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ORIGINAL ARTICLE

Calcium dobesilate prevents cisplatin-induced nephrotoxicity by modulating oxidative and histopathological changes in mice

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Abstract

Cisplatinisoneofthesyntheticcancermedicineswithnephrotoxicitybeingoneofitsmajorsideeffects.Pastresearchshowsthat calciumdobesilate(CaD),asavascularprotectiveagentindiabeticretinopathy,hasantioxidantproperties.Thus,thisstudyaims to evaluate the protective effects of CaD in cisplatin-induced nephrotoxicity in mice. A many as 28 mice, in the present experimentalresearch,wererandomlydistributedintofourgroups,includingcontrol,cisplatin(theintraperitonealadministration of 20 mg/kg cisplatin only on the first day of the experiment), cisplatin + CaD 50 (cisplatin with the oral administration of 50mg/kgCaD),andcisplatin+CaD100(cisplatinwiththeoraladministrationof100mg/kgCaD).Thetreatedgroupsreceived CaDbyoralgavagefor4constitutivedays.Onthefifthday,themiceweresacrificed,andsomebiochemical(serumlevelsofCr andBUN,renaltissuelevelsofMDA,andrenalactivitiesofSODandGPx)andpathologicalparameterswereevaluated.Based ontheresults,therewasasignificantdecreaseintherenalSODandGPxactivities;incontrast,therewasasignificantincreasein the BUN, Cr, and renal MDA levels following administering cisplatin. However, the CaD treatment (100 mg/kg) significantly attenuatedthesealterations.Inaddition,thekidney'shistologicalexaminationofkidneysconfirmedthenephroprotectiveeffects of CaD. The findings proved the protective impact of CaD on cisplatin-induced nephrotoxicity by an improvement in the oxidative stress factors.

Keywords Nephrotoxicity. Cisplatin. Calciumdobesilate. Antioxidant. Mice

Introduction

Cisplatinisawell-knownchemotherapeuticdrugwithcellular alkylating properties, which is used in the treatment of cana cers, such as brain cancer, carcinoma, lung cancer, and ovarc iancancer(Yaoetal.2007).Cisplatin-inducednephrotoxicity is the major side effect that limits its clinical use (Goudarzi et al. 2017b; Sharp and Siskind 2017). There are several mechanisms involved in nephrotoxicity induced by cisplatin. One of the major mechanisms of this type is the overproducO tion of reactive oxygen species (ROS) and tissue oxidative damage (Ozkok and Edelstein 2014; Bazmandegan et al.

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2019). Cisplatin-inducedoxidative stressleads tolipid perox) idation, cell membrane degradation, protein, and nucleic acid oxidation, as well as tissue degradation (Dasari and Tchounwou 2014). It has been shown that damage to renal tissues increases the levels of blood urea nitrogen (BUN) and creatinine(Cr)(Rasoulianetal.2014 ;Boroushakietal.2015 = Ghaznavi et al.2018). Moreover, molecular changes include anincreaseinthemalondialdehyde(MDA)concentrationand a decrease in the antioxidant system enzymes, including glua tathione peroxidase (GPx) and superoxide dismutase (SOD) in renal tissues (Liu et al. 2010; Bazmandegan et al. 2019). Furthermore,histopathologicalchangesincludetubularnecroF sis, leukocyte infiltration, and glomerular injury (Dehnamaki etal.2019).Ithasbeenshowninseveralstudiesthatoneofthe prevention approaches to cisplatin-induced nephrotoxicity is theusedofantioxidantsagentssuchasmagnesiumsulfateand cystone (Hamroun et al. 2019; Casanova et al. 2020). Accordingly, research on finding agents that reduce cisplatin-induced nephrotoxicity could be very helpful in inc creasing cisplatin usage in clinics (Saleh and El-Demerdash 2005; Chirino et al.2008; Ehsani et al.2017).

Calcium dobesilate (CaD) is one of the derivatives of cyclohexadinylbisulfate,whichwasintroducedover40years ago for treating diabetic retinopathy as it reduces vascular permeability (Haller et al.2017). It has been well established thatCaDhaspotentantioxidantproperties(Zhangetal.2015). In vitro studies show this drug has a scavenging effect on oxygen free radicals. However, these results have been cono firmed by in vivo studies as well (Rota et al. 2004). Jafarey et al. showed that CaD reduces free ROS and increases antie oxidant enzymes, such as SOD and GPx in gentamicino induced nephrotoxicity (Jafarey et al. 2014).

