Modulatory Effect of *Echinacea Purpurea* Root Extract on Cisplatin-Induced Renal Toxicity in Rats: Antioxidant and Anti-inflammatory Pathways

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ABSTRACT

Cisplatin (CISP) is a potent chemotherapy antineoplastic drug. Severe adverse effects are the major hampered for prescribed CISP. This study aims to evaluate the modulatory effect of Echinacea purpurea root extract (EPRE) in CISP-induced renal toxicity, with underline the mechanisms. This research conducted on forty male rats that classified into four equal groups. Rats received orally EPRE (500 mg/kg) either separately or in combination with single intraperitoneal (IP) injected of CISP (7.5 mg/kg-1). Rats were sacrificed after 7 days from CISP injection. Renal toxic pretreated (EPRE+CISP)group received orally EPRE for three weeks, on the day 21th receives a single IP injection of CISP. After 28 days, administration EPRE (500 mg/kg) did not alter renal function markers, while had antioxidant and anti-inflammatory effects, thus conformed its safe usage. However, EPRE (500 mg/kg) combined with CISP had a significant protective role against the damage in renal as evidenced by significantly decreased CISP-induced elevates in serum renal function markers and changes in an ionic electrolyte (Na+ and K+). Additionally, it significantly restored renal antioxidant status and significantly decreased serum inflammatory cytokines. Rat's renal in EPRE (500 mg/kg) combined with CISP showed no injury compared with the CISP group. In conclusion, EPRE has protected and ameliorated the nephrotoxicity induced by CISP, thus provides an encouraging way for cancer patients receiving CISP to overcome some of its undesirable side effects.

Key Words:*Cisplatin, nephrotoxicity, Echinacea purpurea root, rats.*

eIJPPR 2019; 9(5):88-96

HOW TO CITE THIS ARTICLE: Arwa M. Turkistani(2019)."Modulatory Effect of Echinacea Purpurea Root Extract on Cisplatin-Induced Renal Toxicity in Rats: Antioxidant and Anti-inflammatory Pathways", International Journal of Pharmaceutical and Phytopharmacological Research, 9(5), pp.88-96.

INTRODUCTION

Cisplatin is widely used for the treatment of solid tumors as bladder, ovarian, testicular, and other cancer types [1, 2]. However, low concentrations of CISP induced genotoxicity, inhibits DNA synthesis, myelosuppression; bone marrow suppression, anaphylaxis, renal toxicity, neurotoxicity, hepatotoxicity, immunosuppression, and hearing loss [3-6]. Overproduction of free radicals, inflammation, and depletion in antioxidant enzymes are the main causes of CISP-toxicity [7, 8]. Approximately one-third of the patients receive CISP therapy to develop renal toxicity after a single dose (50-100 mg/m^2) [9]. The low molecular weight of CISP allows it's free unbound to be filtered by the glomerulus, thus trapping CISP in the renal cortex, which explained the renal toxicity [10, 11].

Due to the presence of several bioactive compounds [12], medicinal plants have been proved to be a notable source of drugs [13].

Recently, herbal therapy used as an alternative form of health care to decrease medicine resistance [14]. Alternative medicine which contains antioxidants compounds offers protection against these deleterious effects of CSP. *Echinacea purpurea* root extract common known as purple coneflower contains several medically bioactive compounds as alkylamides, polyphenols,

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 27 January 2019; **Revised:** 01 October 2019; **Accepted:** 09 October 2019

polysaccharides caffeic acid, glycoproteins, polyacetylenes, phenolic compounds, flavonoids, and others, that have a vital role in its therapeutic effects [15, 16]. The EPRE has immune activation [17, 18], anti-inflammatory [19], and antioxidant properties [20].

However, CISP is the commonly used chemotherapy in many platinum-based therapy regimens [21]. Therefore it is essential to prevent and reduce CISP-nephrotoxicity to increase patient survival [22]. The focus of this research is to evaluate whether EPRE (500 mg/kg) can alleviate CISP-induced renal toxicity in rats, with underline antioxidant and anti-inflammatory pathways.

MATERIAL AND METHODS

Drug, Plant, and Chemicals

Cisplatin ® (CISP)supplied as vials (cis-diamminedichloroplatnum) (CISP), (50 mg/50 ml), Merck Com. Pharma. Germany. *E. purpurea* root extract (USA) in a liquid form was purchased from iHerb, HEARB PHARM, Saudi Arabia. All chemicals were purchased from Al-Saggaf Trading Est., Jeddah, KSA.

Induction of Renal Toxicity

Renal toxicity was induced through intraperitoneal (IP) injected with a single dose of CISP (7.5 mg/kg^{-1}), then rats were sacrificed after 7 days [23].

Experiment Protocol

Male rats Sprague Dawley 180-210g were purchased from the Animal unit of King Fahd Medical Research Center. Forty rats were acclimatized under standard laboratory conditions for one week before experimentation. Rats were separated into four groups (10 each). Control (CON) group; rats received no treatment. Renal toxic (CISP) group; rats received a single IP injection of CISP. *E. purpurea* root extract (EPRE) group; rats received orally EPRE with 500 mg/kg/day for four weeks [24]. Renal toxic pretreated (EPRE+CISP) group; rats received orally EPRE with 500 mg/kg/day for four weeks, on the day 21^{th} received a single IP injection of CISP.

