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ORIGINAL ARTICLE

Analyzing the Biochemical Alterations and Histopathological changes in Oxidative Stress-Induced Tissue Damage. A Study on Antioxidant Therapeutic Interventions

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ABSTRACT

Background: Hexavalent chromium [Cr (VI)] is a toxic industrial chemical that produces oxidative stress, disrupts biochemical pathways, and causes severe organ damage.

Objectives: The study aimed to assess the dose and time-dependent biochemical and histopathological effects of hexavalent chromium [Cr (VI)] exposure, including oxidative stress, hepatotoxicity, and nephrotoxicity.

Methodology: The effects of hexavalent chromium (Cr (VI)) were evaluated on albino rats over 30, 60, and 90 days, at dose and time-dependent conditions. Control and treatment groups (2, 5, and 10 mg/kg [Cr (VI)] were given daily orally to rats. The analysis of oxidative stress markers (MDA, GSH, SOD), liver enzymes (ALT, AST), and renal parameters (creatinine, BUN) was carried out. For formalin fixation and staining, liver and kidney tissues were subjected to histopathological examination. One-way ANOVA ($p < 0.05$) significance was used in statistical analysis, adhering to ethical and international guidelines.

Results: Dose and time dependence of oxidative stress and organ damage were produced after exposure to hexavalent chromium [Cr (VI)]. Decreased glutathione (GSH) and superoxide dismutase (SOD) activity, increased blood levels of lipid peroxidation products, and higher malondialdehyde (MDA), a sign of lipid peroxidation, were demonstrated. Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and blood urea nitrogen (BUN) were high, indicating hepatocellular damage and renal impairment, respectively, and suggesting systemic toxicity and increasing oxidative damage.

Conclusion: Dose and time-dependent oxidative stress (increased lipid peroxidation and decreased antioxidant defenses), causing hepatocellular and renal dysfunction, results from exposure to hexavalent chromium [Cr (VI)]. These results also serve to further demonstrate the cumulative toxicity of [Cr (VI)] and its ability to disrupt biochemical and histopathological homeostasis.

Keywords: Hexavalent chromium, malondialdehyde, glutathione, superoxide dismutase, alanine aminotransferase, aspartate aminotransferase.

INTRODUCTION

An imbalance between the production of Reactive Oxygen Species (ROS) and the antioxidant defense systems is a key aspect of the pathophysiology in various diseases, including cancer, diabetes, cardiovascular disorders, and neurological conditions[1]. Regular cellular metabolism results in byproducts of ROS, including hydrogen peroxide, hydroxyl radicals, and superoxide anions. Nevertheless, overproduction of reactive species or a deficient antioxidant defense system can lead to the formation of oxidative damage to biomolecular species, i.e., lipids, proteins, and nucleic acids, that can detrimentally affect organ and cellular function[2].

Oxidative stress has been of special interest because of its capacity to amplify disease progression through a complex relationship with tissue damage. Oxidative stress is often responsible for the consequences of lipid peroxidation, protein oxidation, and DNA damage, which can lead to the activation of apoptotic and inflammatory cascades. Environmental factors, lifestyle choices, and exogenous toxicants that increase ROS production and decrease antioxidant defenses compound this pathophysiological process[3].

Tissue histopathological changes from oxidative stress are valuable markers of cellular damage and organ dysfunction. Structural alterations in critical organs, the liver, kidney, brain, and heart, induced by oxidative stress are repeatedly studied with important implications for systemic health. Identification of biochemical pathways of oxidative damage and an understanding of possible therapeutic interventions is in order[4]. Oxidative stress-induced tissue damage has become a promising therapeutic avenue where antioxidant therapies are being used. These interventions aim to restore redox balance and prevent cell damage by scavenging ROS and increasing endogenous antioxidant systems. During preclinical and clinical testing, there has been potential for polyphenols, flavonoids, antioxidants, and vitamins. Nevertheless, the efficacy of these therapeutic agents varies by bioavailability, dosing, and the underlying disease context[5, 6].

