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Renoprotective Effect of *Centaurea choulettiana* Pomel (Asteraceae) Leaves on Cisplatin -induced Oxidative Stress and Renal dysfunction in Mice

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ABSTRACT

Several species of *Centaurea* genus are continuously used in traditional medicine. Cisplatin (CP) is still regarded as one of the principal chemotherapeutic agents used in the therapy of many human malignancies. However, the clinical use of CP is limited due to its serious nephrotoxicity. In this study we have investigated the possible renoprotective effects of *n*-BuOH extract of *Centaurea choulettiana* Pomel leaves (BECC) in a cisplatin-induced nephropathy model. The single dose administration of cisplatin (8 mg/kg body weight; ip) resulted in acute renal deterioration as evidenced by the elevation of blood urea nitrogen (BUN) level, creatinine level, renal oxidative stress associated with extensive vacuolization of epithelial cell, swelling, desquamation and necrosis as histopathological alterations. The mice pretreatment with BECC (150 mg/kg; 10 days) attenuated the increase renal dysfunction markers, creatinine (80.15 %), BUN (57.58%) and suppressed malondialdehyde (MDA) (54.90 %). The BECC pretreatment restored GSH level (63.29%) and reversed the antioxidant enzymes, CAT (67.61%), SOD (68.16%), GPX (66.38 %) and the GST activities (70.18 %). The vitamin E pretreatment suppressed MDA level (74.10%) preserved GSH level (80.59 %) and CAT, SOD, GPX, GST activities (84.35%, 85.68 %, 77.90 %, 86.63 %) respectively. These finding indicated the comparable preventive effect of both BECC and vitamin E. The histopathological protection was clearly confirmed by the reduction of renal MPO Level (52.21%). Both biochemical results and histopathological evidence showed the renoprotective potential of *Centaurea choulettiana*, which was able to ameliorate CP-induced and renal dysfunction through its antioxidant capacity.

INTRODUCTION

In Algeria, the genus *Centaurea* (family *Asteraceae*) is represented by 45 species, of which 7 species are distributed in the Sahara (Mabberley, 1987). Several species belonging to this genus are exploited in traditional medicine such as antidiabetics (Kaij-A-Kamb *et al*., 1992), anti-rheumatic (Gonzalez, 1977) and antioxidant antioxidant (Azzouzi *et al*., 2016 a), as well as for the treatment of cancer (Arhoghro, 2012). Favonoids and sesquiterpene lactones as secondary metabolites have been isolated and purified from different species of this genus (Mezache *et al*., 2010). The medical uses of cisplatin (CP) as a chemotherapeutic agents against diverse tumours are often limited due toits adverse effects, mainly the severe nephrotoxicity (Chirino and Chaverri, 2009). Approximately 25-35% of the patients received cisplatin treatment expressed an irreversible renal damage associated with acute tubular necrosis (Arany *et al*., 2004; Yao *et al*., 2007).

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Cellular injury induced by cisplatin is a complex mechanism (Lieberthal, 1996; Dobyan *et al*., 1980; Pabla and Dong, 2008). Oxidative stress and inflammation are the utmost important processes involved in the nephrotoxicity induced by CP (Santos *et al*., 2007; Kuhad *et al*., 2006). A number of chemoprotective agents have been investigated for their potential anti-inflammatory and antioxidant effect in different models of nephrotoxicity induced by cisplatin. A marked renoprotection has been proved with the synthetic agent such as glutamine (Mora *et al*., 2003), the multiple-vitamin supplementation (Ajith *et al*., 2007; Maliakel *et al*., 2008), mirtazapine drug (Sener *et al*., 2012), N-acetylcysteine (Dickey *et al*., 2008; Luo *et al*., 2008; Abdelrahman *et al*., 2010), vitamin E and selenium, (Antunes *et al*., 2001; Naziroglu *et al*., 2004; Nematbakhshand Nasri, 2013). An intensive search for potential natural therapeutic agents for oxidative damage has been carried out in medicinal plants (Yilmaz *et al*., 2013). Medicinal plants and natural herbal products have potential antioxidant such as silymarin (Mansour, 2006), curcumin (Antunes *et al*., 2001; Abdelmaguid *et al*., 2010), quercetin (Francescato *et al*., 2004; Behling *et al*., 2006), Naringenin (Badary *et al*., 2005), grape seed and proanthocyanidin (Saad *et al*., 2009; Yousef *et al*., 2009), lycopene (Atessahin *et al*., 2005; Arhoghro *et al*., 2012), fish oil, (El-Gerbed *et al*., 2013), Royal jelly (Karadeniz *et al*., 2011), ginger extract (Ali *et al*., 2013), green tea (Khan *et al*., 2009), ellagic acid (Yuce *et al*., 2007).

