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Research Article
Protective Effects of Ibudilast Against Cisplatin-Induced Hepatotoxicity and Nephrotoxicity Mediated by Prostacyclin Enhancement

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Abstract

Background and Objective: Cisplatin, a prevalent chemotherapy drug, presents hepatotoxic and nephrotoxic side effects, this study explores ibudilast's potential protective effects against such damage via prostacyclin enhancement. The goal of this research was to assess ibudilast's potential to lessen the negative effects of cisplatin on the hepatic and renal systems. **Materials and Methods:** The 24 adult female rats were divided into three groups: Control, cisplatin-treated (2.5 mg/kg/day, twice weekly for a month) and cisplatin plus ibudilast-treated (5 mg/kg/day intraperitoneally). Oxidative markers, inflammatory cytokines, ALT, creatinine and tissue prostacyclin levels were assessed, along with histopathological analysis. **Results:** Substantial increases in ALT, creatinine, MDA, TNF-α and IL-6 levels were seen after cisplatin treatment. However, all of these measures showed a substantial decline when ibudilast was added to the cisplatin regimen. After receiving ibudilast medication, the histopathology analysis revealed decreased cisplatin-induced hepatic and renal damage. The cytoprotective function of ibudilast was further supported by elevated tissue prostacyclin levels. **Conclusion:** Based on our findings, it is suggested that ibudilast has the potential to safeguard against liver and kidney harm induced by cisplatin. It achieves this by not only reducing oxidative stress and inflammation but also by boosting prostacyclin levels, which supports tissue regeneration.

Key words: Ibudilast, cisplatin, nephrotoxicity, hepatotoxicity, prostacyclin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The cancer therapy landscape has transformed with the advent of tumor-agnostic therapies, which hinge on identifying specific, targetable molecular variants[1]. Despite these advancements, traditional cytotoxic chemotherapy remains a cornerstone in treatment regimens. Cisplatin, an alkylating chemotherapeutic agent, plays a critical role in treating various cancers due to its ability to bind to nuclear DNA, induce apoptosis and promote cell cycle arrest[2,3]. While cisplatin has demonstrated improved survival rates and beneficial outcomes in several malignancies, particularly testicular cancer, its usage is limited due to adverse effects on the nervous, gastrointestinal and renal systems[4]. A multitude of mechanisms, including oxidative stress, inflammation and mitochondrial dysfunction with an emphasis on the overproduction of free radicals has been linked to the development of toxicity caused by cisplatin[5]. Various antioxidants such as hesperidin, melatonin, amifostine, curcumin, ellagic acid, lycopene, vitamin E, Ginkgo Biloba and methylene blue, have been employed to counteract the damage caused by cisplatin[6-8].

Ibudilast, a non-selective phosphodiesterase inhibitor and tiny molecular substance, also inhibits the activity of the molecules Macrophage Migration Inhibitory Factor (MIF) and Toll-Like Receptor 4 (TLR-4)[9,10]. Utilizing its bronchodilator, vasodilator, antioxidant and anti-inflammatory characteristics, it is used clinically for bronchial asthma, post-stroke vertigo and multiple sclerosis[11-13]. Ibudilast, which may cross the blood-brain barrier, has been shown in *in vitro* experiments to reduce the development of oxaliplatin-induced neurotoxicity by attenuating microglial activation in both the central and peripheral nervous systems[14]. Additionally, new research examining ibudilast's ability to prevent myocardial damage brought on by hemorrhagic shock and reperfusion has highlighted its capacity to do so by lowering myocardial levels of malondialdehyde (MDA) and Tumor Necrosis Factor-Alpha (TNF-α), primarily through TLR-4 antagonistic activity[15]. Ibudilast also promotes prostacyclin release from vascular endothelium, which helps to maintain vascular integrity and endothelial function[16].

