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Original Article

Nephroprotective Activity of Marrubiin against Cisplatin-induced Nephrotoxicity in Albino Male Wistar Rats

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ABSTRACT

Background: One of the most effective anti-cancer medications used to treat various cancers is Cisplatin (CP). Due to its nephrotoxicity, its usage is restricted. The purpose of this investigation is to assess Marrubiin's influence in the protection of rats against CP nephrotoxicity. **Materials and Methods:** Animals were divided into five groups. The body weight and kidney weight were measured for all the experimental groups. Urine output and blood samples were collected to assess the Blood Urea Nitrogen (BUN) and Creatinine (Cr) present in the experimental animals. Furthermore, the oxidative stress markers, antioxidant enzymes, inflammatory markers and histopathological studies were carried out to assess the impact of Marrubiin treatment in a dose-dependent manner. **Results:** We observed that treating animals CP-induced animals with Marrubiin aided in improving kidney function. Marrubiin significantly increased the level of antioxidant enzymes, histopathology conditions and body weight of the animals. It also downregulated the inflammatory markers, levels of BUN and Cr, urine output, kidney weight and oxidative stress markers. **Conclusion:** Thus, we conclude that Marrubiin can be used to protect the kidney from injury induced by cisplatin treatment.

Keywords: Cisplatin, Marrubiin, Nephrotoxicity, Oxidative marker.

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INTRODUCTION

One of the initial and most effective metal-based chemotherapy medicines is cisplatin. In the year 1845, cisplatin was identified. Cisplatin's biological characteristic is its ability to prevent cell division. It treats a variety of solid tumors, including cervical, ovarian, lung, testicular, bladder, gastric, head and neck and other types of cancer. The primary target of cisplatin's antitumor action is DNA. The mono or dihydrated platin that enters the nucleus is sufficiently susceptible to DNA base reactions to produce adducts. The created adducts causes cytotoxicity in the cancer cells, which inhibits the progression of the disease.[1] Cisplatin contains multiple cautionary statements, including peripheral neuropathy, nephrotoxicity, extreme nausea and vomiting and myelosuppression, despite its anticancer efficacy.[2]

A fast deterioration in kidney function driven by the adverse effects of medications and substances is known as nephrotoxicity. There are several varieties and certain drugs may have numerous detrimental consequences on renal function.[3] On various areas of the nephron, cisplatin has varying nephrotoxic impacts. It has been reported to induce interstitial inflammation, vascular injury and tubular damage. It is generally recognized that cisplatin kidney damage depends on dosage, duration and frequency. Severe damage is caused by higher plasma levels at higher dosages administered per treatment. Future kidney damage risk has also been demonstrated to rise with a greater cumulative dosage. Patients who already have renal illness and who additionally use nephrotoxic pharmaceuticals are also more vulnerable.[4]

The exact mechanism of nephrotoxicity caused by CP is not clear. According to earlier research, the main ideas include oxidative stress, inflammation, apoptosis and necrosis. Serum indicators of kidney function such as Blood Urea Nitrogen (BUN) and Creatinine (Cr) are elevated in CP-induced renal damage. Additionally, the injection of CP lowers the activities of antioxidant enzymes present in the kidney as Glutathione Peroxidase (GPx), catalase, Superoxide Dismutase (SOD) and Glutathione (GSH).[5]

Even though a variety of medications are being utilized in clinical conditions to treat kidney damage induced by cisplatin, these medications all display varying degrees of insufficiency. The majority of countries employ a range of natural products, including minerals, vitamins, herbs, elements and nutritional

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supplements, as well as traditional and complementary therapies. Ginseng, curcumin and pomegranate are a few examples of foods that have antioxidant and anti-inflammatory properties. They may also provide shields from oxidative stress by boosting the activity of antioxidant enzymes. These organic products can be used as supplements to reduce the nephrotoxicity caused by cisplatin since they may have anti-inflammatory and antioxidant properties.[6]

A well-known diterpenoid lactone by the name of Marrubiin makes up the bitter component of horehound and several other therapeutic plants in the *Lamiaceae* family. It is an ingredient for both medicinal and culinary flavoring uses. It demonstrates strong anti-inflammatory, anti-hematogenic, anti-nociceptive, vasorelaxant, anti-nociceptive, gastroprotective, anti-spasmodic, immunomodulating and analgesic properties.[7]

MATERIALS AND METHODOS

Animals

We acquired 30 male Wistar rats (180-200 g) from an animal shelter. The rats were kept in groups (two to four per cage) with unrestricted accessibility to feed and water and were kept at a temperature of 23±2.0º over a 12 hr alternate light and dark cycle. The procedures for performing the studies were following the Animal Ethics Committee's Guidelines for the use of experimental animals approved by XingTai Third Hospital, Number: 2023-KY-26.

Experimental Design

Cisplatin and other essential chemicals were procured from Sigma-Aldrich. The animals were grouped into 5 groups containing 6 animals in each group. Group I was left untreated for 21 days while receiving normal saline orally. Group II received just cisplatin at a dose of 5 mg/kg intravenously on day 1, which was termed a diabetic-induced group. In the presence of cisplatin-triggered toxicity, Groups III and IV received treatments with Marrubiin at oral dosages of 20 mg/kg and 40 mg/kg once daily, respectively, for 21 days. In the context of cisplatin-triggered toxicity, Group V received treatment for 21 days with Positive control NAC (commercial medication).

