

DOI: <http://dx.doi.org/10.5281/zenodo.16740461>

Protective effects of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis*) peel extracts against lead-induced nephrotoxicity in rats

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Received: 03 February 2025; Revised submission: 12 May 2025; Accepted: 17 June 2025

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ABSTRACT: The present study investigated histological changes in the kidney of lead treated rats and also evaluated role of jamun (*Syzygium cumini*) seed and orange (*Citrus sinensis*) peel extracts in protecting the kidney from lead toxicity. Male Wistar rats were divided into six groups, Group A: Control; Group B: Lead (Pb); Group C: Lead and jamun seed extract (Pb+JSE); Group D: Lead + orange peel extract (Pb+OPE); Group E: Orange peel extract (OPE); Group F: Jamun seed extract (JSE). The lead dose was 50 mg/kg body weight (b wt) whereas orange peel and jamun seed extract dose was 200 mg/kg b wt/day. Kidneys were fixed on 15 and 30 day following the treatment. 15 day Pb (Group B) treated rats exhibited shrunken glomeruli while 30 day Pb treated rats revealed tubular degeneration, and glomerular hypertrophy. In Pb+ JSE (Group C) and Pb+OPE (Group D) treated rats for 15 day and 30 day, the kidney exhibits changes similar to those as noticed in Pb exposed rats but to a lesser extent. Kidney of rats treated for 15 and 30 day with Group E (OPE) and Group F (JSE) have not shown any remarkable histological change. The present study clearly indicates that histological structure of kidney can be altered adversely by lead. Also, the present study revealed that lead toxicity to kidney can be protected by supplementation with extracts of jamun seed and orange peel.

Keywords: Lead; *Syzygium cumini*; *Citrus sinensis*; Antioxidant.

1. INTRODUCTION

Heavy metals are referred to as essential elements because they are needed for a number of physiological and biochemical processes that are vital to life. However, at high concentrations, they have the potential to be toxic. Heavy metals bioaccumulate in our systems when they are ingested or breathed in. They are therefore categorized as dangerous. Physiological and metabolic problems are brought on by this bioaccumulation. They have been accumulated in the environment, including our atmosphere, rivers and soils as a result of their extensive usage in agriculture, industry, medicine and other fields [1, 2].

Heavy metals interact with nuclear proteins and DNA to produce damage that is specific to certain sites. There are two possible kinds of damages: "direct" and "indirect". The metal causes conformational changes in the biomolecules during the "direct" damage. However, the generation of reactive oxygen and

nitrogen species results in "indirect" damage caused by the heavy metal. It has been observed that signaling pathways are activated by heavy metals [3].

Metals cannot be broken down since they are non-biodegradable and hence, exist in the environment for a very long time. Until they are eluted to other compartments, heavy metals that are present in soil and sediments stay there for a long time. They may also generate or deteriorate into more hazardous forms in response to reactions with other components of the soil or sediment. In contaminated areas like abandoned mine sites or areas where metal-containing insect repellents were previously used, anthropogenic activity has left an extremely high concentration of metals. Lead (Pb) is a hazardous heavy metal that can cause poisoning and various adverse effects on humans and other animals [4]. It is released as mixed industrial effluents from mechanical units, contaminating marine biological systems and killing organisms. Lead is a naturally occurring pollutant that is extremely dangerous to human health and causes a substantial renal toxicity [5]. Lead has a tendency to accumulate in biological systems. Lead is frequently added to urban water storage and is typical of water bodies [6].

According to Segal *et al.* [7] the bulk of heavy metals found in marine ecosystems are the result of both natural and man-made processes, and they may be dangerous to living beings. Industrial workers also constantly consume lead and are subject to acute poisoning. They are exposed to lead at work when they work in battery recycling factories or smelters. The greatest public health risk connected with lead is currently exposure of young children to decomposing fragments of leaded paint. Lead exposure in children may now occur from contaminated drinking water due to outdated infrastructure. Consuming heavy metals poses a major risk to human health, especially when lead contaminated food is involved. As a result, it is essential to use methods that lessen lead toxicity [8].

Aerobic organisms have developed an extensive array of antioxidative and repair systems for the prevention of oxidative stress chemicals that break down ROS, like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase (GR) give the primary antioxidant defense. In contrast, ROS-induced damage repair systems eliminate damaged cells through autophagy and apoptosis processes [9]. The potential to protect human organs from oxidative damage by enhancing antioxidant defenses in the body and increasing total antioxidant capacity is demonstrated through use of nutritional antioxidants as complementary substances that delay or prevent oxidation of cellular components [10].

