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Ameliorative effect of zingerone on cadmium-induced nephrotoxicity in adult wistar rats

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ABSTRACT

Exposure to heavy metals like cadmium has been reported to cause severe kidney damage through oxidative stress and inflammation. Zingerone is a bioactive compound present in ginger, it contains significant anti-oxidative and anti-inflammatory properties. This study aims to investigate the anti-oxidative and therapeutic role of zingerone on cadmium-induced nephrotoxicity. Thirty (30) adult male rats were divided into 6 groups (A-F) of 5 rats each (n = 5) randomly [A: normal control (normal saline), B: cadmium-exposed (5 mg/kg of cadmium only), C: zingerone-alone, D-F: 5 mg/kg of cadmium + 50 mg/kg, 100mg/kg, 200 mg/kg of zingerone, respectively]. Nephrotoxicity was induced by oral administration of cadmium chloride ($CdCl_2$), followed by zingerone treatment orally. Renal function markers (serum creatinine and urea level), oxidative stress markers (superoxide dismutases, catalase, malondialdehyde), and histopathological investigations of the kidney were assessed to evaluate the effects. Cadmium administration resulted in significant renal dysfunction, characterized by elevated serum creatinine, urea, and kidney malondialdehyde levels, along with reduced antioxidant enzyme activities (superoxide dismutase and catalase). Histopathological evaluation showed extensive kidney damage characterized by renal tubular damage, necrosis, and inflammation. Zingerone treatment significantly ameliorated these alterations, restoring renal function markers, reducing oxidative stress, and improving the histological architecture of the kidney. These findings suggest that zingerone exerts an anti-oxidative and therapeutic effect against cadmium-induced nephrotoxicity. According to these findings, zingerone shows potential as a therapeutic approach for kidney impairment caused by exposure to heavy metals.

1. Introduction

The kidney is usually a major target of harmful destruction from exposure to chemicals, drugs, and other toxicants, it is a vital organ required to perform several essential functions, such as detoxification, homeostasis, excretion of dangerous compounds, and regulation of extracellular fluids (Augustine et al., 2023; Finn & Porter, 2003; Stevens et al., 2006). Nephrotoxicity is the term used to describe the quick decline in kidney function due to the harmful effects of drugs and chemical exposure. Exposure to heavy metal and accumulation of heavy metal in the body can trigger toxicity to the kidney and result in the decline of several functions of the kidney (Al-Naimi et al., 2019).

Cadmium (Cd) is a toxic heavy metal, reported to be highly dangerous to human health and is, therefore, a serious public health problem (Fatima et al., 2019). In the surroundings, Cd is omnipresent. The primary contamination causes are ambient air, cigarette smoke, welding, and

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polluted food and beverages (Chargui et al., 2011; Munisamy et al., 2013). Its use as a corrosive reagent in industry, and as a stabilizer in color pigments, PVC products and Ni-Cd batteries are continuous sources of Cd (Genchi et al., 2020). House dust is a possible source of Cd exposure in locations with polluted soils (Hogervorst et al., 2007). The metallothioneins (MTs) family of ubiquitous small cysteine-rich proteins, whose specific role is to regulate zinc metabolism, protect humans from long-term exposure to low amounts of Cd (Peana et al., 2022). MTs are crucial for preventing DNA damage, oxidative stress, and ion toxicity from various heavy metals (Matović et al., 2015; Peana et al., 2022). If the body absorbs more Cd than MTs, the metal can accumulate, making the situation even more difficult. This buildup will mostly occur in the kidneys (30%) and liver (30%), with the remaining Cd being distributed across the other organs and has an exceptionally long half-life of 10–30 years (Bernhoft, 2013).

Cadmium is absorbed in the body and accumulates in the kidney and it triggers oxidative stress by generating free radicals. The accumulation of these free radicals will lead to cellular damage to the kidney. The oxidative stress and cellular damage pathways lead to inflammation in the renal tubules, tubular damage, and distortion of the glomeruli, which will result in diminished renal functions (Das & Al-Naemi, 2019; Salama et al., 2019). Cadmium-induced oxidative stress is linked to DNA damage, protein alteration, and lipid peroxidation. Among other illnesses, exposure can result in neurotoxicity, liver damage, and kidney problems (Emeka et al., 2023; Kim et al., 2018; Salama et al., 2019). Research indicates that the widespread low environmental exposure to Cd that now exists in industrialized nations may hurt people's kidneys and bones (Bernard, 2008). Various investigations have revealed that oxidative pressure, inflammation, and apoptosis may be the mechanisms of Cd-induced damage to the kidney and other organs (Alibakhshi et al., 2018; Wachira et al., 2019). Oxidative stress and the generation of reactive oxygen species (ROS) are caused by Cd and are often counteracted by enzymatic and non-enzymatic anti-oxidative barriers (Alibakhshi et al., 2018; Jamakala & Rani, 2014).