Biochemical Measurements

Seven days after CISP injection, renal and blood samples were collected. Serum samples were kept at -80°C until used for measurements of renal function levels (creatinine (Cr), blood urea (BUN) and uric acid (UA)). Ionic sodium and potassium concentrations were determined using colorimetric kits, purchased from Abcam, USA, following the manufactures' procedure.

Estimation of renal oxidative status markers and enzymatic antioxidants

The levels of nitric oxide (NO), thiobarbituric acid reactive substances (TBARS), catalase (CAT) and glutathione peroxidase (GPx) were measured in the renal homogenates using ELISA kits (Abcam, USA) according to the instructions of the manufacturer.

Estimation of renal inflammatory markers

The renal levels of tumor necrosis factor-alpha (TNF-α), and interleukin-10 (IL-10) were determined using ELISA kits from Abcam, USA.

Histopathological hematoxylin and eosin staining examination

Stained renal sections were examined and photographed using a light microscope.

Statistical

All data were expressed as mean ± SE. Differences were done using one-way analysis of variance, post hoc test, LSD test, by SPSS, ver. 24, $p< 0.05$ considered significant.

RESULTS

Serum renal function markers (Cr, BUN, and UA)

Rats treated with CISP revealed appreciably significant ($p<0.001$) renal damage, which noticed through elevates in renal function markers (Cr, BUN, and UA) as compared with CON. Oral given EPRE (500mg/kg) to rats did not induce changes in renal function markers as compared with CON, thus means the safe usage of EPRE. However, before and simultaneous administration of EPRE (500 mg/kg) with CISP showed a protective effect against CISP in rats in the form of significant ($p<0.001$) decreased in renal function markers (Cr, BUN, and UA) as compared CISP group Figure (1).

Serum ionic electrolyte levels (Na+ and K+)

Figure (2) shown the levels of serum ionic electrolyte in different groups. Rats treated with CISP revealed noticeably significant ($p<0.001$) decrease in ionic K+ level with a significant increase in ionic Na^+ level as compared with CON. Oral given EPRE (500mg/kg) to rats did not induce changes in ionic electrolyte levels as compared with CON. However, the group EPRE (500mg/kg) with CISP showed a significant ($p<0.001$) increase in ionic Na+ level with significant ($p<0.001$) decreased in ionic K^+ level as compared CISP group.

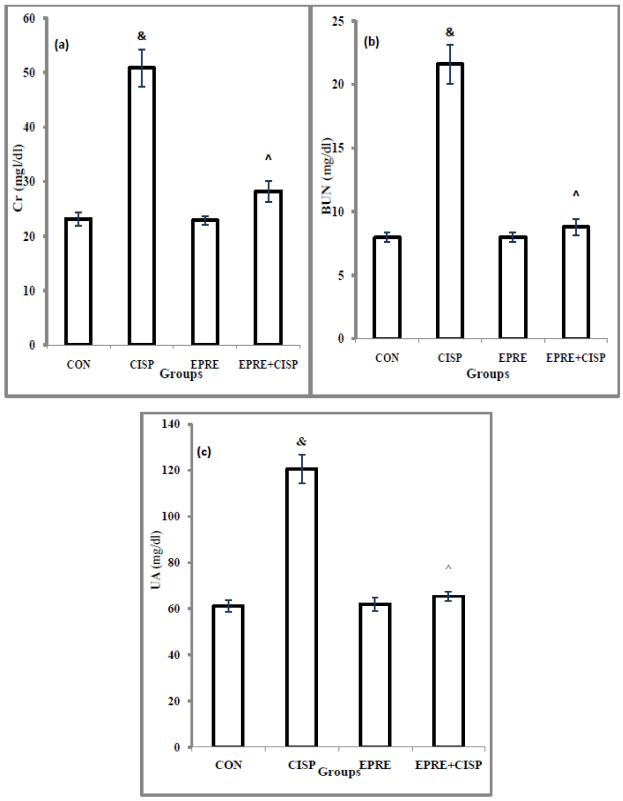

Figure 1: Levels of serum kidney functions (a) Cr , (b) BUN, and (c) UA measured in control (CON), Renal toxic Cisplatin (CISP), *E. Purpurea* root extract (EPRE) (500 mg/kg), and *E. Purpurea* root extract (EPRE) (500 mg/kg)+ Cisplatin (EPRE 500mg/kg + CISP). Results are represented as mean ± SE of 10 rats/ group. & significant compared with CON, and ^ significant compared with the CISP group (p< 0.05).

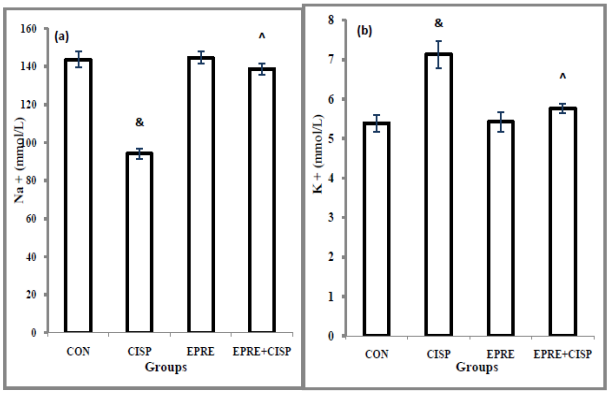

Figure 2: Levels of serum ionic electrolyte (a) Na^+ , and (b) K^+measured in control (CON), Renal toxic Cisplatin (CISP), *E. purpurea*root extract (EPRE) (500 mg/kg), and *E. purpurea*root extract (EPRE) (500 mg/kg)+ Cisplatin (EPRE 500mg/kg + CISP). Results are represented as mean ± SE of 10 rats/ group. & significant compared with CON and ^ significant compared with CISP group (p< 0.05).