With a focus on prostacyclin activation, the aim of this research was to clarify the preventive potential of ibudilast against kidney and liver damage brought on by cisplatin. Additionally, the anti-inflammatory and antioxidant properties of ibudilast were also investigated using a variety of biochemical tests and histological evaluations of liver and kidney tissue.

MATERIALS AND METHODS

Study area: The research was conducted in the Experimental Animals Application and Research Center at Demiroglu Bilim University in Istanbul, Turkey, spanning from September, 2022 to May and January, 2023.

Study subjects: In this investigation, a total of 24 adult Wistar rats, with an average weight of approximately 200 g, were utilized. The rats were taken from the Experimental Animals Application and Research Center at Demiroglu Bilim University in Istanbul, Turkey. The animals were housed in a controlled environment where they experienced a 12 hrs cycle of light and darkness, along with a consistent temperature of 22±2°C. Throughout the duration of the study, the participants were given unrestricted access to standard pellet feed and tap water. All experimental methods adhered to the guidelines set forth by the National Institutes of Health (United States of America) in their Guide for the Care and Use of Laboratory Animals. The Institutional Animal Ethics Committee has granted its approval to the operations, with Ethics Number 28220114. All compounds, unless stated otherwise, were obtained from Sigma-Aldrich Inc.

Experimental design: The research involved a total of 24 rats, which were divided into three groups of equal size. Group 1, consisting of 8 individuals, served as the control group and did not undergo any form of treatment. Group 2 (n = 8) received a dosage of cisplatin (Sigma-Aldrich, St. Louis, Morocco, United States of America) intraperitoneally (i.p.) at a concentration of 20 mg kg^{-1}. Additionally, they were administered 1 mL/kg/day of 0.9% NaCl (Saline, Baxter International Inc., Deerfield, Illinois, United States of America) twice a week for a duration of four weeks. Group 3 (consisting of 8 individuals) was administered an equal dose of cisplatin, in addition to a daily intravenous dosage of 5 mg kg^{-1} ibudilast (Sigma-Aldrich, St. Louis, Morocco, United States of America), for a duration of four weeks. This dosage regimen adhered to the guidelines provided by the Department of Health and Human Services and the FDA, which ensure appropriate conversion of doses between animals and humans. Although there were no casualties among the animals in the cisplatin and ibudilast treatment group during the entire duration of the experiment, 2 mice from group 2, did not survive. After the trial, a method called cervical dislocation was carried out following euthanasia. This method involved using a potent combination of anesthetics, specifically 100 mg kg^{-1} of Ketasol (Richter Pharma, Wels,

Austria) and 50 mg kg^{-1} of Rompun (Bayer, Leverkusen, Germany). The histological investigation involved the extraction of organs, while biochemical analysis was conducted by taking blood samples through a heart puncture.

Plasma lipid peroxidation (MDA) measurement: The measurement of MDA plasma levels was conducted using the TBARS (Thiobarbituric Acid Reactive Substances, Cayman Chemical, Ann Arbor, Michigan, United States of America) test, which detects lipid oxidation. The TBARS is a method used to measure the amount of lipid peroxidation. Lipid peroxidation is a type of oxidative degradation of lipids, in which free radicals "steal" electrons from the lipids in cell membranes, resulting in cell damage. The TBARS assay measures the amount of malondialdehyde (MDA) and other aldehydic products produced during the secondary breakdown of certain oxidized, damaged fats. The MDA, in particular, can react with thiobarbituric acid to produce a pinkish-red colored complex, which is quantified spectrophotometrically. Plasma samples were mixed with trichloroacetic acid (Fisher Scientific, Waltham, Maine, USA) and the TBARS reagent, followed by heating at 100°C for 1 hr. Following the cooling of the mixture, the samples underwent centrifugation (Thermo Fisher Scientific, Waltham, Massachusetts, United States of America) for a duration of 20 min at a speed of 3000 rpm. To calibrate the 535 nm absorbance measurement of the supernatant, tetraethoxypropane (Merck KGaA, Darmstadt, Germany) was employed. The concentrations of MDA were then expressed as nmol g^{-1} protein (nM).

