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RESEARCH ARTICLE

Orientin Attenuates Cisplatin-Induced Renal Toxicity by Reducing Oxidative Stress and Inflammation

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ABSTRACT

Cisplatin (CP), an effective chemotherapeutic drug, has been widely used to treat the several types of tumors. Orientin (ORI) is a flavonoid that shows versatile therapeutic activities. The current research was planned to observe the protective role ORI on CP induced renal injury in rats. Twenty-four male rats were divided into four groups equally and termed as control, CP (10 mg/kg), CP (10 mg/kg) + ORI (40 mg/kg) and ORI (40 mg/kg). After seven days trial, rats were dissected and different parameters were analyzed. Results indicated that the CP administration significantly reduced the activities of catalase, peroxidase, glutathione reductase and glutathione content whereas it increased the level of hydrogen peroxide and TBARS (thiobarbituric acid reactive substances). CP increased the creatinine and urea levels while decreased the creatinine clearance. Moreover, CP significantly increased the inflammatory markers, including nuclear factor kappa-B, tumor necrosis factor-α, Interleukin-6, Interleukin-1β levels, cyclooxygenase-2 activity and histopathological damages. However, co-administration of ORI displayed curative effects against CP-induced renal toxicity and recovered all parameters by bringing them to a normal level. These results revealed that the ORI is a potential bioflavonoid that can potentially counter the CP-induced renal damage.

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INTRODUCTION

Cisplatin (CP) is a cis-diamine-dichloro-platinum, wieldy used as an efficient chemotherapeutic medicine to treat the various types of tumors such as head, neck, breast, colon, lung, liver, kidney, ovary, cervix, bladder and testicular (Elsherbiny *et al*., 2016). The clinical and pharmacological uses of CP are limited due to its severe side effects which includes hair loss, vomiting, nausea, allergic reactions, neurotoxicity, ototoxicity, gastro-toxicity, hepatotoxicity and nephrotoxicity (Li *et al*., 2018). CP accumulates in the renal tissues and causes kidney damage through tubular necrosis and reactive oxygen species (ROS) production (Kumar *et al*., 2017).

CP induced renal damage is directly dependent on platinum concentrations in the kidney (McSweeney *et al*., 2021). The CP usage reduces the antioxidant level in plasma which indicate a failure of defensive mechanism of antioxidant (Nematbakhsh *et al*., 2017). ROS causes cellular damage and necrosis through protein denaturation, lipid peroxidation and DNA damage in tubules of kidney (Ratliff *et al*., 2016). Lipid peroxidation and ROS production have potential to trigger apoptosis in cells (Su *et al*., 2019). So, the nephrotoxicity is the major reason which limits the usage of CP to treat the various tumors (Perše and Večerić-Haler, 2018).

Plants are generally regarded as an active source of medicine (Regginato *et al*., 2021). Flavonoids based herbal medicines have become a major part of recent drug discoveries (Omar *et al*., 2020). Orientin (ORI) is a bioactive flavonoid, abundantly present in millet, dayflower and the peel of passion fruit. It can be extracted

from bamboo and pigeon pea leaves (Lam *et al*., 2016). It has been reported that the ORI exhibits a number of pharmacological properties for example antioxidant, anti-microbial, anti-inflammatory, anti-glycation and radioprotection (Bouchouka, *et al*., 2012). By considering the potential biological activities of ORI current study was planned to assess the protective effects of ORI on CP induced renal damage in male albino rats.

MATERIALS AND METHODS

Chemicals: Both chemicals Orientin and Cisplatin were purchased from Sigma-Aldrich (Germany). All other chemicals used in this study were of analytical grade.

Animals: Mature male albino rats (n=24) weighing 170-200g were kept in the animal house, University of Agriculture, Faisalabad. Stainless-steel cages were used to keep the rats and provided with 25±2ºC temperature and 12 hrs. light/dark cycle. Moreover, rats were given with tap water and standard food throughout the experiment. All the rats were freely provided with standard food pellets and tap water. Before the start of the trial, the rats were made familiarized to the laboratory environment for seven days. Animals were handled in compliance with the NIH guidelines (CEE Council 86/609) protocol.

