original article

Oxytocin ameliorates cisplatin-induced nephrotoxicity in Wistar rats

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BACKGROUND AND OBJECTIVES: The clinical use of cisplatin (CP) is highly limited because of its renal toxicity and the production of reactive oxygen species (ROS) that intensify the cytotoxic effects. Oxytocin (OT) was previously shown to have antioxidant activity.

DESIGN AND SETTING: Experimental study on male Wistar albino rats performed in the Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia.

METHODS: Forty-eight male Wistar albino rats were classified into four equal groups: a control group, OT only-treated group which received OT twice (500 µg/kg intraperitoneally (ip) 30 minutes and just before saline administration), a CP-induced nephrotoxicity group that received a single dose of CP (7.5 mg/kg ip) and treated with saline, and CP+OT group treated with the same previous doses. Seventy-two hours after CP administration, the rats were sacrificed and blood was withdrawn for determination of urea, creatinine, albumin and lactate dehydrogenase (LDH). The kidneys were extracted for histopathological examination and determination of the tissue levels of reduced glutathione (GSH), thiobarbituric acid reactive substances (TBARS) and nitric oxide end product nitrite (NO_2). Glutathione S-transferase (GST), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) and myeloperoxidase (MPO) activities were assessed.

RESULTS: CP-induced renal injury was evidenced histopathologically and manifested by a significant increase in serum LDH activity as well as urea and creatinine levels. Moreover, renal injury was associated with decreased renal tissue activities of CAT, SOD, GPx and GST as well as GSH level. On the other hand, renal tissue content of TBARS and NO_2 as well as the activity of MPO were increased. Alterations in these biochemical and histopathological indices due to CP were attenuated by OT.

CONCLUSION: OT protected rats from CP-induced nephrotoxicity. Such protection is attributed, at least in part, to its antioxidant activity.

Cisplatin (CP) is an inorganic platinum complex that is highly effective against many tumors.[1] Although higher doses of CP are more effective than lower ones, high-dose therapy is associated with irreversible renal dysfunction and cumulative nephrotoxicity.[2] Irreversible renal damage occurs in about one third of CP-treated patients.[3] Thus, prevention of the dose-limiting side effects of CP is one of the major issues in treating cancer patients.[4] Oxidative stress process was reported to contribute to CP-induced nephrotoxicity.[5,6] CP generates reactive oxygen species (ROS) and consequently, depletes glutathione and inhibits the activity of antioxidant enzymes in renal tissues.[7,8] Some antioxidants were tested for their ability to protect against CP-induced nephrotoxicity in experimental animals.[8,9]

Oxytocin (OT) is a neurohypophysial peptide synthesized in the paraventricular and supraoptical nuclei of the hypothalamus. The well-known effect of OT is the stimulation of the uterine contractions at parturition and myoepithelial contractions in the mammary gland during suckling.[10] OT receptors have been identified in many tissues, including the central nervous system, kidney, heart, thymus, pancreas, adipocytes as

well as endothelial and smooth muscle cells of blood vessels.[11-13] Houshmand et al[14] showed that OT possesses a dose-dependent cardioprotective effect against ischemia/reperfusion injury. Moreover, it was shown in brain membranes that secretory peptides, including OT, have antioxidant properties, scavenging free peroxyl radicals, preventing LDL oxidation and inhibiting lipid peroxidation.[15] Recently, Rashed et al[16] showed that OT has a powerful antioxidant effect through inhibition of NADPH oxidase. The current study was designed to investigate the possible protective effect of OT against CP-induced nephrotoxicity.

METHODS

CP was purchased from Bristol-Myers Squibb (New York City, NY, USA) as solution (2mg/mL). OT and all other chemicals used were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Forty-eight male Wistar albino rats (250-300 g) were used in the experiment in accordance with the guidelines of the Biochemical and Research Ethical Committee at King Abdulaziz University, Jeddah, Saudi Arabia. Animals were housed in a well-ventilated temperature-controlled room at 22±3°C with 12 hours light and dark cycles. Food consisted of standard laboratory rat chow with free access to water. All experimental procedures were performed between 08:00 to 10:00 and care was taken to avoid all stressful conditions.

