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Histological evaluation of the liver, kidney, and testes of adult male Wistar rats exposed to heavy metals-contaminated waterways

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Abstract

Background: Human activities continually impact the environment negatively. Some activities are particularly linked to river pollution, and this constitutes a major problem in certain regions of Nigeria. This is a result of economic development, anthropogenic human activities, and agricultural practice that have the potential for adverse health effects. This study evaluated the effect of heavy metals acquired from the waterways on the vital organs of experimental rats.

Methods: Seventy (70) adult male Wistar rats, average weighing between 150-180g, were divided into seven groups of ten animals, each selected by simple randomization. Pooled sampled water and water containing the highest average concentration of singly and combined heavy metals noted in the waterways from three geological zones in Kwara state, Nigeria, were respectively given to the Wistar rats within the treatment groups ad libitum for 65 days. The kidney, liver, and testes were harvested and processed for paraffin embedding, and the effect of the heavy metals was histologically assessed.

Results: Histological staining revealed variable histopathological alterations in the kidney, liver, and testes of rats in the treatment groups in comparison to the control group.

Conclusion: Increased levels of heavy metals in waterways can adversely affect the organs when used for household purposes. Activities in these water bodies must be checked by regulatory agencies, and laws to discriminate against the dumping of waste in water bodies should be enforced.

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Introduction

Water plays an important role in the survival of all organisms, including humans, for food production and economic development (1). Human activities have negatively impacted the environment by introducing toxic waste to the environment via large amounts of heavy metal pollutants, which are being discharged through rivers or via atmospheric deposition into the aquatic environment (2,3). Various activities of humans connected to urbanization, population growth, industrial production, climate change, and other factors reportedly impact the quality of water and often result in water pollution, which is deleterious to the well-being of humans (1). Heavy metals can be derived from natural geological sources or anthropogenic sources, which include smelting, mining, agriculture, aquaculture, and industrial sewage (4). Heavy metals negatively impact the marine environment due to their biotoxicity and non-degradability (5,6). Non-essential metals such as cadmium (Cd) have also been implicated in hurting the growth and development of organisms at low levels (6,7). Heavy metals in the aquatic environment can bioaccumulate in aquatic organisms and biomagnify through the food chain (8). Regular consumption of dietary seafood remains a major route through which heavy metals are absorbed in humans, and the exposure to which is associated with various health problems, including organ damage, endocrine disruption, cancer, and neurological impacts (9). Akinola and Ekiyoyo (10) previously reported Cd pollution along River Ribila located in Odo-nla village off Sagamu road, Ikorodu, Lagos State, Nigeria (10). Haque et al. (11) also reported pollution in the Ganges River, China (11). Soil contamination with heavy metals can ultimately lead to soil pollution and the cultivated plants that are a ready food source for humans as well as other organisms in the food chain. The release of garbage, sewage, and oil spills, regardless of their assimilative capabilities, continually threatens the quality of water in urban environments, and the increased industrial wastes from factories constitute significant sources of toxic pollutants to the water body (12). Food contamination remains a major route of exposure to heavy metals, and increasing dietary heavy metals have been implicated in the development of several diseases, especially after several years of exposure (13). The monitoring of river water quality is important, especially when habitant utilizes water for household purposes such as drinking, cooking, and bathing (14). This study evaluated the effect of heavy metals acquired from the waterways on the vital organs of experimental rats. Furthermore, histopathological analysis was conducted on the kidneys, liver, and testes of adult male Wistar rats upon chronic administration of water from the rivers.

Methods

A cross-sectional surveillance and animal experimentation type of study was conducted. The frequency or prevalence of heavy metal contamination was obtained as the empirical measurement, which enabled the collection of data and provided a basis for making a conclusion, which was then used in the animal experimentation study comprising both control and treatment groups.

Ethical statement

The experimental protocol and procedures used in this study were approved by the College of Medicine Research Ethics Committee, Directorate of Research and Publications, College of Medicine, University of Nigeria, Enugu Campus, State, Nigeria, with protocol number 025/02/2017. This approval is consistent with those set down by the National Institute of Health (NIH) in the “Guide to the Care and Use of Animals in Research and Teaching” (15).

