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Nephroprotective Activity of *Dialium guineense* Aqueous Extract Against Cisplatin-Induced Kidney Damage in Rats

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ABSTRACT

Kidney injury is a health problem that results in organ failure, subsequent dysregulation of body's electrolytes and volume, and abnormal retention of nitrogenous waste. The purpose of this study was to investigate the nephroprotective activity of Dialium guineense aqueous extract against Cisplatin-Induced Kidney Damage in Rats. Kidney damage was induced in animals through intraperitoneal injection of cisplatin (7 mg/kg per day, (i.p.), on the 3rd day while oral administration of aqueous extract of Dialium guineense fruit pulp (ADF) at 100 mg/kg b.wt., 250 mg/kg b.wt, and 500 mg/kg b.wt. and Silymarin (at 100 mg/kg) was for seven consecutive days (Day 1 to Day 7). The nephroprotective potential was determined by measuring organ weight changes, serum biochemical markers (ALT, AST, creatinine, and urea), body electrolytes (Na, K, and Cl), and histopathological observations. The extracts had alkaloids, phenols, flavonoids, saponins, terpenoids, and tannins. Rats treated with cisplatin showed significant increases in relative organ weights, ALT, ALP, creatinine, and urea levels. However, no significant difference was observed in body electrolytes after cisplatin induction or co-treatment with extract. Co-treatment with ADF at all doses, especially 100 mg/kg b.wt., significantly reversed these biomarkers to near-normal levels. Histopathological examination of the kidney confirmed the protective effects of ADF against cisplatin-induced nephrotoxicity damage, with ADF at 100 mg/kg b.wt showing the highest percentage nephroprotection. The results indicate that the aqueous extract of Dialium guineense fruit pulp has nephroprotective properties against cisplatin, which may be partly due to the phytochemicals present in the extract.

Keywords

Nephroprotective, Histopathology, Biochemical, *Dialium guineense*.

Introduction

Globally, a common kidney problem is nephrotoxicity caused by the adverse effects of some toxic chemicals and medications on the kidneys [1-3]. These chemicals and poisonous substances can lead to renal conditions such as acute renal failure, chronic interstitial nephritis, and nephritic syndrome [4,5]. In the 21st century, acute kidney injury has become one of the most recognized causes of death and suffering as a result of an increase in associated risks [6]. For instance, in 2017, the number of patients affected by acute kidney injury kept increasing and affects approximately 843.6

million individuals worldwide [7]. Commonly used drugs known to induce nephrotoxicity include drugs used as chemotherapy agents, which include cisplatin, carboplatin, methotrexate, carmustine, mitomycin. Aminoglycoside antibiotic drugs such as gentamicin, vancomycin, and non-steroidal anti-inflammatory agents which include Ibuprofen, and diuretics are nephrotoxic agents [8,9].

Nephroprotective agents possessing protective activity against nephrotoxins are used for the treatment and prevention of kidney injury [10]. However, the treatment of nephrotoxicity by the use of conventional drugs and dialysis has become expensive, hence the need for reliable, cheaper, and accessible alternatives. One prominent area that has received popularity and very essential in the management of kidney diseases and continues to contribute to a large source of new molecules is the use of medicinal plants [10]. The traditional consumption of some plants as nephroprotective agents has also been reported [11,12]. One plant origin that has received renewed popularity due to its nutritional and medicinal importance is *Dialium guineense*.

Dialium guineense is native to West Africa and primarily found and known in Ghana as 'Yoyi', Icheku in Igbo and Tsamiyar biri in Hausa, 'Assiswe' in Benin, Veludo' in Guinea–Bissau black tombla in Sierra Leone, Awin in Nigeria or 'Igbaru' in Yoruba, 'atchethewh' in Togo [13]. Its health benefit is enormous, some of which include, the ability of the leaf extract to inhibit the development stages of *Plasmodium falciparum* the causative organism of malaria, therefore, consuming a concoction of the leaf can treat malaria [13]. Secondly, the leaf extract of velvet tamarind has the potential to facilitate gastric mucus secretion, which helps enhance the ease of gastric ulcer. It is also an extremely diuretic that stimulates the production of urine, aiding the heart to pump blood, therefore, decreasing the risk of hypertension. It has other medicinal benefits such as anti-inflammatory and anti-microbial properties [14]. The current study was aimed at assessing the nephroprotective effect of aqueous fruits extract on Cisplatin-Induced kidney damage in rats. This will provide additional information on the value and usage of this indigenous fruit.

