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Nephroprotective effect of seed extract and fractions of *Telfairia occidentalis* on doxorubicin-induced kidney injury in rats

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Telfairia occidentalis Hook (Cucurbitaceae) is a vegetable whose seeds are utilised as soup thickener and for medicinal purposes locally in Nigeria was subjected to organ protective study against doxorubicin-induced kidney injury in rodents. Extract and fractions (138 -553 mg/kg) of the seeds were investigated for renoprotective property against kidney injury caused by doxorubicin in rats. Assessment for renoprotective activity was based on effects on indices of renal function, renal oxidative stress markers and kidney histology of the treated rats. Treatment of rats with doxorubicin was observed to elevate levels of creatinine, urea, and electrolytes which were subsequently lowered significantly ($p<0.05$ - 0.001) following *T. occidentalis* seed extract/fractions (276 - 553 mg/kg) administration. The seed extract and fractions coadministration with doxorubicin further improved GSH, GST, SOD, GPx and CAT levels that were lowered by doxorubicin significantly ($p<0.01$) relative to organotoxic control. Pathological observations in extract/fractions-treated rats' kidney sections were prominently reduced relative to the doxorubicin only-treated rats. Chemical pathological effects corresponded with those of the histological observations indicating marked nephroprotective property which may partly be acting through the activities of phytoconstituents of the plant. The plant, *Telfairia occidentalis* seed extract and fractions exhibited antidotal potential which may be beneficial in counteracting doxorubicin related toxicities.

Keywords: *organprotective, Telfairia occidentalis, drug toxicity, vegetable*

Introduction

Doxorubicin has been using the chemotherapy of various types of cancer because of its strong efficacy against various forms of human cancers (Calabresi & Chamber, 1990). Unfortunately, life- threatening associated toxicities such as those that affect the heart, liver, kidney, blood and testes challenge its usefulness in chemotherapy of cancers (Yilmaz et al., 2006). Generation of free radicals leading to oxidative stress resulting from the metabolic activities of its toxic metabolite, have been explained to be responsible for these toxicities (Bachur et al.,1979; Injac et al., 2009; Kalender at al., 2005). The free radicals produced by these metabolic processes attack cell membranes and disrupt their functions and intergrities resulting in organs dysfunctions. Investigations are being carried out on agents especially natural products like *T. occidentalis* that can mitigate or ameliorate the toxic effects of doxorubicin. *Telfairia occidentalis* Hook, a fluted pumpkin (Cucurbitaceae) is a vegetable whose parts;leaves, stem and leaves, are used in parts of Nigeria for the preparation of various meals (Okokon et al., 2009; Usunomena & Okpiabhele, 2023). The nutritious seeds, with history of effectiveness against prostrate disorders is also eaten raw or roasted. Pharmacological activities such as antidiabetic (Eseyin et al., 2007), cellular antioxidant, immunodulatory, anticancer, antiinflammatory (Okokon et al., 2012a), antiplasmodial

(Okokon et al., 2009), antioxidant (Osukoya et al., 2016) and analgesic (Okokon et al., 2012b; Osukoya et al., 2016), genotoxic and cytotoxic (Magnus et al., 2024) and in vivo inhibitory effect alpha amylase and alpha glucosidase (Enin et al., 2023), antiprostatic (Fabian et al., 2025), antiulcer (Umoh et al., 2025), cardioprotective (Nwosu et al., 2025a), and testiculoprotective (Nwosu et al., 2025b) have been reported on the seed extract. Secondary metabolites which include tannins, alkaloids, terpenes, cardiac glycosides and saponins have been found in the seed extract (Ebong et al., 2020), while polyunsaturated fatty acids and some monoterpenes were identified using GCMS analysis of the seed extract by Okokon et al. (2012a). The seed extract has also been reported to be rich in flavonoids, predominant in the polar fractions, as well as some alkaloidal compounds (Umoh et al., 2025). This investigation was carried out to assess the potential of *T. occidentalis* seed extract and fractions against doxorubicin-induced kidney injury in rats.