However, despite the increasing amount of data, a brain gap still exists in the knowledge of the fine relationship of oxidative stress, histopathological changes, and antioxidant treatment potential. The objective of this study was to systematically evaluate biochemical changes and histopathologic features in tissue that is stressed by oxidative stress and to evaluate the efficacy of antioxidant therapeutic interventions. This research combines biochemical, histological, and therapeutic studies to bring the benefit of insight to possible antioxidant strategies to decrease oxidative stress and the pathologies it may cause [7, 8].

MATERIALS AND METHODS

Place and Duration of Study: The current study was conducted in tertiary care Hospital and the animal house of the Institute of Molecular Biology and Biotechnology (IMBB), CRiMM, The University of Lahore, Lahore, Pakistan, from March 2021 to November 2022.

Study Design: This experimental study was carried out to assess the biochemical and histopathological effect of hexavalent chromium (Cr (VI)) exposure in albino rats. The study was set up as control and treatment groups to examine dose and time-dependent toxic effects and therapeutic interventions. The study protocols were approved by the Institutional Animal Ethics Committee (IAEC) of institution, following the ARRIVE guidelines

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and in compliance with the Declaration of Helsinki for animal research

Inclusive and Exclusive Criteria: Inclusive criteria were healthy male albino rats of 8–10 weeks old and weighing 180–220 grams, exposed to Cr(VI) dosed at 2 mg/kg, 5 mg/kg and 10 mg/kg daily and a control and an antioxidant (Cr(VI) (10 mg/kg) + N acetylcysteine (100 mg/kg). The study was performed for 30, 60 and 90 days, assessing oxidative stress markers (MDA, GSH, SOD), liver enzymes (ALT, AST), renal parameters (creatinine, BUN) and histopathology according to IAEC and ARRIVE guidelines. Rats with health conditions, not suitable age or weight, or not treated as per protocol were excluded by the exclusive criteria. Also excluded were groups that were not adhering to ethical standards or proper dosing or did not have enough data to analyze.

Animal Selection and Care: An authorized institution provided the healthy male albino rats, which were 8–10 weeks old and weighed 180–220 g. Under controlled laboratory circumstances (temperature: 22 ± 2°C, humidity: 50–60%, 12-hour light/dark cycle), the animals were housed in stainless steel cages with unrestricted access to standard food and water. The trials were preceded by a 7-day acclimatization phase to ensure stability and health.

Experimental Groups: Five groups (n=8) of rats were randomly assigned to receive different doses of Cr(VI): distilled water (vehicle) as a control group; Cr(VI) at a low dose of 2 mg/kg body weight; Cr(VI) at a medium dose of 5 mg/kg body weight; Cr(VI) at a high dose of 10 mg/kg body weight; and an antioxidant-treated group that received Cr(VI) at 10 mg/kg body weight in addition to oral N-acetylcysteine (100 mg/kg).

Cr (VI) Preparation and Dosing: Cr (VI) was received from a recognized supplier (purity: 99%), and a stock solution was made with distilled water. To maintain stability, dosing solutions were produced fresh every day, and doses were provided once daily via oral gavage for up to 90 consecutive days.

Sample Collection: At 30, 60, and 90 days, rats were anesthetized with ketamine (75 mg/kg) and xylazine (10 mg/kg) delivered intraperitoneally. Blood samples were taken via heart puncture for biochemical analysis, while tissue samples (liver and kidney) were extracted for histological examination.

Biochemical Analyses: Using the thiobarbituric acid reactive substances (TBARS) assay to measure malondialdehyde (MDA) levels, spectrophotometrically measuring reduced glutathione (GSH) levels, and using enzyme-specific assay kits (Sigma-Aldrich, USA) to measure superoxide dismutase (SOD) activity, the biochemical analyses evaluated oxidative stress markers. An automated analyzer was used to test the levels of serum creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) to evaluate renal function.

