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Original Research Article

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Hematological Parameters and Biochemical Evaluation of the Effects of Vitamin C in Swiss Albino Mice Exposed to Chronic Doses of Cadmium

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Abstract: Cadmium toxicity characterizes a global environmental contamination delinquent and a common source of industrial and non-occupational neurological diseases. Cadmium toxicity is common among heavy metal toxicity even at minimum exposure because of slow excretion rate from the body and long biological half-life. The purpose of the present study was to determine the role of vitamin C against cadmium-induced toxicity in Swiss albino mice. This current study was performed by the biochemical parameters and hematological analysis in Swiss albino mice as affected by the oral administration of a single dose equivalent to 1/20 from LD_{50} (100 mg/kg B.W.) of Cadmium individually for 35 days and evaluated the protective role of vitamin C. The results presented a significant reduction ($P < 0.05$) in White Blood Cells count (W.B.C.s) and Red Blood Cell (R.B.C.s) count in Cadmium-treated animals in comparison with the control group. The results from other studies showed a significant reduction of the body weight of cadmium treated mice and were compared with the control group. While total serum protein and total cholesterol significantly decreased ($P < 0.05$) in cadmium-treated animals compared with the control group. Biochemical parameters showed a significant increase ($P < 0.05$) in urea and creatinine levels in cadmium treated mice when compared to the control group. Vitamin C is recognized an essential nutrients for all species of animals. In other words, these vitamins have been shown to have protective effect against heavy metal induced toxicity. In conclusion, this study demonstrates that oral exposure of cadmium caused reduction in biochemical and hematology activities in mice and vitamin C has ameliorative effect against metal-induced toxicity. Vitamin C is a natural antioxidant that prevents the increased production of free radicals induced by oxidative damage to lipid and lipoproteins in numerous tissues and cellular compartments.

Keywords: Cadmium, Toxicity, Protective, Vitamin C, Antioxidant agent.

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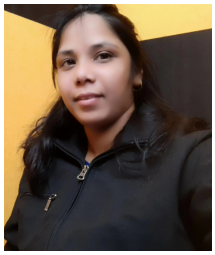

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1. INTRODUCTION

Environmental pollution, specifically by chemicals, is one of the most significant operative factors in destroying the biosphere mechanisms[1]. Among all substances polluted, heavy metals are considered as potential unsafe contaminants in the environment to human health[2]. Heavy metals are metallic components withdensity at least five times more than water[3-4]. In general, heavy metals are not biodegradable, have long biological half-life, and can accumulate in the different vital organs and results in unwanted side effects[5-7]. The numerous harmful health effects upon exposure to toxic heavy metals in the environment are serious concerns[8]. Much importance has been given to elucidate the toxicity mechanism due to collective environmental toxicants and mature a harmless chemotherapeutic method to mitigate the toxic belongings[8]. Cadmium is the most abundant toxic metal in the environment[9]. The anthropogenic activities and vehicular emissions contribute to poisonous metals to humans and other animal food chains[10]. Lead, cadmium, nickel, arsenic, chromium and mercury are the most prevalent metals that can threaten the human at low concentration[11-14]. Cadmium is a significant environmental pollutant present in the soil, water, air and food[15-16]. The primary source of toxic cadmium exposure is the inhalation route of cadmium particles or fumes during industrial operations[17-18]. It is also at present in cigarette smoke[19]. Cadmium-induced tissue has been capable in portion to toxicant-induced oxidative stress[20-21]. Cadmium (Cd) stimulates the development of reactive oxygen species (ROS) and metallothionein, thus causing oxidative damage to erythrocytes and various tissues consequential to the membrane functions[22]. Long-term exposure to Cd rises lipid peroxidation and causes inhibition of SOD (superoxide dismutase) activity, representative oxidative damage in the testes, kidney, and liver[23]. Many studies suggested that the generation of reactive oxygen species (ROS) and its interference with the cellular antioxidant system is one central mechanism by which cadmium's toxic effect is mediated[24]. The antioxidant can play a significant role in the treatment of metal-induced oxidative stress as efficient chelators[25]. Ascorbic acid is a water-soluble dietary antioxidant that plays an essential role in controlling oxidative stress[26]. Ascorbic acid is a necessary constituent in cellular metabolism; biomolecules' interactions give a good idea of toxicant stress and its effect[25]. It has also been demonstrated that vitamin C is one of the greatest influential factors reducing a greater renal and hepatic cadmium problem in pigs fed diet developed with copper[27] Ascorbic acid is a vital phytonutrient for living cells' metabolism in diverse absorptions in natural foods, mostly fruits and their foodstuffs. Vitamin C or ascorbic acid presents a shielding consequence against free radical-induced oxidative damage[28]. Vitamin C acts as a potent water-soluble antioxidant by scavenging reactive oxygen and nitrogen species[29]. It is an excellent source of electrons and thus provides an electron to free radicals such as hydroxyl radical and superoxide radical and quenches their awareness[30]. Vitamin C offers adequate protection against lipid peroxidation[31]. In addition to scavenging action, vitamin C can regenerate other small molecule antioxidants such as α- tocopherol, glutathione and urate from their respective radical species[29]. Vitamin C is an important dietary antioxidant and significantly reduces the effect of reactive oxygen species that can cause oxidative damage such as DNA, protein and lipids which are implicated in various disease and reduces toxic effects of metal[32-33]. This study aimed to investigate a possible protective effect of Vitamin C treatment on the selected biochemical parameters and histological changes of RBCs and WBCs in Swiss albino mice exposed to Cd.

