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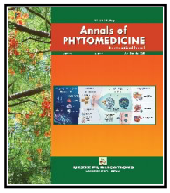

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Comparative protective efficacy of *Colocasia esculenta* (L.) Schott leaf and *Punica granatum* (L.) peel extracts in combating mercuric chloride-induced oxidative and hematobiochemical damage in male Wistar rats

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Abstract

The present study was designed to evaluate the oxidative and hematobiochemical alterations induced by mercuric chloride ($HgCl_2$) and the potential ameliorative effects of *Colocasia esculenta* (L.) Schott leaf extract (CELE) and *Punica granatum* (L.) peel extract (PGPE) in male Wistar rats. A total of eight groups were formed randomly (n = 6). Group I served as the control, while Group II received $HgCl_2$ (2 mg/kg b.wt.) to induce toxicity. To assess plant safety, Groups III and IV were administered CELE and PGPE alone (200 mg/kg b.wt.). Groups V to VII received $HgCl_2$ along with CELE, PGPE, or their combination, respectively. Group VIII (post-treatment), administered $HgCl_2$ for 28 days, followed by both extracts for 14 days. Significant hematological alterations were observed in Group II, including reduced total erythrocyte count, hematocrit, mean corpuscular hemoglobin concentration, total leukocyte count, and platelet count ($p<0.01$). In contrast, neutrophils, MID, mean platelet volume, and platelet-large cell ratio were significantly ($p<0.01$) elevated. These changes indicate inflammatory and oxidative damage due to $HgCl_2$ exposure. Biochemical analysis revealed a significant increase in liver markers (AST, ALT, ALP, bilirubin, cholesterol, triglycerides, and glucose) and kidney markers (BUN, creatinine, and CK-NAC), along with decreased total protein and albumin levels ($p<0.01$). Oxidative stress markers showed a significant ($p<0.01$) increase in MDA levels and a decrease in SOD, CAT, and GR activities in liver and kidney tissues. Treatment with CELE and PGPE, especially in combination (Groups VII and VIII), significantly restored the altered parameters, with the greatest recovery observed in Group VIII (post-treatment). The results suggested that both extracts, due to their antioxidant properties, effectively ameliorate $HgCl_2$ toxicity, particularly upon combined administration.

1. Introduction

Mercury is the 3rd most dangerous heavy metal, constituting a major environmental contaminant ubiquitously detected in water, air, and soil (Nabil *et al*., 2020). This metalloid exists naturally in mineralogical forms but is extensively mobilized by anthropogenic activities, including disposal of batteries, insecticides, dental amalgams, fluorescent lamps, thermometers, cosmetic/herbal products, tattoo inks, and seafood bioaccumulation (Bengtsson and Hylander, 2017; Bjorklund *et al*., 2017; Kuras *et al*., 2017; Ibrahim *et al*., 2019). Among its inorganic compounds, mercuric chloride ($HgCl_2$) is a highly soluble and bioavailable inorganic salt that exerts profound systemic toxicity by physiological and biochemical disruptions. These disruptions include significant body weight loss (cachexia), hematological issues (hemolysis, impaired erythropoiesis), and altered leukocyte profiles (Sharma *et al*., 2007; Durak *et al*., 2010; Berlin *et al*., 2015). Biochemically, $HgCl_2$ exposure elevates hepatic biomarkers (ALT, AST and ALP) and renal biomarkers (creatinine and BUN) levels, indicating organ damage (Uzunhisarcikli *et al*., 2016). Its toxicity is also linked to mitochondrial dysfunction, impaired protein and ATP synthesis, and gastrointestinal irritation (Jarup, 2003; Valko *et al*., 2005; Sandhu and Brar, 2009). A key mechanism of $HgCl_2$ toxicity is oxidative stress, characterized by excessive reactive oxygen species (ROS) generation, antioxidant defenses suppression, and enhanced lipid peroxidation (Valko *et al*., 2005; Rozgaj *et al*., 2005; Franco *et al*., 2007; ATSDR, 2022). This oxidative milieu triggers apoptotic pathways, DNA damage, and inflammatory cascades, exacerbating tissue injury. Recent studies emphasized the neurotoxic potential of $HgCl_2$, where blood-brain barrier disruption facilitates mercury deposition in neural tissues, and provokes neuroinflammation (Zhang *et al*., 2019; Branco *et al*., 2021).

Natural antioxidants are gaining attention for their ability to counteract heavy metal toxicity by reducing oxidative stress. *C. esculenta,* widely used in traditional medicine, is rich in essential vitamins (A, C, E, K), minerals (Ca, Fe, Zn), and diverse phytochemicals like flavonoids,

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phenolics, saponins, and alkaloids (Krishnapriya and Suganthi, 2017; Zubair *et al*., 2023). These bioactive compounds offer potent antioxidant, anti-inflammatory, and hepatoprotective properties, rendering them a promising candidate for mitigating oxidative damage and restoring biochemical homeostasis (Boban *et al*., 2006; Patil and Ageely, 2011; Keshav *et al*., 2019; Rahman and Banu, 2025). Similarly, *P. granatum* peel is also a rich reservoir of polyphenolic compounds (punicalagin, ellagic acid, and flavonoids), which exhibit robust free radical scavenging and anti-inflammatory activities (Jurenka, 2008; Pirzadeh *et al*., 2021). These phytochemicals ameliorate oxidative stress and protect organ dysfunction in various toxicity models (Syed *et al*., 2018; Gil *et al*., 2021; Gull *et al*., 2023). The synergistic effects of these natural antioxidants contribute to cellular defense mechanisms, making both *C. esculenta* and *P. granatum* promising adjuncts in combating $HgCl_2$ -induced oxidative injuries.

2. Materials and Methods

2.1 Plant authentication and ethical approval

Fresh *C. esculenta* leaves and *P. granatum* peels were collected from a local market in Udaipur, Rajasthan, India. Specimens were authenticated by Dr. Y.S. Sarangdevot, Professor of Pharmacognosy and Dean, Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan, India and voucher specimens *C. esculenta* (01) and *P. granatum* (02) were deposited accordingly. The experiment was ethically approved under protocol No. IAEC/RES/04/02, as per CCSEA guidelines.

2.2 Animals experimental design

Forty-eight healthy male Wistar rats (70 to 180 g) were obtained from the Disease-Free Small Animal House, LUVAS, Hisar and acclimatized for one week under standard laboratory conditions. Rats were fed *ad libitum* with pellets and water. They were randomly assigned to 8 groups (n = 6/group). $HgCl_2$ was administered in the morning, followed by plant extracts in the afternoon and evening, as per the protocol outlined in Table 1.

2.3 Preparation of plant extracts

The collected plant materials were thoroughly washed with tap water and dried. Then methanolic extract of *C. esculenta* leaves and aqueous extract of *P. granatum* peels were prepared according to the methods of Ufelle *et al.* (2018) and Kadiyala *et al.* (2023), respectively, with extract yields of 10.55% and 28.72%.

2.4 Administration of extracts and dose selection

Doses were prepared freshly by mixing the dried extracts in distilled water and administered orally *via* gastric intubation at a fixed time daily to minimize circadian variation. The doses were selected as: HgCl, at 2 mg/kg b.wt./day (Bhowmik and Patra, 2015; Ladumor *et al*., 2023), CELE at 200 mg/kg b.wt./day (Saikia *et al*., 2018; Somasekhar Reddy *et al*., 2020), and PGPE at 200 mg/kg b.wt./day (Faddladdeen, 2020).

Table 1: Experimental design illustrating group distribution

Group No.	Experimental groups (6 rats/group)	Treatment duration
I.	Control	Up to 28 days
II.	$HgCl_2$ treatment	Up to 28 days
III.	*C. esculenta* leaf extract (CELE) treatment	Up to 28 days
IV.	*P. granatum* peel extract (PGPE) treatment	Up to 28 days
V.	$HgCl_2$ + CELE treatment	Up to 28 days
VI.	$HgCl_2$ + PGPE treatment	Up to 28 days
VII.	$HgCl_2$ + CELE + PGPE treatment	Up to 28 days
VIII.	Post-treatment $HgCl_2$ for 28 days, then both extracts for 2 weeks	$HgCl_2$ for 28 days, then from 29th day CELE and PGPE up to 42nd day

2.5 Body weight

Rats' individual body weights were recorded initially on day 0 and weekly thereafter (before dosing).

2.6 Hematological and biochemical studies

Just before euthanasia (by cervical dislocation), blood (3 to 4 ml) was drawn from the retro-orbital sinus of each anesthetized (by chloroform) rat. Of this, 1 ml was collected into EDTA-coated vials (1 mg/ml) for hematological evaluation and the parameters listed in Table 2 were measured using an automated hematology analyzer (Mindray, model RM-303-03). The remaining blood was collected in anticoagulant-free sterile glass tubes, and centrifuged at 3000 rpm for 15 min. (at 4°C) to separate the serum. Then serum samples were stored at -20°C until biochemical analyses were performed as listed in Table 2 (Boarescu *et al.,* 2021).

2.7 Oxidative stress assessment

Following euthanasia, liver and kidney tissues (500 mg each) were collected in 5 ml of ice-cold PBS (pH 7.4) and stored at -80°C until further analysis. Tissue homogenates (10%) were prepared in PBS using a Teflon homogenizer (MSW 346, IKA), under ice-cold conditions, then centrifuged at 3000 rpm for 10 min (at 4°C) to purge cellular debris. The resulting supernatant was collected and stored at -20°C. Tissue total protein content was quantified with BSA standard by using the Bradford assay (1976). Oxidative stress markers were then assessed as follows: 1. Lipid peroxidation (LPO): determined as malondialdehyde (MDA) production by using the TBARS (thio-barbituric-acid-reactive-substances) assay (Fernanada *et al.*, 2005), 2. Superoxide dismutase (SOD): activity determined according to Madesh and Balasubramanian (1998), 3. Catalase (CAT): activity determined by monitoring the H_2O_2 decomposition at 240 nm (Aebi *et al.*, 1974), 4. Glutathione reductase (GR): activity determined by following Goldberg and Spooner (1983).

2.8 Statistical analysis

All values are presented as mean ± standard error (SE). Statistical analysis was evaluated by using one-way ANOVA, followed by Duncan's multiple range test (DMRT) as per gautam, (2024), using a custom R script developed with the agricolae package. Differences were considered significant at $p<0.05$ and highly significant at $p<0.01$.

Table 2: List of studied hematological and serum biochemical parameters

S. No.	Hematological parameters	Unit	Biochemical parameters	Unit
1.	Total erythrocyte count (TEC)	10^{12}/l	Alanine transaminase (ALT)	U/l
2.	Hemoglobin (Hb)	g/dl	Aspartate aminotransferase (AST)	U/l
3.	Total leucocyte count (TLC)	10^{9}/l	Alkaline phosphatase (ALP)	IU/l
4.	Different leucocyte count (DLC)	%	Total protein (T.P.)	g/dl
5.	Packed cell volume (PCV)	%	Albumin	g/dl
6.	Mean corpuscular hemoglobin concentration (MCHC)	g/dl	Creatinine	mg/dl
7.	Mean corpuscular hemoglobin (MCH)	pg	Blood urea nitrogen (BUN)	mg/dl
8.	Mean corpuscular volume (MCV)	fl	Cholesterol (Chol.)	mg/dl
9.	Total platelets count (PLT)	10^{9}/l	Triglyceride's (T.G.)	mg/dl
10.	Mean platelet volume (MPV)	fl	Total bilirubin (T.Bil.)	mg/dl
11.	Platelet distribution width (PWD)	%	Glucose	mg/dl
12.	Plateletcrit (PCT)	%	Creatine kinase (CK-Nac)	U/l
13.	Platelet large cell ratio (P-LCR)	%	-	-

3. Results

3.1 Body weight

Daily oral administration of PGPE and CELE, improve body weight in $HgCl_2$ treated rats over a 6-week period, as shown in Table 3 and Figure 1. Although, differences in body weight across groups were not statistically significant overall, slight reductions were observed in toxicity Groups II and VIII throughout the study compared to control Group (I). A significant weight increase was observed in Group IV after the 3rd week compared to toxicity Group II. From the 4th week onward, Groups II and VIII showed significant differences from Groups IV, VI, and VII.