Plasma TNF-α, IL-6 and ALT Level measurements: The levels of TNF-α, Interleukin-6 (IL-6) and Alanine Aminotransferase (ALT) in the plasma were determined using commercially available ELISA kits (SunRed-China, Shandong, China).

Creatinine level determination: An automated analytical system (Roche Diagnostics, Cobas c series, Basel, Switzerland) was used to determine the amounts of creatinine and the findings were expressed in mg dL^{-1}.

Liver and kidney biochemical analysis: Following euthanasia, the organs were promptly extracted and preserved at a temperature of -20°C in preparation for future biochemical analysis. To assess the tissues, the liver and kidney were both homogenized in a phosphate-buffered saline solution with a volume five times that of the sample (pH 7.4). Subsequently, the samples were subjected to centrifugation (Thermo Fisher Scientific, Waltham, Massachusetts, United States of America) at 5000 g for a duration of 15 min. The liquid portion was gathered and the overall protein concentration was determined using the Bradford method (Bio-Rad Laboratories, Hercules, California, United States of America), utilizing bovine serum albumin as a reference. Commercially available rat ELISA kits (SunRed-China, Shandong, China) were utilized to measure the levels of prostacyclin in the supernatants of the liver and kidney.

Histopathological examination of liver and kidney: To conduct histopathological evaluations, every animal received 200 mL of a 4% formaldehyde solution in 0.1 M PBS after being sedated with xylazine (10 mg kg^{-1}, Alfazyme®, Alfasan International B.V., Woerden, Netherlands) and ketamine (100 mg kg^{-1}, Alfamine®, Alfasan International B.V., Woerden, Netherlands). Hematoxylin and Eosin (H&E) (Sigma-Aldrich, St. Louis, Morocco, United States of America) were used to stain the liver and kidney sections (4 µm). Images of each section were captured using an Olympus BX51 microscope with an Olympus C-5050 digital camera (Olympus Corporation, Tokyo, Japan). The morphological assessment of 10 microscopic fields per slide was conducted by a blinded evaluator using an automated image analysis system called Image-Pro Express 1.4.5 (Media Cybernetics, Inc., Rockville, MD, United States of America). The evaluation was done at a magnification of 20X. The kidney sections were assessed for interstitial inflammation, tubular epithelial necrosis, tubular dilation and luminal necrotic debris using a semi-quantitative approach. The grading system was structured in the following manner: A score of 0 is given for a percentage between 0-5%, a score of 1 is given for a percentage between 6-20%, a score of 2 is given for a percentage between 21-40%, a score of 3 is given for a percentage between 41-60%, a score of 4 is given for a percentage between 61-80% and a score of 5 is given for a percentage between 81-100%. Liver damage was evaluated using comparable criteria, which considered factors such as the level of cytoplasmic vacuolization, necrosis, congestion and dilation of sinusoidal and central veins.

Statistical analysis: The SPSS software (version 15.0) (IBM Corporation, Armonk, New York, United States of America) was used to conduct the statistical analysis. With *post hoc* Bonferroni correction done for subgroup analysis, parametric variables were assessed using one-way ANOVA and Student's t-test. The Mann-Whitney U Test is a non-parametric statistical test used to compare two independent groups. The U Test was

employed to compare nonparametric variables. To ascertain how the variables were distributed, the Shapiro-Wilk Test was used. The standard error of the mean (SEM) represents the average value of the data and a significance level of 0.05 was employed to indicate statistical significance.