In India, the deep purple colored, oblong edible fruit with a large centrally located seed is commonly known as Jamun (*Syzygium cumini*). Jamun's fruits pulp and seed extract has been used medicinally for many years. Antigenotoxic effects of the medicinal seed extract are obtained from *Syzygium cumini*, Skeels (Synonym: *Eugenia jambolana*; Family Myrtaceae) [11]. Jamun has anti-ulcer, anti-free radical scavenging, anti-diabetic, anti-malarial, antioxidant, anti-inflammatory, antipyretic, anti-allergic, anti-bacterial, gastro-protective and radio-protective properties [12].

It is also possible to use orange peel extracts in a one step, easy, economical and green strategy for sustainability of dyeing and acquiring wool using high antioxidant activity polyamides or fabrics with multifilament cellulose acetate which has an antioxidant and antibacterial activity [13]. Hesperidin, a component of *Citrus sinensis* that is found in orange peels, has antioxidant, anti-inflammatory, anti-cancer, and antilipidemic properties. Orange peels contain naringin and naringenin, which have antibacterial, antidiabetic, and antitoxic properties [14-16].

2. MATERIALS AND METHODS

Male Wistar rats (40-60 g) were purchased from Asia Scientific Emporium, Varanasi, India. Prior to treatment, rats were acclimatized for at least two weeks in polypropylene cages. Rats were given standard diet and water *ad libitum* throughout the acclimatization and treatment. Rats were randomly divided into 6 groups- A, B, C, D, E and F and each group contained 10 animals. Following treatments were given orally to each group daily at 8:00 AM throughout the experiment:

- Group A: Control
- Group B: (Lead (Pb) - treated): Rats were given daily with lead (50 mg/kg body weight (b wt)).
- Group C: (Lead + jamun seed extract): These rats were given daily lead (50 mg/kg body wt) and jamun seed extract (200 mg/kg b wt) simultaneously.
- Group D: (Lead + orange peel extract): These rats were given daily lead (50 mg/kg b wt) and orange peel extract (200 mg/kg b wt) simultaneously.
- Group E: (Orange peel extract): Rats received daily orange peel extract (200 mg/kg body wt).
- Group F: (Jamun seed extract): Rats received daily jamun seed extract (200 mg/kg body wt).

On the 15th and 30th day after initiation of the experiment, rats (5 from each group at each interval) after overnight fasting, were lightly anesthetized after 24 hours of the last dose.

Seeds of jamun (*Syzygium cumini*) were bought from commercial supplier (M/S SVM Naturals, Tamil Nadu, India). Purchasing of oranges (*Citrus sinensis*) were done locally and separation of peels were done. The jamun seeds and orange peels were washed with tap water and dried at room temperature. They were grinded in powdered form. These powdered forms were mixed with 90% ethanol in 1:20 ratio (w/v) and kept on orbital shaker for 48 h and then filtered with the Whatman No. 1 filter paper and kept in rotatory evaporator at 40 °C. The dried materials were kept at -20 °C for future experiment. Soxhlet apparatus was not used in this process because of heat labile compound present in leaves may be denatured. During the treatment, rats received dose of dried residues mixed with ethanol.

Fixed tissues of kidney were dehydrated in a gradient series of ethanol, cleared with xylene and embedded in paraffin. Sections were cut at 6 µm and placed on slides. The sections were cleared in xylene and rehydrated with graded series of alcohol and stained with hematoxylin and eosin (HE) solution for light microscopic analysis. Photomicrographs of stained slides were taken with the help of Olympus H-20i microscope and Olympus E 420 camera.

Experimental design was approved by the Research Degree Committee, D.D.U. Gorakhpur University, Gorakhpur, India. The study was conducted in accordance with “Guide for the Care and Use of Laboratory Animals”.

3. RESULTS

Kidney of control rats is composed of nephrons. Each nephron consists of a dilated portion, the proximal tubule, distal tubule, loop of Henley and the renal corpuscles. Renal corpuscles consists of tufts of capillaries. Glomerulus is surrounded by the Bowman's capsule. Urinary space is present between the glomerulus and Bowman's capsule (Figure 1).

Shrunken glomeruli were observed at certain places with kidney following 15 day lead treatment (Group B), forming a gap between the glomerulus and Bowman's capsule (Figure 2). In rats from Group C and Group D changes were similar to Group B but to a lesser extent.

After 30 days of lead treatment, swollen glomeruli were observed at certain places, resulting in no space between Bowman's capsule and glomerulus (Figure 3). In addition, there was degeneration of the proximal and distal tubules (Figure 4). In the lumen of proximal and distal tubules, eosin positive deposits have also been observed at certain sites. Few glomeruli appeared to be degenerated (Figure 5). Similar changes were observed except degeneration in proximal and distal tubules of Group C and Group D rats. The renal morphological structure is almost the same as that of control in Group E and Group F rats.