Measurement of heavy metals

Lead (II) acetate trihydrate (Pb(CH3CO2).3H2O), Mercury (II) thiocyanate (Hg(SCN)2), Cadmium acetate dehydrate (Cd(CH3CO2).2H2O), Chromium (III) oxide (Cr2O3) were procured from Sigma-Aldrich (USA). 0.009 g of Pb(CH3CO2).3H2O, 0.001 g of Hg(SCN)2, 0.045 g of Cd(CH3CO2).2H2O and 0.318 g of Cr2O3 were weighed using Meltler sensitive weighing balance and dissolved in 1 liter of double-distilled demineralized water to form 0.009 mg of Pb(CH3CO2).3H2O, 0.001 mg of Hg(SCN)2, 0.045 mg of Cd(CH3CO2).2H2O and 0.318 mg of Cr2O3 per liters solutions, respectively. This was based on the empirical measurement of heavy metals obtained in the waterways of the study area and reported by Adeniyi et al. (16).

Animals and diet

Seventy (70) first filial (F1) generations inbred adult male Wistar rats (Rattus norvergicus) with an average weight of about 150-180 grams were procured from the Institute for Advanced Medical Research and Training (IAMRAT), College of Medicine, University of Ibadan, Nigeria. They were allowed to acclimatize for 14 days and were fed with pelletized rat feed and water ad libitum throughout acclimatization before use. The rats were housed in plastic cages. They were kept in standard laboratory conditions under a natural light-dark cycle at room

temperature and maintained on standard laboratory rat pellets and given water ad libitum. Seventy (70) rats were divided into seven groups of ten animals, each selected by simple randomization using the method of. Hau et al. (17). The duration of treatment lasted 65 days and the animals were euthanized by cervical dislocation. The liver, kidneys, and testes were excised and immediately transferred into 10% neutral buffered formalin for adequate fixation for 72 hours. The fixed tissues were histologically processed using the Thermo Scientific Spin Tissue Processor, STP120, Frankfurt, Germany. The tissue sections obtained were stained using the Haematoxylin and Eosin (H&E) staining technique and evaluated microscopically. Histological analysis was carried out using the H&E staining technique to demonstrate the general architectural profile of the liver, kidneys, and testes. The stained sections were viewed and photographed with an Olympus U-D03 microscope.

Table 1. Grouping and treatment of animals

Group	Treatment
Group 1	The control group had access to diet and double-distilled demineralized water ad *libitum*
Group 2	Treatment group 1 had access to diet and pooled sampled water obtained from the study area ad *libitum*
Group 3	Treatment group 2 had access to diet and dissolved 0.009 mg/L of Pb(CH3CO2).3H2O water ad *libitum*
Group 4	Treatment group 3 had access to diet and dissolved 0.001 mg/L of Hg(SCN)2 water ad *libitum*
Group 5	Treatment group 4 had access to diet and dissolved 0.045 mg/L of Cd(CH3CO2).2H2O water ad *libitum*
Group 6	Treatment group 5 had access to diet and dissolved 0.318 mg/L of Cr2O3 water ad *libitum*
Group 7	Treatment group 6 had access to diet and dissolved mixture of 0.009/L mg of Pb(CH3CO2).3H2O, 0.001 mg/L of Hg(SCN)2, 0.045 mg/L of Cd(CH3CO2).2H2O and 0.318 mg/L of Cr2O3 water ad *libitum*

Results

Histological studies across the various exposed groups revealed varying cytopathic features in the organs of the experimental animals. The kidney, liver, and testes of the control rats were devoid of pathological lesions (Figure 1), while the kidney, liver, and testes of the rats exposed to the pooled sampled water or Lead (II) acetate trihydrate showed a variety of histological changes, including periglomerular inflammation and dilated blood vessels in the kidney, perivascular inflammation and fibrosis in the liver, along with interstitial edema and inflammation of the testes (Figures 2,3).

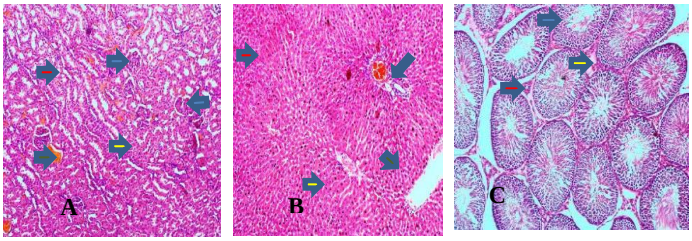

Figure 1A. Group 1 Normal Kidney (Blue arrow – Glomeruli, Yellow arrow – Tubules, Green arrow – Blood vessel, Red arrow – interstitial), **B.** Group 1 Normal liver (Blue arrow: Portal triad, Green arrow- Central vein, Red arrow- hepatocytes, Yellow arrow – Sinusoids). **C.** Group 1 Normal testis: (Blue arrow: Seminiferous tubule, Red arrow- Blood vessel, Yellow arrow – Interstitial). H&E X400.

