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THE PROTECTIVE EFFECT OF CISPLATIN NEPHROTOXICITY IN MICE ON MELATONIN AND GLUTATHIONE

MR AJAY KUMAR, MR NEERAJ KUMAR

SCHOOL OF PHARMACY MONAD UNIVERSITY NH 24 HAPUR (UP)

Abstract:

Cisplatin Nephrotoxicity Several theories have been put forth, but one that stands out is oxidative stress (including glutathione depletion and lipid peroxide generation). This study explains how the antioxidant system contributes to the nephrotoxicity caused by cisplatin and the nephroprotection provided by melatonin. Albino mice (BALB/c) were intravenously injected with: 1) Vehicle management 2) a single 6.5 mg/kg dosage CP group for cisplatin: 3) Melatonin 10 mg/kg for five days following CP injection. CPM team: 4) five days of melatonin (10 mg/kg) before and after CP injection The MCPM group: 5) M group received 10 mg/kg of melatonin daily for 5 days. In order to measure serum creatinine and blood urea nitrogen (BUN) mice were slaughtered five days after receiving CP injections.

KEYWORDS Cisplatin nephrotoxicity lipid peroxidation antioxidant and Glutathione

Introduction

A chemotherapy drug called cisplatin is used to treat a variety of malignancies. This includes esophageal cancer, lung cancer, mesothelioma, breast cancer, bladder cancer, head and neck cancer, testicular cancer, ovarian cancer, cervical cancer, and brain tumors and neuroblastoma. It is administered intravenously. Bone marrow suppression, hearing issues, renal issues, and vomiting are typical adverse effects. Numbness, difficulties walking, allergic reactions, and heart problems are among more major side effects. Baby danger from use during pregnancy is well known. Cisplatin belongs to the class of drugs known as platinum based antineoplastics. After administration water progressively replaces 1 or 2 chloride atoms to create the aqua complex. Cross linking can then take place by replacing the remaining chloride usually with another guanine. DNA is crosslinked by cisplatin in a number of ways which interferes with mitosis the process of cell division. Damaged DNA triggers DNA repair processes which when repair is unsuccessful initiate apoptosis. The one or two intrastrand cross linkages with Purina bases that are the most noticeable among the DNA alterations. These include the less frequent intrastrand adducts and the 1 or 2 intrastrand adducts which together make up about 90% of the adducts. The mainstay of many cancer treatments is the chemotherapy regimen including cisplatin. Although the majority of cancer patients will ultimately have a recurrence with cisplatin resistant illness the initial platinum response is significant. Oxaliplatin is active in extremely cisplatin-resistant cancer cells in the lab but there is minimal proof that it is also active when used to treat cisplatin-resistant cancer patients in a clinical setting. Although the mechanism behind this action is uncertain the medication paclitaxel may be helpful in the treatment of cisplatin-resistant malignancy. Transplatin the trans stereoisomer of cisplatin has the chemical formula trans [PtCl2(NH3)2] but does not have a pharmacological effect that is comparable to that of cisplatin. Transplatin's diminished anticancer efficacy is thought to be caused by two different processes. Transplatin is first assumed to have more chemical reactivity

due to the trans arrangement of the chloro ligands which causes transplatin to become inactive before it reaches the DNA where transplatin exerts its pharmacological action. Second transplatin's stereo conformation makes it possible for it.

Material & Methods

Drug

Cisplatin is a chemotherapeutic medication that is "cytotoxic" or "antineoplastic" against cancer. The medical product in question is categorised as a "alkylating agent" Melatonin and cisplatin were purchased from Mumbai's Himedia Laboratories Pvt.Ltd. and their generosity is recognised the other compounds employed were all of an analytical calibre.

Animal

Male Albino Wister mice were collected from Monad University in Hapur and weighed between 30 and 40 g. The mice were housed in an environment-controlled space with a 12 hr light/dark cycle, constant humidity of 50%, and temperature of 25°C. Prior to the trial, the animals had a one-week acclimatisation period and were given unlimited access to conventional laboratory diet and water. The Monad University Ethics Review Committee for Ethics in Animal Experiments has approved the study, and the Care and Use of Laboratory Animals rules were rigorously adhered to.