Figure 1: *Dialium guineense* Willd plant with fruit.

Materials and Methods

Chemicals

Cisplatin, silymarin, phosphate buffer saline, and formalin were the chemicals used. The phosphate buffer saline was used due to the antioxidant activity and formalin was used for the study (histology). Commercial colourimetric bioassay kits were purchased to estimate serum AST, ALT, urea, and creatinine as well as sodium, chlorine and potassium. All other analytical-grade reagents, chemicals, and strains were purchased.

Collection and Authentication of Plant Materials

Dialium guineense fruit was handpicked from Akatsi in the Volta Region of Ghana. The fruit was identified and authenticated at the Department of Herbal Medicine, KNUST and a voucher specimen was deposited at the faculty's herbarium.

Preparation of Aqueous Fruit Extract

An aqueous extraction was carried out by suspending 400 g of pulverized fruit pulp in 1000 mI of boiled distilled water. The mixture was then allowed to stand for 24 hours in the dark. The liquid extract was then emptied and residue was squeezed in a hygienic white cloth over a pan to get more liquid extract. The liquid extract was filtered by the use of cotton wool and dried over a water bath at 70°C facilitating the evaporation of all the water leaving the crude extract. The fruit pulp extract was dried and then kept in a clean zip-lock bag. Preparation of the doses was done by reconstituting the extract in freshly distilled water.

Phytochemical Screening

The aqueous fruit pulp extract of *Dialium guineense* was screened for the presence of alkaloids, phenols, saponins, tannins, flavonoids and terpenoids according to standard methods [15].

Experimental Animals

Wistar albino rats of similar weight were obtained at the animal facility from the Centre for Plant Medicine Research in Akuapim Mampong. The animals were housed at the Clinical Analyses Laboratory of the Department of Biochemistry and Biotechnology, KNUST-Kumasi in clean plastic cages bedded with wood shavings. The cage beddings, feeding trough, and water bottles were cleaned daily and the animals were housed under standard laboratory conditions of humidity and temperature. They were also given standard feed and water. They were also allowed to acclimatize to their new environment for 7 days before the experiment. The Wistar rats' tails were marked with a permanent marker based on their weights for easy identification. Experiments were carried out according to the guidelines for the consideration and use of animal testing facilities. The groups and treatments are indicated in Table 1

Sacrificing of Animals

All the animals were sacrificed on the 8th day after an overnight fast. Animals were sacrificed by cervical dislocation. With the aid of a sterile blade, incisions were made quickly in the cervical region of the rats, and blood samples were dispensed into a serum operator

for biochemical analyses and EDTA tubes for hematological analyses. The formalin was used to keep the harvested kidney of each rat for histological assessment.

Table 1: Experimental grouping and treatment of Animals.

S/N.	Group	Treatment
1	Normal (control)	Water p.o (1 mL/kg b.wt)
Extracts Only		
2	100 mg ADF only	100 mg/kg ADF only (per day, p.o.) for 7 consecutive days
3	250 mg ADF only	250 mg/kg ADF only (per day, p.o.) for 7 consecutive days
4	500 mg ADF only	500 mg/kg ADF only (per day, p.o.) only for 7 consecutive days
Cisplatin Model		
5	Cisplatin	7 mg/kg b.wt cisplatin intraperitoneally (i.p) on the 3rd day
6	Silymarin+ Cisplatin	100 mg/kg Silymarin (per day, p.o) and 7 mg/kg b.wt cisplatin (i.p) on the 3rd day.
7	100 mg ADF + Cisplatin	100 mg/kg ADF (per day, p.o.) and 7 mg/kg b.wt cisplatin (i.p) on the 3rd day.
8	250 mg ADF + Cisplatin	250 mg/kg ADF (per day, p.o.) and 7 mg/kg b.wt cisplatin (i.p) on the 3rd day.
9	500 mg ADF + Cisplatin	500 mg/kg ADF (per day, p.o.) and 7 mg/kg b.wt cisplatin (i.p) on the 3rd day.