Renal Oxidative Status Markers and Enzymatic Antioxidants

Rats treated with CISP revealed appreciably significant renal oxidative stress, which observed through significant (p<0.001) elevate in renal TBARS, with significant (p<0.001) decline in renal NO, CAT, and GPx as compared with CON group. Oral given EPRE (500 mg/kg) to rats showed a slight improvement in antioxidant status as compared with CON, thus indicated the antioxidant effect of EPRE. However, before and simultaneous administration of EPRE (500 mg/kg) with CISP showed protective effect against CISP in rats in the form of significant (p<0.001) decreased in renal TBARS, with significant (p<0.001) increased in renal NO, CAT, and GPxas compared CISP group Figure (3).

Renal inflammatory cytokine markers

Table (1) shown the levels of serum inflammatory cytokines (TNF-α and IL-10) in different groups. Rats treated with CISP revealed noticeably significant (p<0.001) increased in TNF-α and significant (p<0.001) decreased in IL-10 as compared with CON. However, the group EPRE (500 mg/kg) with CISP showed a significant (p<0.001) decrease in TNF-α and a significant (p<0.001) increased in IL-10 as compared CISP group. Thus indicated the curative effect of EPRE against CISP nephrotoxicity through the anti-inflammatory role of EPRE.

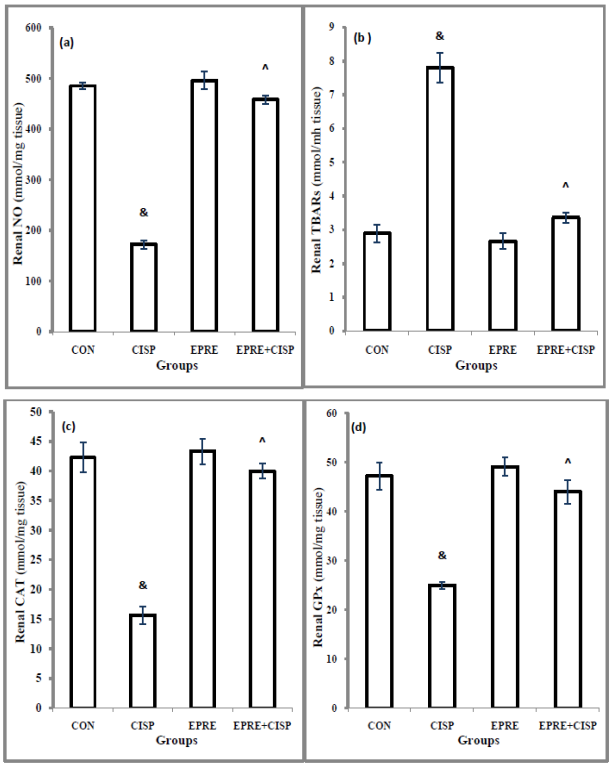

Figure 3: Levels of renal oxidative status markers and enzymatic antioxidants (a) NO ,(b) TBARS, (c) CAT, and (d) (GPx) measured in control (CON), Renal toxic Cisplatin (CISP), *E. purpurea* root extract (EPRE) (500 mg/kg), and *E. purpurea* root extract (EPRE) (500 mg/kg)+ Cisplatin (EPRE 500 mg/kg + CISP). Results are represented as mean ± SE of 10 rats/ group. & significant compared with CON and ^ significant compared with CISP group (p< 0.05).

Table 1: Levels of serum inflammatory markers (tumor necrosis factor alpha (TNF-α), and interleukin-10 (IL-10)) measured in control (CON), renal toxic Cisplatin (CISP), *E. purpurea*root extract (EPRE) (500 mg/kg), and *E. purpurea*root extract (EPRE) (500 mg/kg)+ Cisplatin (EPRE 500mg/kg + CISP).

Groups	TNF-α(Pg/g)	IL-10(pg/g)
Con	403.9 ± 3.73	918.2 ± 6.98
CISP	903.0 ± 8.72[a]	537.1 ± 7.53[a]
EPRE(500 mg/kg)	399.7 ± 4.49	917.2 ± 7.01
EPRE (500 mg/kg)+ CISP	501.6 ±7.31 [b]	801.6± 17.79[b]

Results are represented as mean ± SE of 10 rats/ group. [a] significant compared with CON and b significant compared with the CISP group ($p< 0.05$).

Histological Results

Renal section of rats from control (CON) and *E. Purpurea* root extract (EPRE) (500 mg/kg) groups showing the normal histological structure of renal parenchyma (Fig. 4.A. and Fig. 4. B). Renal sections from renal toxic Cisplatin (CISP) showing interstitial nephritis (Fig. 4.C), thickening of renal capsule and necrosis of subscapular renal tubules (Fig. 4.D), and coagulative necrosis of epithelial lining renal tubules and focal interstitial nephritis (Fig. 5.A). Renal sections from EPRE (500mg/kg) +CISP showing near the normal histological structure of renal parenchyma, expect slight congestion of glomerular tuft and renal blood vessels (Fig. 5.B and Fig. 5.C).