Treatment of Drug

Male Albino Wister mice were separated into five groups, each receiving a different treatment: control, melatonin (10 mg/kg b.w. i.p. for 7 days), cisplatin (6.5 mg/kg b.w., i.p. for 7 days), and melatonin and cisplatin combined. The amounts of serum urea nitrogen and creatinine were assessed. Evaluations of histopathological alterations were made. The current work shows that giving melatonin to mice with nephrotoxicity brought on by a single dose of cisplatin has a kidney protective effect. Cisplatin (6.5 mg/kg b.w.) was administered intraperitoneally (i.p.) once to cause kidney damage. Seven days before to the cisplatin injection, melatonin medication was initiated. Melatonin was mixed with saline and dissolved in ethanol. The final level of ethanol was 1% Day 7 (seven days following the cisplatin therapy) saw all.

Measurement of renal function

Following cisplatin injections, blood samples were obtained at the conclusion of the experiment and centrifuged (2000 x g for 5 min.). Sera were then kept at -80°C until analysis. Commercial tests were utilised to quantify BUN and creatinine concentrations and use them as indicators of renal failure. The diagnostic kit from **Sigma Chemicals Company, Ltd.** was used to determine these results. A homogenate was made in 0.1 M Tris HCl buffer (PH 7.4) as soon as the kidney was removed from the sacrifice and dissected apart.

Statistical analysis

Standard deviation (s.d.) is used to express all values. Analysis of variance (ANOVA) was used to determine the statistical significance, and the Schaffe post hoc test was used to compare each participant individually. Differences were seen as important.

Result

Creatinine and Blood Urea Nitrogen levels

In comparison to the control group (0.930.04mg/dL) and the melatonin group (1.110.03mg/dL), the creatinine level in the cisplatin group (2.350.12mg/dL) was considerably higher. In the CP-M group and the M-CP-M group, the rise was inhibited by the administration of melatonin together with cisplatin (1.17 0.003 mg/dL and 1.09 0.03 mg/dL, respectively). BUN was also elevated in the CP group (control group(46.83±0.54mg/dL)M group (45.5±0.34mg/dL) CP group 67.16±0.47mg/dL) and melatonin was seen to reduce this rise when supplied with cisplatin (CP-M group (56.83±0.94mg/dL) M-CP-M group (62.33±0.84mg/dL).

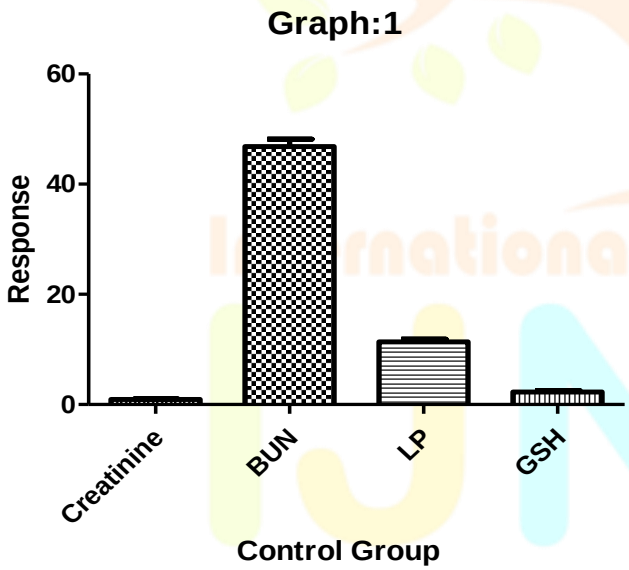
Table : 1.1 Lipid peroxides (nmole MDA/g) and glutathione (nmole GSH/g) levels in kidney homogenates were examined, as well as blood urea nitrogen (mg/dl), creatinine (mg/dl), and values.