Table 3: Mean weekly body weight (g/rat/week) of rats across all experimental groups throughout the study period

Groups	Mean ± S.E. of body weight of rats (g) at weekly intervals (days)						
	0 day	7 days	14 days	21 days	28 days	35 days	42 days
	NS	NS	NS	NS	*	**	**
I.	128.67 ± 4.55	151.33 ± 5.7	170.33 ± 5.96	194.33 ± 6.16	213.67^{ab} ± 6.35	-	-
II.	127 ± 14.48	148.67 ± 11.04	159.67 ± 10.02	179.67 ± 9.2	195.33^{b} ± 7.64	-	-
III.	126.33 ± 10.97	150.67 ± 11.38	173.67 ± 11.2	193.67 ± 7.99	215.33^{ab} ± 6.84	-	-
IV.	126.33 ± 9.9	165.00 ± 8.60	187.67 ± 8.1	206.33 ± 6.86	229.60^{a} ± 6.90	-	-
V.	127.33 ± 7.96	148.00 ± 7.69	168.33 ± 5.55	192.33 ± 4.94	216.67^{ab} ± 4.60	-	-
VI.	127.33 ± 14.51	152.33 ± 11.01	175.33 ± 10.11	198.67 ± 7.58	220.33^{a} ± 5.52	-	-
VII.	128.33 ± 3.91	159.33 ± 4.40	178.67 ± 3.04	201.00 ± 4.28	224.67^{a} ± 4.15	-	-
VIII.	128.17 ± 11.18	150.33 ± 9.67	163.33 ± 10.74	181.67 ± 11.26	198^{b}.33 ± 10	224.33^{a} ± 10.95	251.67^{a} ± 10.44

All data are presented as Mean ± SE (n = 6 per group). Values within the same column bearing different superscripts indicate significant differences at $p<0.05$ or $p<0.01$; identical superscripts denote non-significant differences and values without superscript within a column are also NS. NS = non-significant; * = significant ($p<0.05$); ** = highly significant ($p<0.01$).

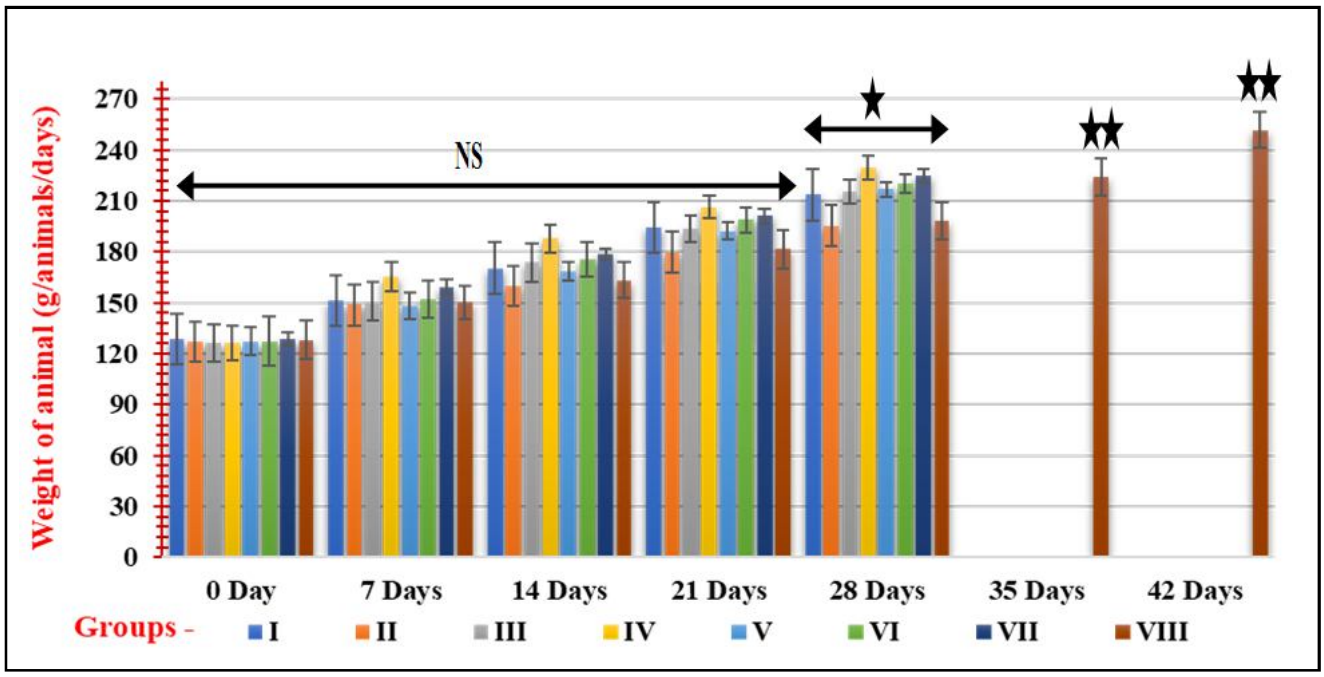

Figure 1: Bar diagram representing mean body weight (g/rat/days) of different experimental groups at weekly intervals (NS = non-significant; * = significant (p<0.05); ** = highly significant (p<0.01)).

3.2 Hematological parameters

Blood cells serve as mobile units of the body's defence system, and they offer vital indicators for evaluating the toxicological effects on body tissues.

3.2.1 Erythrocyte indices

The effects of *C. esculenta*, *P. granatum*, and their combination on erythrocyte indices in $HgCl_2$, exposed rats are depicted in Table 4 and Figures 2-4. A general reduction in erythrocyte indices was observed in $HgCl_2$, -treated groups, except for MCV. TEC, Hb, and HCT levels declined in all $HgCl_2$ -treated Groups (II, V-VIII), and differed significantly (p<0.01) in toxicity Group II (lowest) relative to the control (I), except for Hb (non-significant difference). TEC, Hb, and HCT values were significantly (p<0.01) increased in all treatment Groups (V-VIII) relative to the toxicity Group II, except for Hb (remained statistically non-significant). TEC and Hb levels did not differ significantly among the treatment Groups (V–VIII), while HCT level was significantly (p<0.01) decreased in Groups V and VI compared to VII and VIII. No significant differences were observed in Hb, MCV, and MCH across all Groups (I-VIII). Marked reductions in TEC, Hb, and HCT were noted in all $HgCl_2$, -treated groups, particularly in Groups II and V. Despite these reductions, MCV and MCH remained statistically unchanged across all groups, while MCHC was significantly reduced in Group II compared to control (I). Recovery in erythrocyte indices was observed in all treatment Groups, with the least toxic effect observed in Groups VII and VIII, attributed to the combined use of both plant extracts was more effective in restoring erythrocyte indices than either extract alone.

Table 4: The mean values of RBC, Hb, HCT, MCV, MCH, and MCHC across experimental groups

Groups	Mean ± S.E. hematological erythrocyte indices					
	TEC (10^{12} /l)	Hb (g/dl)	HCT (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)
	**	NS	**	NS	NS	**
I.	7.56^{ab} ± 0.31	14.62 ± 0.56	48.93^{a} ± 0.88	65.21 ± 2.45	19.37 ± 0.36	29.90^{a} ± 1.15
II.	5.87^{c} ± 0.18	9.98 ± 0.43	39.92^{d} ± 1.09	68.39 ± 2.97	17.11 ± 1.01	25.03^{b} ± 1.03
III.	7.66^{a} ± 0.23	14.44 ± 0.26	49.08^{a} ± 0.44	64.34 ± 1.62	18.92 ± 0.50	29.43^{a} ± 0.63
IV.	7.85^{a} ± 0.24	14.75 ± 0.21	49.27^{a} ± 0.93	63.00 ± 1.67	18.91 ± 0.74	30.00^{a} ± 0.75
V.	6.93^{b} ± 0.16	13.56 ± 0.41	43.48^{c} ± 0.55	62.91 ± 1.60	19.64 ± 0.80	31.21^{a} ± 0.97
VI.	7.18^{ab} ± 0.14	13.93 ± 0.23	45.72^{bc} ± 1.37	63.81 ± 2.42	19.44 ± 0.56	30.59^{a} ± 0.95
VII.	7.39^{ab} ± 0.14	14.16 ± 0.28	48.13^{ab} ± 0.56	65.24 ± 1.09	19.18 ± 0.38	29.43^{a} ± 0.60
VIII.	7.32^{ab} ± 0.22	14.22 ± 0.21	47.43^{ab} ± 0.59	65.11 ± 1.93	19.51 ± 0.6	29.98^{a} ± 0.38

All data are presented as Mean ± SE (n = 6 per group). Values within the same column bearing different superscripts indicate significant differences at p<0.05 or p<0.01; identical superscripts denote non-significant differences and values without superscript within a column are also NS. NS = non-significant; * = significant (p<0.05); ** = highly significant (p<0.01).

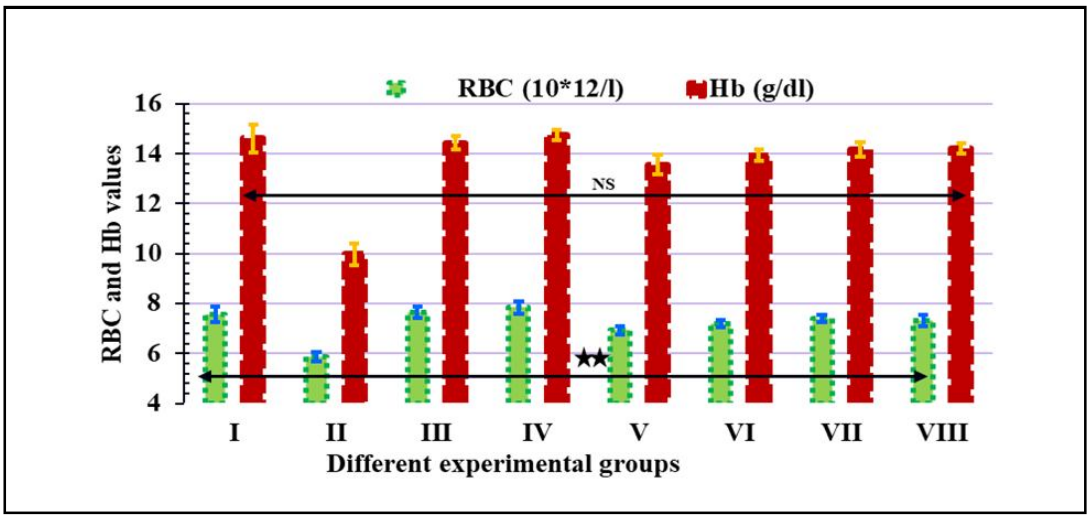

Figure 2: Bar chart illustrating the mean values of RBC (10^{12}/l) and Hb (g/dl) in various experimental groups.

