Research in Pharmaceutical Sciences, December 2017; 12(6): 510-516
Received: December 2016
Accepted: June 2017

School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Original Article

Effects of *Cornus mas* fruit hydro-methanolic extract on serum antioxidants, lipid profile, and hematologic parameters following cisplatin-induced changes in rats

Atefe Mohammadzadeh Vardin[1], Bita Abdollahi[2], Morteza Kosari-Nasab[2], and Mehran Mesgari Abbasi[2,*]

[1]*Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, I.R. Iran.*
[2]*Student Research Committee, Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, I.R. Iran.*

Abstract

Cisplatin (Cis) has serious adverse side-effects that limit its clinical use. The mechanism underlying the effects is complex, including mitochondrial oxidative stress and inflammation. This study investigated whether *Cornus mas*, a fruit with high antioxidant contents, hydro-methanolic extract (CME) can modulate the cisplatin-induced changes. Forty Wistar rats were divided into a control group, Cis group, CME group, CME 300 + Cis group, and the CME 700 + Cis group. After the intervention, blood samples were taken for biochemical and hematological analysis. CME analysis showed noticeable total phenol and total antioxidant contents. The plasma glutathione peroxidase and catalase levels were significantly decreased and malondialdehyde and blood hemoglobin levels were significantly increased in the Cis group, which were reversed to the control levels in the CME + Cis groups. In the CME group, the red blood cell count was significantly lower and the red cell distribution width and hemoglobin distribution width levels were significantly higher. In the Cis-treated group, white blood cells, neutrophils, monocytes, basophils, and large unstained cells were significantly increased and lymphocytes were significantly decreased when compared with the control group that was reached to non-significant levels in CME 700 + Cis group. The blood cholesterol and high density lipoprotein in all CME-treated groups were significantly decreased. The eosinophils increased in the CME group significantly. The results showed considerable total antioxidant and total phenol contents and relative protective effects of CME against Cis-induced antioxidant and hematologic changes in rats.

Keywords: Antioxidant; Cisplatin; *Cornus mas*; Lipid profile; Hematologic parameters

INTRODUCTION

Cisplatin, a platinum-based therapeutic, is a chemotherapeutic agent that is widely used for the treatment of many human solid tumors. However, serious adverse effects, for example its neuro-toxic and nephro-toxic effects, limit its clinical use (1-3). Cisplatin therapeutic effects, as well as its adverse effects, are dose-dependent. The mechanism underlying cisplatin-induced unwanted side effects is complex and has not been fully understood. Mitochondrial oxidative stress, DNA damage, inflammation, and apoptosis of normal tissues are some of the side effects of cisplatin in tissues (3-6).

Cornus mas L. (Cornelian cherry, *C. mas*) is a medicinal plant that belongs to the Cornacea species (7,8). The plant is found in parts of Asia, including the north-west forests of Iran (Arasbaran, East Azerbaijan) and also central and southern Europe (8). The fruit of the Cornelian cherries are typically olive-shaped, 10-23 mm in length, single-seeded red fruits with a sweet-sour taste. The fruits are rich in sugar, organic acids, oxalic acid, tannins, anthocyanins, phenols, flavonoids, and other antioxidants. Fresh Cornelian cherry fruits contain B1, B2, C, and E vitamins, as well as folic acid (7-9). The fruits have been used for the treatment of many disorders in traditional and conventional medicine (8-10).

*Corresponding author: M. Mesgari Abbasi
Tel: +98-9141168681, Fax: +98-4133363231
Email: mesgarim@tbzmed.ac.ir

Access this article online

Website: http://rps.mui.ac.ir

DOI: 10.4103/1735-5362. 217431

The present study was performed to investigate the effects of *C. mas* as a natural antioxidant (11) on the blood lipid profile, antioxidant enzymes, and hematologic parameters of male Wistar rats, as well as to analyze the probable effects of *C. mas* fruit hydro-methanolic extract on the parameters after cisplatin administration.