Histopathological Analysis: Following standard histological techniques, the liver and kidney tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin (H&E). Two blinded pathologists used a semi-quantitative scale (0–4) to measure inflammation, necrosis, and fibrosis to ensure an objective evaluation.[9].

Statistical Analysis: The information was shown as mean ± standard error (SE). Tukey's post hoc test was performed after significant differences between groups were examined using one-way ANOVA. Statistical significance was defined as a p-value of less than 0.05. The analyses were carried out using SPSS software (version 22).

Randomization and Blinding: Animals were randomly allocated to groups using computer-generated random numbers, and researchers performing biochemical and histological investigations were blinded to the group allocations to reduce bias.

Replicability: All tests were carried out in triplicate to guarantee repeatability, and both technical and biological duplicates were used to confirm results.

Compliance with Reporting Standards: The study adhered to ARRIVE guidelines for reporting animal research, ensuring transparency and reproducibility.

RESULTS

In Table 1, after 30 days of hexavalent chromium exposure, oxidative stress markers, liver function tests, and kidney function parameters exhibited significant dose-dependent alterations. Malondialdehyde (MDA) levels, a marker of lipid peroxidation, increased substantially across low, medium, and high doses, with the highest dose group showing a fourfold rise compared to controls ($p < 0.01$). Antioxidant defenses were also weakened, as seen by a marked decline in superoxide dismutase (SOD) and reduced glutathione (GSH) activity. Tests of liver function showed increased levels of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are signs of hepatocellular injury. Renal impairment was also shown by kidney function tests that revealed gradual increases in blood urea nitrogen (BUN) and creatinine. These findings underscore the cumulative toxic effects of hexavalent chromium exposure, with higher doses exacerbating oxidative stress and organ dysfunction in a statistically significant manner ($p < 0.01$).

This histological slide of liver tissue in fig-1 showed hepatocyte nuclei stained dark purple, indicating active cell centers. The sinusoidal capillaries, visible as lighter spaces, facilitate blood flow and the exchange of substances between blood and hepatocytes. The arrangement suggests a well-organized liver lobule structure, which is critical for liver function.

In Table 2, after 60 days of exposure to hexavalent chromium, a significant progression in oxidative stress markers, liver dysfunction, and renal impairment was observed in a dose-dependent manner ($p < 0.01$). Malondialdehyde (MDA) levels, a hallmark of lipid peroxidation, more than tripled in the high-dose group compared to controls, indicating severe oxidative damage. Superoxide dismutase (SOD) activity decreased by more than 50% in the highest dosage group, while reduced glutathione (GSH) levels decreased by 70%, indicating a significant depletion of antioxidant defenses. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were consistently elevated in the high-dose group, surpassing the control by more

than 130%, indicating severe hepatocellular damage, according to liver function tests. In a similar vein, creatinine and blood urea nitrogen (BUN), which are markers of renal impairment, gradually increased in kidney function tests. In comparison to controls, creatinine levels almost doubled in the medium-dose group and tripled in the high-dose group.

These findings provide compelling evidence of the escalating toxic effects of prolonged chromium exposure, emphasizing its potential to induce oxidative stress, disrupt antioxidant defenses, and cause critical organ damage. The slide in Fig-2 represented a section of kidney tissue. The glomerulus, within Bowman's capsule, facilitates filtration, while the surrounding renal tubules process the filtrate for urine formation. The staining highlights the nuclei (dark purple) and cytoplasmic structures.

