

Research Article



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Investigation of the effect of cornelian cherry (*Cornus mas* L.) fruit extract against cisplatin-induced renal cell injury in vitro

Kızılcık (*Cornus mas* L.) meyva ekstraktının sisplatin indüklü in vitro böbrek hücre hasarına etkisinin araştırılması

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Abstract

Objective: The aim of this study was to evaluate the protective effects of cornelian cherry fruit extract against cisplatin-induced nephrotoxicity in vitro.

Materials and methods: African green monkey kidney epithelial cells (Vero) were incubated with 100 mg/mL of cornelian cherry fruit extract, 50 µmol/L of cisplatin or 50 µmol/L of cisplatin plus 100 mg/mL of cornelian cherry fruit extract for 4 h. The wells containing cells without any supplementation served as control. Cell viability was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazoliumbromide assay. Culture mediums were collected, centrifuged and analyzed for malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD) and glutathione peroxidase (GPx).

Results: The cell viability was 59% in cells co-treated with cisplatin and cornelian cherry fruit extract simultaneously and 42% in cisplatin treated cells. The cellular damage ratio was elevated in cells treated with cisplatin. However, when cisplatin combined with cornelian cherry fruit extract the deleterious effects of cisplatin were significantly decreased. The MDA concentration was significantly higher ($p < 0.05$), GSH concentration and GPx and SOD activities were significantly lower ($p < 0.05$) in cisplatin treated group when compared with control group, cornelian cherry group, and cisplatin+cornelian cherry group.

Conclusion: The present study indicated that cornelian cherry fruit extract exert protective effects on oxidative damage in vitro induced by cisplatin.

Keywords: Cisplatin; Cornelian cherry; Oxidative damage; In vitro; Nephrotoxicity.

Özet

Amaç: Bu in vitro çalışmada, kıızılcık meyva ekstraktının sisplatin indüklü nefrotoksisiteye karşı koruyucu etkisinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Çalışmada Afrika yeşil maymun böbrek epitel hücreleri (Vero), 100 mg/mL kıızılcık meyva ekstraktı, 50 µmol/L sisplatin veya 50 µmol/L sisplatin + 100 mg/mL kıızılcık meyva ekstraktı ile 4 saat inkübe edildi. Herhangi bir ekleme yapılmayan, sadece hücre bulunan kuyucuklar kontrol grubu olarak kullanıldı. Hücre canlılığı, 3-(4,5-dimetil-thiazole-2-yl)-2,5-difenil tetrazolium bromide tayini ile belirlendi. Kültür medyumları toplandı ve santrifüj edildi. Malondialdehit (MDA),

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glutatyon (GSH), superoksit dismutaz (SOD) ve glutatyon peroksidaz (GPx) analizleri yapıldı.

Bulgular: Sisplatine maruz bırakılan hücrelerde hücre canlılığı %42, sisplatinle birlikte kıvılcık meyva ekstraktı uygulanan hücrelerde ise hücre canlılığı %59 bulundu. Sisplatin uygulanan hücrelerde hücre hasar oranı yüksekti. Bununla birlikte kıvılcık meyva ekstraktı ile kombine sisplatin grubunda, sisplatinin zararlı etkileri anlamlı derecede azalmıştı. Sisplatin grubu, kontrol grubu, kıvılcık grubu ve sisplatin+kıvılcık grupları ile karşılaştırıldığında MDA konsantrasyonu önemli derecede yüksek, GSH konsantrasyonu, GPx ve SOD enzim aktiviteleri anlamlı derecede düşük bulundu ($p < 0.05$).

Sonuç: Bu çalışma sisplatin ile uyarılan in vitro oksidatif hasar üzerine kıvılcık meyva ekstraktının koruyucu etkileri olduğunu göstermiştir.

Anahtar Kelimeler: Sisplatin; Kıvılcık; Oksidatif hasar; In vitro; Nefrotoksisite.