Morphometric analysis

The Body Weight (BW) of the experimental animals was recorded on the 0^{th}, 7^{th}, 14^{th} and 21^{st} day of the experiment and compared between all experimental groups. The Kidney Weight (KW) of animals was recorded and compared between all experimental groups at the end of the study.

Blood sample collection and serum separation

All animals were given intramuscular injections of xylazine (5 mg/kg) and ketamine hydrochloride (50 mg/kg) before being killed after the experiment. As soon as blood was collected, it was placed in tubes that were dry and without anticoagulant and it was left to clot for 15 min at room temperature (22±2ºC) in a tilted posture. The serum was then separated by centrifuging the tubes for duration of 20 min at 1200 g. After that, the serum was kept at -80ºC for further biochemical evaluation.

Preparation of tissue for homogenate and microscopic observation

At the end of the experiment, each rat in each experimental group was swiftly dissected and the kidneys were weighed. The right kidneys were washed with normal saline before being utilized to make the homogenate. A 0.5 g slice of each kidney was homogenized in 5 mL of pH 7.4 phosphate buffer using an electrical homogenizer and the sample was refrigerated. The supernatants from the centrifugation of the renal homogenates were stored at -80ºC before being used to assess antioxidant and oxidative stress markers. The left kidneys were immediately embedded in paraformaldehyde (4%) at 4ºC for an overnight histological analysis.

Metabolic data collection

On days 0^{th}, 7^{th}, 14^{th} and 21^{st} of the experiment, urine samples from all the experimental groups were taken. Rats were given unrestricted access to tap water while being housed in metabolic cages for a whole day. We consistently measured the urine output and water consumption.

Estimation of Blood urea nitrogen and creatinine

To assess renal tissue damage, Blood Urea Nitrogen (BUN) and Serum Creatinine (Cr) levels were detected. By utilizing commercially available specific kits and the procedure included with the product, they were calorimetrically quantified.

Estimation of antioxidant biomarkers

The antioxidant biomarkers including SOD, CAT, GSH and GPx levels were estimated calorimetrically utilizing commercially available kits and by following the protocol provided by the manufacturer.

Measurement of oxidative stress biomarkers

The estimate of the expression level of the inflammatory marker Myeloperoxidase (MPO) in kidney tissue samples.[8] By quantifying Malondialdehyde (MDA), the methodology developed by Buege and Aust was used to evaluate lipid peroxidation.[9] Griess reagent was used to carry out the nitrite test.[10] The[11] technique was used to measure the Protein Carbonyl (PC) concentration of rat kidneys. The level of NO (Nitric Oxide) was estimated using a NO test kit and by following the protocol available with the kit.

Estimation of pro-inflammatory cytokines

IL6 and IL1β levels on homogenized renal tissues were determined using an ELISA kit to explore the pro-inflammatory

cytokines produced in the kidneys as a result of cisplatin intoxication.

Histoarchitecture study

The kidneys isolated from the experimental animals were cleaned with isotonic saline and preserved in 10% neutral buffered formalin for 48 hr. Following the process, the kidneys were encased in paraffin wax. Using a microtome, the parafilm blocks were sliced into 5–6 µm thick thin slices. A microscope and imaging equipment were utilized to view the thin slices after they had been stained with hematoxylin and eosin.

Statistical analysis

The statistical analysis was completed using GraphPad Prism version 6.01. The results are reported as mean±SD. ANOVA and the Tukey *post hoc* test were used to see whether there were any differences between the groups. If $p<0.05$, differences between means were deemed statistically significant.

RESULTS

Effect of Marrubiin (MB) administration on the Body Weight (BW) in CP-treated rats

Figure 1 depicts the effect of Marrubiin on the body weight in CP-treated rats. On the 0th day, the body weights of the experimental animals in all the groups were the same. In group II (CP-treated) animals showed a reduction in their body weight on the 7th, 14th and 21st day in comparison to the CP-induced animals treated with Marrubiin extract in a dose-dependent manner (group III and group IV). Marrubiin and positive control N-Acetylcysteine (NAC) almost maintained the animal body weight in group III and group IV.

Effect of Marrubiin (MB) on urine output in rats treated with CP

Figure 2 shows the effect of Marrubiin on the urine output in CP-treated rats. On the 0th day, the urine output was considerably the same in all the experimental groups. On the 7th, 14th and 21st day, the urine output was high in group II (only CP-treated) animals, while the Marrubiin-treated animals in dose- based manner (group III and IV) and positive control N-Acetylcysteine (NAC) controlled the urinary output.

Effect of Marrubiin (MB) administration on the Kidney weight and serum levels of blood urea Nitrogen and creatinine in CP-treated Rats

Figure 3A depicts the effect of Marrubiin on the kidney weight in CP-treated rats. When compared to the normal control group, it was found that the kidney weight in the animals treated only with cisplatin was noticeably higher. When animals induced with CP toxicity were treated with positive control N-Acetylcysteine (NAC) group V and Marrubiin extract in a dose-based manner (groups III and IV), the kidney weight decreased considerably.