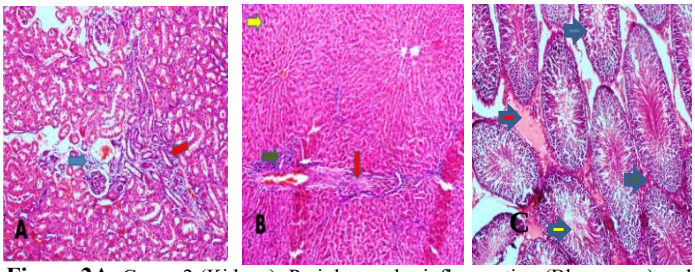

Figure 2A. Group 2 (Kidney): Periglomerular inflammation (Blue arrow) and Interstitial inflammation (Red arrow). **B.** Group 2 (Liver): Ballooning hepatocyte with hyperchromatic nuclei (Yellow arrow), Perivascular inflammation (Green arrow) with Focal fibrosis (Red arrow). **C.** Group 2 (testis): Interstitial edema (Red arrow) and Inflammation (Green arrow). H&E X400.

Rats administered with Mercury (II) thiocyanate displayed sinusoidal dilatation and distention in their livers (Figure 4), while focal hypospermatogenesis was evident in rats administered with either Cadmium acetate dehydrate, Chromium (III) oxide, or a combination of the heavy metals (Figures 5-7).

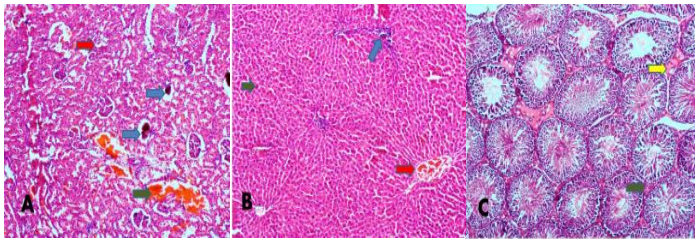

Figure 3A. Group 3 (Kidney): Glomerular degeneration (Blue arrow), Vascular congestion (Green arrow), Tubule degeneration (Red arrow). **B.** Group 3 (Liver): Ballooning hepatocyte with Hyperchromatic nuclei (Green arrow), Congested central vein (Red arrow), Periportal inflammation (Blue arrow). **C.** Group 3 (testis): Interstitial edema (Yellow arrow) and Inflammation (Green arrow). H&E X400.

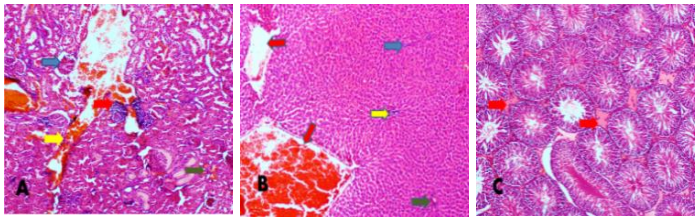

Figure 4A. Group 4 (Kidney): Glomerular degeneration (Blue arrow), vascular distension and congestion (yellow arrow), interstitial inflammation (Red arrow), peritubular inflammation with mild congestion (green arrow). **B.** Group 4 (liver): periportal (blue arrow) and perivascular (yellow and green arrows) inflammation, Sinusoidal dilation, and distension (red arrow). **C.** Group 4 (testis): interstitial edema (Red arrow). H&E X400.

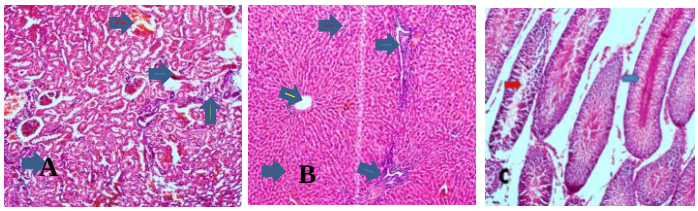

Figure 5A. Group 5 (Kidney): glomerular degeneration (Blue arrow), vascular congestion (Red arrow), peritubular inflammation (Yellow arrow) **B.** Group 5 (liver): Periportal and Perivascular inflammation (Blue arrows), Ballooning hepatocyte with Hyperchromatic nuclei (Green arrow), Central vein (Yellow arrow) **C.** Group 5 (Testis): Seminiferous tubules (Blue arrows) with Focal hypospermatogenesis (Red arrow) H&E X400.

