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ORIGINAL ARTICLE

Assessing Bisphenol A (BPA) Induced Kidney Toxicity in Mammalian Model: A Comparative Study of Biometric, Histochemical, Histological and Behavioral Analyses

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ABSTRACT

Background: These BPA-containing plastics were commonly used to make toys, crockery and digital consumer products. The prime issue was the human exposure to BPA through food contamination from polycarbonate bottles and cars etc.

Methodology: Using a random design, 40 healthy male albino mice were divided into four groups (n=10). Their complementary groups received Kidney High Dose (600 mg/Kg/BW) and Kidney Low Dose (300 mg/Kg/BW) oral BPA doses for four weeks. The Lethal Dose-50 value (2400mg/kg/BW) was used to calculate the intensity of the dosages. The kidney was subjected to biometric, morphometric, histological, histo-chemical, and ultra-structural investigations of control and treated groups.

Results: The investigation showed that the treated groups had seen considerable difference in their biochemical analysis, body weights, particularly kidney weights. In addition, histological studies revealed aberrant mechanisms and renal impairment in the treated groups. Furthermore, it was discovered that BPA harming disrupted the mice's social behavior since aggressive deviations were observed.

Conclusion: This investigation provides convincing evidence that BPA has adverse effects on renal histopathology as well as endocrine disruptor effects. This emerging evidence is also associated with kidney-based pathway malfunctions and daily behavioral activities.

Keywords
Bisphenol A, Biometric, Morphometric, Histochemical, Endocrine Disruptor.

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Article info.
Received: February 12, 2023
Accepted: May 06, 2023

Cite this article: *Nawaz F, Ullah A, Ara C, Zaifat S, Idnan M, Mehboob M, Azmet S. Assessing Bisphenol A (BPA) Induced Kidney Toxicity in Mammalian Model: A Comparative Study of Biometric, Histochemical, Histological and Behavioral Analyses. RADS J Biol Res Appl Sci. 2023; 14(1):1-10.*

INTRODUCTION

Bisphenol A (BPA) is a synthetic chemical compound that has gathered significant attention due to its widespread use in the production in plastic and resins. It belongs to the class of organic compounds known as bisphenols, characterized by two hydroxyphenyl groups connected by bridge. BPA was first synthesized in the 19th century, and its versatility led to its incorporation into various industrial application.

One of the primary applications of BPA is in the production of polycarbonate plastics, which are known for their clarity, durability and shatter-resistances. However, concern about the potential health effects of BPA exposure have led to extensive and public debate. The extensive use of BPA has

become prevalent in the contemporary environment resulting as a potential hazardous pollutant. Consequently, it has been classified as a potentially hazardous contaminant. Regarding its origins, BPA had been detected in diverse range of environments including house hold, soils, and water bodies. This is noteworthy because BPA has been reported as a hazardous component in living creatures[1,2]. In addition food and water BPA contamination are to blame for getting into living things, especially the human body. A sufficient number of sources BPA were identified. The most common was the used in thermal paper in the sales receipts. It's conceivable that this will leak monomers into food and drink. The majority of people were exposed to home daily routines[3]. The impact of BPA on early childhood has spurred a pressing demand for the detection of BPA containing products in Western nations. BPA is often used to make commercial plastic, primarily edible packaging[4]. In developing Nations, a significant population was affected. Over past few years, there has been a substantial and comprehensive scientific endeavor to assess the toxicity of BPA[5]. The campaign was launched to increase awareness about the risk of using BPA plastic to inflict harm and devastation[6]. Swear detrimental destructions in organs and the anomalies in fundamental mechanism of various biological functions elucidated the drastic effect of BPA on cardiac, BPA is linked to neurological, gene toxicity, carcinogenic, abnormal behavior, estrogenic and developmental structures. Developed countries like China, the United States, and Europe were equipped to tackle the problem[7].

Low grade BPA plastic in the various sectors is prevalent in Asia, Notable in Pakistan, India and Bangladesh has raised the concerns about its potential harms to society. In various prominent industries, there has been a reduction in the utilization of BPA. Numerous research inquiries have been conducted, none have yielded convincing results.[8,9].