Treatment Effect on Organ Weights in Rats

The liver and kidney of sacrificed animals were excised, washed in cold buffered saline, and blotted dry. They were weighed to obtain the absolute organ weight (AOW). The relative organ weight (ROW) was calculated as follows:

$$ROW = \frac{AOW}{Body\ Weight\ at\ Sacrifice} \times 100$$

Biochemical Assessment

AST, ALT, urea, creatinine, sodium, potassium, and chloride levels were determined using the COBAS automated chemistry analyzer and commercial kits from ELITECH France. Percentage protection was calculated based on the principal indicators of kidney protection; AST, creatinine, and urea using the formula:

$$Percent\ Protection = \frac{Values\ of\ Toxin\ Control - Values\ of\ Test\ Group}{Values\ of\ Toxin\ Control - Values\ of\ Normal\ Control} \times 100$$

Histological Assessment of Kidney

The excised kidney was defatted, washed in buffered saline, and stored in buffered formalin. The kidney was processed, stained in hematoxylin and eosin, and viewed under high power for histological features such as glomerulosclerosis, tubulointerstitial nephritis, renal necrosis, and fibrosis.

Statistical Analyses

GraphPad Prism 8 for Windows was used in analyzing the data and the results were expressed as a mean ± standard error mean (SEM). Two-way analysis of variance (ANOVA) was used in the assessment of data followed by the Newman-Keuls multiple comparison test. Values for which $p < 0.05$ was considered statistically significant.

Results

Qualitative Phytochemical Constituent of extracts of *D. guineense*

Table 2: Shows the qualitative phytochemical constituents in the aqueous extract of *D. guineense*.

Phytochemicals	Pulp Aqueous Extract
Alkaloids	++
Flavonoids	+
Phenols	+
Saponins	+
Tannins	+
Terpenoids	+

Note: *++=Present In Abundant; +=Present; - =Absent*

Effect of treatment on relative organ weight

The effect of treatment on rats' livers and kidneys compared to cisplatin induction is shown in Figure 2. Relative liver and kidney weight increased significantly when cisplatin was administered. The kidney and liver weights of the toxicant co-treated groups with ADF at all doses significantly decreased to near normal level.

Effects of treatment on Serum Biochemical parameters

Figure 3 shows the effect of the extract on the biochemical profile of normal and Cisp-treated animals. Administration of cisplatin resulted in a significant increase in biochemical parameters such as AST, ALP, creatinine, and urea when compared with the normal group.

Effect of treatment on electrolyte

Table 3 shows the effect of treatment on electrolytes. Cisplatin administration resulted in no significant changes in the electrolytes.

Table 3: Shows the effect of treatment on electrolyte.

Treatment	Potassium (mmol/L)	Sodium (mmol/L)	Chloride (mmol/L)
Normal	6.73±0.48	141.00 ±0.83	100.03 ±2.40
100 mg only	7.20±0.23	146.23 ±2.65	107.53 ±1.64
250 mg only	6.63±0.19	145.53±0.37	104.13 ±0.81
500 mg only	6.90±0.20	147.13 ±0.70	107.00± 0.68
Cisp only	7.37±0.64	139.27 ±3.78	89.23 ±3.64
Sily + Cisp	5.83±0.35	142.00 ±1.45	101.50 ±0.06
100 mg + Cisp	6.37±0.23	147.93 ±2.59	103.1 7±1.03
250 mg + Cisp	6.37±0.23	145.60±1.80	98.67±2.97
500 mg + Cisp	6.97±0.42	144.70 ±1.31	106.70±2.99

Values are expressed as mean ±SEM (n=5)

Percentage Nephroprotection

Percentage protection of the kidney was based on the principal indicators of kidney protection (AST, creatinine and urea). Figure 4 shows the comparative analysis of the nephroprotective effect of Silymarin, and aqueous extract of Dialium *guineense* fruit pulp (ADF) at different doses against cisplatin administration. ADF at 100 mg/kg b.wt offered the best treatment.