Scientific research is increasingly embracing the use of medicinal plants and herbs like ginger, *Curcuma longa* (Akinyemi et al., 2018), *Ficus exasperata* (Oviosun et al., 2023), and garlic (Anusuya et al., 2013) in curbing renal damage caused by toxins (Ekor, 2014). Ginger (*Zingiber officinale* Roscoe, family: Zingiberaceae) is the underground rhizome of the ginger plant (Ahmad et al., 2015; Emeka et al., 2023). Zingerone, also known as vanilla acetone, is found in ginger at about 9.25% (Ahmad et al., 2015). Zingerone is primarily present in dry ginger, but cooking or drying also converts gingerol (another component in ginger) into zingerone by retro aldol reaction (Zhang, 2012). According to reports, zingerone has antioxidant, anti-inflammatory, anti-obesity, oxidative stress antagonist, anti-emetic, anti-diuretic, and anti-nausea properties during chemotherapy (Ahmad et al., 2015; Kumar et al., 2014; Mashhadi et al., 2013).

Zingerone, an antioxidant found in ginger, can prevent kidney damage by decreasing oxidative stress triggered by an imbalance of ROS. ROS, such as superoxide, anions, hydrogen peroxide, and hydroxyl radicals, can harm renal cells, lipids, proteins, and DNA. They can also cause inflammation by activating signaling pathways (Alibakhshi et al., 2018; Türk et al., 2022). Antioxidants-rich bioactive compounds like zingerone can mitigate oxidative stress, inflammation enhanced mitochondrial function, and protect the kidney (Alibakhshi et al., 2018; Kandemir et al., 2019; Türk et al., 2022).

This study explores the ameliorative potential of zingerone, a bioactive compound derived from ginger, in mitigating Cd-induced renal toxicity in rats. Despite extensive research into Cd's nephrotoxic effects and various antioxidants as therapeutic agents, the role of zingerone is greatly underexplored. By investigating its antioxidant mechanisms, this study provides novel insights into various dose-dependent zingerone's efficacy and pathways, contributing to the development of safer and natural therapeutic strategies for heavy metal-induced nephrotoxicity. This study evaluated the ameliorative effect of various doses of zingerone on Cd-induced kidney toxicity.

2. Materials and methods

2.1. Experimental animals

Thirty (30) adult rats (10-12 weeks old) weighing between 180-200 g, were purchased from the animal farm of the University of Nigeria, Nsukka. The rats were kept in a well-ventilated standard animal cage in the Department of Anatomy, University of Nigeria in March 2022. The experimental rats were acclimatized for 2 weeks in standard laboratory conditions, with 37 ˚C temperature and, a 12-hour light/dark cycle, and they were allowed unrestricted access to water and food.

2.2. Chemical procurement

We purchased standard analytic products of cadmium ($CdCl_2$) (CAS No: 7440-439) and zingerone (CAS No: 122-48-5, with purity ≥ 98%) from Sigma-Aldrich USA.

2.3. Preparation of zingerone and cadmium solution

Zingerone and $CdCl_2$ were dissolved in normal saline solution and administered daily. Zingerone was administered at varying doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg (Alam, 2018; Alibakhshi et al., 2018; Amin et al., 2021; Safhi, 2015). $CdCl_2$ was administered at a dose of 5 mg/kg (Vijaya et al., 2020). Both $CdCl_2$ and zingerone were administered orally using an oral cannula.

2.4. Exprimental design

Six groups of five (5) rats each were formed by dividing the rats according to their weight. The sample size was calculated following the ARRIVE guidelines and using the resource equation method. As shown in Table 1, group A received normal saline daily for 21 days as the normal control group. Group B served as the negative control group which received 5mg/kg of Cd for 7 days, group C received 100 mg/kg of zingerone only, groups D, E, and F were treated with 5 mg/kg of Cd for 7 days and treated with 50 mg/kg, 100 mg/kg, 200 mg/kg of zingerone, respectively for (14) fourteen days (Alam, 2018; Alibakhshi et al., 2018; Amin et al., 2021; Safhi, 2015; Vijaya et al., 2020).