Against this background, it is necessary to find a drug that reducestherenaltoxicityofcisplatin.However,itseemsCaD hashighlyprotectiveeffectsintheseconditions.Accordingly, this research aims to investigate if CaD has an impact on cisplatin-inducedkidneyimpairmentinmicethroughexaminc ing oxidative stress indices and histological changes.

Materials and methods

Drugs

in polycarbonate cages at room temperature (24±2 °C), with a 12-h light/dark cycle, and with free access to food (Pars Industrial Company, Iran) and water.

In this study, the animals were randomly divided into 4 groups with 7 animals in each group, including Group 1 served as control and received no particular treatment, Group 2 received 20 mg/kg cisplatin intraperitoneally on the first day, and Groups 3 and 4 received 20 mg/kg cisplatin intraperitoneally on the first day and different doses of CaD (50and100mg/kg/day)orallywhichwasstartedonday1and continued for 3 consecutive days.

Sample collection

Four days after the initial CaD administration, the mice were anesthetized with diethyl ether. Next, blood samples were collected by cardiac puncture and centrifuged at 1000 rpm for 3 min for collecting the serum. The samples of the serum were kept at −80 °C for measuring BUN and Cr levels. The micewerethendecapitatedwithbothkidneysharvestedforthm with.Therightkidneyswerefixedina10%formalinsolution forhistopathologicalstudies.Inaddition,theleftkidneyswere frostedinanitrogentankfortheevaluationofoxidativestress indices (Bazmandegan et al.2019; Taghipour et al. 2019).

Serum parameters

The serum levels of Cr and BUN were measured using an automated analyzer (Mindray, Guangzhou, China) by respeca tive commercial kits (ParsAzmoon Co., Tehran, Iran).

Oxidative parameters

The frozen kidneys were defrosted and homogenized with phosphate-buffered saline and centrifuged 25 min at 6000 rpm at 4 °C for collecting supernatants (Kaeidi et al. 2020a,b). Next, the kidney levels of MDA as well as SOD and GPx activities were evaluated by commercially available kits (ZellBio, Ulm, Germany) in the collected supernatants.

Histopathological evaluation

After preparing the kidney sections using hematoxylin and eosin (H&E), they were stained and observed in a blind mane ner by an pathologist under a light microscope (Nikon Labophot, Japan) (Karimi et al. 2019; Hosseinzadeh et al. 2020

CaD (Doxium®) was obtained from OM PHARMA Company (Switzerland), and cisplatin (CISPLATIN MYLAN®) was purchased from MYLAN Firm (France).

Animals and study groups

In this experimental research, as many as 28 male mice were obtained from the animal house of Rafsanjan University of Medical Sciences, Rafsanjan, Iran. The animals were housed

Statistical analysis

StatisticalanalysiswasperformedusingGraphPadPrism(verS sion 6, USA), and the results were reported as mean ± SEM. Alterations between the groups were defined via a one-way ANOVA followed by a post-hoc analysis of the Tukey's test. $p<0.05$ was considered significant.

Results

Serum parameters

The mean BUN and Cr levels of the serum increased signifiT cantly in the cisplatin group ($p<0.01$ and $p<0.001$, respec< tively) (Fig. 1). The administration of CaD at a dose of 100 mg/kg for 4 constitutive days significantly decreased the BUN and Cr levels of the serum compared with the cisplatin group ($p<0.05$ and $p<0.01$, respectively).

Oxidative parameters

The results of the present work revealed that the MDA conT centration increased significantly via cisplatin administration compared with the control group ($p<0.001$) (Fig. 2). It was alsofoundoutthatthemeanconcentrationofMDAdecreased significantly inthe group thatreceived100 mg/kg of CaD for 4 constitutive days compared with the cisplatin group ($p<0.001$).

According to the results, the activities of GPx and SOD were reduced significantly following cisplatin administration compared with the control group ($p<0.001$) (Fig. 3a and b). The administration of CaD (100 mg/kg) for 4 constitutive days significantly increased the SOD activity compared with the cisplatin-treated mice ($p<0.01$). In addition, CaD at both doses(50and100mg/kg),for4constitutivedays,significantd ly increased the GPx activity compared with the cisplatin group ($p<0.05$ and $p<0.01$, respectively).