Table 1: Biochemical and Organ Function Parameters after 30 Days of Hexavalent Chromium Exposure in Albino Rats

Parameter	Control Group	Low Dose (2 mg/kg)	Medium Dose (5 mg/kg)	High Dose (10 mg/kg)	Statistical Significance
Oxidative Stress Markers after (30 days)					
MDA (nmol/mg protein)	1.25 ± 0.15	2.10 ± 0.20	3.85 ± 0.30	5.25 ± 0.40	$p < 0.01$
GSH (µmol/mg protein)	8.50 ± 0.40	7.20 ± 0.30	5.60 ± 0.50	4.10 ± 0.35	$p < 0.01$
SOD (U/mg protein)	20.50 ± 1.10	18.20 ± 0.90	14.80 ± 1.20	11.00 ± 1.10	$p < 0.01$
Liver Function Tests					
ALT (U/L)	35.0 ± 2.5	42.5 ± 3.0	58.0 ± 4.0	72.0 ± 5.0	$p < 0.01$
AST (U/L)	45.0 ± 3.0	56.0 ± 3.5	68.0 ± 4.5	85.0 ± 6.0	$p < 0.01$
Kidney Function Tests					
Creatinine (mg/dL)	0.80 ± 0.05	0.95 ± 0.08	1.20 ± 0.10	1.50 ± 0.12	$p < 0.01$
BUN (mg/dL)	15.0 ± 1.2	18.0 ± 1.5	24.5 ± 2.0	32.0 ± 2.5	$p < 0.01$

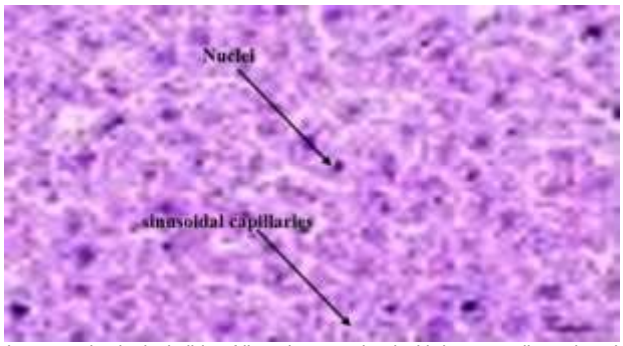

Figure-1: Histological slide of liver tissue stained with hematoxylin and eosin (H&E)

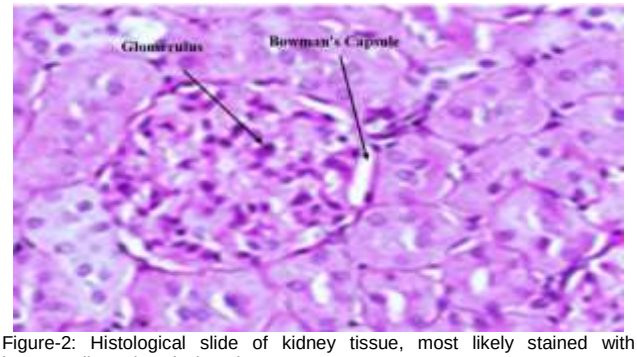

Figure-2: Histological slide of kidney tissue, most likely stained with hematoxylin and eosin (H&E).

Table-2: Biochemical and Organ Function Parameters after 60 Days of Hexavalent Chromium Exposure in Albino Rats

Parameter	Control Group	Low Dose (2 mg/kg)	Medium Dose (5 mg/kg)	High Dose (10 mg/kg)	Statistical Significance
Oxidative Stress Markers After (60 days)					
MDA (nmol/mg protein)	1.30 ± 0.15	2.60 ± 0.20	5.00 ± 0.35	7.50 ± 0.45	$p < 0.01$
GSH (µmol/mg protein)	8.20 ± 0.40	6.00 ± 0.25	4.00 ± 0.35	2.50 ± 0.30	$p < 0.01$
SOD (U/mg protein)	20.20 ± 1.10	16.50 ± 0.80	12.00 ± 1.10	8.50 ± 0.90	$p < 0.01$
Liver Function Tests					
ALT (U/L)	36.0 ± 2.5	48.0 ± 3.2	65.0 ± 4.5	85.0 ± 6.0	$p < 0.01$
AST (U/L)	46.0 ± 3.0	62.0 ± 4.0	80.0 ± 5.5	100.0 ± 7.5	$p < 0.01$
Kidney Function Tests					
Creatinine (mg/dL)	0.82 ± 0.05	1.10 ± 0.10	1.45 ± 0.12	1.80 ± 0.15	$p < 0.01$
BUN (mg/dL)	15.5 ± 1.3	20.0 ± 1.7	28.0 ± 2.2	38.0 ± 2.8	$p < 0.01$

