ARTICLE | OPEN ACCESS

Drug Discovery

To Cite:
Edem G, David J, Okon K, Thompson H. Relationship between cadmium toxicity, kidney function disturbances and urinary bladder inflammation: The role of *Uvaria chamae* in mitigating these effects. *Drug Discovery* 2024; 18: e6dd1968
doi: https://doi.org/10.54905/disssi.v18i41.e6dd1968

Author Affiliation:
[1]Department of Human Anatomy, College of Health Sciences, University of Uyo, Uyo, Nigeria
[2]Department of Medical Physiology, College of Health Sciences, University of Uyo, Uyo, Nigeria

[*]**Corresponding Author**
Department of Human Anatomy, College of Health Sciences, University of Uyo, Uyo,
Nigeria

Peer-Review History
Received: 13 November 2023
Reviewed & Revised: 17/November/2023 to 29/January/2024
Accepted: 01 February 2024
Published: 05 February 2024

Peer-Review Model
External peer-review was done through double-blind method.

Drug Discovery
pISSN 2278–540X; eISSN 2278–5396

DISCOVERY
SCIENTIFIC SOCIETY

Relationship between cadmium toxicity, kidney function disturbances and urinary bladder inflammation: The role of *Uvaria chamae* in mitigating these effects

Gabriel Edem[1*], **Jessica David**[2], **Kingsley Okon**[1], **Hope Thompson**[1]

ABSTRACT

The aim of this study was to investigate the ameliorative effects of *Uvaria chamae* against cadmium-induced toxicity on the urinary bladder and kidney function biomarkers of Wistar rats, considering its recognized local health benefits. Twenty-five adults male Wistar rats weighing between 120g and 350g were assigned into five groups (5 per group). The groups were designated as follows: group 1 (control), rats received standard feed and distilled water; group 2, rats induced with 3mg/kg of cadmium; group 3, rats induced with 3mg/kg of cadmium and given 500mg/kg of extract; group 4, rats induced with 3mg/kg of cadmium and given 1000mg/kg of extract; group 5, rats induced with 3mg/kg of cadmium and given 1000mg/kg of extract; group 5, rats induced with 3mg/kg of cadmium and 1500mg/kg of extract. Cadmium was administered intraperitoneally once a week for four weeks based on the animals' body weight, while *Uvaria chamae* root extract was orally administered daily for twenty-eight days. After the last day of administration, the animals were sacrificed. Samples (comprising blood and urinary bladder tissues) were obtained for biochemical and histopathological analysis respectively. Kidney function biomarkers including serum urea, serum creatinine, and BUN were measured while thin sections of urinary bladder were processed for histopathological screening. The administration of cadmium resulted in urinary bladder damage, indicated by a significant ($P < 0.05$) increase in the assessed indices (serum urea, serum creatinine, and BUN) in the experimental animals when compared to the control animals. Remarkably, the administration of *Uvaria chamae* effectively restored the aforementioned changes to nearly normal levels in rats exposed to cadmium. Furthermore, this treatment ameliorated the histological derangements, including disorganized epithelium, hemorrhagic cystitis, tissue edema and detrusor muscle hypertrophy in the urinary bladder of the experimental rats caused by cadmium.

Thus, the potential therapeutic and ameliorative effects of *Uvaria chamae* extracts against toxicity induced by cadmium are evident.

Keywords: *Uvaria chamae*, urinary bladder, cadmium, toxicity, blood urea nitrogen, serum urea, serum creatinine

1. INTRODUCTION

Cadmium is a chemical element with an atomic number of 48. It is represented with the symbol "Cd". It was discovered in contaminated zinc compounds sold in pharmacies in Germany by Friedrich Stromeyer and Karl Samuel Leberecht Hermann simultaneously in 1817 as an impurity of zinc carbonate. It belongs to the group 12 element in d-block and period 5 with the electronic configuration [Kr] $4d^{10}$ $5s^2$ (Lide, 2005). Cadmium is a heavy metal that occurs as a natural constituent in the earth's crust along with copper, lead, nickel and zinc. The average concentration of cadmium in the earth's crust is between 0.1 and 0.5 parts per million (ppm). The most common cadmium mineral is greenockite. It can be found as a by-product from sulfide deposits, mainly those containing lead, zinc, and copper (Page and Bingham, 1973). Cadmium is a toxic metal and is hazardous to both humans and animals.

Humans are commonly exposed to cadmium by inhalation and ingestion. Cadmium enters the air and binds to small particles where it can combine with water or soil causing contamination of fish, plants and animals. The bioaccumulation of cadmium in the human body leads to acute and chronic intoxications. Adverse health effects of cadmium include diarrhea, stomach pains, bone fracture, reproductive failure, infertility, damage to the central nervous system and immune system, psychological disorders, etc. Cadmium has been extensively studied for its toxic effects on various organs, including the urinary bladder. Its exposure has been linked to urinary bladder inflammation, fibrosis, and an increased risk of urinary bladder cancer. The urinary bladder is part of the urinary system. It is a hollow, spherical-shaped organ and collapsible muscular sac located in the pelvis that stores urine temporarily.

Three openings are seen in the bladder and they are: The two openings of the ureter and a single opening of the urethra (Chummy, 2013). In males, the prostate gland surrounds the bladder's neck, where it empties into the urethra. The empty bladder is 5-7.5 cm long, while the full bladder is about 12.5cm long and holds about 500ml of urine, but it can hold more than thrice that amount (1500ml). It is the reservoir for urine received from the kidneys. Two sphincter muscles (circular muscles) help keep urine from leaking by closing tightly like a rubber band around the bladder's opening. The sensory nerves in the bladder wall relay information about its fullness to the brain, alerting a person when it is time to urinate or empty the bladder and prompting the conscious decision to initiate urination. The complex anatomy and functioning of the urinary bladder are essential for maintaining proper urinary function in the human body.