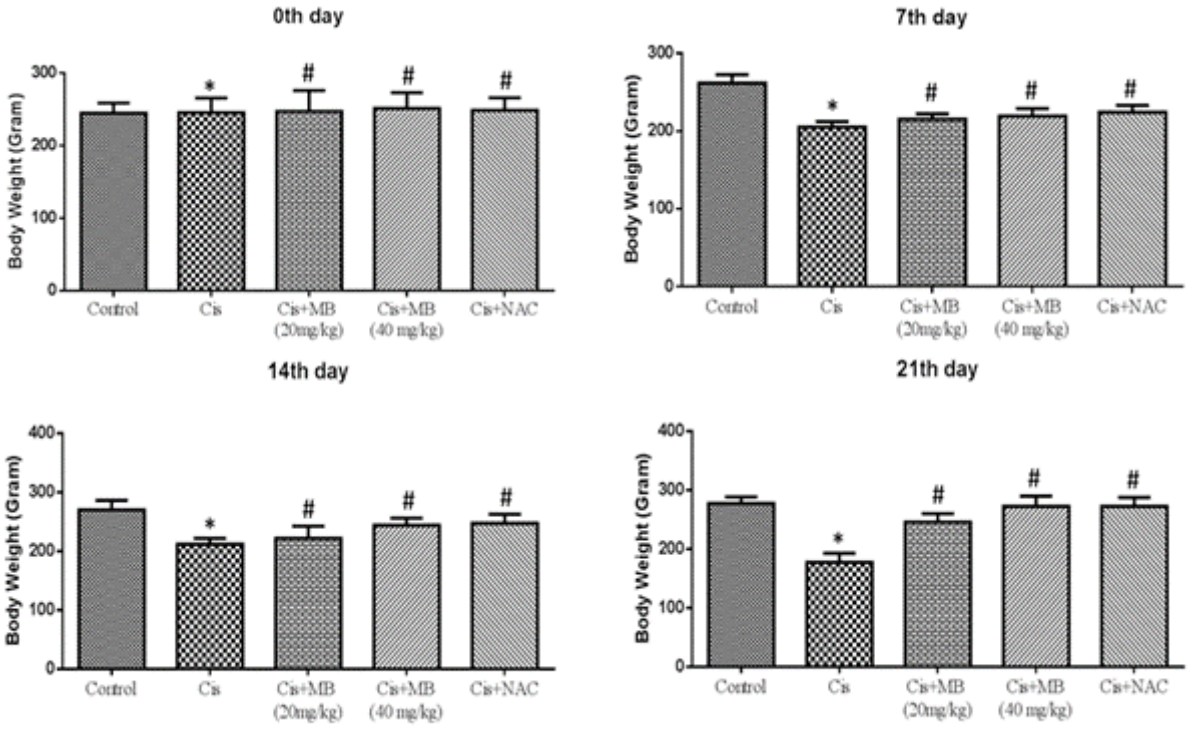

Figure 1: Effect of Marrubiin (MB) administration on the Body Weight (BW) in CP-treated rats. Results were given as mean±SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's *post hoc* assay. '*' $p<0.05$ compared with control and '#' $p<0.01$ compared with CP-intoxicated group.

Figure 3B illustrates the effect of Marrubiin on the serum levels of BUN and Cr in CP-treated rats respectively. The findings revealed those 24 hr after receiving CP; the rats had acute nephrotoxicity as evidenced by a substantial rise in BUN and Cr levels. When rats with nephrotoxicity induced by CP were treated with Marrubiin in a dose-dependent manner (groups III and IV), the levels of blood urea nitrogen and creatinine were considerably lower than in the CP-treated animals (group II).

Effect of Marrubiin (MB) on the activity of antioxidant enzymes in CP-treated rats

Figure 4 depicts the impact of Marrubiin on the expression of kidney antioxidant enzymes. When compared to the control group, the expression of SOD, CAT and GPx activity and GSH content dramatically reduced in CP-treated animals (group II). In comparison to the CP group (group II), treatment of CP-treated rats with Marrubiin in a dose-based manner (group III and IV) significantly elevated these antioxidant enzymes.

Effect of Marrubiin (MB) on oxidative stress biomarkers in CP-treated rats

Figure 5 (a-d) illustrates the effect of Marrubiin on the levels of MDA and NO, the activity of MPO and PC content in CP-treated rats respectively. The findings revealed that animals treated only with CP (group II), expressed high levels of oxidative stress biomarkers in comparison to the control group. When rats with nephrotoxicity induced by CP were treated with positive control N-Acetylcysteine (NAC) and Marrubiin in a dose-dependent manner with Marrubiin in a dose-dependent manner (groups III, IV and V), the levels of oxidative stress biomarkers were significantly reduced than in the CP treated animals (group II).