RESULTS

Ibudilast's impact on plasma MDA, IL-6 and TNF-α values: To investigate the impact of ibudilast, an anti-inflammatory and antioxidant, on organ damage induced by cisplatin in rats, the researchers measured the levels of MDA, TNF-α and IL-6 in the plasma. Following the administration of cisplatin, there was a notable rise in plasma MDA levels, which serve as an indicator of oxidative stress. Additionally, the levels of TNF-α and IL-6, which are associated with inflammation, showed a significant increase (TNF-α, $p<0.001$, MDA and IL-6, $p<0.0001$). Significantly, the administration of ibudilast treatment mitigated the increase in these three biomarkers induced by cisplatin (Table 1).

Ibudilast's impact on cisplatin-mediated renal and hepatic dysfunction: The substantial renal damage caused by cisplatin exposure was shown by the significantly elevated kidney function tests (Table 1). The only group receiving cisplatin had significantly higher levels of creatinine than the control group ($p<0.0001$). This measure did, however, significantly decline after ibudilast therapy ($p<0.001$), indicating ibudilast's preventive efficacy against cisplatin-induced kidney damage.

When compared to the control group, the cisplatin group had raised plasma ALT levels, increasing from 38.2±4.5 to 89.3±12.4 IU L^{-1} ($p<0.001$). With ibudilast therapy, this measure had a significant decrease ($p<0.05$) (Table 1).

Ibudilast's influence on prostacyclin levels in kidney and liver tissues: The prostacyclin levels in the liver and kidney tissues of the cisplatin group were significantly lower when compared to the control group ($p<0.0001$ and $p<0.001$, respectively). It is worth mentioning that the ibudilast therapy group showed a significant recovery in prostacyclin levels compared to the group treated with cisplatin ($p<0.001$ for liver prostacyclin, $p<0.05$ for kidney prostacyclin) (Table 1).

Ibudilast's influence on cisplatin-induced histopathological alterations in kidney and liver tissues: The H&E-stained slices of the liver and renal tissues revealed signs of cellular damage. The histopathological score for the cisplatin group significantly increased, showing interstitial inflammation, luminal necrotic debris and tubular dilatation (Table 2, $p<0.0001$). All tubulointerstitial scores dropped after receiving ibudilast therapy (Fig. 1).

Cisplatin was shown to cause necrosis, cytoplasmic vacuolization, central vein and sinusoidal dilatation and congestion in liver tissue (Table 3). Surprisingly, ibudilast therapy dramatically reduced this severe liver damage (Fig. 2).

Table 1: Comparative analysis of biochemical and inflammatory markers in normal control, cisplatin+saline and cisplatin+5 mg kg^{-1} Ibudilast groups

Markers	Normal control	Cisplatin+Saline	Cisplatin+5 mg kg^{-1} ibudilast
MDA (nM)	49.5±3.08	156.1±10.3**	98.7±6.6$^{\#}$
TNF-α (pg mL^{-1})	21.1±1.9	91.8±3.5*	56.1±8.1$^{\#}$
IL-6 (pg mL^{-1})	13.5±2.6	685.2±19.1**	394.5±17.9$^{\#\#}$
ALT (IU L^{-1})	38.2±4.5	89.3±12.4*	45.6±3.8$^{\#}$
Creatinine (mg dL^{-1})	0.45±0.02	0.87±0.05**	0.65±0.09$^{\#\#}$
Liver prostacyclin (pg mg^{-1} protein)	77.1±8.5	19.3±5.7**	54.8±6.6$^{\#\#}$
Kidney prostacyclin (pg mg^{-1} protein)	109.6±11.8	61.2±9.2*	87.4±7.3$^{\#}$

Results were presented as Mean±SEM, Statistical analyses were performed by one-way ANOVA test, *$p<0.001$, **$p<0.0001$ (different from control group), $^{\#}p<0.05$ and $^{\#\#}p<0.001$ (different from cisplatin and saline group)

Table 2: Comparative evaluation of histopathological parameters in kidney tissues of normal control, cisplatin+saline and cisplatin+5 mg kg^{-1} Ibudilast groups