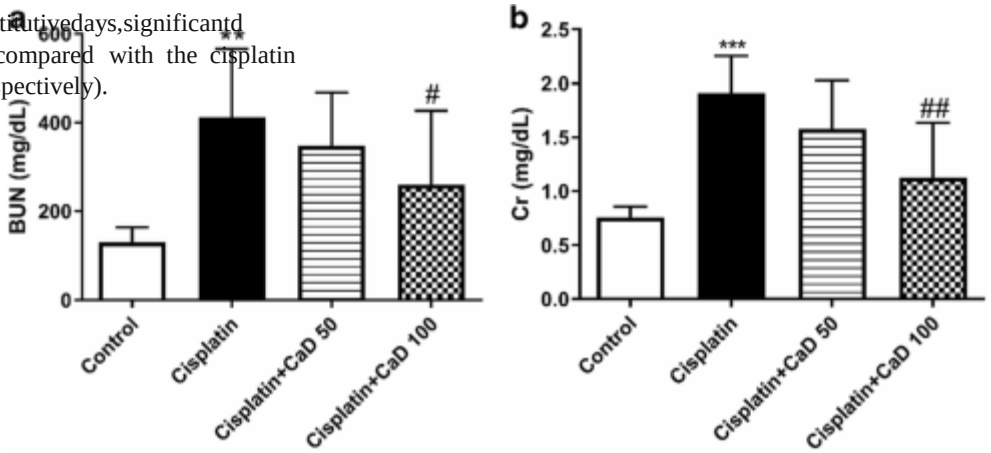

Fig. 1 CaD treatment effects on the levels of BUN (a) and Cr (b) in cisplatin-induced nephrotoxicity. **p<0.01 and ***p<0.001: compared with the control group. #p<0.05 and ##p<0.01: compared with the cisplatin group. CaD calcium dobesilate, BUN blood urea nitrogen, Cr creatinine

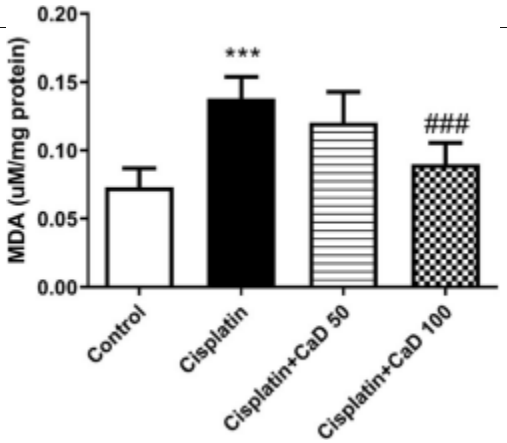

Fig. 2 CaD treatment effects on the concentration of MDA in cisplatinC induced nephrotoxicity. ***p<0.001: compared with the control group. ###p < 0.001: compared with the cisplatin group. CaD calcium dobesilate, MDA malondialdehyde

The effects of CaD on histopathological indices in cisplatin-induced nephrotoxicity

Nopathologicallesionswereseeninthekidneysofthecontrol group (Fig. 1a; Table 1). Extensive pathological lesions, such as tubular degeneration, tubular necrosis, tubular cell vacuoa lation, and case cast, were seen in the cisplatin group due to cisplatinadministration(Fig. 1b;Table 1).Theadministration of CaD (potentially 100 mg/kg) significantly reduced cisplatin-induced pathological lesions in the renal tissues (Fig. 1c and d; Table 1; Fig. 4).

Discussion

Accordingtotheresultsofthepresentinvestigation,theintraA peritoneal administrationofcisplatin (20 mg/kg) significantly increased BUN and Cr levels in the serum. Moreover, it was found out that cisplatin increased MDA levels and decreased SOD and GPx activities in the renal tissues. These