Materials and Methods

Plant collection and extraction

Noni Fresh *Telfairia occidentalis* seeds were procured from Itam market in Itu L. G. A, Akwa Ibom State, Nigeria, in June, 2024. A taxonomist in the Department of Botany, University of Uyo, Uyo, Nigeria had previously identified and authenticated *Telfairia occidentalis* seeds and Herbarium specimens (UUPH 1(b)) were deposited at Pharmacognosy and Natural Medicine Department's Herbarium, University of Uyo. Fresh *Telfairia occidentalis* seeds were left on a table for 14 days to dry and afterwards powdered. Maceration of one kilogram (1Kg) of the seeds powder was carried out for 3 days in 50% ethanol (5000 mL) and filtered. The filtered liquid was concentrated using water-bath at 40˚C to completely remove the ethanol. Twenty grams (20 g) of the crude extract was dissolved in distilled water (500 mL) and dichloromethane (DCM, 5 x 500 mL) was used to partitioned it for five times until there was no change in colour of the solution, in order to prepare DCM and aqueous fractions. The yields of the extract and fractions were calculated. The extract and fractions were preserved at 4˚C in a refrigerator in preparation for the experiment.

Animals

Wistar rats (male and female) weighing 150 - 200 g and obtained from University of Uyo Animal housed were used in this investigation. Plastic cages were used to accommodate them. Standard pelleted Feed (Guinea feed) were fed to the rats and unlimited access to water was given to them. The study was approved by College of Health Sciences Animal Ethics Committee, University of Uyo, (UU/FP/AE/24/055).

Experimental design

Fourteen (14) days experimental treatment model previously reported by Olorundare et al. (2020) and Noah et al. (2023) was employed in this investigation and reduce experimental errors. Groups I rats designated as untreated normal control were administered orally with 10 mL/kg/day of distilled water only. Group 2 consisted of rats (organotoxic group) treated with normal saline (10 mL/kg/day) and concurrently treated intraperitoneally on every 48 hours with doxorubicin hydrochloride (1.66 mg/kg) dissolved in 0.9% normal saline for 14 days. Groups 3-5 designated as extract treated groups consisted of rats groups respectively administered orally with *Telfairia occidentalis* seed extract (138, 276 and 553 mg/kg/day) prepared in 10% Tween 80, two hours before intraperitoneal administration of doxorubicin (1.66 mg/kg) prepared in 0.9% normal saline and given every 48 hours for two weeks. Groups 6 and 7 were the fractions-treated groups orally administered with DCM and aqueous fractions respectively at the dose of 276 mg/kg but given doxorubicin (1.66 mg/kg) prepared in 0.9% normal saline intraperitoneally on every 48 hours for 2 weeks. Group 8 rats pretreated with silymarin (100 mg/kg/day) and representing the positive control group, received doxorubicin (1.66 mg/kg) prepared in 0.9% normal saline intraperitoneally every 48 hours for 2 weeks.

Collection of blood samples and organs

The rats were weighed, twenty-four hours after the completion of the 14 days experimental period. They were then sacrificed under light diethyl ether vapour anaesthesia. Cardiac puncture technique was employed to obtain blood samples from the rats into plain centrifuge tubes which were allowed to clot for two hours before centrifugation at 1500 rpm for 15 mins for serum separation which were used for biochemical parameters assays. The identified kidneys of the sacrificed rats were harvested and thereafter weighed. Formaldehyde (10%) was used to fix one of the harvested kidneys in preparation for histological procedures, while surrounding fat and connective tissue of the other kidney was removed before briskly rinsing it in ice cold KCl solution (1.15%) and stored in ice cold NaCl (0.9%) in a clean sample bottle for assays of oxidative markers.

Kidney function test

The indices for kidney functions such as creatinine, blood urea and electrolytes (Na, K, Cl, and HCO_3) levels were determined at the University of Uyo Teaching Hospital, Chemical Pathology Department, using diagnostic kits.

Oxidative stress markers

The antioxidative stress potentials of *T. occidentalis* seed extract and fractions were investigated utilising the various oxidative stress markers determined from the preserved kidney samples.