The purpose of this study was to accurately estimate the detrimental consequences of BPA on kidneys while also giving insight into the validity and standard quality of BPA used in the polymer industry. When it comes to the grade of plastic used, the majority of underdeveloped countries make concessions. However, political and economic consideration BPA from exposing the lethality of its originalities to the general public.

MATERIALS AND METHODS

BPA was obtained from company brand named "Duskan" USA chemicals, which is 99.9% pure. In the course of the investigation, mature forty male albino Mus musculus mice were employed. Mice typically weigh between 20 and 25 ± 02 grams. On average, the conditions were upheld at a room temperature of 22.2 °C, with humidity level at 50.1%, and a 12/12-hours light and dark cycle. The mice were relocated and housed in the new animal house. The experimental animals were remained undisturbed for few days before the experiment to acclimatize the local environment[10]. Every animal has access to free food and water (ad libitum). The Ethics Committee for Laboratory Animal Care approved all of the study's protocols (Bio-Ethics committee of Punjab University Lahore Pakistan). Instead of using a plastic cage, alternative equipment (such as glass bottles and metallic bowls) and stainless-steel cages were employed to reduce interference[11].

The prescribed dosages were attained using LD50 (2400 mg/Kg/BW)[2, 9]. After being weighed, the mice were separated into four groups of ten at random. Group-KC (Control) remained normal and was not exposed to anything that persisted. Mice in the Group-KHD (High dosage) and Group-KLD (Low Dose) groups were treated at high doses (600 mg/Kg/BW) and low doses (300 mg/Kg/BW), respectively. Soybean oil was delivered to Group-KVC (Vehicle Control), which was designated as such. Oral medications were used for all treatments. For four weeks straight, BPA and soya bean oil were administered orally. G-KVC served as the control group and was left unaltered. Blood samples were taken to conduct a biochemical study. The BPA was given and maintained for four weeks in a row. During the course of trial, consistent assessments were conducted to monitor body weight, measure dietary intake and fecal waste produced by them[12].

Sample Preparation

To prepare the samples, the animals are weighed using a digital weighing scale. After blood sampling, the mice were swiftly slaughtered, and the kidneys were taken out and weighed. For histological analysis, the value of the kidney (KC) coefficient was determined, and the kidneys were fixed and stored in 10% formalin (Figure **1**).

Serum Biochemical Measurement Indices

We followed the manufacturer's instruction to determine the serum level of uric acid, blood urea nitrogen, and creatinine using a conventional commercial kit. (Changchun Huili Biotechnology Co. Ltd. Changechun China) (Figure **1**).

Histopathology Analysis

The tissue mainly kidney was cleaned with saline, processed to ethanol solution with increasing concentration for dehydration, dipped in paraffin wax, paraffin-embedded, and sectioned (5 mm thick) after 48 hours of fixing. Hematoxylin and eosin (H&E) staining method were used[13]. Using a portable camera called the "Ease-i Imageur universal" and a microscope with the model number M4000-D Swift from Japan, microphotographs of histological sections were taken at various magnifications.

Statistical Analysis

Data were evaluated using the parameters' means and standard deviations. As a post-doc test, a one-way analysis of variance (ANOVA) was performed to determine if there were any significant differences between the various groups. A p-value of 0.05 was used to determine statistical significance.

RESULTS

The outcomes of this research were structured into four primary tiers. Biometric, Biochemistry, Histo-pathological analysis, and Behavioral observations.

Biometric Analysis

The biometric observations of the current research revealed the following differences while comparing the treated and control groups (Table **1**).

Table 1. The table shows the comparison in biometric analysis, feed consumptions, fecal waste production between control and BPA treated groups.

Parameters	Group KC (Control)	Group KVC (V. Control) (0/1ml/animal/day)	Group KLD (low dose) (300mg/Kg/body weight)	Group KHD (high dose) (600mg/Kg/body weight)
Mean body weight (Zero day of experiment) (gm)	23.46±0.47	23.40±0.59	24.08±0.53*	23.82±0.06**
Mean body weight (28th day of experiment) (gm)	25.08±0.44	24.90±0.47	22.07±0.52	22.03±0.43*
Mean weight of kidney (mg)	151.1±1.2	150.75±0.75	144.08±0.88**	138.9±1.1*
Mean kidney length (mm)	4.82±0.003	4.70±0.003	4.55±0.003	4.22±0.001
Mean kidney width (mm)	4.44±0.021	4.46±0.001	4.13±0.001	4.06±0.001
K.Coefficient of kidney (gm)x100/body weight (gm)	0.0059±0.001	0.0062±0.003	0.0063±0.025*	0.0063±0.002*
Average (28 days) feed intake (gm)	20.25±0.30	19.79±0.21	21.96±0.41	22.04±0.23**
Average fecal waste (=10) (gm)	3.00±0.00	2.93±0.03	2.86±0.04**	2.39±0.17*