Taking into consideration the popular uses of the Centaurea genus as an anti-inflammatory agent and in addition to our recent study that mentioned *Centaurea choulettiana* as antioxidant agent and has been proved rich in caffeic acid, chlorogenic acid, ferulic acid and in sesquiterpenes, the present investigation was performed for the first time to evaluate the renoprotective effects of the *n*-BuOH extract of *Centaurea choulettiana* (BECC) against nephrotoxicity induced by cisplatin in mice.

MATERIALS AND METHODS

Reagents and Chemicals

Cisplatin (*cis*-dichlorodiammine-platinum II, CP) was obtained from Center of Cancer Chemotherapy, Constantine-3.1,1-3,3-tetramethoxypropane.5,5′-dithio-bis-2-nitrobenzoic acid (DTNB), 1-chloro-2,4-dinitrobenzene (CDNB), GSH, *O*-dianisidine hydrochloride, thiobarbituric acid (TBA), trichloroacetic acid (TCA), malondialdehyde (MDA), hexadecyltrimethylammonium bromide (HTAB) were purchased from Sigma-Aldrich (USA). All other chemicals used were either of analytical grade and of the highest purity.

Plant Material and Extract Preparation

The collected flowers (May 2013) of *Centaurea choulettiana* from the M'Sila region, Algeria, were authenticated by Dr. Sarri Djamel, Department of Biology, M'Sila University, Algeria according to Quezel and Santa (Quezel and Santa, 1963). A voucher specimen has been deposited in the Herbarium of the VARENBIOMOL research unit University of Frères Mentouri Constantine 1 (CCA/05/2013**).**

A quantity of 1370 g of leaves of *Centaurea choulettiana* Pomel were dried at ambient temperature and cut into small pieces then macerated three times (24hours for each time) with methanol / H_2O (70 %). The extract obtained after filtration and evaporation was partitioned with solvents in increasing polarity: chloroform, ethyl acetate and *n*-butanol. Each phase was evaporated under reduced pressure. 14g of *n*-BuOH extract of leaves of *Centaurea choulettiana* Pome (BECC) as dried extract was obtained and subjected for the nephroprotective study. The choice of *n*-BuOHl eaves of *Centaurea choulettiana* extract for the present investigation was based on its richness in bioactive compounds (Azzouzi *et al*., 2016 a).

Animals and Experimental Design

Male *Wistar albino* mice were maintained in the controlled conditions of temperature and humidity with 12 hours light/dark cycle and fed with standard feed and water.The Ethics Committee of Animal Experimentation of Brother Mentouri university Constantine1approved all animal experiments which were in strict compliance with the United States National Institutes of Health.Guidelines for care and use of laboratory animals in biomedical research (Anusuya *et al*., 2013).

Twenty-four male adult mice (weight 30 ± 2 g) were divided into four equal groups (6 mice in each group).

group I (control), received by gavage 1 mL of 0.9 % NaCl saline solution for ten days.

group II (CP-mice group), received orally 1 mL of 0.9 % NaCl saline solution for ten days. At the last day, one hour afterwards the gavage, a single dose (8 mg/kg) of CP was injected intraperitoneally (ip).

group III (Vitamin E-mice group), received orally 100 mg/kg of vitamin E for ten days. One hour after later dose, a single dose (8 mg/kg) of CP was ip injected.

group IV (BECC- mice group), received orally 150 mg/kg of BECC for ten days. One hour after later dose, a single dose (8 mg/kg) of CP was ip injected.

All groups were sacrificed in the day 11by decapitation. After 18 hours of CP challenge, the blood samples were collected and centrifuged at 3000 rpm during 15 minutes at 4 °C. The obtained serum was stored at 4 °C for the assessment of renal function markers, namely blood urea nitrogen (BUN) and plasmatic creatinine level. These assessments were performed according to the standard procedures given along with the analysiskits purchased.The decapsulated renal tissues were quickly removed, rinsed in ice-cold saline and used immediately or stored frozen at -80 °C until further antioxidant parameter analysis.

