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Nephroprotective potential of *Cichorium endivia* L. pretreatment against doxorubicin induced kidney injury

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Abstract: The serious adverse effects, such as nephrotoxicity, limit the clinical utility of anticancer doxorubicin (DOX) drug. *Cichorium endivia* L. is reputed to show antioxidive effectiveness. The present investigation was conducted to explore the nephroprotective potential of crude methanol extract of *Cichorium endivia* (CECE) pretreatment against DOX-induced nephrotoxicity. Randomly, twenty male Wistar rats were assigned into four groups: Control (no-treatment), DOX group (15mg/kg, i.p, once), DOX + CECE (100mg/kg) and DOX + CECE (200mg/kg). All experiments were performed for 15 consecutive days except for DOX, was delivered once on day twelve. Samples of kidney and serum were collected one day after the last treatment for further assays. Pretreatment with CECE significantly protected the kidney function from DOX toxicity. Urea and creatinine levels were reduced in the serum. Furthermore, CECE administration decreased the damage in the renal histological structure. Restoration of the renal corpuscle and tubules structures was more manifested in a high dose (200mg/kg) of CECE. In summary, these findings demonstrate the nephroprotective effect of CECE pretreatment in DOX-treated rats.

Keywords: Doxorubicin, *Cichorium endivia*, nephrotoxicity, creatinine, urea.

INTRODUCTION

Doxorubicin (DOX) is a well-known anthracycline antibiotic reputed as antitumor medication (Abd-Ellatif *et al*., 2022). DOX is extremely efficient and still deeply used in the treatment of a wide variety of cancers (Arunachalam *et al*., 2022). On the other hand, DOX is one of the leading causes of drug-induced multi-organ damage including cardiotoxicity, nephrotoxicity and hepatotoxicity (Yesilkent and Ceylan, 2022). Reports have described that DOX related nephrotoxicity might be via its damaging actions on renal tissue, as it amassed particularly in the kidney leading to higher permeability of glomerular capillary and induction of tubulointerstitial degeneration. Hence, this severe side effect limits its clinical utility as anticancer drug (Soltani Hekmat *et al*., 2021, Wu *et al*., 2021, Xiang *et al*., 2021). Although, the precise mechanism of DOX nephron-destructive effect has not been finally uncovered, it is assumed that DOX may lead to production of free radical and cause lipid per oxidation of organs with less anti-oxidants protective mechanisms like kidney (Nimbal *et al*., 2021). Consequently, it is important to find a new safe candidate to diminish those adverse effects of DOX on kidney and other organs. Recently, medicinal plants including edible herbs offer a plethora of bioactive molecules that constitute biocompatible therapeutic agents, which characterized by diversity of bioactivities and wide safety profiles (Aranaz *et al*., 2019, Khalil *et al*., 2022c). Those acknowledged benefits make such herbs being a functional supplement that provide health benefits, including the prevention and/or treatment of human diseases (Khalil *et al*., 2022a, Khalil *et al*., 2022b). *Cichorium endivia* L. (*C. endivia*) is one of sunflower family (*Asteraceae*), which is a reputed by its high nutritional and medicinal values. *C. endivia* is a widespread vegetable used in salad (Ducrocq *et al*., 2022). Because of the characteristic crunchy and unique slight bitter taste and flavor, *C. endivia* has been preferred in many cookeries. The bitterness and nutraceutical values of *C. endivia* is attributed to various bio-metabolites including sesquiterpene lactones like lactucin and lactucopicrin (Amer, 2018, Zhang *et al*., 2022). *C. endivia* is one of the herbs belongs to Mediterranean regions (Papetti *et al*., 2008). *C. endivia* L. contains a diversity of biomolecules such as derivatives of sesquiterpenes, flavonoids, coumarins, phenolic acids and other nitrogenous constituents (Khalil and Kamel, 2015). Regarding the biological effects, *C. endivia* extract demonstrated a potent liver protective activity (Chen *et al*., 2011, Han *et al*., 2021), substantial antioxidant capabilities, antimicrobial (Amer, 2018), which is imputed to the high levels of phenolic based constituents (Khalil and Kamel, 2015). In view of the reported valuable nutritive, antioxidant and various pharmacological effects of *C. endivia* against various conditions, the work pursues to investigate the potential