Introduction

Cisplatin {cis-diamminedichloroplatinum (II), $[\text{PtCl}_2(\text{NH}_3)_2]$ } is an inorganic platinum compound that highly effective chemotherapeutic agent for the treatment of many cancer types such as ovary, testis, cervix, lung, head, and neck [1–3]. The most common reported side effects of cisplatin therapy is nephrotoxicity [4–10]. The major renal effect of cisplatin exposure is proximal tubular damage [11]. It has been indicated that cisplatin metabolised in proximal tubule cells cause nephrotoxicity [12]. Knowledge of pathogenic mechanisms of cisplatin in kidney is critical to prevent cisplatin-induced renal impairment.

Several hypotheses have been proposed to explain the mechanism of cisplatin-induced nephrotoxicity. These include tubular cell toxicity, reactive intermediates, inflammation and apoptosis-related mechanisms [11, 13–16]. Studies have suggested that exposure to cisplatin induce oxidative stress in the kidney [17–21]. Reactive oxygen species, specifically superoxide radical, has been stated in the mechanism that underlies cisplatin-induced renal injury [22]. Because oxidative stress plays a crucial role in cisplatin-induced hepatic toxicity, antioxidant supplements may be useful in the prevention and treatment of cisplatin-induced renal injury. Plants particularly horticulture section are raw material and used by people for food, either as edible products, or for culinary ingredients, for medicinal use or ornamental and aesthetic purposes. They are genetically very diverse group and play a major

role in modern society and economy. Fruits and vegetables are an important component of traditional food, but are also central to healthy diets of modern urban population [23–27]. It is well documented through in vivo and in vitro studies that natural products provides powerful protection against cisplatin-induced nephrotoxicity through reduced oxidative stress [28–34]. Studies have shown that the strong antioxidant properties of cornelian cherry are attributed to specific compounds, such as ascorbic acid, anthocyanins, and polyphenols [35–42]. *Cornus mas L.* has been reported to reduce oxidative stress and related damage [41, 43]. However, much less is known with regard to protective effect of cornelian cherry fruit extract against cisplatin-induced nephrotoxicity. The aim of this study was to evaluate the protective effect of cornelian cherry fruit extract on cisplatin-induced nephrotoxicity in vitro.

Materials and methods

Materials

Cornelian cherry fruits were collected from Samsun, Turkey in September 2014, and kept frozen at -20°C until analysis (about 5 months). Some properties of the materials can be seen in Table 1.

Extractions

For extraction, about 100 g of frozen cornelian cherry fruits were thawed in refrigerator. The fruits were crushed for 5 min in a Waring blender after removing the stones. An aliquot of 50 g pulp was mixed with 300 mL of deionized water. The mixture was sonicated (Bandelin Sonorex, Germany) for 30 min at 20°C and then filled up to the final volume of 500 mL with the water. The extract was centrifuged at 1550 g for 15 min at 4°C . The supernatant was used for analysis.

Determination of some physical and chemical properties of cornelian cherry fruits

Fruit weight was determined by using a digital balance with a sensitivity of 0.001 g, and flesh/stone ratio was calculated using $[(\text{fruit weight} - \text{stone weight}) / \text{stone weight}]$ formula. Length and width of the fruit were measured by using caliper with a sensitivity of 0.01 mm. The colour of the cornelian cherry fruits was recorded by a Minolta

Table 1: Some properties of the cornelian cherry fruits analysed.

