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Research Article

Protective Role of Icariin Against Oxidative Renal Damage in Cisplatin Induced Nephrotoxicity

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ABSTRACT

Icariin (ICA), a flavonol glycoside derived from several species of plants belonging to genus Epimedium, family berberidaeceae. It is well known for its antioxidant properties. Its antioxidant potential against cisplatin induced nephrotoxicity is not yet reported. The present study is hypothesized and proposed to evaluate the antioxidant potential of ICA against cisplatin induced nephrotoxicity. Male Wistar rats were divided into five groups of eight each. Group I served as control; Group II received single intraperitoneal injection of 7 mg/kg body weight of Cisplatin; Group III received Cisplatin and ICA (50 mg/kg/p.o); Group IV received Cisplatin and ICA (100 mg/kg/p.o); Group V received ICA (100 mg/kg/p.o) alone. Cisplatin administration significantly altered the levels of renal function markers in the serum such as serum Creatinine (SCr), blood urea nitrogen (BUN), which were significantly restored with ICA treatment. Increase in urinary total protein (U_{TP}), urinary clearance (U_{Cr}) and kidney lipid peroxides (MDA) along with concomitant reduced levels of antioxidant enzymes, were also reversed upon ICA treatment. ICA protective effect was confirmed with histopathological studies. These results clearly demonstrate that the antioxidant effect of ICA might contribute to its nephroprotective effect against Cisplatin.

Key words: Cisplatin, Nephrotoxicity, Icariin, Nephroprotection, Antioxidant potential

INTRODUCTION

Cisplatin is widely used antineoplastic drug, effective for a large number of tumors. Indeed, nephrotoxicity has limited the clinical use of cisplatin[1]. The cisplatin induced nephrotoxicty involves a complex cascade such as oxidative stress, inflammation and apoptosis of renal cells as it is accumulated in the renal cells than other organs[2,3]. Nephrotoxicity is characterized by alterations in urine and renal functions by depleting antioxidant defense system[4,5]. Oxidative stress has been implicated as key pathogenic mechanism causing renal apoptosis and its prevention would reduce the morbidity and improve the therapeutic outcome of cisplatin[6,7]. Current research has been focused on the development of plant derived compounds with antioxidant potential against cisplatin induced nephrotoxicity[8].

Icariin (ICA), a compound derived from plant genus epimedium, family berberidaeceae. It has been shown to be effective in inflammation[9], osteoporosis[10], neurotoxicity[11], oxidative stress[10], depression[12], rheumatoid arthritis[13] and erectile dysfunction[14]. However, its antioxidant potential against cisplatin induced nephrotoxicity is not yet reported. Hence, the present study was designed to evaluate the nephroprotective activity of ICA against cisplatin induced nephrotoxicity.

MATERIALS AND METHODS

Chemicals

Icariin (ICA) was obtained from SV Agro Foods Private Limited, Mumbai, India. Cisplatin was purchased from Sigma Chemicals, India. Blood urea nitrogen and Creatinine kits were purchased from Span diagnostics, India. All other chemicals were of analytical grade.

Animals

Male Albino rats weighing 160-180 g (about 6-8 weeks old) were used. The animals were housed 5 per cage (440 mm × 270 mm × 178 mm) under controlled conditions of light (12h light / dark cycle, lights on at 7:00 AM), temperature (22 ± 2 ^{0}C) and humidity 50–60% with free access to food and water. The animals were acclimatized to the laboratory for at least 7 days. All the experiments were carried out according to the committee for the purpose of control and supervision of experiments on animals (CPCSEA), Government of India and approval was obtained from Institutional Animal Ethical Committee No.1677/PO/a/12/CPCSEA/16.

Experimentation

After acclimatization, the rats were randomly divided into five groups of eight animals in each group. The experimental design is as follows

- Normal Control (N): Rats received water as a vehicle.
- Cisplatin control (Cis): Rats received a single dose of cisplatin (7 mg/kg) intraperitoneally on 1st day.
- Icariin control (ICA-100): Rats received ICA (100 mg/kg) alone orally by gavage once daily for 15 days
- Icariin (50 mg/kg)+ Cisplatin (Cis+ICA-50): Rats received a single dose of cisplatin (7 mg/kg/i.p) on 1st