From time immemorial, medicinal plants have been used to treat, cure, and manage several ailments and one of such plant is *Uvaria chamae*. It is commonly known as finger root or bush banana and is a climbing medicinal plant that belongs to the family *Annonaceae* and genus *chamae*. The plant is commonly found in West Africa (Oluremi et al., 2010). *Uvaria chamae* is traditionally used to treat conditions such as bronchitis, gastroenteritis, amenorrhea, menorrhagia, abdominal pain, and wound healing. The plant contains bioactive compounds such as alkaloids, flavonoids, phenols, tannins, and saponins. Kidney function biomarkers are vital for diagnosing and monitoring various kidney conditions, including chronic kidney disease, acute kidney injury, kidney infections, and other renal disorders.

The choice of test may depend on the patient's specific symptoms and medical history and results are interpreted to determine the appropriate treatment and management. Understanding the histopathological changes in the urinary bladder induced by cadmium is essential. This can shed more light on the cellular and tissue-level modifications that occur in response to cadmium exposure, which may be helpful in understanding the mechanisms of toxicity. Study on the therapeutic properties of *Uvaria chamae* in the context of cadmium-induced bladder damage and its impact on kidney function biomarkers is limited. Kidney function test can provide helpful information about the effect of cadmium exposure and *Uvaria chamae* administration. Research on these aspects can help us understand whether *Uvaria chamae* has any therapeutic potential in alleviating the detrimental effects of cadmium on the urinary bladder and overall kidney function.

2. MATERIALS AND METHODS

Materials

Materials used in this study include the following: Twenty-five adult male Wistar rats, clean wooden cages, water bowls, standard feed, sawdust, masking tapes, temporary and permanent markers, iodine, electric weighing balance, insulin syringe, distilled water, cadmium, *Uvaria chamae* extract, big and small size plain sample bottles, and buffered formalin.

Collection and Extraction of *Uvaria chamae*

The roots of *Uvaria chamae* were collected from a local farm in Ikot Efre Itak in Ikono Local Government Area of Akwa Ibom State. They were ascertained and processed in the Department of Biochemistry, Faculty of Sciences, University of Uyo, Nigeria. The roots were washed and air-dried for some days. The roots were then grinded into fine powder using an electric blender and brewed in about 70% alcohol and then kept for 72 hours, after which they were filtered with the use of a filter paper. The filtrate was kept in a water bath to dry. The dry matter was weighed and preserved in a refrigerator for the experiment.

Preparation of Cadmium Solution and *Uvaria chamae* Root Extract

Cadmium was dissolved in sterile distilled water to ascertain the required concentration and was administered intraperitoneally. *Uvaria chamae* extract was reconstituted in distilled water to achieve the desired doses for the animal experiment.

Animals for the Experiment

Twenty-five adults male Wistar rats weighing between 120g and 350g were acquired from the animal house of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Uyo, Uyo. They were divided into five groups of five rats and maintained under standard environmental conditions with free access to water and standard feed. The cage beddings and water bottles were cleaned daily and the animals were allowed to adapt (acclimatized) for two weeks to the laboratory conditions before the beginning of the experiment. Acclimatization of the animals took place at the animal house of the Faculty of Basic Medical Sciences, University of Uyo, Nigeria. Group two to group five served as the experimental groups, while group one served as the control with the administration of just feed and water.

Administration of Cadmium and Extract

Cadmium was administered intraperitoneally once a week for four (4) weeks according to the body weight of the animals and the extract of *Uvaria chamae* was administered orally and daily for twenty-eight (28) days. The animals were divided into five groups (5 rats per group) arranged as follows:

Group one (control)- given standard feed and distilled water.

Group two- induced with 3mg/kg of cadmium.

Group three- induced with 3mg/kg of cadmium and given 500mg/kg of *Uvaria chamae* extract.

Group four- induced with 3mg/kg of cadmium and given 1000mg/kg of *Uvaria chamae* extract. Group five- induced with 3mg/kg of cadmium and given 1500mg/kg of *Uvaria chamae* extract.

Experimental Design

The rats were allowed to acclimatize for two weeks before the commencement of administration. The animals were marked and divided into five groups (1-5) of five (5) rats per group (Table 1).

Table 1 Grouping and Dosage of Administration

Groups	Dosage	Duration
Group one(control)	Feed + water	
Group two	3mg/kg of cadmium	Once weekly for four weeks
Group three	3mg/kg of cadmium + 500mg/kg of *Uvaria*	Once daily for four weeks +

	chamae	28 days respectively
Group four	3mg/kg of cadmium + 1000mg/kg of *Uvaria chamae*	Once daily for four weeks + 28 days respectively
Group five	3mg/kg of cadmium + 1500mg/kg of *Uvaria chamae*	Once daily for four weeks + 28 days respectively

Histological Studies

At the end of the experiment, the animals were sacrificed. The urinary bladder was harvested and fixed in 10% buffered formalin. The tissues were processed and stained using hematoxylin/eosin dye. The tissue sections were viewed under a Primo star microscope (3150012146).

Determination of Kidney Function Parameters

Blood sample was taken into plain sample bottles and centrifuged for about 15 minutes to obtain the serum. Serum was used to analyze the following kidney function biomarkers: serum creatinine, serum urea, and blood urea nitrogen.

Statistical Analysis

Data obtained was expressed as mean ± SEM and statistically analyzed using one-way analysis of variance (ANOVA) with the help of GraphPad Prism statistical software (version 8.0.2). $P< 0.05$ was considered statistically significant.

3. RESULTS

Effects of *Uvaria chamae* Extract on the levels of kidney Function Biomarkers in Cadmium-Induced Adult Male Wistar Rats

The administration of cadmium resulted in elevated levels of serum creatinine (SC), serum urea (SU), and blood urea nitrogen (BUN). The results showed that *Uvaria chamae* extract dose-dependently reduced the serum levels of these parameters (Table 2).