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nephro-protective effect of its crude extract against DOX-induced nephrotoxicity in experimental rats as complementary natural candidate to control such side effect, which is one of the prevalent problems in the clinical use of DOX. The investigations included histopathological evaluation of renal tissues, Furthermore to assess the different biochemical and oxidative stress parameters including assessment of levels of serum urea, creatinine, reduced glutathione (GSH) and level of lipid peroxidation marker malondialdehyde (MDA)

MATERIALS AND METHODS

Plant material

The leaves of *C. endivia* L. were collected from the Botanical Garden Assuit, Assuit governorate, Egypt (during April 2007). A voucher specimen of the plant was kept in Department of Pharmacognosy, Faculty of Pharmacy, Minia University, Egypt (Coded: Minia-07-July-*CE).* The specimen was kindly identified by Professor Mohamed Salah Kamel, Department of Pharmacognosy, Faculty of Pharmacy, Minia University, Egypt.

Preparation of crude extract

The air-dried leaves of *C. endivia* L. (1.0 kg) were powder and extracted with 70% methanol (Sigma-Aldrich, Germany), (using 5 L of 70% methanol, at room temperature for ten days. The collected extracts were combined concentrated under vacuum using rotary evaporator (Heidolph Instruments, Germany) to yield 100.0g viscous extract (CECE).

Experimental animals

Twenty healthy adult male Wister rats (7-8 weeks old) weighing (170-210g) were obtained from the animal house of the College of Science, King Faisal University. Animals were acclimatized to the environmental conditions of laboratory for seven days prior to the work, using standard conditions of 12 hours of light/dark cycle at a temperature of 22-25°C. Animals get free access to water and food. The protocol of study was approved by Research Ethics Committee, Deanship of Scientific Research, King Faisal University (#KFU-REC-2023-May-ETHICS910).

Experimental design

Animals were randomized into four groups each of five animals. The study groups was designed to be according to the following. Control group (A) received 1% carboxymethyl cellulose (CMC) (Sigma-Aldrich, Germany) by oral gavage for 14 days, followed by isotonic saline via intraperitoneal (i.p.) injection once on 12th day of study. DOX group (B) received 1% CMC via oral gavage for 14 days, during a single dose of DOX (15 mg/kg, i.p.) (Sigma-Aldrich, USA) on 12th day of study will be given. DOX + CECE (100mg/kg, dissolved in 1% CMC) (C) and DOX + CECE (200mg/kg, dissolved in 1% CMC) (D) groups received the doses via oral gavage for 15 days, followed by a single injection of DOX (15 mg/kg, i.p.) on day 12^{th} was injected for both groups. At the end of the experiment (after 14 days), rats were fasted overnight and anaesthetized with urethane (1 g/kg, i.p.) (Sigma-Aldrich, Germany) to collect blood samples by cardiac puncture, then rats were scarified. Blood samples were kept for 30 min and centrifuged (Eppendorf AG, Germany) at 3000 rpm for 15 min. Sera were collected and stored at -20°C for kidney function tests. Kidneys were harvested, rinsed with cold saline and defatted (for histological analysis).

Assessment of kidney function

The collected samples of blood were centrifuged at 2000 rpm for 15 min using refrigerated centrifuge to obtain serum samples. Subsequently, the levels of urea and creatinine levels were assessed in the serum using colorimetric kits according to the manufacturer's protocols (Biomed Diagnostics, Egypt) (Khalil *et al*., 2022a).

Measurement of oxidative stress parameters

The homogenate of kidney (1:5 w/v) was prepared in 0.1 mM PBS buffer (at pH of 7.4), then centrifuged and the supernatant was used to estimate the renal MDA and GSH. The level of MDA was determined chemically as thiobarbituric acid reactive substances according to the prescribed method by Khalil *et al* (Khalil *et al*., 2022c). The GSH was assessed following the procedures of the manufacturer (Biomed Diagnostic, Egypt).

Kidney histopathological examinations

Fixed tissues of kidney were dehydrated using alcohol of ascending concentrations, followed by clearing with the aid of xylene, followed by rapid embedding in paraffin wax. Sections were prepared at 4µm thickness. The sections were stained with hematoxylin and eosin (H&E) (Khalil *et al*., 2022b). The carefully adjusted slides were scrutinized under light microscopy to study the histopathological alterations.

STATISTICAL ANALYSIS

Data were expressed as the mean ± standard error of the mean (Mean ± SEM). The multiple analyses were done by One Way Analysis of Variance (ANOVA) test followed by Tukey-Kramer Post Hock test were applied. Statistically significant results were considered if the P-value was less than 0.05. Statistical analysis was conducted with Graph Pad Prism (version 7.0; San Diego, CA, USA).