Parameters	Values
Length (mm)	15.11
Width (mm)	11.20
Average fruit weight (g)	3.52
Flesh/stone ratio	5.29
L^a	25.04
$+a^a$	21.57
$+b^a$	6.59
Dry matter (%)	22.14
Soluble solids (%)	13.0
Titrateable acidity (%)	1.22
pH	3.67
Total sugar (%)	8.20
Reducing sugar (%)	7.56
Unreducing sugar (%)	0.61
Total phenolics (μg gallic acid equivalents) ^a	83.01
Oleanolic acid (mg/kg)	45.60
Ascorbic acid (mg/kg)	215.62
Total anthocyanins (μg cyanidin 3-glucoside equivalents) ^a	27.70
Individual anthocyanins (%) ^b	
Cyanidin-3-glucoside	45.20
Pelargonidin-3-glucoside	47.78
Cyanidin-3-rutinoside	3.50
FRAP ($\mu\text{mol Fe}^{2+}$) ^a	1031.08
EC_{50} (mg/mL) ^a	1.10

^aIn 100 mg/mL of the extract, ^bIndividual compounds presented as percentage of total peak area monitored at 515 nm.

CR-400 (Japan) Chromameter and reported on the Hunter $L^*a^*b^*$ method, where lightness L^* and two colour coordinates, a^* and b^* . The dry matter content of the fruits was conducted by heating in a vacuum oven at 70°C until a constant weight. The total soluble solid content of the fruits was assessed by refractometry, using an Abbe refractometer (Atago, Japan). Titrateable acidity was measured with 0.1 M NaOH up to pH 8.2 and expressed as percentage of malic acid. The pH value was measured using a pH meter (Eutech Cyberscan, Singapore) for a 10% (w/v) solution of the fruit prepared in deionized water. Sugar contents were determined according to the Lane-Eynon method [44].

Determination of antioxidant properties of the extracts

Total phenolics was quantified using Folin-Ciocalteu reagent [45]. The oleanolic acid was quantified using HPLC according to the procedure described by Zhang et al. [46]. Ascorbic acid content was performed by high performance liquid chromatography (HPLC) [47]. Total anthocyanin content was carried out using the pH differential

absorbance method [48]. The anthocyanin profile of the fruit was carried out by means of HPLC–UV as mentioned by Tural and Koca [42]. The antioxidant activity test was performed by two different methods. One was based on the evaluation of the free radical scavenging capacity (DPPH) of the extracts [42], and the other measured their ferric-reducing antioxidant power (FRAP) [49].

Cell culture

An established cell line, African green monkey kidney epithelial cells-Vero (ATCC, CCL-81) (American Type Culture Collection [ATCC], USA) was cultivated in Dulbecco's modified Eagle's medium (DMEM) supplemented with 2 mM L-glutamine and Earle's BSS adjusted to contain 1.5 g/L sodium bicarbonate, 0.1 mM nonessential amino acids, and 1.0 mM sodium pyruvate, 90%; and fetal bovine serum (FBS), 10%. No antibiotics were added. Cells were grown to confluence in flasks (75 cm²) over 6–7 days. Cells were subcultured by treatment with 0.25% trypsin containing 0.1 mM EDTA in PBS. Cells were diluted in fresh medium and seeded into 96-well plates (1.5 × 10⁴ cells/well). After incubation for 24 h, the medium was aspirated from all wells and replaced with 100 μL /well extraction mix or control medium and incubated for another 24 h before cytotoxicity was addressed (8 wells/dilution/incubation period).

Cell treatment with cisplatin and cornelian cherry fruit extract

The preliminary assays were performed by adding 50 $\mu\text{mol/L}$, 100 $\mu\text{mol/L}$, 200 $\mu\text{mol/L}$, 300 $\mu\text{mol/L}$, 400 $\mu\text{mol/L}$ and 500 $\mu\text{mol/L}$ for cisplatin and 1 mg/mL, 10 mg/mL, 100 mg/mL, 200 mg/mL for cornelian cherry fruit extract to cultures to obtain a significant effect in cell viability after 4 h without excess cell death at 24 h. The concentration of 50 μM of cisplatin was selected to induce cell injury since it allowed to obtain after 4 h a decrease of at least 42% of both cell lines viability. Although, the higher concentration (200 mg/mL) of cornelian cherry fruit extract was toxic for cell culture, lower concentration of cornelian cherry fruit extract did not show any toxic effect on cell viability. Due to this reason, the concentration of 100 mg/mL of cornelian cherry fruit extract was selected for assay. Vero cells were seeded in 24-well plates at a density of 1 × 10⁵ cells/mL in Dulbecco's modified minimum essential medium containing 10% FBS. After 24 h, they were incubated with 50 $\mu\text{mol/L}$ of cisplatin or

50 $\mu\text{mol/L}$ of cisplatin plus 100 mg/mL of cornelian cherry fruit extract for 4 h. The wells containing cells without any supplementation served as control.