Effect of Marrubiin (MB) on pro-inflammatory cytokines and histopathology in CP-treated rats

Figure 6A shows the effect of Marrubiin on the activity of pro-inflammatory cytokines (IL1β and IL6) in CP-treated rats. The findings revealed that animals treated only with CP (group II), expressed high levels of IL1β and IL6 in comparison to the control group. When rats with nephrotoxicity induced by CP were treated with Marrubiin in a dose-dependent manner (group III and group IV), the levels of IL1β and IL6 were considerably reduced than in the CP-treated animals (group II). The kidney morphology of control rats was normal (Figure 6a). The CP-treated animals (group II) kidney tissue displayed severe damage, including leukocyte infiltrations, cellular deterioration, congestion, glomerular atrophy and tubular dilation (Figure 6b). When rats with nephrotoxicity induced by CP treated with Marrubiin in a dose-dependent manner (group III and group IV) had considerably reduced kidney damage as shown in Figure

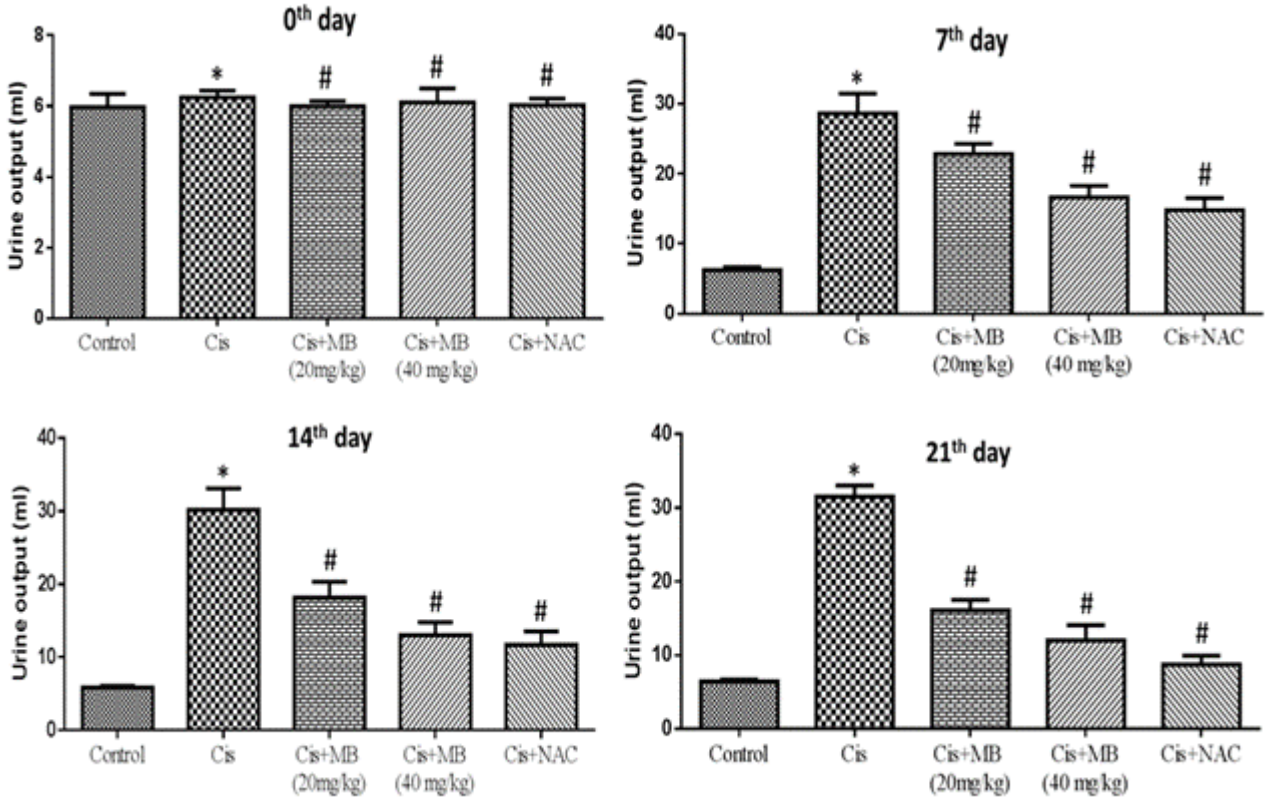

Figure 2: Effect of Marrubiin (MB) on urine output in rats treated with CP. Results were given as mean±SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's *post hoc* assay. '*' $p<0.05$ compared with control and '#' $p<0.01$ compared with CP-intoxicated group.