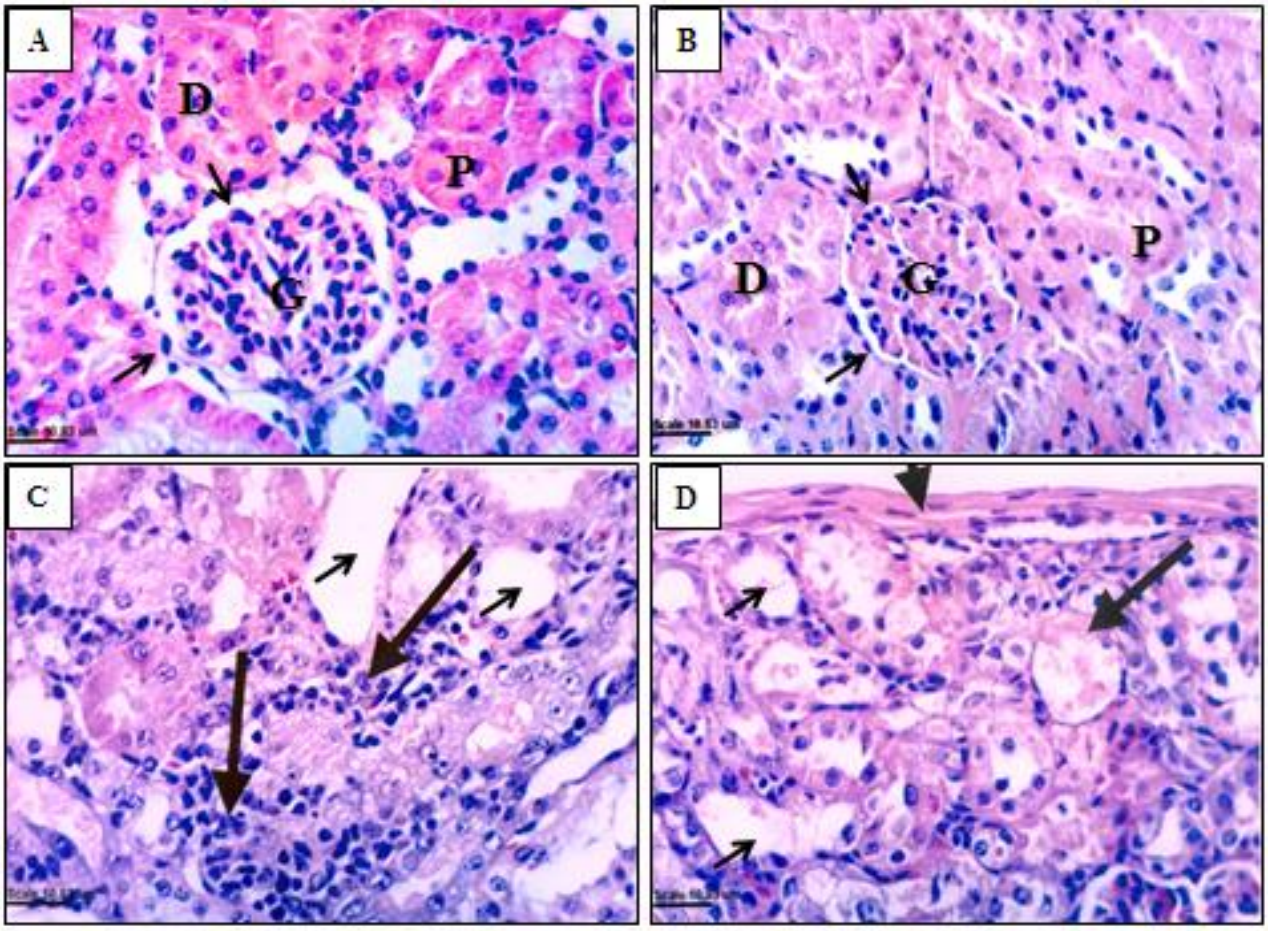

Figure 4: A photomicrograph of a renal section from control (CON) and *E. Purpurea* root extract (EPRE) (500 mg/kg) groups showing the normal histological structure of renal glomerulus (G), narrow Bowman's capsular (arrows) normal proximal (P) convoluted tubules with distal (D) tubule has many cubical cell lining with apical nuclei (Fig. 4.A. and Fig. 4. B). Renal section from toxic Cisplatin (CISP)group showing interstitial nephritis (large arrows), widespread of the dilated tubules, swelling and hydropic of the degenerated cytoplasmic (small arrows) (Fig. 4.C), thickening of renal capsule (arrowhead), widespread of the dilated tubules (small arrows), and necrosis of subscapular renal tubules (large arrows) (Fig. 4.D).

