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Protective Role of Vitamin C Pretreatment in Acute Nickel Nephrotoxicity in Mice

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Abstract

Pretreatment with Vitamin C (VC) has been identified as a viable therapeutic approach for reducing acute Nickel (Ni) Nephrotoxicity in mice. During oxidative stress and inflammation, the hazardous heavy metal Ni is known to cause Renal Failure (RF). This study was carried out to examine the preventative benefit of VC consumption and its effects on Ni-induced RF. This study used 60 lab mice weighing between 30 and 35 grams. After being weighed, 44 adapted mice were chosen from among the 58 male mice. Six experimental categories made up of eight mice each were created from these 44 animals. The 30-day course of medication for the lab mice was continued. This study revealed no substantial variations in the weights of the Renal System (RS) in mice that had previously received VC, but there was a significant increase in the weight of the RS in mice that had received Nickel Chloride ($NiCl_2$) injections while compared with the controls and the sample that received VC orally. The mice's blood levels of urea, creatinine, and uric acid were able to rise concurrently. Although VC treatment can protect the RS from these NC poisons, this was supported by changes in the mice's renal tissues. According to the study, taking VC supplements may work as an antioxidant to shield renal and hematological components from deterioration.

Keywords: Necrosis, Vitamin C (VC), Nickel chloride ($NiCl_2$), Nephrotoxicity, Mice, Renal failure (RF).

Introduction

The VC is a necessary nutrient that is needed for sustaining general health. It is well known for its antioxidant effects and its contributions to iron absorption, immune system health, and collagen formation. Even while VC is often regarded as safe and well-tolerated, consuming too much of it might have negative effects on the function of the renal system. VC is a significant and well-known antioxidant. Large dosages of VC intravenous supplements have shown to be highly efficient in therapies for cancers and life-threatening conditions linked to oxidative stress by enhancing the body's antioxidant capacity (1). The nephrotoxicity caused by cisplatin in mice may be successfully reduced by pre-treatment with a particular intervention. This treatment, that was given before the drug cisplatin was given, showed exceptional promise for minimizing kidney damage. The pre-treatment method of action reduced the toxic effects of cisplatin on renal tissues, protecting their structural integrity and functional ability. This encouraging discovery shows that the use of this pre-treatment technique may hold significant promise in preventing cisplatin-induced nephrotoxicity, presenting a possible route for enhancing the safety and acceptability of cisplatin-based chemotherapy regimens (2). Nephrotoxicity in mice has a protective effect by preserving the essential renal function of these creatures. Mice may undergo nephrotoxicity while exposed

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to drugs or agents that are known to be harmful to the renal, such as certain pharmaceuticals or chemicals. Although this illness briefly damages the renal tissue, it also triggers several safeguards meant to keep the renal healthy in general. These mechanisms include cellular repair processes being triggered, immune cells being drawn to the location of the damage, and antioxidant defenses being strengthened (3). Cisplatin-induced nephrotoxicity has been associated with substantial morbidity and fatality rates. Because of the high concentration of cisplatin in the renal, renal functions are particularly impacted by cisplatin. Maintaining the urine flow by hydrating with saline both before and after cisplatin chemotherapy is the suggested method for preventing renal impairment in cisplatin-based chemotherapy (4). Ni poisoning in mice shows the damaging effects of this heavy metal on renal function and is a serious disease. Mice exposed to nickel may suffer substantial RF that compromises their ability for maintaining the equilibrium of electrolytes and fluids and filter waste materials. Oxidative stress, inflammation, and disruption of cellular communication pathways all occur as a result of Ni-induced nephrotoxicity in the renal tissue. These processes aid in the degeneration of kidney tissue and the development of renal failure (5). Mice depend heavily on VC, an important nutrient that supports a wide range of physiological processes and has some positive health effects.VC, a strong antioxidant, aids in preventing oxidative stress, which is brought on by the buildup of harmful free radicals, in mice's cells and tissues. VC also plays a role in the manufacturing of collagen that is necessary for preserving the structural integrity of a variety of tissues including the skin, blood vessels, and bones. VC strengthens the immune system in mice by encouraging the development and operation of immune cells to fend against infections and illness (6).