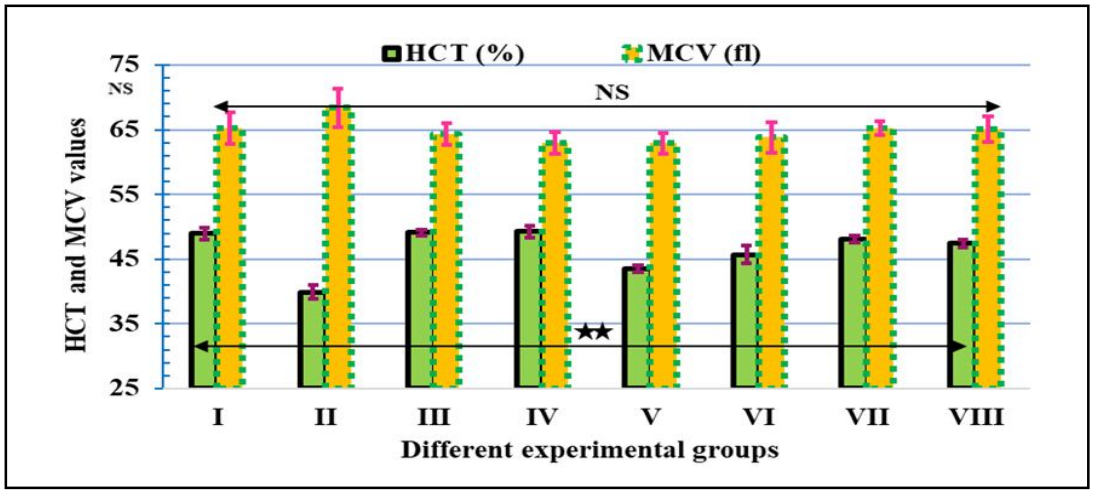

Figure 3: Bar chart illustrating the mean values of HCT (%) and MCV (fl) in various experimental groups.

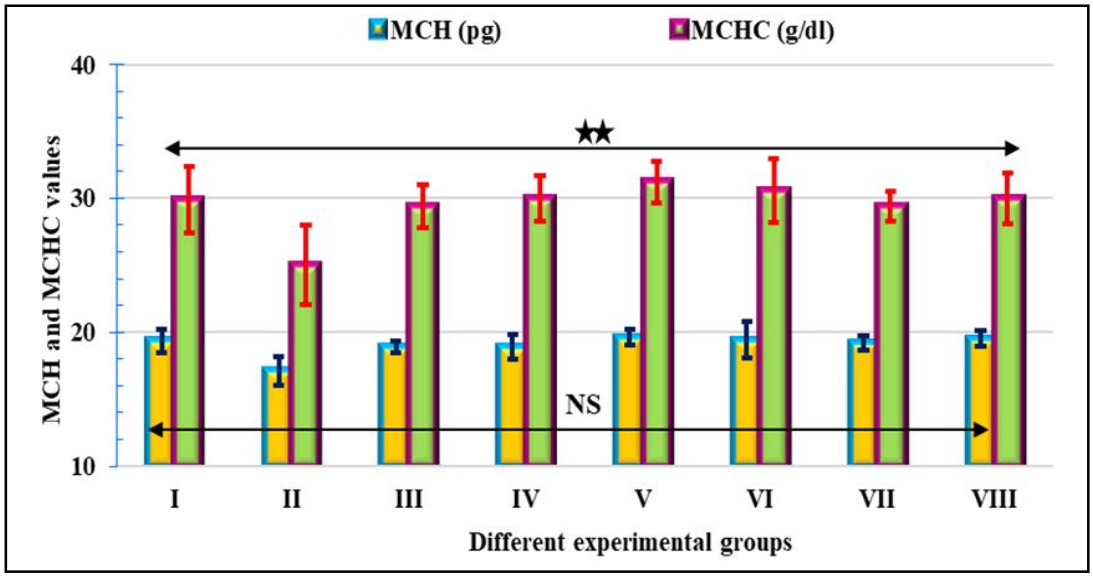

Figure 4: Bar chart illustrating the mean values of MCH (pg) and MCHC (g/dl) in various experimental groups.

3.2.2 Leucocyte indices

The effects of *C. esculenta* leaves, *P. granatum* peel, and their combination on leukocyte indices, in $HgCl_2$ exposed rats are depicted in Table 5 and Figures 5-6. TLC values remained non-significant across experimental Groups, except for a significant ($p<0.01$) decrease in the toxicity Group II. LYM% was significantly ($p<0.01$) lower in the toxicity Group II relative to control (I). Among the treatment groups, only Groups VII and VIII exhibited a significant ($p<0.01$) increase in LYM% relative to Group II. MID% was significantly ($p<0.01$) elevated in the Group II relative to all other groups, while significant ($p<0.01$) lower was observed in all treatment groups compared to Group II. NEUT% in toxicity Group II was also significantly ($p<0.01$) elevated than control (I). These findings align with Ranveer (2015), who attributed such hematological changes to inflammatory responses from $HgCl_2$ induced oxidative and degenerative damage in blood and tissues. Mercury accumulation in visceral organs (liver and kidneys) may trigger an inflammatory cascade (Sheikh *et al*., 2013). Elevated MID values observed here likely reflect increased monocyte activity, as similarly reported by Sheikh *et al*. (2013) and Ranveer (2015) in $HgCl_2$ -exposed rats. The highest recovery in TLC and DLC values was observed in treatment Group VIII, followed by Groups VII, VI, and V.

Table 5: The mean values of TLC and DLC percentage across experimental groups

Groups	Mean ± S.E. hematological WBC parameters			
	TLC (10^9 /l) **	LYM (%) **	MID (%) **	NEUT (%) **
I	$13.58^{a} \pm 0.3$	$60.00^{ab} \pm 0.37$	$2.99^{cd} \pm 0.2$	$37.00^{cd} \pm 0.18$
II	$10.07^{b} \pm 0.46$	$55.00^{e} \pm 0.71$	$5.00^{a} \pm 0.15$	$40.00^{ab} \pm 0.58$
III	$13.46^{a} \pm 0.29$	$61.50^{a} \pm 0.82$	$3.50^{b} \pm 0.10$	$35.00^{e} \pm 0.75$
IV	$13.74^{a} \pm 0.41$	$61.00^{a} \pm 0.67$	$2.80^{cd} \pm 0.07$	$36.20^{de} \pm 0.69$
V	$12.82^{a} \pm 0.26$	$56.20^{de} \pm 0.73$	$3.00^{cd} \pm 0.1$	$40.80^{a} \pm 0.75$
VI	$12.98^{a} \pm 0.37$	$57.00^{cde} \pm 0.61$	$2.70^{d} \pm 0.07$	$40.30^{a} \pm 0.59$
VII	$13.21^{a} \pm 0.21$	$58.60^{bc} \pm 0.50$	$3.20^{bc} \pm 0.06$	$38.20^{bc} \pm 0.48$
VIII	$13.34^{a} \pm 0.21$	$57.50^{cd} \pm 0.82$	$3.20^{bc} \pm 0.25$	$39.30^{ab} \pm 0.91$

All data are presented as Mean ± SE (n = 6 per group). Values within the same column bearing different superscripts indicate significant differences at $p<0.05$ or $p<0.01$; identical superscripts denote non-significant differences and values without superscript within a column are also NS. NS = non-significant;* = significant ($p<0.05$);** = highly significant ($p<0.01$).

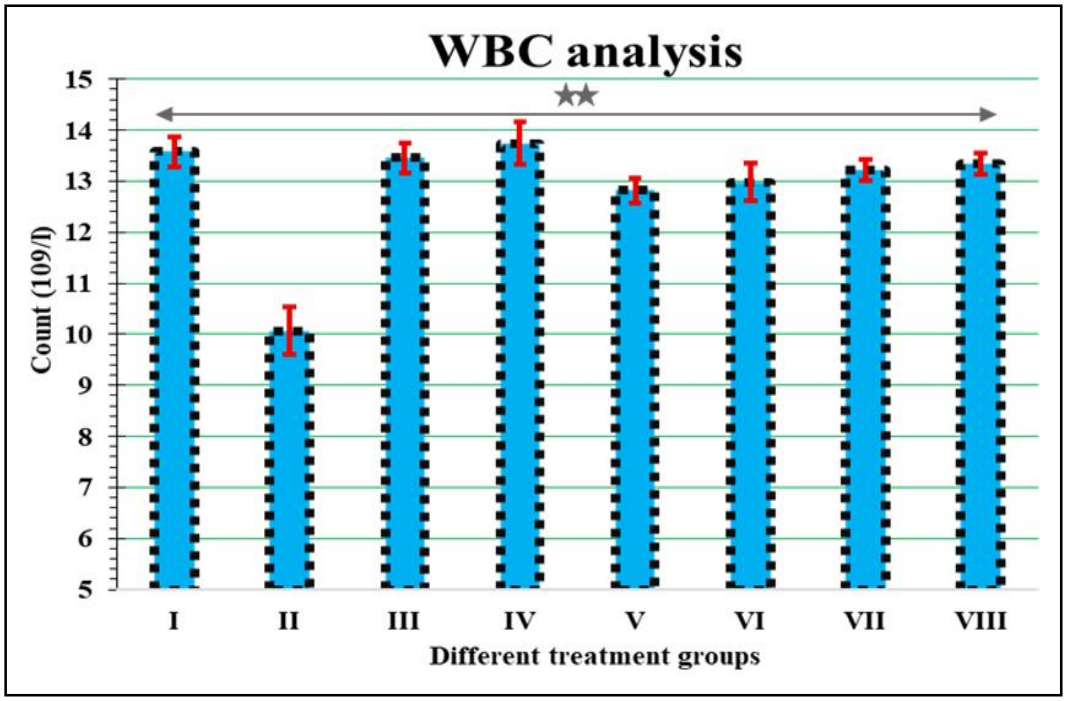

Figure 5: Bar chart representing the mean values of WBC count (10^9/l) in various experimental groups.

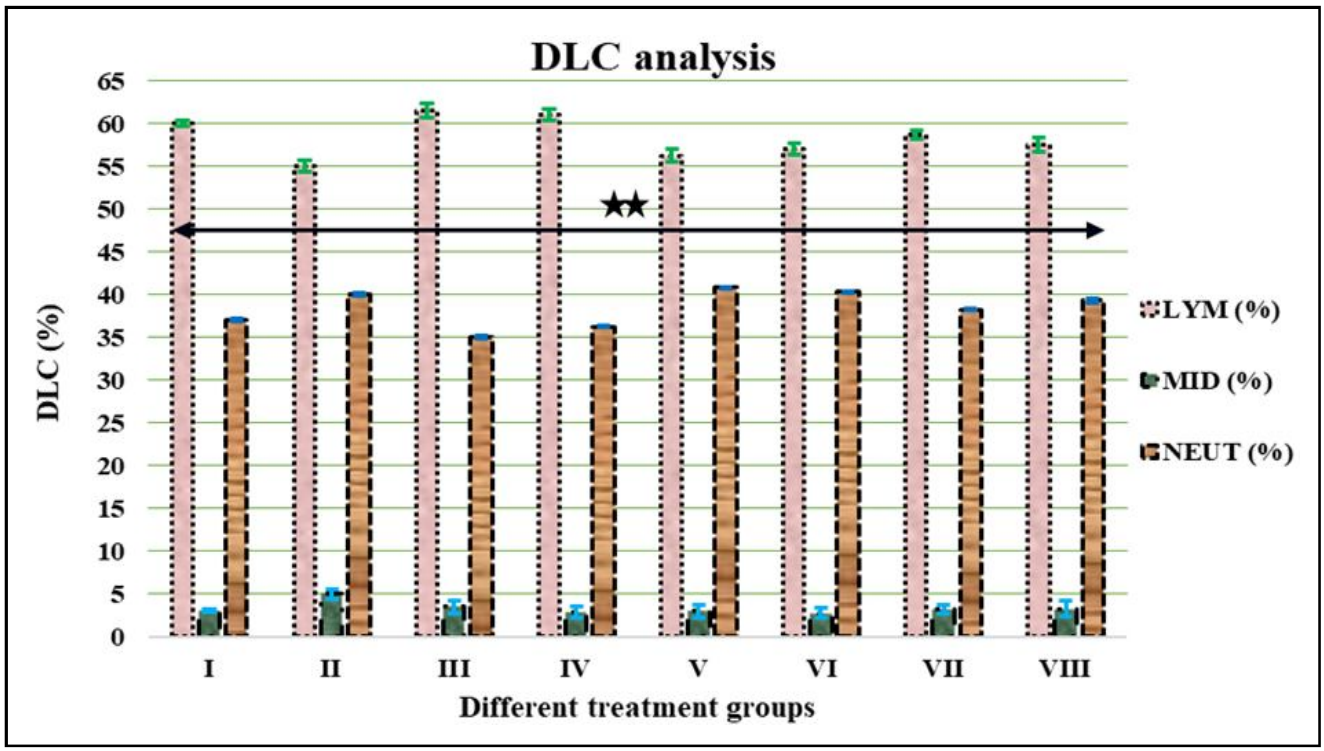

Figure 6: Bar chart representing the mean values of DLC (%) in various experimental groups.