Rats were divided into four equal groups in separate cages. Group I (control group) received saline (1 mL/kg; intraperitoneally (ip). Group II (OT group) received OT alone (500 µg/kg; ip) twice; 30 minutes and immediately before saline administration (instead of CP). The dose of OT was based on our preliminary study and a previous study by Düşünceli et al.[17] Group III (CP group) received saline (1 mL/kg) 30 minutes and immediately before CP administration. CP was given in a dose of 7.5 mg/kg once ip, the dose which is documented to induce nephrotoxicity in rats.[2] Group IV (OT + CP group) received both OT and CP in the same previous doses.

Seventy-two hours after CP administration, rats were sacrificed using ether anesthesia and blood was collected directly by a cardiac puncture from the heart of each animal. The blood was centrifuged at 3000×*g* for 10 minutes to obtain clear sera which was stored at –70°C for further analysis. The abdomen of each rat was opened and kidneys were rapidly dissected out, washed in ice-cold isotonic saline and blotted between two filter papers. The right kidneys from each animal were fixed in 10% formalin for histopathological examination. For subsequent analysis, a 10% homogenate was prepared from a part of the left kidney in phosphate buffer (0.05mol/L, pH 7.0) using a polytron homogenizer (PT 10/35) obtained from Brinkmann Instruments Inc. (Westbury, NY, USA) at 4°C. The homogenate was centrifuged at 1000×*g* for 10 minutes at 4°C to remove the cell debris.

Serum albumin concentrations were determined by a spectrophotometric bromocresol green method described by Doumas et al.[18] Serum lactate dehydrogenase activity (LDH), blood urea nitrogen (BUN) and serum creatinine levels were determined spectrophotometrically by the methods described by Martinek,[19] Talke and Schuber[20] and Slot,[21] respectively. Reduced glutathione (GSH) was determined according to the method of Moron et al[22] based on the formation of a yellow-colored complex with Ellman reagent. Lipid peroxidation was determined by measuring thiobarbituric acid reactive substances (TBARS) in tissue homogenates referring to the malondialdehyde (MDA) standard calibration curve according to the method of Uchiyama and Mihara.[23] Nitric oxide (NO) end product nitrite production (NO_2) was used to assess relative values of the NO. Nitrites assay was determined by a colorimetric method based on the Greiss Reaction.[24]

The activity of glutathione S-transferase (GST) was measured according to the method of Habig et al.[25] P-nitrobenzylchloride was used as a substrate. The absorbance was measured spectrophotometrically at 310 nm using a UV-double beam spectrophotometer obtained from Labomed Inc. (Culver City, CA, USA). Catalase (CAT) activity was determined from the rate of decomposition of H_2O_2, monitored by a decrease of 240 nm following the addition of tissue homogenate. Superoxide dismutase (SOD) levels in the kidney tissue were determined according to the modified method of Kakkar et al.[27] Glutathione peroxidase (GPx) activity was determined by the method of Hafeman et al[28] based on the degradation of H_2O_2 in the presence of GSH. Myeloperoxidase (MPO) activity was determined using a 4-aminoanipyrine/phenol solution as a substrate for MPO-mediated oxidation by H_2O_2 and changes in absorbance at 510 nm (A510) were recorded.[29] The protein content of tissue homogenates was determined by the Lowry protein assay using bovine serum albumin as a standard.[30]

Histopathological sections of kidney from all groups were evaluated using Meiji light microscope model 109-L (Meiji Techno. Co., Ltd., Saitama, Japan). Tissues were fixed in 10% formalin, embedded in paraffin, sectioned at 5 µm and stained with hematoxylin and eosin.