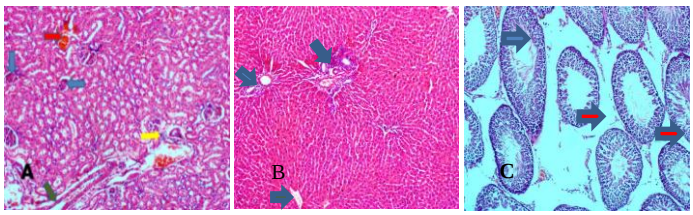

Figure 6A. Group 6 (Kidney): Focal glomerular degeneration (Blue arrow), Thickened vessel (Green arrow), Vessel congestion (Red arrow), and Mild peritubular inflammation (Yellow arrow). **B.** Group 6 (Liver): Periportal and Perivascular inflammation (Blue arrows). **C.** Group 6 (Testis): Seminiferous tubules (Blue arrows) with Focal hypospermatogenesis (Red arrow). H&E X400.

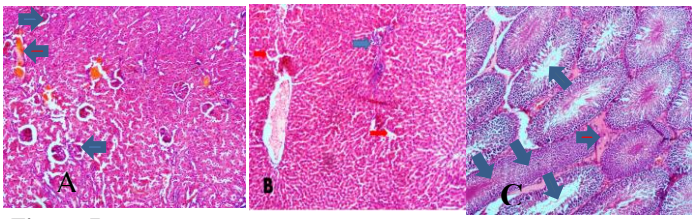

Figure 7A. Group 7 (Kidney): Focal glomerular degeneration (Blue arrow), Vascular congestion **B.** Group 7 (Liver): Periportal inflammation (Blue arrow), sinusoidal dilation (red arrow) **C.** Group 7 (Testis): Edema (Red arrow) with Inflammation (Green arrows). Focal hypospermatogenesis (Yellow). H&E X400.

