

ORIGINAL CONTRIBUTION

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Effect of onions tunic extract on sodium oxalate-induced acute kidney injury

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Abstract

Acute kidney injury (AKI) is one of the global health concerns afflicting the human population and urolithiasis (kidney stone), especially the calcium oxalate stone is the most prominent amongst the stone formers with a huge recurrence rate. This study elucidates the ameliorative potential of the tunic of onions against Wistar kidney rats toxified with sodium oxalate.

Ethylacetate extract of the tunic of onions otherwise regarded as Onions peel extract (OPE) in this study was prepared to get the flavonol-rich extracts. Adult male Wistar rats received 70 mg/kg body weight sodium oxalate with or without co-treatment with OPE, quercetin or cystone. Biochemical analyses were carried out on the plasma and urine, followed by a histopathological assessment of the kidney. Intoxication with sodium oxalate brought about electrolyte imbalance, nephrotic syndrome (high concentrations of total protein and albumin in the urine and low concentrations in the plasma) reduced renal function (low renal clearance of creatinine and urea) and damage to the kidney as well as fluid accumulation. Treatment with flavonol extract from onion tunic mitigated these deleterious changes as a result of sodium oxalate intoxication. The finding suggests that onion peel has the potential to prevent damage arising from oxalate toxicity in the kidney.

Keywords Acute kidney injury, Kidney stone, Onion tunic, Nephrotic syndrome, Toxified

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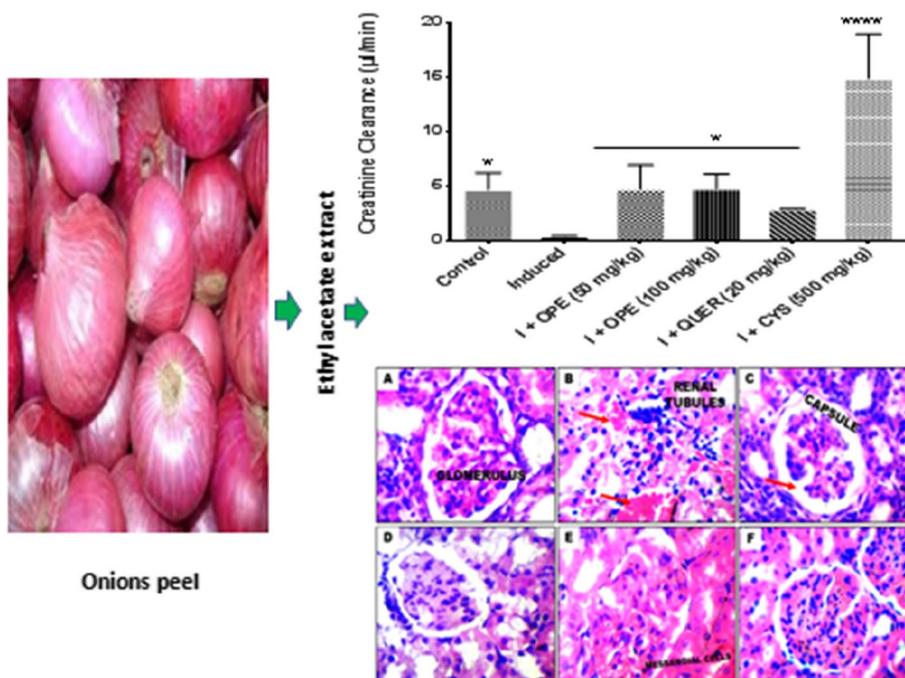
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Graphical Abstract



Introduction

Acute kidney injury (AKI) is a global health concern, affecting about 13 million globally per year, 85% of which are in developing countries, and can be attributed to > 2.3 million deaths despite advances in therapeutic strategies and nursing measures, including dialysis and kidney transplantation [1].

The mechanisms underlying the aetiology and pathogenesis of AKI are very complex and may include nephrolithiasis, nephrotoxicants, sepsis, mitochondrial dysfunction, ROS, ER stress, autophagy, ischemia/reperfusion injury (I/R), inflammation, apoptosis and necrosis [2].

Sudden loss of kidney function is known as acute kidney injury which can occur as a result of traumatic injury with blood loss, sudden reduction of blood flow to the kidneys, damage to the kidneys from shock during severe infection called sepsis, obstruction of urine flow, such as with enlarged prostate or kidney stone, damage from certain drugs or toxins and pregnancy complications, such as eclampsia and pre-eclampsia [3]. When the kidney becomes damaged, waste products and fluid can build up in the body, causing swelling of the ankles, vomiting, weakness, poor sleep, and shortness of breath [4].

Kidney stone disease is a recurrent and lifelong disease that causes significant health and financial burden. The basic mechanism of kidney stone formation is still not clear but is connected with inflammation, oxidative stress and recruitment of crystal-forming or binding molecules [5–7].