MATERIALS AND METHODS

Plant ingredients and extraction

The *C. mas* fruits were purchased from the suburbs of Kaleibar (East Azarbaijan, Iran). The fruits were washed and their seeds were removed manually. The fruit parts were air-dried and then turned into a coarse powder. Then, 500 g of the fine powder was extracted by methanol (Merck, Germany) and water mixture in the ratio of 7:3 at 25 ± 2 °C. The mixture was then filtered (0.45 µ pore size) and the solvents were completely removed by a rotary vacuum evaporator (Hidolf, Germany) at 40 °C. Finally, the *C. mas* methanolic extract (CME) was frozen and stored at -80 °C until it was ready to use (8).

Analyses of Cornus mas hydro-methanolic extract

The total phenolic contents of the CME were assayed using Folin-Ciocalteu reagent and gallic acid standard curve, and expressed as mg of gallic acid equivalents (GAE) per gram of the extract (12). The total flavonoids of the CME were determined using the spectrophotometric method as described by Vador, *et al.* (13,14). The antioxidant properties of the CME were assayed by the DPPH assay method (13) and the 50% reduction capacity (RC_{50}) was expressed as mg/mL.

Animals

Forty male Wistar rats, weighing 200 ± 20 g, were obtained from Pasteur Institute (Karaj, Iran). The animals were housed in a temperature-controlled room (22 ± 2 °C) with 12/12 h of light/dark cycles with a standard rat pellet diet and clean drinking water *ad libitum*. All the animal procedures were approved by the Animal Research Ethics Committee of Tabriz University of Medical Sciences (ethical approval code: 5-4-1171) and were carried out in accordance with the related guidelines.

Experimental design

The animals were randomly divided into five groups (n = 8) as follows: (1) the normal control group; orally received distilled water (DW) daily by gavage needle for 16 days and an IP injection of sterile DW water on day 11; (2) the CME group, orally received 700 mg/kg bw CME daily for 16 days and an IP injection of DW on day 11; (3) the CME 300 + Cis group, orally received 300 mg/kg bw CME daily for 16 days and an IP injection of 5 mg/kg bw cisplatin on day 11; (4) the CME 700 + Cis group, orally received 700 mg/kg bw CME daily for 16 days and an IP injection of 5 mg/kg bw cisplatin on day 11; (5) the Cis group, orally received DW daily for 16 days and an IP injection of 5 mg/kg cisplatin on day 11 (15-17).

At the end of the experimental period, the blood samples were taken from each animal by cardiac puncture. The samples were transferred into tubes containing ethylenediaminetetraacetic acid (EDTA) as the hematology anticoagulant and clot tubes for biochemical analyses.

The clot tubes were centrifuged at 2000 g at 4 °C for 10 min. The blood serum samples were separated and stored in a freezer at -80 °C until use.

Biochemical analyses

The blood triglyceride, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were determined by the enzymatic methods using commercial kits (Pars Azmun, Karaj, Iran). The total antioxidant capacity (TAC), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were assayed by commercial kits (Randox, Italy). Catalase activities were determined by a Cayman kit (USA). Malondialdehyde (MDA) contents were analyzed by a barbituric acid method. After calibrating and validating these tests using several calibrators, the automated Abbott biochemistry analyser (Alcyon 300, USA) was used for performing the tests.

Hematological analyses

The hematology indices including hemoglobin (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red blood cells (RBC), packed cell volume (PCV), red cell distribution width (RDW), hemoglobin distribution width (HDW), platelet, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), basophil, eosinophil, lymphocyte, leucocyte, monocyte, neutrophil, and white blood cells (WBC) were assayed by the Technicon-H1 (Bayer, Germany) hematology analyzer (8). The results of the analyzer were checked by microscopic analyses of the stained blood smears (May-Grünwald and Giemsa-Romanowski).

Statistical analyses

Statistical analyses were performed using SPSS (V. 20) for Windows (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) followed by Tukey post-hoc multiple comparison tests was used to compare the parameters between the groups. The data were expressed as mean ± standard deviation (SD). *P*-values less than 0.05 and 0.01 were considered statistically significant.

RESULTS

Antioxidant indices of Cornus mas hydro-methanolic extract

Composition of the CME in terms of poly-phenolic and flavonoid compounds and antioxidant properties are represented in Table 1.