Discussion

Most rivers and reservoirs are prone to pollution because of the indiscriminate

disposal of domestic, agricultural, and industrial wastes into water bodies (18). Due to environmental contamination brought on by industrial processes and products, human exposure to heavy metals like mercury (Hg), lead (Pb), and cadmium have considerably increased over the past 50 years (19). Soil and water pollution has significantly impacted food safety and quality and remains a major concern to human health (20). This study utilized the highest concentration of identified heavy metals in fifteen rivers sampled in different seasons across three geological zones in Kwara state, Nigeria (16), to further observe histopathological changes in organs of rats administered with water containing the identified heavy metals. The anthropogenic activities of humans have been indicated to predispose humans to various maladies due to the release of toxic substances into the environment, with the incidence of cancers and infertility increasing in the last fifty years (21). Additionally, the ratio of heavy metal's beneficial and harmful effects depends on their concentrations within living cells; thus requiring that the levels of metal ions have to be maintained within an appropriate range to prevent nutritional deficiencies, whereas higher concentrations can cause health concerns (22). Mercury (Hg) can induce organ toxicity in the central nervous system, hepatotoxicity, gastrointestinal alterations, and renal dysfunction with disruption of macromolecules or mechanism of actions involving aquaporin mRNA reduction, glutathione peroxidase inhibition, enzyme inhibition, production of reactive oxygen species, and Thiol binding (23,24). Lead can also induce organ toxicity, including central nervous system (CNS) injury, Hematological changes such as anemia (25), pulmonary dysfunction, reduced pulmonary function (26), Liver damage as well as cardiovascular dysfunction with the mechanism of action involving enhanced levels of inflammatory cytokines such as interleukin -1 (IL-1), tumor necrosis factor-alpha (TNF-α) and IL-6 in the CNS (27), Increased serum Endothelin 1 (ET-1), nitric oxide (NO), and erythropoietin (EPO) levels, Inactivation of Delta-aminolevulinic acid dehydratase (δ-ALAD) and ferrochelatase (inhibition of heme biosynthesis), reduced Glutathione (GSH), Superoxide dismutase (SOD), catalase (CAT), and Glutathione peroxidase (GPx) levels (28) . The liver, kidneys, and testes of the control group were devoid of pathological lesions (Figure 1 a, b, c). Pathological lesions in the organs of rats administered with Cadmium, Chromium, and a combined (Lead, Mercury, Cadmium, and Chromium) cocktail of the metals used in this study showed significant lesions when compared with organs of rats administered with pooled sampled water only. Chromium-induced toxicity has been documented by (29,30) with the mechanism of damage involving DNA damage, genomic instability, oxidative stress, and reactive oxygen species (ROS) generation. Gastrointestinal disorders, dermal diseases, kidney dysfunction, as well an increase in the occurrence of cancers, including bladder, kidneys, lungs, larynx, testicular, bone, and thyroid. Heavy metal concentration in the blood is of significant consideration for public health (19), and excessive dietary intake of lead is implicated in several cancers (31). Matouke and Lami (32) reported elevated levels of Cd, and Chromium (Cr), in Clarias gariepinus, further suggesting that consuming these fishes could predispose humans to various chronic diseases. Pb, Cd, and Hg are natural heavy metals found in geological formations in the earth's crust with characteristic high densities (>5g/cm3) (33) with exposure to these chemicals confirmed to be toxic to the reproductive systems; thus, requiring standard public health monitoring and interventions (34). Several organs, such as the Kidney, Liver, and Lung, are damaged by cadmium exposure, metabolic syndromes associated with Zn and Cu, degenerative bone disease, and various cancers have also been reported (22). The mechanism of action by which cadmium induces these disruptions includes miRNA expression dysregulation (35), endoplasmic reticulum stress, Cd-MT absorption by the kidneys, dysregulation of Ca, Zn, and Fe homeostasis, low serum parathormone (PTH) levels, ROS generation, and altered phosphorylation cascades (36,37). Environmental and occupational exposure to heavy metals remains a global health issue as it alters the biological system, thus predisposing humans to infertility and affecting 15% of couples of reproductive age (21). The toxic mechanisms include the disruption of cell signaling pathways, oxidative stress, altered gene expression, epigenetic regulation of gene expression, apoptosis, and disruption of the testis–blood barrier, inflammation, endocrine disruption, and ion mimicry (38). Water pollution remains a global potential threat to humans and animals that interact with the aquatic environment (39). Aquatic animals can accumulate pollutants directly from contaminated water, with fish storing these pollutants in various organs (18). These contaminants could bioaccumulate and transcend into human diets, thus leading to several chronic diseases (8). Stout et al. (40) reported that hexavalent chromium orally administered induced small intestinal tumors in B6C3F1 mice and tumors of the oral cavity in rats (40). The kidneys of rats administered with the pooled water sample showed the presence of periglomerular inflammation and distended blood vessels coupled with interstitial inflammation (Figure 2a). Deterioration of water bodies and the genotoxic potential of pollutants in rivers and reservoirs in north-central Ilorin has also been reported by Anifowoshe et al. (18). Rats administered with the pooled water sample displayed localized fibrosis and perivascular inflammation in their liver (18). Also, hyperchromatic nuclei and ballooning hepatocytes were evident (Figure 2b). This conforms with a study by Oladipo et al. (41), who reported distorted liver tissue architecture with infiltration and uneven sinusoidal distribution in rats exposed to automobile waste leachates in Ilorin (41). The testes of rats in this category showed the presence of interstitial edema and inflammation when compared with the control (Figure 2c). This is similar to the report of Oladipo et al. (41), who described cytopathic changes such as reduced vascular lumen, vacuolation of tubule germinal epithelium, well as degeneration of the tubular epithelium accompanied by acute vacuolation and atrophy of the germinal epithelium in the testes of rats exposed to leachates in Ilorin West local government area of Kwara state (41). This change has the potential to induce infertility in the animals. Akintunde et al. (42) also documented idiopathic infertility in male Wistar rats exposed to leachates from batteries of electronic devices via induction of peroxidation, impaired cell membrane, and reduced sperm membrane fluidity leading to injury of spermatozoa in the testes of rats (42). The kidneys' histological examination of the rats administered with lead-containing water showed tubular degeneration, vascular congestion, and glomerular degeneration (Figure 3a), while the liver showed ballooning hepatocytes with hyperchromatic nuclei with congested central vein coupled with periportal inflammation (Figure 3b). Jarrar and Taib (43) reported that these features are consistent with lead toxicity (43). The testes of rats in this group were characterized by the presence of interstitial edema and inflammation (Figure 3c). Yakubu and Omar (44) reported reduced sperm count and motility as well as testicular distortion of the seminiferous tubules and cellular degeneration in the testes of adult male rats exposed to groundwater samples and leachates from Gbagede dumpsite, Amoyo, Kwara State, Nigeria (44). The administration of mercury revealed a kidney characterized by severe glomerular degeneration coupled with vascular distortion and congestion (Figure 4a), while the liver revealed periportal and perivascular inflammation coupled with sinusoidal dilation and distention (Figure 4b). The testes of rats in this category appeared moderately normal; however, edema was observed within the tissue (Figure 4c). This is consistent with the findings of Akintunde et al. (42), who indicated that leachate containing lead and cadmium might be harmful to the testicular cell membrane on exposure to the mixed metal, which could serve as an agent of testicular damage and infertility in males (42). The kidney of cadmium administered group showed the presence of glomerular degeneration, vascular congestion as well as peritubular inflammation (Figure 5a), while the liver showed ballooning hepatocytes with hyperchromatic nuclei; periportal and perivascular inflammation was also evident (Figure 5b).