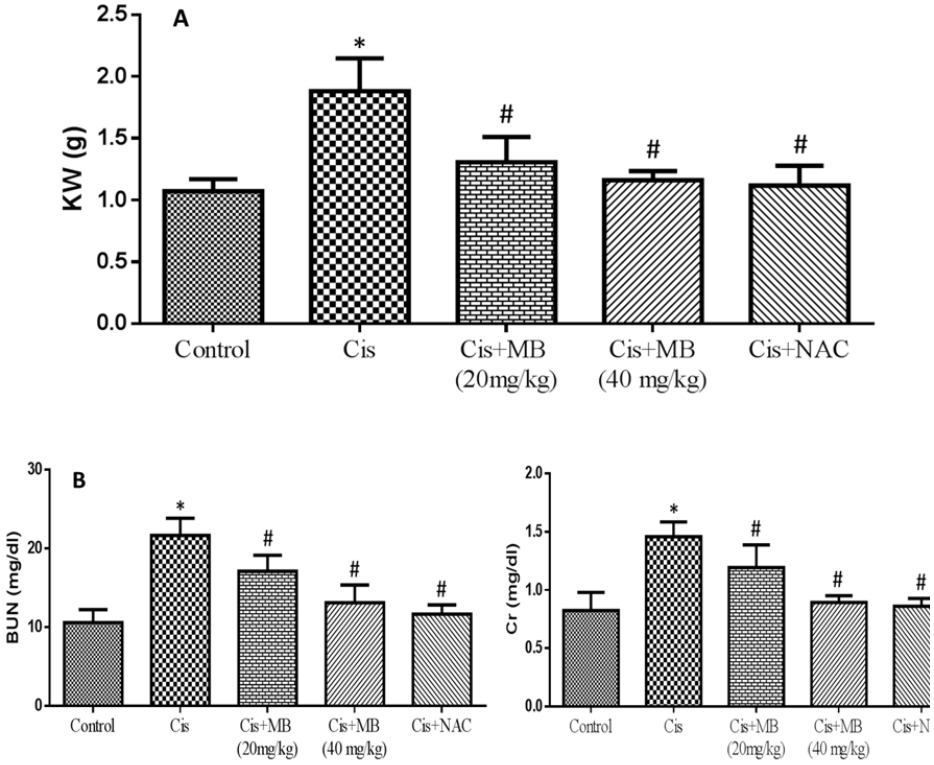

Figure 3: (A): Effect of Marrubiin (MB) on kidney weights (KW g). Results were given as mean±SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's *post hoc* assay. '*' $p<0.05$ compared with control and '#' $p<0.01$ compared with CP-intoxicated group. (B): Effect of Marrubiin (MB) on serum levels of BUN (a) and Cr (b) in rats with CP-induced nephrotoxicity. Results were given as mean±SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's *post hoc* assay. '*' $p<0.05$ compared with control and '##' $p<0.01$ compared with CP-intoxicated group.

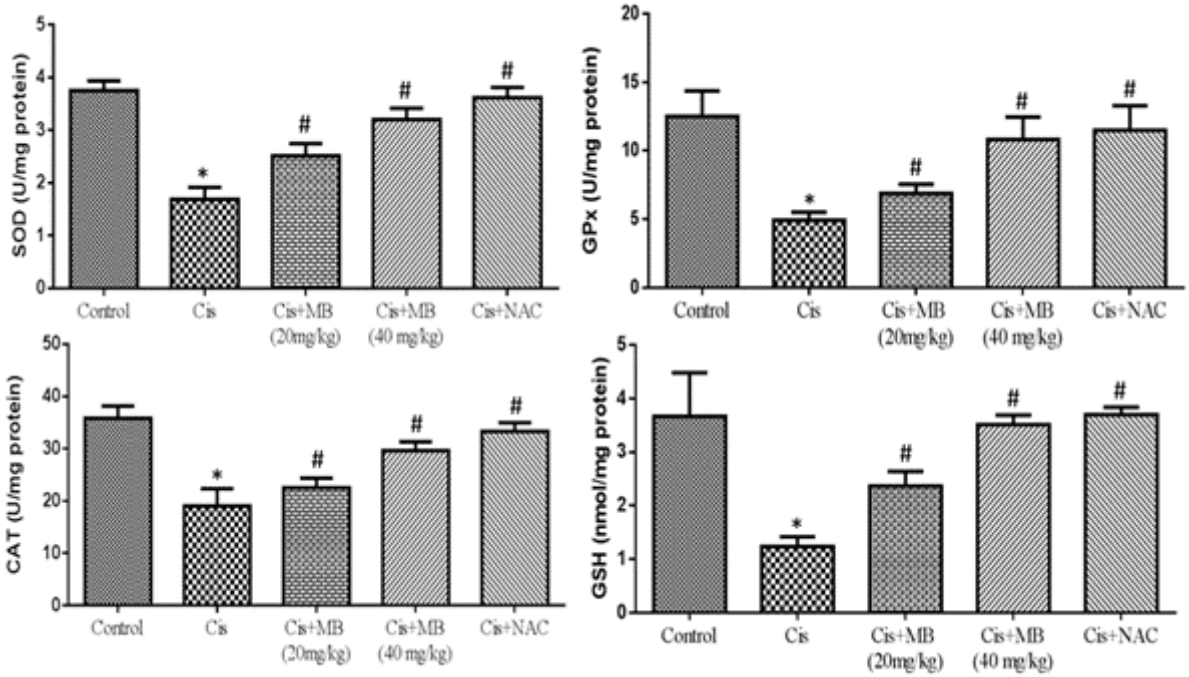

Figure 4: Effect of Marrubiin (MB) on the estimation of antioxidant enzymes against CP-induced nephrotoxicity in rats. Results were given as mean±SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's *post hoc* assay. '*' $p<0.05$ compared with control and '#' $p<0.01$ compared with CP-intoxicated group.

6c-d. The animals with nephrotoxicity induced by CP treated with NAC also showed similar pathology to group V (Figure 6e).