Effects on lipid profile and antioxidant enzymes

Table 2 displays the status of all biochemical parameters measured in this research. The effects of the cisplatin on blood serum triglyceride, cholesterol, HDL, and LDL levels were not statistically significant ($P > 0.05$). However, the lowering effect of CME on blood cholesterol and HDL in all CME-treated groups was significant ($P < 0.01$). The serum GPx ($P < 0.05$) and catalase ($P < 0.01$) levels were significantly decreased and the MDA level ($P < 0.05$) was significantly increased in the Cis group when compared with the control. The administration of CME, together with Cis, reversed the GPx, catalase, and MDA results to the values that were not significantly different from the control levels (Table 2).

Effects on red blood cell parameters

Table 3 displays the status of red blood cell parameters explored. The Hb of the rats in the Cis group was significantly higher than that of the control group ($P < 0.01$). However, in the co-treated groups, the Hb levels were not significant ($P > 0.05$). On the other hand, in the CME group, the RBC counts were significantly lower ($P < 0.01$) and the RDW, ($P < 0.01$) and HDW, ($P < 0.05$) levels were significantly higher than those of the control group (Table 3).

Effects on platelet parameters

Table 4 displays the values of platelet parameters measured in this study. Significant increase of platelet in the CME 300 + Cis group ($P < 0.01$), a decrease of MPV in the Cis group ($P < 0.05$) and an increase of PCT in the CME and CME 300 + Cis groups ($P < 0.01$) in comparison with the control group were observed.

Effects on white blood cell parameters

Table 4 displays the values of WBC parameters assayed in this study. In the cisplatin-treated group, WBCs ($P < 0.05$), neutrophils ($P < 0.01$), monocytes ($P < 0.01$), basophils (count, $P < 0.05$), and large unstained cells ($P < 0.01$) were significantly increased, while lymphocytes (percent, $P < 0.01$) were significantly decreased when compared with the control group. The CME co-administration showed no significant reduction on the WBC levels when compared to the Cis group ($P > 0.05$). However, the neutrophil, monocytes, basophils (count), large unstained cells, and lymphocytes (percent) values reached control non-significant levels in the CME 700 + Cis group (Table 5). On the other hand, CME administration in the CME group caused a significant enhancement of the eosinophil values when compared to the control group ($P < 0.01$).

Table 1. Composition of *Cornus mas* hydro-methanolic fruit extract (CME) (n = 3).

	Antioxidant activity (RC_{50}, µg/mL)	**Total phenolic content (mg GAE/g extract)**	**Total flavonoid (%)**
CME	252.4 ± 0.4	136.5 ± 0.4	0.09 ± 0.02

Table 2. Blood serum lipid profile and antioxidant parameters of the *Cornus mas* hydro-methanolic fruit extract and cisplatin treated rats (n = 8).

Parameter/Group	**Control**	**CME**	**CME 300 + Cis**	**CME 700 + Cis**	**Cis**
Cholesterol (mg/dL)	92.1 ± 14.1	66.3 ± 7.8^{**+}	66.8 ± 3.3^{**+}	66.2 ± 5.1^{**+}	83.0 ± 7.9
HDL (mg/dL)	61.0 ± 3.3	52.7 ± 4.3^{**++}	51.0 ± 3.3^{**++}	52.0 ± 3.7^{**++}	63.0 ± 3.7
LDL (mg/dL)	10.8 ± 4.1	10.1 ± 5.0	12.3 ± 4.1	6.0 ± 2.8	17.3 ± 7.0
Triglyceride (mg/dL)	51.0 ± 13.9	76.3 ± 23.4	110.8 ± 44.7	67.6 ± 10.5	81.3 ±
GPx (U/mL)	3.1 ± 0.2^{+}	2.9 ± 0.2	3.3 ± 0.2^{++}	3.0 ± 0.2	2.8 ± 0.2*
SOD (U/mL)	26.8 ± 3.7	28.2 ± 3.3	29.9 ± 3.7	28.2 ± 4.4	40.0 ± 2.8
CAT (nmol/min/mL)	11.4 ± 1.9^{++}	10.9 ± 2.5^{++}	10.1 ± 1.8^{+}	7.5 ± 2.0*	6.1 ± 1.2**
MDA (nmol/mL)	5.5 ± 0.7^{+}	5.4 ± 0.4^{+}	6.0 ± 0.7	5.6 ± 0.2	6.6 ± 0.9*
TAC (mmol trolox equivalent/mL)	0.6 ± 0.2	0.8 ± 0.2	0.6 ± 0.1	0.4 ± 0.1^{+}	0.7 ± 0.2