Table 2 Effects of *Uvaria chamae* Extract on the levels of kidney Function Biomarkers in Cadmium-Induced Adult Male Wistar Rats

Groups	SC (mg/dl)	SU (mg/dl)	BUN (mg/dl)
Control	0.89 ± 0.03	30.05 ± 0.97	14.10 ± 1.47
3mg/kg Cd	1.79 ± 0.03#	54.39 ± 0.70#	24.05 ± 0.28#
500mg/kg UC	1.65 ± 0.00	46.28 ± 0.31	21.71 ± 0.30
1000mg/kg UC	1.45 ± 0.02**	44.77 ± 0.23**	19.27 ± 0.15**
1500mg/kg UC	1.41 ± 0.02**	39.95 ± 0.62**	16.47 ± 0.24**

Values are expressed as mean ± standard error of mean, Cd- cadmium, UC- *Uvaria chamae*, SC- serum creatinine, SU- serum urea, BUN-blood urea nitrogen

** indicates a significant difference between group two and other treated groups @p<0.05.

#indicates a significant difference between control and other treated groups.

Hematoxylin and Eosin Method for General Demonstration of the Urinary Bladder

The urinary bladder of the control animals given feed and water, showed a well-defined urothelium with transitional epithelium, lamina propria with blood vessels, detrusor muscle layer, and normal lumen (Plate 1). The urinary bladder of group two animals given 3mg/kg of cadmium only for four weeks showed a disorganized epithelium, hemorrhagic cystitis, tissue edema, and detrusor muscle hypertrophy (Plate II). The urinary bladder of group two animals was severely affected due to inflammation. The urinary bladder of group three animals given 3mg/kg of cadmium for four weeks and 500mg/kg of *Uvaria chamae* extract for 28 days, showed a well-defined urothelium, reduced tissue edema but with the presence of detrusor hypertrophy in the muscle layer (Plate III). This indicated the commencement of the healing process.

The urinary bladder of group four animals given 3mg/kg of cadmium for four weeks and 1000mg/kg of *Uvaria chamae* extract for 28 days showed a well-defined urothelium, reduced tissue edema and reduced detrusor muscle hypertrophy (Plate IV). This indicated the progression of the healing process. The urinary bladder of group five animals given 3mg/kg of cadmium for four weeks and 1500mg/kg of *Uvaria chamae* extract for 28 days showed a well-defined urothelium, absence of tissue edema in the lamina propria, and non-hypertrophied detrusor muscle. Here, the healing process was completed (Plate V).

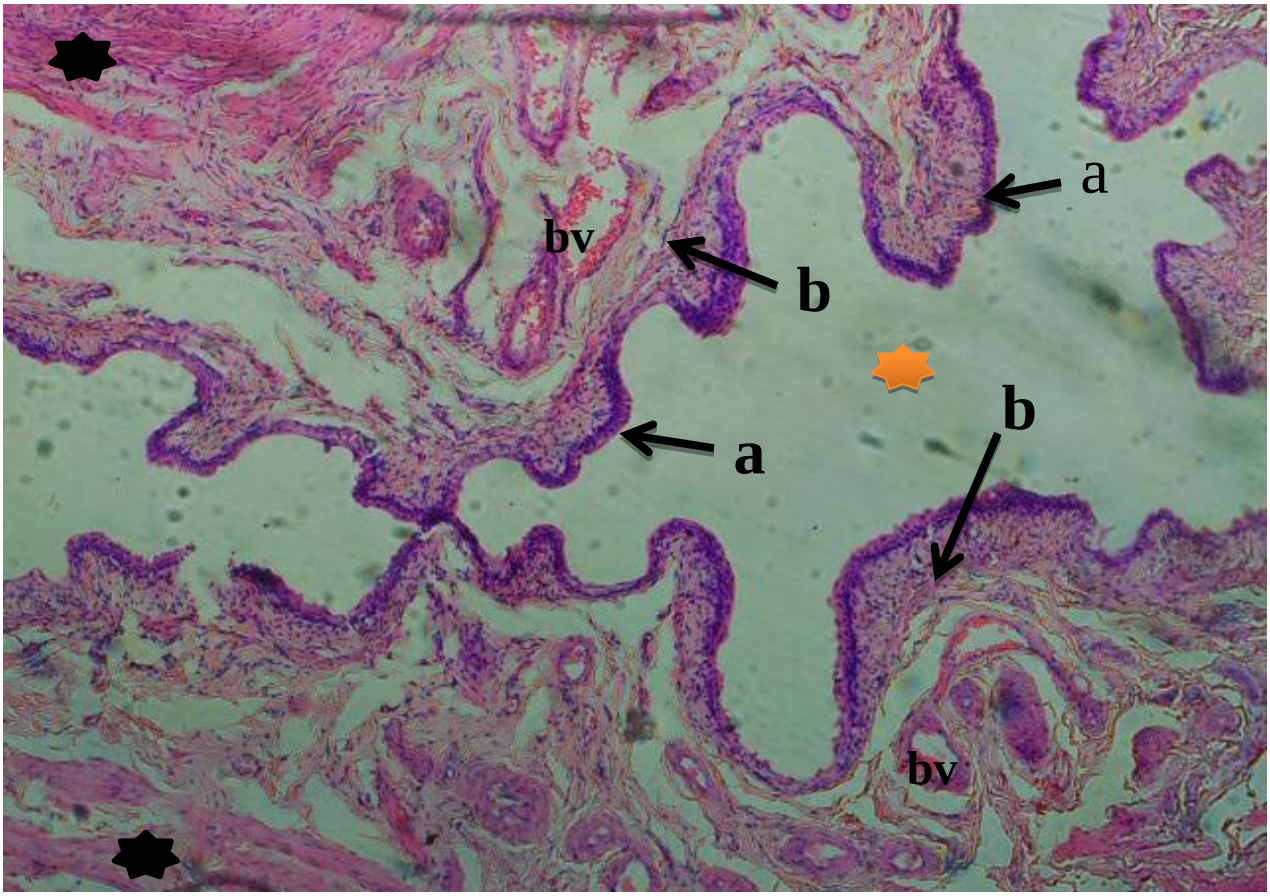

Plate I Photomicrograph of the urinary bladder of control animals given water and feed alone (H & E) showing, well-defined urothelium with transitional epithelium (a), lamina propria with blood vessels (b), detrusor muscle layer (black star) and the lumen (yellow star). x100 magnification. Inference: Normal histology.