*Asterisks shows the significant differences among the groups. Level of significant p>0.05

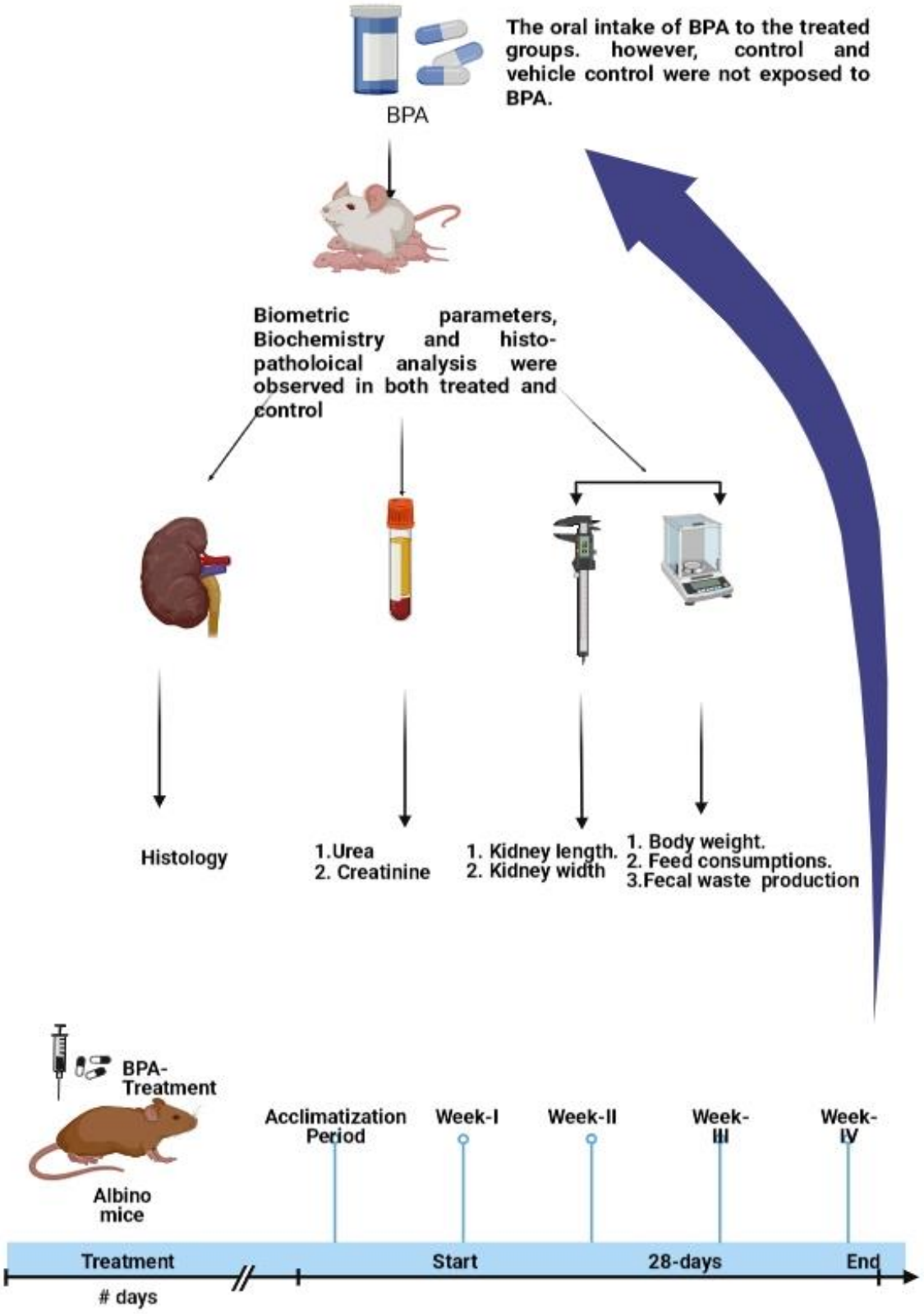

Figure 1. Schematic representation of research study, created at BioRender.com.

