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Protective Effects of Jamun (*Syzygium cumini*) Seed and Orange (*Citrus sinensis*) Peel Extracts against Cadmium Induced Nephrotoxicity in Rats

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Abstract: The aim of the present study was to investigate histological changes in the kidney of rats induced by cadmium and to evaluate the protective role of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis*) peel extracts. Male Wistar rats were divided into six groups – Group A: Control; Group B: Cadmium (Cd); Group C: Cadmium and jamun seed extract (Cd+ JSE); Group D: Cadmium + orange peel extract (Cd + OPE) ; Group E: Orange peel extract (OPE); Group F: Jamun seed extract (JSE). The Cadmium dose was 10 mg/kg b wt whereas orange peel and jamun seed extract dose was 200 mg/kg b wt/ day for 14 day. For light microscopy kidney were fixed on 7 and 14 day following the treatment. 7 day Cd (Group B) treated rats exhibited shrunken glomeruli . In Cd+ JSE (Group C) and Cd + OPE (Group D) treated rats for 7 days, similar changes were noticed but to a lesser extent. Kidney of rats treated for 7 day with OPE and JSE have not shown any remarkable histological change. The kidney of 14 day Cd (Group B) treated rats revealed tubular degeneration and glomerular hypertrophy. In Cd+ JSE (Group C) and Cd + OPE (Group D) treated rats for 14 day, the kidney exhibited changes similar changes (as noticed in Cd treated rats) except degeneration of renal tubules. Kidney of rats treated for 14 day with OPE and JSE have not shown any remarkable histological change. From the present study it can be concluded that Cd caused histological changes in the kidney of rats. These changes can be protected by supplementing with OPE and JSE.

Keywords: Cadmium, *Syzygium cumini*, *Citrus sinensis*, Antioxidant, Nephrotoxicity, Heavy metal, Glomerulus

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Introduction

Heavy metals are high atomic weight elements with a density of at least five times that of water. Heavy metals (HMs) are naturally occurring, dense substances that can accumulate in the

environment and in organisms, posing health risks (Tchounwou *et al.*, 2012; Rajkumar *et al*., 2024).

Heavy metal contamination is a serious environmental issue that occurs when they are released into the soil, water and atmosphere. Heavy metals are toxic and can persist in the environment for a long time. They can harm the health of plants and animals and can cause serious disorders. Some common heavy metals are Pb, Hg, As, Cd and Tl. Heavy metals can enter the environment through a number of sources including industrialization, air deposition, farm yard manure, sewage sludge, synthetic fertilizers and improper waste disposal. Heavy metals can contaminate the foods including cereals, rice and wheat and the animal food like fish, crustacean and mollusc. Metallic chemical elements and metalloids that are hazardous to both organisms and the environment are referred to as "heavy metals" (Duffus, 2002; Briffa *et al*., 2020).

Numerous biological processes, such as signal transduction pathways, cell division, proliferation, and apoptosis, have been affected by exposure to cadmium. The harmful non-essential transition metal cadmium (Cd) is a major global health concern for both humans and animals (Genchi *et al*., 2020). Cadmium is found in cigarette smoke, metal plating and batteries. Cadmium is present in soil, water bodies, and food chains as a result of human activity. Its toxicity poses a potential threat to the environment in which we live. According to Pajewska-Szmyt *et al*. (2019) the exposure to cadmium causes allergies, endocrine system problems, and has a major negative impact on an infant's neurodevelopment. Exposure to cadmium provoke nephrotoxicity (Orisakwe *et al*., 2014; Tripathi and Srivastav, 2011).

According to Ponce *et al*. (2013), cadmium is a widespread environmental pollutant linked to the development of breast cancer. As a potent carcinogen and inducer of antioxidant enzymes, cadmium (Cd) is a non-essential transition metal that complexes with glutathione (GSH) and metallothionein (MT). The most effective defense against oxidative stress caused by Cd is provided by these enzymes. Moreover, chaperone expression and the avoidance of mitophagy, metabolic stress, and endoplasmic reticulum (ER) stress are protective strategies (Sandbichler *et al.*, 2016). According to several reports, antioxidants such as vitamin C and E can shield various experimental animals against cadmium-induced damage (Flora *et al*., 2008). A combination of selenium, alpha-tocopherol, and ascorbic acid may be useful in preventing cadmium toxicity in rats. In the intestine of rats, this led to an increase in lipid peroxidation and a drop in glutathione levels. This combination demonstrated a shielding effect against intestinal cadmium poisoning. (Bolkent *et al*., 2008). Vitamins A, C, E, and selenium can, in fact, prevent or lessen the harmful effects of cadmium on a variety of tissues and organs, including the kidney, liver, skeleton, and blood. The other elements, magnesium and zinc, have a wide range of therapeutic uses.

Reactive oxygen species (ROS), such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals, are produced by aerobic organisms during oxidative metabolism. Hydroxyl can start the lipid peroxidation (LPO) process in tissues (Halliwell and Gutteridge, 1984). Reactive oxygen species (ROS) or free radicals specific to heavy metals are produced by the metal and put cells under oxidative stress. These lead to Carcinogenesis, apoptosis of the cells, damaged DNA, and poor DNA repair, cell injury and peroxidation of lipids in the cell membrane, the protein enzymes become inactive, stopping the folding of protein, aggregation of proteins, modifications in conformation that impair their structure and function and harm cells (Rajkumar *et al*., 2024).