Nephrotoxicity is a significant concern in pre-clinical toxicological research because it may result in direct damage to cells and tissues, blockage of renal excretion, alterations in hemodynamics, and inflammation. Infiltrating plasma and ensuring that metabolic equilibrium is maintained are two of the kidney's primary responsibilities. Depending on the method and length of exposure, acute Ni poisoning may have serious health repercussions and result in a variety of symptoms. High concentrations of Ni dust or fumes may cause coughing, bronchitis, and lung irritation as inhaled (7). Pretreatment may comprise a variety of treatments, including pharmaceutical medications, environmental conditioning, or dietary changes, depending on the particular circumstances. These pretreatment tactics have been shown to elicit adaptive responses, including the upregulation of antioxidant defenses, immune system vigor, and tissue healing mechanisms. The pretreatment reduces the negative effects of following shocks, such as chemical exposures, pathogenic agents, or physical stresses, in mice by enhancing these defense systems (8). The maintenance of kidney health and function depends heavily on a specific chemical or treatment that shields mice against nephrotoxicity. This protective factor aids in protecting renal tissue from the negative effects of nephrotoxic substances by using some ways. Through its antioxidant characteristics, it may function by lowering oxidative stress, which is a frequent underlying factor in kidney damage. Additionally, it could increase the activity of enzymes that cleanse the body and neutralize nephrotoxins' damaging effects (9).

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The adverse effects of Ni exposure on the renal of laboratory mice are referred to as Ni-induced nephrotoxicity. Ni exposure in mice, whether by eating, inhalation, or injection, may cause serious kidney dysfunction and damage. Numerous pathological alterations, such as inflammation, oxidative stress, and disruption of cellular function within the renal tissue, are indicative of Ni-induced nephrotoxicity in mice. These processes, such as tubular necrosis, interstitial fibrosis, and glomerular destruction, help to cause renal injury (10). Pretreatment with VC is an effective therapeutic method for reducing acute nickel Ni nephrotoxicity in mice. This study examined the preventative effects of VC consumption on RF brought on by nickel. The study (11) assessed the effects of heavy metals, a group of continuous and persistent ecological pollutants capable of causing a wide range of dysfunctions in exposed human and animal target tissues. 60 male Wistar mice were split into control and experimental groups for the current experimental investigation. The purpose of the current investigation was to track the effects of Cd-toxicity in the tissues of wistar mice. The protective advantages of sulforaphane (SFN) against arsenic-induced kidney damage are investigated. The study focuses on the PI3K/Akt signaling that is mediated by the Nrf2 pathway. There are 32 male albino Randomly allocated to one of four groups, control, arsenic (Ar), and sulforaphane plus arsenic (SFN+Ar), Wistar mice were given oral dosages of arsenic (5 mg/kg BW) and sulforaphane (80 mg/kg BW) every day for a period of 28 days (12).

In a rat model of renal ischemia-reperfusion (IR) damage, the preventive potential of the Moringa oleifera (MO) methanol extract was examined. 42 Wistar mice were divided into six groups of seven at random and placed as follows: A represents the control group, B the sham operation group, C the IR group, D the IR + low dosage MO, E the IR + high dose MO, and F the IR + VC (13). Ni is a natural element that can be found in a range of settings, such as water, soil, and even in the air. Nickel metallic compounds and elements Ni are used for a wide range of industrial and commercial purposes, including as the production of alloys, luster, Ni-cadmium batteries, and catalytic agents in the chemical and food sectors. Ingestion, either via the lungs or the digestive tract, has been related to the majority of instances of acute and serious poisoning in animals. There are two types of acute toxic effects from ingesting Ni carbonyl (14). The study (15) determined that the antioxidant vitamins C, E, and zinc protected Wistar mice against the negative effects of cadmium (CD). Male albino Wistar strain mice weighing 22510 g received CD along with co-administrations of VC, E, and Zinc, both alone and in combination. After 45 days of testing, key enzymatic parameters were measured in plasma serum to determine the impact of CD and the preventive effects of VC, vitamin E, and zinc. Aminoglycosides have been utilized for bacterial therapy for a very long time and are still widely used today. Although aminoglycosides have a wide range of applications and beneficial effects, drug-related toxicity is thought to be their principal drawback. Through endocytosis and antibiotic buildup in the proximal tubule epithelial cells, aminoglycosides cause nephrotoxicity. The most significant finding, however, was that a variety of pharmaceutical substances had protective effects against nephrotoxicity in test animals (16).