Preparation of renal homogenate

The enzymatic and non-enzymatic endogenous antioxidant activities and levels were determined from the preserved kidney samples homogenates of the sacrificed rats used in this study. The renal cortex were stored at -8°C after being separated from the kidneys which were sectioned longitudinally. Homogenization of each was carried out in cold potassium phosphate buffer (0.05M,Ph 7.4) and centrifuged at 5000 rpm for 10 min at 4°C. Recovered supernatant of each kidney was used for assays of catalase (CAT) (Sinha,1972), glutathione peroxidase (GPx) (Lawrence & Burk,1976), malondialdehyde (MDA) content (Esterbauer & Cheeseman, 1990), superoxide dismutase (SOD) (Marklund & Marklund, 1974), and reduced glutathione (GSH) (Ellman,1959).

Histopathological studies

The 10% formaldehyde-fixed kidney samples of the rats were prepared and stained with haematotoxylin and eosin (H&E) according to standard protocols following the method of Drury & Wallington (1980), at Chemical Pathology Department, University of Uyo Teaching Hospital, Uyo. Alteration in the morphology if any was identified and recorded, while histological pictures were taken as micrographs.

Results

Effect of seed extract and fractions of *Telfairia occidentalis* on body and organs weights of rats

Concomitant treatment of rats with *T. occidentalis* seed extract/fractions and doxorubicin improved rats' body weights relative to the doxorubicin only treated group. High body weight gains were recorded in crude extract (276 mg/kg) and dichloromethane fraction treated groups relative to the organotoxic group. In doxorubicin only treated group, the kidney weights were observed to increased relative to untreated control group but not significant ($p>0.05$). However, not significant improvement of kidney weights ($p>0.05$) relative doxorubicin only-treated group was observed in *T. occidentalis* seed extract and fractions treated group (Table 1).

Table 1. Effect of *T. occidentalis* seed extract and fractions on body and kidneys weights of rats with doxorubicin-induced toxicity

Parameters/ Treatment	Dose mg/kg	kidney	Body weight		
			Before	After	% gain in body weight
Normal control	-	1.29±0.07	176.28±17.97	198.25± 6.61	12.46
Doxorubicin	1.66	1.52±0.07	175.33± 8.46	181.66±13.24	3.61
Silymarin+DOX	100	1.38±0.18	180.33± 10.86	190.66± 13.24	5.72
Extract+DOX	138	1.40±0.03	176.0± 11.13	191.0± 6.08	8.52
	276	1.35±0.05	167.0± 7.57	185.0 ± 8.73	10.77
	553	1.29±0.04	177.66± 7.42	193.33 ± 5.48	8.82
Aqueous fraction	276	1.45±0.08	187.66± 17.89	195.33± 17.70	4.08
DCM fraction	276	1.13±0.18	162.66± 12.66	180.33± 9.56	10.86

Data are expressed as mean ±SEM. n = 5.

Effect of seed extract and fractions of *T. occidentalis* on the kidney

Evaluation of effect of seed extract and fractions of *T. occidentalis* on kidney function parameters

Table 2 depicts the effect of *T. occidentalis* seed extract/fractions and doxorubicin on kidney function indices of rats. Significantly ($p<0.05$ - 0.001) high levels of serum urea, creatinine and electrolytes (K^+, Na^+, Cl- and HCO^-_3) relative to

normal control were recorded in rats treated with doxorubicin (1.66 mg/kg) only. However, concomitant treatment of rats with T. *occidentalis* seed extract and fractions (138 -553 mg/kg) as well as silymarin produced a significantly ($p<0.05$ - 0.001) lowered levels of serum urea, creatinine and electrolytes were relative to doxorubicin only-treated group, with the aqueous fraction exerting the most pronounced effect in some cases. (Table 2).

Table 2. Effect of *T. occidentalis* seed extract and fractions on kidney function parameters of rats with doxorubicin-induced toxicity