Experimental protocol: 24 rats were randomly distributed into four equal groups, having 6 male rats in each group. The experiment was conducted for seven days. Group-1 was considered as control and received normal saline. Group-2 was treated with CP (10mg/kg) intraperitoneally only on the day first of the trial. Group-3 was considered as co-treated group and administrated with CP (10mg/kg) injection on the first day of trial and ORI (40mg/kg) orally on the daily basis till the completion of the trial. The 10 mg/kg dose of CP was chosen in accordance with Ijaz *et al*. (2020), while 40 mg/kg dose of ORI was selected in accordance to Liu *et al*. (2015). Rats of group-4 were treated only with oral dose of ORI (40 mg/kg) throughout the experiment. After seven days of treatment, rats were anesthetized with chloroform, dissected and blood was collected for biological estimation of serum profile. After dissection both the kidneys were separated; one of them was packed in zipper bags and stored at -80^{0}C for biochemical analysis. Other kidney was preserved in formalin (10%) for histological examination. The stored kidney was homogenized in 3 ml of PBS (pH 7.4), then centrifuged for 15 minutes at 12000 rpm before analysis.

Assessment of antioxidant enzymes: Catalase (CAT) and peroxidase (POD) activities were evaluated according to the process of Chance and Maehly (1955). Activity of superoxide dismutase (SOD) was assessed through the process of kakkar *et al*. (1984). Carlberg and Mannervik (1975) protocol was followed for the evaluation of glutathione reductase (GSR) activity. The Glutathione (GSH) content was assessed by spectrophotometric protocol explained by Jollow *et al*. (1974).

Evaluation of TBARS and H_2O_2: Analysis for thiobarbituric acid reactive substances (TBARS) was performed by following the methodology of Iqbal *et al*. (1996). Concentration of hydrogen peroxide (H_2O_2) was assessed by following the method of Pick and Keisari (1981).

Kidney function markers evaluation: Concentrations of urea, creatinine and creatinine clearance were assessed using laboratory procedures defined by the guide provided in the Randox-standard-laboratory kit (Crumlin Company, Antrim, UK). Urinary KIM-1 and Serum NGAL were assessed by following the manufacturer's command using KIM-1 Quantikine ELISA Kits and NGAL Quantikine ELISA-Kits (R and D Systems company Ltd. Changning, China).

Inflammatory markers assessment: Commercially available kits were used to assess the inflammatory markers of the renal tissues. Tumor necrosis factor-α (TNF-α), Nuclear factor kappa-B (NF-κB), Interleukin-6 (IL-6), Interleukin-1β (IL-1β) levels, cyclooxygenase-2 (COX-2) activity were determined with rat ELISA kit (Shanghai YL Biotech Co. Ltd., China). Analyses were accomplished by following the manufacturer's instructions through Elisa Plate Reader (BioTek, Winooski, VT, USA).

Histopathological assessment: Kidney samples were preserved in 10% formalin buffer solution for the fixation. Tissue specimens were dehydrated through ascending grades of alcohol (80, 90 and 100%), and embedded in paraffin. Thin sections (4-5 mm) of each sample were prepared by using a microtome. Hematoxylin & eosin (H&E) stain was used to stain the sections. Microphotography was conducted through a compound microscope (Nikon-187842, Japan) at 40X.

Statistical evaluation: All experimental data were displayed as Mean±SEM. To check the statistical significance, one-way analysis of variance (ANOVA) followed by Tukey-test was applied for multiple comparisons between treatments by using GraphPad prism 5 software. Level of significance was considered at $P<0.05$.