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The purpose of the study was to find that VC does in fact protect Swiss albino mice against cadmium-induced harm. In the present investigation, the protective effects of VC were examined in Swiss albino mice after oral administration of a single dosage of cadmium corresponding to 1/20 of the LD50 over 35 days. To ascertain the effects, hematological testing and biochemical measurements were performed. The cadmium-treated animals had a substantially reduced White Blood Cell (WBC) and Red Blood Cell (RBC) count than the control group (P 0.05) (17). The nephrotoxicity of colistin caused by oxidative stress is connected to the reduced activity of nuclear factor erythroid 2-related factor 2 (Nrf2), which is primarily related to cellular PH domain and leucine-rich repeat protein phosphatase (PHLPP2) levels. The study looked at the potential for rosuvastatin (RST) to alter the trajectory of PHLPP2/protein kinase B (Akt), a crucial regulator of Nrf2 stability, to protect mice from colistin-induced oxidative kidney injury (18). The study (19) determined that Phyllanthus emblica extract (PE) may reduce contrast-induced acute kidney damage (CI-AKI) via inhibiting apoptosis. Male Sprague Dawley mice were given either saline (control) or PE extracts (500 mg/kg/day) for 5 days before to the induction of CI-AKI. Immunohistochemistry (IHC) analysis of gene expression was performed on renal tissues. Biochemical and oxidative stress indicators to assess the impact of Nigella sativa ethanol extract (ENS) on $NiCl_2$ induced hepato-renal damage. HPLC and GC-MS were also used to measure the antioxidant strength and phytochemical components of ENS. The improvement in hepato-renal health in co-exposed mice may have been due to ENS's strong antioxidant capacity and its abundance of antioxidants such as gallic acid, quercetin, eucalyptol, and levomenthol (20). Examining taxifolin's (TA) capacity to protect against renal damage brought on by Cd was the major goal of this investigation. In five equal groups of adult male mice, the following was done: For 14 days, animals were given the following treatments: control, TA-treated, CdCl2-treated (4 mg/kg body weight (BW), p.o.), pretreated with TA an hour before receiving CdCl2 injection, and prepped with TA an hour before receiving CdCl2 injection. The blood urea and creatinine levels of cd-intoxicated mice were greater, and the renal tissues had significant histopathological changes (21).

Purslane ethanolic extract (PEE) was used for this work to shed further light on its hapa-to-nephroprotective properties against cadmium poisoning. Intoxicated mice with Cd displayed significant degeneration and necrosis in the hepatic and renal tissues, along with severe congestion and multifocal hemorrhages. Comparing mice treated with Cd and purslane extract to control mice, all metrics and tissues exhibited no differences (22). The paper (23) determines in the event selenium and zinc might prevent pregnant Wistar mice from $NiCl_2$-induced thyrotoxicity. On the third day of pregnancy, female mice were given subcutaneous (s.c.) injections of NaCl , which served as the control, $NiCl_2$, alone, or in combination with Se, ZnCl2, or all of them at once. ACR-induced kidney injury in mice was the focus of this investigation and aimed to determine if N-acetylcysteine (NAC) and Vitamin E (Vit E) may be of assistance. ACR increased the blood's amounts of glucose, urea, and creatinine. ACR also decreased levels of albumin and protein (24). The study (25) determined that lycopene (LP) and/or N-acetylcysteine (NAC) had any beneficial effects on mice with CP-induced hepatic and renal damage. Mice were randomly assigned to one of seven groups, each with

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seven mice, including the control vehicle group (saline alone), the LP group, the NAC group, the CP group, the LP-CP group, the NAC-CP group, and the LP-NAC-CP group.