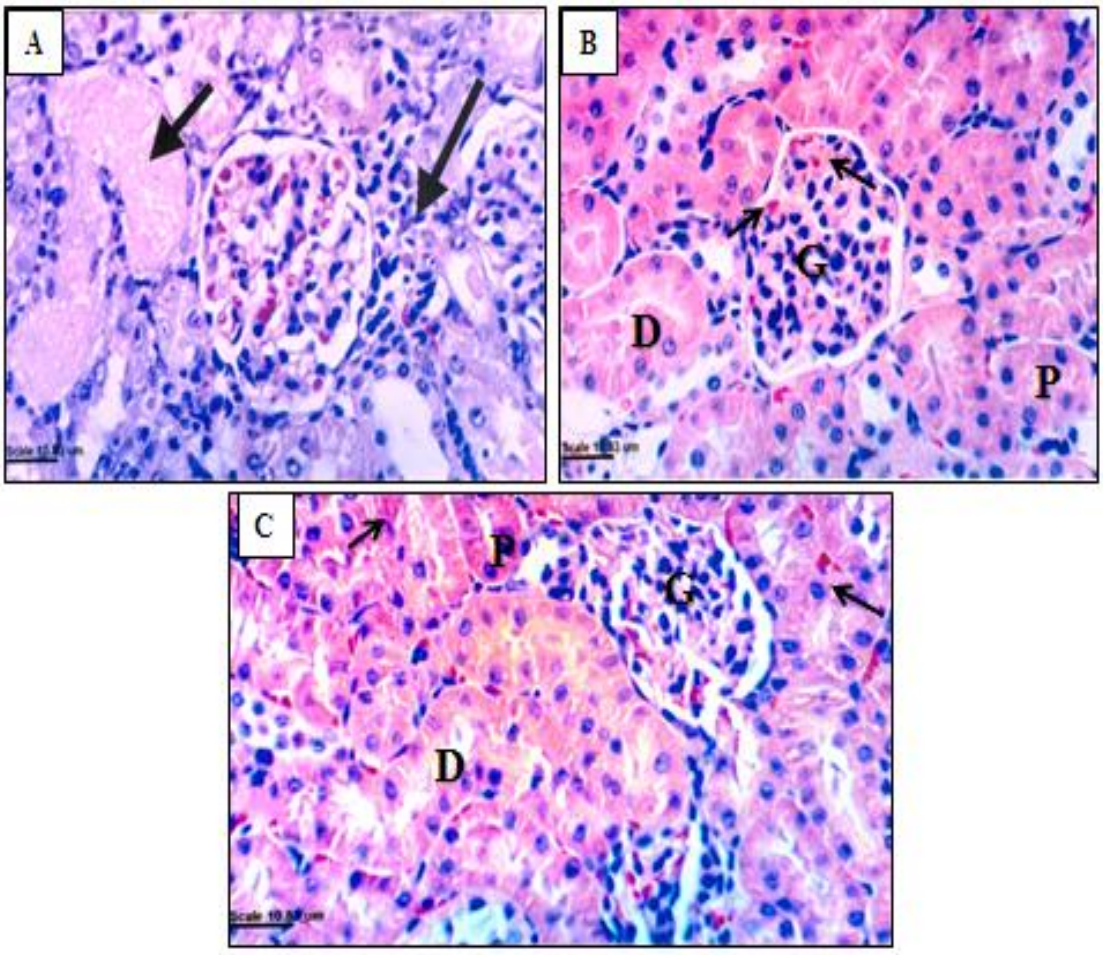

Figure 5: A photomicrograph of a renal section from the CISP group showing coagulative necrosis of epithelial lining renal tubules (small arrows), and focal interstitial nephritis (large arrows) (Fig. 5.A). Renal section from EPRE (500mg/kg) +CISP showing near control structure appearance of renal parenchyma, expect mild congestion of glomeruli (G) and renal blood vessel (Fig. 5.B and Fig. 5.C).

DISCUSSION

Cisplatin used to treat many types of cancer and autoimmune diseases. However, the usage of CISP is restricted due to its renal toxicity [25]. Natural traditional medicine products, which contain bioactive antioxidant compounds, used as an alternative form of health care to decline drug resistance and prevent its side effects [14]. The current research assessed the potential pathways responsible for the renal-protective effects of EPRE in CISP-induced renal toxicity in rats.

Rats injected CISP revealed appreciably renal damage as detected through significant elevations in serum renal function markers (Cr, BUN, and UA), ionic K^+ with a significant reduction in serum ionic Na^+ level. The CISP group revealed noticeably inflammation detected through a significant increase in renal TNF-α and a significant decrease in renal IL-10, as well as renal oxidative stress which observed through a significant elevation in renal TBARS, with a significant decline in renal NO, CAT, and GPx as compared with CON group. The biochemical results confirmed with histopathological results which showed many damage changes including interstitial nephritis, thickening of renal capsule, and necrosis of subscapular renal tubules in the CISP group.

Following our results, other researchers found an increase in kidney function parameters in CISP treated group [25-27]. Ozkok and Edelstein [22] reported that CISP induced severe renal toxicity evidenced by the increase of serum BUN and Cr, as well as decrease of creatinine clearance value along with noticeable histopathological changes. Administration of CISP resulted in an up-regulation of free radicals, thus induced destruction of cellular structures [28, 29]. The elevation of renal oxidative stress as reported in the present study could be explained through the reduction of antioxidants in renal tissue [30].

Oxidative stress, cytokine activity, and inflammation have been concerned in the pathogenesis of CISP-induced renal toxicity [31-33]. CISP is converted metabolically to potent toxin-induced DNA damage, oxidative damage, apoptotic activation, and pro-inflammatory cytokines elevation, thus could be explained through elevation of

myeloperoxidase and transcription factor-kappa B cells (NF-κB) [34-36]. Furthermore, activation of caspase-3-induced tubular epithelial cell apoptosis is an important mechanism that explained renal injury [37, 38].

The TNF-α and IL-10 have a role in explaining the CISP renal toxicity through linking three mechanisms; inflammation, oxidative stress and apoptosis [39, 40]. Several investigations revealed that CISP induced remarkable inflammatory reactions, which evidenced by increased TNF-α and decreased IL-10 levels [39, 41]. The increase of renal TNF-α level explained through inflammatory cytokines activation and elevating the chemotaxis of the immune cells [42], while a decrease of renal IL-10 level explained through the downregulation of antigen and pro-inflammatory liberation [43].

