The kidneys of rats in group C, D and E showed no significant histological alterations when compared with the control group.







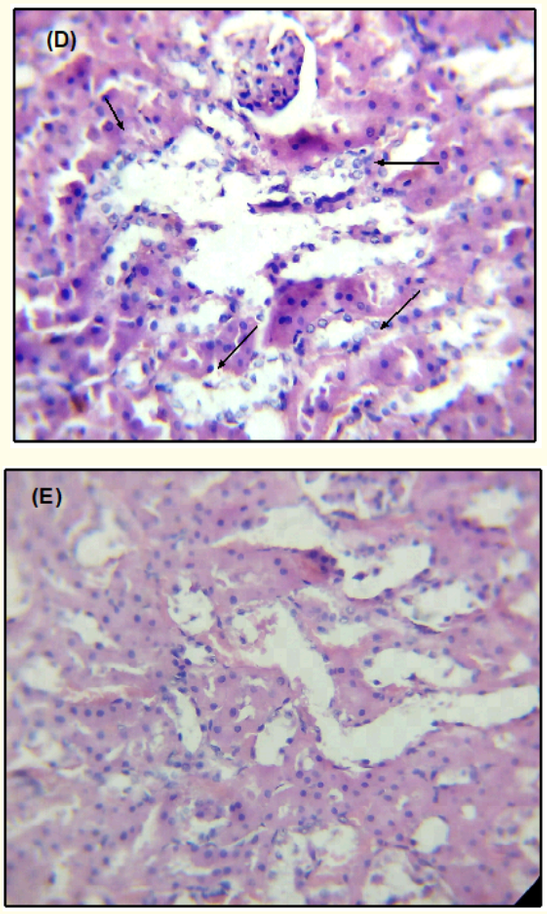


Figure 3: Histopathology and photomicrograph of kidney from group: (A) Histopathology and photomicrograph of kidney from group (A) normal control rats showing no histopathological alteration [Stain: H and E; ×200]. (B) Histopathology and photomicrograph of kidney from group (B) rats, gentamycin treatment only showing severe interstitial degeneration and tubular necrosis [Stain: H and E; ×200]. (C) Histopathology and photomicrograph of kidney from group (C) rats, pre-treatment with tomato extract showing mild or no significant tubular degeneration [Stain: H and E; ×200]. (D) Histopathology and photomicrograph of kidney from group (D) rats, post-treatment with tomato extract showing minor or no significant tubular degeneration [Stain: H and E; ×200]. (E) Histopathology and photomicrograph of kidney from group (E) rats, co-treatment with tomato extract showing minor or no significant tubular degeneration [Stain: H and E; ×200].

Discussion

The role of the kidney in the body cannot be overemphasized. Like the liver, the kidney is also a major organ which functions in maintaining a steady state in the body. It also excretes waste product of metabolism, including drugs and their metabolites. However exposure of the kidney to some of these toxic substances may damage the renal tubules. Naglaa., *et al.* [17], report that about 10% - 15% of the cases of acute kidney injury is associated with the use of gentamycin. Furthermore, Safa., *et al*. [18], state that at therapeutic doses, gentamycin could cause damages to kidney tissues. In order to avoid these damages, various substances such as amrinone, silymarin, celecoxib, dexmedetomidine and rosmarinic, have been used as protective agents [19]. The aim of this study was to evaluate the effect of tomato extract on acute kidney injury induced by gentamycin.

The phytochemical analysis of *Lycopersicon esculentum* (tomato) fruit (table 1) revealed the presence of flavonoids (++), alkaloids and reducing sugars (+++), then carbohydrate and resins (trace amounts). This agrees with the work of Rafiqkhan., *et al.* [20], which showed additional presence of phytochemicals such as: glycosides, phenols, terpenoids and tannins. The difference in tomato constituents could be due to the different methods of extraction. Rafiqkhan., *et al.* [20] extracted with methanol. In this present study, extraction was done with water.

Flavonoids are described as group of natural substances found in plants, with different phenolic structures [21]. They are placed into categories which includes flavones, flavonols, flavanones, catechins, isoflavonoids and anthocyanidins [22]. Flavonols includes quercetin, kaempferol and myricetin, which functions in the effective removal of free oxygen radicals [23]. Furthermore, alkaloids have been shown to possess anti- inflammatory effect [23].

Biochemical results obtained showed that gentamycin effected damage by altering renal biochemical markers (Figures 1and 2). It caused the injury by generating reactive oxygen species, with resultant tubular damage [5]. Serum level of creatinine and urea were significantly elevated in group B (negative control), which received gentamycin alone when compared to the normal group. This increase maybe due to renal injury induced, and agrees with the work of Rashod., *et al.* [24], that induced renal injury with gentamycin is complex and it is characterised by an increase in serum creatinine and blood urea nitrogen concentration. Factors affecting the serum level of creatinine; such as age and gender, were kept constant in this present study. Pre-administration, post-administration

and coadministration of tomato extract significantly reduced the level of creatinine and urea. This reduction could be as a result of the antioxidant effect of flavonoids [23]. This is in agreement with Adel., *et al.* [25], that flavonoids up-regulates antioxidant defenses and reduce free radical formation, hence exhibiting their powerful antioxidant activity. The affected group (negative control) showed increase serum K^+ level and decrease in Na^+ level when compared to the normal. This maybe as a result of damage to the proximal tubules [26], and is in tandem with the work of Vallon [27], which states that damages to the proximal tubules affect the basolateral Na^+/K^+ ATPase transporter and reduces Na^+ reabsorption. Furthermore, this disagrees with the study by Ullah., *et al.* [28], which state that treatment with gentamycin alone decreased serum K^+ level.

The histological findings showed no changes in the normal group, but tubular interstitial degeneration and necrosis were observed in the affected group. In the groups that were pretreated, post-treated and co-treated with tomato, no significant alterations were observed. This agrees with Almaghrab [29], who reports that quercetin improved histological alterations and normalized the kidney biochemical. Some recent studies have shown that antioxidant-rich foods or food products have potential bioactive substances that exhibit protective properties against toxicant xenobiotics [30-41].

Conclusion

The present study showed that gentamycin induced renal Injury and that the administration of tomato extract ameliorated the effects in the test group. Hence, tomato extract possesses renal protective effect against gentamycin.

Thus, this observation suggests that the intake of tomato extract could be of health benefit to patients suffering from drug-induced Kidney Injury.

- Enriching our diet daily with tomato fruits is highly recommended, especially for those at the risk of life threatening diseases, in order to obtain the nutritional benefits contained in them.
- Further study should be done to identify and characterize other phytochemicals in tomato which are of pharmacological benefit.

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Competing Interests Statement

The authors declare no competing interests.

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