Materials and Methods

During the development of nephrotoxicity, mice in the pretreatment group received daily injections of VC for a set amount of time. The controls and pretreatment categories received an appropriate amount of $NiCl_2$ intraperitoneally to cause acute nickel nephrotoxicity. The appearance of nephrotoxic symptoms and the progression of renal damage were extensively watched in the mice. The technique used to investigate VC pretreatment affected acute nickel nephrotoxicity in mice gave important insights into the antioxidant's protective actions against RF brought on by exposure to Ni. The development of possible therapeutic approaches aiming at preventing or treating Ni toxicity-related nephrotoxicity in humans may be significantly impacted by these results. Animals for the first selection were divided into the following categories: category I, category II, category III, category IV, category V, category VI, category VII, and category VIII. Following the categorization, biochemical experiments to evaluate certain criteria have been carried out immediately. To check for any pathological alterations in the tissue samples, a histological study was then carried out. To assess the animals' total performance based on predefined criteria, a performance evaluation was lastly conducted (Figure 1).

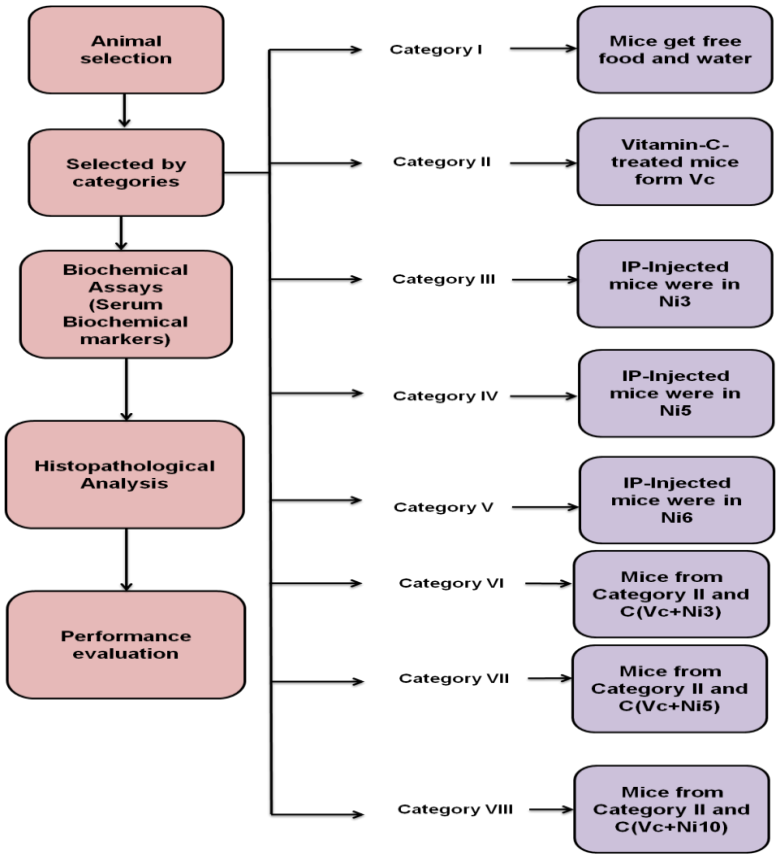

Figure (1): Procedures for the Experimental Method and Evaluation

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Chemicals

Numerous substances were utilized in St. Louis, Missouri, USA experiment, including VC and nickel sulfate (NiSO4 7H2O). To expose mice to Ni and analyze the effects on them, it is possible that NiSO4, a compound comprising NiSO4 ions, was used.

Animal's selection

The weight range of the 58 male Swiss albino mice used in this study was between 30 and 35 grams. The food and water for these mice were placed in plastic cages were mice could easily and freely access them. The living circumstances included a cycle of 11 hours of light and 11 hours of darkness, together with a 36% humid environment and a temperature of 218 degrees Celsius. In every single experiment that was carried out, every single humane and ethical guideline and procedure was adhered to. The Sigma Chemical Company (St. Louis, France) provided all of the substances that were used for this study.