DISCUSSION

The kidneys are essential for living. By purifying and eliminating metabolites (such as urea) and minerals from the blood, they play a crucial role in preserving the homeostatic equilibrium of bodily fluids. It also helps to regulate blood pressure, glucose metabolism and erythropoiesis by eliminating nitrogenous wastes and water from the body. Renal failure might result from severe kidney toxicity.[12] Although cisplatin is a powerful chemotherapeutic drug for a variety of solid tumors, its usage is constrained by unfavorable side effects on healthy organs. Particularly, it is nephrotoxic and capable of inflicting both acute renal damage and chronic kidney disease.[13] According to reports, when cisplatin enters the proximal tubules of the kidney, it causes a significant quantity of ROS to be generated, which could disrupt the body's redox system's delicate equilibrium. In previous studies, it has been reported that antioxidants can ameliorate cisplatin-triggered cytotoxicity by lowering inflammatory responses and apoptosis. Due to the high ROS generation caused by cisplatin, antioxidant enzymes including GSH, CAT and SOD are decreased by cisplatin. The nephrotoxicity of this substance may be caused by membrane lipid peroxidation. The peroxidation of membrane lipids is thought to be the cause of the nephrotoxicity brought on by cisplatin.[14] In the current work, we attempted to elucidate the possible renoprotective activities of Marrubiin against cisplatin-caused nephrotoxicity via biochemical, histopathological and immunohistochemical analyses.

According to various preclinical studies, the treatment of several nephrotoxic drugs (such as cisplatin) in animals significantly reduced the body weight of the animals.[15] Similar to this, we discovered in our study that the mean body weight of the cisplatin-triggered control-treated animals (group II) had significantly decreased when tallied after the investigation. The weight of the cisplatin-induced animals treated with Marrubiin in a dose-dependent manner (groups III and IV) remained the same until the end of the investigation additionally; it was shown that cisplatin-treated animals have higher urine volumes, which is associated with cisplatin-triggered renal failure. Due to diminished gene expression of aquaporin and thickness in the proximal tubule, cisplatin causes a surge in urine production. As was previously reported rats with nephrotoxicity caused by cisplatin showed a rise in urine volume.[16] Similarly, in our study it was observed that the urine output of the cisplatin-triggered control-treated animals (group II) was high. However, the animals treated with Marrubiin in dose dose-dependent manner (group III and group IV) reduced the urine output.

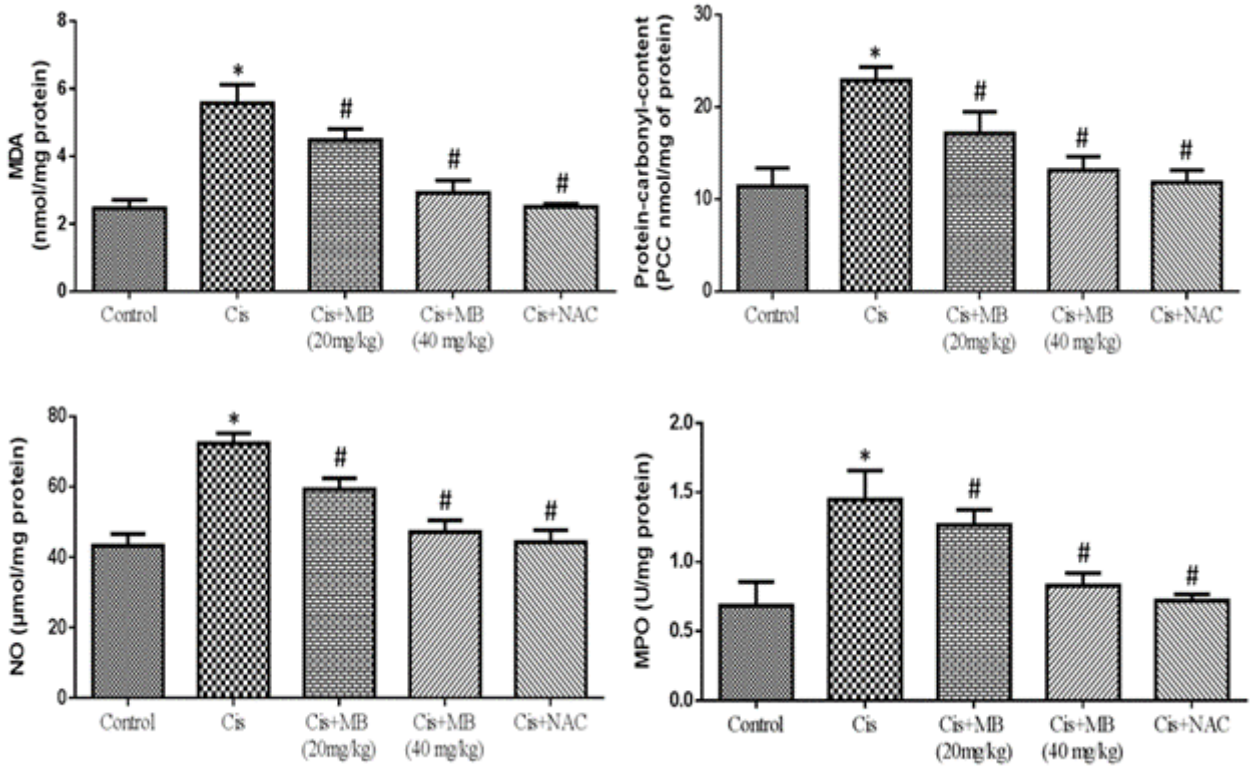

Figure 5: Effect of Marrubiin (MB) on MDA, NO levels, MPO activity and PC content in rats with CP-induced nephrotoxicity. Results were given as mean±SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's *post hoc* assay. '*' $p<0.05$ compared with control and '##' $p<0.01$ compared with CP-intoxicated group.