Reactive oxygen and nitrogen species are produced by heavy metals inside the body, which leads to an imbalance between prooxidant and antioxidant (reducing) components. It has been found that heavy metals affect the signaling cascade and related apoptotic components (Pompilio *et al*., 2021).

Vertebrates have an antioxidant defense (AD)

system that uses both enzymatic and non-enzymatic mechanisms to counteract the harmful effects of reactive oxygen species (ROS). Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GR) are examples of enzymatic defenses; vitamins E, C, and A, carotenes and ubiquinol 10 are examples of non-enzymatic defenses (Filho, 1996). Oxidative stress is caused by either an increase in ROS generation or a decrease in the activity of these antioxidant defense systems (Packer, 1995). It has been documented that oxidative stress in vertebrates is induced by microcystins (Wiegand *et al*., 1999; Li *et al*., 2003), pesticides (Sayeed *et al*., 2003), metals (Almeida *et al*., 2002), and pulp mill effluents (Filho *et al*., 1997).

The aim of the present study was to investigate histological changes in the kidney of rats induced by cadmium and to evaluate the protective role of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis*) peel extracts.

Materials and Methods

Male Wistar rats (40- 65 g) were purchased from Asia Scientific Emporium (Varanasi, India). The rats were housed in polypropylene cages in a hygienic environment and acclimatization was done for 2 weeks prior to the initiation of experiment. During acclimatization and experimental period, the rats were fed with the standard laboratory diet and water *ad libitum*.

Six groups (A-F) of rats (n = 10 for each group) were randomly selected for the experiment. These groups were treated as follow (daily at 8 a.m. through orally) for 14 day:

Group A (Control): No treatment was given.

Group B (Cadmium treated rats): These rats received daily only cadmium (10 mg/kg b wt).

Group C (Cadmium + jamun seed extract): These rats received daily cadmium (10 mg/kg b wt) and jamun seed extract (200 mg/kg b wt) simultaneously.

Group D (Cadmium + orange peel extract): These rats received daily cadmium (10 mg/kg b wt) and orange peel extract (200 mg/kg b wt) simultaneously.

Group E (Orange peel extract): Rats were given daily orange peel extract (200 mg/kg b wt).

Group F (Jamun seed extract): Rats were given daily jamun seed extract (200 mg/kg b wt).

Rats (5 from each group on each interval) were sacrificed on 7th and 14th day 24 h after the last dose under light anesthesia. Prior to the sacrifice, the animals were fasted overnight.

Syzygium cumini (jamun) seeds were acquired from a commercial supplier (M/S SVM Naturals, Tamil Nadu, India). Oranges (*Citrus sinensis*), were bought locally and the peels were separated. The orange peels and jamun seeds were washed thoroughly with tap water and were dried at 40°C in a hot air oven. These were ground into powder. The powdered orange peel and jamun seeds were mixed with 90% ethanol in a 1:20 (w/v) ratio and left for 48 h on an orbital shaker. The samples were then put through a Whatman Grade No. 1 filter paper. 40°C was used to dry the filtrates in a rotary evaporator. For later use, the dried residue was weighed and stored at -20°C. To keep the heat-labile compounds found in orange peels and jamun seeds from becoming denatured, Soxhlet extraction was not utilized in this extraction procedure. Rats were given the appropriate dosage by reconstituting the dried residues of orange peels and jamun seeds with ethanol.

Kidney tissues were fixed in Bouin's fluid. The kidney tissues were processed following routine histological procedure after paraffin embedding. Sections were cut at 6 µm and stained with hematoxylin and eosin (HE). Olympus CH20i microscope and Olympus E420 camera was used to obtain photomicrographs.

Results

The kidney of control rats contains many nephrons. The nephron consists of a dilated portion, the renal capsule, the proximal tubule, Loop of Henle and the distal tubule. The renal

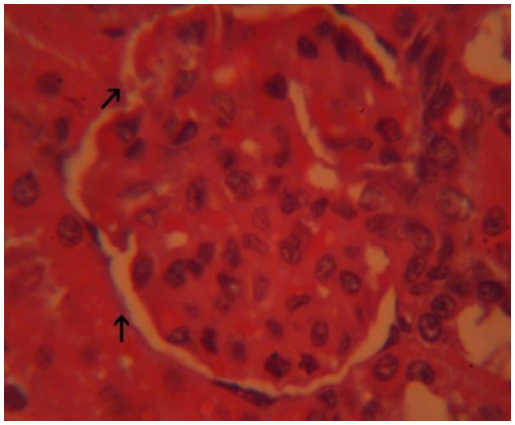

Fig. 1: Kidney of control rat showing glomerulus. HE×500

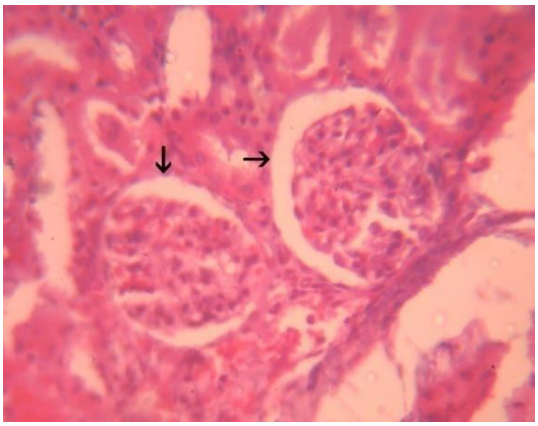

Fig. 2: Kidney of 7 day Cadmium exposed rat showing shrunken glomerulus (arrows). HE×100