In table-3, after 90 days of hexavalent chromium exposure, oxidative stress markers, hepatic function, and renal parameters exhibited pronounced and progressive deterioration, consistent with cumulative toxic effects. Lipid peroxidation, assessed via malondialdehyde (MDA) levels, showed a sevenfold increase in the high-dose group compared to controls ($p < 0.01$), indicating severe oxidative membrane damage. Concurrently, antioxidant defenses were profoundly depleted, with reduced glutathione (GSH) levels declining by over 80% and superoxide dismutase (SOD) activity reduced by more than 70% in the high-dose group. These findings highlight a significant disruption in redox homeostasis.

Liver enzyme levels exhibited a marked dose-dependent rise, with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increasing by 170% and 155%, respectively, in the high-dose group, reflecting extensive hepatocellular damage. Similarly, renal function parameters were significantly impaired, as evidenced by creatinine and blood urea nitrogen (BUN) levels, which increased three- and fourfold, respectively, in the high-dose group relative to controls. These changes underscore a critical loss of renal filtration capacity and structural damage. Overall, the data demonstrate a stark amplification of oxidative damage, hepatotoxicity, and nephrotoxicity with prolonged exposure to hexavalent chromium. The findings provide mechanistic insights into chromium-induced toxicity, emphasizing its potential for severe organ-specific and systemic pathological consequences.

The comparative analysis across 30, 60, and 90 days of hexavalent chromium exposure reveals a progressive and dose-dependent escalation in oxidative stress, hepatotoxicity, and nephrotoxicity. Malondialdehyde (MDA) levels consistently increased over time, indicating cumulative lipid peroxidation, while antioxidant markers, including glutathione (GSH) and superoxide dismutase (SOD), declined sharply, particularly in the high-dose group. Liver function markers, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) exhibited a significant upward trend, with 90-day high-dose levels exceeding the 30-day values by 140–170%, reflecting sustained and worsening

hepatocellular damage. Creatinine and blood urea nitrogen (BUN) levels also rose significantly, suggesting more progressive renal dysfunction. They found that chromium's toxic effects were amplified by prolonged exposure, becoming increasingly severe over time and with increasing doses, and that higher doses magnified oxidative damage and organ impairment.

Table 3: Biochemical and Organ Function Parameters after 90 Days of Hexavalent Chromium Exposure in Albino Rats

Parameter	Control Group	Low Dose (2 mg/kg)	Medium Dose (5 mg/kg)	High Dose (10 mg/kg)	Statistical Significance
Oxidative Stress Markers after (90 days)					
MDA (nmol/mg protein)	1.35 ± 0.15	3.50 ± 0.30	6.80 ± 0.40	9.50 ± 0.50	$p < 0.01$
GSH (µmol/mg protein)	8.00 ± 0.30	4.50 ± 0.20	3.00 ± 0.30	1.50 ± 0.25	$p < 0.01$
SOD (U/mg protein)	20.00 ± 1.00	14.00 ± 0.70	9.50 ± 0.90	5.50 ± 0.80	$p < 0.01$
Liver Function Tests					
ALT (U/L)	37.0 ± 2.8	55.0 ± 3.8	75.0 ± 5.0	100.0 ± 7.5	$p < 0.01$
AST (U/L)	47.0 ± 3.5	70.0 ± 4.5	92.0 ± 6.0	120.0 ± 8.5	$p < 0.01$
Kidney Function Tests					
Creatinine (mg/dL)	0.85 ± 0.06	1.30 ± 0.12	1.75 ± 0.15	2.20 ± 0.18	$p < 0.01$
BUN (mg/dL)	16.0 ± 1.5	25.0 ± 2.0	35.0 ± 2.5	45.0 ± 3.5	$p < 0.01$