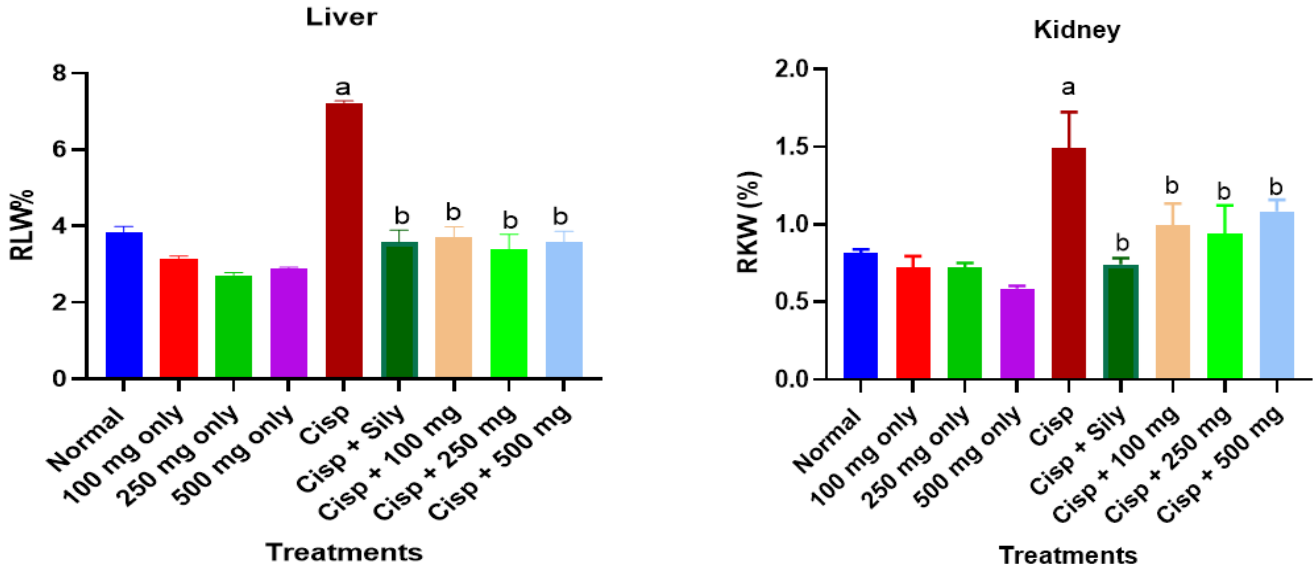

Figure 2: Effect of Extract Treatment on Relative Organ Weight. Values are expressed as mean ±SEM (n=5). Statistical significance "a" at p<0.05-0.001 compared to Normal; "b" at p<0.05-0.001 when compared to cisplatin treated group only.