2. MATERIALS AND METHOD

2.1 Chemical

Cadmium, Vitamin C (Ascorbic acid), and all the chemicals used in the experiments were of the analytical grade and purchased from Himedia Laboratories Private Limited. (Mumbai, India).

2.2 Animals

Swiss albino mice (5-6 weeks old, weighing almost 20-25 gm) were housed in polypropylene cages (3-4 animals per cage; B.I.K Industries). The animals were kept throughout the experiment for full accommodation in an air-conditioned animal room (28±2°C)[34] and controlled light room with a photoperiod of under a 12 h light/dark cycle and given a standard pellet diet (obtained from Hindustan Lever Limited, Mumbai, India) and RO water *ad libitum.* All experimental processes were completed following the recommendations found in the Guide for the Care and Use of Laboratory Animals (Refer) and permitted by committee Institutional Animal Ethics Committee (IAEC) (R. No. 1402/a/10/CPCSEA) of the Jayoti Vidyapeeth Women's University of Jaipur. Established ethical strategies were also followed in all Experiments.

2.3 Experimental design

The Swiss albino mice were divided into three groups comprising of 4 animals in each group as follow:-
Group I: - Control (normal) swiss albino mice, fed with standard pellet diet and water.
Group II: - Were given 100mg/kg body weight of Cadmium chloride.
Group III:- was given 100mg/kg body weight of the Vitamin C after exposure to Cadmium.

2.4 Blood Sample Collection

The mice were carefully monitored every day. Animals defined as fasted were destitute from food for at least 12 h but an acceptable free entree to drinking water. Blood samples were collected at weekly intermissions till the end of the research work[34]. During the 7th, 14th, 28 and 35 week of treatment, the body weight, Serum Total Cholesterol, Total serum protein, Total blood urea, and serum creatinine of all the Swiss albino mice were determined. The blood samples were poised from the tail vein puncture. Throughout the experiment, blood samples were been obtained overnight from the tail vein of all the animals. Blood was left to clot and centrifuged (REMI CM12;2009) at 3000 rpm for 15 min, at 4°C for separating the serum, frozen and stored at -20°C[34]. for biochemical analysis and hematological analysis.

2.5 Bodyweight Estimation

All animals were weighed every week until the end of the experiment.

2.6 Biochemical Estimation

The blood sample was collected for Hematological
Parameters: red blood cells count (RBCs), and white blood cell count (WBCs) was determined according to the methods described by previous research studies[35]. Serum was collected for estimation of biochemical parameters, such

as serum cholesterol[36], total serum protein[37]; serum creatinine[38] and blood urea level[39].