Treatment	Dose mg/kg	Urea (mMol/L)	Creatinine (µmol/L)	Chloride (mMol/L)	Potassium (mMol/L)	Sodium (mMol/L)	Bicarbonate (mMol/L)
Control	10	3.00± 0.17	65.66±2.33	68.0±1.52	3.36± 0.17	126.0± 6.24	22.00± 0.57
Doxorubicin	1.66	7.80±0.30^{c}	114.0±6.65^{b}	92.0±1.73^{c}	5.80± 0.20^{c}	168.3± 3.52^{c}	28.33± 1.52
Crude extract	138	4.70±0.34	96.66± 7.26	68.00±0.57^{f}	5.13± 0.23^{c}	153.3±5.54^{b}	24.66± 1.45
	276	2.80±0.17^{e}	60.0±1.73^{e}	62.66±1.20^{f}	4.13± 0.20^{f}	138.3± 2.40^{e}	23.0± 1.15
	553	1.96±0.14^{f}	62.33± 1.45^{f}	57.33±1.45^{f}	3.96± 0.17^{f}	137.0±2.88^{f}	22.0± 0.57
Aqueous Fraction	276	4.43±0.63	91.33±13.11	57.33±0.88^{f}	4.33± 0.27^{f}	142.0± 3.78^{e}	24.33± 1.76
DCM fraction	276	5.63±0.40^{b}	100.33±13.24^{c}	52.33±1.45^{f}	4.40± 0.20^{e}	142.6±2.33^{e}	24.0± 1.15
Silymarin	100	3.90±0.17	80.66±2.33	64.66±1.45^{f}	4.46± 0.20^{e}	141.3±2.33^{e}	24.0± 1.15

Data are expressed as MEAN ± SEM, Significant at *a*p<0.05, *b*p<0.01, *c*p<0.001 vs control;Significant at *d*p<0.05, *e*p<0.01, *f*p<0.001 vs doxorubicin group. (n=5)

Effect of *T. occidentalis* seed extract and fraction on kidney oxidative stress markers

Table 3 depicts the effect of *T. occidentalis* seed extract/fractions on kidney oxidative stress markers of the treated rats. Significant ($p<0.05$ - 0.001) lowering of activities of GPx, CAT, and GSH levels relative to normal control was observed except in SOD level following doxorubicin-only treatment every 48 hours for 2 weeks, while MDA level was not significantly ($p>0.05$) elevated relative to control. However, subacute treatment with seed extract/fractions of *T. occidentalis* (138 - 553 mg/kg) concomitantly with doxorubicin for 2 weeks exhibited dose-dependent increase of SOD concentration with the extract's high dose (553 mg/kg) followed by DCM fraction exerting the highest significant effect ($p<0.001$) relative to control. Non-dose-dependent elevated CAT activity was observed following extract/fractions treatment with extract low dose (138 mg/kg) followed by middle dose (276 mg/kg) having the most significant ($p<0.01$) effect. Furthermore, GPx activity was non-dose-dependently elevated especially at high extract dose (553 mg/kg) followed by DCM fraction causing the highest significant ($p<0.001$) effect relative organotoxic group. Silymarin similarly caused a pronounced elevation of GPx activity. GSH activity was significantly ($p<0.001$) and non-dose-dependently increased especially in the extract (553 mg/kg), aqueous fraction as well as silymarin treated groups. Dose-dependent but non significant ($p>0.05$) decreases in MDA levels were observed following extract/fraction treatment when compared to doxorubicin only treated group. The highest decrease was recorded in the group treated with the extract's high dose (553 mg/kg) (Table 3).

Table 3. Effect of *T. occidentalis* seed extract and fractions on kidney oxidative stress markers of rats with doxorubicin-induced toxicity

Treatment	Dosemg/kg	SOD (µol/mL)	CAT (µmol/mL)	GPx (µmol/mL)	GSH (µmol/mL)	MDA (µmol/mL)
Control	10	0.21±0.02	3.55±0.69	0.044±0.0001	1.98±0.04	0.43±0.01
Doxorubicin	1.66	0.14±0.01	1.34±0.01^{c}	0.030±0.0005^{c}	1.72±0.01^{b}	0.59±0.02
Crude extract	138	0.20±0.01	3.48± 0.10^{f}	0.039±0.0008^{f}	1.79± 0.01^{a}	0.55±0.02
	276	0.26±0.06^{f}	3.47±0.56^{f}	0.038±0.0005^{c}	1.73±0.02^{b}	0.48±0.10
	553	0.32±0.04^{b,f}	1.60± 0.32^{c}	0.043±0.0020^{f}	1.95± 0.08^{e}	0.43±0.03
Aqueous Fraction	276	0.18±0.03	1.64±0.80^{c}	0.042±0.003^{f}	1.91± 0.01^{d}	0.58± 0.04
DCM fraction	276	0.28±0.04^{f}	3.12±0.44^{f}	0.039±0.0005^{f}	1.75± 0.01^{a}	0.49± 0.04
Silymarin	100	0.24±0.04^{e}	3.30±0.13^{f}	0.046±0.0001^{f}	2.08±0.06^{f}	0.51±0.04