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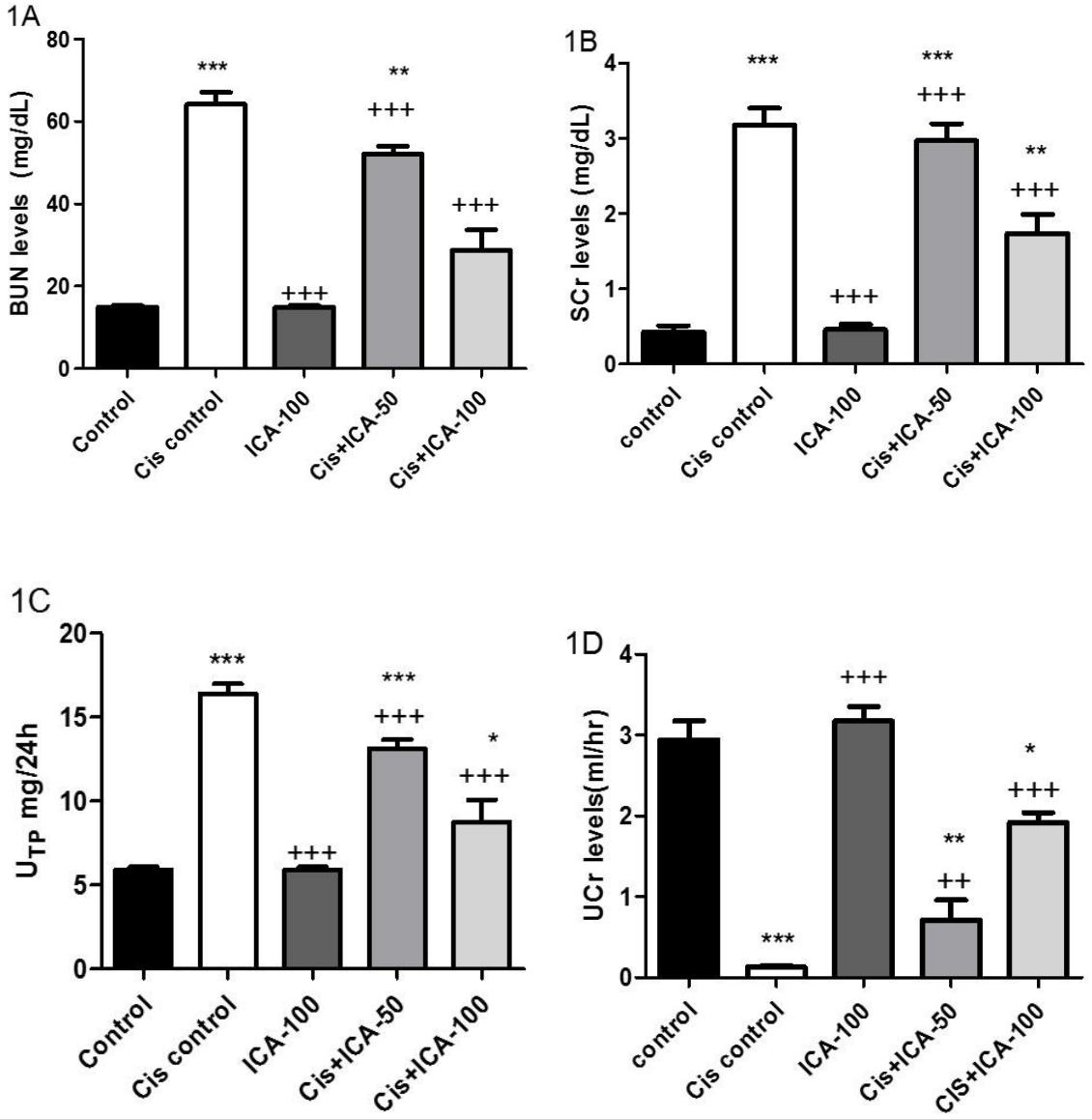

Figure 1. Effect of ICA on (A) BUN levels (B) SCr levels (C) U_{TP} levels (D) UCr levels. Values are expressed as mean±SEM (n=6). Analyzed by one-way ANOVA followed by post hoc Dunnetts test. *(p<0.05), **(p<0.01), ***(p<0.001) *vs.* control group. +(p<0.05), ++(p<0.01), +++(p<0.001) *vs.* Cis control group.