The GraphPad InStat 3 (graphPad Software Inc,

La Jolla, CA, USA) computer program was used to conduct regression analysis and to plot the collected data. All data were expressed as means and standard deviation. Assessment of these results was performed using one-way ANOVA procedure followed by Tukey-Kramer multiple comparisons tests using Software GraphPad Prism, Version 4. Statistical significance was determined as a *P* value <.05.

RESULTS

Effect on serum markers

Administration of CP to rats significantly increased BUN and serum creatinine levels and significantly reduced serum albumin compared to the control group (P<.05). Pretreatment with OT significantly reduced (P<.05) BUN and nearly normalized serum creatinine and albumin levels (**Figures 1 and 2 and Table 1**). Moreover, serum LDH activity significantly increased in CP group compared to the control group. Pretreatment with OT significantly inhibited CP-induced increase in serum LDH activity (**Figure 2**).

Effect on tissue markers

In CP rats, significant (*P*<.05) depletion of GSH and an increase in TBARS and NO_2 levels were observed compared to the control group. Pretreatment with OT significantly attenuated these changes in OT+CP group compared to CP group (**Table 2**).

Effect on tissue enzymatic activity

Renal tissue activities of the antioxidant enzymes (GST, SOD, CAT and GPx) were significantly decreased (*P*<.05) in CP group compared to control group. Pretreatment with OT significantly elevated these levels (**Table 3**). MPO activity, an indicator of neutophil infiltration, was significantly higher in the renal tissue of CP group compared to control group. On the other hand, OT pretreatment significantly decreased the renal tissue activity of MPO approximating the control group activity (**Figure 3**).

Histopathological results

The light microscopic study of the control and OT groups revealed a regular morphology of renal parenchyma with well-designated glomeruli and tubules (**Figure 4A and 4B**). In the CP group, CP caused severe widespread tubular and interstitial damage evidenced by tubular lumen dilatation due to flattening of tubular cells with brush border loss, cast formation and inflammatory cell infiltration (**Figure 4C**). Pretreatment with OT significantly improved the histological features of the CP-induced nephrotoxicity. Kidneys of rats pretreated with OT showed reduced tubular damage and interstitial inflammation indicating regeneration and improvement (**Figure 4D**).

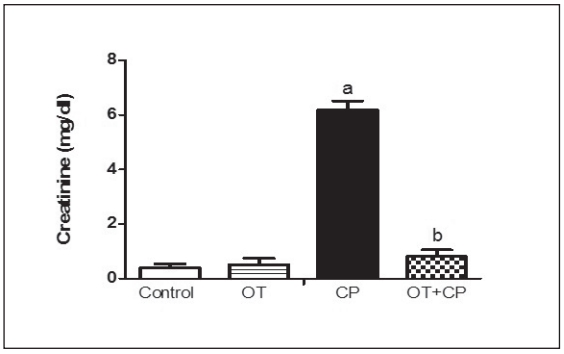

Figure 1. Effect of oxytocin (OT) treatment on serum creatinine in cisplatin (CP)-induced nephrotoxicity.

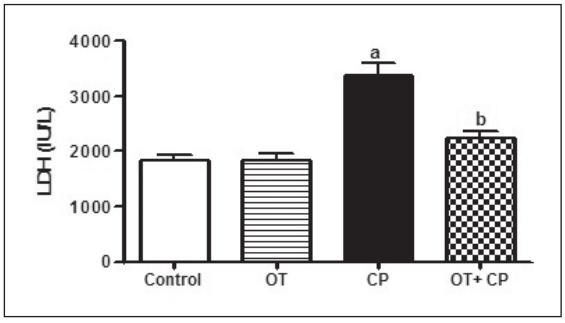

Figure 2. Effect of oxytocin (OT) on serum lactate dehydrogenase (LDH) level in cispaltin (CP)- induced nephrotoxicity (n=12 each group). [a]*P*<.05 vs. control group; [b]*P*<.05 vs. CP group.

