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Protective effects of pretreatment or concomitant treatment with *Hypericum* extract on renal function and renal toxicity in cisplatin-induced nephrotoxicity

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ABSTRACT

Introduction: Cisplatin is a strong anticancer medicine, but its use is limited due to the potential nephrotoxicity induction.
Objectives: The present study seeks to determine the impact of *Hypericum* hydroalcoholic extract on cisplatin-induced nephrotoxicity.
Materials and Methods: Thirty-two male rats were assigned to groups 1 to 4. Group 1, control (Cont); treated by saline (IP). Group 2, Cis; cisplatin [intraperitoneal (IP), 7.5 mg/kg]. Group 3, CisH; cisplatin + *Hypericum* (70 mg/kg, IP, for one week). Group 4, HCis; first treated with *Hypericum* for a week, followed by cisplatin. Renal tissue and blood samples were obtained a week after cisplatin injection for tissue assay and biochemical analysis. Kidney tissue damage score (KTDS), plasma creatinine (Cr), blood urea nitrogen (BUN), serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) were measured.
Results: Kidney weight showed significant differences between the treated groups and the Cont group ($P<0.001$). Serum BUN, Cr, SGOT, and SGPT increased significantly in Cont ($P<0.01$). BUN decreased in CisH and HCis groups compared to Cis group, although there was no significant difference. Serum Cr, SGOT, and SGPT decreased significantly in CisH and HCis groups compared to the Cis group ($P<0.05$). MDA and KTDS increased in the Cis group and decreased significantly in the CisH and HCis groups compared to the Cis group ($P<0.05$). Serum SOD and CAT decreased significantly in Cis compared to Cont ($P<0.05$) and increased in CisH and HCis groups compared to Cis. There was no significant difference between the CisH and HCis groups in any of the measured parameters.
Conclusion: This study reveals that pretreatment with *Hypericum* extract or its concomitant administration with cisplatin can moderate the side-effects of cisplatin, improve renal function and decrease lipid peroxidation, renal toxicity and the KTDS.

Implication for health policy/practice/research/medical education:
In the current study, 32 male rats were assigned to four groups to determine the impacts of *Hypericum* hydroalcoholic extract on cisplatin-induced nephrotoxicity. This study reveals that pretreatment with Hypericum extract or its concomitant administration with cisplatin can moderate the side effects of cisplatin, improve renal function and decrease lipid peroxidation, and also renal toxicity.

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Original

Introduction

Cisplatin (cis-diamminedichloroplatinum II) is a strong anticancer medicine that is administered as a therapy for a spectrum of solid tumors, including in the testicles, bladder, ovary, lungs, head and neck (1). Cisplatin mainly accumulates in the renal proximal tubule cells and causes renal failure in 20%-30% of the patients (2). Clinically, the grade of cisplatin-induced nephrotoxicity depends on the administered dose. Cases treated with a single dose of cisplatin might experience reversible renal injury, while treatment with large doses or numerous courses may lead to irreversible alterations (3). Based on a pharmacokinetic study, cisplatin-induced nephrotoxicity mostly occurs because of an increase in cisplatin distribution and its longtime aggregation in the kidneys (4).

The mechanisms of induction of nephrotoxicity as the main restricting cause of cisplatin utilization are still not entirely understood, although studies have revealed the main pathways involved to include oxidative stress, apoptosis, inflammation, and autophagy (3,5). A large number of studies have confirmed the detrimental role of reactive oxygen species (ROS) as well. Cisplatin stimulates the production of ROS such as hydroxyl radical and superoxide anion (1,6) and causes the inactivation of glutathione, augments lipid peroxidation and protein oxidation, and also inhibits the activities of antioxidant enzymes (7).

Previous studies have shown that malondialdehyde (MDA) levels are increased in cisplatin-induced nephrotoxicity. MDA is produced by fatty acid peroxidation and helps indicating the oxidative stress in the renal cells (8). In contrast, antioxidant enzymes are a leading category in protecting against ROS. Cisplatin can weaken the renal antioxidant defense system by reducing glutathione levels and antioxidant enzyme functions in the renal tissue, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Antioxidants have also been shown to protect against cisplatin-induced nephrotoxicity (8).