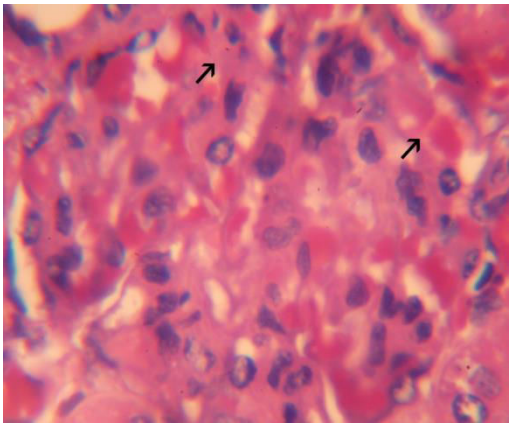

Fig. 3: Kidney of 14 day Cadmium exposed rat showing glomerular hypertrophy. HE×500

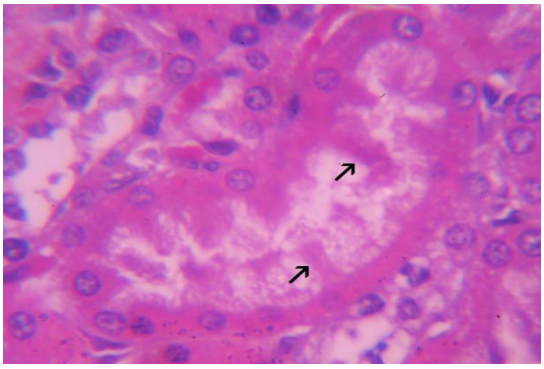

Fig. 4: Kidney of 14 day Cadmium exposed rat showing tubular degeneration (arrows). HE×500

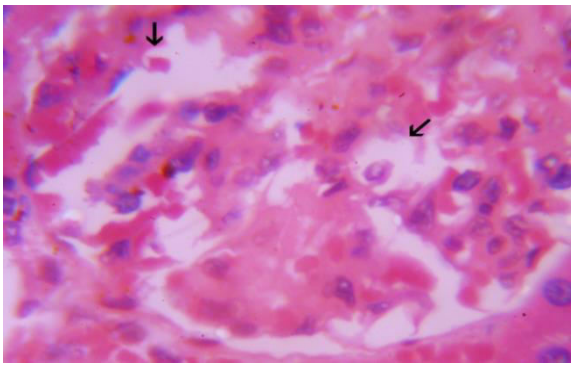

Fig. 5: Kidney of 14 day Cadmium exposed rat showing degenerated glomerulus (arrows). HE×500

capsules contain a tuft of capillaries, the glomerulus surrounded by Bowman's capsule (Fig. 1). Urinary space is present between gomerulus and Bowman's capsule. Proximal tubule is lined by cuboidal or columnar epithelium while the distal tubule is lined by cuboidal epithelium.

After 7 day following cadmium treatment (Group B), certain shrunken glomeruli were visible, creating more gap between the glomerulus and Bowman's capsule (Fig. 2). In rats from Group C (Cd + OPE) and Group D (Cd + JSE) similar changes were observed but to a lesser extent. In Group E (OPE) and Group F (JSE) rats, no alterations in the kidney morphology were noticed.

After 14 day of cadmium treatment (Group B), hypertrophied glomeruli were visible at few places (Fig. 3). The proximal and distal tubules were also degenerating (Fig. 4). In Cd treated rats glomerulus showed degeneration at certain places (Fig. 5). Group C (Cd + JSE) and Group D (Cd + OPE) rats showed similar changes (as observed in Cd treated rats) except degeneration of tubules. No change in glomerulus is noticed in Group E (OPE) and Group F (JSE) rats.

Discussion

In the current investigation, rats exposed to cadmium showed histological changes in kidney. Exposed rats exhibited glomerular shrinkage on day 7. In accordance with present study glomerular shrinkage was also seen in rats by other investigators after exposure to different toxicants/drugs - paraquat (Abdel-Mageid, 1994); Lithium (Sharma and Iqbal, 2005); Aluminium chloride (Okail *et al.*, 2005); chlorpyrifos (Tripathi and Srivastav, 2010, Rekha *et al.*, 2013); cadmium (Tripathi and Srivastav, 2011); 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (Ciftci *et al.*, 2012); Triazophos (Sharma and Sangha, 2014); Endosulfan (Khan, 2014); Silver (Roda *et al.*, 2014); Malathion (Mamun *et al.*, 2015); Abmactin (Moqbel *et al.*, 2017); Mercuric chloride (Langeswaran *et al.*, 2018); 2,4-D (Upadhyay *et al.*, 2018); MCLR (Srivastava *et al.*, 2020);

Cypermethrin (Srivastava *et al.,* 2021) and Bisphenol-A (Ishtiaq *et al.*, 2022).