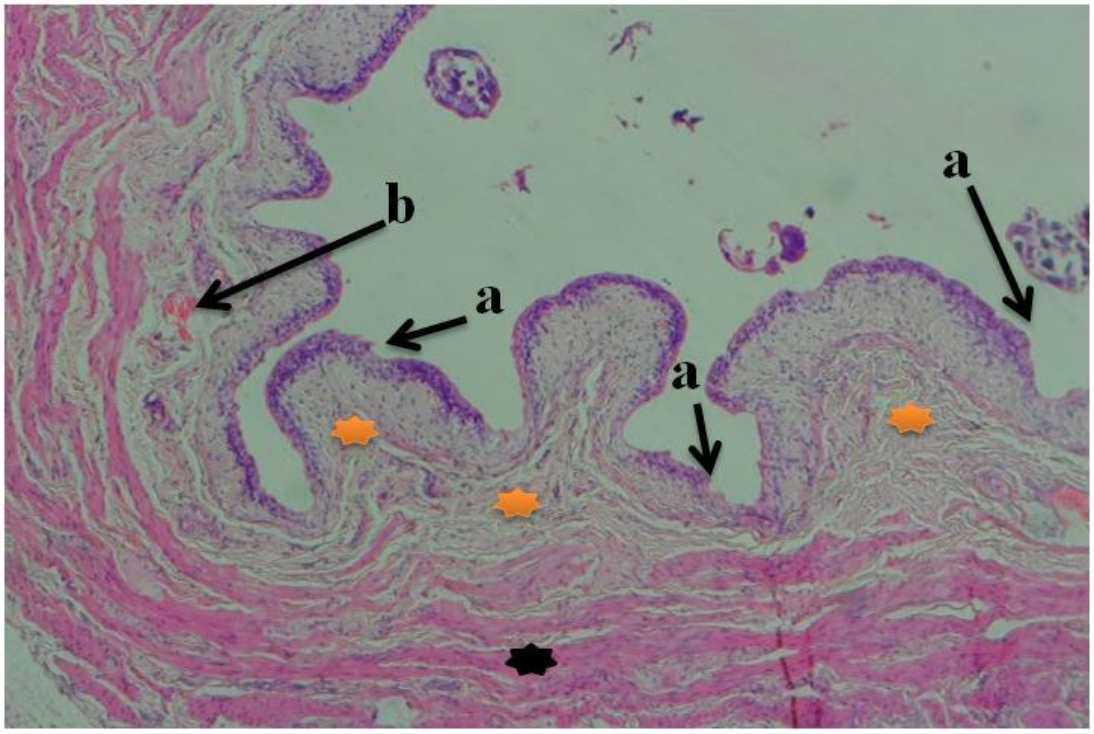

Plate II Photomicrograph of the urinary bladder of group 2 animals given 3mg/kg of cadmium alone for four weeks (H & E) showing, disorganized epithelium (a), hemorrhagic cystitis (b), tissue edema (yellow star) and detrusor muscle hypertrophy (black star). x100 magnification. Inference: Severely affected due to inflammation

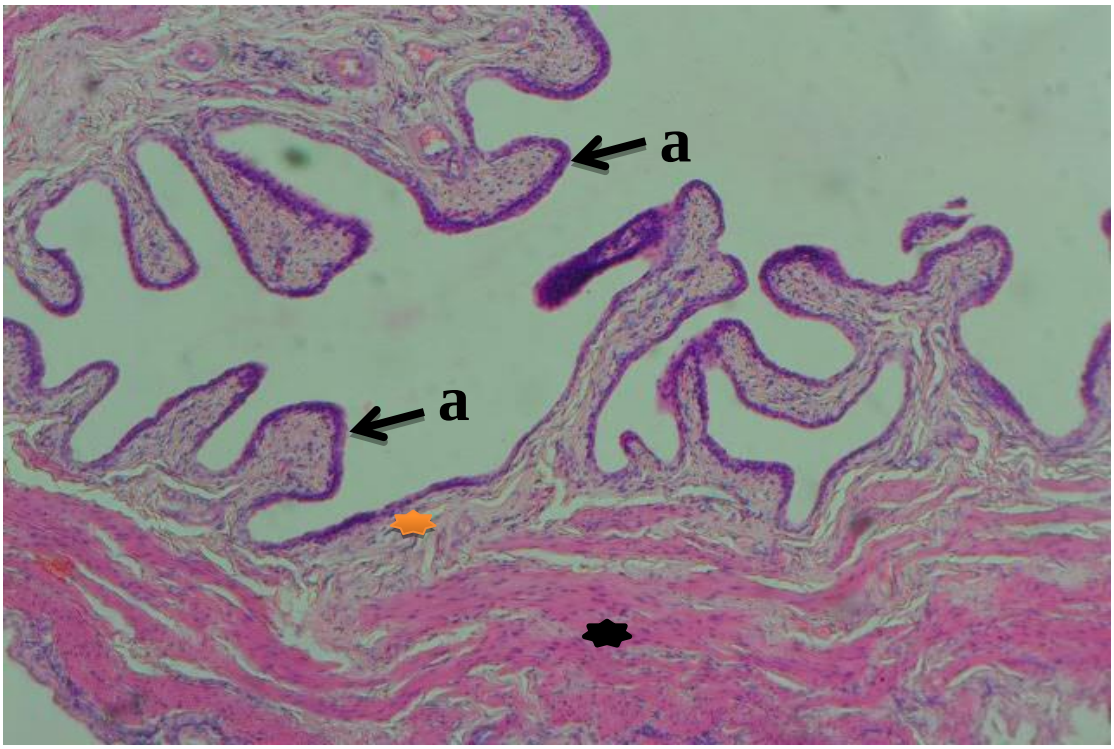

Plate III Photomicrograph of the urinary bladder of group 3 animals given 3mg/kg of cadmium alone for four weeks and 500mg/kg of *Uvaria chamae* for 28 days (H & E) showing, well-defined urothelium (a), reduced tissue edema (yellow star) but with the presence of detrusor hypertrophy in the muscle layer (black star). x100 magnification. Inference: Initiation of the healing process