Experimental procedure

After weighing each of the 58 male mice, a category of 44 mice that had successfully acclimated was chosen. Eight mice overall from these 44 mice were distributed at random to each of the six experimental categories.

Category I

The mice in the category that serves as the control category are allowed unrestricted mobility and access to food and water.

Category II

VC is comprised of mice that were administered VC orally over seven days at a dosage that was equivalent to 17 grams per kilogram of mice weight.

Category III

The Intraperitoneal Injections (IPI) of $NiCl_2$ at a concentration of 4 mg per kg of BW were given to mice that had Ni3 implanted.

Category IV

Ni5-containing mice received an IPI of $NiCl_2$ at a dosage of 6 mg per kg of BW.

Category V

The mice used in the Ni6 study were given an IPI of $NiCl_2$ at a concentration of 11 mg per kg of BW. After 24 hours, the administration of Ni to these mice resulted in the death of some of the mice in categories III, IV, and V.

Category VI

The experiment used category II mice that were dosed with a mixture of VC and nickel sulfate (Ni3).

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Category VII

Mice from category II were those that participated in the experiment and were exposed to a combination of VC and nickel sulfate (Ni5).

Category VIII

Mice from the second classification were used to test the effects of VC combined with nickel sulfate (Ni10).

The final three categories each received IP VC for six days. These last three categories received dosages of $NiCl_2$ through IP on day seven that were 4, 5, and 11 milligrams per kilogram of the mice's BW. 24 hours following the Ni injection operation, mice were likewise put to death using chloroform, and their blood was collected into tubes containing lithium heparin before being immediately set in an ice bath and processed for ten minutes at a speed of 2500 revolution per minute and a temperature of 5 ° C.

The blood of the dead mice was extracted, the serum was examined histologically, and the kidneys were utilized to determine the amounts of uric acid, urea, and creatinine in the blood. Among the blood components examined were the quantity of hemoglobin, the number of white blood cells, the total number of RBC, and the volume of RBC bundles.

Calculating the Ni concentration

Depending on the source, different amounts of Ni may be discovered in mice's RF. A single gram of clean tissue is weighed and then placed in a tissue homogenizer with cold KCl for the RF. The homogenizer is then agitated after 2 ml of an acidic solution comprised of ($HClO4/HNO_3$, 1:3, v/v) is added. The homogeneous samples are digested in a microwave, and the homogeneous extract is then obtained, with the Ni content being determined by an automated absorption spectrometer.

Biochemical assays Serum biochemical markers

A biochemical test offered by the Biolabo firm, the Total Protein Biuret Method, may be used to evaluate functional indicators for nephrotoxicity. Utilizing this technique, total protein levels in biological materials may be quantified and used as a measure of renal function. The Total Protein Biuret Method made available by Biolabo makes use of the biuret reaction; in copper, ions interact with protein peptide bonds to create a colorful complex. The amount of total protein may be calculated by gauging the strength of this development.

Histopathological analysis

The experiment involves preserving the kidneys of dead mice for 24 hours in formalin and an eleven percent salt solution. The tissue eye is prepared for microscopic examination by being cut into sections with a section thickness of five to six millimeters, colored with hematoma xylene and eosin, and then placed in a medium consisting of paraffin-free xylene. The present study's findings in category II revealed that while VC levels were high and significantly important, the mice's eating or behavior did not alter. According to the findings, mice in categories III, V, and IV had a variety of symptoms, such as decreased activity and a

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diminished appetite for food and liquids that resulted in weight loss as compared to controls 24 hours after the Ni injection. Additionally, categories III, V, and IV had higher levels of urea, uric acid, and creatinine than categories VI, VII, and VIII, which did not exhibit the same clinical symptoms.
Observe that there is a reduction in the significance of the Ni and VC concentrations relative to the results in categories VI, VII, and VIII and that the mice exhibit normal behavior. In a research, it was discovered that mice's renal tissue accumulated more Ni in the III, IV, and V categories than in the other categories.