RESULTS

Effect of C. endivia on kidney function and renal oxidative stress

Serum creatinine and serum urea levels were assessed as indicators for kidney function in different experimental

groups. Administration of DOX for four days resulted in a significant increase in serum creatinine (3-fold) and serum urea (2-fold). The protective effect of CECE (100 and 200mg/kg) for 12 days resulted in decrease of levels of serum creatinine and urea (fig. 1A and B). DOX resulted in a significant increase in renal MDA with a significant reduction in renal GSH compared to the control group. These effects emphasized renal oxidative stress associated with exhaustion of some of the antioxidant mechanisms in the kidney (GSH). CECE (100 and 200mg/kg) significantly attenuated MDA level compared to DOX group. Renal GSH level activity was significantly higher than those observed in the DOX group, which indicate partial restoration of the oxidative balance by CECE (100 and 200mg/kg) treatments (fig. 1C and D).

Histopathological changes in renal cortex

Renal histology was examined using H&E staining. Renal cortex section from control Group (fig. 2A) revealing the standard histological structure of renal cortex including renal corpuscle (arrow) with intact endothelial lining (arrowhead), proximal (wave arrow) and distal (curvy arrow) convoluted tubules. Fig. 2B demonstrated the section of renal cortex from DOX treated group. It showed serious renal deteriorations encompassing dilated glomerular space (arrow) and thinning in Bowman's capsule (arrowhead). Renal tubules existed with collapse, apoptotic-lining cells (wave arrow) as well as epithelial desquamation (curvy arrow). Moreover, congested blood vessels (arrow with tail), interstitial edema (star), hemorrhage (rectangle) and inflammatory cells infiltration (circle) were also detected. Fig. 2C showed the section of renal cortex from CECE (100 mg/kg) treated group, which demonstrating partial tissue enhancement displayed by restored renal corpuscle (wave arrow) with few ones highlighted with vacuolations (arrowhead) and thin bowman's capsules (arrow). Most renal tubules displayed in intact form (curvy arrow) and others with dilated tubules (star). Moderate interstitial hemorrhage (rectangle) plus few inflammatory cells infiltrations (circle). Fig. 2D expressed the section of renal cortex from CECE (200 mg/kg) treated group, that highlighting obvious enhancement with clear disappearance in renal cortex damage. Section reveals a restoration of most histological structure of renal corpuscle except some vacuolations (star) and few with incomplete Bowmen's capsule (arrow). Renal tubules assembled mostly with normal architecture (curvy arrow) except few still suffered with vacuolations (arrowhead) and epithelial desquamation (wave arrow). Scarce interstitial hemorrhage (rectangle) were noticed.

Histopathological changes in renal medulla

Renal medulla section from control group (Fig. 3A) displaying the typical histological assembly of renal medulla constructing as collecting ducts (arrow) and vasa recta (arrowhead). Fig. 3B demonstrated the section of renal medulla from DOX treated group, that signifying critical renal tubules damage with loss of their organization (wave arrow), collapsed renal tubules (arrowhead), deep basophilic apoptotic lining cells (arrow), interstitial hemorrhage (arrow with tail), edema (star) as well as inflammatory cells aggregation (rectangle). Renal medulla section from CECE (100 mg/kg) Fig. 3C represented the section of the renal medulla from CECE (100mg/kg) treated group, that revealing limited tissue development distinguished by areas with degenerated renal tubules with edema (star) while others marked in an intact form (arrow). In addition, some tubules detected with apoptotic lining cells (arrowhead) in addition to some injury along vasa recta (wave arrow). Reasonable interstitial hemorrhage and inflammatory cells infiltrations (rectangle) were also noticed. Fig. 3D showed the section of renal medulla from CECE (200mg/kg) treated group, which highlighting obvious progress with restored renal tubules (arrow) except few with epithelial desquamation and collapsed lumen (curvy arrow). Few injuries along vasa recta (rectangle) along with interstitial hemorrhage (wave arrow) and edema (arrowhead).