Parameters	Normal control	Cisplatin+Saline	Cisplatin+5 mg kg^{-1} ibudilast
Tubular epithelial necrosis	0.3±0.2	3.5±0.3*	1.8±0.2$^{\#\#}$
Luminal necrotic debris	0.2±0.1	2.2±0.3*	1.5±0.3$^{\#}$
Tubular dilatation	0.1±0.1	3.0±0.4*	1.6±0.4$^{\#\#}$
Interstitial inflammation	0.1±0.1	1.3±0.4*	0.6±0.4$^{\#}$

Results were presented as Mean±SEM, Statistical analyses were performed by one-way ANOVA test, *$p<0.0001$ (different from control group), $^{\#}p<0.01$ and $^{\#\#}p<0.0001$ (different from cisplatin and saline group)

Table 3: Comparative analysis of histopathological parameters in liver tissues of normal control, cisplatin+saline and cisplatin+5 mg kg^{-1} Ibudilast groups

Parameters	Normal control	Cisplatin+Saline	Cisplatin+5 mg kg^{-1} ibudilast
Sinusoidal and central vein dilatation	0.1±0.1	3.4±0.5*	1.1±0.5##
Congestion	0.3±0.2	3.0±0.4*	1.3±0.4#
Necrosis	0.2±0.1	2.5±0.3*	0.9±0.3##
Cytoplasmic vacuolization	0.1±0.1	3.4±0.5*	0.8±0.1#

Results were presented as mean±SEM, Statistical analyses were performed by one-way ANOVA Test, *p<0.001 (different from control group), #p<0.01 and ##p<0.0001 (different from cisplatin and saline group)