Cadmium treatment to rat showed glomerular degeneration on day 14. Tripathi and Srivastav (2011) have also reported glomerular degeneration after exposure to cadmium. In vertebrates few researchers have observed glomerular degeneration caused by various toxicants/drugs in rat- paraquat (Lamfon and Al-Rawi, 2007); chlorpyrifos (Tripathi and Srivastav, 2010, Mansour and Mossa, 2010, Rekha *et al.*, 2013); lead (EI-Newesy and EI-Sayed, 2011); gentamicin (Alrifi *et al.*, 2012); deltamethrin (EI-Gerbed, 2014); triazophos (Sharma and Sangha, 2014); abmactin (Moqbel *et al.*, 2017); MCLR (Srivastava *et al.*, 2020) and cypermethrin (Srivastava *et al.,* 2021). After treatment with chlorpyrifos (Srivastava *et al.*, 1990); cadmium (Wangsongsak *et al.*, 2007); deltamethrin (Cengiz, 2006); microcystin (Atencio *et al.*, 2008, Suput, 2011); and cypermethrin (Korkmaz *et al.*, 2009) glomerular degeneration have been reported in fishes. Aslam *et al.* (2009) reported glomerular degeneration in chick after cypermethrin exposure. Rats exposed to paraquat exhibited amorphous cellular debris in their glomerulus (Lamfon and Al-Rawi, 2007). Due to glomerular degeneration in cadmium-treated rats in the present study, there may be a decrease in GFR, as observed by Barrouillet *et al.* (1999) in their *in vitro* cadmium exposure study.

Rats treated with cadmium showed tubular degeneration and vacuolization on day 14. Earlier, other researchers have also reported tubular degeneration in vertebrates exposed to other toxicants - fish (chlorpyrifos- Srivastava *et al.*, 1990; cadmium- Rabergh *et al.*, 1991; Kotak *et al.*, 1996; Wangsongsak *et al.*, 2007; microcystin- Atencio *et al.*, 2008; cypermethrin - Ayoola and Ajani, 2008); quail (lead– Almansour *et al.*, 2008); chick (cypermethrin- Aslam *et al.*, 2009); wood mouse and whitetoothed shrew (landfill leachates containing toxic metals- Sanchez-Chardi *et al.*, 2009); monkey (lead- Colle *et al.*, 1980); mice (chlorpyrifos- Thijssen *et al.*, 2007; microcystin-Rangel *et al.*, 2014; Al-Sultan *et al.*, 2015; Al-Majeed *et al.*, 2016); rabbit (fluoride – Shashi *et al.*, 2002). In rat, tubular degeneration has also been noticed after treatment with different toxicants/drugs - chlorpyrifos (Aughey *et al.*, 1984; Karmakar *et al.*, 1986; Gatta *et al.*, 1989; Brzoska *et al.*, 2003; Abdel-Moneim and Said, 2007; Kukner *et al.*, 2007; Jihen *et al.*, 2008; Tripathi and Srivastav, 2010; Rekha *et al.*, 2013; Tanvir *et al.*, 2016); microcystin (Hooser *et al.*, 1989; Suput *et al.*, 2011, Srivastava *et al.*, 2020); metal mixture (Jadhav *et al.*, 2007); paraquat (Damain *et al.*, 1992; Abdel Mageid, 1994; Lamfon and Al-Rawi, 2007); fenthion (Kerem *et al.*, 2007); cigarette smoke (Kuru *et al.*, 2009); cadmium (Brozska *et al*., 2003; Tripathi and Srivastav, 2011); cypermethrin (Muthuviveganandavel *et al.*, 2008; Srivastava *et al*., 2021); Lead (EI-Newesy and EI-Sayed, 2011); Gentamicin (Abdel-Raheem *et al.*, 2009; Alrifi *et al.*, 2012; 2,4-D-Tayeb *et al.*, 2012; Upadhayay *et al.*, 2018); zinc (Faddah *et al.*, 2012); streptozotocin (Omara *et al.*, 2012); Monosodium glutamate (Dixit *et al.*, 2014); Deltamethrin (EI- Gerbed, 2014); Endosulfan (Khan,2014); Lead acetate (Aksu *et al.*, 2017); Abmactin (Moqbel *et al.*, 2017); Cymoxanil (Ahmed *et al.*, 2020). However, Velisek *et al*. (2009) did not find any alterations in the kidneys of fish treated with bifenthrin.

In the present investigation, rats treated with cadmium showed glomerular hypertrophy after 14 day which is supported from the observations by other researchers who have reported glomerular hypertrophy in the kidney in vertebrates exposed to different toxicants: cadmium – (Aughey *et al*., 1984; Brzoska *et al*., 2003; AbdelMoneim and Said, 2007; Tripathi and Srivastav, 2011); Gentamicin – (Abdel-Raheem *et al.*, 2009; 2,4 D - Tayeb *et al.*, 2012); chlorpyrifos – (Mansour and Mossa, 2010; Rekha *et al.*, 2013; Tripathi and Srivastav, 2011); *Acacia nilotica* pod extract - (Omara *et al.*, 2012); heterogenous chemical mixture– (Morya and Vachhrajani, 2014); fenitrothion– (Afshar *et al.*, 2008); malathion – (Hafez *et al*., 2017). Similar observations were also noticed in rabbit (fluoride

– Shashi *et al.,* 2002) and quail (lead – Almansour *et al*., 2008).