Onion (*Allium cepa* L.) has been valued as a food and medicinal plant since ancient times. It is widely cultivated, second only to tomato, and is a vegetable bulb crop known to most cultures and consumed worldwide [8]. The dry outer layers of an onion, which are discarded before food processing such as cooking, contain large amounts of polyphenols and have been found to possess antioxidant, hypotensive and inhibition of angiotensin-1 converting enzyme (ACE) [9, 10].

Recently, dietary polyphenols have been used as a target to mitigate nephrolithiasis/ AKI basically due to their antioxidant, anti-inflammatory, diuretic and ACE-inhibitory activities [11].

Therefore, the interest of this research is to investigate the effect of the ethyl acetate extract of onion tunic in the kidney of animals induced with sodium oxalate with a major interest in the biochemical and histopathological parameters.

Methods

Chemicals and reagents

Chemicals, reagents and solvents used during this research were of analytical status. Quercetin, sodium oxalate, urea, creatinine, albumin, and total protein estimation kits were procured from Sigma-Aldrich Co, St Louis, USA. Calcium, sodium and chloride kits were purchased from AGAPPE Diagnostics Switzerland GmbH. All other chemicals used in the experiment were of the highest grade commercially available. Standard chow diet (Vital feeds) was procured from local vendors.

Plant material

Red onions (*Allium cepa* L) were bought from Sabo market, Okitipupa metropolis, Nigeria, in March 2021. Botanical identification and authentication were carried out at the herbarium of the Olusegun Agagu University of Science and Technology Okitipupa, Nigeria. The plant was identified by Mr. M. Oluwatubosun Aturu and a voucher number (OAUSTECH/H/0678) was assigned.

Preparation of ethylacetate extract of red onions (*A. cepa*) tunic

The flavonol-rich extract of the Onion tunic was prepared following the procedure of Olayeriju et al. [9]. Briefly, the tunics of onions were hand-picked to remove dirt and fleshy part of the onions, cleaned, air-dried and pulverized. Exactly (80 g) of the powdered tunic was macerated in 600 mL of ethyl acetate (Sigma Chemicals; USA) for 4 h at 40 °C, during which there was constant agitation. The mixture of the solvent and the ground sample was filtered first with mesh cloth, and then with filter paper (Whatman No. 1) and concentrated using a rotary evaporator.

Experimental animals

Thirty-six healthy male Wistar rats (age 6 weeks old; body weight 150 ± 20 g) obtained from a private breeder in the Ibadan metropolis of Oyo State, Nigeria, were used for the study. The animals were housed at standard housing conditions (27 ± 3 °C) under a 12-h light/dark cycle in polypropylene pathogen-free cages and fed standard rodent chow (Vital Feeds Nigeria Limited) and water ad libitum. The experimental protocol and procedures for the animal experiments were approved following the Committee for Control and Supervision of Experiments on Animals guidelines after the approval of the experimental protocol by the Institutional Animals Ethics Committee of the Biochemistry programme in the

Department of Chemical Sciences, Olusegun Agagu University of Science and Technology, Okitipupa.

Induction of experimental toxicity/ urolithiasis in Wistar rats

Sodium oxalate was used to induce toxicity/ nephrolithiasis and was administered for 5 consecutive days intraperitoneally and co-administered with or without (Onion peel extract (OPE), quercetin and cystone) orally for 7 consecutive days.

Study protocol

The experimental design consisted of 48 rats divided into eight groups consisting of six animals per group and was placed on the following treatment.

Group I: (Control) – Animals in this group were allowed access to distilled water ad libitum throughout the experiment, and administered vehicle for 7 days.

Group II: (Induced) – Animals in this group were administered 70 mg/kg body weight sodium oxalate (NaOx).

Group III: (50 mg/kg) – Animals in this group were administered 70 mg/kg body weight sodium oxalate and co-administered with 50 mg/kg OPE.

Group IV: (100 mg/kg) – Animals in this group were administered 70 mg/kg body weight sodium oxalate and co-administered with 100 mg/kg OPE.

Group V: (20 mg/kg) – Animals in this group were administered 70 mg/kg body weight sodium oxalate and co-administered with 20 mg/kg quercetin.

Group VI: (500 mg/kg) – Animals in this group were administered 70 mg/kg body weight sodium oxalate and co-administered with 500 mg/kg standard cystone.

All animals were kept in individual metabolic cages on the 8th day of sodium oxalate induction and treatment. Thereafter, 24 h urine samples were collected. Blood was collected via cardiac puncture after euthanizing with cervical dislocation; plasma was separated by centrifugation at 10,000 g for 10 min. The tissues (kidney) were removed and prepared for histopathological analysis.