- day and ICA (50 mg/kg/p.o) from 5th day onwards for 10 days.
- Icariin (100 mg/kg) + Cisplatin (Cis+ICA-100): Rats received a single dose of cisplatin (7 mg/kg/i.p) on 1st day and ICA (100 mg/kg/p.o) from 5th day onwards for 10 days.

Sampling and biochemical analysis

On 15th day, blood samples were collected from retro-orbital plexus, serum was separated by centrifugation at 4000 rpm for 15 min and used for assessment of BUN and SCr. The animals were placed in metabolic cages for urine collection. Urine was centrifuged at 3000 rpm for 30 min and supernatant was used for the measurement of urinary total protein (U_{TP}) and Urinary Creatinine (UCr). After the collection of urine, rats were sacrificed by cervical decapitation and kidney tissue was obtained for biochemical and histological studies. A 10% homogenate of kidney tissue was prepared in phosphate buffer.

Assessment of renal functions

The development of nephrotoxicity was assessed in rats using commercially available kits (Span diagnostics Ltd, India) on day 5 and 10 of cisplatin administration by measuring serum Creatinine (SCr), serum blood urea nitrogen (BUN), urinary total protein (U_{TP}), urinary Creatinine (UCr).

Assessment of renal oxidative stress

Measurement of protein concentration in kidney homogenate

Protein was determined according to the method of Lowry et al.[15] using bovine serum albumin (BSA) as standard protein.