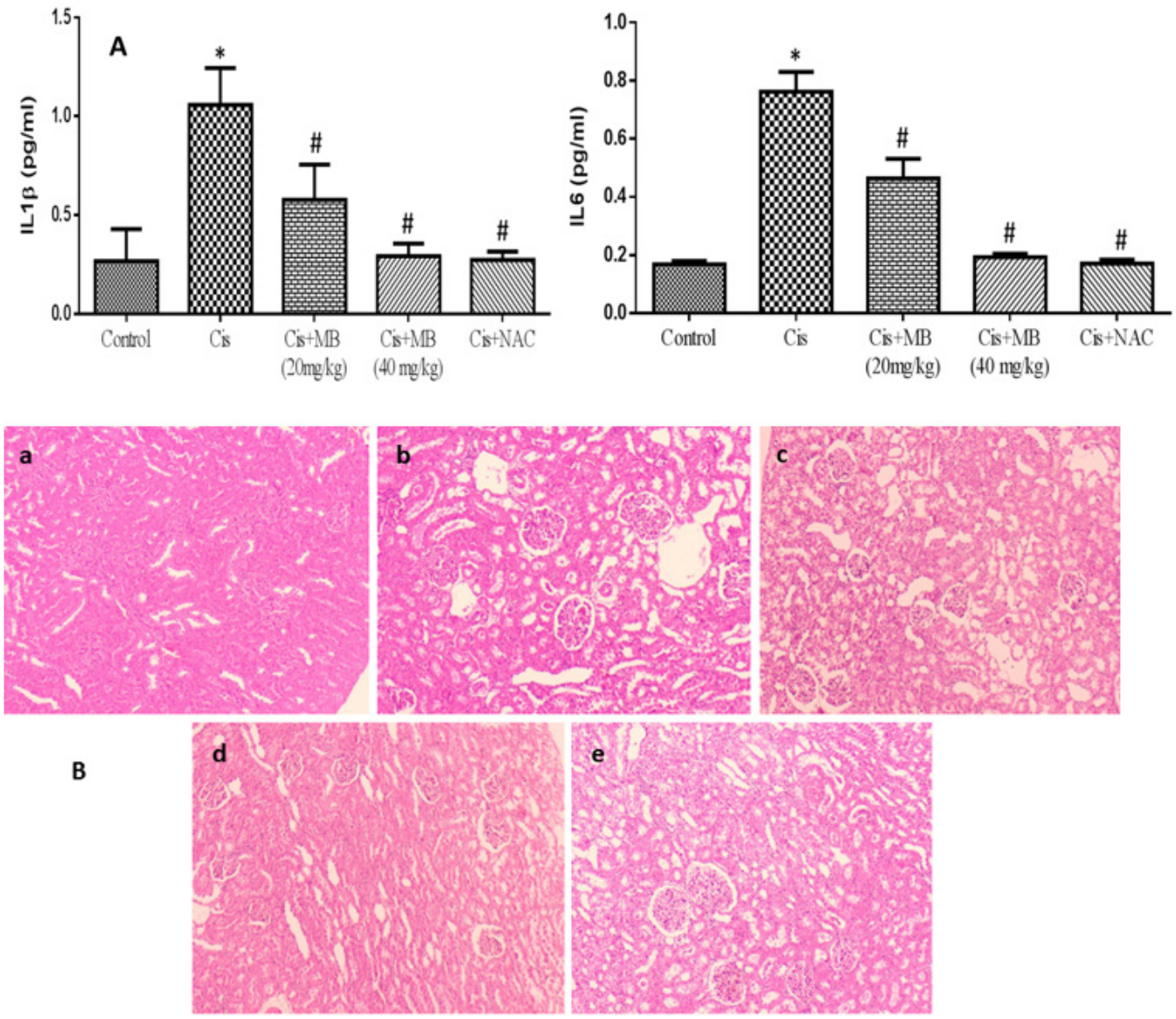

Figure 6: (A): Effect of Marrubiin (MB) administration on pro-inflammatory cytokines IL-1β and IL-6 in CP-treated rats. Results were given as mean±SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's *post hoc* assay. '*' $p<0.05$ compared with control and '##' $p<0.01$ compared with CP-intoxicated group. (B): Effect of Marrubiin (MB) administration on histopathological alterations of the rat kidney. Control (a); cisplatin (b); cisplatin+Marrubiin (MB) 20 mg/kg (c); cisplatin+Marrubiin (MB) 40 mg/kg (d); Cisplatin+N-Acetylcysteine (NAC) Positive control (e).

Likewise, cisplatin-triggered control-treated animals (group II) showed an increase in kidney weight that was connected with edema or inflammation brought on by the drug's ability to cause tubular necrosis.[17] The animals treated with Marrubiin in a dose-dependent manner (group III and group IV) exhibited a substantial decrease in kidney weight in comparison to the group II animals, which may be related to the anti-inflammatory property of Marrubiin.[18] Previous studies reported that cisplatin treatment in rats induced a spike in the level of Creatinine (Cr) and Blood Urea Nitrogen (BUN) which in turn indicates the impairment of kidney function.[19] In the present study, we observed that on treatment with Marrubiin in a dose-based manner, (group III and IV) to the CP-treated animals, the level of Cr and BUN significantly reduced. This indicates the antioxidant activity of Marrubiin.