Table 1. Effect of oxytocin treatment on blood urea and serum albumin in cisplatin-induced nephrotoxicity.

	Urea (mg/dL)	Albumin (g/dL)
Control	24.3 (3.5)	5.3 (0.10)
OT	29.6 (4.2)	5.1 (0.24)
CP	130 (9.7)[a]	3.8 (0.5)[a]
OT+CP	62.0 (5.7)[b]	4.1 (0.13)

Data are the mean (SD) of 12 rats in each group. OT: oxytocin; CP: cisplatin. [a]*P*<.05 vs. control group; [b]*P*<.05 vs. CP group.

DISCUSSION

Nephrotoxicity limits the clinical use of CP as a chemotherapeutic agent in 25% to 30% of patients, even after the first dose.[31] The current study investigated the

Table 2. Effect of oxytocin (OT) treatment on the levels of reduced glutathione (GSH), thiobarbituric acid-reactive substances (TBARS) and nitrite (NO_2) in cisplatin (CP)-induced nephrotoxicity.

	GSH (µ mol/g protein)	TBARS (n mol/ g protein)	NO_2 (µ mol/mg protein)
Control	1.80 (0.53)	20.6 (3.30)	0.10 (0.14)
OT	1.43 (0.29)	23.2 (5.70)	0.11 (0.17)
CP	0.20 (0.10)[a]	51.3 (5.11)[a]	0.38 (2.20)[a]
OT+CP	1.20 (0.41)[b]	25.8 (4.93)[b]	0.18 (0.20)[b]

Data are the mean (SD) of 12 rats in each group. OT: oxytocin; CP: cisplatin. [a]*P*<.05 vs. control group; [b]*P*<.05 vs. CP group.

Table 3. Effect of oxytocin (OT) treatment on the activities of glutathione S-transferase (GST), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in cisplatin (CP)-induced nephrotoxicity.

	GST (U/mg protein)	CAT (U/ mg protein)	SOD (U/ mg protein)	GPx (U/ mg protein)
Control	0.82 (0.19)	5.13 (0.57)	53.1 (4.10)	29.12 (2.82)
OT	0.88 (0.08)	5.05 (0.53)	58.6 (4.51)	30.03 (3.07)
CP	0.36 (0.08)[a]	2.46 (0.37)[a]	30.6 (3.41)[a]	19.82 (2.01)[a]
OT+CP	0.58 (0.1)[b]	3.72 (0.26)[a]	39.1 (3.14)[b]	23.26 (2.07)[b]

Data are the mean (SD) of 12 rats in each group. [a]*P*<.05 vs. control group; [b]*P*<.05 vs. CP group.