Data are expressed as MEAN ± SEM, Significant at *a*p<0.05, *b*p<0.01, *c*p<0.001 vs control;Significant at *d*p<0.05, *e*p<0.01, *f*p<0.001 vs doxorubicin group (n=5)

Effect of seed extract and fractions of *T. occidentalis* on histology of rat kidney

Histological examination of H&E-stained kidney sections of rats at magnification (x100) in the different treatment groups revealed that group 1 (CONT) receiving distilled water (10 mL/kg) only showed a normal renal micro-architecture with well-presented glomeruli without any evidence of pathology (Figure 1).

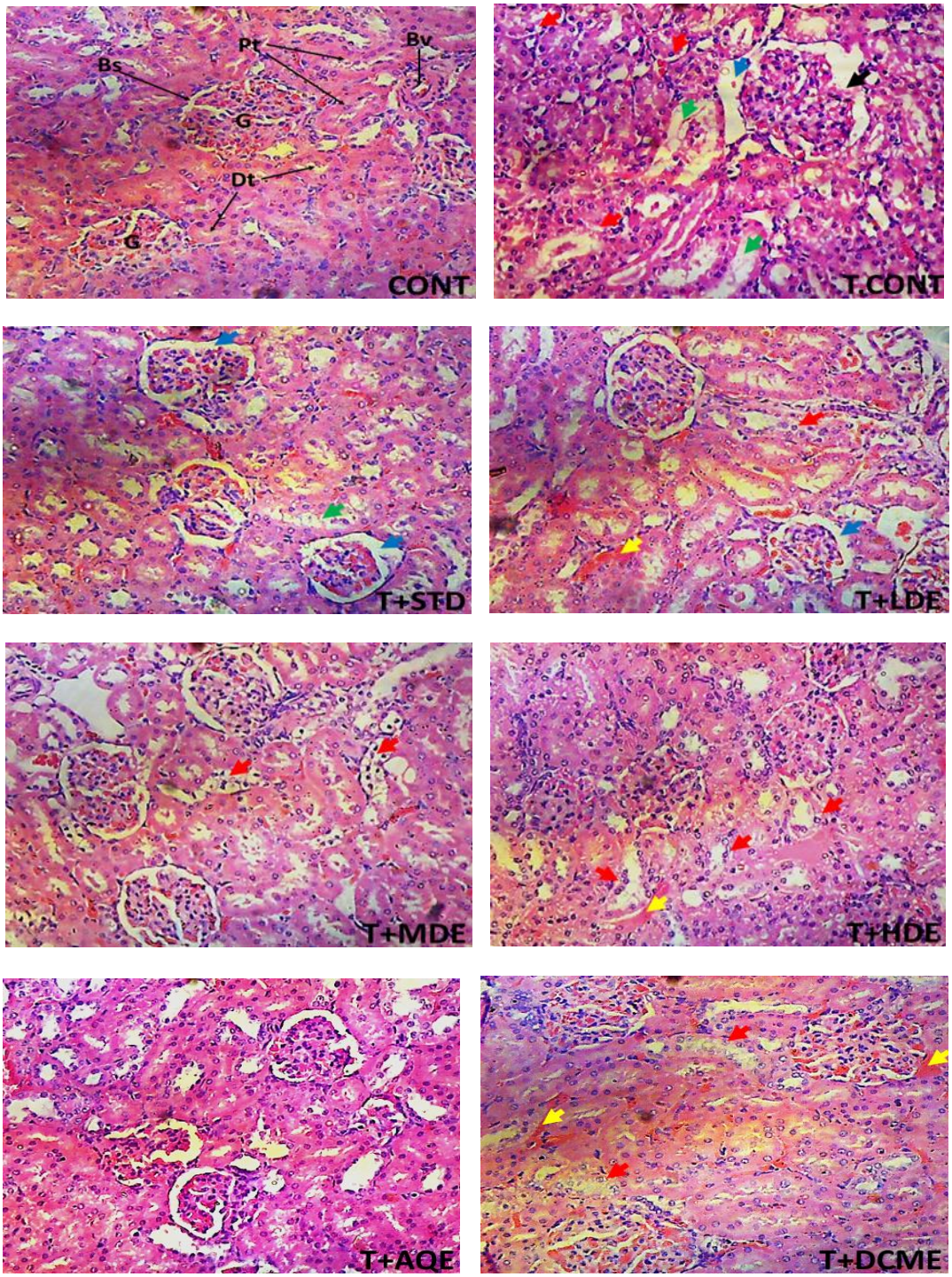

Figure 1. Photomicrographs of sections of kidneys of rats treated with distilled water (**CONT**), doxorubicin only, 1.66 mg/kg (**T.CONT**), Sylimarin, 100 mg/kg and DOX (**T+STD**), *T. occidentalis*, 138 mg/kg and DOX (**T+LDE**), *T. occidentalis*, 276 mg/kg and DOX (**T+MDE**), *T. occidentalis,* 553 mg/kg and DOX (**T+HDE**), Aqueous fraction,276 mg/kg and DOX (**T+AQE**) and DCM fraction, 276 mg/kg and DOX (**T+DCME**) showing well-presented glomeruli (G), Bowman's space (Bs), proximal convoluted tubules (Pt) and the distal convoluted tubules (Dt), vacuolated and degenerating tubules (red arrow), degenerating glomerular tuft cells (black arrow), widened bowman space (blue arrow) and dilated renal tubules (green arrow) (H&E x100).