2.5 Animal sacrifice, blood collection, and tissue collection

Under mild anesthesia using chloroform, the animals were sacrificed by cervical dislocation twenty-four hours after their last treatment. A midline surgical incision was made in the abdominal cavity to expose the abdominal viscera. The right and left kidneys were isolated and excised. The excised kidneys were rinsed in distilled water and preserved in 10% formal saline solution before histological examination. Blood samples were obtained through retro-orbital puncture using a capillary tube. Using capillary tubes we collected blood retro-orbitally, this was done before using chloroform for mild anesthesia to enable us to collect samples that would be free from any possible contamination. The blood sample was sent to the

laboratory for a standard biochemical analysis of a kidney function test (Augustine et al., 2023; Oviosun et al., 2023).

2.6. Biochemical analysis (oxidative stress markers- SOD, MDA, CAT)

For biochemical analysis of SOD, MDA, and CAT activity, harvested kidney samples were frozen immediately by placing them on ice (−70 ˚C) and thereafter homogenized. The level of SOD in the kidney homogenate was calculated using the method of Bannister and Calabrese (1987) as reported by Ceretta et al. (2012). CAT levels in the kidney were determined by the methods of Aebi (1984) as previously described by Ceretta et al. (2012). The lipid peroxidation was measured in the homogenate from kidney by quantifying the level of MDA formed by 2-thiobarbituric acid (TBA) reaction as thiobarbituric acid reactive substances (TBARS) using the method of Conti et al. (1991) previously reported by (Chiş et al., 2016; Sevastre-Berghian et al., 2017).

Table 1. Experimental grouping and design

Experimental group	Number of rats	Administration	Treatment
A	5	Normal saline	Normal saline (5ml) for 21 days
B	5	5 mg/kg $CdCl_2$ only	5 mg/kg of $CdCl_2$ for 7 days
C	5	100 mg/kg of zingerone only	100 mg/kg of zingerone only for 21 days
D	5	5 mg/kg $CdCl_2$ +50 mg/kg of zingerone	5 mg/kg $CdCl_2$ for 7 days + 50 mg/kg of zingerone for 14 days
E	5	5 mg/kg $CdCl_2$ +100 mg/kg of zingerone	5 mg/kg $CdCl_2$ for 7 days + 100 mg/kg of zingerone for 14 days
F	5	5 mg/kg $CdCl_2$ +200 mg/kg of zingerone	5 mg/kg $CdCl_2$ for 7 days + 200 mg/kg of zingerone for 14 days

2.7 Kidney function test (serum urea and serum creatinine level)

The blood samples were allowed to clot for about 2-3 hours and centrifuged to obtain serum. Serum creatinine and urea levels were measured using standard laboratory procedures and measurements were recorded as mg/dl. The method outlined by Kandemir et al. (2019) was used to measure the levels of urea and creatinine in the serum.

2.8 Histological evaluation

The kidney was fixed with 10% phosphate-buffered formaldehyde for 24 hours and subjected to routine histological investigation using standard procedures according to Spencer et al. (2012). The tissue was then subjected to the routine method of fixation, dehydration, clearing, filtration, and embedding. Embedded tissue was sectioned at 5 microns using a rotatory microtome to obtain tissue ribbon sections, stained with routine hematoxylin and eosin, and examined with the aid of an Olympus binocular light microscope (Olympus USA).

2.9. Data analysis

GraphPad Prism version 8.01 for Windows (GraphPad Software, USA) was used to analyze data obtained from this study. One-way analysis of variance (ANOVA) was used to compare the differences between groups followed by Tukey's Post Hoc test. Values were presented as mean ± standard Error (SEM) and $p < 0.05$ was considered statistically significant.

3. Results and discussion

3.1. The effect of zingerone on serum creatinine and urea level

Figure 1 and Figure 2 show the effect of zingerone on serum creatinine and urea levels respectively, with values expressed as mean ± SEM.