DISCUSSION

Although DOX has strong antitumor effectiveness, it is limited as a chemotherapeutic drug due to its vast side effects including renal toxicity (Baothman *et al*., 2023). Obviously, using DOX results in a torrent of interactions producing reactive oxygen species, which can rapidly interact with kidney leading to severe renal injury (Abbasnezhad *et al*., 2022). Its destructive effect is defined through increasing glomerular capillary penetrance, cellular injury of renal proximal tubules and tubulointerstitial degeneration (Grant *et al*., 2019, Wu *et al*., 2021). Hence, it is important to develop effective strategies in order to discover a safe renoprotective herbal candidate as an adjuvant therapy with DOX chemotherapy. *Cichorium* is a reputed genus for its beneficial and medicinal importance. Traditionally, its members are used as medicine and edible food vegetable (Khalil and Kamel, 2015). One of the most important member of this genus is *C. endivia*. Recent reports demonstrated its importance as an herbal remedy in treatment of various health conditions, including Liver, skin and cancer issues (Eltamany *et al*., 2022). In this work, we focused on the protective effect of *C. endivia* using DOX-induced nephrotoxicity rat model, which is well-established reproducible experimental model of kidney injury. The evaluation of biochemical key functions of kidney revealed substantial deterioration of kidney functions in the DOX group. Interestingly, the study confirmed DOX-induced nephropathy, as demonstrated by a significant rise in the levels of serum urea and creatinine concentrations in the DOX group in comparison with the normal control group and supported by toxic histopathological variations.

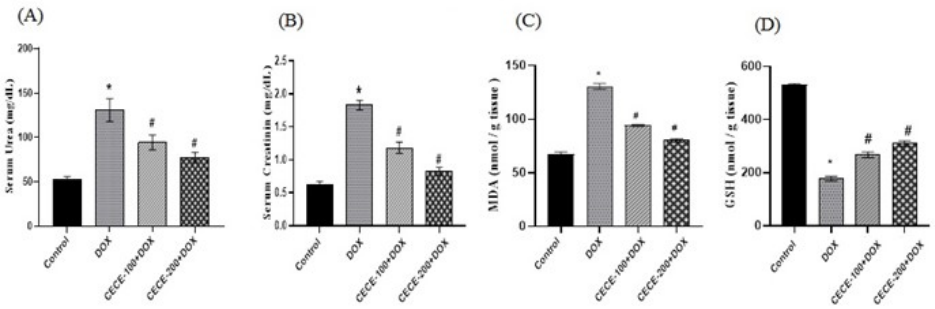

Fig. 1: Effect of *C. endivia* crude extract on serum creatinine and urea in DOX-induced nephrotoxicity. The serum levels of (A) Urea,(B) Creatinine, (C) MDA and (D) GSH in different groups. Data are presented as mean ± S.D. * Significant difference from control at $p < 0.05$, #Significant difference from DOX at $p < 0.05$. *C. endivia* crude extract (CECE), Doxorubicin (DOX), Malondialdehyde (MDA), Reduced glutathione (GSH).

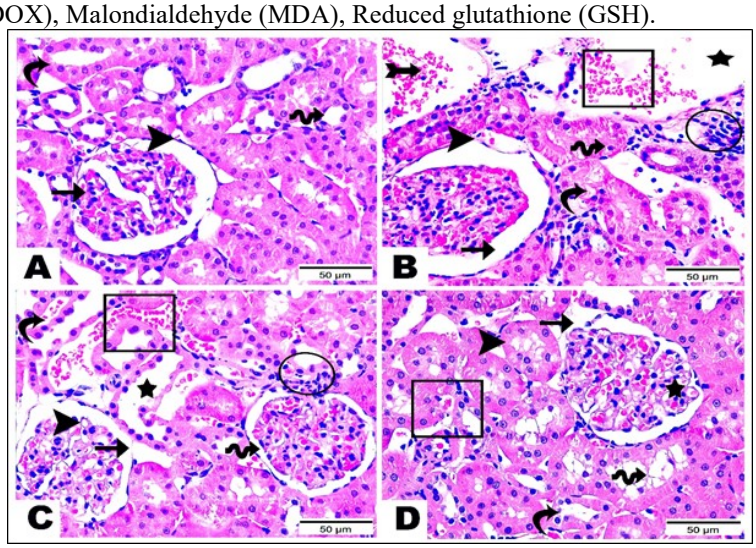

Fig. 2: Photomicrographs emphasized the histopathological alterations in kidney tissue sections (Renal Cortex Area) among studied groups (Hematoxylin & Eosin Stain, Magnification Power= x400 & Scale Bar= 50µm). (A) Control group, (B) Untreated DOX group, (C) DOX+CECE (100 mg/kg) and (D) DOX+CECE (200 mg/kg). *C. endivia* crude extract (CECE), Doxorubicin (DOX).