Biochemical assays

Urine and plasma nephrochemical assays

Urine and plasma nephrochemical assays (creatinine, urea, total protein, albumin, calcium, sodium and chloride as well as a procedure for estimating urine volume) were carried out as previously described by Olayeriju et al. [7].

Histopathological analysis

Histopathological analysis was carried out as described by Sikarwar et al. [12]. The slides were examined under a light microscope to study the light microscopic architecture of the kidney and calcium oxalate deposits using H and E (hematoxylin and eosin) staining.

Statistical analysis

The data were analyzed with one-way ANOVA followed by Duncan multiple comparisons post hoc tests. A statistical difference of $p < 0.05$ was considered significant in all cases.

Results

Nephroprotective study of OPE against sodium oxalate administered rats

The effect of OPE on nephrochemical assays is presented in Figs. 1, 2, 3, 4, 5, 6, 7, 8 and 9 and Tables 1 and 2.

There was a significant $p < 0.05$ increase in the plasma concentration of creatinine in the animals administered sodium oxalate compared with control animals. Treatment with OPE (50 and 100 mg/kg) brought about a decrease in the plasma creatinine concentration. This is a reflection of the calculated creatinine clearance as less creatinine output was observed in the animals toxified with sodium oxalate compared with treated groups (OPE, Quercetin and cystone). Also, the plasma urea concentration of the induced group shows a significant $p < 0.05$

decrease compared with the control group, but administration of the extract ameliorated the effect as seen and corroborated by the calculated urea clearance.

The significant imbalance in the plasma and urine electrolyte concentrations in the group administered sodium oxalate only was reversed by the treatment groups (Tables 1 and 2).

Damage to the kidney glomerulus is often measured by estimating the amount of proteins in the urine and plasma. Figures 3, 4, 5 and 6 show an obvious statistical increase in the concentration of total protein and albumin in the urine and a reciprocal effect in the plasma of animals administered sodium oxalate compared with control. Treatment with the extracts brought about a significant reduction in the concentration of these macromolecules in the urine vis-avis the plasma.

The increased concentration of calcium in the urine and concomitant decrease in the plasma of animals administered sodium oxalate is indicative of a supersaturated calcium oxalate medium i.e. a stone-forming environment. Administration of OPE significantly ameliorated this effect as shown in Figs. 7 and 8. Also, there was a significant reduction in the 24 h urine of animals administered sodium oxalate while groups administered with onions tunic reversed the effect on the reduction of urine output as shown in Fig. 9.

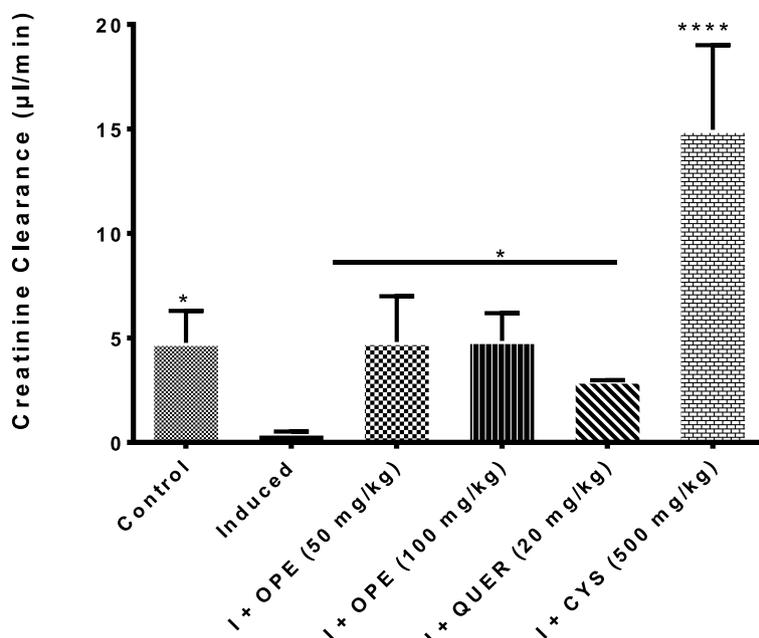


Fig. 1 Effect of Onion tunic extract on creatinine clearance in animals administered sodium oxalate. Data are expressed as mean ± SEM of 6 rats ($n = 6$); * $p < 0.1$, and **** $p < 0.0001$; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