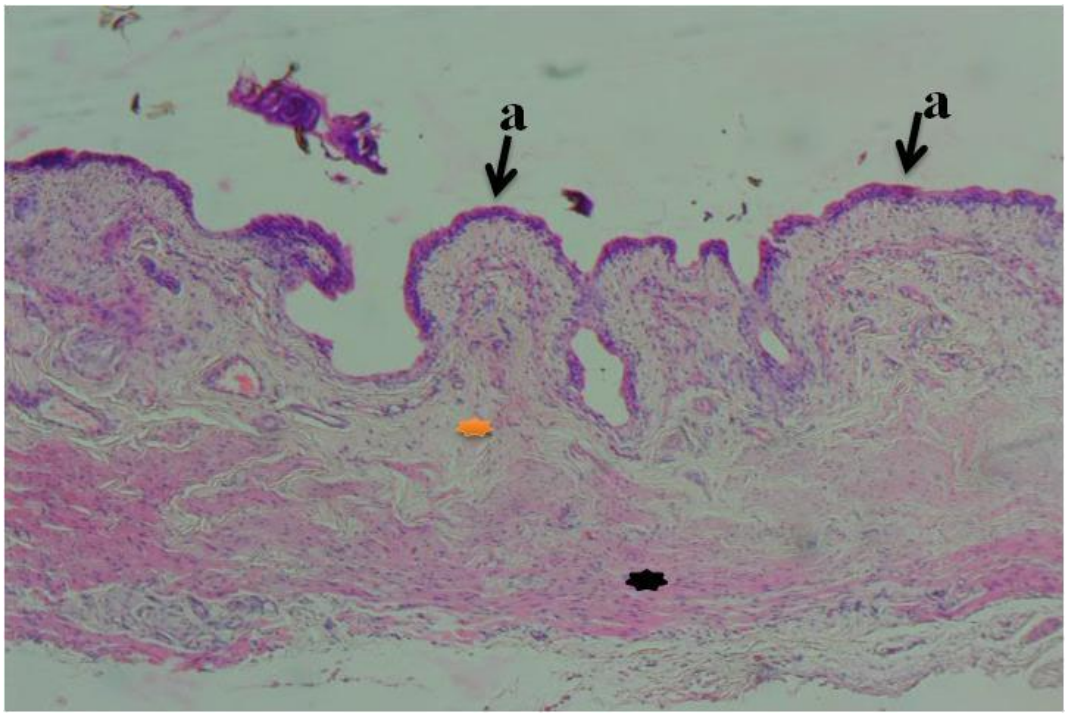

Plate IV Photomicrograph of the urinary bladder of group 4 animals given 3mg/kg of cadmium alone for four weeks and 1000mg/kg of *Uvaria chamae* for 28 days (H&E) showing, well-defined urothelium (a), reduced tissue edema (yellow star) and reduced detrusor muscle hypertrophy (black star). x100 magnification. Inference: Progression of the healing process

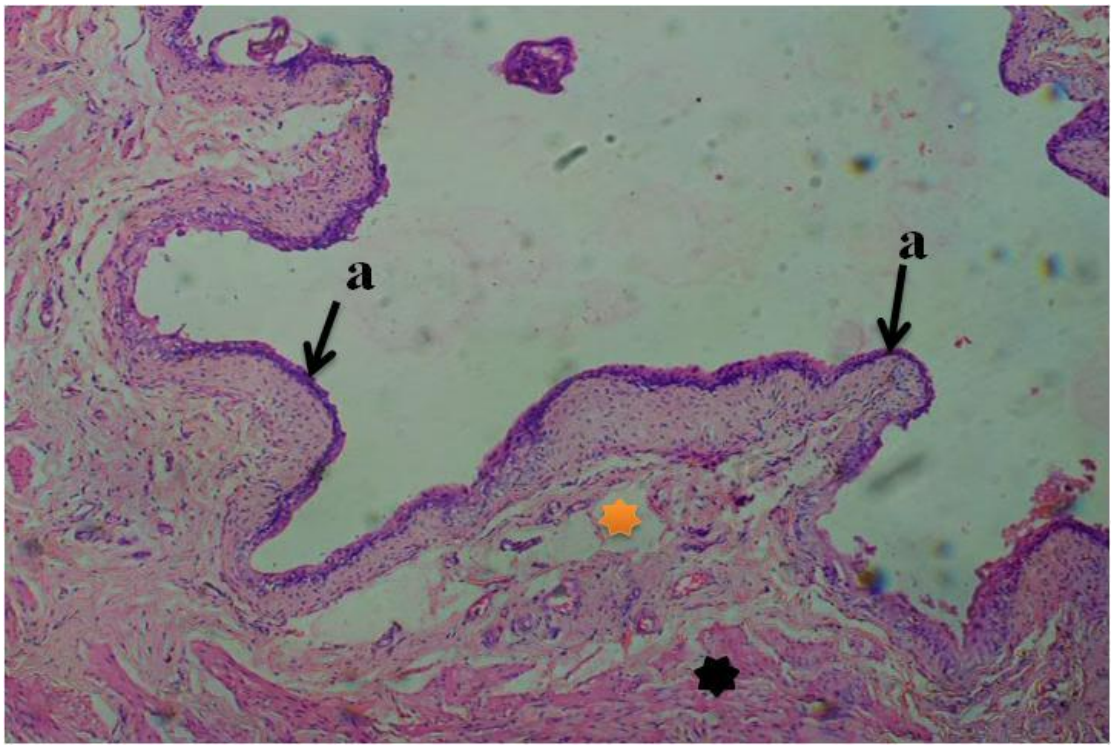

Plate V Photomicrograph of the urinary bladder of group 5 animals given 3mg/kg of cadmium alone for four weeks and 1500mg/kg of *Uvaria chamae* for 28 days (H & E) showing, well-defined urothelium (a), absence of tissue edema in the lamina propria (yellow star) and non-hypertrophied detrusor muscle (black star). x100 magnification. Inference: Completion of the healing process.