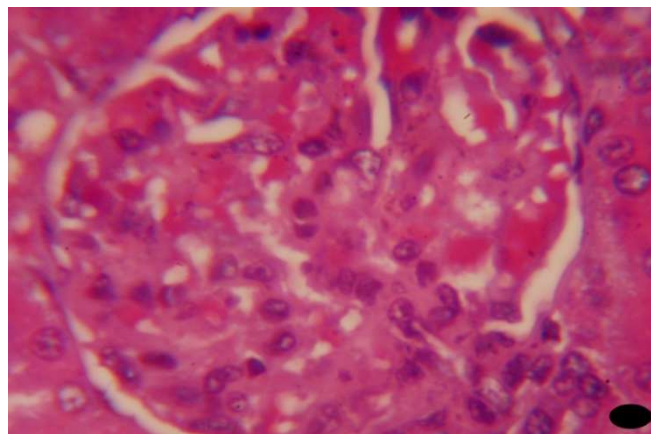


Figure 1. Kidney of control rat. Hematoxylin-eosin X 500.

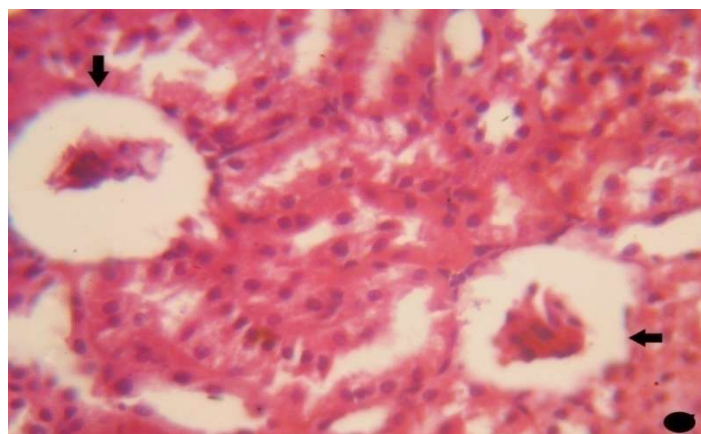


Figure 2. Kidney of 15 day lead exposed rat showing shrunken glomeruli (arrows). Hematoxylin-eosin X 100.

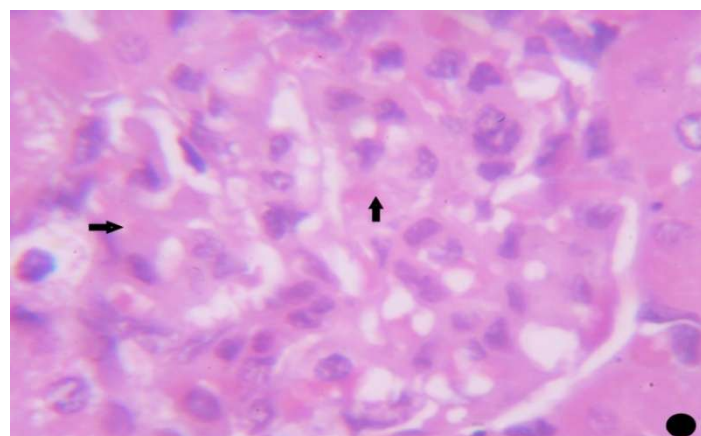


Figure 3. Kidney of 30-day lead exposed rat showing glomerular hypertrophy (arrows). Hematoxylin-eosin X 500.

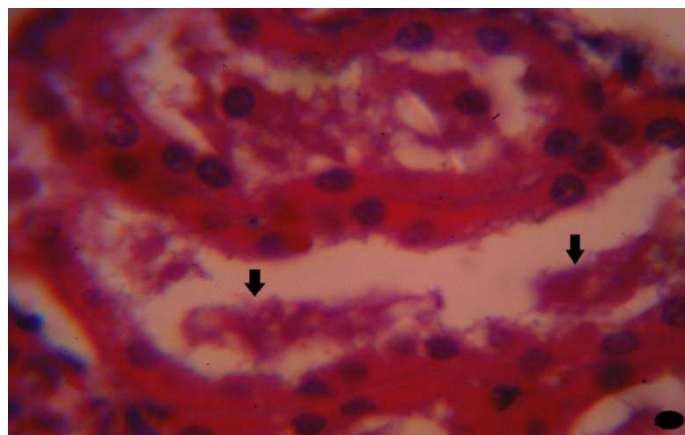


Figure 4. Kidney of 30 day lead exposed rat showing tubular degeneration (arrows). Hematoxylin-eosin X 500.