Tissue Preparation and Assessment of Renal Oxidative Stress Markers

The renal cortex tissue was carefully separated from medulla. A 10% (w/v) homogenate was prepared using 0.25 M

sucrose, 1 mM EDTA and 0.05 M Tris-HCl solution, pH 7.4.A part of the homogenate was used for assessment of MDA (indicator of lipid peroxidation) measured by using 1,1,3,3-tetramethoxypropane as standard. The results were expressed as nmol MDA/g liver tissue (Ohkawa *et al*., 1979).

Another part of homogenate was centrifuged at 9600 rpm/min for 15 min at 4 °C to separate cytosolic fraction. The obtained fraction was subsequently used for determination of renal antioxidant markers. Reduced glutathione (GSH) was measured by the method of Sedlak and Hanus (1982), GSH levels were expressed as nmole of GSH/mg protein.The activity of glutathione S-transferase (GST) was determined on the basis of conjugation of GSH with CDNB, the GST activity was monitored at 340nm for 3min (Habig *et al*., 1974), and expressed as µmol/mg protein. Glutathione peroxidase (GPx) activity was assessed by the method of (Rotruck *et al*., 1975) based on the degradation of H_2O_2 in the presence of GSH, the GPx activity was expressed as nmol/min/mg protein. Catalase (CAT) activity was determined from the rate of decomposition of H_2O_2, monitored by a decrease of absorbance at 240nm (Aebi, 1984), the CAT activity was expressed asnmol/min/mg protein.Superoxide dismutase (SOD) activity was measured as the inhibition of autoxidation of pyrogallol, according to the method of Marklund and Marklund (1974) and expressed as (U/mg protein, one unit of SOD activity was defined as the enzyme amount causing 50% inhibition in pyrogalol auto-oxidation per minute.Renal MPO activity was measured according to Bradley *et al*. (1982). In brief, the renal cortex tissue was suspended in 6 mL of 50 mmol/Lphosphate buffer (pH 6.0) containing 1% HTAB. The homogenized samples werefrozen and thawed, and centrifuged at 4.500 x g for 15 minutes at 4 °C. The evaluation of MPO activity was estimated after adding of 0.6 mL of phosphate buffer (pH 6.0) which contains 0.167 mg/mL *O*-dianisidinedihydrochloride and 0.0005 % H_2O_2. The change in absorbance at 460 nm was recorded spectrophotomecally over 10 minutes. (One unit of MPO activity was defined as the amount of enzyme able to reduce 1 µmol of H_2O_2 per minute). Protein concentration was estimated by the method of Lowry *et al.* (1951).

Histopathological Analysis

Renal fragment tissues were fixed in 10% formalin and were performed by standard method. The sections were stained with haematoxylin-eosin (H&E),

Statistical Analysis

All data were expressed as means ± SD (n=6) and compared by means of ANOVA test, values of P<0.05 was regarded as significant.

RESULTS

Renal Function Markers

Administration of CP to mice induced a marked renal impairment, as evidenced by a significant ($p < 0.01$) elevations in serum BUN and creatinine levels when compared to control group. BECC (150 mg/kg) and vitamin E (100mg/kg) pretreatment daily for 10 days, significantly ($p < 0.01$) reserved the renal function as indicated by the reduction in serum creatinine (80.15 %) and BUN (57.58%) as compared with vitamin E-group (84.61,74.24%) respectively (Figure 1; a,b).

Renal Oxidative Stress Markers

Exposure mice to CP caused a significant ($p <0.01$) depletion of cortex renal GSH accompanied with a significant ($p <0.05$) increase in MDA level (Table 1). In both BECC-group and vitamin E-group there was a significant ($p <0.01$) reserve in GSH level (63.29 %, 80.59%; $p< 0.01$) respectively, and in MDA level (54.90 %, 74.10 %; $p < 0.01$) respectively, indicating the comparable preventive effect of both BECC and vitamin E (Table1). A significant ($p <0.01$) decline was observed in both CAT, SOD activities and in both GPX,GST activities in CP-exposure mice (Table 1). The pretreatment with BECC and vitamin E significantly reversed the CAT activity (67.61 %, 84.35 %; $p < 0.01$) respectively, and the SOD activity (68.16%, 85.68 %; $p< 0.01$) respectively and the GPX activity (66.38 %, 77.90 %; $p <0.01$) respectively and the GST activity (70.18%, 86.63; $p <0.01$) respectively (Table 1).