Hydrolic changes in the renal tissue may be the cause of kidney abnormalities brought on by toxicants, such as tubular degeneration and vacuolization.. These alterations clearly show that toxicants cause both renal dysfunction and induce renal failure via pump transport of tubular cells (Srivastava *et al*., 2020, 2021).

Conclusion

It is concluded that cadmium exposure adversely affects the histological structure of the kidney of the rats. The alterations observed in the structure of kidney after cadmium exposure could be protected by the supplements obtained from the extracts of jamun seed and orange peel. It is suggested that living beings after their exposure to cadmium should intake supplements of these given extracts (which contain phytochemicals) which would help in the reduction of cadmium toxicity.

References

Abdel-Mageid SA. (1994) Structural changes in the kidney of albino rat in response to the administration of paraquat herbicide. J Egypt Germ Soc Zool. 15: 153-175.

Abdel-Moneim AM, Said KM. (2007) Acute effect of cadmium treatment on the kidney of rats: biochemical and ultrastructural studies. Pak J Biol Sci. 10: 3497-3506.

Abdel-Raheem IT, Abdel-Ghany AA and Mohamed GA. (2009) Protective effect of quercetin against gentamicin-induced nephrotoxicity in rats. Biol Pharma Bull. 32(1): 61-67.

Afshar S, Farshid AA, Heidari R and Llkhanipour M. (2008) Histopathological changes in the liver and kidney tissues of Wistar albino rat exposed to fenitrothion. Toxicol Indust Hlth. 24: 581-586.

Ahmed MS, Massoud AH, Derbalah AS, Al-Brakati A, Al-Abdawani MA, Eltahir HA and Elmahallawy EK. (2020)Biochemical and histopathological alterations in different tissues of rats due to repeated oral dose toxicity of cymoxanil. Animals 10(12): 2205.

Aksu DS, Saglam YS, Yildirim S and Aksu T. (2017) Effect of pomegranate (*Punica granatum* L.) juice on kidney, liver, heart and testis histopathological changes, and the tissues lipid peroxidation and antioxidant status in lead acetate-treated rats. Cell Molec Biol. 63(10): 33-42.

Alarifi S, Al-Doaiss A, Alkahtani S, Al-Farraj SA, Al-Eissa MS, Al-Dahmash B and Mubarak M. (2012) Blood chemical changes and renal histological alterations induced by gentamicin in rats. Saudi J Biol Sci. 19(1): 103-110.

Al-Majeed MIA, Al-Sultan EYA and Abbas AAK. (2016) Toxic effects of low concentration of cyanotoxin (Microcystin-LR) on mice and study of protective efficacy of the antioxidants vitamins (C&E) and *Capparis spinosa* L. root extract. J Natural Sci Res. 6: 34-42.

Almansour MI, Al-Otaibi NM, Alarifi SA, Ibrahim SA and Jarra BM. (2008) Histological and histochemical alterations induced by lead in the kidney of the quail *Coturnix coturnix*. Saudi J Biol Sci. 15: 307-313.

Almeida JA, Diniz YS, Mmarwues SFG, Faine LA, Ribas BO, Burneiko RC and Novelli ELB. (2002) The use of the oxidative stress responses as biomarkers in Nile tilapia (*Oreochromis niloticus*) exposed to *in vivo* cadmium contamination. Environ Int. 27: 673-679.

Al-Sultan EYA, Al-Majeed MIA and Abbas AAK. (2015) Study of physiological and histological effects under very low concentration of cyanobacterial toxin MC-LR on lab Mice (*Mus musculus*). Res J Pharma Biol Chem Sci. 6: 1064-1072.

Aslam F, Khan A, Khan MZ, Sharaf S, Gul ST and Saleemi MK. (2009) Toxico-pathological changes induced by cypermethrin in broiler chicks: Their attenuation with vitamin E and selenium. Exp Toxicol Pathol. 62: 451-450.

Atencio L, Moreno I, Prieto A, Moyano R, Molina AM and Camean AM. (2008) Acute effects of microcystins MCLR and MCRR on acid and alkaline phosphatase activities and pathological changes in intraperitoneally exposed tilapia fish (*Oreochromis sp*.). Toxicol Pathol. 36: 449-458.

Aughey E, Fell GS, Scott R and Black M. (1984) Histopathology of early effects of oral cadmium in rat kidney. Environ Hlth Perspect. 54: 153-161.

Ayoola SO and Ajani EK. (2008) Histopathological effects of cypermethrin on juvenile African catfish (*Clarias gariepinusi*). World J Biol Res. 1:1-14.

Barrouillet MP, Potier M and Cambar J. (1999) Cadmium nephrotoxicity assessed in isolated rat glomeruli and cultured mesanglial cells: Evidence for contraction of glomerular cells. Exp Nephrol. 7: 251-258.

Bishak YK, Payahoo L, Osatdrahimi A and Nourazarian A. (2015) Mechanisms of cadmium carcinogenicity

in the gastrointestinal tract. Asian Pac J Cancer Prev. 16(1): 9-21.

Bolkent S, Sacan O, Yanardag R and Bolkent S. (2008) Effects of vitamin E, vitamin C, and selenium on gastric fundus in cadmium toxicity in male rats. Int J Toxicol. 27(2): 217-222.