Determination of GSH level in kidney homogenate

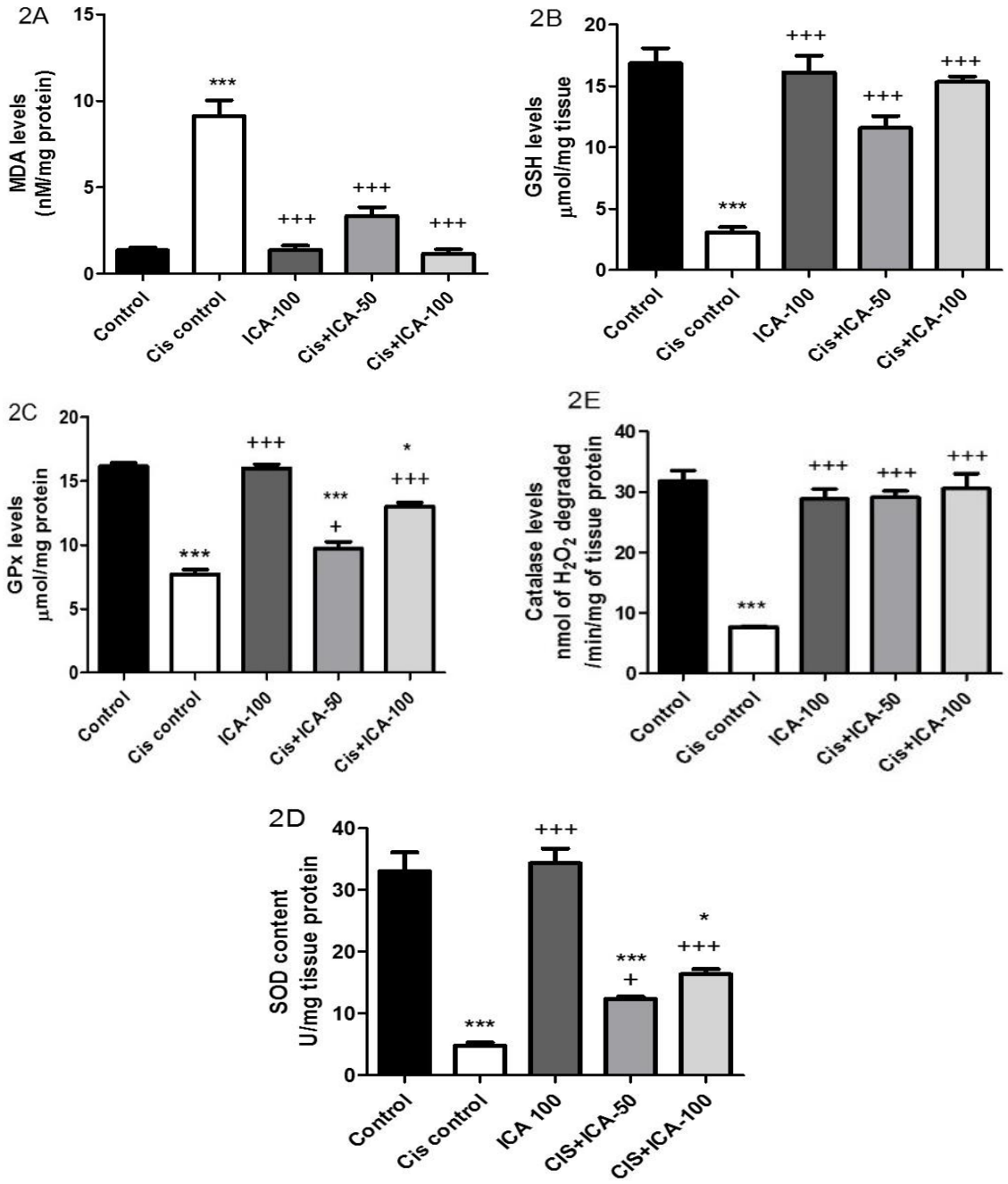

Figure 2. Effect of ICA on (A) MDA levels (B) GSH levels (C) GPx levels (D) catalase levels (E) SOD content. Values are expressed as mean±SEM (n=6). Analyzed by one-way ANOVA followed by post hoc Dunnetts test. *(p<0.05), **(p<0.01), ***(p<0.001) *vs.* control group. +(p<0.05), ++(p<0.01), +++(p<0.001) *vs.* Cis control group.

Reduced glutathione content was measured according to the method of Ellman[16]. Briefly, 0.75 ml of supernatant was mixed with 0.75 ml of 4% sulphosalicylic acid and then centrifuged at 1,200 rpm for 5 min at 4^0C. From this 0.5 ml of supernatant was taken and added to 4.5 ml of 0.01 M DTNB (5′,5′dithiobis 2- nitrobenzoic acid), and the yellow color developed was read Spectrophometrically at 412 nm immediately. The GSH content was calculated as µmol GSH/mg protein.

Measurement of MDA level in kidney homogenate

Malondialdehyde (MDA) formation was estimated by the method of Ohkawa et al.[17]. Briefly, 200 µl of supernatant was added to 50 µl of 8.1% sodium dodecyl sulphate, vortexed and incubated for 10 min at room temperature. 375 µl of thiobarbituric acid (0.6%) was added and placed in a boiling water bath for 60 min and then the samples were allowed to cool at room temperature. A mixture of 1.25 ml of butanol: pyridine (1.5: 1 ratio), was added, vortexed and centrifuged at 1000 rpm for 5 min. The optical density of the colored layer was measured at 532 nm on a Spectrophotometer against reference blank and the rate of MDA formed is expressed as nmol/mg protein.