The testes of the exposed rats revealed hypospermatogenesis (Figure 5c). Yakubu and Omar (44) also reported the presence of groundwater leachate from Gbagede dumpsite in Amoyo, Kwara State, with the testicular histology revealing distortion of the seminiferous tubules and cellular degeneration in groups exposed to groundwater and leachates (44). Oladipo et al. (41) documented the structural abnormalities in the kidney, liver, and testes of albino mice exposed to automobile waste leachate. The kidneys of rats administered with the chromium-containing solution revealed focal glomerular degeneration with thickened vessels as well as congestion coupled with mild inflammation (Figure 6a), while the liver revealed peripheral and perivascular inflammation (Figure 6b). The testes of rats in this group were characterized by focal hypospermatogenesis (Figure 6c). The occurrence of cadmium in nature is low, and it is mainly associated with the ores of lead, zinc, and copper, with a biological half-life in humans ranging from 7 to 26 years in the kidney and 3 to 4 months in the blood (33).

Long-term exposure to cadmium through the air, water, soil, and food may be associated with cancer and organ system toxicity, such as skeletal, urinary, reproductive, cardiovascular, central and peripheral nervous, and respiratory systems (45). Thorne et al. (46) previously reported a failure in spermiation in a single low dose of cadmium administration in adult male Wistar rats, while De Souza Predes et al. (47) also documented that slight variation in cadmium doses could cause a surge in testicular damage, to include vacuolization of the seminiferous epithelium accompanied by diminished height and azoospermia in rats (46,47) further buttressing our findings in this study. The final group administered with the combined heavy metal solution (Pb, Hg, Cd, and Cr) revealed focal glomerular degeneration and vascular congestion in the kidneys, with the interstitial spaces appearing normal and not inflamed (Figure 7a). However, periportal inflammation, sinusoidal dilation, and mild congestion of the central vein were evident in the liver of rats in this group (Figure 7b), while the testes of rats were mildly inflamed with focal hypospermatogenesis evident (Figure 7c).

Conclusion

This study revealed the effects of variations in the water quality on vital organs of the body. It is relevant for the control and management of heavy metals in Kwara state, Nigeria. Individuals who utilize water directly from these rivers for household purposes must take precautions to prevent the possible adverse health effects that may be associated with these metals. Additionally, regulatory agencies must constantly monitor activity on these water bodies, and regulations that strictly forbid dumping waste in water should be enforced.

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Ethical statement

The study was performed in accordance with the "the National Institute of Health (NIH) in the "Guide to the Care and Use of Animals in Research and Teaching published by the National Academic Press (Eighth edition, International Standard Book Number-13: 978-0-309-15400-0). The experimental protocol and procedures used in this study were approved by the College of Medicine Research Ethics Committee, Directorate of Research and Publications, College of Medicine, University of Nigeria, Enugu Campus, State, Nigeria, with protocol number 025/02/2017.

Conflicts of interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Author contributions

The authors confirm contribution to the paper as follows: Study conception and design: Temidayo Daniel Adeniyi: Data collection: Temidayo Daniel Adeniyi, Akinpelu Moronkeji; Analysis and interpretation of results: Akinpelu Moronkeji, Temidayo Daniel Adeniyi, Victor Olukayode Ekundina; Draft manuscript preparation: Akinpelu Moronkeji. All authors reviewed and approved the final version of the manuscript.

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