Briffa J, Sinagra E and Blundell R. (2020) Heavy metal pollution in the environment and their toxicological effects on humans. Heliyon 6(9): e04691.

Brzoska MM, Moniuszko-Jakoniu J, Pilat-Marcinkiewicz B and Sawicki B. (2003) Liver and kidney function and histology in rats exposed to cadmium and ethanol. Alcoh Alkoholism 38: 2-10.

Cengiz EI. (2006) Gill and kidney histopathology in the freshwater fish *Cyprinus carpio* after acute exposure to deltamethrin. Environ Toxicol Pharmacol. 22: 200-204.

Ciftci O, Ozdemir I, Vardi N, Beytur A and Oguz F. (2012) Ameliorating effects of quercetin and chrysin on 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-induced nephrotoxicity in rats. Toxicol Indust Hlth. 28(10): 947-954.

Colle A, Grimaud JA, Boucherat M and Manuel Y. (1980) Lead poisoning in monkeys: functional and histopathological alterations of the kidneys. Toxicol. 18:145-158.

Damain F, Frank H, Win Fried M, Hartmut M and Laus W. (1992) Failure of radiotherapy to resolve fatal lung damage due to paraquat poisoning. Chest 100: 1146- 1165.

Dixit SG, Rani P, Anand A, Khatri K, Chauhan R and Bharihoke V. (2014) To study the effect of monosodium glutamate on histomorphometry of cortex of kidney in adult albino rats. Renal Failure 36(2): 266-270.

Duffus JH. (2002) Heavy metals a meaningless term? Pure Appl Chem. 74: 793-807.

El-Gerbed, MS. (2014) Protective effect of lycopene on deltamethrin-induced histological and ultrastructural changes in kidney tissue of rats. Toxicol Indust Hlth. 30(2):160-173.

El-Neweshy MS and El-Sayed YS. (2011) Influence of vitamin C supplementation on lead-induced histopathological alterations in male rats. Exp Toxicol Pathol. 63(3): 221-227.

Faddah LM, Baky NAA, Al-Rasheed NM, Al-Rasheed NM, Fatani AJ and Atteya M. (2012) Role of quercetin and arginine in ameliorating nano zinc oxide-induced nephrotoxicity in rats. BMC Complem Alternat Med. 12(1): 1-14.

Filho W. (1996) Fish antioxidant defenses: A comparative approach. Braz J Med Bio Res. 29: 1735-1742.

Filho W, Baptista L, Soares C and Pedrosa R. (1997) The effect of pulp mill effluent on two fish species. In: Proc Fifth Brazilian Symposium on Chemistry of Lignins and other Wood Components, Curitiba. Brazil, October 15-17, pp. 612-619.

Flora SJ, Mittal M and Mehta A. (2008) Heavy metal induced oxidative stress and its possible reversal by chelation therapy. Indian J Med Res. 128: 501-523.

Gatta A, Bazzerla G, Amodio P, Menon F, Angeli P, Schiaffino E and Schmicd C. (1989) Detection of the early steps of cadmium nephropathy – comparison of light and electron-microscopical patterns with the urinary enzymes excretion. Nephron 51: 20-24.

Genchi G, Sinicropi MS, Lauria G, Carocci A and Catalano A. (2020) The effects of cadmium toxicity. Int J Environ Res Public Hlth. 17(11): 3782.

Hafez EHH, Afaf MEA, Ahmed ANM and Mohammed FAA AA. (2017) The impact of the organophosphate insecticide “Malathion" on rat and the possible ameliorating role of “Thymoquinone". Egyptian J Exp Biol (Zoology) 13(2): 309-318.

Halliwell B and Gutteridge JMC. (1984) Oxygentoxicity, oxygen radicals, transition metal and disease. Biochem J. 219: 1-14.

Hooser SB, Beasley VR, Lovell RA, Carmichael WW and Haschek WM. (1989) Toxicity of microcystin-LR, a cyclic hepatopeptide hepatotoxin from *Microcystis aeruginosa* to rats and mice. Vet Pathol. 26:246-252.

Ishtiaq A, Ijaz MU, Ehsan N, Imran M, Naz H, Alvi K and Zhu GP. (2022). Therapeutic effect of oroxylin A against bisphenol A-induced kidney damage in rats: a histological and biochemical study. Pak Vet J. 42(2): 511-516.

Jadhav SH, Sarkar SN, Patil RD and Tripathi HC. (2007) Effects of subchronic exposure via drinking water to a mixture of eight water-contaminating metals: a biochemical and histopathological study in male rats. Arch Environ Contam Toxicol. 53: 667-677.

Jihen H, Imed M, Fatima H and Abdelhamid K. (2008) Protective effects of selenium (Se) and zinc (Zn) on cadmium (Cd) toxicity in the liver and kidney of the rat: histology and Cd accumulation. Food Chem Toxicol. 46: 3522-3527.

Karmakar N, Saxena R and Anad R. (1986) Histopathological changes in rat tissues by oral intake of lead acetate. Environ Res. 41: 23-28.

Kerem M, Bedirli N, Gurbuz N, Ekinci O, Akkaya T, Sakrak O and Pasaoglu H. (2007) Effects of acute fenthion toxicity on liver and kidney function and histology in rats. Turk J Med Sci. 37: 281-288.