Data are expressed as mean ± SD, the parameters with significant differences ($P < 0.05$). CME, *Cornus mas* hydro-methanolic fruit extract; Cis, cisplatin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GPx, glutathione peroxidase; SOD, superoxide dismutase; CAT, catalase; MDA, malondialdehyde; TAC, total antioxidant capacity. * and ** significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the control group. $^{+}$ and $^{++}$ significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the Cis-treated rats.

Table 3. Red blood cell parameters of the *Cornus mas* fruit hydro-methanolic extract and cisplatin treated rats (n = 8).

Parameter/Group	**Control**	**CME**	**CME 300 + Cis**	**CME 700 + Cis**	**Cis**
RBC (10^{12}/L)	7.74 ± 0.14	7.0 ± 0.2^{**++}	7.7 ± 0.3	7.8 ± 0.4	7.8 ± 0.5
Hb (g/dL)	13.90 ± 0.48^{++}	13.6 ± 0.2^{++}	14.3 ± 0.5^{+}	14.1 ± 0.9^{+}	15.3 ± 0.4**
PCV (%)	42.90 ± 0.80	40.0 ± 2.3	43.6 ± 1.2	43.0 ± 1.5	43.4 ± 3.5
MCV (fL)	55.40 ± 1.10	56.3 ± 4.8	57.2 ± 2.6	55.0 ± 2.8	55.3 ± 1.8
MCH (pg)	18.10 ± 0.60	19.4 ± 1.6	18.7 ± 0.8	18.0 ± 0.7	19.8 ± 3.0
MCHC (g/dL)	32.60 ± 0.59	34.9 ± 5.7	32.6 ± 0.4	32.8 ± 0.7	36.0 ± 6.4
RDW (%)	14.10 ± 0.80	16.8 ± 1.8^{**++}	13.8 ± 0.3	14.2 ± 0.4	14.1 ± 0.3
HDW (g/dL)	3.20 ± 0.21	3.9 ± 0.6*	3.0 ± 0.1	3.5 ± 0.2	3.4 ± 0.5

Data are expressed as mean ± SD, the parameters with significant differences ($P < 0.05$). CME, *Cornus mas* fruit hydro-methanolic extract; Cis, cisplatin; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV; mean corpuscular volume; RBC, red blood cell count; PCV, packed cell volume; RDW, red cell distribution width; HDW, hemoglobin distribution width. * and ** significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the control group. $^{+}$ and $^{++}$ significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the Cis-treated rats.

Table 4. Platelet parameters of the *Cornus mas* fruit hydro-methanolic extract and cisplatin treated rats (n = 8).

Parameter/Group	**Control**	**CME**	**CME 300 + Cis**	**CME 700 + Cis**	**Cis**
PLT (10^{9}/L)	667.5 ± 57.3	780.8 ± 114.0	885.0 ± 68.4^{**++}	770.8 ± 55.4	652.5 ± 108.0
MPV (fL)	4.3 ± 0.1^{+}	4.3 ± 0.2^{++}	4.3 ± 0.2^{+}	4.1 ± 0.2	3.9 ± 0.1*
PDW (%)	56.1 ± 2.1	58.5 ± 4.0	55.7 ± 1.6	56.4 ± 2.7	59.1 ± 4.8
PCT (%)	0.32 ± 0.02	0.40 ± 0.04^{**++}	0.43 ± 0.04^{**++}	0.35 ± 0.04	0.31 ± 0.02

Data are expressed as mean ± SD, the parameters with significant differences ($P < 0.05$). CME, *Cornus mas* fruit hydro-methanolic extract; Cis, cisplatin; PLT, platelet; MPV; mean platelet volume, PCT; total platelet mass, PDW; platelet distribution width. * and ** significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the control group. $^{+}$ and $^{++}$ significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the Cis-treated rats.