The result shows that there was a statistically significant elevation in the values of serum creatinine and urea levels in group B (administered with 5 mg/kg of Cd only) ($p \leq 0.05$) compared to rats in group A (normal saline). Elevated levels of Cd can accumulate in the body leading to dysfunction of the mitochondria and ROS production. Cd toxicity may lead to damage to various organs through mechanisms like oxidative stress and inflammation (Das & Al-Naemi, 2019). The accumulation of Cd within the body system triggers toxic effects and damage to the kidney function and structure (Kim et al., 2018; Lee et al., 2014; Vukićević, 2012). The result of this study showed that there was a remarkable elevation in the values of serum creatinine and urea level in rats exposed to only Cd, this findings are in concurrence with previous reports which reported that Cd toxicity can relatively affect the kidney and lead to elevation of serum creatinine and urea (Kim et al., 2018; Lee et al., 2014; Shati, 2011). The level of serum creatinine and serum urea remarkably reduced in groups C-F and post-treatment groups which received 5 mg/kg of Cd + 50 mg/kg, 100 mg/kg and 200 mg/kg of zingerone compared to the rats in group B ($p \leq 0.05$). This suggests that administration of zingerone to rats in other treatment groups improved renal function, with serum creatinine and urea levels significantly reduced. Various studies reported zingerone's role in regulating kidney function parameters like serum creatinine and urea level (Dawood et al., 2022; Hosseinzadeh et al., 2020).

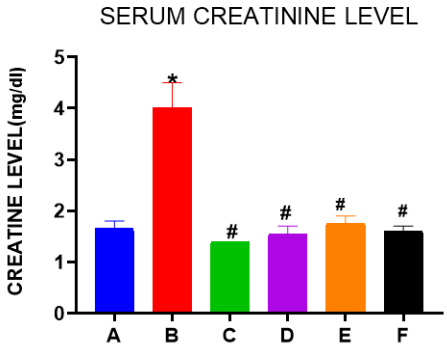

Figure 1. Effect of zingerone on serum creatinine level
Values expressed as mean ± SEM.* indicates significant difference compared with group A at $p \leq 0.05$. # indicates significant difference compared with group B at $p \leq 0.05$

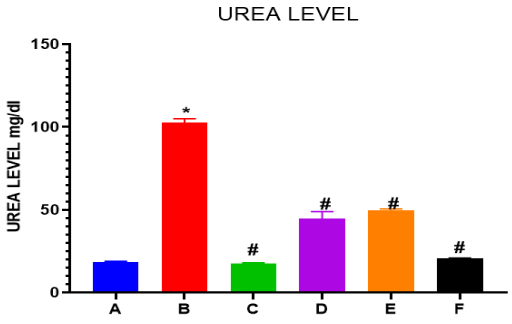

Figure 2. Effect of zingerone on urea level
Values expressed as mean ± SEM.* indicates significant difference compared with group A at $p \leq 0.05$. # indicates significant difference compared with group B at $p \leq 0.05$

3.2. The effect of zingrone on anti-oxidative parameters (SOD, CAT and MDA)

Figures 3-5 show the level of SOD, CAT and MDA. In this study, it was observed that there was a reduction in the level of SOD and CAT in Group B (Cd of 5 mg/kg only) compared to group A. The MDA level in group B was significantly elevated, when statistically compared to group A. Groups C-F treated with various doses of zingerone showed a significant reduction in the level of MDA.

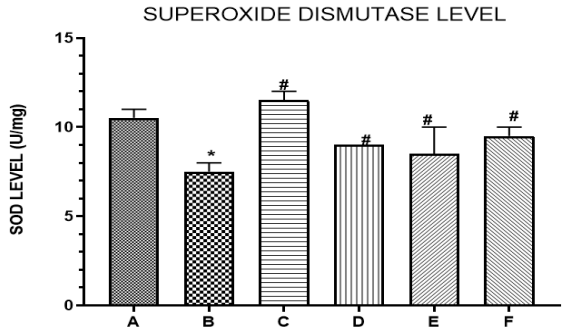

Figure 3. Effect of zingerone on SOD activity
Values expressed as mean ± SEM. * differs significantly compared with group A at $p \leq 0.05$. # differs significantly compared with group B at $p \leq 0.05$