3.2.3 Platelet indices

The effects of both plant extracts on platelet indices in HgCl, -exposed rats are depicted in Table 6 and Figures 7-10. Platelet count (PLT) was significantly (p<0.01) decreased in the toxicity Group II compared to control (I). Treatment Groups (V-VIII) showed significantly (p<0.01) elevated PLT relative to Group II, indicating the extracts restorative effects. MPV and PDW were significantly (p<0.01) increased in toxicity Group II versus the control (I), suggesting platelet activation or destruction. While treatment Groups (V-VIII) revealed significantly elevated (p<0.01) PLT, except Group VI revealed no significant change versus the toxicity Group II. PCT levels were significantly (p<0.01) decreased in the toxicity Group II versus control (I), whereas treatment Groups (V-VIII) showed significantly increased values compared to toxicity Group II. P-LCR was significantly (p<0.01) elevated in toxicity Group II compared to control (I), while treatment Groups (V-VIII) showed a non-significant decrease versus Group II, indicating a mild normalization of platelet size variation with treatment.

Table 6: The mean values of PLT, MPV, PDW, PCT and P-LCR parameters across experimental groups

Groups	Mean ± S.E. hematological platelet indices				
	PLT (10^9/µl) **	MPV (fl) **	PDW (%) **	PCT (%) **	P-LCR (%) **
I.	492.67^{ab} ± 15.34	7.18^{c} ± 0.13	9.45^{bc} ± 0.17	0.35^{b} ± 0.01	25.33^{bc} ± 0.31
II.	405.67^{c} ± 23.84	8.32^{a} ± 0.3	10.89^{a} ± 0.4	0.33^{c} ± 0.01	27.66^{a} ± 0.51
III.	509.50^{a} ± 10.78	7.03^{c} ± 0.11	9.21^{c} ± 0.15	0.36^{ab} ± 0.00	25.15^{c} ± 0.29
IV.	497.67^{ab} ± 9.84	7.15^{c} ± 0.12	9.36^{c} ± 0.15	0.36^{b} ± 0.00	25.39^{bc} ± 0.33
V.	478.50^{ab} ± 16.36	7.55^{bc} ± 0.22	9.88^{bc} ± 0.29	0.36^{ab} ± 0.00	27.13^{a} ± 0.71
VI.	453.17^{b} ± 13.17	7.82^{ab} ± 0.19	10.23^{ab} ± 0.24	0.35^{b} ± 0.00	27.58^{a} ± 0.50
VII.	466.83^{ab} ± 19.51	7.60^{bc} ± 0.24	9.95^{bc} ± 0.32	0.35^{b} ± 0.00	26.74^{ab} ± 0.59
VIII.	504.83^{a} ± 11.93	7.32^{bc} ± 0.17	9.58^{bc} ± 0.22	0.37^{a} ±0.00	26.96^{a} ± 0.64

All data are presented as Mean ± SE (n = 6 per group). Values within the same column bearing different superscripts indicate significant differences at p<0.05 or p<0.01; identical superscripts denote non-significant differences and values without superscript within a column are also NS. NS = non-significant; * = significant (p<0.05); ** = highly significant (p<0.01).

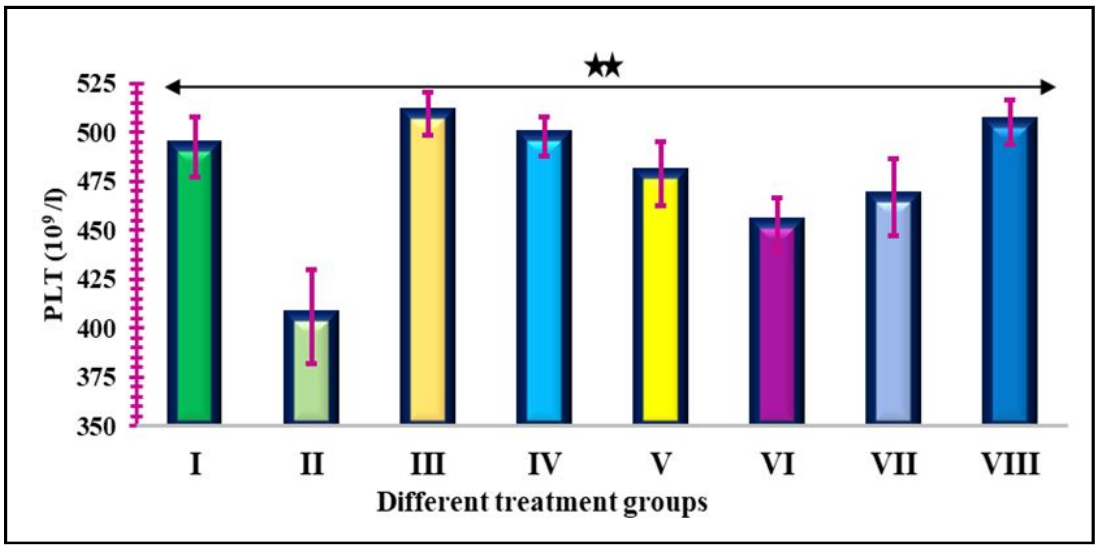

Figure 7: Bar chart displaying the mean values of PLT (10^9/l) in various experimental groups.

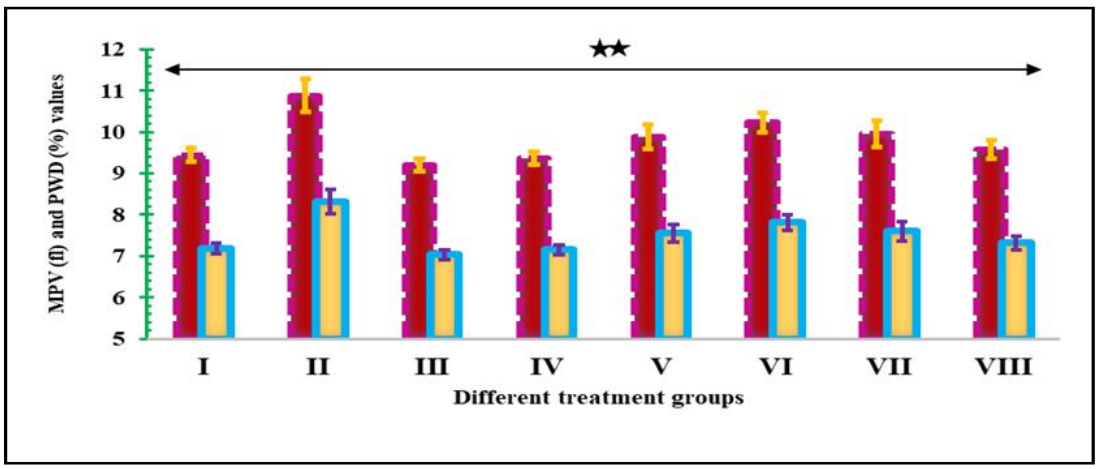

Figure 8: Bar chart displaying the mean values of MPV (fl) and PWD (%) in various experimental groups.

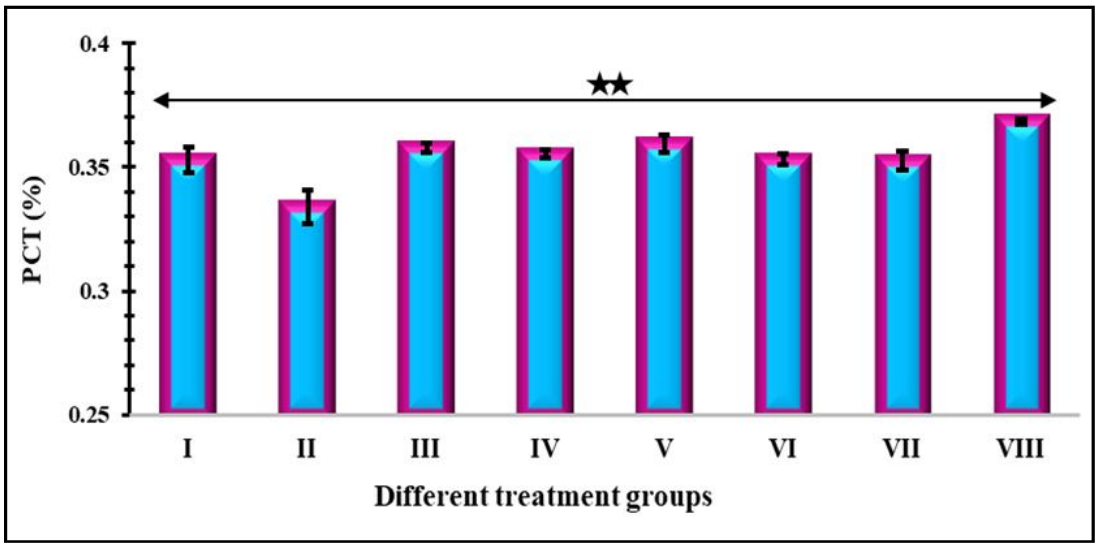

Figure 9: Bar chart displaying the mean values of PCT (%) in various experimental groups.

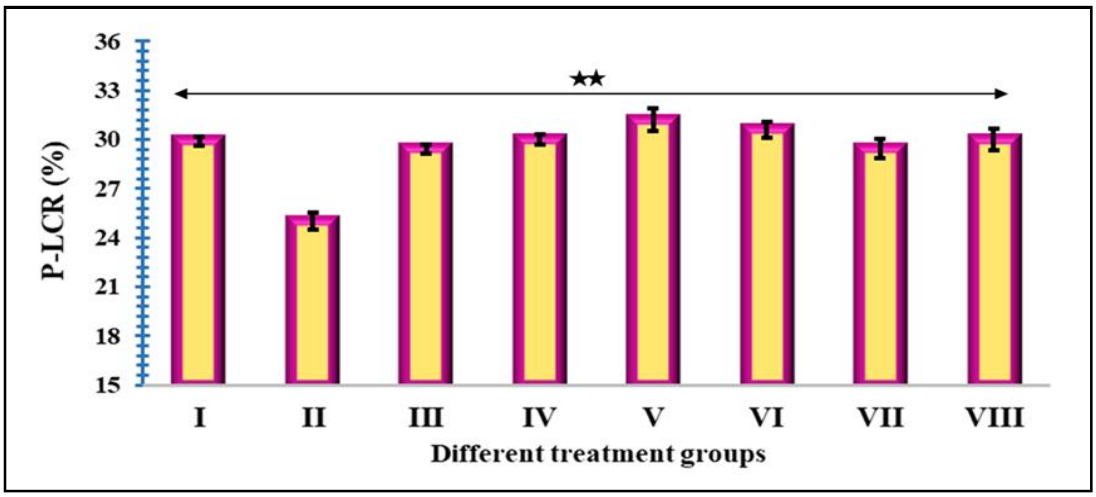

Figure 10: Bar chart displaying the mean values of P-LCR (%) in various experimental groups.