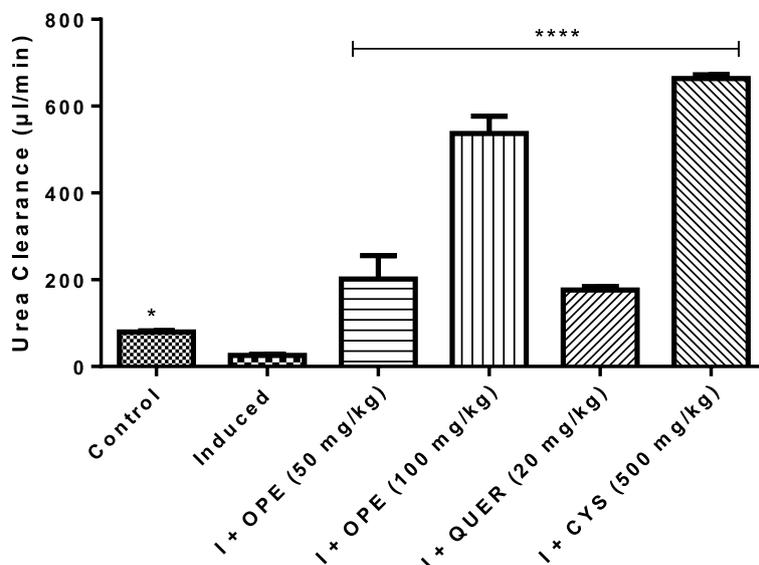


Fig. 2 Effect of Onion tunic extract on urea clearance in animals administered sodium oxalate. Data are expressed as mean ± SEM of 6 rats (n=6); **p* < 0.1, and *****p* < 0.0001; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

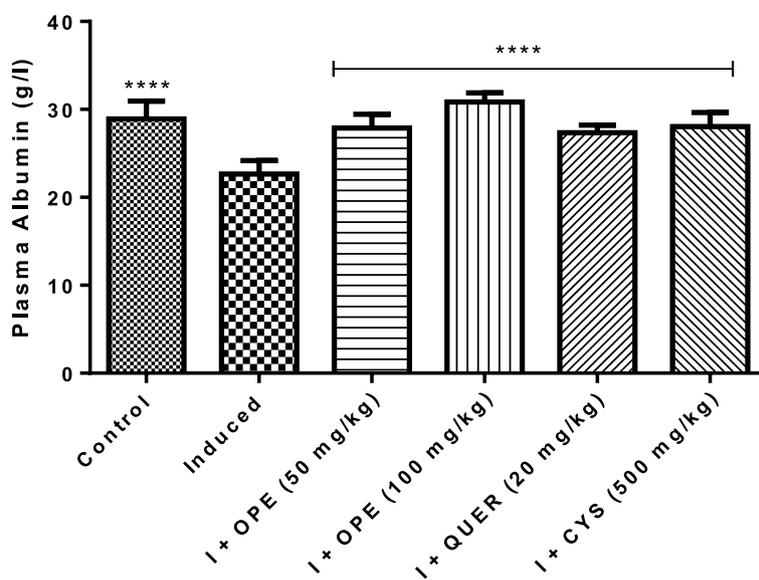


Fig. 3 Effect of Onion tunic extract on Plasma Albumin in animals administered sodium oxalate. Data are expressed as mean ± SEM of 6 rats (n=6); *****p* < 0.0001; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

Histopathology

From the histopathology analysis, no visible lesion was seen in the control animals (A). Severe degenerative changes characterized by congested renal tubules (proximal and distal convoluted tubules), infiltrated renal parenchyma by red inflammatory cells and dilated renal tubules which are signs of glomerulosclerosis and

glomerulonephritis, pyknotic renal parenchymal cells or signs of haemorrhage, concentrated mesangial cells towards a point was found in the animals administered sodium oxalate only (B). Mild degenerative architecture, the renal cortex shows glomeruli with mild fluid accumulation, the renal tubules appear mildly congested in the lumen, the interstitial spaces appear normal with

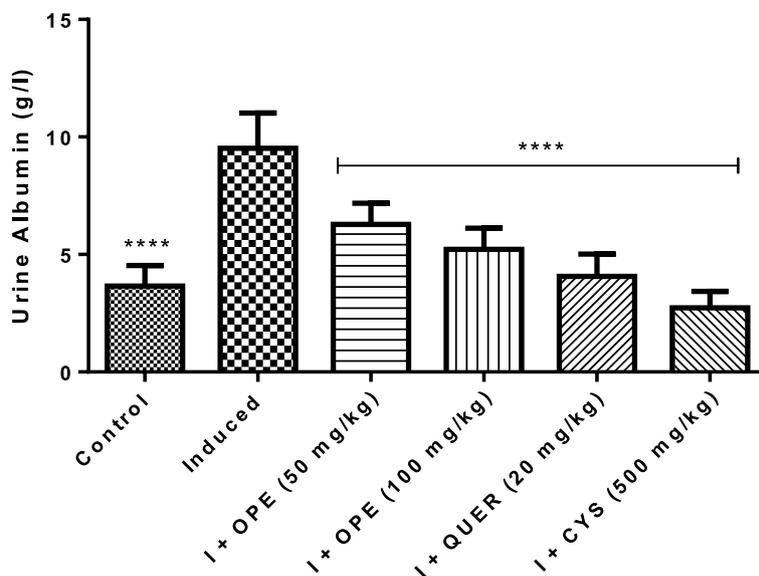


Fig. 4 Effect of Onion tunic extract on Urine Albumin in animals administered sodium oxalate. Data are expressed as mean \pm SEM of 6 rats ($n=6$); **** $p < 0.0001$; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