During comparison to the mice of the III, IV, and V categories with the VI, VII, and VIII categories, determine that there's an apparent rise in food intake in the latter categories, and these latter categories do not show statistically significant variations while compared with the control category. But the mice of the III, IV, and V categories consumed significantly less water and food than the mice of the control category.
Blood element data revealed lower levels in the III, IV, and V categories compared with the control category and the VI, VII, and VIII categories, although there were no statistically significant changes between the last three categories. The use of eosin in the renal generated findings that were positive in the structural stability configuration of the brain and the configuration of the cortex of the RF in each of the control categories I and II, and the results in the categories III, IV, and V were changed in the RF, involving necrosis and tubular degenerative conditions with interstitial hemorrhaging as a result of inflammation, as well as the observations of perivascular pickling of spots of mononuclear cells. The VC therapy, which lowers the amount of Ni in the renal, did not improve the condition of the renal, contrary to the findings of the research above, which indicated improvements and the development of new renal tissue.

Results

Pretreatment with VC significantly decreased the renal damage brought on by Ni poisoning and substantially reduced oxidative stress. Additionally, VC has anti-inflammatory qualities that reduced the levels of inflammatory markers in the renal tissues. The relevance of VC in the maintenance of renal health is highlighted by these results, in addition to its potential therapeutic role as a means of preventing or reducing acute Ni-induced nephrotoxicity.

Correlation between Ni and VC Concentrations and their Impact on Renal Weight

Mice in the Ni + VC categories had lower Ni concentrations than mice in the Ni category, a finding consistent with a reduction in renal weight. The nephrotoxic effects of Ni may have been reduced by VC pretreatment, supporting the maintenance of healthy renal function. VC pretreatment may lessen the negative effects on renal weight and help to maintain renal health by lowering the concentration of Ni in the renal (Table 1 and Figure 2).

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Table (1): Numerical outcomes of the relationship between the concentrations of Ni, VC, and the combined impact on renal weight

Renal weight				
	Control means	**VC means**	**Ni means**	**Ni+ VC Mean**
Absolute	0.06	0.03	0.08	0.04
Relative	0.032	0.021	0.031	0.045

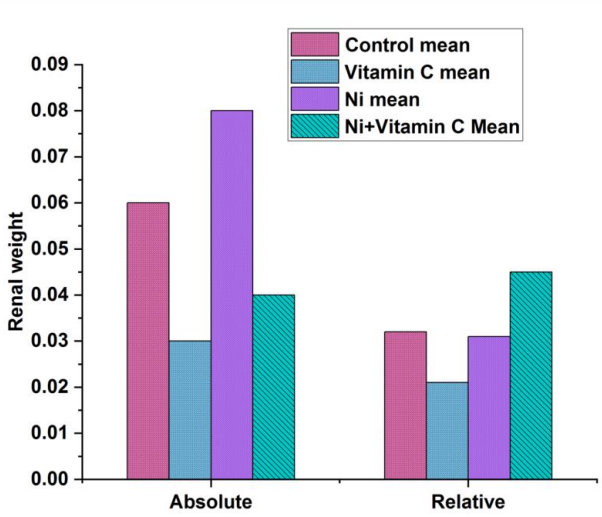

Figure (2): The relationship between the concentrations of Ni, VC, and the combined impact on renal weight

Correlation between Ni and VC Concentrations and their Impact on BW

Mice in the Ni + VC categories had lower Ni concentrations than those in the Ni category, which was associated with less significant weight loss. This demonstrates that pretreatment with VC reduced the harmful effects of Ni and aided in maintaining the mice's healthy BW. The possibility of VC as a preventative strategy against acute nickel nephrotoxicity in mice is highlighted by these results. Pretreatment with VC may improve the harmful effects on BW and support maintaining general health by lowering the concentration of Ni in the body (Table 2 and Figure 3).