3.3 Biochemical parameters

Liver and kidney function tests serve as crucial enzymatic markers, offering vital insights into systemic toxicity. The effects of *C. esculenta* leaves, *P. granatum* peel, and their combination on biochemical parameters in $HgCl_2$ exposed rats are depicted in Tables 7-8 and Figures 11-15. In the toxicity Group (II), levels of AST, ALT, ALP, Chol., triglycerides, total bilirubin, glucose, BUN, creatinine, and CK-NAC were significantly ($p<0.01$) elevated compared to the control (I), indicating hepatic and renal dysfunction. Conversely, total protein and albumin levels were significantly ($p<0.01$) low.

Treatment with plant extracts led to significant ($p<0.01$) reductions in AST, ALT, ALK, total bilirubin, Chol., triglycerides, BUN, creatinine, and CK-NAC levels in treatment Groups (V-VIII) compared to toxicity Group (II). Glucose levels also declined significantly ($p<0.01$) in Groups VI, V, VII, and VIII, respectively. Conversely, total protein and albumin levels significantly ($p<0.01$) rise in the same Groups (V-VIII). Globulin levels showed a non-significant rise in treatments Groups (V-VIII). For AST, only treatment Groups V and VI was differed significantly ($p<0.01$). For ALT levels, only Group V differed significantly ($p<0.01$) from Group VIII. For ALK and triglyceride levels varied significantly ($p<0.01$) across treatment Groups (V-VIII). Regarding total bilirubin, Chol., BUN and creatinine levels, treatment Groups V and VI, as well as VII and VIII, showed non-significant differences within pairs, but differed significantly ($p<0.01$) between pairs.

For glucose values, Group V differed significantly ($p<0.01$) from Group VIII, and Group VI from Group VII. Regarding total protein, only Group VIII differed significantly ($p<0.01$) from Groups V and VI. For albumin values, Group V differed significantly ($p<0.01$) from Groups VII and VIII, while Group VI differed significantly ($p<0.01$) from Group VIII but not from Group VII. Regarding globulin levels, no significant differences was found among treatment Groups (V-VIII). For CK-NAC levels, Group V differed significantly ($p<0.01$) from Groups VI to VIII. Group VI differed significantly ($p<0.01$) from Group VII, but not from Group VIII, while Group VII differed significantly ($p<0.01$) from Group VIII.

Table 7: The mean values of ALT, AST, ALK, total bilirubin, cholesterol, triglycerides and glucose levels across experimental groups

Groups	Mean ± S.E. biochemical parameters						
	AST (U/l) **	ALT (U/l) **	ALK (U/l) **	Total Bilirubin (mg/dl) **	Cholesterol (mg/dl) **	Triglycerides (mg/dl) **	Glucose (mg/dl) **
I.	$51.79^{fg} \pm 1.11$	$29.23^{e} \pm 1.59$	$84.12^{g} \pm 1.37$	$0.34^{d} \pm 0.02$	$42.16^{d} \pm 1.77$	$146.25^{f} \pm 2.24$	$43.18^{ef} \pm 2.55$
II.	$79.72^{a} \pm 1.63$	$49.78^{a} \pm 1.68$	$146.63^{a} \pm 1.57$	$0.62^{a} \pm 0.01$	$82.81^{a} \pm 1.54$	$270.06^{a} \pm 2.49$	$81.94^{a} \pm 1.79$
III.	$53.24^{ef} \pm 1.11$	$33.28^{de} \pm 1.48$	$89.9^{f} \pm 1.28$	$0.30^{d} \pm 0.01$	$40.87^{de} \pm 1.28$	$130.63^{g} \pm 1.67$	$39.11^{f} \pm 1.28$
IV.	$48.49^{g} \pm 1.72$	$28.73^{e} \pm 1.64$	$75.61^{h} \pm 1.86$	$0.29^{d} \pm 0.02$	$37.04^{e} \pm 1.12$	$126.70^{g} \pm 2.05$	$47.80^{e} \pm 2.04$
V.	$67.41^{b} \pm 1.57$	$40.61^{b} \pm 1.34$	$128.36^{b} \pm 1.73$	$0.51^{b} \pm 0.02$	$64.88^{b} \pm 1.29$	$225.49^{b} \pm 1.82$	$64.93^{bc} \pm 1.62$
VI.	$62.82^{c} \pm 1.54$	$38.59^{bc} \pm 1.80$	$121.75^{c} \pm 1.67$	$0.48^{b} \pm 0.02$	$61.21^{b} \pm 1.72$	$212.19^{c} \pm 2.20$	$69.96^{b} \pm 1.96$
VII.	$58.80^{d} \pm 1.09$	$36.05^{bcd} \pm 1.51$	$106.90^{d} \pm 1.40$	$0.42^{c} \pm 0.02$	$55.64^{c} \pm 1.61$	$199.40^{d} \pm 2.30$	$59.87^{cd} \pm 1.43$
VIII.	$57.11^{de} \pm 1.16$	$35.46^{cd} \pm 1.47$	$101.66^{e} \pm 1.90$	$0.40^{c} \pm 0.02$	$52.79^{c} \pm 1.24$	$186.48^{e} \pm 2.54$	$57.04^{d} \pm 1.86$

All data are presented as Mean ± SE (n = 6 per group). Values within the same column bearing different superscripts indicate significant differences at $p<0.05$ or $p<0.01$; identical superscripts denote non-significant differences and values without superscript within a column are also NS. NS = non-significant; *= significant ($p<0.05$); ** = highly significant ($p<0.01$).

Table 8: The mean values of BUN, creatinine, total protein, albumin, globulin and Ck-NAC levels across experimental groups

Groups	Mean ± S.E. biochemical parameters					
	BUN (mg/dl) **	Creatinine (mg/dl) **	Total Protein (mg/dl) **	Albumin (mg/dl) **	Globulin (mg/dl) *	Ck-NAC (U/l) **
I	$30.45^{e} \pm 1.09$	$0.28^{d} \pm 0.01$	$7.60^{b} \pm 0.15$	$5.11^{b} \pm 0.12$	$2.49^{c} \pm 0.12$	$918.53^{g} \pm 10.65$
II	$51.96^{a} \pm 1.83$	$0.52^{a} \pm 0.02$	$4.93^{e} \pm 0.19$	$2.15^{g} \pm 0.10$	$2.78^{bc} \pm 0.22$	$2213.81^{a} \pm 9.99$
III	$35.32^{cd} \pm 1.72$	$0.32^{d} \pm 0.01$	$7.29^{b} \pm 0.16$	$3.88^{c} \pm 0.12$	$3.41^{a} \pm 0.24$	$1030.54^{f} \pm 14.10$
IV	$33.03^{de} \pm 1.32$	$0.30^{d} \pm 0.01$	$8.04^{a} \pm 0.14$	$5.48^{a} \pm 0.12$	$2.56^{c} \pm 0.23$	$849.27^{h} \pm 13.23$
V	$45.57^{b} \pm 1.58$	$0.46^{b} \pm 0.01$	$6.07^{d} \pm 0.12$	$2.86^{f} \pm 0.12$	$3.22^{ab} \pm 0.12$	$1604.15^{b} \pm 12.79$
VI	$42.60^{b} \pm 1.68$	$0.44^{b} \pm 0.02$	$6.16^{d} \pm 0.16$	$3.08^{ef} \pm 0.09$	$3.08^{abc} \pm 0.19$	$1493.26^{c} \pm 9.86$
VII	$38.07^{c} \pm 1.46$	$0.39^{c} \pm 0.02$	$6.52^{cd} \pm 0.14$	$3.36^{de} \pm 0.09$	$3.15^{ab} \pm 0.22$	$1408.22^{c} \pm 9.43$
VIII	$36.46^{cd} \pm 1.41$	$0.38^{c} \pm 0.02$	$6.70^{c} \pm 0.14$	$3.52^{d} \pm 0.10$	$3.18^{ab} \pm 0.16$	$1315.63^{e} \pm 10.32$

All data are presented as Mean ± SE (n = 6 per group). Values within the same column bearing different superscripts indicate significant differences at $p<0.05$ or $p<0.01$; identical superscripts denote non-significant differences and values without superscript within a column are also NS. NS = non-significant; * = significant ($p<0.05$); ** = highly significant ($p<0.01$).

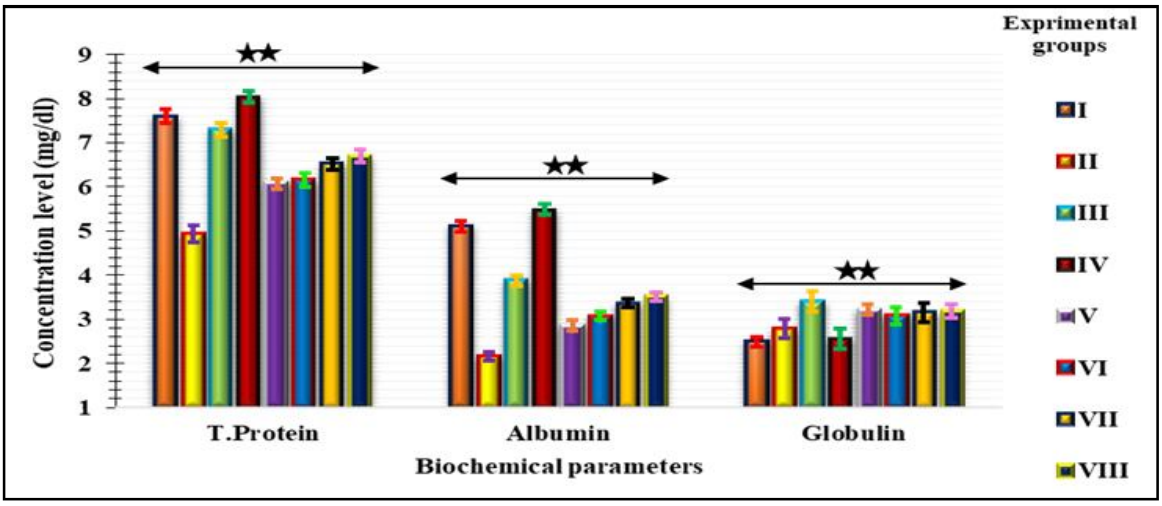

Figure 11: Bar diagram depicting the mean values of serum AST, ALT and ALK (U/l) in across experimental groups.