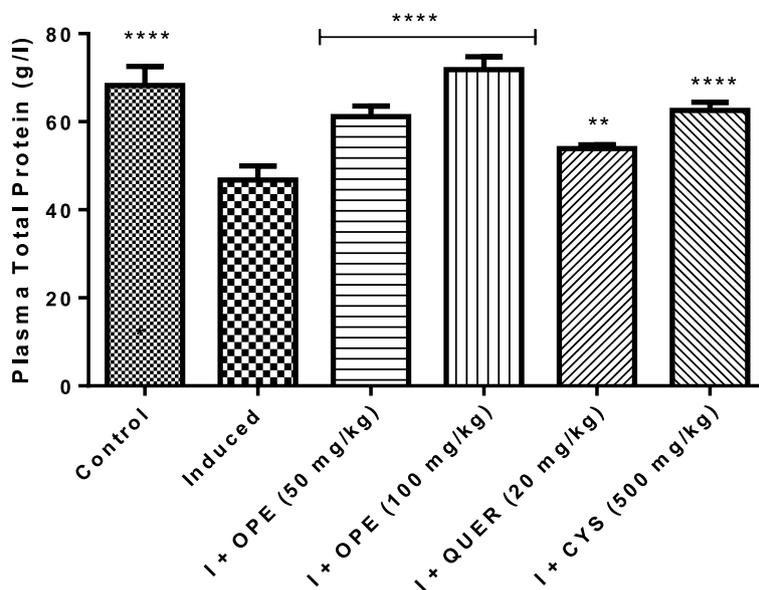


Fig. 5 Effect of Onion tunic extract on Plasma Total Protein in animals administered sodium oxalate. Data are expressed as mean \pm SEM of 6 rats ($n=6$); ** $p < 0.01$, and **** $p < 0.0001$; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

mild signs of haemorrhage, the glomerulus appears mildly sclerotic with a wider capsular space and a well outlined renal parenchymal cells was seen in animals co-treated with (50 mg/kg) OPE (C). The group(s) administered (100 mg/kg) OPE (D), (20 mg/kg) QUER (E) and the standard (500 mg/kg) Cys (F) shows normal

architecture; the renal cortex shows normal glomeruli with normal mesangial cells and capsular spaces, the renal tubules appear normal; clear and not congested and the interstitial spaces appear normal with a well-defined profile (Fig. 10).

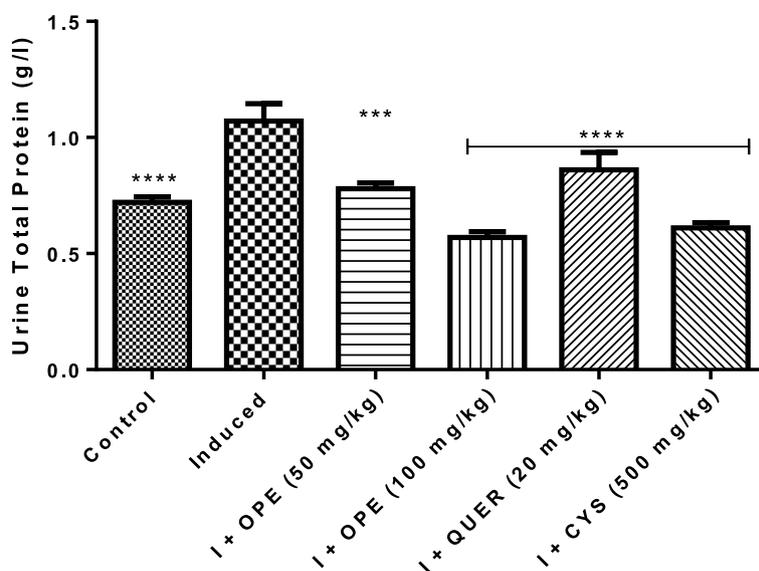


Fig. 6 Effect of Onion tunic extract on Urine Total Protein in animals administered sodium oxalate. Data are expressed as mean \pm SEM of 6 rats ($n=6$); *** $p < 0.001$, and **** $p < 0.0001$; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