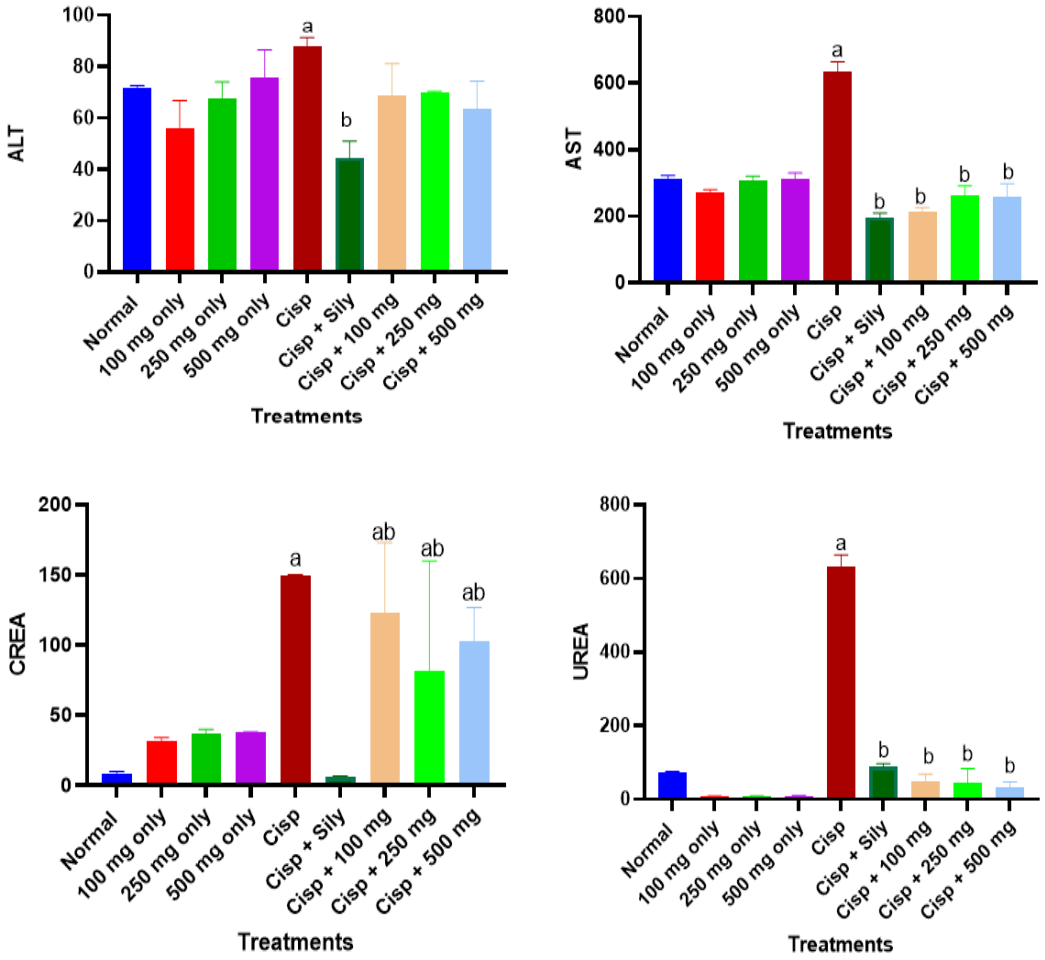

Figure 3: Effect of Extract Treatment on Serum Biochemical parameters. Values are expressed as mean ±SEM (n=5). Statistical significance "a" at p<0.05-0.001 compared to Normal; "b" at p<0.05-0.001 when compared to cisplatin treated group only.

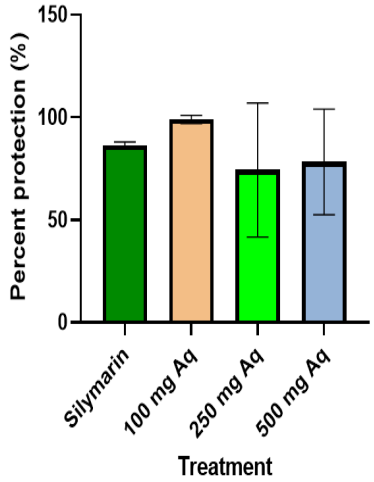

Figure 4: The figure shows the percentage nephroprotection of the various doses of aqueous extract of *D. guineense* against cisplatin. Each bar is the mean percentage protection of kidney protection indicators (creatinine and urea).

Effect of treatments on kidney histology

Figure 5 shows the kidney micrographs of both normal and cisp-treated rats. While there were no significant morphological changes in the normal group, the group treated with only cisplatin had significant random tubular epithelial coagulation, necrosis and mild inflammation. Animals co-treated with either ADF at 100 mg/kg bwt or silymarin had their kidney tissues reverted to near-normal architecture.