Assessment of cell viability

The colorimetric assay (the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide-MTT) developed by Mosmann and modified by Edmondson et al. was used as a test for cell proliferation and survival [50, 51]. A 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide dye solution (MTT) (Sigma, St Louis, MO) was prepared as 0.5 mg/mL in PBS at 37°C just before use. A total of 20 μL MTT dye was added to each well and incubated at 37°C in air containing 5% CO_2 and at 95% relative humidity for 4 h in the dark. After incubation, the MTT was aspirated and the formazan product was solubilized in 50 μL dimethyl sulfoxide (DMSO) (Sigma-Aldrich, St Louis, MO, USA). The plates were shaken before the optical densities were measured at 570 nm using a microplate reader (Infinite F50, Tecan Austria GmbH, Grödig, Austria). All assays were repeated at least twice to ensure reproducibility. The absorption value obtained with the control was deemed to indicate 100% viability. The percentage of viable cells was determined using the following formula:

$$\text{percentage of viable cells} = (A/B) * 100,$$

where A = viable cells in the experimental well and B = viable cells in the control well. More than 90 % cell viability was considered as noncytotoxic, 60% to 90% as slightly cytotoxic, 30% to 59% as moderately cytotoxic, and less than 30% cell viability was considered as strongly cytotoxic [50].

Preparation of cell medium for analyses of oxidative-stress biomarkers

The cell culture mediums were centrifuged at 1550 g for 5 min and then supernatants were collected separately for analyses of oxidative-stress biomarkers.

Determination of MDA concentration

Culture medium malondialdehyde concentration was determined according to Yoshioka et al. [52]. Briefly, 0.5 mL of medium samples were mixed with 2.5 mL of 20% trichloroacetic acid and 1 mL of 0.67% thiobarbituric acid then the mixture boiled at 95°C for 30 min. After cooling,

the mixture was extracted in 4 mL n-butanol and centrifuged at 1550 g for 10 min. Then, the n-butanol phase was separated and absorbance of the supernatant was measured at 535 nm by spectrophotometer (Thermo Scientific, Genesys 10S UV-VIS, Madison, WI, USA) against n-butanol. The results were evaluated from the standard curve obtained using 1,1,3,3 tetraethoxypropane of 0.1, 0.5, 1, 5 and 10 nmol/mL. The results were expressed as nmol/mL.

Determination of GSH concentration

The glutathione concentration of culture medium was determined by the method of Beutler et al. [53]. Briefly, a 500 μL aliquot of culture medium was mixed 3 mL of the precipitating solution (1.67 g metaphosphoric acid, 0.2 g EDTA and 30 g NaCl in 100 mL distilled water), kept in ice bath for 5 min and centrifuged at 1550 g for 10 min at 4°C. Then, 500 μL supernatant was mixed with 2 mL of 0.3 M disodium hydrogen phosphate solution and 250 μL of 0.001 M freshly prepared 5,5'-dithiobis (2-nitrobenzoic acid) dissolved in 1% w/v sodium citrate was added in assay tube. The standard solutions containing 0–5 nmol/mL of reduced glutathione was treated similar procedure for a standard curve, simultaneously. A blank tube was prepared with 2 mL buffer, 500 μL of diluted precipitating solution (three parts to two parts of distilled water) and 250 μL of DTNB reagent. The absorbance of test tubes were measured by spectrophotometer at 412 nm against a blank. GSH concentration was calculated from the GSH standard curve and results were expressed as nmol/mL.