Average Body Weight: Treating mice with BPA dose, irrespective of concentration, (G-KHD, G-KLD), depicted substantial reduction in average body weights. ($p < 0.01$) when compared to the positive and negative control groups.

Average Kidney Weight: Similarly, the trends of variation in BPA-induced kidney weight were same as in body weights. The BPA-exposed groups showed a significant loss in weight when compared with the control groups (Table **1**).

Kidney Length and Width: Similarly, the morphometric analysis revealed a significantly decreased in the width and length of the BPA-exposed mice's kidneys. However, there were no such differences in the control groups.

Kidney Coefficient: It is calculated by using following formula:

K.Coff = weight of Kidney (gm) ×100/ body weight (gm)

The net change in gain or loss in body and kidney weights of the mice after consuming BPA is easily sought out using the kidney coefficient. This will give insight into the degree of destruction in the induced kidney.

Food Consumption: Feed (National Feed No.14) consumption was changed and measured on daily basis for all groups. It was found that both treated groups exhibited a significant increase in their diet consumption in the 2nd week, which periodically decreased as the experiment proceeded, but in the end, it was found an average increase when compared with control groups (Table **1**). The consumption of large-size pellets was more than the smaller ones of the same diet.

Fecal Waste: The wet fecal waste (Aluminum foil was used for temporary storage while processing) was collected from each cage (n=10) and measured on weekly basis. In the end, it was calculated that the amount of fecal material produced in treated groups was more than that of the vehicle (positive) and control (negative) groups (Table **1**).

Biochemical Analysis

Changes in Serum Biochemical Indicators: It was observed that in the treated groups (G-KHD, G-KLD) there was a significant upraise inthe level of blood Urea and Creatinine when compared with control and vehicle control (Figure **2 & 3**).

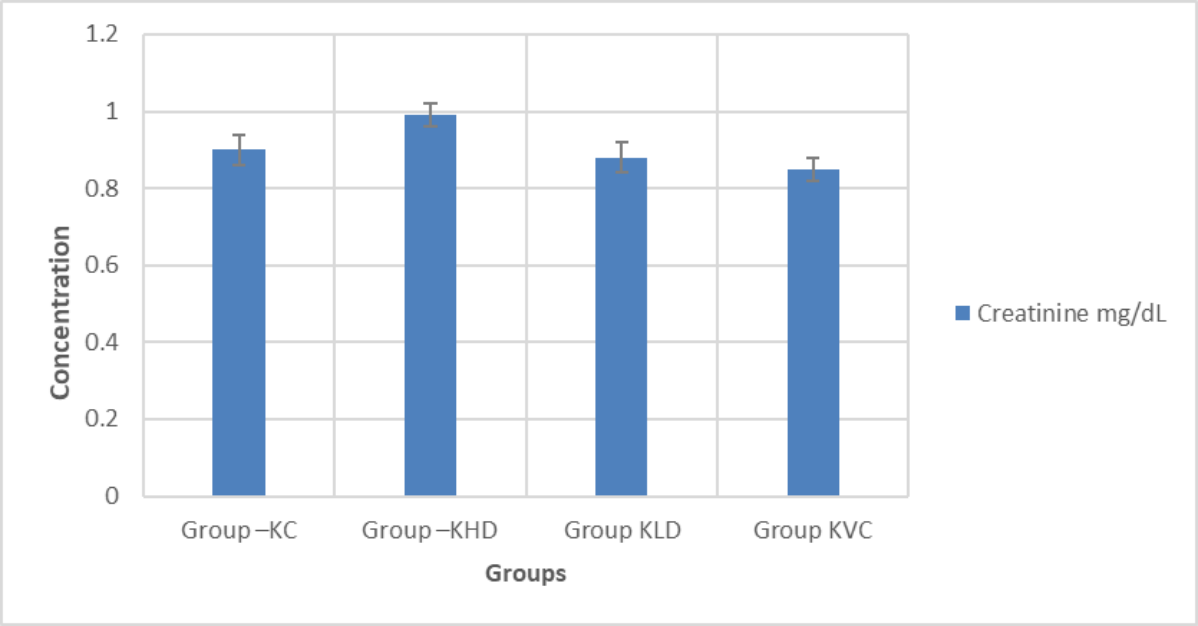

Figure 2. Variation in the value of creatinine the control and BPA treated groups.