Table 1: The effect of BECC (150 mg/Kg) on renal oxidative stress markers in CP-mice.

Groups	MDA (nmol/g tissue)	CAT (nmol/min/mg protein)	GSH (nmol/mg protein)	GPx (nmol/ min/mg protein)	GST (µmol/ mg protein)	SOD (U/mg protein)
control	39,17±3,05	100,18±8,25	23,49±1,62	33,69±3,11	8,39±1,24	27,06±2,28
CP	97,99±7,38**	47,278±4,54**	8,5±0,79**	14,24±2,34** ŤŤ ¥¥	4,49±0,64**	13,495±0,95**
CP + vit E	54,4±5,72** ŤŤ (74.10 %)	81,91±2,08** ŤŤ (84.35 %)	20,58±1,59* ŤŤ (80.59 %)	29,4±1,38** ŤŤ (77.90 %)	7,87±0,7** ŤŤ (86.63 %)	25,11±1,71** ŤŤ (85.68 %)
CP + BECC	65,7±3,31** ŤŤ ¥¥ (54.90 %)	74,71±5,43** ŤŤ¥ (67.61 %)	17,98±1,16** ŤŤ ¥¥ (63.29 %)	27,16±1,99* ŤŤ ¥ (66.38 %)	7,235±0,77ŤŤ (70.18 %)	22,74±1,98** ŤŤ ¥¥ (68.16 %)

Values are mean ± SD, (n = 6), * : all groups vs Control; Ť : CP vs CP + vitamin E and CP + BECC; ¥ : CP + vitamin E vs CP + BECC . ¥Ť*P<0.05; ¥¥ ŤŤ **P<0.01. Values in parentheses indicate percent protection. The % of protection is calculated as: 100 x (values of CP) -values of samples/ (values of CP) -values of control.

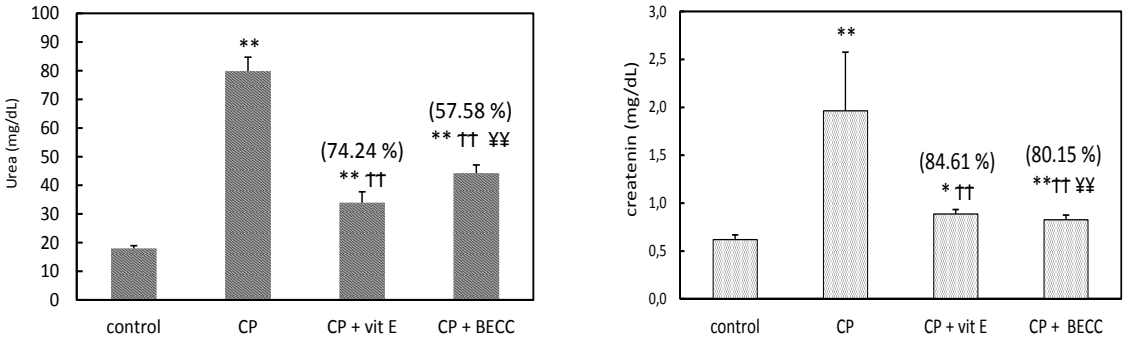


Fig. 1: The effect of BECC (150 mg/Kg) on renal function markers in CP-mice : (a) BUN and (b) creatinine. Values are mean ± SD, (n = 6) , *all groups vs Control; † : CP vs CP + vitamin E and CP + BECC; ¥ : CP + vitamin E vs CP + BECC . ¥†*P<0.05; ¥¥ †† **P<0.01. Values in parentheses indicate percent protection. The % of protection is calculated as : 100 x (values of CP) -values of samples/ (values of CP) -values of control.