Determination of GPx activity

GPx activity of culture medium was measured by the method suggested by Paglia and Valentine [54]. An aliquot of 20 μL culture medium was mixed with 800 μL of the reaction mixture, containing 0.1 M phosphate buffer, pH 7.0, 1 mM ethylene diamine tetra-acetic acid (EDTA), 10 mM GSH, 1 mM sodium azide, 1 unit of glutathione reductase, 1.5 mM nicotinamide adenine dinucleotide phosphate (NADPH). After incubation for 5 min at 37°C, 10 μL of the 30 mM tert-butyl hydroperoxide was added to the assay mixture for initiation of reaction. GPx activity was measured as the rate of NADPH oxidation was monitored in a spectrophotometer at 340 nm for approximately 5 min. The GPx activities were expressed as U/mL.

Determination of SOD activity

Superoxide dismutase activity was measured by the method based on Sun et al. [55]. Briefly, 100 μ L of culture medium was mixed with 2.45 mL of assay reagent which containing 0.3 mM xanthine, 0.6 mM disodium ethylene diamine tetraacetic acid, 0.15 mM nitroblue tetrazolium, 0.4 M sodium carbonate, 1 g/L bovine serum albumin. The reaction was initiated by the addition 20 μ L of xanthine oxidase to the mixture, incubated at 25°C for 20 min. The reaction was terminated by the addition of 1 mL of 0.8 mM copper (II) chloride to the mixture. The SOD activity was monitored at 560 nm by detecting the inhibition of the nitroblue tetrazolium reduction rate. One unit of SOD activity was defined as the amount of enzyme required to cause 50% inhibition of NBT reduction to formazan. The SOD activities were expressed as U/mL.

Cytological examination of cell cultures

Vero cell culture samples were fixed for 10 s in absolute methanol. Following fixation cell culture samples stained with Giemsa for 10 s and then rinsed with tap water. Vero cell culture samples were examined under light microscope (Nikon Eclipse E600, Nikon Instruments Inc., Tokyo, Japan).

Cytological evaluation of cell cultures

Cell culture samples stained with Giemsa were scored semiquantitatively for cellular degeneration and damage. Cells were evaluated at x200 final magnification with an eyepiece showing grids of 100 squares from a total of 10 different adjacent fields measuring a total area of 0.15 mm². On average a total of 1100 cells from each sample were scanned for evaluating cellular degeneration and results are reflected as percentage score. Cells showing signs of cytoplasmic basophilia, cellular shrinkage, loosing cellular contours, nuclear condensation, nuclear fragmentation, cytoplasmic budding were considered as degenerated or showing signs of apoptosis.

Statistical analysis

The statistical significance of the differences between groups was analyzed by One-Way ANOVA analysis of variance and Duncan's multiple range test using SPSS Statistics V21.0 (IBM Corporation, Armonk, NY, USA).

Each value was the mean of two replications obtained from 4 independent experiments. Data are expressed as mean \pm standard deviation (SD) and p value of <0.05 was considered statistically significant.

Results

Cytological findings

The cell viability was 59% in cells co-treated with cisplatin and cornelian cherry fruit extract simultaneously and 42% in cisplatin treated cells. In Vero cell culture without any application, and Vero cell culture treated with only 100 mg/mL of cornelian cherry fruit extract, a few cells showing signs of cytoplasmic basophilia, nuclear and cellular condensation were observed (Figures 1 and 2). The cellular damage ratio was elevated with treatment of 50 μ mol/L of cisplatin. Cells showing cytoplasmic basophilia, nuclear and cellular condensation were high in 50 μ mol/L cisplatin treated cells (Figure 3). However, when 50 μ mol/L of cisplatin combined with 100 mg/mL of cornelian fruit cherry extract the deleterious effects of cisplatin were significantly decreased (Figure 4).