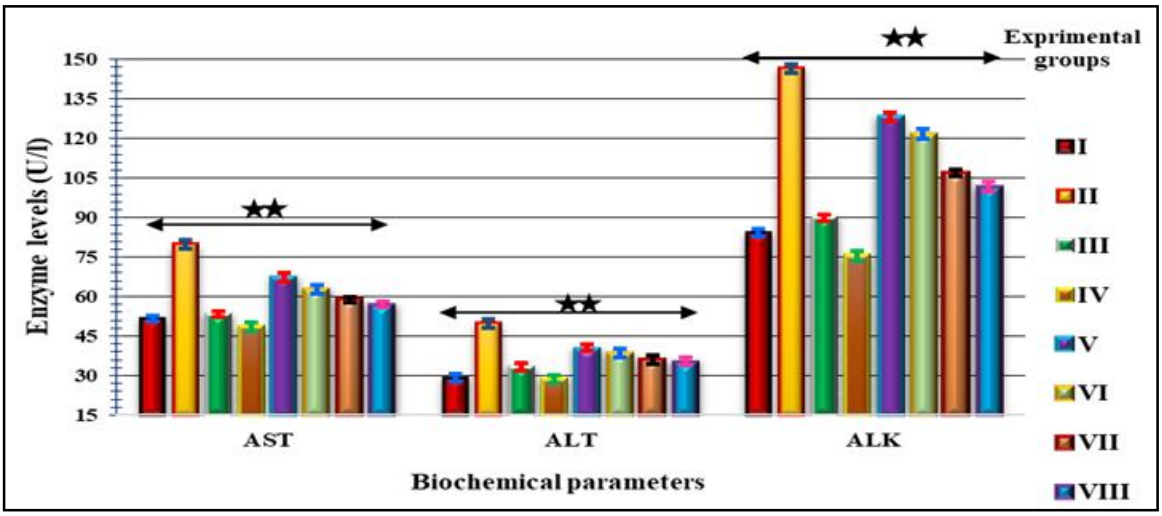

Figure 12: Bar diagram depicting the mean values of serum Total protein, Albumin and Globulin (mg/dl) in across experimental groups.

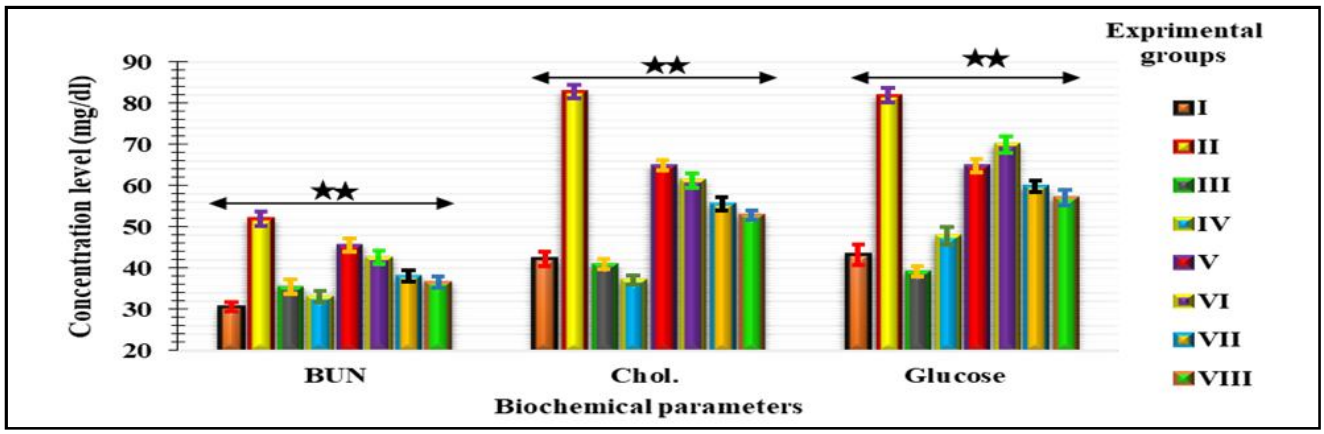

Figure 13: Bar diagram depicting the mean values of serum BUN, Cholesterol and Glucose (mg/dl) in experimental groups.

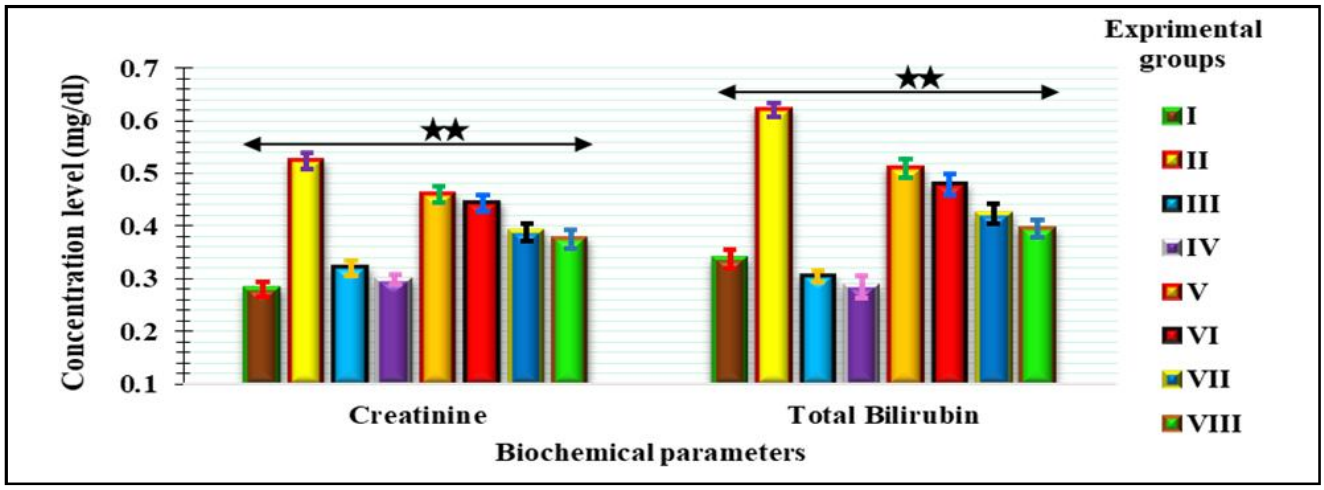

Figure 14: Bar diagram depicting the mean values of serum Creatinine and Total bilirubin (mg/dl) in experimental groups.

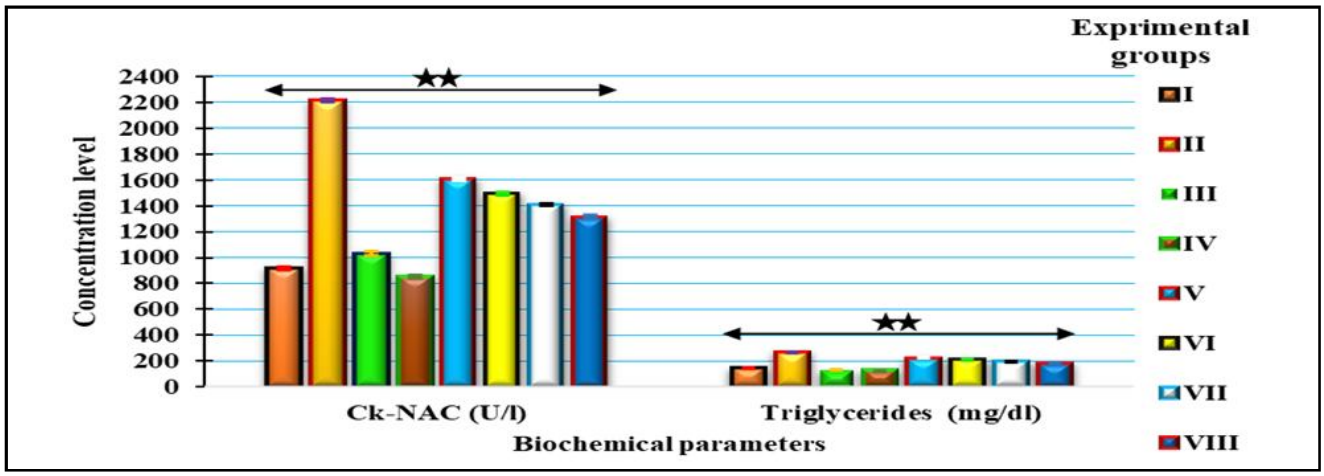

Figure 15: Bar diagram depicting the mean values of serum Ck-NAC (U/l) and triglycerides (mg/dl) in experimental groups.

3.4 Evaluation of oxidative stress parameters

The impact of $HgCl_2$ toxicity and the therapeutic potential of plant extracts on antioxidant status were assessed in liver and kidney tissues by measuring LPO (*via* MDA production), SOD, CAT, and GR activities. The results are summarized in Table 9 and Figures 16-19.

3.4.1 Oxidative stress markers in liver tissue

In liver tissue, oxidative stress markers revealed a significant ($p<0.01$) decrease in SOD, CAT, and GR activities, along with a significant ($p<0.01$) increase in MDA levels in the toxicity Group (II) relative to the control (I). Conversely, all treatment Groups (V-VIII) showed a

significant ($p<0.01$) reduction in MDA levels and a significant ($p<0.01$) rise in SOD, CAT, and GR activities compared to toxicity Group II. Treatment Groups V and VI differed significantly ($p<0.01$) from Groups VII and VIII, for MDA levels and SOD activity. For CAT activity among the treatment Groups (V-VIII), only Group V differed significantly ($p<0.01$) from Groups VII and VIII, while GR activity remained statistically similar across all treatment Groups (V-VIII). Notably, $HgCl_2$ exerted a more pronounced effect on SOD and CAT activities than on GR.

3.4.2 Oxidative stress markers in kidney tissue

Renal oxidative stress markers showed a significant ($p<0.01$) reduction in SOD, CAT, and GR activities, alongside a significant ($p<0.01$) rise in MDA levels in the toxicity Group II relative to control (I). In contrast, all treatment Groups (V-VIII) exhibited a significant ($p<0.01$) decrease in MDA levels and a significant ($p<0.01$) increase in SOD, CAT, and GR activities compared to toxicity Group II. Regarding MDA levels, Groups V and VI differed significantly ($p<0.01$) from Groups VII and VIII, indicating a stronger antioxidant effect in the combined extract treatments. In terms of SOD and CAT activity, Group V differed significantly ($p<0.01$) from Groups VII and VIII, while Group VI differed significantly ($p<0.01$) from Group VIII. For GR activity, no significant differences were observed in all treatment Groups (V-VIII).

Table 9: The mean values of LPO, SOD, CAT and GR in liver and kidney tissue of male Wistar rats from different experimental groups

Groups	Mean ± S.E. oxidative stress assay in liver and kidney tissue							
	LPO (nmole MDA/gm)		SOD (U/mg of protein)		Catalase (mmoles /min/mg protein)		Glutathione reductase (µmole/mg of protein/min)	
	Liver **	Kidney **	Liver **	Kidney **	Liver **	Kidney **	Liver **	Kidney **
I.	$55.74^{d} \pm 0.96$	$34.35^{f} \pm 0.71$	$21.25^{a} \pm 0.40$	$12.31^{a} \pm 0.35$	$38.27^{ab} \pm 1.21$	$44.67^{a} \pm 1.09$	$8.55^{ab} \pm 0.65$	$2.90^{a} \pm 0.07$
II.	$72.08^{a} \pm 1.26$	$59.55^{a} \pm 0.93$	$13.58^{d} \pm 0.21$	$7.18^{f} \pm 0.1$	$21.89^{f} \pm 1.39$	$28.35^{f} \pm 1.13$	$5.68^{e} \pm 0.32$	$1.68^{c} \pm 0.06$
III.	$57.80^{d} \pm 0.92$	$40.37^{d} \pm 0.85$	$20.16^{a} \pm 0.70$	$11.24^{b} \pm 0.21$	$35.45^{bc} \pm 0.9$	$41.04^{b} \pm 0.99$	$8.32^{abc} \pm 0.41$	$2.81^{a} \pm 0.07$
IV.	$55.11^{d} \pm 0.92$	$37.18^{e} \pm 0.71$	$21.13^{a} \pm 0.61$	$11.58^{b} \pm .016$	$38.73^{a} \pm 0.87$	$43.00^{ab} \pm 0.67$	$9.10^{a} \pm 0.48$	$2.95^{a} \pm 0.09$
V.	$66.45^{b} \pm 0.74$	$53.30^{b} \pm 0.46$	$15.74^{c} \pm 0.40$	$8.64^{e} \pm 0.09$	$27.17^{e} \pm 1.26$	$32.71^{e} \pm 0.96$	$6.92^{d} \pm 0.39$	$2.10^{b} \pm 0.11$
VI.	$64.96^{b} \pm 0.38$	$51.83^{b} \pm 0.74$	$16.95^{c} \pm 0.25$	$8.81^{de} \pm 0.11$	$29.82^{de} \pm 1.00$	$34.43^{de} \pm 0.83$	$7.11^{cd} \pm 0.24$	$2.14^{b} \pm 0.1$
VII.	$61.86^{c} \pm 0.57$	$48.40^{c} \pm 0.40$	$18.29^{b} \pm 0.45$	$9.18^{cd} \pm 0.09$	$32.40^{cd} \pm 0.89$	$36.79^{cd} \pm 0.37$	$7.35^{bcd} \pm 0.39$	$2.23^{b} \pm 0.06$
VIII.	$61.40^{c} \pm 0.59$	$47.19^{c} \pm 0.76$	$18.64^{b} \pm 0.32$	$9.41^{c} \pm 0.09$	$33.07^{cd} \pm 1.05$	$37.65^{c} \pm 0.72$	$7.66^{bcd} \pm 0.64$	$2.22^{b} \pm 0.08$

All data are presented as Mean ± SE (n = 6 per group). Values within the same column bearing different superscripts indicate significant differences at $p<0.05$ or $p<0.01$; identical superscripts denote non-significant differences and values without superscript within a column are also NS. NS = non-significant; * = significant ($p<0.05$); ** = highly significant ($p<0.01$).