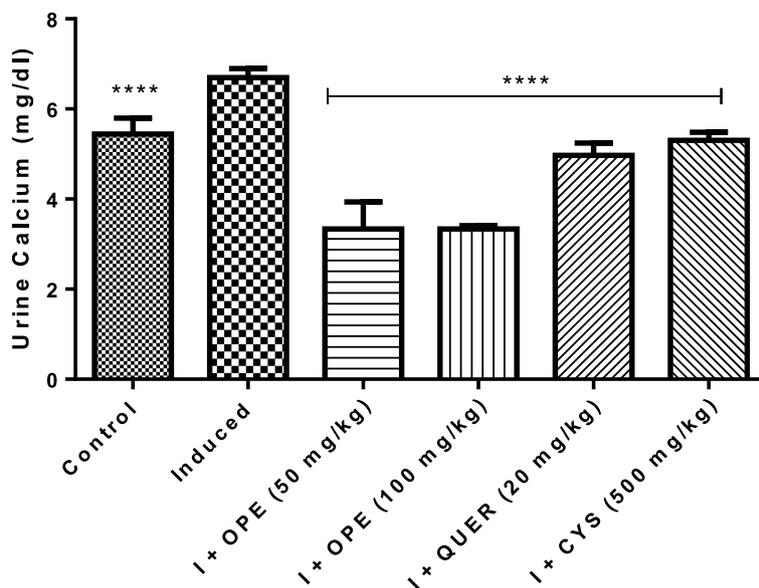


Fig. 7 Effect of Onion tunic extract on calcium in animals administered sodium oxalate. Data are expressed as mean \pm SEM of 6 rats ($n=6$); **** $p < 0.0001$; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

Discussion

The experimental model of nephrolithiasis used in this study utilizes the toxic mechanism of oxalate overload whereby increased oxalate in the system chelates calcium ions forming insoluble calcium oxalate (CaOx)

in the kidney being the major excretory route and ultimately leading to nephrotoxicity and renal failure [13]. This was evident in the present study as there was a significant decrease in the plasma concentration of calcium, an indication of the chelating power of oxalate leading to a concomitant increase in the

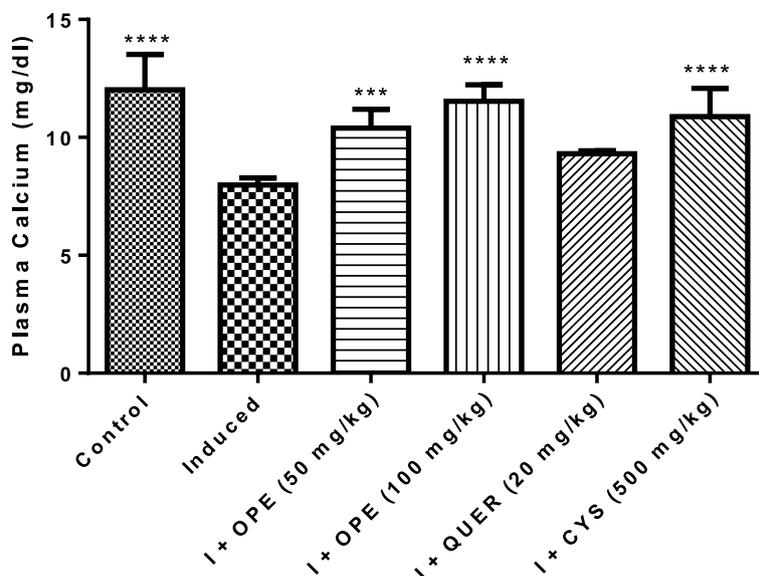


Fig. 8 Effect of Onion tunic extract on plasma calcium in animals administered sodium oxalate. Data are expressed as mean ± SEM of 6 rats (n=6); ****p* < 0.001, and *****p* < 0.0001; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

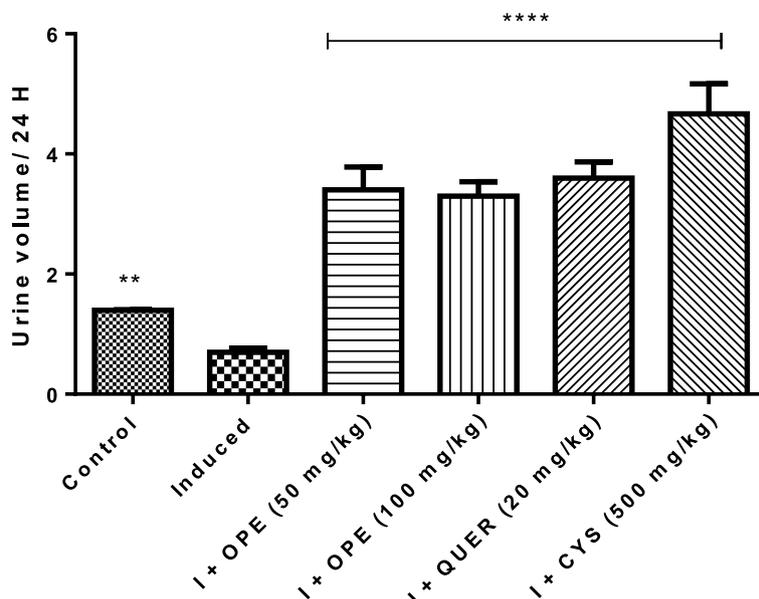


Fig. 9 Effect of Onion tunic extract on Urine volume/ 24 h in animals administered sodium oxalate. Data are expressed as mean ± SEM of 6 rats (n=6); ***p* < 0.01, and *****p* < 0.0001; *denotes that data were compared with induced. OPE: Onion peel extract; I: induced; QUER: Quercetin; CYS: cystone