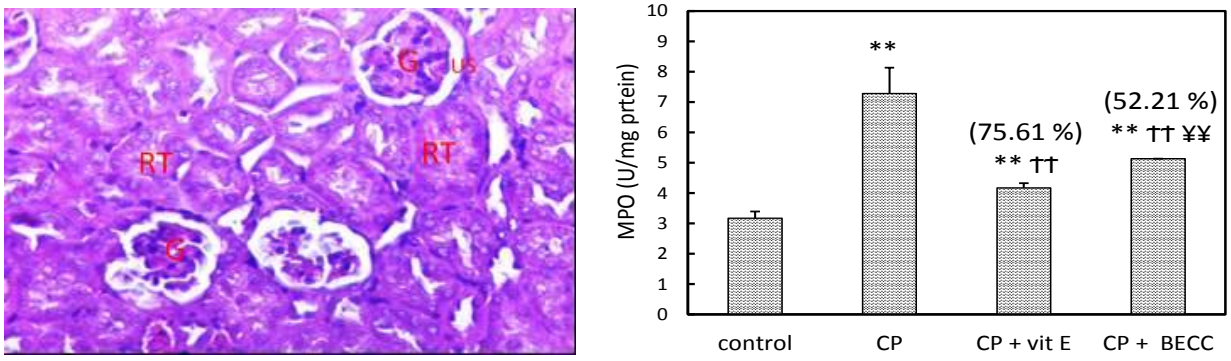
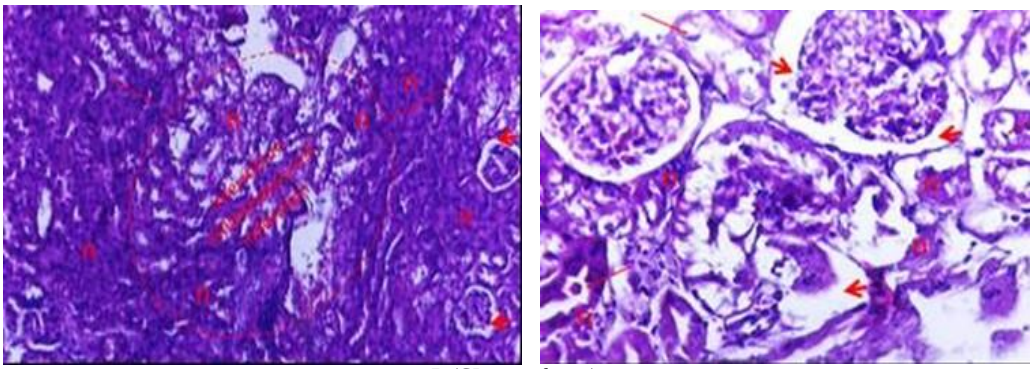
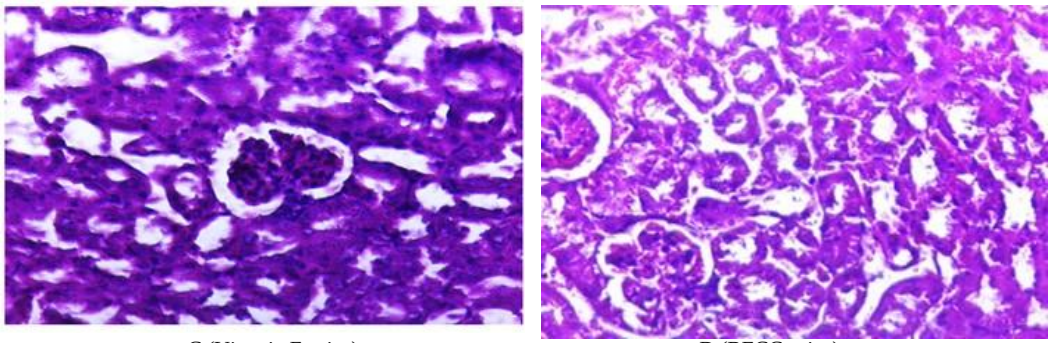


Fig. 2: The effect of BECC (150 mg/Kg) on renal MPO in CP-mice.Values are mean ± SD, (n = 6), *: all groups vs Control; †: CP vs CP + vitamin E and CP + BECC; ¥ : CP + vitamin E vs CP + BECC . ¥†*P<0.05; ¥¥ †† **P<0.01. Values in parentheses indicate percent protection. The % of protection is calculated as : 100 x (values of CP) -values of samples/ (values of CP) -values of control.