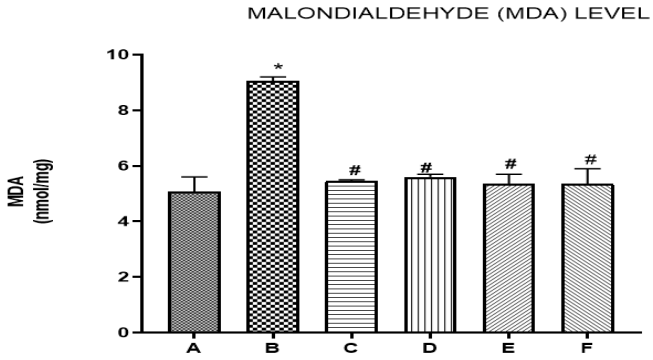

Figure 4. Effect of zingerone on MDA activity
Values expressed as mean ± SEM. * differs significantly compared with group A at $p \leq 0.05$. # differs significantly compared with group B at $p \leq 0.05$

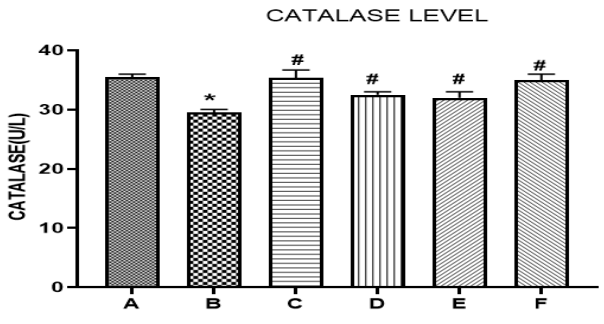

Figure 5. Effect of zingerone on CAT activity
Values expressed as mean ± SEM. * indicate significant difference compared with group A at $p \leq 0.05$. # indicate significant compared with group B at $p \leq 0.05$

Nephrotoxicity arising from Cd exposure is a complex process that has been reported to trigger oxidative stress, inflammation, and cellular damage to the kidney (Onwuka et al., 2011; Yan & Allen, 2021). The significant decrease in SOD, CAT levels and increase in MDA levels observed in rats administered only Cd are consistent with the findings of previous authors who reported that Cd causes oxidative damage as a result of mitochondrial dysfunction, DNA damage, inflammation, decreased activity of antioxidant enzymes and increased lipid peroxidation (Das & Al-Naemi, 2019; Salama et al., 2019). An increase in redox imbalance, DNA damage, and oxidative degradation of proteins and lipids are the primary underlying mechanisms of Cd-related renal impairment (Yan & Allen, 2021). Administration of zingerone in rats treated with zingerone only, post-treated with 50 mg/kg, 100 mg/kg, and 200 mg/kg of zingerone shows a significant increase in antioxidant enzyme activities (SOD, CAT) and decrease lipid peroxidation (MDA). This highlights the zingerone's reportedly strong antioxidant qualities for scavenging free radicals and enhancing tissue structure (Ahmad et al., 2015; Alibakhshi et al., 2018; Kandemir et al., 2019; Mehrzadi et al., 2021).

3.3. The role of zingerone on histological examination of the kidney tissue

Group A (normal control group) showed normal kidney histology with the glomeruli, renal tubules, and cortex clearly shown to be normal. Histological examination of the kidney showed that there were structural changes in the kidney of rats administered with 5mg/kg of Cd only, with histology of the kidney showing tubular necrosis, inflammation degeneration of renal tubules, basal membrane disruption, and congestion of red blood vessels (Figures 6-7). These histological findings of rats treated with Cd only are also linked with the significant increase in the level of serum creatinine, urea, and deregulation of antioxidant enzymes observed. The histological alterations observed in rat's exposure to Cd may also be linked to the accumulation of free radicals in the renal tissue of the rats treated with cadmium (Kandemir et al., 2019; Olubunmi et al., 2017). This observation conforms with previous studies which reported that Cd distorts kidney histology, reduces renal function, and induces oxidative stress (Olubunmi et al., 2017; Onwuka et al., 2011). Group C (treated with zingerone only) showed normal histology of the kidney. Experimental rats in Group C were given only zingerone and rats in the treatment group were treated with 5 mg/kg Cd and 200 mg/kg zingerone. The microanatomical features of the kidneys were found to be very normal with no signs of necrosis or deterioration in the glomeruli and renal tubules. However, in the groups post-treated with low doses (50 mg/kg, 100 mg/kg of zingerone) after Cd administration, there were mild alterations in the histology of the kidney, with signs of cellular improvement in the degeneration compared to the group exposed to Cd only. These observations show that a high dose of zingerone exhibits great potency for restoring the histology of the kidneys of Cd-induced nephrotoxic rats.