Severely injured kidney with atrophying renal micro-architecture visible as vacuolated and degenerating tubules, degenerating glomerular tuft cells, widened bowman space and dilated renal tubules were observed in group 2, (T+CONT) treated with doxorubicin (1.66 mg/kg) only. Moderately distorted kidney micro-architecture, observed with vacuolated and degenerating tubules, widened bowman space and areas of hemorrhagic blood vessels within the renal cortical matrix were observed in group 3 (T+STD) and group 4 (T+LDE) rats respectively treated with silymarin (100 mg/kg) and doxorubicin (1.66 mg/kg) as well as *T. occidentalis* seed extract (138 mg/kg) and doxorubicin (1.66 mg/kg). Also, moderately affected kidneys having atrophying renal micro-architecture, with widespread vacuolated and degenerating tubules, within the renal cortical matrix were found group 5 rats (T+MDE) treated with 276 mg/kg of *T. occidentalis* seed extract and doxorubicin (1.66 mg/kg), while group 6 rats (T+HDE) treated with 276 mg/kg of *T. occidentalis* seed extract and doxorubicin (1.66 mg/kg), also showed moderately affected kidneys but with altered renal micro-architecture, with vacuolating and degenerating tubules, and areas of hemorrhagic blood vessels within the renal cortical matrix. Aqueous fraction (276 mg/kg) and doxorubicin (1.66 mg/kg) treated rats in group 7 (T+AQE), showed a normal renal micro-architecture without any pathological sign, while moderately distorted renal micro-architecture, having vacuolating and degenerating tubules and areas of hemorrhagic blood vessels within the renal cortical matrix was observed in kidney sections of rats in group 8 (T+DCME) treated with dichloromethane fraction (276 mg/kg) of *T. occidentalis* seed and doxorubicin (1.66 mg/kg).