4. DISCUSSION

This study evaluated the effect of cadmium on the urinary bladder and kidney function parameters of Wistar rats and the role of *Uvaria chamae* in mitigating these effects. Cadmium is a known contaminant that poses a risk to human health. Nearly everyone in the universe is exposed to this contaminant through food supply, and it accumulates in the body over a lifetime. Ingestion of cadmium poses a major concern as it is a nonessential trace element that does not play a role in the growth of humans or plants but is toxic to humans (Clemens et al., 2013; EFSA, 2009; Khan et al., 2017; Smolders, 2001). Cadmium toxicity is contingent on exposure route, quantity, and rate. In humans, the kidney bears the brunt of toxic effects, particularly the S1 segment of the proximal tubule. This region becomes a major site for cadmium deposition, manifesting clinically as defects in the reabsorption of proteins, amino acids, glucose, bicarbonate, and phosphate. This condition is collectively termed Fanconi syndrome.

These defects arise from cadmium-induced oxidative damage to transport proteins and mitochondria, potentially triggering apoptosis of tubular cells (Thévenod, 2003; Sabath and Robles-Osorio, 2012). Cadmium could also hinder the metabolism of Vitamin D in the kidney, leading to adverse effects on bone (Kjellstrom, 1992). This combined with cadmium's direct interference with the absorption of calcium in the gut and disruption of collagen metabolism, may result in osteomalacia and, or osteoporosis (Nordberg et al., 2007). A notable manifestation of this sequence is itai-itai disease in Japan, characterized by intense pain from osteomalacia, osteoporosis, renal tubular dysfunction, anemia, and calcium malabsorption (Ogawa et al., 2004). In contrast, *Uvaria chamae* is a plant with arrays of medicinal and therapeutic properties. It is a plant that has both medicinal and nutritional values. The root barks, stem barks, and leaves are extensively used because of their medicinal properties.

The root bark is employed in treating respiratory catarrh, and in phytomedicine, the root extract proves beneficial for addressing ailments like piles, menorrhagia, epistaxis, hematuria, and hemolysis (Oliver, 1986). The root extract serves to alleviate abdominal pains, while the juice extracted from roots, stems, or leaves is commonly applied to wounds or sores and this helps in promoting swift and effective healing (Irvin, 1961). Also, in Sierra Leone and Nigeria, the root is renowned for its purgative and febrifugal properties. In traditional medicine, concoctions of roots, barks, and leaves are used to address and treat various ailments such as gastroenteritis, vomiting, diarrhea, dysentery, wounds, sore throats, inflamed gums, etc. Studies on the root extract of *Uvaria chamae* showed the presence of bioactive components comprising of flavonoids, alkaloids, tannins, saponins and phenols (Okwu and Iroabuci, 2009; Olufunmilayo et al., 2010).

Bioactive compounds, particularly flavonoids, form the core of *U. chamae's* medicinal properties in Nigerian herbal medicine. Their diverse biological functions, encompassing protection against allergies, platelet aggregation, microbes, ulcers, viruses, and tumors, underscore the significance of these compounds. By impeding the enzymes involved in estrogen production, flavonoids lower the risk of estrogen-induced cancers. Moreover, specific flavonoids exhibit robust protective properties against inflammatory disorders and decrease edema formation, suppress the synthesis of prostaglandin E2 as well as thromboxane B2. Okwu and Iroabuchi, (2009) found that the root extract of *U. chamae* exhibits a higher concentration of flavonoids than alkaloids, tannins, saponins, and phenols. Alkaloids are nerve stimulants, convulsants and muscle relaxant.

The abundant presence of saponins and tannins in *U. chamae* roots may contribute to the plant's hemostatic activity, potentially arresting bleeding from damaged or injured vessels through the precipitation of proteins to form vascular plugs. Indicative of its diverse potential, the plant contains phenols that may serve as anti-clotting agents, antioxidants, immune enhancers, and hormone modulators. Extensive research has focused on phenols as bioactive compounds employed in disease prevention (Duke, 1992). Phenols exhibit the capability to inhibit specific enzymes associated with inflammatory disorders and modify prostaglandin pathways, safeguarding platelets from clumping (Duke, 1992). The ethanolic extract from *Uvaria chamae* roots exhibited significant anti-inflammatory properties in the urinary bladder, possibly attributed to the presence of bioactive compounds like flavonoids, saponins, and phenolic compounds (Okwu and Iroabuchi, 2009).

This current study aimed to evaluate the potency of *Uvaria chamae* extract at different doses against cadmium-induced urinary bladder toxicity and disturbances in the kidney function biomarkers. Evaluating kidney function relies on blood chemistry analyses, specifically measuring concentrations of serum urea, serum creatinine, and blood urea nitrogen (BUN), which are widely employed for this purpose. Serum urea, serum creatinine, and blood urea nitrogen serve as established clinical indicators reflecting the physiological and functional status of the kidneys, each with its defined normal concentration range. Any deviation from these values is considered

indicative of kidney morbidity. Our findings, which are consistent with Bekheet et al., (2011), indicate that exposure to cadmium resulted in significant ($p< 0.05$) increases in the concentrations of the mentioned indices (serum urea, serum creatinine, and blood urea nitrogen) when compared to the control group.

Wang et al., (2009) supported these findings by documenting that cadmium toxicity induces tubular necrosis, loss of the brush border, and damage in the small tubules of the kidney. Additionally, the increase in serum urea and serum creatinine due to cadmium toxicity may be linked to disturbances in protein catabolism, a consequence of elevated synthesis of the arginase enzyme involved in urea production (Tormanen, 2006). In assessing kidney function, creatinine, a by-product of creatine phosphate in muscles, assumes a crucial role. Produced consistently by the body, creatinine is predominantly cleared from the bloodstream by the kidneys. As the foremost endogenous marker, creatinine holds significant importance in evaluating glomerular function (Lujambio et al., 2014). Estimating the glomerular filtration rate (GFR) is the clinically preferred method for assessing renal function, representing the rate (mm/min) at which substances are filtered or cleared from the blood through the kidney glomerulus.