Herbal medicines or active herbal substances have been extensively used for combating health problems. Numerous natural antioxidants and radical scavengers have been proposed for reducing cisplatin-induced nephrotoxicity, such as breviscapine, berberine, resveratrol, *Apodytes dimidiata*, and *Nigella sativa* oil (3). Sunny Hypericum (Zagros Hypericum, scientific name: Hypericum helianthoides) is a herbaceous perennial herb found in Ilam province, Iran. *Hypericum* contains compounds such as phenolic acids (chlorogenic acid) and phloroglucinol (hyperforin, adhyperforin) (9). Numerous experiments have confirmed different biological functions for the members of this genus, including cytotoxic, antioxidant, anti-inflammatory, anti-ulcer, analgesic, antiproliferative, antimicrobial, and antiviral effects as well as antitumor, antiangiogenic, and immunomodulatory activities (10,11). Hypericum reportedly contains five predominant flavonoids, including taxfolin-7-O-α-l-rhamnoside, isoquercitrin, quercitrin, quercetin-7-O-α-l-rhamnoside and quercetin (12).

Objectives

This study was conducted to investigate and determine the antioxidant and protective effects of Hypericum extract on cisplatin-induced nephrotoxicity and assess kidney function under these conditions.

Materials and Methods

Animals

For this experimental study, 32 male Wistar rats (weighing 200 ± 5 g) were procured from the animal house of Ilam university of medical sciences, Ilam, Iran. The rats were kept in a controlled room (temperature: 23 ± 1°C, light-dark cycles: 12 hours, and humidity: 50%). The animals were fed by a standard rodent chow diet with free access to tap water.

Experimental groups

The animals were randomly assigned to four groups (n=8 per group) as follows:

- Group 1 (Cont): These rats were taken as the control group and treated by saline via intraperitoneal (IP) injection.
- Group 2 (Cis): These rats were treated with a single dose of cisplatin (7.5 mg/kg) via IP injection.
- Group 3 (CisH): These rats were treated with a single dose of cisplatin (7.5 mg/kg) + *Hypericum* (70 mg/kg) via IP for a week.
- Group 4 (HCis): The rats in this group were first treated with *Hypericum* (70 mg/kg), IP, for a week, followed by a single dose of cisplatin (7.5 mg/kg).

Extract preparation

Hypericum was picked up from the Zagros Mountains, Iran. First, the dried herbal samples were grinded to a powder. Then, 20 g of the powder was used for preparing the extract. Powder degreasing was performed with hexane and the Soxhlet extraction procedure was carried out with a water-methanol solvent. Finally, the solvent was eliminated through rotation (ILK HB 10) and the derived extract (1.88 g with a yield of 9.40%) was lyophilized and stored at -20°C.

Induction of nephrotoxicity

In order to induce nephrotoxicity, the rats were injected a single dose of cisplatin 7.5 mg/kg, IP, and they were allowed one week to develop nephrotoxicity.

Blood sampling and serum preparation

A week after cisplatin injection, the animals were anesthetized (by ketamine and xylazine, based on their weight) and blood samples were collected from their heart, and the plasma was then separated by centrifugation (at

3000 rpm for 15 minutes) and stored at −20°C to measure the biochemical parameters.

Histopathological examination

For the histological examination, the kidneys were removed and immediately weighed and placed in phosphate-buffered formalin (10%), then kept at room temperature. After dehydration in ethanol (70%-100%), the tissue samples were cleared in xylene and embedded in paraffin. The 3-µm thick paraffin-embedded tissue sections were prepared and stained via the hematoxylin-eosin (H&E) method. All samples were interpreted blindly, as the pathologist was unaware of the administered treatment. The pathologist determined the rats' kidney tissue damage score (KTDS) on a scale of 0 to 4, based on the intensity renal damages (hyaline cast, debris, vacuolization, flattening and degeneration of tubular cells, and dilatation of tubular lumen); zero was assigned to the normal tubules without damage.

Renal function laboratory tests

In order to determine renal function and monitor the liver enzyme levels, serum creatinine (Cr), blood urea nitrogen (BUN), serum glutamate oxaloacetate transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) levels were measured by kits according to their manufacturer's instructions using an auto-analyzer (the BUN, Cr, SGOT, and SGPT laboratory kits were purchased from Pars Azmoon Co., Tehran, Iran).