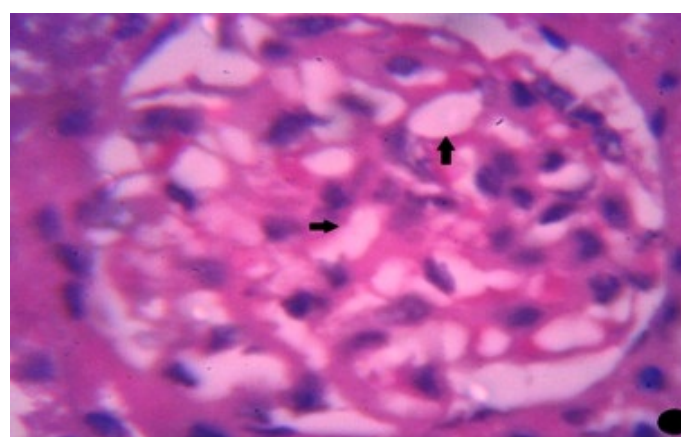


Figure 5. Kidney of 30 day lead exposed rat showing glomerular degeneration (arrows). Hematoxylin-eosin X 500.

4. DISCUSSION

The shrinkage of glomeruli observed in rats exposed to lead treatment is in conformity with the findings of few workers who have also observed glomerular shrinkage in rats after exposure to toxicants/chemicals- paraquat [17], lithium [18], aluminium chloride [19], chlorpyrifos [20], cadmium [21, 22], 2,3,7,8-tetrachlorodibenzo-p-dioxin [23], endosulfan [24], silver [25], malathion [26], mercuric chloride [27], 2,4-dichlorophenoxyacetic acid (2,4-D) [28], MCLR [29], cypermethrin [12] and bisphenol-A [30].

Glomeruli in rats treated with lead showed degeneration after 30 days of treatment. In past few researchers have observed similar results following toxicant exposure in fish after treatment with chlorpyrifos [31], deltamethrin [32], cadmium [33], microcystin [34] and cypermethrin [35]; in chick- after treatment with cypermethrin [36] and in rat- after treatment with paraquat [37], chlorpyrifos [20] and cadmium [22,23], lead [38], MCLR [29] and cypermethrin [12]. Additionally, Barrouillet *et al.* [39] observed a decrease in GFR following lead exposure and proposed that glomerular degeneration is the cause of decrease in GFR.

In rats tubular degeneration following lead treatment after 30 days were noticed. Similar findings were reported by other researchers in vertebrates after exposure to chemicals or toxicants to fish: chlorpyrifos [31], cadmium [33], microcystin [34], cypermethrin [40]; to chick: cypermethrin [36]; to quail: lead [41]; to wood mouse and white-toothed shrew (landfill leachates containing toxic metals [42]; to mice: chlorpyrifos [43], microcystin [44]; to rabbit: fluoride [45]; to rat: chlorpyrifos [20, 46], microcystin [29,47], metal mixture [48], paraquat [17,37], cypermethrin [12,49], fenthion [50], cigarette smoke [51], cadmium [21,22], lead [38],

gentamicin [52], 2,4-D [53], zinc [54], streptozotocin [55], monosodium glutamate [56], endosulfan [24], lead acetate [57]. However, when fish are exposed to bifenthrin, kidney morphology does not change [59].

After 30 day of treatment with lead rats exhibited glomerular hypertrophy which is in conformity with the reports of other investigators who have also noticed similar changes after exposure to different toxicants in rats: cadmium [21,22], gentamicin [52], 2,4-D [53], chlorpyrifos [20], *Acacia nilotica* pod extract [55], heterogenous chemical mixture [60], fenitrothion [61], malathion [62]. In rabbits fluoride exposure resulted in glomerular hypertrophy [45].

The hydrolytic alterations that kidney tubules may experience following toxicant exposure could be the plausible cause of the tubular vacuolization and degeneration observed in rats treated with lead. Similar suggestion has also been proposed [11, 29] for the alteration noticed in toxicant exposed rats.

Author Contributions: AS conducted the data collection and primary investigation for the study, and writing manuscript; SKS and AKS supervised the research, provided guidance throughout the study; SKS, AKS and NS assisted in manuscript writing, formatting and reviewed the final draft. All authors have read and agreed to the published version of the manuscript.

Ethical Approval: Experimental design was approved (RC/ F.Sc./Zoo/2019-20/13/22) by the Research Degree Committee, D.D.U. Gorakhpur University, Gorakhpur, India. The study was conducted in accordance with “Guide for the Care and Use of Laboratory Animals”.

Conflict of Interest: The authors of this work declare that they have no conflicts of interest.

Source of Funding: The research work has not been funded by any funding agency.

Acknowledgements: Authors are thankful to Prof. Ravi Kant Upadhyay, Head of Department of Zoology, DDU Gorakhpur University, Gorakhpur, India, for providing laboratory facilities.

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