During the study, it was evident that the cadmium-induced rats experienced a substantial elevation in serum creatinine concentration compared to the control group. Remarkably, *Uvaria chamae* treatment appears to boost the kidney's capacity to inhibit creatinine buildup in the bloodstream, suggesting a potential ameliorative role against cadmium-induced damage in rat bladder thus, affecting the overall kidney function. Serum urea is the final metabolite of protein nitrogen balance, these measurements which permit the assessment of the overall metabolism of proteins and amino acids through the exclusive hepatic urea cycle. Once in the bloodstream, urea is predominantly excreted by the kidneys. After undergoing glomerular filtration, a substantial percentage, varying between 40% and 60%, is reabsorbed at the tubular level, establishing it as a marker for renal function. Serum urea concentration increases with reduced glomerular filtration rate (GFR), and vice versa.

This means that serum urea increases in conditions where renal clearance decreases due to renal impairment. In this study, it was observed that cadmium-induced rats showed heightened serum urea levels compared to the control group, suggesting potential kidney damage. Similar to serum creatinine and serum urea, BUN significantly increased in rats induced with cadmium, indicating renal disturbances. Blood Urea Nitrogen (BUN) denotes the nitrogen content, primarily in the form of urea, circulating in the bloodstream. In the case of healthy animals, the renal glomerulus filters urea from plasma. Although some urea returns to the blood through renal tubules, the major route of elimination is through urine. If the kidney is not operating effectively, it results in insufficient removal of urea from plasma, causing elevated BUN levels that vary in response to various physiological conditions like increased protein intake, intestinal bleeding, infection, fever, dehydration, medications, burns, and poisoning (Levey, 1990).

This study revealed a significant improvement in kidney function through the administration of ethanolic extract of *Uvaria chamae* at doses of 500, 1000, and 1500 mg/kg respectively. The observed effects included decreased levels of serum urea and serum creatinine, along with a reduction in BUN. Remarkably, *Uvaria chamae* treatment appears to boost the kidney's capacity to inhibit creatinine buildup in the bloodstream, suggesting a potential ameliorative role against cadmium-induced damage in the urinary bladder, thus, affecting the overall renal function. It also indicates that *Uvaria chamae* has the potential to enhance renal function in experimental animals by curbing the increase in serum urea and BUN levels. The ameliorative effect of *Uvaria chamae* extract was related to the antioxidant and biological activities of its bioactive compounds.

Our study is in support of the findings of Okwu and Iroabuchi, (2009), and Olufunmilayo et al., (2010), who showed the anti-inflammatory effects of *Uvaria chamae* extract was attributed to the presence of bioactive compounds comprising of flavonoids, alkaloids, tannins, saponins and phenols. The histopathological findings in this study align with the observations of Romaniuk et al., (2017), which demonstrated significant morphological changes in the tissue wall structures of the urinary bladder caused by heavy metal salts. The study reveals a buildup of cadmium in urinary bladder tissue, providing an explanation for the observed histological alterations. According to studies by Feki-Tounsi and Hamza-Chaffai, (2014) and Golabek et al., (2009), bladder cancer tissues exhibited statistically elevated cadmium concentrations compared to those in control animals. Due to the kidneys' function of expelling toxic substances, such as metal salts, through urine, heavy metals can be held in the bladder, leading to their accumulation in its walls and potentially causing impairment of its function, indicating the detrimental effects of excessive heavy metal exposure on the urinary bladder.

Concerning the histological modifications observed in the urinary bladder, rats induced with cadmium showed disorganized epithelium, hemorrhagic cystitis, tissue edema, and detrusor muscle hypertrophy. Lining the walls of the urinary bladder is a specialized stratified epithelium called the urothelium. The urothelium appeared rough and scattered due to cadmium induction. There

was damage to the inner lining of the bladder and the blood vessels that supply blood to the bladder. The bladder was shown to be inflamed, and blood was seen in the lining of the bladder. The tissue of the bladder appeared swollen due to fluid accumulation caused by leakage of blood vessels in the bladder. The fibres of the detrusor muscle of the bladder were hypertrophic (presenting as prominent trabeculae) to compensate for increased workload of the bladder emptying. This is very common in conditions that obstruct the urine outflow, such as benign prostatic hyperplasia. The urinary bladder was severely affected due to inflammation caused by cadmium toxicity.

The pathogenesis of chemical-induced bladder damage hinges on oxidative damage, where free radicals play a central role in the mechanisms leading to urinary bladder toxicity. The study suggests that cadmium inflicted considerable bladder impairments on experimental rats, while *Uvaria chamae* alleviated the damage caused by cadmium. This claim was supported by examining photomicrographs from the histopathological analysis of bladder sections taken from control and experimental animals. Histological examinations revealed enhanced bladder tissues, aligning with improved kidney functional markers. This correlation strongly supports the potential ameliorative effect of *Uvaria chamae* against cadmium-induced bladder toxicity. This study conclusively reveals that, the administration of *Uvaria chamae* at 500, 1000, and 1500 mg/kg doses respectively, significantly impedes cadmium-induced toxicity and shields against damage to bladder tissue. This correlation may be linked to the anti-oxidative and chelating properties of bioactive compounds, including flavonoids, alkaloids, tannins, saponins and phenols present in *Uvaria chamae*.

5. CONCLUSION

In conclusion, the study suggests that *Uvaria chamae* played ameliorative role in shielding experimental rats from cadmium-induced bladder toxicity. This plant-based product, *Uvaria chamae*, may offer a certain degree of therapeutic efficacy against acute or bladder impairments in humans. Thus, the ethanolic extract of *Uvaria chamae* can be a potential remedy for alleviating toxicity induced by cadmium.

Author's Contribution

All authors were actively involved from the commencement of the work till the completion. They were involved in the work design, execution, interpretation, writing and editing of the manuscript.

Acknowledgement

We sincerely want to appreciate the laboratory staff for their technical support and assistance.

Ethical Approval

The animal ethical guidelines were closely followed in this study for experimentation as per the animal regulations of Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Uyo, Nigeri. The ethical guidelines for plants & plant materials are followed in the study for species collection, identification & experimentation.