According to Kandemir et al. (2019) and Mani et al. (2016), zingerone mitigated drug and chemically induced kidney toxicity, by enhancing the histology of the kidney tissue, reducing serum creatinine, and urea levels, and decreasing oxidative stress. This aligns with the findings of this current study, as our data showed that administration of zingerone greatly improved Cd-induced toxicity by regulating serum levels of creatinine, urea level, and oxidative stress and greatly improving the microanatomy of the kidney. The modulatory effect of zingerone on Cd toxicity was also observed to be dose-dependent, as our result showed that 200 mg/kg of zingerone proved to be more effective.

4. Conclusions

The result from this study revealed that Cd-induced nephrotoxicity was characterized by increased levels of serum creatinine, urea, oxidative stress, and a decrease in renal function. However, zingerone administration showed great potential in modulating Cd-induced renal damage, evidenced by a reduction in serum creatinine, and urea levels, a decrease in oxidation of lipids, and increased activity of antioxidant enzymes in kidney tissue of rats administered

with Cd. Zingerone also restored the histology of the kidneys of Cd-induced nephrotoxic rats. The outcome of our research indicates that zingerone possesses a dose-dependent therapeutic effect against Cd-induced renal toxicity. This highlights the role of zingerone as a promising therapeutic agent in mitigating heavy metal-induced renal damage.

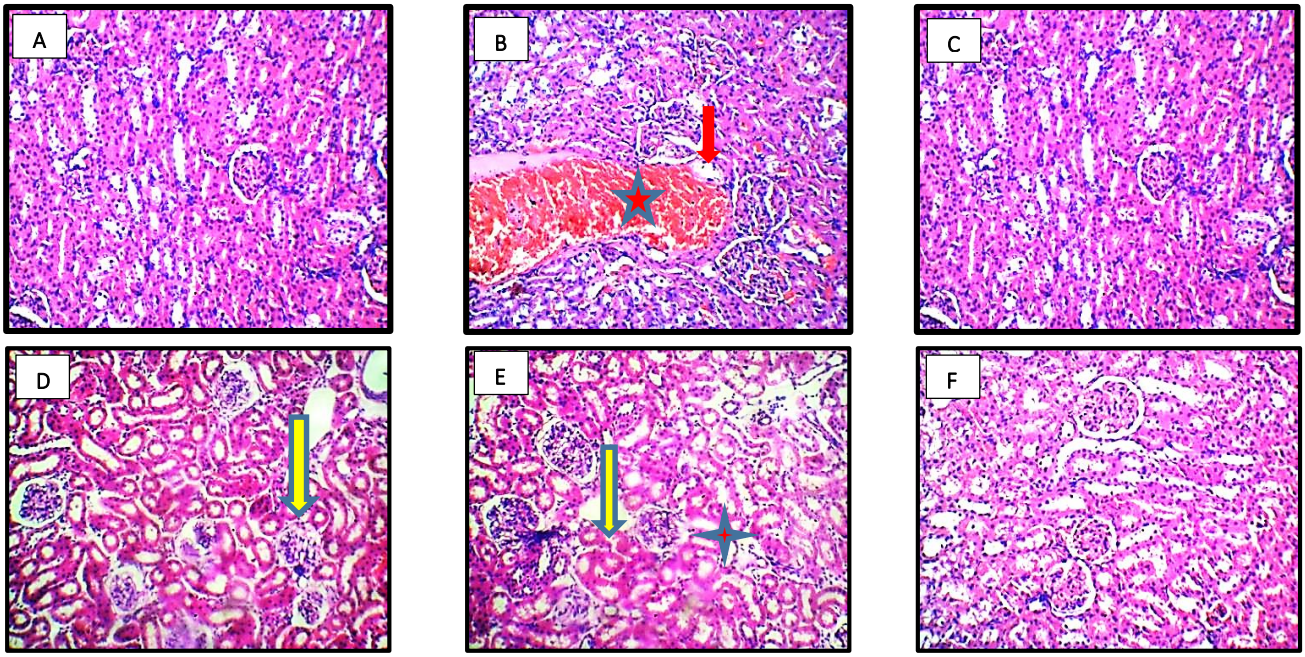

Figure 6. Kidney histology demonstrated by H&E (x 100, scale bar: 100 µm)

The renal tubules, renal cortex, glomeruli and mesangial cells as well as renal parenchyma are clearly seen across the treatment groups. **Group A** showed normal kidney, **group B** animal treated with Cd only showed tubular necrosis, inflamation of the tubules, glomeruli distortion and alterations in renal tubules (indicated by red arrow and star), **group C** showed a normal histology of the kidney, **groups D & E** showed mild strutural alteration in the kidney (indicated by yellow arrow and star symbol), **group F** showed a normal histoloy of the kidney with no signs of necrosis or distortion of the glomeruli and renal tubules.