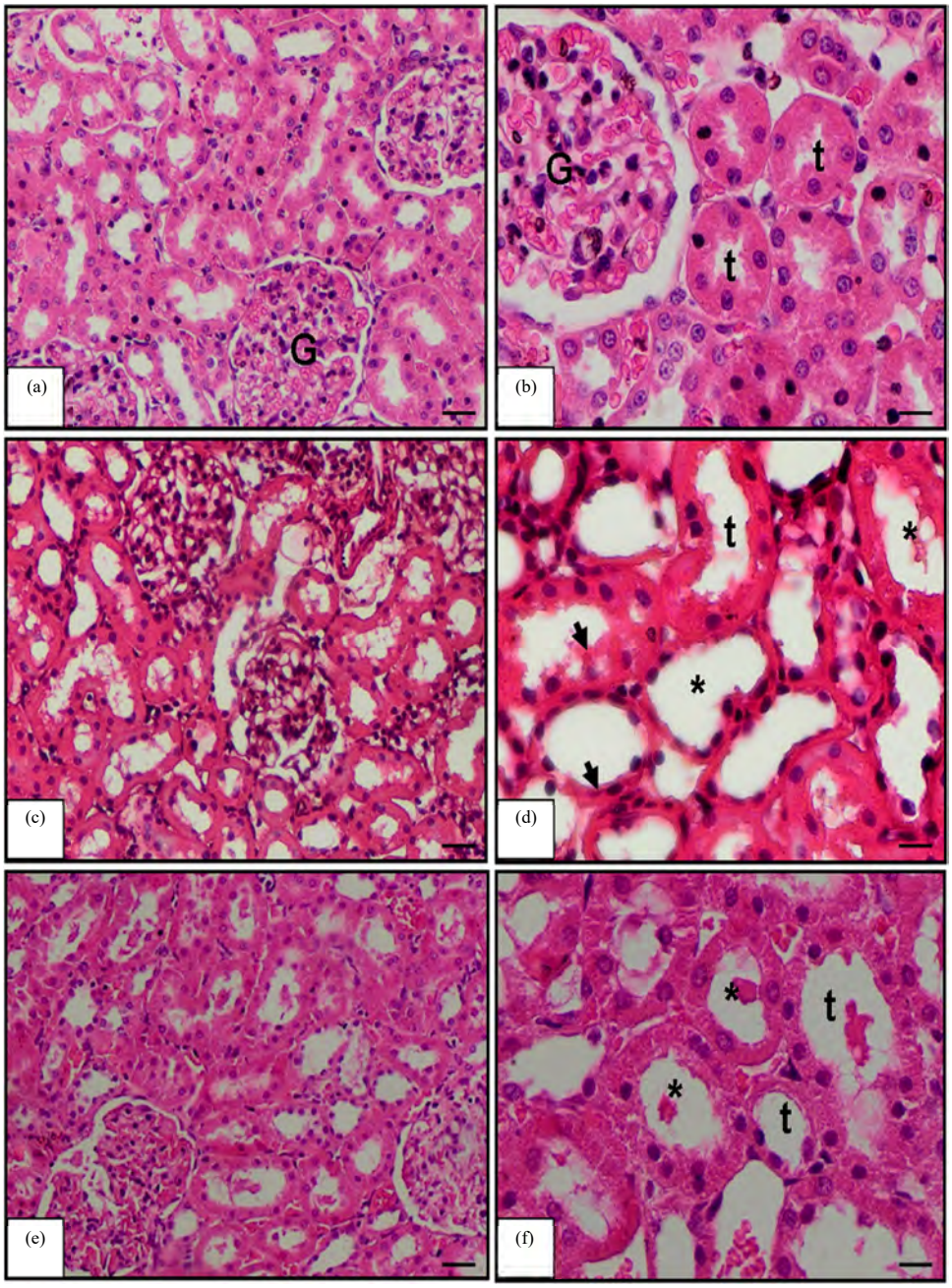

Fig. 1(a-f): Kidney histopathology H&E (X10 and X40 magnification), (a-b) Normal kidney (control group), glomerul (G) and tubules (t), (c-d) Cisplatin and saline group kidney have tubular cell necrosis (arrow) and tubular dilatation (*) and (e-f) Cisplatin and ibudilast group kidney decreased on tubular dilatation (*) and tubular cell necrosis