Determination of GPx level in kidney homogenate

GPx was measured according to the method previously

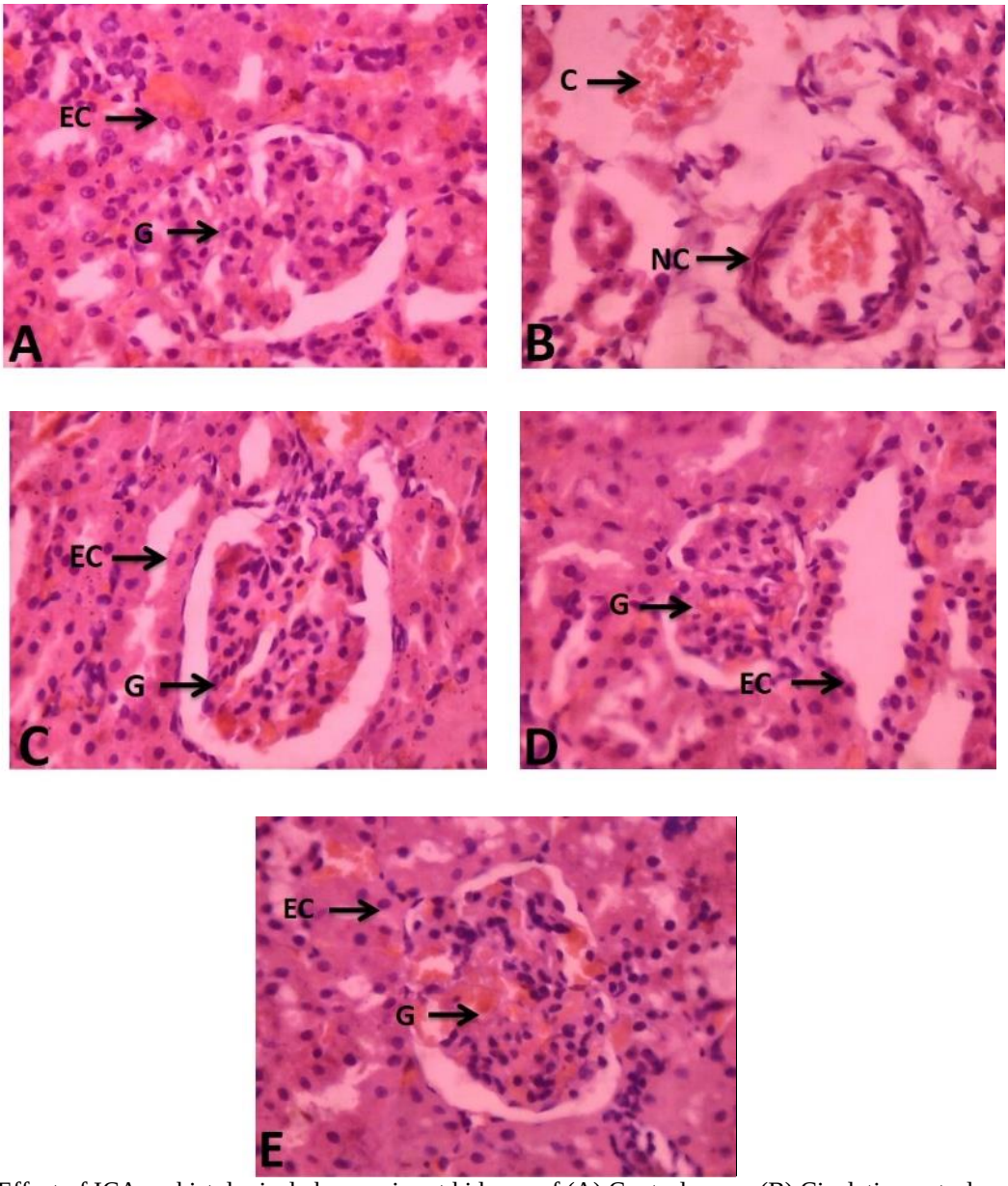

Figure 3. Effect of ICA on histological changes in rat kidneys of (A) Control group (B) Cisplatin control group (C) ICA control group (D) Cis+ICA-50 mg/kg treated group (E) Cis+ICA-100 mg/kg treated group.

described with minor modifications[18]. Briefly, 5 µl of brain supernatant was mixed with 10 µl of each of 5 mM EDTA, 10 mM sodium azide, 10 mM GSH, 0.2 mM hydrogen peroxide (H_2O_2) and 20 µl of phosphate buffer. The reaction mixture was incubated at 37^0C for 10 min and 10% TCA was added to the mixture. The mixture was subjected to centrifugation at 1400×g for 10 min, the supernatant was collected and mixed with 150 µl of 0.01M dihydrogen phosphate and 50 µl 0.04% DTNB. The absorbance was measured at 412 nm. GPx is expressed as µmol/mg protein.

Determination of catalase activity in kidney homogenate

Catalase activity was measured by a slightly modified version of Aebi[19]. Briefly, 100 µl of brain supernatant was added to 10 µl of 100% ethanol and placed in ice bath for 30 min. The tubes were allowed to attain room temperature followed by the addition of 10 µl of Triton X-100. To 50 µl of mixture, 200 µl of phosphate buffer (pH 7.0) and 250 µl of 0.066 M H_2O_2 (hydrogen peroxide) in phosphate buffer was added. The decrease in optical density was measured at 240 nm for 60 sec in UV Spectrophotometer. The molar extinction coefficient of 43.6 Mcm^{-1} was used to determine catalase activity which is equal to the moles of H_2O_2 degraded/mg protein/min.

Determination of SOD activity in kidney homogenate

SOD activity was measured according to the method of Misra and Fridovich[20] by monitoring the autooxidation of (-) – epinephrine at pH 10.4 for 4 min at 480 nm. Briefly, 100 µl of brain supernatant was added to 880 µl of 0.05 M carbonate buffer containing 0.1 mM EDTA (disodium edetate) (pH 10.4), and to this mixture, 20 µl of 30 mM epinephrine (in 0.05% acetic acid) was added and the optical density values were measured at 480 nm for 4 min on a UV-Visible Spectrophotometer, activity is expressed as the amount of enzyme that inhibits the oxidation of

epinephrine by 50% which is equal to 1 unit. The SOD activity is expressed as U/mg protein.