3 STATISTICAL ANALYSIS

The results were expressed as mean ± SEM (Standard Error of Mean). The data were analyzed by one-way ANOVA followed by student t-test at the level of significance was described as P<0.05 and P<0.01. All statistical data were performed using IBM SPSS Statistics 20 (File version 22.0.0.0).

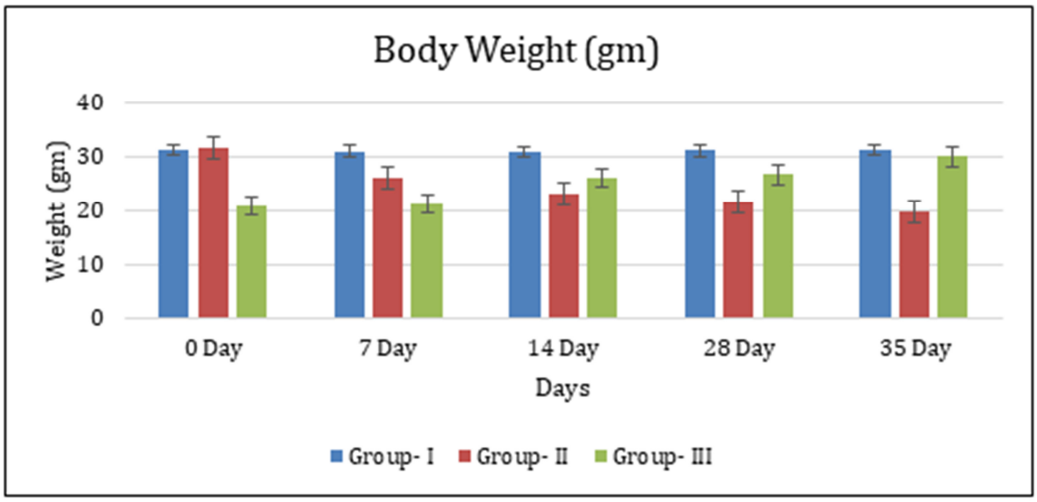
4 RESULT

In this investigation, the bodyweight of albino mice subjected to treatment is shown in Table 1 and Graph 1. In Cd-treated Animals, the results showed a significant decrease ($p < 0.05$) in body weight compared to the control group. However, vitamin C supplements the body weight gain significantly ($p < 0.05$) than in albino mice exposed to cadmium $p < 0.05$. In the present study, the Red Blood cell (RBC) and White Blood cell (WBC) of Swiss albino mice subjected to Cadmium treatments are shown in Table 2 and Figure 2. During the experiment, the White Blood cell (WBC) and Red Blood cell (RBC) of the Swiss albino mice group (9.06±0.001; 8.08±0.004) slightly significantly decreased as compared with the control group (3.79±0.001; 3.53±0.009) ($p<0.05$). Vit C treatment increased ($p<0.05$) the lowered RBC counts. It was also found that the WBC counts increased ($p<0.05$) in Cd-treated rats.

Table 1: The effect of Vitamin C on Body Weight (gm) in Cadmium treated Mice.

Days	Group- I	Group- II	Group- III
	Control	Cadmium treated Mice	Vitamin C treated Mice
0 Day	31.18±0.09	31.56±0.09	20.79±0.02
7 Day	31.09±0.07	26.17±0.05	21.18±0.04
14 Day	30.81±0.06	23.19±0.04	25.97±0.05
28 Day	31.13±0.07	21.62±0.04	26.67±0.05*
35 Day	31.25±0.09	19.79±0.01	29.98±0.06*

*Values (In Gram) are shown as the Mean±SEM. Values are statistically significant at * p<0.05 when compared to control group.*