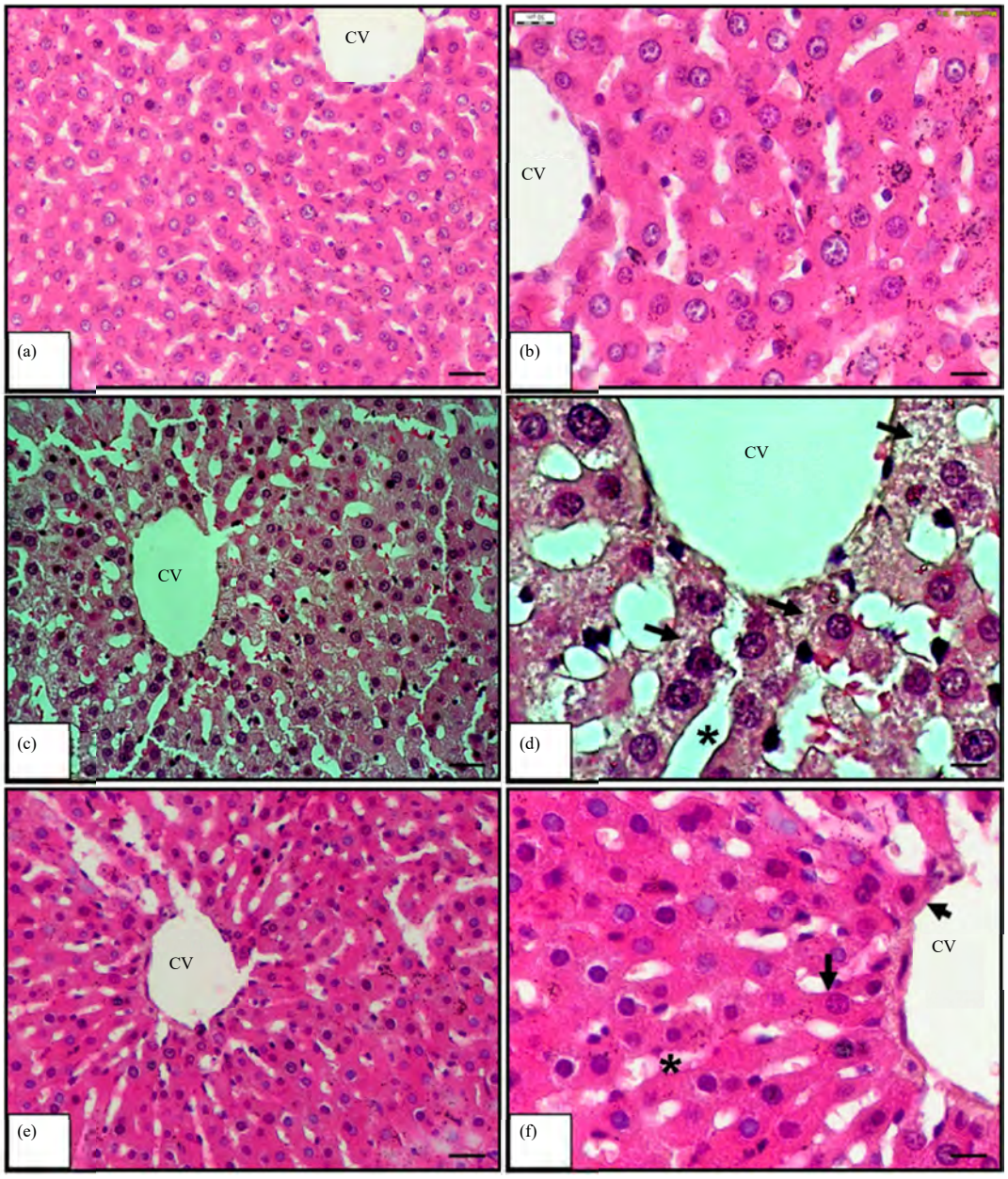

Fig. 2(a-f): Liver histopathology H and E (X10 and X40 magnification), (a-b) Normal liver (control group), (c-d) Cisplatin and saline group liver have vacuolar changes of pericentral hepatocytes, central venous (cv) and sinusoid dilatation (*) and hepatocyte necrosis (arrow) and (e-f) Cisplatin and ibudilast group liver decreased central venous and sinusoid dilatation (*) and hepatocyte necrosis (arrow)

DISCUSSION

Microscopic examinations and biochemical indicators supported the current research, which showed that ibudilast has protective qualities against cisplatin-induced liver and kidney damage in animal models. Due to its negative effects, cisplatin, a powerful cytotoxic drug used in the treatment of cancer, is only sometimes used. The nephrotoxicity and less commonly, the hepatotoxicity caused by cisplatin thought to be caused by lipid peroxidation and oxidative stress, which result in elevated reactive oxygen products[17]. Additionally, cisplatin-induced inflammation causes kidney and liver damage[18]. Levels of TNF-α, MDA and IL-6 are used as indicators of inflammation and lipid peroxidation. In a study conducted by Hama *et al.*[19], it was found that Ibudilast effectively decreased neuropathic pain in rats with spinal cord

injuries. This was achieved by inhibiting TNF-α production in spinal microglia. Ibudilast, on the other hand, was shown to be protective against brain aneurysms, according to research by Yagi *et al.*[20], in large part because of its powerful suppression of Phosphodiesterase-4 Isoenzyme (PDE-4) and decrease in TNF-α expression.