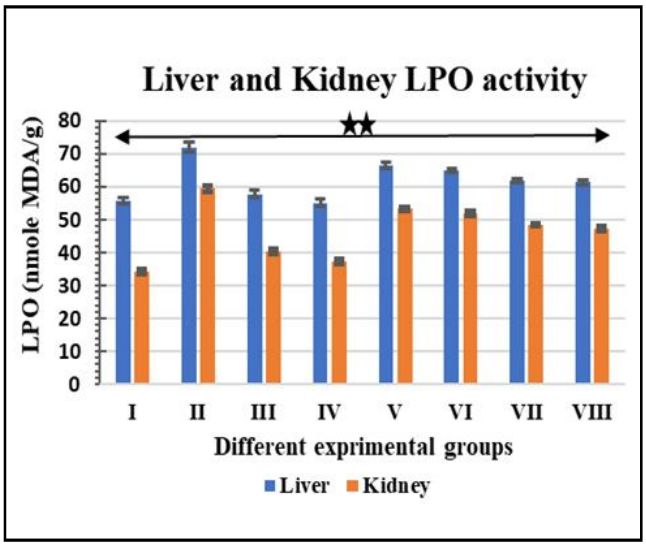

Figure 16: Bar diagram showing the mean LPO levels (nmole MDA/gm) in liver and kidney tissue across experimental groups.

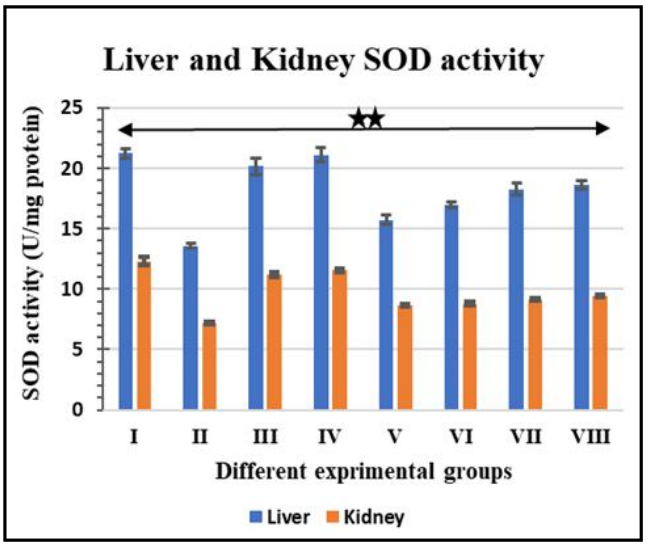

Figure 17: Bar diagram showing the mean SOD activity (U/mg protein) in liver and kidney tissue across experimental groups.

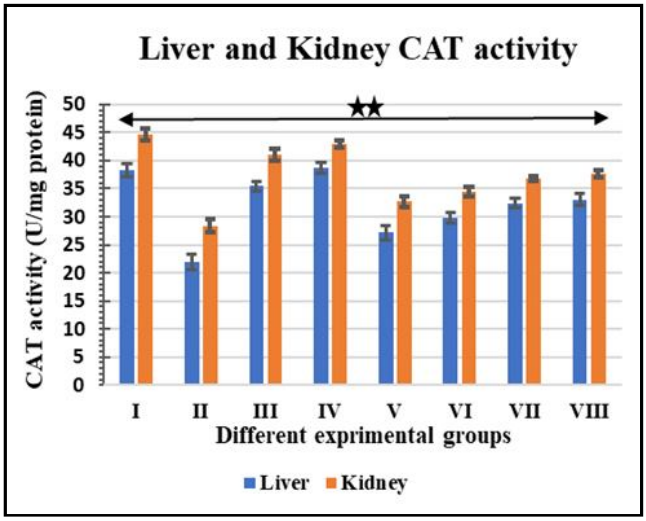

Figure 18: Bar diagram showing the mean catalase activity (mmoles/min/mg protein) in liver and kidney tissue across experimental groups.

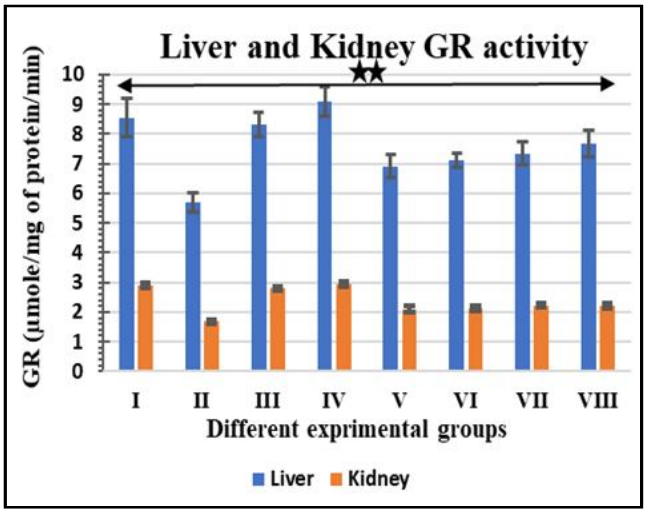

Figure 19: Bar diagram showing the mean glutathione reductase activity (µmole/mg protein/min) in liver and kidney tissue across experimental groups.

4. Discussion

The slight reductions in body weight were observed in toxicity Groups II and VIII throughout the study, likely due to decreased feed and water intake, renal tubular damage impairing water reabsorption and dehydration, and poor nutrient absorption by $HgCl_2$ -induced gastrointestinal injury, as confirmed by histopathological findings. The observed body weight reduction aligns with previous studies (Jalili *et al*., 2020; Domiaty, 2022; Maria Francis *et al*., 2023; Abubakar *et al*., 2024). In contrast, plant extract-treated groups showed improved weight gain by mitigating $HgCl_2$ toxicity, with Group IV exhibiting the highest body weight (Figure 1), indicating greater efficacy of PGPE over CELE. The weight gain effect of *P. granatum* aligns with previous reports (Faddladdeen, 2020; Jebur *et al*., 2023). Furthermore, the combined treatment of both extracts showed a greater protective effect against $HgCl_2$ induced weight loss than either extract alone.

In hematological parameters, non-significant TEC and Hb levels among treatment Groups (V-VIII), and significantly ($p<0.01$) decreased HCT level in Groups V and VI compared to VII and VIII, indicating that the combined administration of *C. esculenta* and *P. granatum* may offer better protection against $HgCl_2$ -induced toxicity. While, marked reduction in TEC, Hb, and HCT in Groups II and V and non-significant levels of MCV and MCH across all groups, suggesting that $HgCl_2$ primarily affects RBC quantity rather than their size or Hb content. Significantly reduced MCHC in Group II compared to control (I), indicates the presence of hypochromic anemia, characterized by reduced Hb concentration within RBCs. These findings align with Brandao *et al*. (2009), who reported decreased RBC counts by mercury-induced erythrocyte destruction.

$HgCl_2$ binds to RBCs, increasing their fragility by promoting LPO and inhibiting heme synthesis, thereby lowering Hb levels (Jomova and Valko, 2011; Lodia and Kansala, 2012). Mercury also disrupts lysosomal and mitochondrial membranes, alters protein synthesis, and contributing to cellular damage and anemia (Chauhan *et al*., 2014). Ololade *et al*. (2010) further associated decreased RBC counts with reduced iron and Hb levels, which impair blood's oxygen-carrying capacity. The hypochromic microcytic anemia observed here likely results from $HgCl_2$ induced oxidative stress and free radical generation, which inactivate Naz /Kz -ATPase, promote calcium influx into cells, and enhances membrane fragility and shortens RBC lifespan. As a result, TEC declines, leading to reduced Hb and HCT levels. Similar outcomes in mercury-exposed rats were also reported by Ladumor (2019) and Domiaty (2022). The reductions in TEC, Hb, HCT, and MCHC, along with increased MCV, align with Ibegbu *et al*. (2014). Similar decreases in TEC and Hb were reported by Shalan (2022), while Chauhan *et al*. (2014) also observed declines in TEC, Hb, HCT, MCH, and MCHC under $HgCl_2$ induced toxicity. Group VI demonstrated better recovery than Group V, indicating that *P. granatum* is more effective in mitigating $HgCl_2$ induced hematotoxicity than *C. esculenta*. These protective effects are attributed to the polyphenolic compounds in both plants, which possess strong free radical scavenging and metal-chelating properties. Supporting this, Ufelle *et al*. (2018) showed that methanolic extract of *C. esculenta* leaves promotes hematopoiesis in rats, while aqueous aqueous *P. granatum* peel extract reduces hemolysis (Aksu *et al*., 2012; Hasan *et al*., 2016).

TLC values remained non-significant across experimental groups, except for a significant ($p<0.01$) decrease in the toxicity Group II, indicating mercury-induced immunosuppression. This suppression was mitigated by plant extract treatments. Similar observations were reported in mercury-exposed mice (Brandao *et al*., 2009; Hounkpatin *et al*., 2013) and rats (Ibegbu *et al*., 2014; Ranveer, 2015; Ladumor, 2019). The low TLC values may reflect leukopenia and thrombocytopenia associated with mercury-induced hepatic dysfunction (Lee, 2004), likely due to mercury bioaccumulation in the liver and kidneys (Ololade *et al*., 2010). Histopathological findings in this study also corroborates HgCl, -induced organ damage in both toxicity and treatment groups.

Among the treatment Groups (V-VIII), only Groups VII and VIII exhibited a significant ($p<0.01$) increase in LYM% relative to Group II, indicating a stronger protective effect of the combined plant extracts, while significant ($p<0.01$) lower MID% was observed in all treatment Groups VIII, VII, V, and VI (lowest), respectively, compared

to Group II, indicating plant extracts mitigation on immune dysregulation. In all treatment groups, NEUT% remained elevated relative to control, reflects partial recovery and ongoing but reduced inflammation.The highest recovery in TLC and DLC values was observed in treatment Group VIII, followed by Groups VII, VI, and V. This improvement is attributed to the antioxidant properties of phenol and flavonoid-rich fractions from *P. granatum* peel and saponin and alkaloid-rich fractions from *C. esculenta* leaves, which likely shield blood cells from $HgCl_2$ induced damage. Notably, Group VI outperformed than Group V, suggesting PGPE is more effective in countering HgCl, toxicity. Similar leukocyte restoration with PGPE was reported by Hasan *et al*. (2016) in lead toxicity, while Ufelle *et al*. (2018) noted hematopoietic and leukocytic effects of CELE in both anemic and healthy rats.