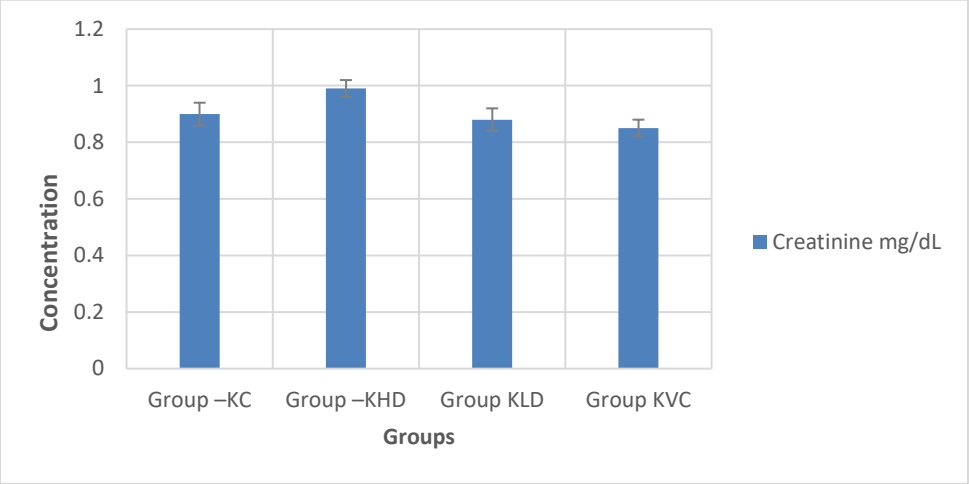

Figure 3. Variations in the value of urea in the control and BPA treated groups.