B (CP-treatedmice)



C (Vitamin E-mice) D (BECC-mice)

Fig 3: Photomicrograph of Histopathological analysis renal cortex of mice (H&E X400): A: (control): normal glomerular (G) and tubular: renal tubule RT (the proximal tubule and distal tubule) and urinary space (US). B (CP-treated mice): disrupted renal parenchyma showing loss of structural arrangement of renal tubules (arrows). Severe degeneration in atrophied glomerulus, dilation of Bowmn's space (head arrow), wide spread proximal tubular necrosis (n). C (Vitamin E-mice): Vit E pre-treatment preserved glomerular architecture and showed a regular epithelial cell of some tubules, moderate tubular necrosis. D (BECC-mice): showed slight degeneration in proximal tubule with a moderate degree of histopathological alteration with some healthy tubules.

Cortex Renal MPO Level and Histological Analysis

MPO activity, which is an indicator of neutrophil infiltration, was significantly (P<0.01) higher in the cortex renal tissue of CP-mice (7.282±0.848 U/mg protein) than that of the control group (3.173±0.2178U/mg protein). In BECC-group (5.137±0.128 U/mg protein) and vitamin E-group the (4.175±0.154 U/mg protein) MPO activity significantly (P<0.01) was normalised (52.21 %) in comparison to vitamin E (75.61 %) (figure 2).

The histopathological analysis of the cortical region of control kidney mice showed the normal glomerular and tubular histo-architecture (figure3A) the CP-treated mice showed an in the renal tubules oedema and congested blood vessels and interstitial damage evidenced by tubular lumen dilatation with variable degrees of tubular necrosis and inflammatory cell infiltration that confirmed the MPO finding (figure 3B). Administration of BECC and vitamin E, greatly ameliorated the histopathological lesions, minimized the degenerative changes and the renal parenchyma attained nearly normal structure and organization (figure 3C,D).

DISCUSSION

CP is an inorganic platinum compound characterized by a broad spectrum anti-neoplastic effect against a wide variety of tumours (Daugaard and Abildgaard, 1989; Siddik, 2003). However many side effects mainly the nephrotoxicity in 25-30% of patients were clinically occurred (Saad *et al*., 2009). In the present investigation, nephrotoxicity of CP was clear from the elevated levels of serum creatinine and BUN levels that might be resulted from renal dysfunction, which could be explained by the reduction of the glomerular filtration (Yao *et al*., 2007). It has been reported that the accumulated CP in the tubular epithelial cells reached its highest level in the proximal tubular cells of the inner cortex especially in the S3 segment (Townsend *et al*., 2003) and may form a reactive metabolite intracellular hydration by platinum complexes which could cause the humans nephrotoxicity (Matsushima *et al*., 1998; Baek *et al*., 2003). BECC administration clearly attenuated increases in serum BUN and creatinine that may reflect its renal function restoration, this effect is comparable to that of vitamin E, which considered as positive control. Cisplatin-induced nephrotoxicity is a complex process and multiple mechanisms which include oxidative stress and inflammation (Arany *et al*., 2004, 1993; Jordan and Carmo-Fonseca, 2000). The impaired renal functions could be attributed to the direct toxic effect of CP on the glomerular and tubular structures through the generation of reactive oxygen species (ROS) (Cetin *et al*., 2006; Yao *et al*., 2007). In our study, CP administration produces MDA in the renal cortex, affecting cellular structure and function. The MDA production was associated with a sequence of events such as the cortex renal GSH depletion, SOD, CAT, GPx and GST activity reduction in renal cortex tissues. The diminution of SOD activity could provoke the initiation and propagation of lipid peroxidation in the CP-treated rat (Davis *et al*., 2001). It is well recognised that excessive lipid peroxidation augments GSH consumption (Karthikeyan *et al*., 2007; Gonzales *et al*., 2005). The biotransformation of CP has been mentioned as a part of the cisplatin-induced renal damage (Townsend *et al*., 2003; Wainford *et al*., 2008). It has been indicated that the CP nephrotoxicity is initiated by the inhibition of protein synthesis and protein-SH depletion (Sadowitz *et al*., 2003; Pabla and Dong, 2008). The depletion of the intracellular GSH may be explained by conjugation of CP with GSH, which lead to detoxifying electrophilic compounds. These compounds pass afterwards to the kidney where they would be cleaved by the γ-glutamyl-transpeptidase to cysteinyl-glycine-conjugates on the surface of the proximal tubule cells (Townsend *et al*., 2003). The dissociation of one chlorine from CP results in a positive charge on the platinum which would attract the negatively charged sulfur on the cysteine moiety of the GSH. Some heavy metals including CP have been reported to induces renal damage by ROS generation (Kawai *et al*., 2006), the CP administration in different experimental model resulted in the generation of $O^{\cdot-}_2$ in both cell-free system (Masuda *et al*., 1994) and male Wistar rats (Chirino and Chaverri, 2009) and °OH in cell-free system in both female and male Wistar rats (Kadikoylu *et al*., 2004; Jiang *et al*., 2007). The contribution of hydrogen peroxide (H_2O_2) in cisplatin-induced nephrotoxicity in cortical tubule cells was demonstrated in a previous study, principallyin S3 cells of the proximal kidney tubules (Tsutsumishita *et al*., 1998). Thus, both CAT and GPx enzymes that detoxify hydrogen peroxide could be reduced (Kadikoylu *et al*., 2004). The reduction in the of the antiperoxidative enzymes activities (CAT and GPx) may be attributed to the increased generation of ROS, which in turn lead to the inhibition of these enzymes (Gaetani, *et al*., 1996). In our study, the activities of GSH-dependent antioxidant enzymes GPx and GST also were significantly diminished in cisplatin group. The activities reduction of GPx and GST could be due to the decreased availability of their GSH substrate (Karthikeyan *et al*., 2007; Ran *et al*., 2007). In our study, the histopathological finding confirmed the biochemical results, the decline in antioxidant enzymes activities was accompanied by a remarkable reduction in the glomerular capillary tufts size and associated with the proximal tubular necrosis that could be related to inflammation process as an another mechanism of CP-induced nephrotoxicity (Pratibha *et al*., 2010), CP administration elevated the MPO activity in the cortex tissue, indicating the enhanced polynuclear (PN) migration to in the renal cortex tissue (Tsuji *et al*., 1999; Ahmed Elberry *et al*., 2012).