Abd Elghani *et al*. (2020) and Calmday-Ombo and Innih (2025) reported a non-significant drop in PLT due to $HgCl_2$ toxicity, whereas this study found a significant reduction in both PLT and PCT values. This decline is attributed to $HgCl_2$ induced oxidative stress and bone marrow suppression, leading to leukopenia and thrombocytopenia. Elevated MPV suggests impaired bone marrow function and reduced platelet turnover, resulting to a more heterogeneous platelet population as reflected by increased PDW and P-LCR. Similar platelet count recovery with *P. granatum* peel was observed by Hasan *et al*. (2016) under lead toxicity. The highest recovery in PLT was seen in treatment Group VIII, followed by Groups V-VII. This improvement is attributed to the synergistic antioxidant effects from *P. granatum* peel and *C. esculenta* leaves. Interestingly, treatment Group V outperformed Group VI, suggesting CELE may be more effective than PGPE in mitigating $HgCl_2$ induced platelet toxicity.Serum analysis revealed a marked rise in AST, ALT, ALK, total bilirubin, Chol., T.G., and glucose in all $HgCl_2$-treated Groups (II, V-VIII) compared to the control (I), indicating $HgCl_2$ induced hepatic damage, corroborated by elevated oxidative stress value, histopathological alterations, and liver ultrastructural changes from this study. The significant rise in AST, ALT, and ALK levels is likely due to mercury binding to sulfhydryl groups on enzymes, disrupting their activity, and damaging hepatocyte membranes. This disruption leads to leakage of hepatic enzymes and other biomolecules into the bloodstream, reflecting impaired liver function and biosynthetic capacity (Kumar *et al*., 2005; Uzunhisarcikli *et al*., 2016). The significant rise in serum AST and ALT levels confirms $HgCl_2$ -induced hepatic injury, aligning with previous reports (Tripathi *et al*., 2021; Makena *et al*., 2022; Shalan, 2022; Mohamed *et al*., 2023). However, Ajibade *et al*. (2019) and Abubakar and Agbon (2024) reported non-significant increases in these enzymes. Similarly, the significant rise in ALK levels also supports hepatic injury, in agreement with previous studies (Makena *et al*., 2022; Sabir *et al*., 2022; Mohamed *et al*., 2023; Abubakar and Agbon, 2024). However, Chauhan *et al*. (2014) reported a non-significant rise in ALK levels.

The significant elevated total bilirubin levels were supported by Chauhan *et al*. (2014) and Sabir *et al*. (2022). Similarly, elevated Chol. and T.G. levels also suggest hepatic damage, consistent with Tripathi *et al*. (2021) and Mohamed *et al*. (2023). The significant rise in glucose levels reflects oxidative stress-induced pancreatic islet cell apoptosis and glucose dysregulation (Chen *et al*., 2012). The highest recovery in liver biochemical parameters was seen in treatment Group VII, followed by Groups VIII, VI, and V, suggesting that the combined plant extracts were more effective than either alone. This improvement is attributed to phenol and flavonoid rich fractions from *P. granatum* peel, as well as alkaloid and saponin-rich fractions from *C. esculenta* leaves. Group VI outperformed Group V, indicating *P. granatum* was more effective in mitigating $HgCl_2$ toxicity, except for glucose levels where *C. esculenta* performed better. These antioxidant compounds likely contributed to hepatocyte protection against $HgCl_2$ induced damage.

Serum analysis revealed a significant increase in creatinine, BUN, and CK-NAC levels, along with decreased total protein and albumin in $HgCl_2$ treated Groups (II, V-VIII) compared to control (I), indicating $HgCl_2$ induced renal damage. These findings are corroborated by oxidative stress value, histopathological alterations, and ultrastructural kidney damage observed in this study. Elevated ROS in kidney may reduce filtration surface area, and glomerular filtration, that led to creatinine and urea buildup in the blood (Amber *et al*., 2020). Increased creatinine level serves as a key marker of glomerular injury, and the overall rise in these renal biomarkers reflects $HgCl_2$ -induced nephrotoxicity due to nitrogenous waste buildup.

The reduced protein levels in $HgCl_2$ -treated Groups (II, V-VIII) are likely due to impaired hepatic synthesis and enhanced renal excretion (Youcef *et al*., 2014; Aqeel *et al*., 2019). Furthermore, Hosseini *et al*. (2018) and Sabir *et al.* (2022) also reported elevated urinary albumin levels, suggesting tubular damage and decreased glomerular filtration, which aligns with the observed drop in serum total protein and albumin levels. Elevated Ck-NAC levels may reflect enzyme leakage into systemic circulation because of renal cellular damage (Maria Francis *et al*., 2023). Mercury ion enters into renal tubular cells *via* sodium ion channels, and induce nephrotoxicity by binding to nucleophilic sites, especially sulfur-containing groups in amino acids, proteins, and peptides mainly in the renal cortex and proximal tubules (Almeer *et al*., 2019).

Serum creatinine concentration serves as a key indicator of kidney function and structural integrity (Sheikh *et al.,* 2013). Elevated urea and creatinine levels are closely associated with renal damage and oxidative stress (Zhang *et al*., 2020; Goudarzi *et al*., 2023). The significant rise in BUN and creatinine levels in this study confirms $HgCl_2$ -induced nephrotoxicity, aligning with earlier studies (Makena *et al*., 2022; Sabir *et al*., 2022; Shalan, 2022; Mohamed *et al*., 2023). While, Chauhan *et al.* (2014) and Abubakar *et al.* (2024) reported a non-significant rise in creatinine levels. The increased globulin levels in all $HgCl_2$ treated groups were likely due to the toxic accumulation of $HgCl_2$ in various organs and triggering an inflammatory response, as supported by histopathological evidence of tissue damage and inflammation in this study.

The highest recovery in kidney biochemical parameters was seen in treatment Groups VII and VIII, indicating that the combination of both plant extracts was more effective against $HgCl_2$ toxicity than either individual plant extract. This improvement is attributed to the antioxidant compounds present in both plants, which likely protected renal cells by reducing $HgCl_2$ -induced oxidative stress and cellular injury. Group VI outperformed than Group V, indicating that PGPE was more effective than CELE.

Notable improvements in liver enzyme levels following PGPE treatment were observed in previous studies. Jebur *et al*. (2023) reported improved AST, ALT, and ALP levels with PGPE in fenpropathrin toxicity, attributing to its potent anti-inflammatory

and antioxidant phytochemicals. Faddladdeen (2020) also observed reductions in AST, ALT, ALP, and glucose levels with PGPE in type 1 diabetes. El-Daly (2016) noted significant decreases in urea, creatinine, and BUN levels following PGPE administration in CdCl, toxicity. Additionally, Saikia *et al*. (2018) demonstrated the hepatoprotective potential of the methanolic extract of *C. esculenta* in iron overload-induced mice, with significant reductions in ALT and AST levels.

Lipid peroxidation, a key indicator of cellular toxicity, was significantly elevated in all $HgCl_2$ -treated Groups (II, V-VIII) due to $HgCl_2$ induced ROS generation, which promotes oxidative stress and LPO (Karapehlivan *et al*., 2014; Ahmad and Mahmood, 2019). These findings are aligned with previous studies (Hosseini *et al*., 2018; Ladumor, 2019; Nabil *et al*., 2020). The significant reduction in SOD, CAT, and GR activities in $HgCl_2$ treated groups is linked to ROS generation by $HgCl_2$, which consequently led to decreased antioxidant enzyme levels in liver tissue (Ahmad and Mahmood, 2019). The decline in CAT activity may result from its utilization in neutralizing free radicals and H_2O_2 accumulation (Rao and Chhunchha, 2010; Joshi *et al.,* 2014). These results are consistent with earlier studies (Joshi *et al*., 2017; Ladumor, 2019; Nabil *et al*., 2020).

The highest recovery was seen in Groups VII and VIII, indicating that the combination of both plant extracts was more effective against $HgCl_2$, induced oxidative stress than either individual extract. Group VI outperformed than Group V, suggesting that PGPE offers stronger protection. Both CELE and PGPE effectively reduced LPO and enhanced SOD, CAT, and GR activities, while preserving hepatocellular architecture. Their protective effects are attributed to bioactive constituents (flavonoids, terpenoids, coumarins), with potent antioxidant, free radical scavenging, ROS-neutralizing, and membrane-stabilizing properties. Similar increases in SOD and CAT activities from *C. esculenta* were reported by Saikia *et al.* (2018) and Gomaa *et al*. (2022).

This study showed a significant rise in MDA levels in renal tissues of all $HgCl_2$, treated Groups (II, V-VIII) compared to controls, due to excessive ROS generation induced by $HgCl_2$. These ROS promote oxidative stress, lipid peroxidation, and DNA damage (Boroushaki *et al*., 2014; Ahmad and Mahmood, 2019). Mercury also binds to low molecular weight proteins and metallothioneins in the kidney, that further exacerbates oxidative damage and cellular dysfunction by increased ROS production (Caglayan *et al.,* 2019). The resulting ROS attack membrane lipids, and raising MDA levels (Hosseini *et al.,* 2018; Mohamed *et al.,* 2023). Similar observations are consistent with prior studies (Yadav *et al*., 2019; Francis *et al*., 2020; Nabil *et al*., 2020; Sabir *et al.,* 2022).

The significant reduction in SOD, CAT, and GR activities in all $HgCl_2$ treated groups is attributed to excessive ROS generation and oxidative stress induced by $HgCl_2$, which impaired antioxidant enzyme function in renal tissue (Ahmad and Mahmood, 2019). The decline in SOD activity promoted oxygen intolerance in tissues and triggering several deleterious reactions. CAT, which detoxifies H_2O_2 and superoxide radicals, showed reduced activity possibly due to enhanced hydroxyl ion formation, that elevated LPO levels in renal tissues (Joshi *et al.,* 2014). The declines in SOD and CAT activities are align with previous reports (Ladumor, 2019; Nabil *et al*., 2020; Sabir *et al*., 2022; Mohamed *et al*., 2023), as well as reductions in CAT and GR activities (Ge *et al.*, 2022; Mohamed *et al.*, 2023; Maria Francis *et al*., 2023).

Notably, $HgCl_2$ exposure led to a greater decrease in SOD and CAT activities compared to GR activity in renal tissue. The most significant recovery of renal oxidative stress parameters was seen in treatment Groups VII and VIII compared to Groups VI and V, indicating that the combined plant extracts were more effective against HgCl, toxicity, and Group VI outperformed Group V, suggesting that PGPE is more effective than CELE. This protective effect is likely due to antioxidant constituents of plant extracts, which scavenge free radicals, neutralize ROS, and preserve cell membrane integrity. In this study, both CELE and PGPE effectively attenuated $HgCl_2$ induced oxidative stress, evidenced by decreased LPO and increased SOD, CAT, and GR activities. Moreover, these extracts also contributed to maintaining the structural integrity of renal cells. The enhancement in SOD and CAT activities by *C. esculenta* aligns with findings by Saikia *et al*. (2018) and Gomaa *et al*. (2022).

5. Conclusion

This study demonstrates that *C. esculenta* leaf and *P. granatum* peel extracts effectively mitigate mercuric chloride-induced toxicity in rats, as reflected by improvements in body weight, hematobiochemical profiles, and oxidative stress markers. Notably, the combined extract exhibited the most pronounced protective effect, followed by the aqueous *P. granatum* peel extract and then the methanolic *C. esculenta* leaf extract.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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