concentration of calcium in the urine believed to have been attracted by the movement of oxalate to urine. This is a major factor in the formation of kidney stones i.e. the calcium oxalate stone [14]. Although, the interest of this research was to investigate sodium oxalate

toxicity in the kidney of rats, not necessarily leading to kidney stone.

The presence of oxalate in the kidney or urinary system is been known to cause oxidative damage and reduction in the functionality of the kidney [15]. These damages

Table 1 Effect of onion tunic extract on plasma biochemistry parameters in animals administered sodium oxalate

Groups	Control	Induced	I + OPE (50 mg/kg)	I + OPE (100 mg/kg)	I + QUER (20 mg/kg)	I + CYS (500 mg/kg)
Creatinine (mg/dl)	0.72 ± 0.02****	1.07 ± 0.08	0.78 ± 0.03****	0.57 ± 0.03****	0.86 ± 0.08****	0.61 ± 0.02****
Urea (mg/dl)	15.14 ± 1.69***	25.57 ± 2.49	13.88 ± 4.16***	7.67 ± 1.89****	15.31 ± 5.29***	10.40 ± 5.19****
Sodium (mEq/dl)	136.97 ± 5.40*	124.88 ± 8.40	138.95 ± 7.64*	154.74 ± 3.40****	144.30 ± 8.45***	150.56 ± 4.78****
Chloride (mMol/l)	68.57 ± 5.34****	84.05 ± 2.56	73.38 ± 2.16***	69.53 ± 3.21****	75.06 ± 5.32**	76.91 ± 3.65*

Data are expressed as mean ± SEM (n = 6)

OPE Onion peel extract, I induced, QUER Quercetin, CYS cystone

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

**** $p < 0.0001$

* denotes that data were compared with induced

Table 2 Effect of onion tunic extract on urine biochemistry parameters in animals administered sodium oxalate

Groups	Control	Induced	I + OPE (50 mg/kg)	I + OPE (100 mg/kg)	I + QUER (20 mg/kg)	I + CYS (500 mg/kg)
Creatinine (mg/dl)	3.22 ± 0.17****	0.92 ± 0.05	1.48 ± 0.06****	1.10 ± 0.01**	1.02 ± 0.05 ^{ns}	2.58 ± 0.02****
Urea (mg/dl)	184.71 ± 7.34*	196 ± 5.34	186.56 ± 6.50 ^{ns}	179.33 ± 6.50**	156.79 ± 4.60****	173.27 ± 8.50****
Sodium (mEq/dl)	82.79 ± 12.6****	183.49 ± 7.6	157.91 ± 4.49*	150.00 ± 2.42**	129.07 ± 22.97****	122.09 ± 16.92****
Chloride (mMol/l)	149.44 ± 6.43****	111.41 ± 1.46	129.53 ± 5.00**	134.00 ± 3.24****	170.69 ± 12.45****	152.13 ± 7.99****

Data are expressed as mean ± SEM (n = 6)

OPE Onion peel extract, I induced, QUER Quercetin, CYS cystone

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

**** $p < 0.0001$

* denotes that data were compared with induced

are oftentimes related to the inability to excrete wastes like creatinine and urea as well as nephrotic syndrome (increased urinary protein and albumin) as observed in this study.

Others such as electrolyte imbalance and fluid retention as a result of decreased urine volume as seen in this study are a result of oxalate intoxication which is corroborated by the damage observed from the histology of the kidney of animals administered oxalate.

The phytochemicals present in Onion's tunic have been reported in our laboratory by Olayeriju et al. [9]. The arrays of flavonols present in the ethyl acetate extract of the thin back of onions possess the ability to mitigate the effect of oxalate intoxication as observed in this study. Therefore, the ameliorative potentials of the extract can be alluded to by the presence of these flavonol phytochemicals in the extract. The powerful antioxidant potentials of these specific flavonols; kaempferol,

quercetin and quercetin glycosides (isoquercitrin, quercitrin and rutin) can prevent kidney damage [16]. The mitigating antioxidant power of the flavonols present in onion tunic extract confers on the kidney the ability to excrete waste (increased urinary creatinine and urea or decreased plasma creatinine and urea), prevent nephrotic syndrome (increased urine total protein, and albumin or decreased plasma total protein and albumin), and prevent electrolyte imbalance and water retention as well as prevent the degenerative changes observed in the kidney architecture.