Determining the MDA and antioxidant enzyme activity in the kidneys

In order to measure lipid peroxidation (MDA) and antioxidant enzyme activity in the kidneys, the kidney tissues were removed immediately after killing the rats on the final day of the examination. Then, 100 mg of the renal tissues were homogenized in cold phosphate buffered saline (PBS), and after centrifugation, the supernatants were collected and consumed for the measurements. SOD and CAT activities were determined by colorimetry at 420- and 412-nm wavelengths, respectively, based on the manufacturer's instructions (Navand Salamat Biotechnology Co., Iran).

Statistical analysis

Data were presented as mean ± SEM and analyzed by one-way ANOVA and Tukey post hoc tests using SPSS software version 22. The results were considered significant if $P < 0.05$.

Results

Kidney weight per body weight showed a significant difference between the treatment groups and the control group ($P < 0.001$), as shown in Figure 1.

Serum BUN and Cr

As demonstrated in Figure 2, significant differences were also observed in BUN between the groups ($P = 0.001$). BUN increased significantly in group 2 (Cis) compared to Cont ($P < 0.01$). Meanwhile, BUN decreased in CisH and HCis groups compared to Cis, although not significantly. No significant difference was observed in BUN between CisH and HCis groups. Figure 3 reveals significant differences in Cr between the groups ($P = 0.001$). Serum Cr increased significantly in group 2 (Cis) compared to Cont ($P < 0.01$). Nonetheless, Cr decreased significantly in CisH and HCis groups compared to Cis ($P < 0.007$ and 0.02, respectively). Meanwhile, no significant difference in Cr was observed between CisH and HCis groups.

Serum SGOT and SGPT

According to Figures 4 and 5, significant differences in SGOT and SGPT were observed between the groups ($P < 0.01$). SGOT and SGPT levels increased significantly in Cis compared to Cont ($P < 0.001$ and $P < 0.003$). Meanwhile, SGOT and SGPT levels decreased significantly

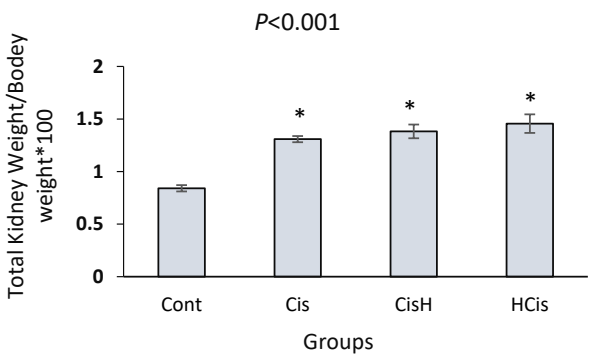

Figure 1. Total kidney weight/body weight*100. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin + *Hypericum*, HCis: first treated with *Hypericum* for a week and after that cisplatin. * is equal to significant difference with Cont group.

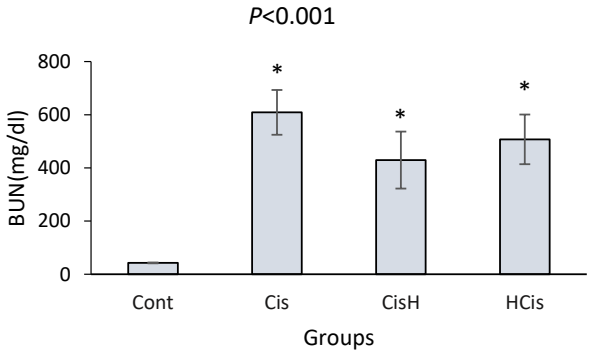

Figure 2. BUN. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin+Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. * is equal to significant difference with Cont group.

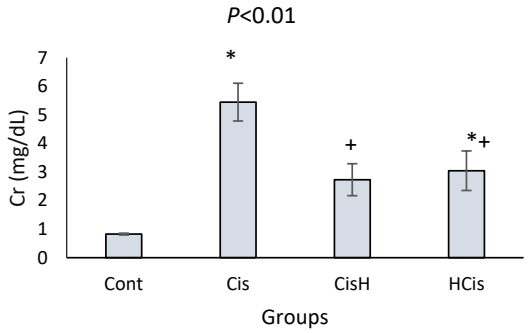

Figure 3. Creatinine. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin + Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. * is equal to significant difference with Cont group. + is equal to significant difference with Cis group..