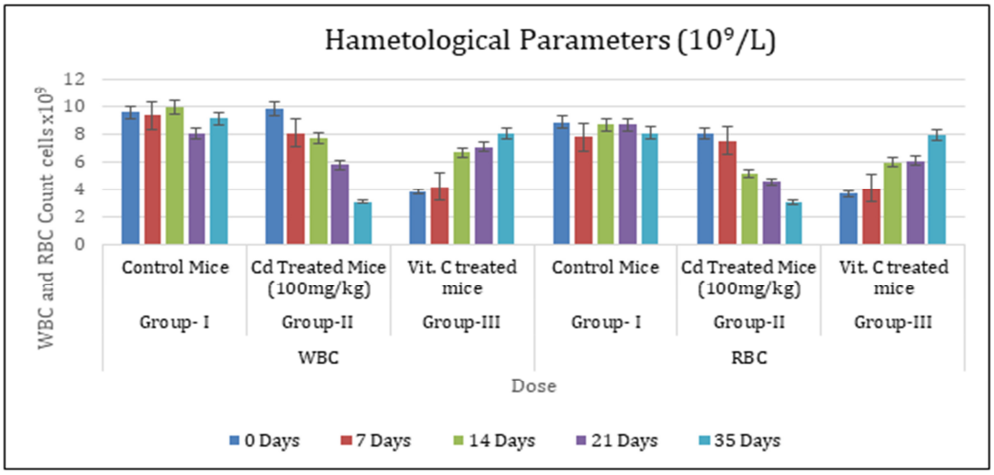


Graph 1: Showing the effect of Vitamin C on Body weight in Cadmium treated mice

Table 2: The effect of Vitamin C on Hematological Parameters in Cadmium treated Mice.

Days	WBC			RBC		
	Group- I	Group-II	Group-III	Group- I	Group-II	Group-III
	Normal Mice	Cd Treated Mice (100mg/kg)	Vitamin C treated mice	Control Mice	Cd Treated Mice (100mg/kg)	Vitamin C treated mice
0 Days	9.57±0.009	9.85±0.009	3.78±0.003	8.88±0.007	8.02±0.007	3.64±0.003
7 Days	9.36±0.008	8.09±0.007	4.18±0.004	7.78±0.006	7.53±0.005	4.07±0.005
14 Days	9.95±0.011	7.75±0.006	6.67±0.005	8.68±0.008	5.16±0.004	5.98±0.006
21 Days	8.08±0.007	5.76±0.004	7.08±0.006*	8.67±0.008	4.54±0.004	6.08±0.006*
35 Days	9.13±0.008	3.07±0.003	8.02±0.007*	8.09±0.007	3.02±0.002	7.98±0.008*

*Values are shown as the Mean±SEM. Values are statistically significant at * p<0.05 when compared to the Normal group.*



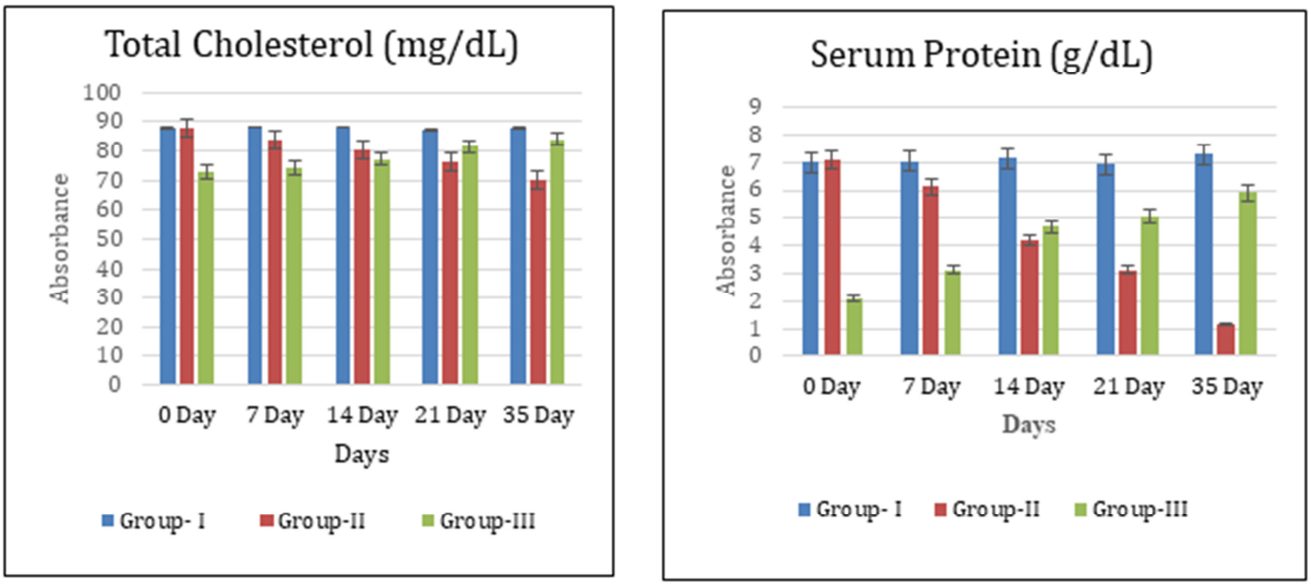
Graph 2: Effect of Vitamin C on Hematological parameters in Cadmium treated mice