RESULTS

Effect of CP and ORI on markers of oxidative stress: The activities of antioxidants such as CAT, POD, SOD, GSR and GSH content were significantly ($P<0.05$) reduced in CP administration rats in comparison to control. Furthermore, the activities of antioxidants were improved substantially ($P<0.05$) when rats were co-administrated with CP and ORI when compared with CP intoxicated rats. ORI alone treatment showed normal activity of antioxidant enzymes near to control group (Table 1).

The levels of TBARS and H_2O_2 were significantly ($P<0.05$) increased in CP administered animals as compared to the control. Nevertheless, level of TBARS and H_2O_2 were remarkably decreased when rats were co-treated with CP+ORI as compared to CP treated group. ORI alone treatment maintained the TBARS and H_2O_2 levels near to the control (Table 2).

Table 1: Effects of Orientin on the activity of CAT, SOD, POD, GSR and GSH in the kidneys of CP treated rats.

Groups	CAT (U/mg protein)	POD (U/mg protein)	SOD (nanomole)	GSR (Nm NADPH oxidized/min/mg tissues)	GSH (µM/g tissue)
Control	8.84±0.31[a]	5.53±0.15[a]	7.18±0.09[a]	4.26±0.16[a]	15.20±0.36[a]
CP (10 mg/kg)	5.21±0.26[b]	2.55±0.12[b]	3.56±0.12[b]	2.38±0.19[b]	15.19±0.25[b]
CP (10 mg/kg) + ORI (40 mg/kg)	7.48±0.22[a]	4.92±0.11[a]	6.34±0.19[a]	3.85±0.10[c]	12.34 ±0.21[c]
ORI (40 mg/kg)	8.92±0.20[a]	5.59±0.16[a]	7.07±0.10[a]	4.29±0.11[a]	15.04±0.47[a]

Values in a same column that do not share a superscript are significantly different.