Oxidative stress parameters

The results of oxidative stress parameters of the treatment groups were presented in Table 2. The MDA concentration was significantly higher ($p < 0.05$) in the cisplatin

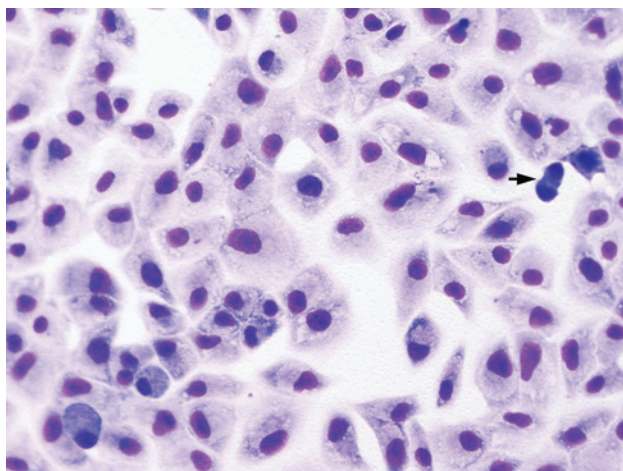


Figure 1: Vero cell culture without any application. A few cells are showing signs of cytoplasmic basophilia, nuclear and cellular condensation (arrow). Giemsa x20.

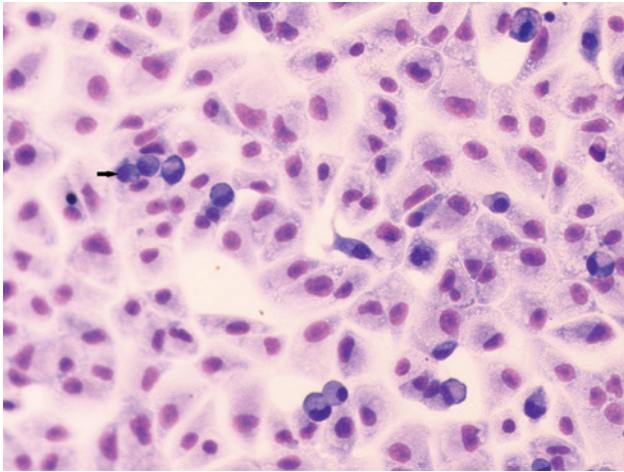


Figure 2: Vero cell culture treated with only 100 mg/mL of cornelian cherry fruit extract for 4 h.

A few cells are showing signs of cytoplasmic basophilia, nuclear and cellular condensation (arrow). Giemsa x20.

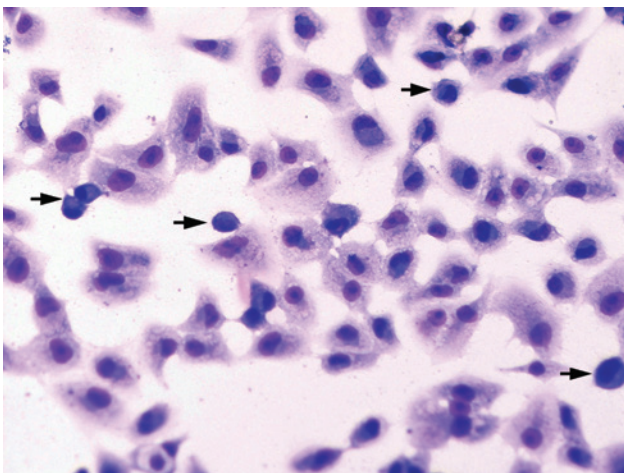


Figure 3: Vero cell culture treated with 50 µmol/L of cisplatin for 4 h. Increased number of cells are showing cytoplasmic basophilia, nuclear and cellular condensation (arrows). Giemsa x20.