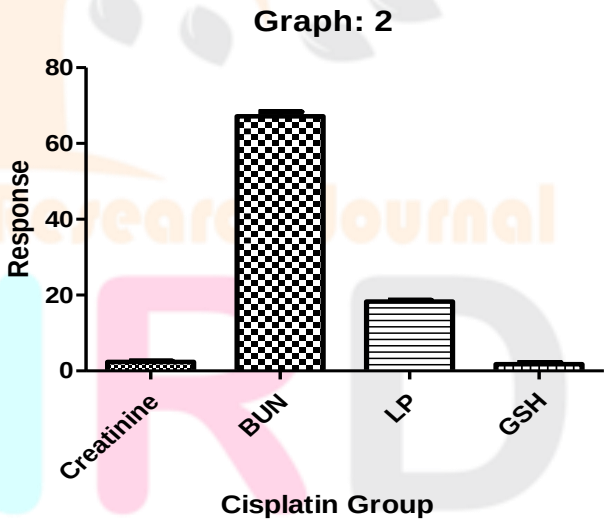
Group Name	Serum Creatinine (mg/dl)	BUN (mg/dl)	LP nmole MDA/g	GSH nmole GSH/g
C	0.93±0.04	46.83±0.54	11.4±0.19	2.3±0.08
CP	2.35±0.12	67.16±0.47	18.31±0.14	1.76±0.18
M	1.11±0.03	45.5±0.34	9.43±0.11	2.38±0.10
CP – M	1.17±0.003	56.83±0.94	14.93±0.18	1.55±0.11
CP – M – CP	1.09±0.03	62.33±0.84	12.16±0.15	2.43±0.10

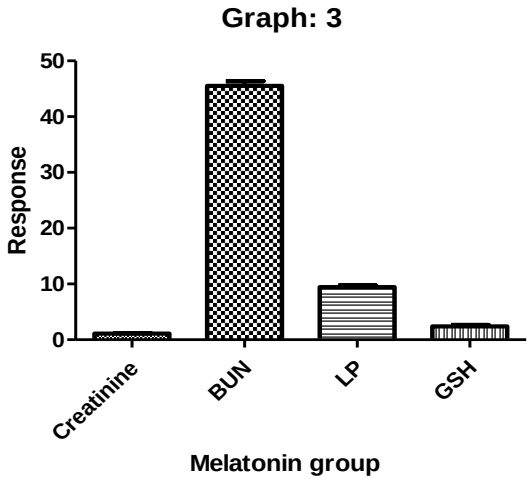
C – Control , CP- Cisplatin , M – Melatonin

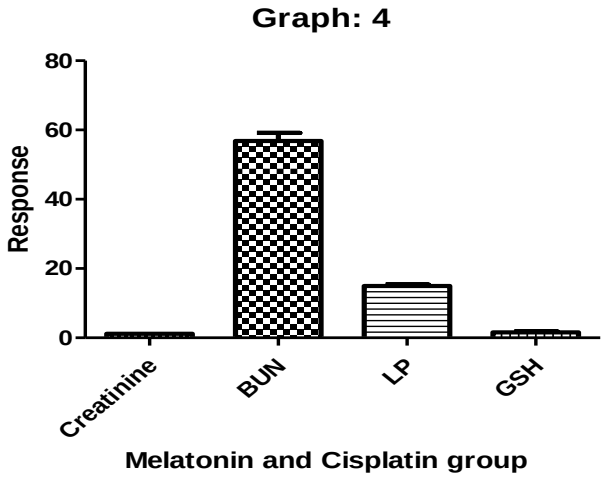
Lipid peroxide(LP) and Glutathione (GSH) levels

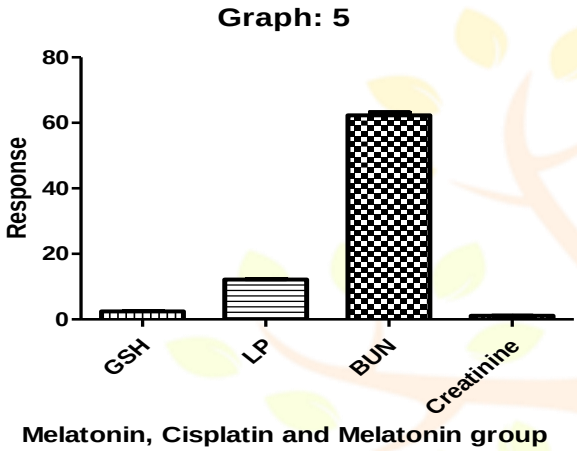
In comparison to the control group (11.40.19nmolMDA/g) and the melatonin group (9.430.11nmol MDA/g), the renal LP was found to be considerably greater in the cisplatin group (18.310.14nmol MDA/g). Melatonin lowered MDA values an index of LP to (14.930.18nmol MDA/g in the CP-M group and (12.160.15nmol MDA/g in the M-CP-M group, both of which were substantially lower than CP group (P O.OOl) (table I) when given in combination with cisplatin. When compared to the control group (2.30.08mol GSH/g) and the melatonin group (2.380.10mol GSH/g), cisplatin significantly reduced renal GSH to 1.760.18 (mol GSH/g). While melatonin therapy boosted it to (1.550.11mol GSH/g) in the CP-M group and (2.430.10mol GSH/g) in the M-CPM group when combined with cisplatin.