Informed consent: Not applicable.

Conflicts of interests: The authors declare that there are no conflicts of interests.

Funding: The study has not received any external funding.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES

1. Bekheet SH, Awadalla EA, Salman MM, Hassan MK. Bradykinin potentiating factor isolated from *Buthus occitanus*

venom has a protective effect against cadmium induced rat liver and kidney damage. Tissue cell 2011; 43(6):337-343. doi: 10.1016/j.tice.2011.07.001
2. Chummy SS. Last's anatomy: regional and applied, 12th edn. Ann R Coll Surg Engl 2013; 95(3):230
3. Clemens S, Aarts M, Thomine S, Verbruggen M. Plant science: The key to preventing slow cadmium poisoning. Trends Plant Sci 2013; 18(2):92-9. doi: 10.1016/j.tplants.2012.08.003
4. Duke JN. Handbook of biological active phytochemicals and their activities. CRC Press, BICA Ration (FL) 1992; 99-131.
5. European Safety Authority (EFSA). Scientific opinion of the panel on contaminants in the food chain on a request from the European commission on cadmium in food. EFSA J 2009; 980: 1-139.
6. Feki-Tounsi M, Hamza-Chaffai A. Cadmium as a possible cause of bladder cancer: a review of accumulated evidence. Environ Sci Pollut Res Int 2014; 21(18):10561-73. doi: 10.1007/s 11356-014-2970-0
7. Golabek T, Darewicz B, Borawska M, Markiewicz R, Socha K, Kudelski J. Lead concentration in the bladder tissue and blood of patients with bladder cancer. Scand J Urol Nephrol 2009; 43 (6):467-470. doi: 10.3109/00365590903198991
8. Irvin FR. Woody plants of Ghana with Special Reference to their Uses. Oxford University Press, London 1961; 143-144.
9. Khan M, Khan S, Khan A, Alam M. Soil contamination with cadmium, consequences and remediation using organic amendments. Sci Total Environ 2017; 601-602:1591-1605. doi: 10.1016/j.scitotenv.2017.06.030
10. Kjellstrom T. Mechanism and epidemiology of bone effects of cadmium. IARC Sci Publ 1992; (118):301-10.
11. Levey AS. Measurement of renal function in chronic renal disease. Kidney Int 1990; 38(1):167-84. doi: 10.1038/ki.1990
12. Lide DR. Magnetic susceptibility of the elements and inorganic compounds. CRC Handbook of Chemistry and Physics 86th edition. Boca Raton (FL): CRC Press. ISBN 0-8493-0486-5 2005.
13. Lujambio I, Sottolano M, Luzardo L, Robaina S, Krul N, Thijs L, Carusso F, da-Rosa A, Ríos AC, Olascoaga A, Garau M, Gadola L, Noboa O, Staessen JA, Boggia J. Estimation of glomerular filtration rate based on serum cystatin C versus creatinine in a Uruguayan population. Int J Nephrol 2014; 9. doi: 10.1155/2014/837106
14. Nordberg GF, Nogawa K, Nordberg M, Friberg L. Cadmium. In: Nordberg GF, Fowler BF, Nordberg M, Friberg L, editors. Chapter 23 in Handbook of the Toxicology of Metals. 3rd edition. Amsterdam, The Netherlands: Elsevier; 2007; 479.
15. Ogawa T, Kobayashi E, Okubo Y, Suwazono Y, Kido T, Nogawa K. Relationship among prevalence of patients with Itai-itai disease, prevalence of abnormal urinary findings, and cadmium concentrations in rice of individual hamlets in the Jinzu River basin, Toyama prefecture of Japan. Int J Environ Health Res 2004; 14(4):243-52. doi: 10.1080/09603120410001725 586
16. Okwu DE, Iroabuci F. Phytochemical Composition and Biological Activities of Uvaria *chamae* and *Clerodendoron splendens*. E-J Chem 2009; 6(2):553-560.
17. Oliver B. Medicinal plants in Tropical West Africa. Cambridge University Press, Cambridge 1986; 117-168. doi: 10.1017/cbo9 780511753114
18. Olufunmilayo EA, Adelodun LK, Oladimeji PR, Lateef SK. In vitro antisickling activities and phytochemical evaluation of *Plumbago zeylanica* and *Uvaria chamae*. Afr J Biotechnol 2010; 9 (53):9032-9036. doi: 10.5897/AJB10.521
19. Oluremi BB, Osungunna MO, Omafuma OO. Comparative assessment of antibacterial activity of *Uvaria chamae* plants. Afr J Microbiol Res 2010; 4(13):1391-1394.
20. Page AL, Bingham FT. Cadmium residues in the environment. Residue Rev 1973; 48(0):1-44. doi: 10.1007/978-1-4615-8498-8_1
21. Romaniuk A, Sikora V, Lyndin M, Smiyanov V, Sikora V, Lyndina Y, Piddubnyi A, Gyryavenko N, Korobchanska A. The features of morphological changes in the urinary bladder under combined effect of heavy metal salts. Interv Med Appl Sci 2017; 9(2):105-111. doi: 10.1556/1646.9.2017.2.09
22. Sabath E, Robles-Osorio ML. Renal health and the environment: heavy metal nephrotoxicity. Nefrologia 2012; 32(3):279-86. English, Spanish. doi: 10.3265/Nefrologia.pre201 2.Jan.10928
23. Smolders E. Cadmium uptake by plants. Int J Occup Med Environ Health 2001; 14(2):177-83
24. Thévenod F. Nephrotoxicity and the proximal tubule: insights from Cadmium. Nephron Physiol 2003; 93(4):87-93. doi: 10.1 159/000070241
25. Tormanen CD. Inhibition of rat liver and kidney arginase by cadmium ion. J Enzyme Inhib Med Chem 2006; 21(1):119-23. doi: 10.1080/14756360500483420
26. Wang L, Chen D, Cao J, Liu Z. Protective effect of N-acetylcysteine on experimental chronic cadmium nephrotoxicity in immature female rats. Hum Exp Toxicol 2009; 28(4):221-9. doi: 10.1177/0960327109102365