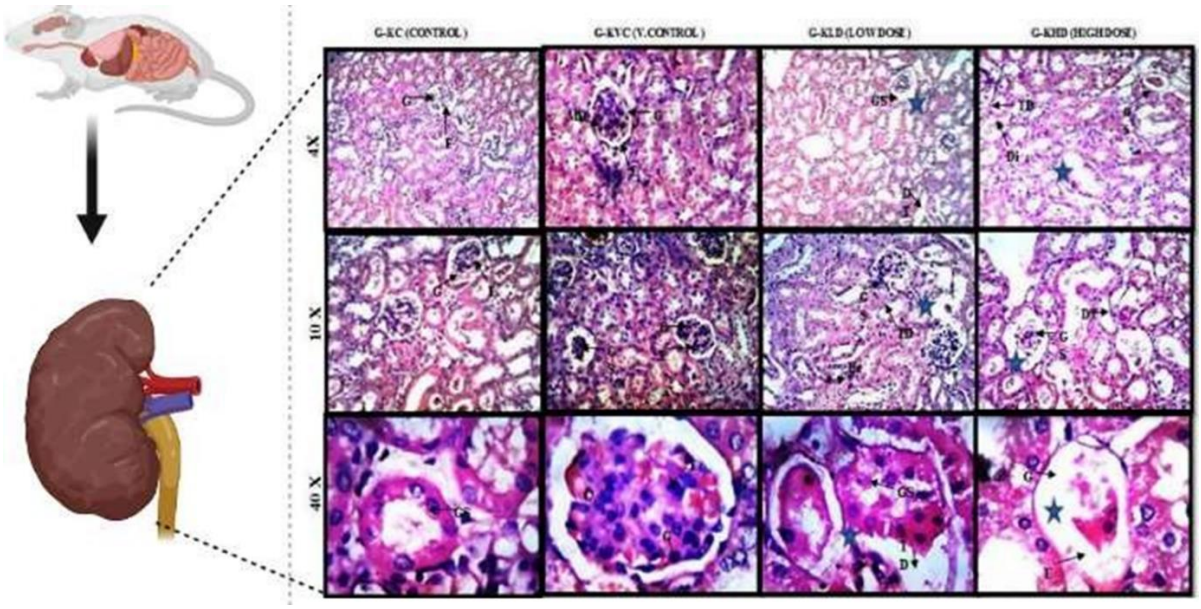

Figure 4. Kidney sections from mice display the following renal tubules: G- KC (Control) (Control) G-KVC (Vehicle Control) groups, proximal tubules (star) displaying intact pyramidal cells encircled by a restricted lumen, the cytoplasm extremely acidophilic and acidophilic, and rounded, vesicular (active) nuclei (arrows) are H-E, 40X,100X,400X. G2: A modest dosage of KLD dye reveals minor alterations in the proximal tubules, including an increase in cytoplasmic acidophilia and a density of nuclei staining (signs of early apoptosis). Dilated lumina and a reduction in lining epithelium height were seen in distal tubules. In several tubular cells (H-E, 400), the cytoplasm was not stained. G2-a: A modest dosage of KLD dye reveals minor alterations in the proximal tubules, including an increase in cytoplasmic acidophilia and a density of nuclei staining (signs of early apoptosis). Distal tubules displayed dilated lumina and a shorter lining epithelium. G2-b: Loss of tubular outlines was seen with KLD dye. The lumina vanished completely. Cells' cytoplasm is intensely pigmented, and their nuclei get smaller and more stained with time (signs of apoptosis). (H-E, × 400). G3: KHD dye (high dosage) demonstrates tubular shape disorder, dilatation (arrows), and evidence of cell degeneration (unstained cytoplasm, dotted circles, and decreased nuclear size, arrows) (H-E 400).

Histopathology: In the control kidney cells, the renal small cystic lumen maintained a consistent, unbroken size while the proximal tubule epithelial cells were densely arranged with a notable enlargement of the lumen width. The lumen displayed irregularities, and the cell bodies were comparatively large. The glomerular structure also appeared intact, displaying discernible hematoxylin and eosin staining with the cytoplasm. The nucleus prominently rounded was situated near base of the cell. This cell exhibited a light and distal tubule lumen was prominent and well define. The rounded nucleus was positioned on the proximal cavity surface. Subsequent to BPA G-KHD and G-KLD treatment, the renal tubules exhibited enlargement as compared to the control cells. Tubular capillaries experiences expansion or even complete disappearance. Notable morphological changes included granule and vesicular degeneration, nuclear condensation and nuclear lysis within the renal tubular epithelial cells. The count apoptotic cells were notably higher after BPA treatment compared to the control group, as indicated by the result of microscopic staining slides (Figure **4**).

DISCUSSION

BPA is a lethal material and injurious to health if inhaled orally. It is also recognized as a global ecological pollutant and potentially induce kidney toxicity. These issues need to be thoroughly investigated and confirmed to determine whether the administration of BPA resulted in significant kidney toxicity. The current study was authenticated by findings reported by Rahman *et al.,* (2021) and Dökmeci *et al.* (2021) [14,15]. Overall, the results of this primary study showed that administration of BPA with varied concentrations caused renal injury. It was suggested that even when administered at its lowest dose, BPA consistently led to a decrease in kidney efficiency and caused a notable degree of injury[16]. Similar results were also validated by Moreno-Gómez-Toledano *et al.* (2022)[17]. In addition to the toxicity, administration of BPA with varied concentrations of doses causes a significant ($p<0.05$) reduction in body and renal masses. However, the adverse effects of BPA were proportional to the inhaled concentration of dose.

Afzal *et al.* (2022) concluded that BPA damage caused a significant reduction in body and kidney weight[18]. In comparison to the control and vehicle controls mice subjected to BPA treatment exhibited passive increases in body weight. This trend of diminished weight gain became more pronounced with escalating BPA concentrations, which in turn contributed to hormonal disruption. These results were corroborated by the findings of Kobroob *et al.* (2018); Karabulut *et al*., (2022) in their respective studies[19,20]. Faheem *et al*., (2021) also reached the same conclusion and validated the current research findings stating that BPA toxicity significantly reduced organ weights[2].