Histological examination

For histopathology, the kidney from each animal was promptly fixed in a 20% neutral buffered formalin solution. According to established protocol, kidneys were progressively dehydrated, embedded in paraffin, cut into 5-m sections, and stained with hematoxylin and eosin for histological analysis [20]. A pathologist who was not informed of the type of therapy examined the histological alterations semi-quantitatively. Each kidney slide had a minimum of 10 fields that were analysed, and the degree of the alterations was determined using the following scale: none + mild damage +++ moderate damage and +++ severe damage [32].

Microscopic Examination

Results from both light and transmission electron microscopy showed that the renal parenchyma in the control and melatonin groups was normal (figures 1). Extreme cortical destruction with multiple vacuolated proximal and distal tubular cells was visible in the light micrograph of the cisplatin group. Glomeruli shrank, and there was noticeable leukocyte infiltration (figure 2). By using transmission electron microscopy, it was possible to see that the mitochondria of proximal tubular cells were deteriorated and had irregular microvilli. Figure 2 shows enlarged short pedicels in the glomerulus and thickened uneven basal lamina (figure2). Investigations using light microscopy on the Cisplatin-Melatonin group revealed little damage to the proximal and distal tubular cells. The parenchyma showed significant leukocyte infiltration (figure 3). The proximal tubular cells in that group's transmission electron microscopy micrographs had a degraded ultrastructure with disrupted irregular microvillus and many vacuoles. There appeared to be mitochondria.

Figure:-1.1 A photomicrograph of the control group glomerulus proximal and distal tubules demonstrates their normal shape.

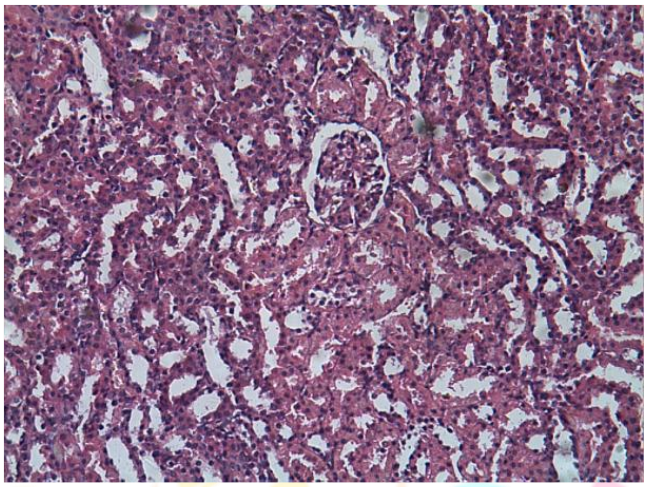
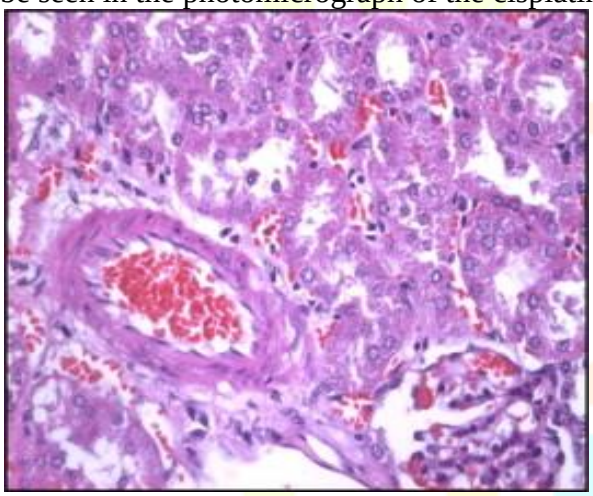


Figure:-1.2, 1.2.1 Extreme cortical destruction with multiple vacuolated proximal and distal tubular cells can be seen in the photomicrograph of the cisplatin group.