DISCUSSION

This study systematically investigates the dose- and time-dependent effects of hexavalent chromium. The effects of chromium (Cr(VI)) exposure on oxidative stress, hepatic function, and renal integrity over 30, 60, and 90 days were studied.[10]. The results show a progressive increase in the biochemical and functional alterations in key organs of Cr (VI) -induced cumulative oxidative damage and organ toxicity. Prolonged exposure is associated with a marked increase in malondialdehyde (MDA) levels, a robust marker of lipid peroxidation, indicating intensification of oxidative stress. MDA levels in the high-dose group increased nearly fourfold by 30 days and sevenfold by 90 days, consistent with continued ROS-mediated damage to cellular membranes[6]. Concomitantly, time-dependent significant depletion of glutathione (GSH) and superoxide dismutase (SOD) activity signifies a collapse of the antioxidant defense system and makes tissues more prone to oxidative insults. Consistent with previous studies showing ROS generation and direct mitochondrial electron transport chain interference by Cr (VI) through Fenton-like reactions, these findings suggest that Cr (VI) has the potential to act as a mitochondrial oxidant[11, 12].

Sustained hepatocellular injury from prolonged Cr (VI) exposure can be evidenced by a progressive rise in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. By 90 days, ALT and AST increased in the high dose group above 170% of control, indicating significant hepatocyte membrane disruption and necrosis[13]. As expected, these findings correspond to the known hepatotoxic properties of Cr (VI), involving oxidative DNA damage and ROS-induced lipid peroxidation in hepatocytes, resulting in inflammation and apoptosis. This is further corroborated by histological studies in previous research, which show extensive necrosis, fibrosis, and inflammatory cell infiltration in chromium-exposed livers. Renal function was also significantly impaired, as evidenced by increased creatinine and blood urea nitrogen (BUN) in medium- and high-dose groups after 60 and 90 days. These findings indicate progressive nephrotoxicity, presumably regulated by chromium accumulation in renal tissues that disturbs tubular reabsorption and filtration mechanisms[14, 15].

The observed biochemical markers are consistent with the hypothesis that Cr (VI) -induced nephrotoxicity is due to oxidative damage to renal tubular cells and glomerular structures. Consistent with these findings, earlier studies demonstrate histopathological evidence of tubular necrosis, interstitial inflammation, and glomerular damage in models exposed to Cr (VI). Depletion of antioxidant defenses in a dose- and time-dependent manner and sustained increase in oxidative stress markers indicate that if the body is exposed for a prolonged period, the capacity to neutralize ROS is overwhelmed [13]. This imbalance leads to a vicious cycle of oxidative damage, inflammation, and cellular dysfunction, which then results in systemic toxicity. Our findings support the key role of oxidative stress as a central mechanism of Cr (VI) toxicity and agree with other environmental and occupational exposure studies.[16]. The observed effects were markedly more severe in the high-dose group than in the low-dose group at all time points, demonstrating the dose-dependent toxicity of Cr (VI). The cumulative and chronic effects of chromium exposure are emphasized by the progressive worsening of biochemical and functional markers over time. This temporal pattern provides evidence for the need to prevent long-term organ damage through early intervention and mitigation strategies in exposed populations [17, 18].

CONCLUSION

Finally, this study shows clear evidence that Cr (VI) can induce oxidative stress, hepatotoxicity, and nephrotoxicity in a dose and time-dependent manner. The results demonstrate the importance of more stringent regulation of Cr (VI) exposure in environmental and industrial settings. The precise molecular pathways of chromium-induced damage should be elucidated in future research, as should possible therapeutic strategies, including antioxidant supplementation, to modify the toxic effects.

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Authors contribution:

MNS: Conducted research and obtained IRB approval.

RS: Drafted the manuscript.

MAA: Designed statistical models and revised the manuscript.

QAS: Validated statistical models and assisted in manuscript revision.

FAM: Performed English editing and collected relevant data, Research supervision.

AA: Collected clinical data.

AS: Collected molecular data.

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