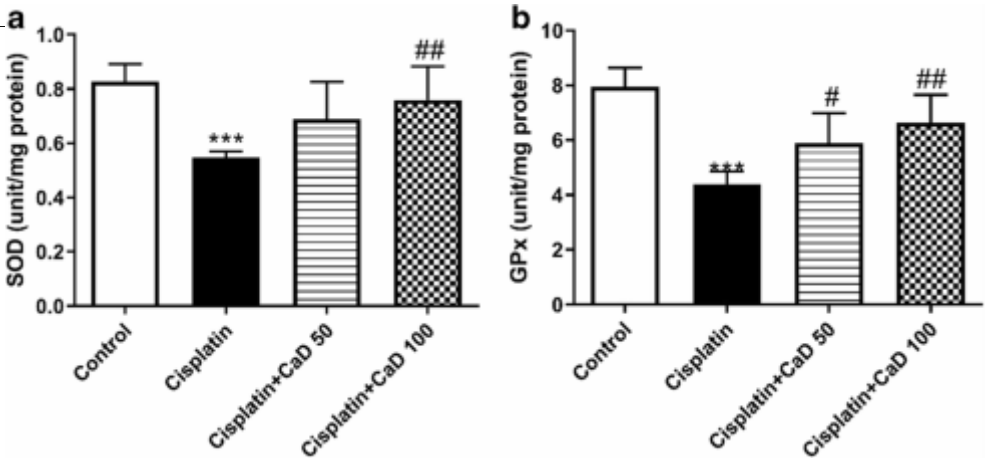

Fig. 3 The effects of treatment with CaD on SOD (a) and GPx (b) in cisplatin-induced nephrotoxicity. ***p<0.001: compared with the control group. #p<0.05 and ##p<0.01: compared with the cisplatin group. CaD calcium dobesilate, SOD superoxide dismutase, GPx glutathione peroxidase

biochemical alternations were in line with histopathological lesionsinthekidney.Accordingtotheresults,theoraladminl istration of CaD (100 mg/kg) for 4 constitutive days signifii cantly mitigated the deleterious effects of cisplatin on the kidney.

Although cisplatin is a potent antineoplastic agent, it has certain serious side effects, including nephrotoxicity (Yao et al.2007; Goudarzi et al.2017b). It is well established that cisplatin induced nephrotoxicity causes functional disorders characterized by a rise in BUN and Cr levels (Saleh and Elc Demerdash 2005; Ghaznavi et al. 2018; Mehrzadi et al. 2018a,b .Consistentwithpastreports,thepresent study dem. onstrated that cisplatin administration increases Cr and BUN levels in the serum. Moreover, it was shown that treatment with 100 mg/kg CaD for 4 constitutive days reduced the inw crement levels of Cr and BUN in cisplatin-treated animals. Some reports indicate that antioxidant compounds such as ellagic acid, lycopene, and cashew phenolic exhibit similar protective effects in cisplatin-induced renal injuries (Atessahin et al.2005; Atessahin et al.2007; Chandrasekara andShahidi2011).Atpresent,itiswelldocumentedthatCaD exerts antioxidant effects by increasing the level and activity of antioxidant enzymes or/and scavenging free radicals (Berthet et al. 1999; Haller et al. 2017; Solà-Adell et al. 2017). In a human study, it was shown that CaD could im) prove renal functions, including Cr and BUN levels, in pap tients with diabetic nephropathy (Qin et al. 2017). Jafarey et al. reported that CaD at the doses of 50 and 100 mg/kg reduced serum levels of BUN and Cr in nephrotoxicity inr duced by gentamicin in rat (Jafarey et al. 2014).

Itisbelievedthatcisplatin increaseslipid peroxidationand MDA levels in renal tissues by inducing oxidative stress (Priyamvadaetal.2008).MDAhashighlyreactiveproperties that were increased in the present and similar investigations following cisplatin administration (Priyamvada et al. 2008; Ghaznavi et al. 2018). The overproduction of MDA induces functionalchangesandhistopathologicallesionsinthekidney (Goudarzi et al.2017a; Mehrzadi et al.2018a,b; Dehnamaki et al. 2019; Karimi et al. 2019). We also demonstrated that treatmentwithCaDatthedoseof100mg/kgfor4constitutive days significantly decreased MDA levels in the renal tissue. Bogdanovetal. found out thattheoraladministrationofCaD (200 mg/kg/day) for 15 days reduced oxidative stress bio(markers, such as MDA in the retina of diabetic mice (Bogdanov et al. 2017). Moreover, CaD reduces MDA levels in the human's isolated varicose veins (Alda et al. 2011). Furthermore, CaD reduces liver damages in experimental obF structive jaundice by reducing the MDA levels of the liver (Unal et al.2019). Hence,it seems that CaD exerts its benefi) cial effects by reducing MDA levels.

Previousreportsindicatethatcisplatinreducesthecapacity of antioxidant enzymes, such as SOD and GPx (Atessahin et al. 2005, Atessahin et al. 2007, Chirino et al. 2008). Consistent with these reports, the present study demonstrated

Groups	Histological criteria		
	Tubular necrosis	Tubular degeneration	Tubular cells vacuolation
0	0	0	0
+++	+++	+++	+++
+	+	+	+
0	+	+	+
0	+	+	+

Table 1 Effect of CaD on kidney histopathology in cisplatinh induced nephrotoxicity in mice