Khan S. (2014) Study of histopathological changes induced by endosulfan in kidney of albino rats. J Drug Deliv Therapeut. 4(3): 125-128.

Korkmaz N, Cengiz EI, Unlu E, Uysal E and Yanar M. (2009) Cypermethrin-induced histopathological and biochemical changes in Nile tilapia (*Oreochromis niloticus*), and the protective and recuperative effect of ascorbic acid. Environ Toxicol Pharmacol. 28:198-205.

Kotak BJ, Semalulu S, Friytz DL, Prepas EE, Hrudey SE and Coppock RW. (1996) Hepatic and renal pathology of intraperitoneally administered microcystin LR in rainbow trout (*Oncorhynchus mykiss*). Toxicon. 34: 517-525.

Kukner A, Colakoglu N, Kara H, Oner H, Ozogul C and Ozan E. (2007) Ultrastructural changes in the kidney of rats with acute exposure to cadmium and effects of exogenous metallothionein. Biol Trace Elem Res. 119: 137-146.

Kuru M, Ugras M and Esrefoglu M. (2009) Effect of resveratrol on tubular damage and interstitial fibrosis in kidneys of rats exposed to cigarette smoke. Toxicol Indust Hlth. 25: 539-544.

Lamfon HA and Al-Rawi MM. (2007) Effect of antox and paraquat-induced histological and biochemical changes in kidney of albino rats. J Appl Sci Res. 3: 988-993.

Langeswaran K, Selvaraj J, Ponnulakshmi R, Mathaiyan M and Vijayaprakash S. (2018) Protective effect of Kaempferol on biochemical and histopathological changes in mercuric chloride induced nephrotoxicity in experimental rats. J Biol Active Prod Nat. 8(2): 125-136.

Mamun MAA, Rahman A, Belal SH, Islam MA, Sarker MEH, Arman MSI and Hoque KMF. (2015) Histological study of the effect of malathion on liver and kidney tissues of mice model. Int J Pharm Sci Res. 6(3): 1043.

Mansour SA and Mossa ATH. (2010) Oxidative damage, biochemical and histopathological alterations in rats exposed to chlorpyrifos and the antioxidant role of zinc. Pest Biochem Physiol. 96(1): 14-23.

Mohamed HZ and Shenouda MB. (2021) Amelioration of renal cortex histological alterations by aqueous garlic extract in gentamicin induced renal toxicity in albino rats: a histological and immunohistochemical study. Alexandria J Med. 57(1): 28-37.

Moqbel FS, Al-Eryani MA and Abd Al Galil FM. (2017) Histopathological and biochemical effects of abamectin on kidney in male albino rats. J Entomol Zool Stud. 5: 245-249.

Morya K and Vachhrajani KD. (2014) Impairment of renal structure and function following heterogeneous chemical mixture exposure in rats. Indian J Exp Biol. 52: 332-343.

Muthuviveganandavel, V, Muthuraman P, Muthu S and Srikumar K. (2008) A study on low dose cypermethrin induced histopathology, lipid peroxidation and marker enzyme changes in male rat. Pest Biochem Physiol. 91: 12-16.

Okail HA, Ibrahim AS and Badr AH. (2020) The protective effect of propolis against aluminum chloride-induced hepatorenal toxicity in albino rats. J Basic Appl Zool. 81: 1-11.

Omara EA, Nada SA, Farrag ARH, Sharaf WM and El-Toumy SA. (2012) Therapeutic effect of *Acacia nilotica* pods extract on streptozotocin induced diabetic nephropathy in rat. Phytomed. 19(12): 1059-1067.

Orisakwe OE. (2014) Lead and cadmium in public health in Nigeria: physicians neglect and pitfall in patient management. North American J Med Sci. 6(2): 61-70.

Packer JE. (1995) Oxidative stress, antioxidants, aging and disease. In: Oxidative Stress and Aging, (eds.) Gulter R.G., Packer L.B., Eratum J. and Mori A., Birkhauser Verlag, Basle, pp. 152-163.

Pajewska-Szmyt M, Sinkiewicz-Darol E and Gadzała-Kopciuch R. (2019) The impact of environmental pollution on the quality of mother's milk. Environ Sci Pollut Res Int. 26(8): 7405-7427.

Pompilio NCG, Francisco CS, Marco Tulio FM, Sergio Samuel SM and Fernanda Eliza GJ. (2021) Heavy metals in blood, milk and cow's urine reared in irrigated areas with wastewater. Heliyon. 7(4): e06693.

Ponce E, Aquino NB and Louie MC. (2013) Chronic cadmium exposure stimulates SDF-1 expression in an ERα dependent manner. PLoS One 8(8): e72639.

Rabergh CMI, Bylund G and Eriksson JE. (1991) Histopathological effects of microcystin-LR, acyclic peptide toxin from the cyanobacterium (blue-green alga) *Microcystis aeruginosa*, on common carp (*Cyprinus carpio* L.). Aquat Toxicol. 20: 131-145.

Rajkumar V, Lee VR and Gupta V. (2024) Heavy Metal Toxicity. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

Rangel M, Martins JCG, Garcia AN, Conserva AA, Costa Neves A, Anna CLS and Carvalho LR. (2014) Analysis of the toxicity and histopathology induced by the oral administration of *Pseudanabaena galatea* and *Geitlerinema splendidum* (Cyanobacteria) extracts to mice. Mar Drugs 12: 508-524.