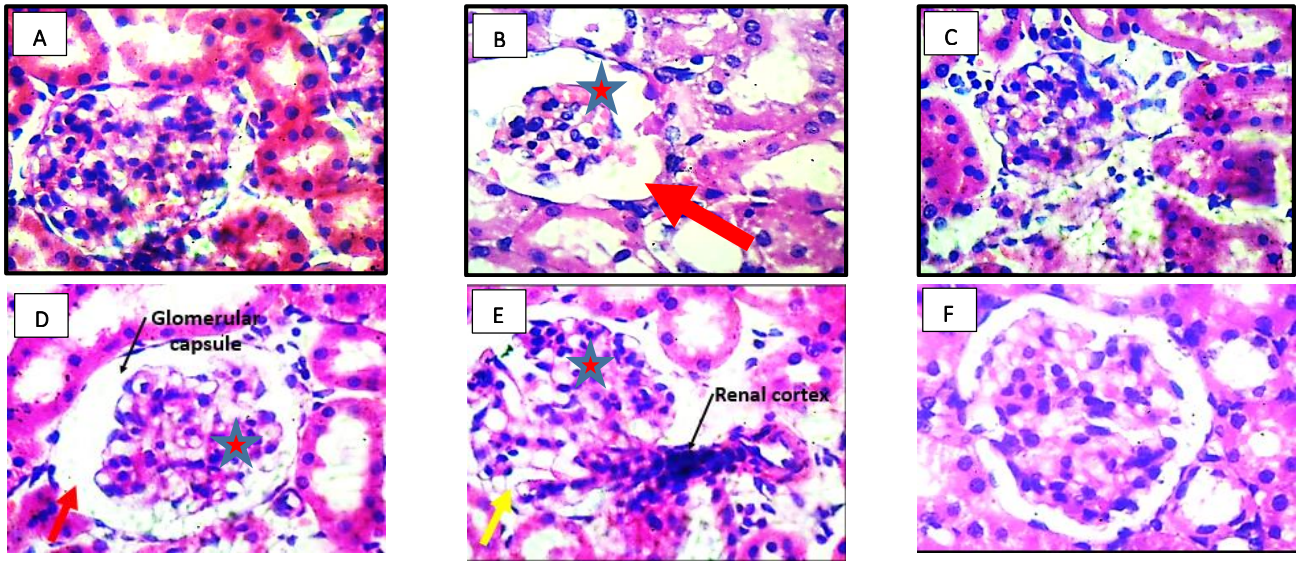

Figure 7. Histology section of kidney (H&E staining at x 400, scale bar: 100µm) showing the cortex,renal tubules, glomeruli, renal parenchymal cells, and mesangial cells across the treatment groups

Group A: The kidney shows normal micro-anatomical features. **Group B:** Animal treated with Cd only showed tubular necrosis,basal membrance disrution, glomeruli damage,inflamation and alterations in renal tubules (indicated by red arrow and star). **Group C:** The kidney appears normal, with normal microanatomical features. **Groups D & E:** Showed mild strutural alteration in the kidney microanatomy (indicated by yellow arrow and star). **Group F:** Showed a normal histology of the kidney with no signs of necrosis or distortion of the glomeruli and renal tubules.

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Conflict of interest

The authors confirm that there are no known conflicts of interest.

Statement of ethics

The current investigation adheres to the procedures established by the Institutional Animal Ethics Committee (IAEC) and the ARRIVE Guideline. Ethical approval for this study was obtained from the Research Ethics Committee of the College of Medicine, University Of Nigeria (2020-NNHREC/05/01/2008-FWA00002458-1RB00002323).

Availability of data and materials

All data generated or analyzed during this study are included in this published article. On request, the associated author can provide more information.

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CRediT authorship contribution statement

Augustine Oviosun: Research design, Resources, Investigation, Data collection, Original draft, Methodology
Godson Emeka Anyanwu: Research design, Supervision, Formal Analysis, Investigation, Methodology
Ezinne Chidinma Oviosun: Writing, Original Draft, Resources, Formal analysis
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Supplementary File

None.

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