Table (2): Numerical outcomes of the association between Ni and VC concentrations and their combined effect on BW

BW				
	Control means	**VC means**	**Ni means**	**Ni + VC Mean**
Initial	0.81	0.78	1.06	0.97
Final	1.17	0.25	0.16	0.24

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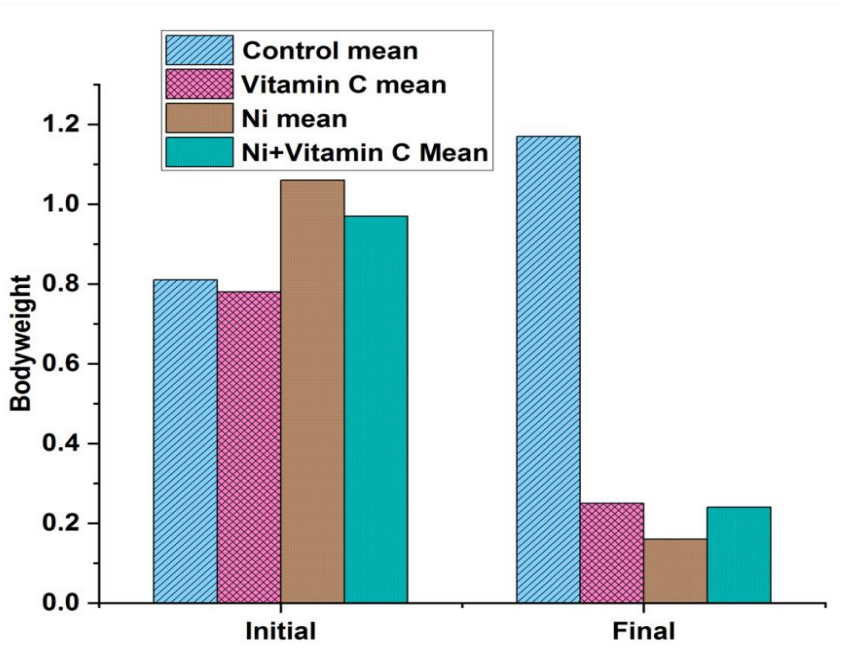

Figure (3): Association between Ni and VC concentrations and their combined effect on BW

Mice Blood Parameters in Control, VC, Ni, and Ni + VC categories

Mice in the VC categories received VC before being exposed to Ni, but mice in the Ni category had no pretreatment before being exposed to Ni. Both Ni exposure and VC pretreatment were given to the Ni + VC categories. All categories levels of Packed Cell Volume (PCV), Hemoglobin (Hb), WBCs, and RBCs were assessed. WBCs are essential for the immune response, and variations in their number might signify infection or inflammation. The findings would provide light on the possible advantages of VC in reducing the negative effects of Ni on mice's renal (Table 3 and Figure 4).

Table (3): Numerical outcomes of the WBC, RBCs, Hb, and PCV in mice blood parameters in the control, VC, Ni, and Ni + VC categories

Parameter				
	Control means	**VC means**	**Ni means**	**Ni + VC Mean**
WBC	5.97	5.8	11.3	5.95
RBC	6.95	6.39	4.05	6.55
HB	14.88	14.77	8.72	14.87
PCV	56.29	55.91	31.95	54.85

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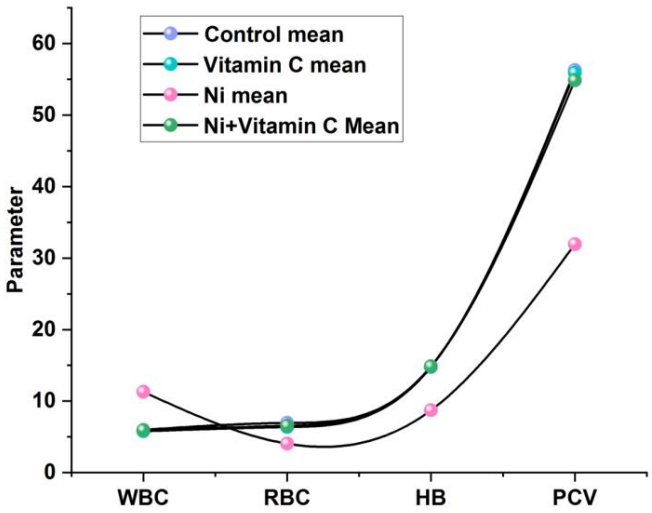