The abnormal reduction in the body weight observed in mice exposed to BPA could stem from reduced food consumption and/or increased energy expenditure. Notably, the quantity of food ingested by the BPA treated groups markedly differed from that of the control's groups, despite a discernibly inclination towards decreased food intake with increasing of BPA level[21]. The results suggested a catabolic effect of BPA rather than a disruption in the feeding mechanism. Despite the low rate of growth development in mice, renal hypertrophy still occurred in BPA-contaminated treated groups. This was demonstrated by a dose-dependent increase in kidney weight when standardized to the corresponding body weight. These effects of BPA on the feed trends coincides with the findings of Kobroob *et al.* (2018); Ismail *et al.* (2022)[19, 22].

The reduction in the feed consumption correlated with the corresponding decrease in waste/fecal production by the BPA-induced groups. When compared to the untreated animals, BPA triggered the hormone disruptor leading to abnormality in the digestive activity of the animals[23, 24].

In the present study, it was experimentally elucidated that BPA persuaded toxic histopathological effects. The cytological evaluation of the kidney sections in BPA groups (with low and high doses) indicated glomerular degeneration, congestion, and mononuclear cell infiltration. Oral administration of BPA for 28 days revealed histological renal changes, including dilation and propagation of glomeruli and degeneration of epithelium of proximal tubule, along with a remarkable rise of serum creatinine and urea levels. The microscopic examination of the renal tissue had showed a focal loss of brushy tubular cover observed in the cortex, with minor tubal dilatation in the group, while these variations were insignificant in the low-dose group[16]. These present results validated by the work of Aboelhassan *et al.* (2022)[25], which demonstrated

that BPA produced vital vein obstruction and congestion, swelling, and edema leading to the breakdown and necrosis of hepatocytes. In protein-uric conditions, Podocytes are commonly affected sites, eventually causing renal function impairment and detrimental effects on the kidney glomeruli. Histological examination revealed a variation of glomerular abnormalities in BPA-exposed groups which was further confirmed by their irregular podocyte foot progressions. The present findings align closely with the referenced study, which showcased the emergence of podocytopathy and proteinuria in mice due to BPA exposure. These findings further exhibited discernible damage to the renal proximal tubules in the BPA-exposed groups, as evidenced by dose-depended alterations in their typical ultrastructure[26].

The initial outcomes of the various research studies indicated an elevation in urea and creatinine level among the groups subjected to BPA treatment, in contrast to the control group representing the normal conditions. It was additionally noted that continuous exposure to BPA over a span of 4 weeks can lead to the development of azotemia *i.e.*, a condition in which an organism is unable to effectively eliminate nitrogenous wastes from the body, resulting in a simple increase in blood urea nitrogen and serum creatinine levels[27]. The aforementioned cytological observations collectively demonstrated that BPA induces kidney damage along with a decline in renal function. This compromised the capacity and capability to eliminate waste material (fecal) could potentially underlie the disruption in both glomerular filtration and tubular function[28].

Strong evidence authorizes those social behaviors in experiments, are susceptible to exposure to BPA, leading to male mice exhibiting aggressive abnormalities. These effects are likely multifactorial, disrupting normal pathways. Early exposure of animals and humans to these widely prevalent chemicals may result in subtle interactive and social effects. Social behavioral insufficiencies resulting from BPA exposure include any behaviors involving interaction among members of the same species, such as various forms of communication (i.e., courtship behaviour, pair bonding, social interest, social grooming, copulation, and aggression) [29, 30].

CONCLUSION

This study has unequivocally unveiled the detrimental repercussions of oral administration of BPA, manifesting oxidative damage lead to nephrotoxicity. In consonance, BPA is affirmed as a potent toxicant with far reaching implications for living organism.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the Ethical Board of the University of Punjab, Lahore Pakistan.

CONFLICT OF INTEREST

There is no conflict of interest of any kind.

FUNDING SOURCE

University of the Punjab, Lahore Pakistan

ACKNOWLEDGEMENT

We acknowledge the efforts of all the contributors.

LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
BPA	Bisphenol A
H & E	Hematoxylin and Eosin
LD50	Lethal Dose 50
SPSS	Statistical Package for the Social Sciences

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