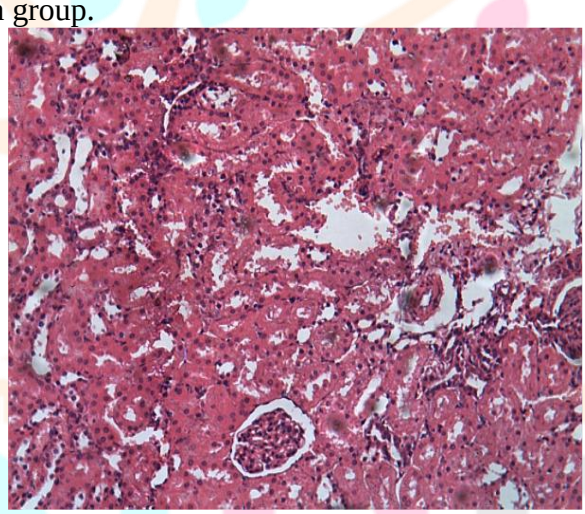
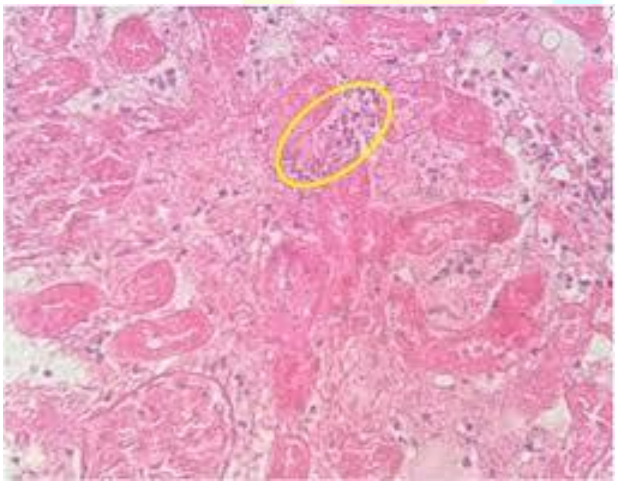


Figure :-1.3 ,1.3.2 The proximal and distal tubular cells show considerable damage in the CP-M group photomicrograph.



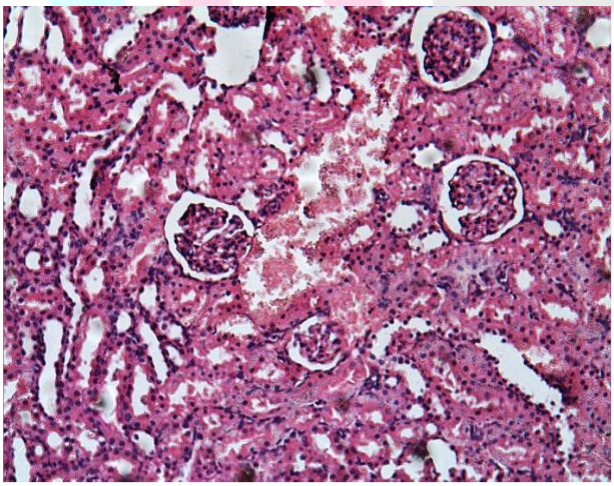
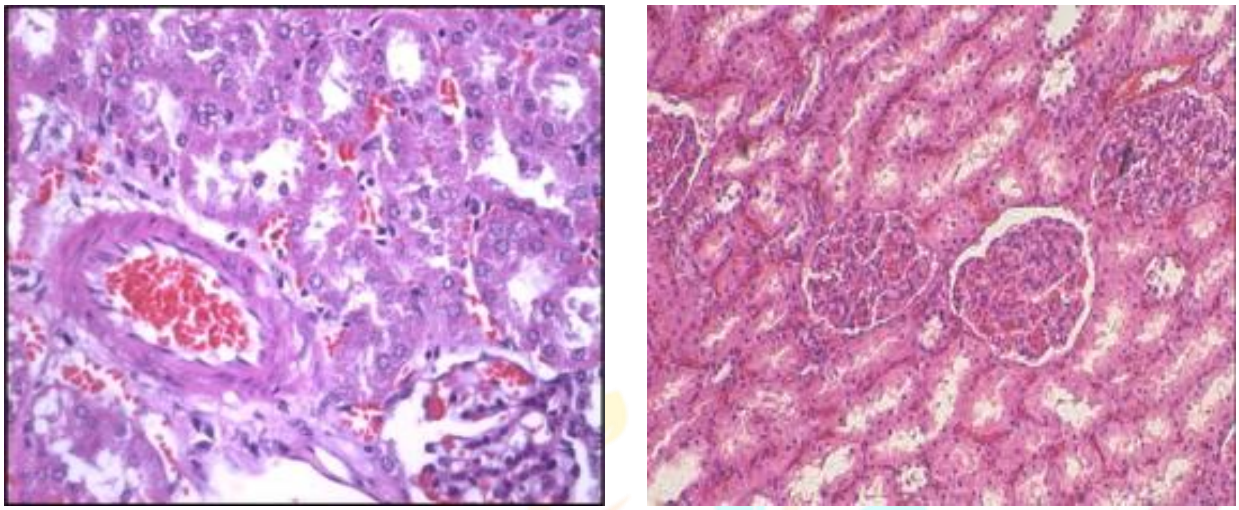