The renoprotective effect of BECC was associated with preservation of GSH concentration, upregulation of GPx, SOD and prevention renal cortex from increased MDA and MPO concentration.In the present study, our investigation also revealed that the renoprotective effect of BECC was comparable to that of vitamin E which is known to be the major lipophilic chain-breaking antioxidant present within cell membranes (Packer and Landvik, 1989). These findings are in line with earlier studies that reported that the use of vitamin E in combination with selenium treatment ameliorate cisplatin side effects by preserving renal GSH

and up-regulated the GPx activity in cisplatin-rats (Naziroglu *et al*., 2004; Nematbakhsh and Nasri, 2013). In the current investigation the vitamin E as standard references, clearly prevented CP induced proteinuria and oxidative stress.A comparable data were reported by Maliakel *et al.* (2008), that indicated α-tocopherol monoglucoside as nephoprotective agent against cisplatin-induced nephrotoxicity. Our previous phytochemical studies carried out on this plants characterize the presence of many bioactive compound among them caffeic acid (10.07 mg/kg), chlorogenic acid (5.04mg/kg), ferulic acid (4.81 mg/kg) (Azzouzi *et al*., 2016 a) that being the highest in concentration and have been proved antioxidant effect (Dos Santos *et al*., 2006). From this study, the caffeic acid has been proved earlier as the most abundant phenolic acid in the *n*-BuOH extract of leaves from *Centaurea choulettiana* (Azzouzi *et al*., 2016 a). Thus, the enhancement of this renoprotective effect of BBCC seems to be dependent on the antioxidant activities exerted by phenolic acid (caffeic acid, chlorogenic acid, ferulic acid) contained in BBCC. These compounds are mentioned to be a chain-breaking antioxidants acting through radical scavenging activity which could be attributed to their hydrogen or electron donating aptitude (Azzouzi *et al*., 2016a, Farah *et al*., 2008).

Our finding are in agreement with those declared by Ozen *et al.* (2004) that mentioned the caffeic acid phenethyl ester as a potent reducer of oxidative stress in rat tubular damage induced with CP and confers good renoprotection.

CONCLUSION

From our findings, we can conclude that both biochemical results and histopathological evidence showed the renoprotective potential of BECC, which was able to ameliorate CP-induced and renal dysfunction through its antioxidant capacity.

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