Doxorubicin, a different common drug used to treat hematological and solid tumors, causes cardiotoxicity in 3-26% of instances. By preventing the breakdown of nicotinamide adenine dinucleotide phosphate oxidase 2, research by Nishiyama *et al.*[21] shown that ibudilast reduces the rise in reactive oxygen products after the injection of doxorubicin and cisplatin[22]. Their findings supported the hypothesis that pre-emptive ibudilast usage before doxorubicin treatment prevents left ventricular diastolic dysfunction by lowering myocardial TLR4, TNF-α and MDA levels. These results were supported by the findings of this study, which demonstrated the anti-inflammatory and antioxidant properties of ibudilast by dramatically lowering the increased TNF-α, MDA and IL-6 levels related to cisplatin.

In comparison to the control group, this study revealed a significant rise in serum creatinine levels as well as higher ratings for tubular epithelial necrosis, tubular dilatation, interstitial inflammation and luminal necrotic debris, but after receiving ibudilast medication, all metrics showed a considerable decline. Following ibudilast therapy, Li *et al.*[23] research in rats with folic acid-induced renal tubular damage and acute renal failure revealed significantly lower blood creatinine and BUN levels as well as tubulointerstitial damage scores in the kidney tissue. Their results demonstrated that ibudilast protects against acute renal failure by inhibiting Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor Kappa B (NF-kB) signaling pathways mediated by TLR-4.

The current study findings, in contrast to other studies, was the first to show that ibudilast may protect against CIN, principally through enhancing prostacyclin release from the endothelium[24]. The literature is replete with papers that describe the liver damage caused by cisplatin. To monitor cisplatin-induced hepatotoxicity, liver function tests often measure blood ALT and AST levels[25-27]. Present study investigation discovered around double the ALT levels in the cisplatin group compared to the control and these levels reverted to control group levels after receiving ibudilast medication, which is consistent with the literature.

According to research by Martin *et al.*[28], cisplatin-induced hepatotoxicity was caused by oxidative damage, lipid peroxidation and protein sulfhydryl groups. After receiving cisplatin therapy, the liver tissue underwent a histological analysis and the results showed substantial increases in the levels of necrosis, cytoplasmic vacuolization, sinusoidal and central venous dilatation and congestion. This cisplatin-induced liver damage was significantly prevented by ibudilast therapy (Fig. 2). With the addition of ibudilast to the treatment regimen, the cisplatin-induced drop in liver prostacyclin levels also approached control group values. This suggested that the protective effect of ibudilast against cisplatin-induced toxicity on the liver may be attributed to the production of prostacyclin or nitric oxide from the endothelium, rather than inhibiting PDE.

The limited sample size of the current research poses a significant drawback due to ethical considerations, necessitating larger preclinical studies. Additionally, it's important to assess how different ibudilast doses affect bigger populations. Finally, ibudilast's ability to lessen the antitumor effects of cisplatin as well as its adverse effects needs to be further tested.

CONCLUSION

Current study emphasizes the potential protective effects of ibudilast against cisplatin-induced kidney and liver damage. These effects are primarily attributed to the anti-inflammatory and antioxidant properties of ibudilast. The significance of current findings lies in the demonstration of ibudilast's ability to safeguard against liver and kidney damage induced by cisplatin in animal models, achieved through the enhancement of prostacyclin levels. This evidence supported the argument for the utilization of ibudilast in reducing the nephrotoxicity and hepatotoxicity associated with cisplatin.

SIGNIFICANCE STATEMENT

Cancer's high global mortality rate emphasizes the importance of chemotherapeutic agents like cisplatin. However, its adverse effects, especially hepatotoxicity and nephrotoxicity, restrict its use. Ibudilast's potential protective properties against cisplatin-induced damage is a less-explored territory. This study, through a controlled animal model, evaluated cisplatin's damage and Ibudilast's protective response, focusing on MDA, TNF-α and IL-6 levels and prostacyclin enhancement. The research illuminates Ibudilast's potential in countering cisplatin's harmful effects and paves the way for human clinical trials, offering a promising direction to enhance cancer treatment safety and efficacy.

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