treated group (4.49 ± 0.31 nmol/mL) when compared with control group (0.96 ± 0.07 nmol/mL), cornelian cherry group (0.90 ± 0.07 nmol/mL) and cisplatin+cornelian cherry group (1.09 ± 0.26 nmol/mL). The concentration of GSH was significantly lower ($p < 0.05$) in the cisplatin treated group (0.73 ± 0.08 nmol/mL) compared to control group (2.51 ± 0.37 nmol/mL), cornelian cherry group (2.64 ± 0.39 nmol/mL) and cisplatin+cornelian cherry group (2.33 ± 0.42 nmol/mL). The activities of GPx and SOD were significantly lower ($p < 0.05$) in the cisplatin treated group (0.31 ± 0.07 U/mL and 1.16 ± 0.13 U/mL, respectively) when compared with control group (0.96 ± 0.13 U/mL and 2.42 ± 0.30 U/mL, respectively), cornelian cherry

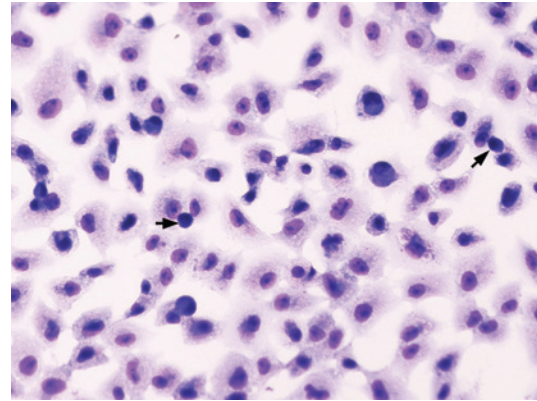


Figure 4: Vero cell culture co-treated with 50 µmol/L of cisplatin and 100 mg/mL of cornelian cherry fruit extract simultaneously for 4 h. Decreased number of cells are showing cytoplasmic basophilia, nuclear and cellular condensation (arrows). Giemsa x20.

group (1.09 ± 0.15 and 2.78 ± 0.34 U/mL, respectively), and cisplatin+cornelian cherry group (0.83 ± 0.15 U/mL and 2.18 ± 0.32 U/mL, respectively).

Discussion

It is well known that cisplatin causes nephrotoxicity [4–10]. In cisplatin therapy, pathological changes in kidney have been described as focal acute tubular necrosis, affecting primarily the distal convoluted tubules and collecting ducts, dilatation of convoluted tubules and formation of casts [7]. Previous studies have demonstrated that exposure to cisplatin caused renal injury through oxidative stress [17, 19, 21, 56].

The potential beneficial effects of natural antioxidants in the treatment and prevention of various disease have been well established. Growing body of evidence indicate that natural substances derived mainly from plants may play a crucial role to alleviate cisplatin-induced renal oxidative stress. Badary et al. (2005) reported the protective effect of naringenin, a natural dietary antioxidant, against cisplatin-induced alterations in renal cortex antioxidant defense system in rats [28]. Tangeretin reduced renal oxidative stress due to cisplatin by decreased lipid peroxides with concomitant augmentation of glutathione and glutathione peroxidase, so that attenuated cisplatin-induced renal injury in rats [57]. Quercetin, a common bioflavonoid in fruit and vegetables, has been shown to reduce cisplatin toxicity in cultured tubular epithelial cells by scavenging of free oxygen radicals [31]. It has been demonstrated that anthocyanin-rich *Seoritae* extract may ameliorate renal oxidative stress via activation of adenosine

Table 2: Oxidative stress parameters of the treatment groups (n = 4).