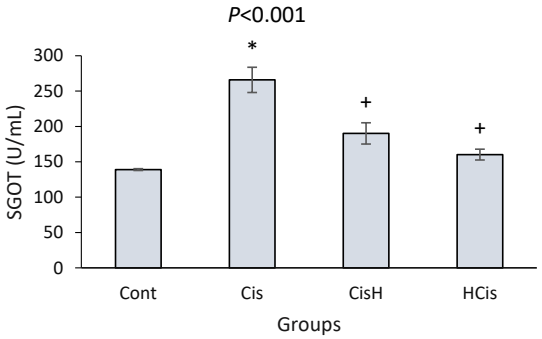

Figure 4. SGOT. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin + Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. * is equal to significant difference with Cont group. + is equal to significant difference with Cis group.

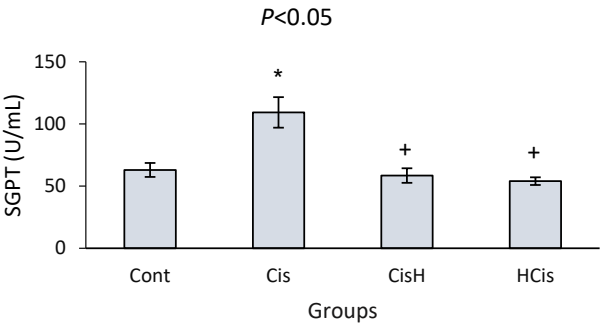

Figure 5. SGPT, Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin+Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. * is equal to significant difference with Cont group. + is equal to significant difference with Cis group..

in CisH and HCis groups compared to Cis ($P<0.01$). There was no significant difference in SGOT and SGPT levels between CisH and HCis groups.

Kidney tissue damage score and serum MDA

Figure 6 presents the tissue samples. There were significant differences between the groups in KTDS ($P<0.05$) and

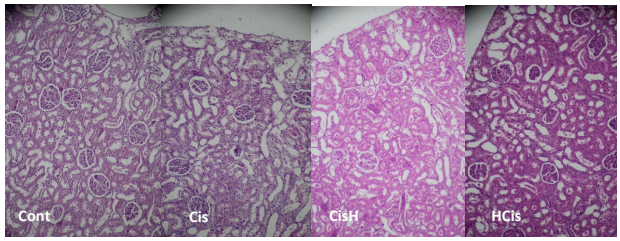

Figure 6. Kidney tissue. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin+ Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin.

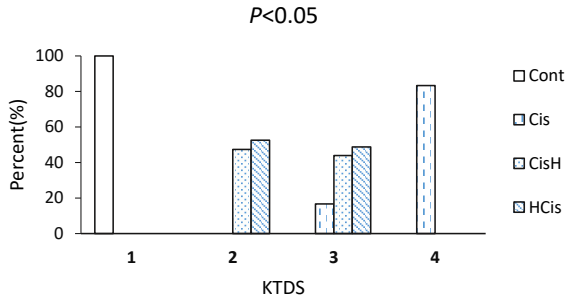

Figure 7. Kidney tissue damage score (KTDS). Cont; control group, Cis: cisplatin, CisH: concomitant cisplatin + Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. (Grade 0= no damage, grade 1= mild damage, grade 2= moderate damage and grade 3 = severe damage and grade 4= very severe damage).

MDA ($P<0.01$). KTDS increased in Cis, as shown in Figure 7, while it decreased significantly in CisH and HCis groups compared to the Cis group. MDA also increased in Cis group, as shown in Figure 8, while it decreased significantly in CisH ($P<0.01$) and HCis ($P<0.01$) groups compared to the Cis only group.

SOD and CAT

As shown in Figures 9 and 10, there were significant differences in SOD ($P<0.02$) and CAT ($P<0.024$) between the groups. SOD ($P<0.01$) and CAT ($P<0.03$) decreased significantly in Cis compared to Cont ($P<0.01$), and SOD and CAT increased in CisH and HCis groups compared to group 2 (Cis), and it did not show any significant difference with Cont. There was no significant difference in SOD and CAT levels between the CisH and HCis groups either.