Oral given EPRE (500 mg/kg) to rats did not induce changes in renal functions and ionic electrolyte levels, while it improves antioxidant status compared with CON, thus means the safe usage of EPRE. However, before and simultaneous administration of EPRE (500 mg/kg) with CISP showed protective against CISP renal damage in rats in the form of significant decreased in serum renal function markers (Cr, BUN, and UA), ionic K^+, renal anti-inflammatory cytokines (decreased in TNF-α and increased in IL-10) with significant increase renal antioxidant status, as well as resulted in normalize the histological structure of renal parenchyma as compared CISP group. Thus indicated the curative effect of EPRE against CISP nephrotoxicity *via* the anti-inflammatory, antioxidant and inhibition apoptosis.

Several studies on the anti-inflammatory and antioxidant of EPRE were done [44, 45]. The restoration of antioxidant, inhibition of inflammation, and apoptosis are the key to renal protective caused by EPRE. This protective effect was concurrent with other researchersHuntimer*et al*. [46] and Sullivan *et al*. [47], they confirmed the antioxidant of EPRE through free radicals scavenger and protect cellular macromolecules, thus attributed to its potent antioxidant and anti-inflammatory compounds such as polysaccharides, phenolic acids, alkylamides, phenolic diterpenes polyacetylene, glycoproteins, tannins, inulin, flavonoids, and isohytylamides [44, 48-52]. Polysaccharides and alkamides in EPRE have anti-inflammatory and immune-modulatory effects [53]. Polyphenolic compounds in the EPRE resulted in a decline of renal dysfunction and improve antioxidant status in renal tissue [54]. Cichoric acid in *Echinacea r*oot decreases apoptosis and has free radicals scavenging properties [55, 56]. Bayramoglu *et al*. [57] found that EPE induced a decrease in hepatotoxicity and nephrotoxicity in ischemia/reperfusion injury in rats. Angouti and Mashayekhi [58] revealed that *E. purpurea* extracts declined significantly nephrotoxicity induced by gentamicin, and protect against its side effects on renal function.

CONCLUSION

The results of the present study revealed that EPRE has a protective effect against CISP exert renal toxicity, evidenced by improving in renal dysfunction, declining renal inflammation and increasing renal antioxidant status with a noticeable improvement in the histopathological results. Thus suggests EPRE act as potent renal protective agents, the mechanisms by which EPRE could prevent against CISP-nephrotoxicity through antioxidant, and anti-inflammatory properties.

REFERENCES

[1] Dubey A, Park DW, Kwon JE, Jeong YJ, Kim T, Kim I, Kang SC, Chi KW. Investigation of the biological and anti-cancer properties of ellagic acid-encapsulated nano-sized metalla-cages. International journal of nanomedicine. 2015;10(Spec Iss):227.

[2] Cui W, Yazlovitskaya EM, Mayo MS, Pelling JC, Persons DL. Cisplatin-induced response of c-jun N-terminal kinase 1 and extracellular signal-regulated protein kinases 1 and 2 in a series of cisplatin-resistant ovarian carcinoma cell lines. Molecular carcinogenesis. 2000 Dec;29(4):219-28.

[3] Florea AM, Büsselberg D. Occurrence, use and potential toxic effects of metals and metal compounds. Biometals. 2006 Aug 1;19(4):419-27.

[4] Pabla N, Dong Z. Cisplatin nephrotoxicity: mechanisms and renoprotective strategies. Kidney international. 2008 May 1;73(9):994-1007.

[5] Tsang RY, Al-Fayea T, Au HJ. Cisplatin overdose. Drug safety. 2009 Dec 1;32(12):1109-22.

[6] Olszewski U, Hamilton G. A better platinum-based anticancer drug yet to come?. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2010 May 1;10(4):293-301.

[7] Kim YK, Jung JS, Lee SH, Kim YW. Effects of antioxidants and Ca2+ in cisplatin-induced cell injury in rabbit renal cortical slices. Toxicology and applied pharmacology. 1997 Oct 1;146(2):261-9.

[8] de Oliveira Mora L, Antunes LM, Francescato HD, Bianchi MD. The effects of oral glutamine on cisplatin-induced nephrotoxicity in rats. Pharmacological Research. 2003 Jun 1;47(6):517-22.

[9] Shiraishi F, Curtis LM, Truong L, Poss K, Visner GA, Madsen K, Nick HS, Agarwal A. Heme oxygenase-1 gene ablation or expression modulates cisplatin-induced renal tubular apoptosis. American

Journal of Physiology-Renal Physiology. 2000 May 1;278(5):F726-36.

[10] Launay-Vacher V, Rey JB, Isnard-Bagnis C, Deray G, Daouphars M. Prevention of cisplatin nephrotoxicity: state of the art and recommendations from the European Society of Clinical Pharmacy Special Interest Group on Cancer Care. Cancer chemotherapy and pharmacology. 2008 May 1;61(6):903-9.

[11] Kodama A, Watanabe H, Tanaka R, Kondo M, Chuang VT, Wu Q, Endo M, Ishima Y, Fukagawa M, Otagiri M, Maruyama T. Albumin fusion renders thioredoxin an effective anti-oxidative and anti-inflammatory agent for preventing cisplatin-induced nephrotoxicity. Biochimica et Biophysica Acta (BBA)-General Subjects. 2014 Mar 1;1840(3):1152-62.