Rekha, Raina S and Hamid S. (2013) Histopathological effects of pesticide-cholopyrifos on kidney in albino rats. Int J Res Med Sci. 1(4): 465-475.

Roda E, Barni S, Milzani A, Dalle-Donne I, Colombo G and Coccini T. (2017) Single silver nanoparticle instillation induced early and persisting moderate cortical damage in rat kidneys. Int . Molec Sci. 18(10): 2115.

Sanchez-Chardi A, Penarroja-Matutano C, Borras M and Nadal J. (2009) Bioaccumulation of metals and effects of a landfill in small mammals Part III: Structural alterations. Environ Res. 109: 960-967.

Sandbichler AM and Höckner M. (2016) Cadmium protection strategies--A hidden trade off?. Int J Molec Sci. 17(1): 139.

Sayeed I, Parvez S, Pandey S, Bin-Hafeez B, Haque R and Raisuddin S. (2003) Oxidative stress biomarkers of exposure to deltamethrin in freshwater fish, *Channa punctatus* Bloch. Ecotoxicol Environ Saf. 56: 295-301.

Sharma D and Sangha GK. (2014) Triazophos induced oxidative stress and histomorphological changes in liver and kidney of female albino rats. Pest Biochem Physiol. 110: 71-80.

Sharma SD and Iqbal M. (2005) Lithium induced toxicity in rats: a hematological, biochemical and histopathological study. Biol Pharma Bull. 28(5): 834-837.

Shashi A, Singh JP and Thapar SP. (2002) Toxic effects of fluoride on rabbit kidney. Fluoride 35: 38-50.

Srivastava BD, Srivastav M, Srivastav SK, Urata M, Suzuki N and Srivastav Ajai K. (2021) Protective effects of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis*) peel extracts against cypermethrin induced nephrotoxicity in rats. Egypt J Basic Clin Pharmacol. 11: 101492.

Srivastava BD, Srivastava M, Urata M, Suzuki N and Srivastav Ajai K. (2020) Efficacy of jamun *Syzygium cumini* seed and orange *Citrus sinensis* peel extracts against microcystin LR induced histological damage in the kidney of rat. Brazilian J Biol Sci. 7(17): 247-259.

Srivastava SK, Tiwari PR and Srivastav Ajai K. (1990) Effects of chlorpyrifos on the kidney of freshwater catfish, *Heteropneustes fossilis*. Bull Environ Contam Toxicol. 45: 748-751.

Suput D. (2011) Effects of microcystins, cyanobacterial toxins, on mammalian cells and organs. Acta Chim Slov. 58: 708-716

Tanvir EM, Afroz R, Chowdhury MAZ, Gan SH, Karim N, Islam M N and Khalil MI. (2016) A model of chlorpyrifos distribution and its biochemical effects on the liver and kidneys of rats. Human Exp Toxicol. 35(9): 991-1004.

Tayeb W, Nakbi A, Trabelsi M, Miled A and Hammami M. (2012) Biochemical and histological evaluation of kidney damage after sub-acute exposure to 2, 4-dichlorophenoxyacetic herbicide in rats: involvement of oxidative stress. Toxicol Mech Methods 22(9): 696-704.

Tchounwou PB, Yedjou CG, Patlolla AK and Sutton DJ. (2012) Heavy metal toxicity and the environment. Exp Suppl. 101: 133-164.

Thijssen S, Maringwa J, Faes C, Lambricht I and Van Kerkhove E. (2007) Chronic exposure of mice to environmentally relevant, low doses of cadmium leads to early renal damage, not protected by blood or urine cadmium levels. Toxicol. 229: 145-156.

Tripathi S and Srivastav Ajai K. (2010) Nephrotoxicity induced by long-term oral administration of different doses of chlorpyrifos. Toxicol Indust Hlth. 26: 439-447.

Tripathi S and Srivastav Ajai K. (2011) Cytoarchitectural alterations in kidney of Wistar rat after oral exposure to cadmium chloride. Tissue Cell 43: 131-136.

Upadhyaya AM, Rao MV and Jhala DD. (2018) Ameliorative effects of melatonin against 2, 4-dichlorophenoxyacetic acid toxicity in kidney of mice-A histological study. Asian J Pharm Clin Res. 11(1): 78-82.

Velisek J, Svobodova Z and Piackova V. (2009) Effects of acute exposure to bifenthrin on some haematological, 142 biochemical and histopathological parameters of rainbow trout (*Oncorhynchus mykiss*). Veterinarni Medicina 54: 131-137.

Wangsongsak A, Utarnpongsa S, Kruatrachue M, Ponglikitmongkol M, Pokethitiyook P and Sumranwanich T. (2007) Alterations of organ histopathology and metallothionein mRNA expression in liver barb, *Puntius gonionotus* during subchronic cadmium exposure. J Environ Sci. 19: 1341-1348.

Wiegand C, Pflugmacher S, Oberemm A, Meems N, Beattie KA, Steinberg CEW and Codd GA. (1999) Uptake and effects of microcystins-LR on detoxication enzymes of early life stages of the zebra fish (*Danio rerio*). Environ Toxicol. 14: 89-95.