Treatment with Cd caused a significant decrease of cholesterol (70.09±0.11) when ($p<0.05$) compared to the control group (87.09±0.24). Meanwhile, the concentration of total serum protein was reduced (2.11±0.001) ($p < 0.05$) as compared to the control group (7.13±0.009). The administration of vitamin C in cadmium-treated mice increased cholesterol level and the serum protein levels were in compared to cadmium treated mice. The results showed the serum creatinine Cd-treated mice group significantly increased (6.76±0.21) concerning the control group (0.98±0.08) ($P<0.05$). However, vitamin C supplies the serum creatinine became significantly decrease ($p < 0.05$) than in albino mice exposed to cadmium $p < 0.05$. Cadmium induced mice were found to have significantly elevated blood urea level (57.09±0.28) with the respect to the control group (38.99±0.13) ($p<0.05$) Table 3; Figure 3. The administration of vitamin C in cadmium treated albino mice increased blood urea level was significantly decreased as compared to normal mice. ($p<0.05$) Table 4; Figure 4.

Table 3: The effect of Vitamin C on Total Cholesterol and Total Serum Protein in Cadmium treated Mice.

Days	Total Cholesterol (mg/dL)			Total Serum Protein (g/dL)		
	Group- I	Group-II	Group-III	Group- I	Group-II	Group-III
	Control	Cadmium treated Mice	Vit. C treated mice	Control	Cadmium treated Mice	Vit. C treated mice
0 Day	87.92±0.17	88.02±0.18	72.78±0.11	6.98±0.007	7.09±0.008	2.11±0.001
7 Day	88.34±0.19	84.05±0.14	74.12±0.12	7.03±0.009	6.11±0.008	3.12±0.003
14 Day	88.08±0.18	80.15±0.13	77.08±0.12	7.13±0.009	4.19±0.005	4.68±0.004
21 Day	87.16±0.17	76.16±0.11	81.56±0.14*	6.92±0.008	3.12±0.003	5.08±0.004*
35 Day	87.68±0.17	70.09±0.10	84.11±0.15*	7.29±0.009	1.14±0.001	5.91±0.005*