Discussion

Herbs and natural products offer a supplementary health measure for preventing, managing, and treating diseases. People with renal diseases may seek natural products to improve their condition (13). The present study was designed to examine *Hypericum* as a remedy for cisplatin-induced nephrotoxicity. In clinical terms, cisplatin is a very effective and advanced drug that is utilized as an anticancer agent to treat various solid tumors, such as in the stomach, lungs, and ovaries. In practice, however, nephrotoxicity

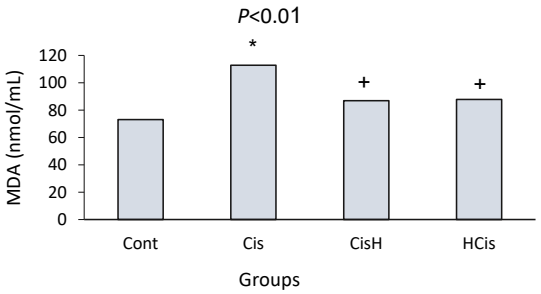

Figure 8. MDA. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin + Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. * is equal to significant difference with cont group. + is equal to significant difference with Cis group.

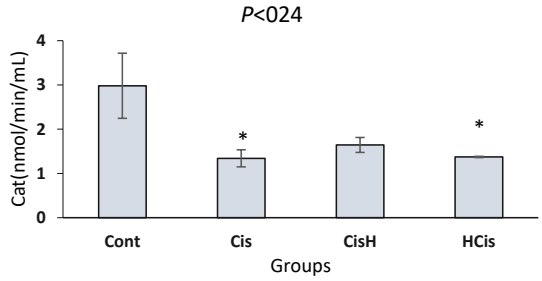

Figure 9. CAT. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin + Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. * is equal to significant difference with cont group.

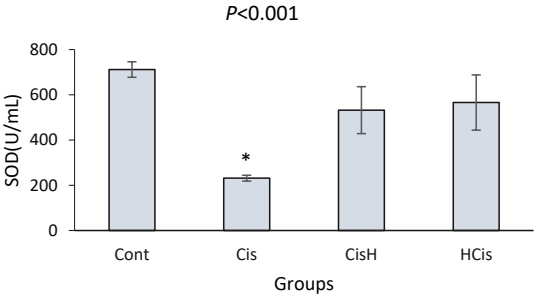

Figure 10. SOD. Cont; control group, Cis: cisplatin group, CisH: concomitant cisplatin + Hypericum, HCis: first treated with Hypericum for a week and after that cisplatin. * is equal to significant difference with Cont group.

is a major reported side-effect of that. From a clinical perspective, the probability of nephrotoxicity caused by cisplatin exceeds 20-35% and can be fatal in acute kidney injury (AKI) cases. The clinical characterization of AKI patients includes kidney tubular dysfunction, renal failure, anemia, somatic trembling, colon dysfunction, and decreased body weight, which give ample reason to discourage the use of cisplatin as an antitumor agent (3).

In this study, BUN and Cr increased significantly in Cis compared to Cont and decreased in the groups with the co-administration of cisplatin and *Hypericum* extract (i.e., the CisH and HCis groups) compared to the Cis group, although not significantly. No significant difference was observed between the CisH, HCis and Cont groups in BUN and Cr. The present findings are consistent with those by Abd El-Kader et al, who confirmed that the injection of cisplatin (7 mg/kg) induces AKI noticeably in rats. Based on their results, serum levels of Cr and BUN increased with cisplatin injection compared to the controls (14), which is indicative of glomerular destruction and shows renal function impairment compared to the controls. Cisplatin injection is associated with vessel congestion, glomerular dysfunction, and dilatation in the proximal and distal tubules and also neutrophil infiltration into the renal cortex. Proximal and distal tubule dysfunction in cisplatin-induced nephrotoxicity resulted in impaired reabsorption, followed by elevated serum BUN and Cr levels, perturbations in renal hemodynamics, and increased renal vascular resistance (15, 16). Senturk et al also reported that plasma levels of BUN (non-significantly) and Cr decreased after *Hypericum* administration in animal models of ischemia/reperfusion injury (IRI) compared to the controls (17).

Izol et al also demonstrated that elevated BUN and Cr levels in gentamicin-induced nephrotoxicity models decreased significantly when gentamicin was administered along with *Hypericum* extract. This effect shows that decreased glomerular filtration related to ROS leads to increased serum BUN and Cr levels. *Hypericum* extract prevents ROS production by way of its antioxidant effects and thus leads to decreased BUN and Cr values (18).