[12] Althaiban MA. Evaluation of Renaoprotective Effect of Costus Afer Leaf Extract on Rats exposed to Cyclosporine: Antioxidant and Anti-inflammatory Pathways. Journal of Biochemical Technology. 2019 Jun 1;10(2): 1-7.

[13] Rezaei, E., Nazari, N., Nowrouzi, A., Pakdel, A., Nazari, H. The Effect of Aqueous and Hydro-Alcoholic Extract of Prosopis Farcta on the Glucose Uptake in L6 Muscle Cell Lines. J Biochem Tech, 2018; Special Issue (2): 159-165.

[14] Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life sciences. 2005 Dec 22;78(5):431-41.

[15] Tanaka T, Kojima T, Kawamori T, Yoshimi N, Mori H. Chemoprevention of diethylnitrosamine-induced hepatocarcinogenesis by a simple phenolic acid protocatechuic acid in rats. Cancer research. 1993 Jun 15;53(12):2775-9.

[16] Abdullah T. A strategic call to utilize Echinacea-garlic in flu-cold seasons. Journal of the National Medical Association. 2000 Jan;92(1):48.

[17] Ahmed HS, Kamel KI, El-Sabeiy ME, Zeitouny MH. Effect of Echinacea extract supplementation on growth performance and hemo-biochemical traits of growing rabbits. Egypt Poultry Science. 2008;28:1165-80.

[18] Kumar KM, Ramaiah S. Pharmacological importance of Echinacea purpurea. International Journal of Pharma and Bio Sciences. 2011 Oct;2(4):304-14.

[19] Heidari M, Rezaie A, Broojeni MP, Najafzadeh H, Mohammadian B. Histopathologic effects of Echinacea purpurea extract on sodium arsenite-induced hepatic disorders. Comparative clinical pathology. 2012 Dec 1;21(6):1629-32.

[20] Masteikova R, Muselik J, Bernatonienė J, Bernatonienė R. Antioxidative activity of Ginkgo, Echinacea, and Ginseng tinctures. Medicina. 2007;43(4):306.

[21] Hanigan MH, Devarajan P. Cisplatin nephrotoxicity: molecular mechanisms. Cancer therapy. 2003;1:47.

[22] Ozkok A, Edelstein CL. Pathophysiology of cisplatin-induced acute kidney injury. BioMed research international. 2014;2014.

[23] El-Sharouny SH, Rizk AA, Rashed LA, Sayed WM, Elmoneam MD. Analysis of the therapeutic role of platelet-rich plasma against cisplatin-induced hepatotoxicity in rats: controversy between oxidative and apoptotic markers. European Journal of anatomy. 2019;23(3):201-13.

[24] Abdalla, O., Abdelhamid, F., El-Boshy, M., Mohammed, F. H. and Othaman, H. Studying the effect of Echinacea purpurea root on hematological, biochemical and histopathological alterations in cyclo-phosphamide treated rats. Annals of Veter Animal Sci, 2015; 3(2):62-75.

[25] Mostafa RE, Dalia OS, Dina FM. Cisplatin-induced nephrotoxicity in rats: modulatory role of simvastatin and rosuvastatin against apoptosis and inflammation. Journal of Applied Pharmaceutical Science. 2018 Apr;8(04):043-50.

[26] Shimeda Y, Hirotani Y, Akimoto Y, Shindou K, Ijiri Y, Nishihori T, Tanaka K. Protective effects of capsaicin against cisplatin-induced nephrotoxicity in rats. Biological and Pharmaceutical Bulletin. 2005;28(9):1635-8.

[27] Palipoch S, Punsawad C, Koomhin P, Suwannalert P. Hepatoprotective effect of curcumin and alpha-tocopherol against cisplatin-induced oxidative stress. BMC complementary and alternative medicine. 2014 Dec;14(1):111.

[28] Conklin KA. Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. Nutrition and cancer. 2000 May 1;37(1):1-8.

[29] Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. European journal of pharmacology. 2014 Oct 5;740:364-78.

[30] El-Shitany NA, Eid B. Proanthocyanidin protects against cisplatin-induced oxidative liver damage through inhibition of inflammation and NF-κβ/TLR-4 pathway. Environmental toxicology. 2017 Jul;32(7):1952-63.

[31] Deng J, Kohda Y, Chiao H, Wang Y, Hu X, Hewitt SM, Miyaji T, Mcleroy P, Nibhanupudy B, Li S, Star RA. Interleukin-10 inhibits ischemic and cisplatin-induced acute renal injury. Kidney international. 2001 Dec 1;60(6):2118-28.

[32] Ramesh G, Reeves WB. TNF-α mediates chemokine and cytokine expression and renal injury

in cisplatin nephrotoxicity. The Journal of clinical investigation. 2002 Sep 15;110(6):835-42.

[33] Ramesh G, Reeves WB. Salicylate reduces cisplatin nephrotoxicity by inhibition of tumor necrosis factor-α. Kidney international. 2004 Feb 1;65(2):490-8.

[34] Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of cisplatin nephrotoxicity. Toxins. 2010 Nov;2(11):2490-518.

[35] Rao AM, Anand U, Anand CV. Myeloperoxidase in chronic kidney disease. Indian Journal of Clinical Biochemistry. 2011 Jan 1;26(1):28-31.

[36] Amirshahrokhi K, Khalili AR. Thalidomide ameliorates cisplatin-induced nephrotoxicity by inhibiting renal inflammation in an experimental model. Inflammation. 2015 Apr 1;38(2):476-84.

[37] Wei Q, Dong G, Franklin J, Dong Z. The pathological role of Bax in cisplatin nephrotoxicity. Kidney international. 2007 Jul 1;72(1):53-62.