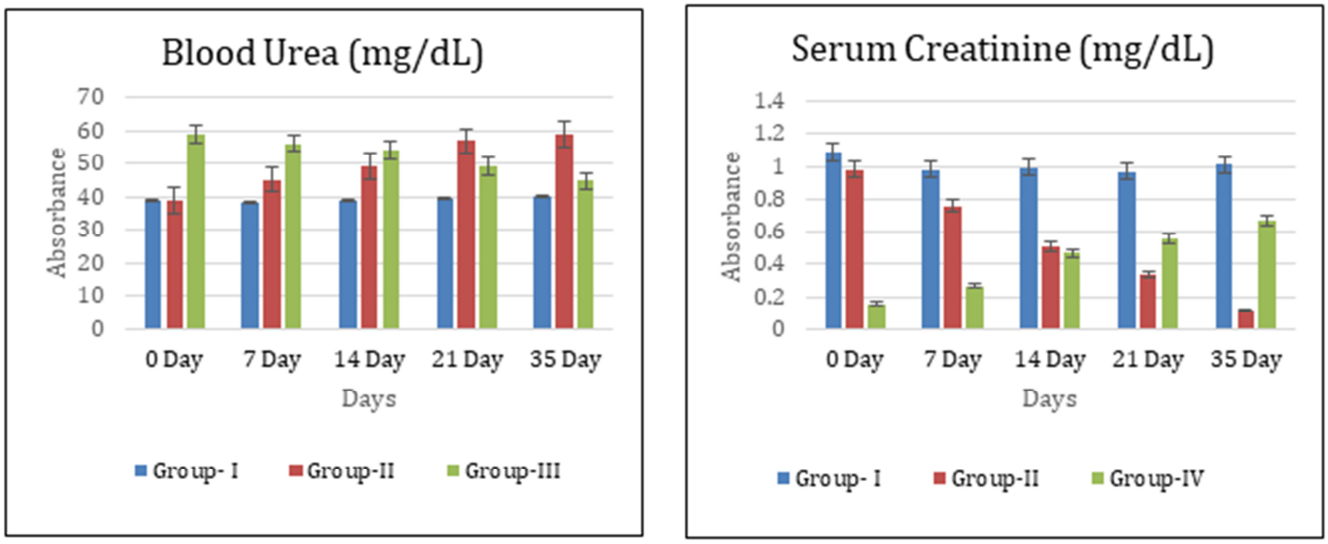
Values are shown as the Mean±SEM. Values are statistically significant at * p<0.05 when compared to the normal group.



Graph 3: Effect of Vitamin C on Total Cholesterol and Total Serum Protein in normal mice, Cadmium treated mice and Vitamin treated mice

Table 4: The effect of Vitamin C on Serum Blood Urea and Serum Creatinine in Cadmium treated Mice.

Days	Serum Blood Urea (mg/dL)			Serum Creatinine mg/dL)		
	Group- I	Group-II	Group-III	Group- I	Group-II	Group-IV
	Control	Cadmium treated Mice	Vit. C treated mice	Control	Cadmium treated Mice	Vit. C treated mice
0 Day	39.08±0.11	38.97±0.09	58.98±0.19	1.09±0.006	0.98±0.006	0.16±0.001
7 Day	38.19±0.09	45.09±0.14	56.03±0.17	0.98±0.005	0.76±0.005	0.27±0.002
14 Day	38.91±0.09	49.17±0.15	54.01±0.16	0.99±0.005	0.51±0.005	0.47±0.003
21 Day	39.78±0.10	56.98±0.18	49.18±0.15*	0.97±0.004	0.34±0.003	0.56±0.004*
35 Day	40.01±0.12	59.01±0.19	44.77±0.13*	1.01±0.007	0.12±0.001	0.67±0.005*



Graph 4: Effect of Vitamin C on Serum Blood Urea and Serum Creatinine in normal mice, Cadmium treated mice and Vitamin treated mice