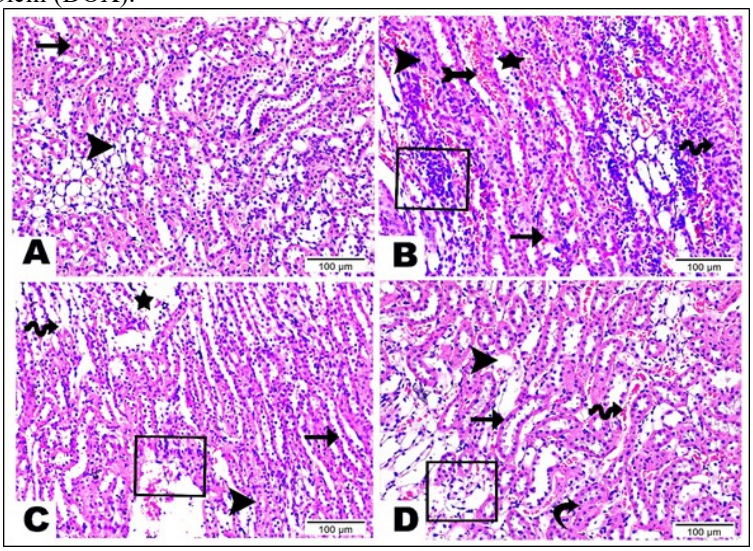

Fig. 3: Photomicrographs emphasized the histopathological alterations in kidney tissue sections (Renal Medulla Area) between examined groups (Hematoxylin & Eosin Stain, Magnification Power= x200 & Scale Bar= 100µm). (A) Control group, (B) Untreated DOX group, (C) DOX+CECE (100 mg/kg) and (D) DOX+CECE (200 mg/kg). *C. endivia* crude extract (CECE), Doxorubicin (DOX).

Orally administered CECE (100 and 200mg/kg) lessened the nephrotoxic effect created by DOX inoculation through substantial decreases in the serum levels of urea and creatinine, compared with the DOX-treated group' renal function restoring toward the normal levels (fig. 1A and B). In The current study, rats injected with DOX demonstrated a high level of lipid peroxidation marker (MDA, fig. 1 C) with a low level of GSH (fig. 1D) in the renal homogenate, indicating that the renal cells were shifted to the toxic redox status induced with DOX. Here, CECE (100 and 200mg/kg) pretreatment demonstrated improvement in the oxidative balance of the renal homogenate in the form of reduction of MDA level as well as improvement of level of GSH activity. These results support the amelioration effect of CECE against oxidative stress induced by DOX in the renal tissue. This could be attributable to antioxidant capability of *C. endivia* (Eltamany et al., 2022, Khalil and Kamel, 2015, Mikropoulou *et al.,* 2018). The results showed that DOX-treated group has serious renal cortex and medulla deteriorations encompassing dilated glomerular space, thinning in Bowman's capsule and collapsed renal tubules with apoptotic-lining cells in comparison with control group (figs. 2 and 3). Renal cortex section from CECE (100 and 200mg/kg) reveals a restoration of most histological structure of renal corpuscle except some vacuolations and few with incomplete Bowmen's capsule. Renal tubules assembled mostly with normal architecture; on the other hand, renal medulla section demonstrated obvious progress with restored renal tubules (figs. 2 and 3). Noteworthy, the current results are consistent with several previous studies, which were conducted to evaluate the effect of Date palm fruits (Baothman *et al*., 2023), *Rosa centifolia* (Nimbal *et al*., 2021) and *Chromolaena odorata* (Ikewuchi *et al*., 2021). Hence, the current histopathological microscopic scrutinization of renal tissue in addition to the kidney functions recognized a substantial improvement in rats administered with crude extract of *C. endivia* by increasing dose from 100 to 200 mg/kg.

CONCLUSION

In summary, the conducted investigation demonstrated that, CECE as an adjuvant therapy for DOX treatment, has a promising nephroprotective potential. It diminished the DOX-induced increase of kidney functions related key biomarkers (urea and creatinine serum levels). Notably, it ameliorated the histopathological damage caused by DOX. Future studies are recommended to assess the possible contributing mechanisms mediating the nephroprotective activity.

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