Groups	MDA (nmol/mL)	GSH (nmol/mL)	GPx (U/mL)	SOD (U/mL)
Control	0.96 ± 0.07 ^a	2.51 ± 0.37 ^a	0.96 ± 0.13 ^{a,b}	2.42 ± 0.30 ^{a,b}
Cornelian cherry	0.90 ± 0.07 ^a	2.64 ± 0.39 ^a	1.09 ± 0.15 ^a	2.78 ± 0.34 ^a
Cisplatin	4.49 ± 0.31 ^b	0.73 ± 0.08 ^b	0.31 ± 0.07 ^c	1.16 ± 0.13 ^c
Cisplatin + cornelian cherry	1.09 ± 0.26 ^a	2.33 ± 0.42 ^a	0.83 ± 0.15 ^{a,b}	2.18 ± 0.32 ^b

^{a,b,c}Means with different superscripts within a column differ significantly ($p < 0.05$, Duncan's multiple range test).

monophosphate-activated protein kinase [58]. Sahu et al. (2013) demonstrated that hesperidin attenuates cisplatin-induced acute renal injury by decreasing oxidative stress which the major patho-mechanisms of cisplatin induced nephrotoxicity [59]. Natural antioxidant extract supplementation was also shown to prevent cisplatin-induced kidney failure through strengthening the renal antioxidant system and eliminating oxidation reactions [60]. These studies may suggest that natural antioxidants have a potential nephroprotective role.

Cornelian cherry has been indicated as valuable source of substances including ascorbic acid, anthocyanins and polyphenols with high antioxidant activity [35–42, 61]. It is increasingly thought that cornelian cherry may play preventive and therapeutic roles in oxidative stress-related diseases. In a recent study, freeze-dried cornelian cherry fruit addition to diet has been evaluated to verify the hypothesis of protective impact of cornelian cherry as an antioxidant. Researchers demonstrated elevated catalase activity upon cornelian cherry supplementation in the brain tissue of Wistar rats [62]. Cornelian cherry treatment ameliorated myocardial injury and enhanced the antioxidant defense against carbon tetrachloride-induced cardiotoxicity in rats and exhibited cardioprotective properties. Treatment of cornelian cherry in carbon tetrachloride-treated rats significantly decreased the increased levels of myocardial lipid peroxides and significantly increased the myocardial endogenous antioxidants (glutathione peroxidase, superoxide dismutase and catalase) levels [63]. The protective effect of cornelian cherry fruit extract in carbon tetrachloride-induced hepatotoxicity has been demonstrated by decreased liver MDA concentration in male rats [43]. Es Haghi et al. (2014) reported that treatment of rats with 300 mg/kg and 700 mg/kg doses of cornelian cherry fruit extract improved the level of antioxidant enzymes such as SOD, CAT and GPx, protected kidney from oxidative stress induced by carbon tetrachloride and also they suggested the protective effects of cornelian cherry fruit extract in attenuating carbon tetrachloride induced morphological abnormalities in the glomerular and tubular compartments [64]. Furthermore,

cornelian cherry has been shown to decrease MDA and increase GSH concentrations in the liver of hypercholesterolemic rabbits [41]. However, there is, as yet, no evidence about the effect of cornelian cherry fruit extract on cisplatin-induced nephrotoxicity. In the present in vitro study, we have demonstrated that cornelian cherry fruit extract supplementation significantly reduced cisplatin-induced oxidative stress in Vero cell culture. There was a significant increase of MDA concentration in cisplatin-exposed group as compared to the control group, cornelian cherry group and cisplatin + cornelian cherry-exposed group. The administration of cornelian cherry fruit extract to cisplatin-exposed Vero cell culture significantly increased the GSH concentration. In this study, decreased activities of GPx and SOD in culture medium exposed to cisplatin indicates that these enzymes were consumed due to increased oxidative stress. However, GPx and SOD activities significantly elevated following cornelian cherry administration.

Conclusions

In conclusion, the present study indicate that cornelian cherry fruit extract supplementation significantly alleviates the cisplatin-induced oxidative stress in Vero cell culture. Cornelian cherry could be an effective strategy to prevent cisplatin-induced renal damage. However, further experimental studies are prerequisite on this issue before clinical application can be recommended.

Conflict of interest statement: The authors have no conflict of interest.

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