[38] Liu H, Gu LB, Tu Y, Hu H, Huang YR, Sun W. Emodin ameliorates cisplatin-induced apoptosis of rat renal tubular cells in vitro by activating autophagy. Acta Pharmacologica Sinica. 2016 Feb;37(2):235.

[39] Tadagavadi RK, Reeves WB. Endogenous IL-10 attenuates cisplatin nephrotoxicity: role of dendritic cells. The Journal of Immunology. 2010 Oct 15;185(8):4904-11.

[40] Shaw J, Chen B, Huang WH, Lee AR, Valeriote FA. The small-molecule TNF-α modulator, UTL-5g, reduces side effects induced by cisplatin and enhances the therapeutic effect of cisplatin in vivo. Journal of experimental therapeutics & oncology. 2011 Jun 1;9(2).

[41] Rehman MU, Ali N, Rashid S, Jain T, Nafees S, Tahir M, Khan AQ, Lateef A, Khan R, Hamiza OO, Kazim S. Alleviation of hepatic injury by chrysin in cisplatin administered rats: probable role of oxidative and inflammatory markers. Pharmacological Reports. 2014 Dec 1;66(6):1050-9.

[42] Lawrence T. The nuclear factor B pathway in inflammation. Inflammation biology group. Cold Spring Harbor Laboratory Press. 2009;1(6):1-0.

[43] Knolle PA, Uhrig A, Hegenbarth S, Löser E, Schmitt E, Gerken G, Lohse AW. IL-10 down-regulates T cell activation by antigen-presenting liver sinusoidal endothelial cells through decreased antigen uptake via the mannose receptor and lowered surface expression of accessory molecules. Clinical and experimental immunology. 1998 Dec;114(3):427.

[44] Pellati F, Benvenuti S, Melegari M, Lasseigne T. Variability in the composition of anti-oxidant compounds in Echinacea species by HPLC. Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques. 2005 Mar;16(2):77-85.

[45] AH E. Protective effects of Echinacea on cyproterone acetate induced liver damage in male rats. Pakistan Journal of Biological Sciences. 2008;11(21):2464-71.

[46] Huntimer ED, Halaweish FT, Chase CC. Proliferative activity of Echinacea angustifolia root extracts on cancer cells: Interference with doxorubicin cytotoxicity. Chemistry & biodiversity. 2006 Jun;3(6):695-703.

[47] Sullivan AM, Laba JG, Moore JA, Lee TD. Echinacea-induced macrophage activation. Immunopharmacology and Immunotoxicology. 2008 Sep 1;30(3):553-74.

[48] Block KI, Mead MN. Immune system effects of echinacea, ginseng, and astragalus: a review. Integrative cancer therapies. 2003 Sep;2(3):247-67.

[49] Miller SC. Echinacea: a miracle herb against aging and cancer? Evidence in vivo in mice. Evidence-Based Complementary and Alternative Medicine. 2005;2(3):309-14.

[50] Stanisavljević I, Stojičević S, Veličković D, Veljković V, Lazić M. Antioxidant and antimicrobial activities of Echinacea (Echinacea purpurea L.) extracts obtained by classical and ultrasound extraction. Chinese Journal of Chemical Engineering. 2009 Jun 1;17(3):478-83.

[51] Ezz MK. The ameliorative effect of Echinacea purpurea against gamma radiation induced oxidative stress and immune responses in male rats. Australian Journal of Basic and Applied Sciences. 2011;5(10):506-12.

[52] Murthy HN, Park SY, Lee EJ, Paek KY. Biosafety and Toxicological Evaluation of Tissue-Cultured Echinacea purpurea Adventitious Roots. Horticultural Science & Technology. 2015 Feb 1;33(1):124-32.

[53] Gertsch J, Schoop R, Kuenzle U, Suter A. Echinacea alkylamides modulate TNF-α gene expression via cannabinoid receptor CB2 and multiple signal transduction pathways. FEBS letters. 2004 Nov 19;577(3):563-9.

[54] Wongmekiat O, Leelarugrayub N, Thamprasert K. Beneficial effect of shallot (Allium ascalonicum L.) extract on cyclosporine nephrotoxicity in rats. Food and chemical toxicology. 2008 May 1;46(5):1844-50.

[55] Thygesen L, Thulin J, Mortensen A, Skibsted LH, Molgaard P. Antioxidant activity of cichoric acid and alkamides from Echinacea purpurea, alone and in combination. Food chemistry. 2007 Jan 1;101(1):74-81.

[56] Tsai YL, Chiu CC, Chen JY, Chan KC, Lin SD. Cytotoxic effects of Echinacea purpurea flower extracts and cichoric acid on human colon cancer cells through induction of apoptosis. Journal of ethnopharmacology. 2012 Oct 11;143(3):914-9.

[57] Bayramoglu G, Kabay S, Ozden H, Ustuner MC, Uysal O, Bayramoglu A, Senturk H, Kutlu A, Ustuner D, Canbek M. The effect of Echinacea on kidney and liver after experimental renal ischemia/reperfusion injury in the rats. African Journal of Pharmacy and Pharmacology. 2011 Oct 8;5(13):1561-6.

[58] Angouti M, Mashayekhi M. Effect of Echinacea purpura extract on gentamicin-induced nephrotoxicity in sheep. Journal of Livestock Science (ISSN online 2277-6214). 2017 Jan 1;8:221-4.