Cast

Control
Cisplatin
Cisplatin + CaD 50
Cisplatin + CaD 100

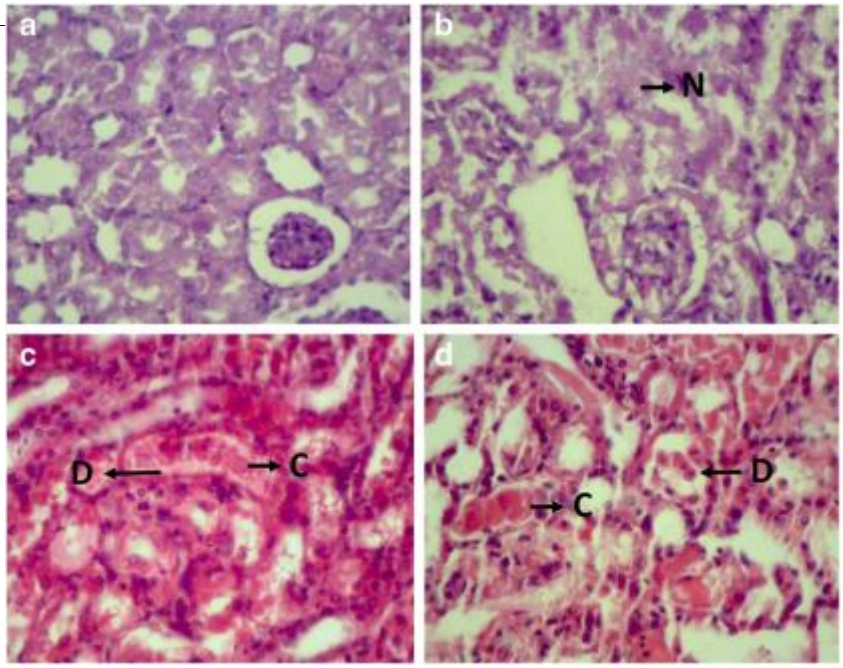

Fig. 4 Histopathological observations (sections of the kidney were stained using hematoxylin and eosin, at a magnification of ×400) indicate CaD effects on cisplatin-induced nephrotoxicity alterations in the kidney. a Control group; b cisplatin group; c cisplatin + CaD 50 group; d cisplatin + CaD 100 group. CaD calcium dobesilate, C cast, N tubular necrosis, D tubular degeneration

that cisplatin decreased the activity of these enzymes in the antioxidant system. In addition, we demonstrated that CaD administration (especially 100 mg/kg) for 4 constitutive days in cisplatin-treated rats restored the activities of SOD and GPx. CaD reduces free radicals and strengthens the body's antioxidant defense system, including SOD and GPx (Jafarey et al. 2014). According to a human study, CaD en) hanced the levels of SOD and GPx and reduced MDA levels in cardiac surgery (Cerrahoglu et al. 2009). In another report, itwasshownthatCaDhadprotectiveeffectsonthedamageto diabeticrats'retinabyincreasingtheactivityofGPx(Heetal. 2019).

It has been demonstrated that cisplatin induces tubular damages, including tubular cell vacuolation, tubular necrosis, tubular degeneration, and cast (Atessahin et al. 2005; Bazmandegan et al. 2019). In the same vein, we found these tubular lesions in the kidney samples of cisplatin-treated anit mals.ItwasalsoshowninthepresentstudythatCaDreduced these pathological lesions in the kidney at the dose of 50 mg/kg and more potentially at the dose of 100 mg/kg. Previous reports also verified the nephroprotective effects of CaD through histopathological studies. For example, Gao etal.foundoutthatCaDdecreasedrenalpathologicaldamage and protected the kidney from fibrous degeneration in early diabetic nephropathy (Gao et al. 2009).

to protection against cisplatin-induced oxidative stress possit blythroughitsantioxidantactivities.Therefore,thesefindings indicate that treatment with CaD could act as a beneficial strategy for reducing cisplatin-induced renal damage in pas tients with cancer.

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Authors' contributions Conceived and designed the experiments: GB and MA. Performed the experiments: BG, AK, MK, and AF. Analyzed thedata:GBandMA.Contributedreagents/materials/analysistools:AK, GB,andIF.Wrotethepaper:IFandGB.Theauthorsdeclarethatalldata were generated in-house and that no paper mill was used.

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Compliance with ethical standards All experiments were performedinaccordancewiththeguidelinessetbytheethicalcommittee under ethics code IR.RUMS.REC.1397.028.

Conflict of interest The authors declare that they have no conflict of interest.

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Conclusions

It is concluded that cisplatin causes oxidative stress-induced damageinthekidneytissueofrats.TreatmentwithCaDleads

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