Table 5. White blood cell parameters of the *Cornus mas* fruit hydro-methanolic extract and cisplatin treated rats (n = 8).

Parameter/Group	Control	CME	CME 300 + Cis	CME 700 + Cis	Cis
WBC ($\times10^9$/L)	$5.84 \pm 0.51^{+}$	7.01 ± 0.50	$7.78 \pm 0.58^{*}$	$7.54 \pm 1.92^{*}$	$7.70 \pm 0.75^{*}$
NEUT ($\times10^9$/L)	$0.58 \pm 0.08^{++}$	$0.68 \pm 0.11^{++}$	$0.74 \pm 0.17^{++}$	$0.66 \pm 0.09^{++}$	$1.08 \pm 0.27^{**}$
NEUT (%)	$10.1 \pm 1.0^{++}$	$9.9 \pm 1.2^{++}$	$9.6 \pm 0.9^{++}$	$9.8 \pm 0.6^{++}$	$13.4 \pm 1.1^{**}$
LYMP ($\times10^9$/L)	4.2 ± 0.5	4.8 ± 0.4	4.8 ± 0.2	$5.2 \pm 0.6^{*}$	4.3 ± 0.7
LYMP (%)	$72.4 \pm 5.9^{++}$	$67.9 \pm 6.9^{+}$	62.4 ± 8.8	$67.7 \pm 7.0^{+}$	$54.6 \pm 6.9^{**}$
MONO ($\times10^9$/L)	$0.78 \pm 0.18^{++}$	$0.94 \pm 0.19^{++}$	$1.60 \pm 0.38^{**}$	$1.17 \pm 0.19^{+}$	$1.82 \pm 0.58^{**}$
MONO (%)	$13.0 \pm 2.5^{++}$	$13.8 \pm 2.4^{++}$	$20.6 \pm 4.9^{**}$	$16.3 \pm 1.6^{++}$	$25.2 \pm 3.6^{**}$
EOS ($\times10^9$/L)	0.10 ± 0.02	$0.33 \pm 0.18^{**++}$	0.20 ± 0.11	0.21 ± 0.07	0.07 ± 0.04
EOS (%)	1.56 ± 0.41	$4.88 \pm 1.21^{**++}$	2.55 ± 1.04	$2.88 \pm 0.79^{+}$	1.15 ± 0.93
BASO ($\times10^9$/L)	$0.02 \pm 0.00^{+}$	$0.02 \pm 0.00^{+}$	0.03 ± 0.00	0.03 ± 0.01	$0.04 \pm 0.02^{*}$
BASO (%)	0.27 ± 0.08	0.23 ± 0.13	0.40 ± 0.14	0.34 ± 0.11	0.58 ± 0.44
LUC ($\times10^9$/L)	$0.16 \pm 0.02^{++}$	$0.21 \pm 0.02^{+}$	$0.35 \pm 0.06^{**}$	0.22 ± 0.04	$0.31 \pm 0.09^{**}$
LUC (%)	$2.65 \pm 0.58^{++}$	$3.05 \pm 0.56^{++}$	$4.45 \pm 1.14^{*}$	$3.14 \pm 1.04^{+}$	$4.98 \pm 1.07^{**}$

Data are expressed as mean ± SD, the parameters with significant differences ($P < 0.05$). CME, *Cornus mas* fruit hydro-methanolic extract, Cis, cisplatin; BASO, basophils; *C. mas*, *Cornus mas*; EOS, eosinophils; LYMP, lymphocytes; LUC, large unstained cells; MONO, the monocytes; NEUT, the absolute neutrophils; WBC, white blood cell. * and ** significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the control group. + and ++ significantly different at $P < 0.05$ and $P < 0.01$ (respectively) when compared with the Cis-treated rats.