Discussion

This study was aimed at investigating whether the administration of aqueous fruit pulp extracts of *Dialium guineense* could help protect the kidney from cisplatin-induced nephrotoxicity. The aqueous extract was screened through phytochemical analyses phytochemical screening of the aqueous extract revealed the presence of alkaloids, flavonoids, phenols, saponins, tannins, and terpenoids. Kidney injury could occur as a result of oxidative stress and inflammation [16-19]. Generally, plants possessing secondary metabolites including alkaloids and terpenoids protect against injuries including kidney injuries [20]. This attests that aqueous

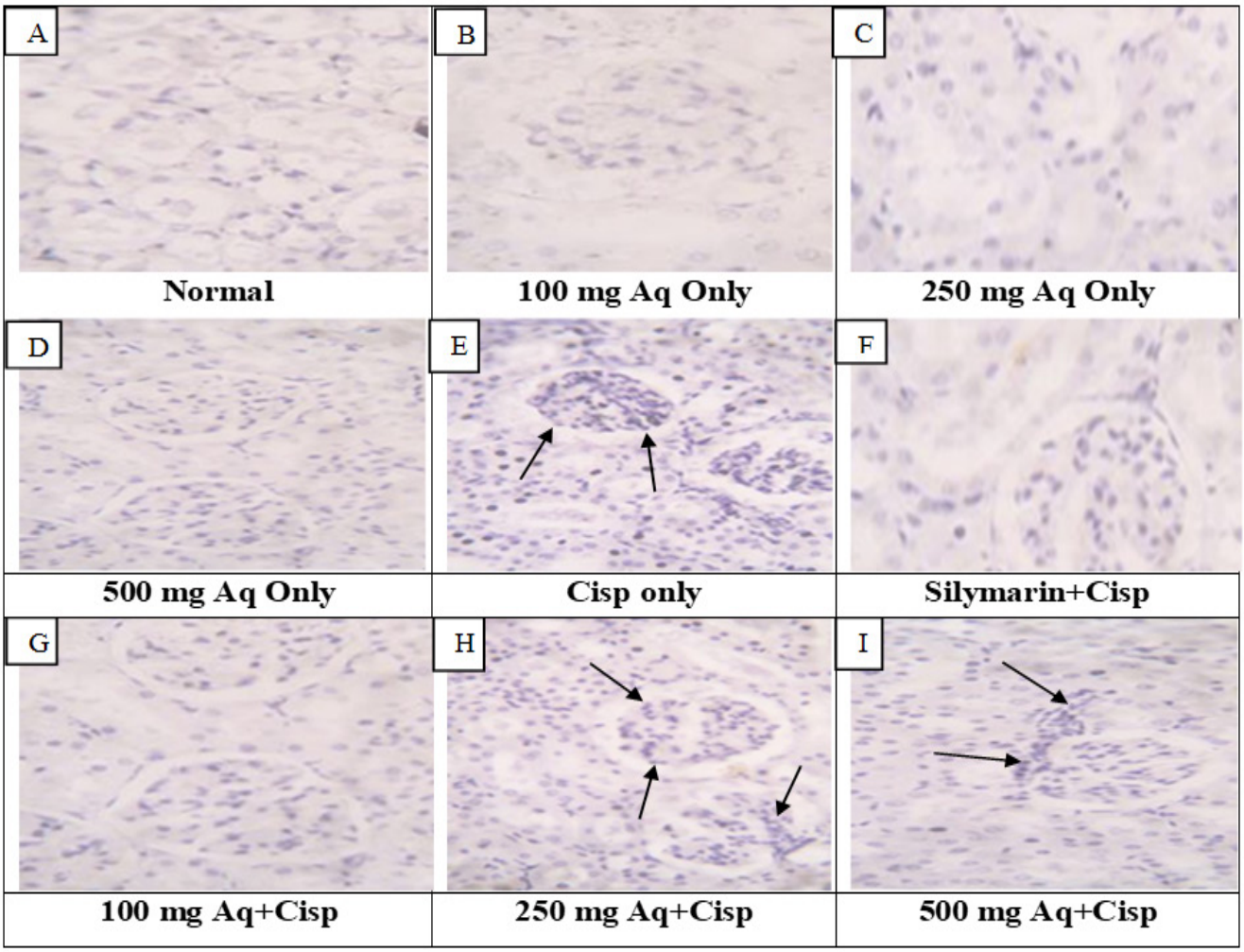

Figure 5: Photomicrograph (A) – (D) shows no observable lesion; (E) shows random tubular epithelial coagulation necrosis and mild inflammation (black arrows); (F) shows mild coagulation necrosis of tubular epithelium (black arrows); (G) shows no observable lesion. (HandE x 400).

extract of *D. guineense* fruit pulp may possess a protective ability against nephrotoxicity.