Figure (4): The WBC, RBCs, Hb, and PCV in mice blood parameters in the control, VC, Ni, and Ni + VC categories

Discussion

Heavy metals and other elements that are improperly used or released into the environment have detrimental effects on various bodily organs, including the RS and blood components. This drop in a patient's BW is brought on by an aberrant rise in the degradation of proteins and lipids, which is thought to be caused by an increased buildup of Ni in the renal tissues (26). Due to the deposition of Ni or $NiCl_2$, exposure to these metals increases the BW of the RS. This makes the patient eat and drink less, which lowers their weight. VC administration to Ni -injected mice has a preventive effect against any potential physiological alterations brought on by Ni buildup in the mice's renal (27).

This kind of metal ions' presence together with minerals raises the amount of ROS in the renal system, creating the development of hydroxide and oxidized lipids that are seen in high concentrations in instances of renal damage. VC is very useful in treating acute renal failure because it serves to lessen the impact of inflammation. Additionally, VC is crucial for the development and maintenance of functional collagen as well as for preserving the decrease of active sites in minerals (28). Any VC deficit hinders blood vessel walls' ability to repair and delays wound healing.

The hormone cytoplasmic hydroxylase that regulates both pro-survival and angiogenic genes, uses ascorbic acid as a cofactor. Ascorbic acid's inhibitory efficacy against the oxidation of biomolecules has been shown repeatedly in lab settings. Ascorbic acid may also stop certain types of reactive oxidation from having negative effects on nucleic acids by protecting lipids and proteins from the inside out of the cell (29). Despite advances in medical technology, individuals with renal insufficiency have higher death rates, particularly those who have chronic renal illness. Still, antioxidant use has been shown to significantly lower renal injuries and improve renal function by reducing inflammation and Reactive Oxygen Species (ROS).

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The RS is compromised as a result of increased levels of urea, uric acid, and creatinine found in the blood of Ni-treated mice as well as histological anomalies discovered during a renal histological investigation. The type of histological and functional damage may be brought on by an increase in the creation or breakdown of amino acids, or it may result from renal failure to excrete. Mice treated with $NiCl_2$ had lower hemoglobin levels than controls (30). This is according to their research into the minerals that prevent the body from producing hemoglobin pigment because they obstruct the biochemical pathways involved in creating heme, which lowers the rate of biosynthetic heme synthesis. In addition, $NiCl_2$ therapy causes mice to produce more WBC than usual, which suggests that the metal may boost and promote the formation of WBC as a consequence of inflammation in the renal cells.

Conclusion

In the context of acute nickel nephrotoxicity in mice, VC pretreatment refers to the administration of VC to mice before their exposure to Ni to reduce the negative consequences of Ni-induced RF. A therapeutic strategy, pretreatment with VC has been demonstrated to be beneficial in lowering acute nickel Ni nephrotoxicity in mice. In this study, examined to consuming VC before being exposed to RF from nickel was protective. A supplement dosage of VC, which is well-known for its antioxidant abilities and capacity to scavenge free radicals, is given to mice as part of this pretreatment technique. According to the results of the study investigation, VC is both efficacious and resistant to the toxicity brought on by Ni buildup in mice's renal. As a consequence, it is regarded as a biological antioxidant substance produced by hazardous metals like Ni. Pretreatment with VC could not completely address all of the underlying causes of acute Ni nephrotoxicity, such as oxidative stress-independent pathways or inflammation. Future studies on VC pretreatment in acute Ni nephrotoxicity in mice may improve knowledge and therapy. First, determining the best VC dose, duration, and timing would help reduce Ni-induced RF. The molecular pathways by which VC protects may also provide new therapeutic targets.

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