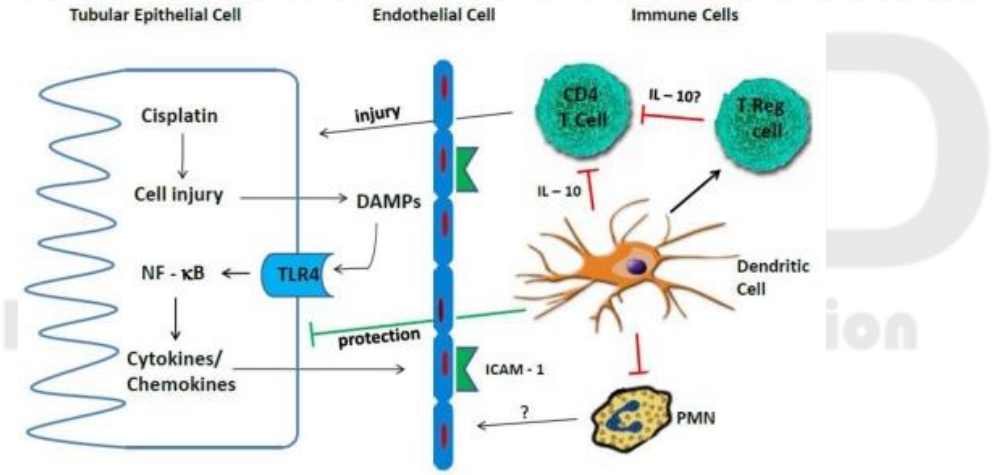
Figure: 1.4 A photomicrograph taken by the M-CP-M group shows damage to the proximal and distal tubular cells. Low-grade tubular cell degeneration is seen, but the glomerulus appears to be unaffected.



Inflammation in Cisplatin Nephrotoxcicty

The role of inflammation in the pathophysiology of cisplatin nephrotoxicity is becoming more recognised, along with the role of direct cellular toxicity. A number of the mediators of inflammatory renal damage have been discovered during the past ten years, as shown in (Figure 5). Immune mechanisms causing nephrotoxicity from cisplatin. Renal epithelial cells damaged by cisplatin generate DAMPs, which activate TLR4. TNF- is one of the chemokines and cytokines that are produced when TLR4 is activated. These chemokines and cytokines stimulate the production of adhesion molecules, luring neutrophils and T cells into the area of damage. The anti-inflammatory cytokine IL-10 is produced by tissue-resident dendritic cells, which at least in part prevent kidney damage. Treg cells also lessen renal damage, despite

Figure 1.5



Discussion

Antitumor medications are being used more often as adjuvant treatment for individuals with high-risk conditions [24]. The complications related to chemotherapy are a serious worry. Recent developments in medicine have demonstrated the connection between oxygen radicals and hydrogen peroxides and the emergence of numerous pathogenic processes, including the unfavourable effects of anti-tumor medications [24, 25]. The drawback of nephrotoxicity caused by the anticancer medication cisplatin is that it is extremely

effective [2, 3, 5]. The purpose of this effort was to offer a logical plan for preventing or treating the clinical renal failure brought on by CP. It is thought that the production of free radicals and the consequent lipid peroxidation of membrane lipids are what causes certain substances, such as cephaloridine parquet.

Conclusion

The harmful and dose-limiting toxicity of cisplatin is nephrotoxicity. The transport of cisplatin into renal epithelial cells, damage to nuclear and mitochondrial DNA, activation of several cell death and survival pathways, and induction of a significant inflammatory response all contribute to the development of cisplatin nephrotoxicity. Although this plan offers a wide range of potential treatment targets, single therapies in animal models have often.

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