Therefore, it can be proposed that the plant prevented kidney stone formation and kidney damage via the diuretic potential of onion tunic, and the ability to mitigate oxidative stress a major risk factor for nephrotic syndrome, electrolyte imbalance and decreased kidney functionality.

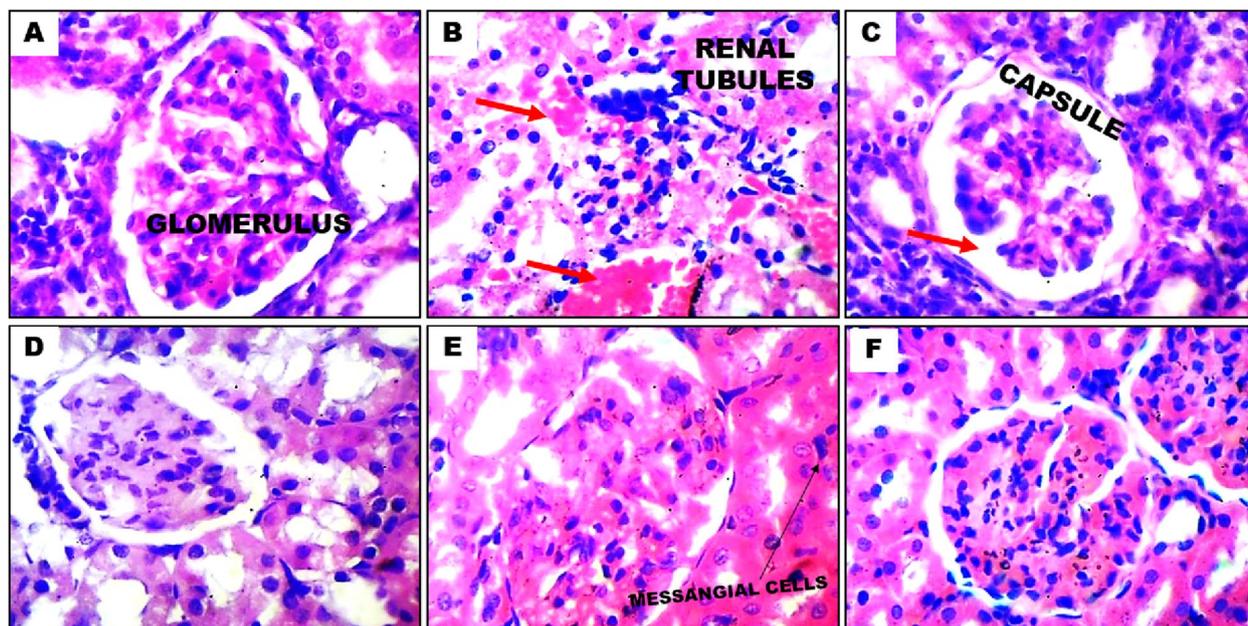


Fig. 10 Magnified views of kidney micromorphological section demonstrated by Haematoxylin and Eosin staining at high magnification (X400). The renal cortex, renal tubules, glomeruli and mesangial cells as well as proximal and distal renal convoluted tubules are all visible across the various groups. **A** Control; **B** Induced; **C** I+OPE (50 mg/kg); **D** I+OPE (100 mg/kg); **E** I+QUER (20 mg/kg); **F** I+CYS (500 mg/kg)

Conclusion

The results from this study highlight the ameliorative effect of the tunic of onions in oxalate-toxified albino rats. The protective effect of the flavonols in the thin back of onions which are discarded during use was observed in this study to prevent nephrotic syndrome, electrolyte imbalance, kidney damage and improved kidney function. The mechanism of action of these flavonols and the possible effect of combination therapy with other compounds or extracts against kidney disease will be addressed in future research.

Abbreviations

AKI	Acute kidney injury
OPE	Onions peel extract
ACE	Angiotensin-1 converting enzyme
NaOx	Sodium oxalate
QUER	Quercetin
CYS	CYSTONE
CaOx	Calcium oxalate

Acknowledgements

Not applicable.

Authors' contributions

Olanrewaju Sam Olayeriju; Concept development, experiment proceeding, manuscript writing and editing, proofreading and approved the final manuscript. Damilola Alex Omoboyowa; Manuscript proof reading and Approved the corrected manuscript.

Funding

There is no financial support from any source.

Availability of data and materials

The dataset analyzed during our current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving animals were in accordance with the ethical standards of the Department of Chemical Sciences (Biochemistry Programme), Olusegun Agagu University of Science and Technology where this study was conducted and ethical consent was given (OAU/STECHEM.SCI/BCH/2021/05).

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interests.

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Received: 22 June 2023 Accepted: 29 January 2024

Published online: 17 February 2024

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