DISCUSSION

Using an experimental rat model, we evaluated the lipid profile, hematologic parameters, and the activity of the antioxidant enzymes in cisplatin-treated rats with and without CME co-administration. The cisplatin caused no significant difference to the lipid profile when compared to the control group. The results are consistent with those of Ellis, *et al*., who found no significant adverse effects on the plasma lipid profile after cisplatin chemotherapy in patients (18). There are, however, some findings that are not in line with our findings. In a study by Abdel-Gayoum, *et al*., on serum total cholesterol, triglyceride concentrations were increased, but no severe changes in LDL- or HDL-cholesterol fractions were observed in nephrotic rats five days after a single cisplatin IP injection (19). On the other hand, the significant total cholesterol and HDL lowering effects of CME were demonstrated in our findings, which were in agreement with the current understandings of traditional medicine specialists with regard to the cardiovascular protective effects of *C. mas* (8). There were some reports about the hypolipidemic effects of natural products anthocyanins (20).

In our study, some results showed an increasing effect of cisplatin on Hb and a decreasing effect of CME on RBCs in rats (Table 3). Platelet parameters indicated the enhancement effects of cisplatin on MPV in the Cis group ($P < 0.05$), and CME on PCT in the CME and CME 300 + Cis groups ($P < 0.01$). MPV increases during the platelet activation and also during the platelet swelling (21). Increased MPV indicate a large number of larger and younger platelets in the blood, probably due to the bone marrow rapid production and release into the blood circulation. The MPV values reached non-significant levels in the CME + Cis groups. It is demonstrated that antioxidants reduce the platelet activity through stimulation of prostacyclin synthesis and by scavenging of the peroxides (22,23). It is evident that polyphenols can stop NADPH oxidase enzyme of platelets. Therefore, inhibiting the production of O_2^- and increasing the biological power of NO consequently regulates glycoprotein pine receptors on the platelet membrane surface; this, in turn, inhibits the activation of platelets and their adherence during inflammation and thrombosis processes (24). As a result, it is probable that the antioxidant and phenolic compounds of *C. mas* fruits prevent the platelet activity without bone marrow depression.

In the findings of WBC-related parameters, a significant enhancement in WBC and inflammatory cells (neutrophils, monocytes, basophils, and large unstained cells), as well as a reduction in lymphocytes, was observed in the cisplatin-treated group when compared to

the control group. The values of the parameters had a trend to non-significant levels in the co-treated (CME + Cis) groups (Table 5). There is evidence to show that the myeloperoxidase (MPO) activity increases in cisplatin-treated rats, indicating that there is high neutrophil infiltration in tissues (25). The MPO inhibition and interaction activity of the polyphenols, and other antioxidants, were also reported by some researchers (26,27). Inflammation has an important role in cisplatin-induced pathophysiology and our findings are in accordance with previous studies (28). Oxidative stress induced by cisplatin can activate the nuclear factor kappa beta (NF-kβ) transcription factor that promotes the production of TNF-α mRNA and TNF-α as the pro-inflammatory cytokines. In cisplatin-induced adverse effects, the levels of the cytokines increase (29). On the other hand, CME caused a significant increase on eosinophils in the CME-treated group. This may be due to a reduction in the eosinophil apoptosis. Apoptosis of eosinophils is mediated by stimulators of cellular oxidative metabolisms and can be inhibited by antioxidants (30). The results suggest that the antioxidant properties of CME may inhibit the eosinophil apoptosis.

The findings of the present study showed a significant reduction in GPx and catalase activities and an enhancement in serum MDA values in the cisplatin group, but which were reversed in the control levels in the CME co-treated groups. These results indicate oxidative stress induced by cisplatin, which can protects by CME administration.

The oxidative stress induction by cisplatin has been proven to be involved in cisplatin-induced toxicity (31-33). Oxidative stress, apoptosis, inflammation, and fibrogenesis are involved in the *in vivo* mechanism of cisplatin-induced changes and injuries. Reactive oxygen species (ROS) can directly act on cell components, such as lipids and proteins, and destroy their structure. Cisplatin can increase the presence of the produced ROS through all these pathways, resulting in the pathogenesis of acute cisplatin-induced adverse effects (31). The increase of the rats' serum MDA content after cisplatin administration suggests lipid peroxidation, which is in agreement with the results of the previous studies (2,33). This could be as a result of an increased hydrogen peroxide concentration produced due the depletion of antioxidant enzymes, such as catalase and GPx activities (32). In the CME analysis, we established that CME has high antioxidant and polyphenol contents (Table 1). However, the restoration of GPx and catalase activities and the reduced serum MDA content in the CME co-treated rats suggest an improvement in the *in vivo* antioxidant status, which may be a function of the antioxidant properties of the CME phenolic and antioxidant contents.