KTDS and MDA also increased in the Cis group. The present findings are consistent with the results reported by Hu et al, they revealed that tissue injury is induced by cisplatin and results in AKI model (19). Several studies have reported that cisplatin administration increases oxidative stress markers such as MDA and inflammatory mediators such as cyclooxygenase-2 (COX-2) as well as inducible nitric oxide synthase (iNOS) considerably (14). Based on the present findings, KTDS and MDA decreased significantly in the CisH and HCis groups compared to the Cis only group. The present findings are in line with some other findings; for instance, in a study on ischemia/reperfusion injury (IRI) rat models, the group that received Hypericum (n=8) showed mild parenchymal hemorrhage in 1 rat, mild hyaline cast in 4 rats, and normal histopathological results in 3 rats; meanwhile, the IRI control group showed hyaline cast in all the rats (severe in 1, moderate in 4, and mild in 3 cases) as well tubular dilation and parenchymal hemorrhage in 7 animals (moderate in 4 and mild in 3 cases) (17).

In another study, Izol et al showed that gentamicin administration results in edematous injury, which was attenuated by Hypericum extract administration. In addition, the MDA level decreased significantly in the renal tissue in the gentamicin group by Hypericum

extract administration. MDA is a typical marker of lipid peroxidative damage (18). This study showed that Hypericum plant possesses multiple active factors, such as apigenin and hyperforin, which modify apoptosis (18). In the present study, SOD and CAT decreased significantly in the Cis group compared to Cont but increased in the CisH and HCis groups compared to Cis. The cell apoptosis pathway is mediated by oxidative stress. Previous studies on the subject have mostly been focused on oxidative stress in the process of cisplatin-induced kidney damage. Cisplatin can significantly decrease the concentration of SOD and glutathione (GSH) and increase the renal content of MDA (20). Cisplatin aggregation in the renal tissue cells causes malfunction (as observed in this study and reported by similar studies), and augments ROS production and reduces antioxidant enzymes. ROS then attacks and damages the membrane lipids and increase lipid peroxidation, finally causing reduced GSH and antioxidant enzyme levels (21). Izol et al also showed that gentamicin-induced nephrotoxicity results in decreased GSH levels due to the increased free radicals' production (superoxide anion and hydrogen peroxide) and increased consumption of sulfhydryl (SH) groups of proteins. Enhanced ROS production leads to an increased consumption of renal antioxidant enzymes (for instance CAT). Gentamicin has been shown to decrease the expression of CAT. Additionally, Izol et al reported that GSH and CAT levels decreased significantly in the gentamicin group but increased significantly when gentamicin was co-administered with Hypericum extract, so this regime keeps the cells safe from free radical injuries (18).

Finally, in the present study, SGOT and SGPT levels increased significantly in Cis compared to Cont group. The study by Kim et al also stated, SGOT and SGPT levels were elevated significantly in the cisplatin-treated group compared to the controls, which shows the considerable oxidative stress and toxicity were induced. High liver enzyme activities (SGOT, SGPT) are markers of hepatic damage, and increased liver enzyme levels (and increased chemicals such as Cr) suggest hepatic damage or inflammation (22). In this study, SGOT and SGPT decreased significantly in the CisH and HCis groups compared to Cis. In agreement with our study, another research also reported that the increased levels of SGOT and SGPT in an IRI group decreased after Hypericum administration compared to the control (17).

Conclusion

Pretreatment with Hypericum extract or its concomitant administration with cisplatin can moderate the side effects of cisplatin; improve renal function and decrease lipid peroxidation, renal toxicity and KTDS. Corroborated by the results of further studies on the use of the active ingredients of Hypericum, the present findings can be helpful and practical in reducing the side-effects associated with cisplatin use.

Authors' contribution

MM, MK and HG planned, conducted, observed and analyzed the study. MM, MK, HG, AS, NM, NA, SP, NA and AK participated in the running of experimental part and gathered the data. All authors participated in preparing the final report of the study and approved the manuscript content.

Conflicts of interest

The authors declare no conflict of interests in this study.

Ethical issues

All experimental protocols in this study were conducted according to the guidelines of animal studies (National Institutes of Health Guide (NIH), 1978) and was approved by Ethics Committee of Ilam University of Medical Sciences (Ethical code #IR.MEDILAM.REC1397.149). In addition, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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