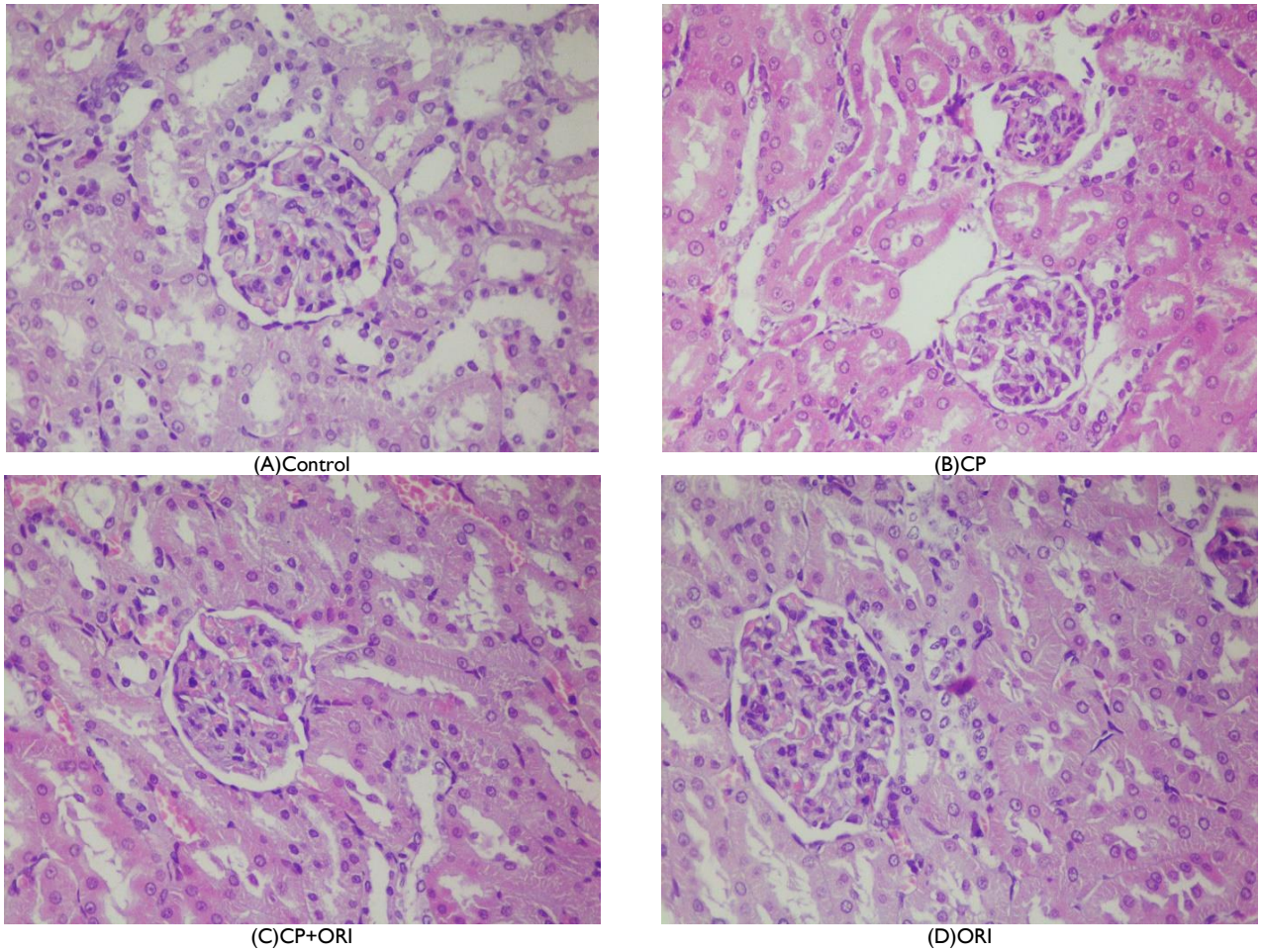

Fig. 1: Histopathological examination of renal tissues (H&E/40X) (A) Kidney section of control group rats, displaying normal histology of glomeruli and renal-tubules. (B) Renal section of CP treated rats, demonstrating tubular necrosis indicated by condensed and pycnotic nuclei of tubular epithelial cells (C) Kidney section of CP+ORI treated rats showing reduced degenerative variations in renal epithelium and granular deposits in their lumens (D) Kidney section of ORI only treated rats displaying normal histological structure of glomeruli and renal tubules.

Table 2: Effects of Orientin on the level of TBARS and H_2O_2 in the kidneys of CP-treated rats.

Groups	H_2O_2 (µM/min/ mg protein)	TBARS (nM/mg tissue)
Control	1.64±0.06[a]	12.09±0.80[a]
CP (10 mg/kg)	4.21±0.17[b]	23.72±0.55[b]
CP (10 mg/kg) + ORI (40 mg/kg)	2.24±0.14[c]	15.69±0.54[c]
ORI (40 mg/kg)	1.73±0.09[a]	12.23±0.81[a]

Values in a same column that do not share a superscript are significantly different.

Effect of CP and ORI on kidney function markers: In the experimental rats, administration of CP resulted in a significant ($P<0.05$) rise in the level of creatinine, urea, KIM-1 and NGAL while reduced the creatinine-clearance as matched with control. Whereas, co-administration of CP with ORI prevented any change in the serum level creatinine, urea, creatinine clearance, KIM-1 and NGAL as compared to CP alone treated rats. When rats were treated with ORI alone, serum values of all these parameters remained near to control group (Table 3).

Effect of CP and ORI on inflammatory markers: CP treatment significantly ($P<0.05$) raised the levels of inflammatory markers, i.e., TNF-α, NF-κB, IL-6, IL-1β and COX-2 activities in contrast to the control group. Whereas the co-treatment of CP with ORI reduced the TNF-α, NF-κB, IL-1β, IL-6 levels and COX-2 activities in cotreated rats in contrast to the CP treated rats. ORI alone treatment maintained the NF-κB, TNF-α, IL-1β, IL-6 levels and COX-2 activities near to the control (Table 4).