According to much research, the elevated formation of superoxide anion, hydrogen peroxide and hydroxyl radicals is that causes cisplatin nephrotoxicity. Excessive formation of these ROS depletes GSH, increases lipid peroxidation in renal tissue and lowers the activity of the antioxidant enzymes catalase, SOD and glutathione peroxidase.[20] Similarly, in the present investigation the cisplatin-triggered control-treated animals (group II) exhibited low levels of antioxidant enzymes including SOD, CAT, GSH and GPx. We observed that on treatment with Marrubiin in a dose-based manner, (group III and IV) to the CP-treated animals, the level of antioxidant enzymes including SOD, CAT,

GSH and GPx elevated indicating the antioxidant property of Marrubiin. It is well-recognized that oxidative stress contributes significantly to CP-induced nephrotoxicity.

It has been shown that CP raises kidney oxidative stress markers such as MDA, NO, MPO and PC levels. Malondialdehyde (MDA), a by-product of lipid peroxidation and one of the primary indicators of oxidative stress, has been observed to rise following cisplatin administration. According to reports, exposure to cisplatin is associated with higher concentrations of neutrophils and macrophages. It has been demonstrated that these activated neutrophils can cause tissue damage by building up and releasing cytotoxic proteins (such as myeloperoxidase) and ROS into the extracellular fluid. Myeloperoxidase activity (MPO), an indirect indicator of neutrophil infiltration, is a key indicator of an acute inflammatory response. Tissue damage and inflammation are brought on by a rise in MPO brought on by cisplatin toxicity.[21] Studies on protein oxidation in many human diseases have been conducted. Through accumulation, disintegration and the creation of cross-links in the polypeptide chain, oxidative damage to proteins altered their symmetrical organization, which accelerated the production of superoxide anions. PC (protein carbonyl) is a biomarker that is universally preferred and is now the most widely utilized to detect PC build-up and oxidation of protein. We found that cisplatin promoted oxidation of protein in kidney mitochondria, which is supported by a boost in superoxide radical generation.[22] In correspondence to the previous study, we observed that the cisplatin-triggered control-treated animals (group II) exhibited elevated levels of MDA, NO, MPO and PO. However on treatment with Marrubiin in a dose-based manner (group III and IV) to the CP-treated animals, the level of MDA, NO, MPO and PO was reduced. This indicates the antioxidant property of Marrubiin.[23]

A recognized immunological process in nephrotoxicity is the upregulation of the generation of cytokines inside renal tissue caused by cisplatin-triggered pro-inflammatory damage. Significant inflammatory mediators produced in an animal model of nephrotoxicity include IL-1β, IL-6 and TNF-α. These pro-inflammatory mediators are known to be extremely important in the occurrence of cisplatin-triggered nephrotoxicity.[24] The elevation of pro-inflammatory cytokines by cisplatin is due to the upregulation of intracellular ROS in the kidney, which in turn induces the transcription factor NF-κB. The NF-κB in turn induces the activation of TNF-α which in turn activates the other inflammatory mediators.[25] In the present study, the cisplatin control animals (group II) exhibited elevated levels of IL-6 and IL-1β, indicating nephrotoxicity. The CP-induced animals treated with Marrubiin in a dose-based manner (groups III and IV) exhibited reduced levels of inflammatory markers indicating the antiinflammation property of Marrubiin.

In line with the biochemical data and those from previous studies, our histological findings revealed degenerative lesions in the renal tissue of CP-treated rats, including RBC congestion, leukocyte infiltration, glomerular atrophy and larger epithelial cells in proximal convoluted tubules. On treatment with Marrubiin in dose dose-dependent manner, there was a considerable reduction in the histopathological changes.

CONCLUSION

The results of the current study indicate that administering Cisplatin to rats resulted in renal tissue damage brought on by oxidative stress. Through its antioxidant and anti-inflammatory properties, Marrubiin therapy in a dose-dependent manner has the potential to offer protection against CP-induced oxidative damage. These results suggest that Marrubiin therapy may be used as a preventative measure to lessen CP-induced kidney impairment in cancer patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CP: Cisplatin; **BUN:** Blood urea nitrogen; **Cr:** Creatinine; **SOD:** Superoxide dismutase; **GSH:** Glutathione; **BW:** Body weight; **MDA:** Malondialdehyde.

SUMMARY

The kidneys are essential for living. By purifying and eliminating metabolites (such as urea) and minerals from the blood, they play a crucial role in preserving the homeostatic equilibrium of bodily fluids. It also helps to regulate blood pressure, glucose metabolism and erythropoiesis by eliminating nitrogenous wastes and water from the body. The purpose of this investigation is to assess Marrubiin's influence in the protection of rats against cisplatin nephrotoxicity. The body weight and kidney weight were measured for all the experimental groups. Urine output and blood samples were collected to assess the blood urea nitrogen and creatinine present in the experimental animals. Furthermore, the oxidative stress markers, antioxidant enzymes, inflammatory markers and histopathological studies were carried out to assess the impact of Marrubiin treatment in a dose-dependent manner. We observed that treating animals CP-induced animals with Marrubiin aided in improving kidney function. Marrubiin significantly increased the level of antioxidant enzymes, histopathology conditions and body weight of the animals. It also down-regulated the inflammatory markers. Thus, we conclude that Marrubiin can be used to protect the kidney from injury induced by cisplatin treatment.

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