5 DISCUSSION

Different people have clarified the mechanism of cadmium-induced hepatotoxicity which includes contact with membrane components and lipid peroxidation[40]. Cadmium induces oxidative stress and lipid peroxidation by reducing GSH (Glutathione) or by inhibition of antioxidant enzymes[40]. Cadmium becomes accrued in liver and causes tissue damage[41]. Cadmium indirectly generates various radicals like superoxide, hydroxyl and nitric oxide and induces oxidative stress and tissue damage[42]. These reactive oxygen species generated indirectly by Cd, attack on the cell membrane and causes destabilization and disintegration of the cell membrane resulting in lipid peroxidation[43,16]. Because of its oxidative stress inducing nature the cadmium induced toxicity can be restored by the treatment of various antioxidant[44-45]. The present study also confirmed that the administration of vitamin C significantly reduces the toxicities induced by cadmium. The increase in the pollution of our daytime is an important and worldwide problem. It is outstanding for using xenobiotic substances or deadly chemicals or by certain synthetic compounds such as heavy metals[46-47]. Cadmium and lead are very toxic heavy metals and a significant environmental pollutant that causes extermination in numerous tissues of animals and human[48-49]. Vitamin C is an effective water solvable antioxidant created in human plasma. It scavenges reactive oxygen and nitrogen species including hydroxyl radical, peroxyl radicals, superoxide anion, nitrogen dioxide as well as non-radical species such as hypochlorous acid, ozone and singlet oxygen[50]. In the current study, Cadmium fed mice were exposed to a substantial and constant decrease in body weight at different intervals over the control group's experiment period. An earlier report has been described that in swiss albino mice, that significantly reduces body weight[51-52]. The reduction in body weight content in the Cd-treated mice group correlates with other author's work[53-54]. In the current work, the investigation of samples obtained from animals treated with vitamin C showed enhancement in the body weight as compared to the cadmium mice group. These results agreed with the further study, which found that the ascorbic acid prohibited the free radicals caused oxidative impairment of the cell membrane[39]. The treatment with vitamin C to the Cadmium-treated animals enhanced body weights[55,1]. This outcome agrees with other results[56-57]. Vitamin C supplementation facilitated a significant increase in body weight compared to cadmium treated mice[58,53]. The observed rats reduced weight gain in this study is reliable with some earlier published reports[59]. The present study result exposed a significant decrease in WBC and RBC of treated mice with Cadmium compared with the control mice group. It has been described that RBC and WBC count significantly reduced in the swiss albino mice administered $CdCl_2$[60,51]. On the other hand, These outcomes approve with those found by early studies[54,58]. They specified that the RBC count significantly reduced in Wistar Rats, showing the Cd concentration relative to the control mice group. Other authors revealed this outcomes[61-62] conducted on mice poisoned with lead. In the current search, the Vitamin C treated group showed a rise in hematological parameters compared to cadmium-treated mice. Another work found that hematological parameters significantly increased by dietary vitamin C[54]. On the other hand, it was also shown that pre-treatment with vitamin C showed a defensive role on the toxicityof Cadmium on hematological value[63]. Similar outcomes were obtained by earlier published works[64], which exposed the protective effect of vitamin C on

anemia produced by heavy metals in rats. The previous report showed that treatment with Vitamin C showed meaningfull reduction of the toxic effects of Cadmium on hematological standards[58]. In Our current study cadmium treated mice presented a significant reduction in Cholesterol, serum protein , increased serum creatinine and blood urea level compared to the control mice group. In the present work, examining specimens obtained from animals treated with vitamin C showed improvement in the biochemical parameters compared to the cadmium group. A similar result has been reported a significant decrease in total serum protein level and increased urea and creatinine levels in albino rats[65-67,1]. These results are in coincidence with those previously obtained study[1]. They found that rats treated with vitamin C showed a significant increase in total serum protein level and decreased urea and creatinine levels in albino rats. The reduction in cholesterol content in the Cd-treated mice group agrees with other authors' work[67,68-71]. Reduced protein content was observed in the Cd-treated group. Some authors also reported a similar trend in their research findings[69-71,72-75]. This result agrees with other findings[76,65]. On the other hand, the results obtained showed a significant increase in total serum protein level by the treatment of vitamin C on Cadmium-induced rats[77]. Another worker reported that the administration of vitamin C significantly decreases urea and creatinine levels in Wistar rats[78].

6 CONCLUSION

The outcomes of this current study showed that cadmium present in the atmosphere and in the specific products are the cause of hematological and biochemical disorders in the blood. Vitamin C has a protective effect on biochemical and hematological induced cadmium toxicity. The present work also presented that Vitamin C has a significant result on the aberrations of biochemical and hematological parameters. Thus vitamin C can be used as natural sources of antioxidants and as essential components for reduction of cadmium toxicity

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8 AUTHORS CONTRIBUTION STATEMENT

Both the authors have contributed equally.

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10 CONFLICT OF INTEREST

Conflict of interest declared none.

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