Effect of CP and ORI on renal histopathology: Control and ORI treated group showed normal histology of renal tissue. Both groups exhibited normal glomeruli with normal distal and convoluted tubules and Bowman's capsule. Histopathological abnormalities were observed in the CP administered group. The malpighian body showed irregular damaged corticular segments and aggregation of necrotic cells. There was also an inflammatory cell's penetration in corticular and medullary sections, constriction

Table 3: Effects of Orientin on the level of urea, creatinine, creatinine clearance, KIM-1 and NGAL in the kidneys of CP-treated rats

Groups	Urea (mg/dl)	Creatinine (mg/dl)	Creatinine clearance (ml/min)	Urinary KIM-1 (ng/day)	NGAL (mg/ml)
Control	18.22±0.57[a]	1.90±0.05[a]	1.73±0.05[a]	0.27±0.03[a]	0.41±0.04[a]
CP (10 mg/kg)	44.59±2.39[b]	4.86±0.06[b]	0.75±0.06[b]	1.37±0.02[b]	1.63±0.05[b]
CP (10 mg/kg) + ORI (40 mg/kg)	27.88±0.84[a]	2.85±0.05[a]	1.46±0.07[a]	0.69±0.03[c]	0.83±0.07[c]
ORI (40 mg/kg)	18.86±0.81[a]	1.93±0.08[a]	1.70±0.06[a]	0.25±0.03[d]	0.36±0.04[d]

Values in a same column that do not share a superscript are significantly different.

Table 4: Effects of Orientin on inflammatory parameters (TNF-α, NF-κB, IL-1β, IL-6 levels and COX-2 activities) in the kidneys of CP-treated rats

Groups	NF-κB (ng/g tissue)	TNF-α (ng/g tissue)	IL-1β (ng/g tissue)	IL-6 (ng/g tissue)	COX-2 (ng/g tissue)
Control	14.0±0.93 [a]	8.22±0.26 [a]	26.3±0.53 [a]	6.49±0.30 [a]	23.5±0.71 [a]
CP (10 mg/kg)	73.6±1.78 [b]	18.4±0.76 [b]	91.4±2.48 [b]	17.1±0.29 [b]	73.3±2.71 [b]
CP (10 mg/kg) + ORI (40 mg/kg)	21.6±1.08 [c]	9.37±0.44 [c]	42.2±2.03 [c]	7.42±0.18 [a]	31.9±1.46 [c]
ORI (40 mg/kg)	13.9±0.76 [a]	8.05±0.27 [a]	25.3±0.32 [a]	6.08±0.14 [a]	23.9±0.58 [a]

Values in a same column that do not share a superscript are significantly different.

of blood vessels, stretching of tubules, and constriction of Bowman's capsule space. CP and ORI co-administration protected the renal damages with improved glomerular degradation and inflammatory cells infiltration and normal renal tissues like the control group (Fig. 1).

DISCUSSION

In the current study, a remarkable decline was observed in antioxidant enzyme activities, including CAT, POD, SOD, GSR and GSH content. CP administration increased the level of H_2O_2 and TBARS in renal tissues. SOD supports the conversion of O^{-2} into H_2O_2 and oxygen (Jalilov *et al*., 2010). CAT converts the H_2O_2 into H_2O and O_2 and shields the cells from the oxidative damage caused by H_2O_2 and OH^- (Smirnoff and Arnaud, 2019). CP produces ROS, containing hydroxyl radicals (OH^-) and superoxide anion (O_{2-}), and triggers lipid peroxidation (Rehman *et al*., 2020). Earlier studies have shown that increased MDA and reduced antioxidant levels are potential indicator of renal oxidative damage (Ma *et al*., 2017). Our findings revealed that CP induced renal damage by increasing the levels of H_2O_2 and TBARS and reducing the GSH content and the activities of antioxidant enzymes in the kidney of CP intoxicated rats. ORI improves the damage by bringing the activities of antioxidant enzymes at normal levels. This may be attributed to antioxidant potential of ORI.