Discussion

This investigation aimed to evaluate the kidney protective potentials of seed extract and fractions of *T. occidentalis* on doxorubicin-induced kidney injuries in rats in order to assess its antidotal activity. Doxorubicin, though active against various cancers, has limited clinical usefulness due to associated diverse organ toxicities (Calabresi & Chamber, 1990; Yilmaz et al., 2006) resulting from metabolic activities of its toxic metabolite which produces free radicals that is responsible for doxorubicin-induced organ toxicity (Injac et al., 2009; Kalender et al., 2005). This study showed that doxorubicin administration was accompanied by raised serum urea, creatinine and electrolytes (K^+, Na^+, Cl^- and HCO^-_3) levels relative to normal control, which indicated a serious kidney injury. This observation agrees with earlier findings of Rajasekaran (2019), which elevations due to doxorubicin activity were reported. Previous study had shown that raised serum creatinine and urea levels (Lakshmi & Sudhakar, 2010) as well as elevated serum electrolytes (Na, K, Cl and bicarbonate) levels (Okokon et al., 2024) are cardinal signs of kidney injury. However, these high levels were reduced significantly by co-administration with *Telfairia occidentalis* seed extract and fractions. According to Mohan et al. (2010), doxorubicin causes kidney injury through production of free radicals by its semiquinone metabolite, which precipitates oxidative stress resulting in injury to the kidney which can be through cumulative dose and duration of treatment dependent lipid peroxidation and biological macromolecules damage (Rashid et al., 2013). *T. occidentalis* seed extract and fractions may have counteracted the activities of doxorubicin induced oxidative stress by scavenging the generated free radicals leading to protection of the kidney as demonstrated in the reduced urea, creatinine and electrolytes levels. Previous reports have shown antioxidative burst and antioxidant activities of seed extract and fractions of *T. occidentalis* (Okokon et al., 2012a; Osukoya et al., 2016), which may be the probable mechanism of nephroprotective action of the seed extract and fractions considering the rich flavonoid compounds and strong antioxidant activity reported on the seed extract (Umoh et al., 2025). The findings of this study further support the antioxidant potentials of the seed extract and fractions. Lowering of kidney's enzymatic and non-enzymatic endogenous antioxidants (SOD, CAT, GPx and GSH) levels relative to control, with raised MDA level was observed in this investigation following repeated treatment with doxorubicin (1.66 mg/kg, i.p) to rats every two days for 2 weeks in this study. Oxidative stress marked by high MDA level, a product of lipid peroxidation, has been reported to increase following doxorubicin administration (Rashid et al., 2013, Rehman et al., 2014, Khames et al., 2019). However, concurrent treatment rats with *T. occidentalis* seed extract/fractions (138 - 553 mg/kg) and doxorubicin resulted in elevation of antioxidant enzymes (SOD, CAT, GPx) and GSH levels of the extract/fractions-treated rats relative to doxorubicin only group though non-dose-dependently. These results corroborate other investigations that previously documented inhibitory potential of doxorubicin on endogenous enzymatic and nonenzymatic antioxidants as was the case in this study, resulting in kidney injury (Abushouk et al., 2017; Abdel-Daim et al., 2017; Abushouk et al., 2019). The considerably lowered MDA level following the *T. occidentalis* seed extract and fractions treatment may have been due to free radicals scavenging potentials of the phytoconstituents and therefore, lipid peroxidation further confirming the antioxidant potentials of the seed extract and hence its kidney protective property. Histological examinations in the present investigation showed that pathological features of injury depicted as vacuolated and degenerating tubules, degenerating glomerular tuft cells, widened bowman space and dilated renal tubules within the renal cortical matrix among others were obvious in kidneys of doxorubicin (1.66 mg/kg) alone treated rats However, following co-administration of *T. occidentalis* seed extract/fractions and doxorubicin these pathological signs were significantly reduced or absent when the kidney sections of some extract/fraction-treated rats were examined. This further supports the kidney protective property of the seed extract which suggest the involvement of antioxidant and antioxidative stress potentials of its phytoconstituents especially the flavonoids as reported previously

(Okokon et al., 2012a; Umoh et al., 2025). These observations further corroborate the kidney protective potential of the seed extract earlier reported by Usunomena & Okpiabhele, (2023) against paracetamol-induced kidney toxicity.

Conclusion

The results of this investigation revealed that the seed extract and fractions of *T. occidentalis* can counteract doxorubicin-induced injury on the kidney. This activity can be attributed to activities of its phytoconstituents. Thus, the seed extract can be used to ameliorate doxorubicin-induced renotoxicity.

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Author contributions

This work was carried out in collaboration among all authors. Authors JEO, GEE and UQN conceived and designed the research and conducted the animal studies. Authors JEO and CCO performed the data analysis and interpretation. Authors JEO, UUF, CCO, and GEE contributed to writing the article. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no conflict of interest. The manuscript has not been submitted for publication in other journal.

Ethics approval

This investigation on experimental animals was duly approved by the College of Health Sciences Animal -Ethics Committee, University of Uyo (UU/FP/AE/24/055). All the experiments were carried out according to National Institute of Health Guide for Care and Laboratory Animals (pub. No. 85-23, revised 1985).

AI tool declaration

The authors have not used AI and it's related to tools to write this manuscript. The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

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