CONCLUSION

In summary, the results of the present study demonstrate that *C. mas* fruit extract can provide significant protection against unwanted cisplatin-induced changes in serum antioxidant enzymes, lipid profile, and hematologic parameters. There is no evidence to show that natural antioxidants interfere with cancer therapeutics *in vivo*. Moreover, co-administration of natural antioxidants, such as *C. mas*, and chemotherapy drugs, may enhance the effectiveness of the treatment and reduce the unwanted side effects.

ACKNOWLEDGEMENTS

The authors would like to thank the heads, members and staffs of the Student Research Committee and Drug Applied Research Center for their financial and technical support.

REFERENCES

1. Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney Int. 2008;73(9):994-1007.
2. Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. Toxins (Basel). 2010;2(11):2490-518.
3. Almaghrabi OA. Molecular and biochemical investigations on the effect of quercetin on oxidative stress induced by cisplatin in rat kidney. Saudi J Biol Sci. 2015;22(2):227-231.
4. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014;740:364-378.
5. Ozkok A, Edelstein CL. Pathophysiology of cisplatin-induced acute kidney injury. Biomed Res Int. 2014;2014:967826.

6. Pabla N, Dong Z. Curtailing side effects in chemotherapy: a tale of PKCdelta in cisplatin treatment. Oncotarget. 2012;3(1):107-111.
7. Zarei L, Shahrooz R, Sadrkhanlou R, Malekinejad H, Ahmadi A, Bakhtiary Z. Protective effects of cornus mas extract on *in vitro* fertilization potential in methotrexate treated male mice. Vet Res Forum. 2015;6(1):55-61.
8. Abdollahi B, Mesgari Abbasi M, Zakeri Milani P, Nourdadgar AS, Banan Khojasteh SM, Nejati V. Hydro-methanolic extract of cornus MAS L. and blood glucose, lipid profile and hematological parameters of male rats. Iran Red Crescent Med J. 2014;16(5):e17784.
9. Alavian SM, Banihabib N, Es Haghi M, Panahi F. Protective effect of *Cornus mas* fruits extract on serum biomarkers in CCl4-induced hepatotoxicity in male rats. Hepat Mon. 2014;14(4):e10330.
10. Vareed SK, Reddy MK, Schutzki RE, Nair MG. Anthocyanins in *Cornus alternifolia*, *Cornus controversa*, *Cornus kousa* and *Cornus florida* fruits with health benefits. Life Sci. 2006;78(7):777-784.
11. Francik R, Kryczyk J, Krosniak M, Berkoz M, Sanocka I, Francik S. The neuroprotective effect of *cornus* MAS on brain tissue of Wistar rats. Scientific World J. 2014;2014: Article ID 847368, 9 pages.
12. Ghasemi Pirbalouti A, Siahpoosh A, Setayesh M, Craker L. Antioxidant activity, total phenolic and flavonoid contents of some medicinal and aromatic plants used as herbal teas and condiments in Iran. J Med Food. 2014;17(10):1151-1157.
13. Mesgari Abbasi M, Heidari R, Amini afshar R, Zakeri Milani P, Ghamarzad Shishavan N. Effects of pomegranate seed methanolic extract on methotrexateinduced changes in rat liver antioxidant compounds. Curr Top Nutraceutical Res. 2015;13(3):153-159.
14. Vador N, Vador B, Hole R. Simple spectrophotometric methods for standardizing ayurvedic formulation. Indian J Pharm Sci. 2012;74(2):161-163.
15. Eshaghi M, Zare S, Banihabib N, Nejati V, Farokhi F, Mikaili P. Cardioprotective effect of cornus mas fruit extract against carbon tetrachloride induced-cardiotoxicity in albino rats. J Basic Appl Sci Res. 2012;2(11):11106-11114.