The kidney is one of the many organs that play important roles in the body. However, its roles become compromised after exposure to certain toxicants. Synthetic drugs are part of those toxicants, with cisplatin being an example. Mitochondrial dysfunction is regarded as the main mechanism in cisplatin-induced nephrotoxicity [21,22]. A reduction in membrane electrochemical potential, disturbance in calcium homeostasis, reduced ATP synthesis and impaired mitochondrial respiration have been studied to be mechanisms attributed to cisplatin-induced nephrotoxicity [23,24]. Apart from that, it has also been studied that cisplatin can lead to a breakdown in complexes I, II, III, and IV of the mitochondrial respiratory chain, leading to an increase in the production of superoxide anions at complexes I, II, and III [25]. The production of superoxide anions could be from the hydroxyl radicals. Hydroxyl radicals are very strong oxidants; therefore, their induction has been associated with cisplatin [26,27]. Oxidative stress by cisplatin has been linked to the depletion of non-enzymatic (GSH and NADPH) and the enzymatic antioxidant defence system (superoxide, dismutase, catalase, glutathione transferase, glutathione peroxidase, glutathione reductase, glutathione peroxidase) in the kidneys of rats [28-30], with the most serious cisplatin nephrotoxicity being acute nephrotoxicity.

From Figure 2, the administration of cisplatin caused significant gain in relative liver and kidney weights. The increase in the relative liver and kidney weight of rats treated with cisplatin could be due to organ enlargement, indicating organ inflammation. However, co-treatment with the extracts resulted in a decrease in these parameters. Biochemical markers such as ALT, AST, urea, and creatinine are very relevant in the diagnosis of kidney injuries. Treatment with cisplatin led to an appreciable increase in the levels of ALT, AST, urea, and creatinine, an indication of nephrotoxicity. Induction of nephrotoxicity by cisplatin has been associated with cellular uptake and efflux, oxidative and endoplasmic reticulum stress, and apoptosis, leading to proximal tubular injury [31]. Proximal tubular injury is said to be involved in other mechanisms such as autophagy, dysregulation of cell-cycle proteins, DNA damage, mitochondrial dysfunction, and activation of mitogen-activated protein kinase [32]. Co-treatment of the animals with the aqueous extract of *D. guineense* lowered the levels of urea and creatinine at all levels when compared to the normal group. The extract or toxicant did not have any adverse effect on the levels of measured electrolytes as shown in table 3. Studies have indicated that kidney injury could result in changes in the levels of electrolytes [33]. However, there was no effect on the levels of chloride, potassium, and sodium ions after treatment with cisplatin and co-treatment with the aqueous extract.

The results of the histopathological examination of sections of kidney tissues of normal, nephrotoxic-induced groups and groups treated with extracts are presented in Figure 5. The histopathology also confirms the nephroprotective activities of the aqueous extract of *D. guineense* as micrographs of kidney sections of rats treated with ADF at 100 mg/kg b.wt showed no kidney damage with no observable lesion as compared to the toxicants-only group, which showed severe kidney damage. These confirm the nephroprotective effects of the aqueous extract of *Dialium guineense* fruit pulp.

Conclusion

The aqueous extract of *Dialium guineense* contains certain phytochemicals with potent antioxidant activities, an indication that it can be used to protect the body against diseases that are caused by oxidative stress. The ability of the extract to reduce biomarkers such as ALT, AST, urea, and creatinine in cisplatin-induced kidney injury implies that it possesses nephroprotective activity. These observations were confirmed by histopathological observations.

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