The results of present study revealed that CP intoxication increased the urea and creatinine levels, while reduced the creatinine clearance in the kidney of CP treated rats. Oh *et al*. (2014) demonstrated that CP accumulates in the kidney and reduces the glomerular filtration rate (GFR) by decreasing the creatinine clearance and increasing the creatinine and urea levels. The use of creatinine and urea as a marker to determine renal function is justified because their plasma/serum levels reflect GFR. Renal disease is connected with decrease in GFR, and the intensity of renal disease relates significantly but adversely with GFR (Higgins, 2016). These abnormalities cause renal damage that results in renal failure. However, ORI administration normalized the concentration of these markers by diminishing ROS production and reduced renal injuries which may be attributed towards its antioxidant potential.

CP administration raised the KIM-1 and NGAL levels in treated rats. KIM-1 and NGAL are the biomarkers of acute kidney injury (AKI). KIM-1 is a transmembrane protein and initial diagnosis marker of AKI. In the healthy renal tissue, it is not expressed; however, its presence can be detected during the early stages of nephrotoxicity at lower to higher levels (Song *et al*., 2019). NGAL normally discharges into the blood in greater extents after damage and it gets eliminates through the urine (Khawaja *et al*., 2019). CP is a cytotoxic agent which may disrupt the integrity of renal cells, that leads to increased levels of KIM-1 and NGAL. ORI treatment decreased the KIM-1 and NGAL levels in cotreated rats, which confirmed that ORI treatment recovered the renal injuries.

In this study, CP administration increased the NF-κB, TNF-α, IL-6, IL-1β levels and COX-2 activity. NF-κB stimulation is fundamental in the expression of pro-inflammatory cytokines like NF-κB, IL-1β, TNF-α, IL-6 and COX-2 that are linked with acute inflammatory responses and other ROS related disorders (Kandemir *et al*., 2018). NF-kB activation leads to increased secretion of TNF-α, IL-6, IL-1β through gene upregulation, which contributes to acute kidney injury (Kandemir *et al*., 2018). COX-2 is an additional critical inflammation marker, which plays an important biological role in inflammation (Gandhi *et al*., 2017). In this analysis, the activity of COX-2 was escalated in CP treated renal tissues which indicates the inflammatory responses in CP treated rats. ORI treated rats showed decreased levels of NF-κB, IL-1β, TNF-α, IL-6, and COX-2 activities. This normalization may be attributed to the anti-inflammatory potential of ORI. These results substantiate the anti-inflammatory role of ORI in renal tissues.

Renal histopathology showed that CP induced tubular dilation and focal epithelial cell destruction throughout restricted areas in the cortex. At the same time, in the outer medulla, it provoked chronic and pronounced decline in epithelial cells. Capillaries interacted with tubules were dilated and dilation of tubules was also observed in the inner medulla. Elevated levels of KIM-1 and NGAL in CP treated rats also endorse the histopathological damages. The patho-physiology of CP induced acute kidney injury includes proximal tubule damage, oxidative stress, vascular injury and inflammation in the kidney (Ozkok and Edelstein, 2014). However, ORI protected the renal tissues and tubules from abnormalities in the cotreated group. This potential of ORI may be credited to its anti-inflammatory and antioxidant properties which eventually attenuated the renal tissue damages.

Conclusions: The current study showed the renoprotective capability of ORI against CP induced renal damage. The

results showed that ORI revealed a remarkable protective role against oxidative stress and inflammation, which are a principal representative of CP-induced renal damage. ORI administration effectively prevented the disturbance in the level of antioxidants, renal damage markers, inflammatory markers, and histopathological damages. This renoprotective ability of ORI may be linked to its antioxidant and anti-inflammatory abilities.

Authors contribution: MUI, SA and MI designed and performed the study. MF, SN and TR Interpreted the results. KA and AA helped in statistical analysis. MUI, SA and HN wrote the manuscript. All authors approved the final version of manuscript.

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