16. Naghizadeh B, Boroushaki MT, Vahdati Mashhadian N, Mansouri MT. Protective effects of crocin against cisplatin-induced acute renal failure and oxidative stress in rats. Iran Biomed J. 2008;12(2):93-100.
17. Tikoo K, Bhatt DK, Gaikwad AB, Sharma V, Kabra DG. Differential effects of tannic acid on cisplatin induced nephrotoxicity in rats. FEBS Lett. 2007;581(10):2027-2035.
18. Ellis PA, Fitzharris BM, George PM, Robinson BA, Atkinson CH, Colls BM. Fasting plasma lipid measurements following cisplatin chemotherapy in patients with germ cell tumors. J Clin Oncol. 1992;10(10):1609-1614.
19. Abdel-Gayoum AA, El-Jenjan KB, Ghwarsha KA. Hyperlipidaemia in cisplatin-induced nephrotic rats. Hum Exp Toxicol. 1999;18(7):454-459.
20. Kwon SH, Ahn IS, Kim SO, Kong CS, Chung HY, Do MS, *et al*. Anti-obesity and hypolipidemic effects of black soybean anthocyanins. J Med Food. 2007;10(3):552-556.
21. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia. 2010;14(1):28-32.
22. Salonen JT. Antioxidants and platelets. Ann Med. 1989;21(1):59-62.
23. Sobotkova A, Masova-Chrastinova L, Suttnar J, Stikarova J, Majek P, Reicheltova Z, *et al*. Antioxidants change platelet responses to various stimulating events. Free Radic Biol Med. 2009;47(12):1707-1714.
24. Pignatelli P, Di Santo S, Buchetti B, Sanguigni V, Brunelli A, Violi F. Polyphenols enhance platelet nitric oxide by inhibiting protein kinase C-dependent NADPH oxidase activation: effect on platelet recruitment. FASEB J. 2006;20(8):1082-1089.
25. Aydin B, Unsal M, Sekeroglu ZA, Gulbahar Y. The antioxidant and antigenotoxic effects of pycnogenol((R)) on rats treated with cisplatin. Biol Trace Elem Res. 2011;142(3):638-650.
26. Kohnen S, Franck T, Van Antwerpen P, Boudjeltia KZ, Mouithys-Mickalad A, Deby C, *et al*. Resveratrol inhibits the activity of equine neutrophil myeloperoxidase by a direct interaction with the enzyme. J Agric Food Chem. 2007;55(20):8080-8087.
27. Kurutas EB, Cetinkaya A, Bulbuloglu E, Kantarceken B. Effects of antioxidant therapy on leukocyte myeloperoxidase and Cu/Zn-superoxide dismutase and plasma malondialdehyde levels in experimental colitis. Mediators Inflamm. 2005;2005(6):390-394.
28. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci. 2007;334(2):115-124.
29. Ramesh G, Reeves WB. TNF-alpha mediates chemokine and cytokine expression and renal injury in cisplatin nephrotoxicity. J Clin Invest. 2002;110(6):835-842.
30. Wedi B, Straede J, Wieland B, Kapp A. Eosinophil apoptosis is mediated by stimulators of cellular oxidative metabolisms and inhibited by antioxidants: involvement of a thiol-sensitive redox regulation in eosinophil cell death. Blood. 1999;94(7):2365-2373.
31. Silici S, Ekmekcioglu O, Kanbur M, Deniz K. The protective effect of royal jelly against cisplatin-induced renal oxidative stress in rats. World J Urol. 2011;29(1):127-132.
32. Akomolafe SF, Akinyemi AJ, Anadozie SO. Phenolic acids (gallic and tannic acids) modulate antioxidant status and cisplatin induced nephrotoxicity in rats. Int Sch Res Notices. 2014;2014: Article ID 984709, 8 pages.
33. Verma PK, Raina R, Sultana M, Singh M, Kumar P. Total antioxidant and oxidant status of plasma and renal tissue of cisplatin-induced nephrotoxic rats: protection by floral extracts of *Calendula officinalis* Linn. Ren Fail. 2016;38(1):142-150.