Histological examination

The kidney tissue was isolated, fixed in 10% neutral buffered formalin and subsequently embedded in paraffin and sliced into slices of 5 µm thickness followed by staining with hematoxylin and eosin.

Statistical analysis

Data was expressed as mean± standard error of the mean (S.E.M.). Statistical difference was analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's test using GraphPad Prism version 5 software (GraphPad Software, Inc. La Jolla, CA, USA). A value of $p<0.05$ is considered as statistically significant.

RESULTS

Effect of ICA on renal functions

To assess the renal function, parameters such as BUN, SCr, U_{TP}, UCr were estimated in all the groups. Cisplatin administration significantly ($p< 0.001$) increased BUN, SCr, U_{TP} as well as UCr levels in cisplatin control group compared to normal control group. Treatment with ICA at a doses of 50 and 100 mg/kg for 10 days significantly ($p<0.001$) attenuated the increased levels of BUN, SCr, U_{TP}, UCr as compared to cisplatin control group. No significant statistical difference was observed in the levels of BUN, SCr, U_{TP}, UCr between normal and ICA control groups (Figure 1).

Effect of ICA on kidney MDA levels

Cisplatin administration significantly increased ($p<0.001$) the levels of MDA in kidney tissues of cisplatin control group, indicating development of oxidative stress. However, ICA (50 and 100 mg/kg) treated groups showed significant ($p<0.001$) reversal in the levels of MDA as compared with cisplatin control group (Figure 2A). But, no significant change in MDA levels was observed in ICA alone treated groups when compared with normal control group indicating that ICA is effective only in presence of oxidative stress.

Effect of ICA on kidney GSH levels

An endogenous antioxidant GSH levels were significantly decreased ($p<0.01$) after cisplatin administration as observed in cisplatin control group when compared with normal control group, which was significantly improved ($p<0.001$) in ICA treated groups when compared with cisplatin control group (Figure 2B). No significant difference in GSH levels was observed in rats treated with ICA alone.

Effect of ICA on kidney GPx levels

Cisplatin administration significantly decreased ($p<0.001$) the levels of GPx in cisplatin control group compared with normal control group. ICA treated groups showed significant increment ($p<0.001$) in the decreased levels of GPx when compared with cisplatin control group (Figure 2C). However, no significant change in GPx levels was observed in ICA alone treated group.

Effect of ICA on kidney catalase levels

Renal catalase levels are significantly decreased after cisplatin administration ($p<0.001$) in cisplatin control group compared with normal control, in which the decreased catalase levels is restored significantly ($p<0.001$) upon treatment with ICA when compared with cisplatin control group (Figure 2D). But, ICA alone treated group showed no significant change in these catalase levels.

Effect of ICA on kidney SOD levels

Cisplatin control group showed significantly decreased ($p<0.001$) levels of SOD as compared with normal control group indicating the depletion of antioxidant defense system after cisplatin administration (Figure 2E). Interestingly, ICA treated groups showed significant increment ($p<0.001$) in SOD levels as compared with cisplatin control group. However, ICA alone treated group showed no significant change in SOD levels.

Histological studies

Kidney sections from normal and ICA control group showed normal glomerulus and tubule with regular morphology. Cisplatin control group showed degenerative glomeruli, interstitial hemorrhages, enlarged renal tubule with hemorrhages, congestion and vacuolization of renal tubule indicating renal toxicity. ICA (50 and 100 mg/kg) treat group showed normal kidney morphology with less vacuolation, reduced glomeruli congestion with regenerated tissue indicating the protective effect of ICA against cisplatin induced renal damage (Figure 3).

DISCUSSION

Nephrotoxicity is the dose limiting complication which limited the clinical use of cisplatin, a major chemotherapeutic drug of choice for wide range of tumors[21]. Oxidative stress is recognized as a key pathogenic mechanism of cisplatin induced nephrotoxicity and its prevention is an important therapeutic approach[22-25]. ICA is a natural flavonoid and is well known for its antioxidant potential. Hence the present study proposed to demonstrate the protective effect of ICA against oxidative stress in cisplatin induced nephrotoxicity. ICA attenuated the renal damage as evident from restored BUN, SCr, U_{TP}, UCr, morphological changes as well as redox status.

Renal damage is indicated by marked increase in BUN, SCr, U_{TP}, UCr[26,27,21]. In congruent with this, we observed significant increment in BUN, SCr, U_{TP}, UCr, levels after cisplatin administration in cisplatin control group indicating the development of renal tissue damage by cisplatin. These results are confirmed with histological examination where pathological changes of degenerated glomeruli, hemorrhages, vacuolation were observed in kidney tissue. ICA treatment attenuated cisplatin induced nephrotoxicity as evidenced by attenuation of increased BUN, serum creatinine, urinary creatinine, urinary total protein and kidney/body weight ratio as well.

Accumulating evidence suggested that there is robust production of reactive oxygen species (ROS) after cisplatin administration[28-30]. The ROS such as superoxide, hydroxyl radicals and nitric oxide accumulated in the renal tissue overwhelms the antioxidant dense mechanism, thus lead to oxidative stress (oxidant/antioxidant balance). Oxidative stress has been implicated as critical pathogenic mechanism in cisplatin induced nephrotoxicty[31,32,21]. The renal content of peroxynitrite and nitric oxide is increased

in cisplatin treated rats[33]. Free radicals damage the lipid components of the cell membrane by peroxidation and denaturation of proteins, which lead to enzymatic inactivation.

Antioxidant enzymes are inhibited by cisplatin and renal activities of superoxide dismutase, glutathione peroxidase and catalase are significantly decreased[34,35]. LPO are generated naturally in small amounts in the body mainly by the effect of several ROS i.e., hydroxyl radical and hydrogen peroxide. An increase in the concentration of end products of LPO is the evidence for the involvement of free radicals in human disease[36]. After cisplatin treatment, decreased level of protein, succinate dehydrogenase activity, and increased level of lipid peroxides were noted in kidney. In this study, cisplatin-induced animals showed increased LPO level in kidney comparable to the control and icariin control animals. Icariin significantly reduced the kidney LPO levels and counteracted the formation of free radicals induced by cisplatin-mediated nephrotoxicity, indicating its protective role in the prevention of renal damage. GSH is an important antioxidant tripeptide in the cells, preventing damage to important cellular components caused by ROS[37]. GSH detoxifies many endogenous toxins, including cisplatin, through the formation of GSH adducts to protect cells from the potential nephrotoxicity[38]. In this study, ICA with graded doses (50mg/kg & 100mg/kg) prevented renal damage by significant increase in the kidney GSH level which effectively protects renal cells from the exposure to free radicals and peroxidase induced by cisplatin.

CAT is a common enzyme that catalyzes the decomposition of hydrogen peroxide to water and oxygen[33]. CAT is highly effective in inhibiting various ROS-mediated injuries and could protect the kidney from cisplatin induced nephrotoxicity. Icariin (50mg/kg & 100mg/kg) significantly restored the kidney tissue CAT level that shows its anti-oxidant activity during nephrotoxicity. Superoxide is converted to a far less reactive product, hydrogen peroxide by a family of metalloenzymes known as SOD which constitute a front line of defense against ROS-mediated injury[39].The cisplatin-induced animals showed a decrease in tissue SOD levels, which may be due to the depletion of copper and zinc in the kidney which are essential for the activity of SOD. The levels of superoxide were significantly improved in ICA (50mg/kg & 100mg/kg) treated animals. Glutathione peroxidase (GPx) protect cells from oxidative damage. The biochemical function of GPx is to reduce lipid hydroperoxides to their corresponding alcohols and to reduce free hydrogen peroxide to water. Cisplatin alone treated animals showed marked decrease in GPx levels, whereas, animals treated with icariin (50mg/kg & 100mg/kg) has reverted the change of cisplatin by restoring GPx levels.

In conclusion, ICA, a natural flavonoid found in Epimedium reduced cisplatin-induced functional and histological renal damage. Furthermore, it attenuated cisplatin induced oxidative stress as evident by attenuation of cisplatin induced changes in MDA, SOD, GSH, GPx and catalase levels. These results indicate the protective effect of ICA on cisplatin induced renal injury and may be used as an adjunct with cisplatin therapy to maintain normal kidney function.

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