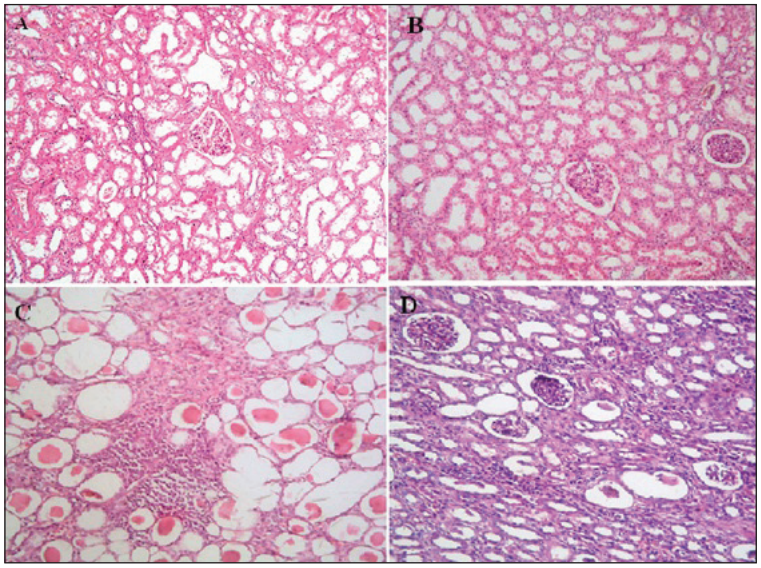

Figure 4. Histopathological finding (Hematoxylin and eosin, ×200) from (A) control group and (B) oxytocin (OT) only treated group showing normal histopathological distribution; (C) cisplatin-treated (CP) group showing prominent tubular dilatation with flat epithelial lining, cast formation and interstitial inflammation (D) OT plus CP group displaying remarkable improvement in the histological appearance with marked reduction in CP-induced tubular damage, compared to samples treated with CP alone.

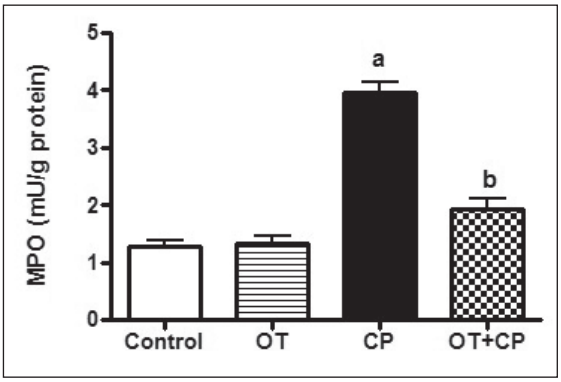

Figure 3. Effect of oxytocin (OT) treatment on Myeloperoxidase (MPO) activity in in cisplatin (CP)-induced nephrotoxicity (n=12 each group). [a]*P*<.05 vs. control group; [b]*P*<.05 vs. CP group.

possible protective effect of OT against CP-induced nephrotoxicity. CP induced renal injury as evidenced by the histopathological features as well as serum and tissue parameter changes. Townsend et al[32] showed that renal toxicity from CP is usually localized to the proximal tubular cells. This is consistent with the findings of the present study that showed tubular necrosis with interstitial inflammation.

BUN and serum creatinine were elevated with a significant decrease in serum albumin, indicating renal impairment in CP-treated rats. Similarly, LDH was significantly elevated following CP administration, indicating nonspecific cellular injury. The exact mechanism of CP-induced nephrotoxicity is not completely understood. However, oxidative stress and free radical production in renal tubular cells have been suggested as reasons for the oxidative renal damage.[33] A significant decline in antioxidant enzyme activities and an increase in free radicals in experimental models as well as in human studies is typical during CP treatment.[34] Mansour et al[35] demonstrated that CP induces ROS by depleting the antioxidant system whether enzymatic as GST, GPx, SOD and CAT or non-enzymatic as intracellular GSH. These findings are in accordance with the results of the present study. Pretreatment with OT obviously ameliorated these alterations in the antioxidant system.

The present study supports the hypothesis that the mechanism of CP toxicity is related to exhaustion of the antioxidant defense system. A significant increase in renal TBARS and a decrease in the activities of antioxidant enzymes were reported by many researchers following CP treatment of rats.[8,36,37] In the present study, CP-elevated tissue MPO activity indicating the presence of enhanced polymorphonuclear leukocytes recruitment in the inflamed tissue, while the increased renal TBARS level, an indicator of lipid peroxidation,

verified the oxidative damage in the renal tissue. OT pretreatment inhibited the increase in MPO activity and TBARS levels as well as the inflammatory cell infiltration induced by CP. These data are in accordance with Çetinel et al,[38] who reported similar effects of OT on both MPO and MDA in stress-induced colitis.

Previous studies indicated that CP undergoes metabolic activation in the kidney to a more potent toxin with highly reactive thiols.[39] This process begins with the formation of glutathione conjugates in the circulation, perhaps mediated by GST.[32,40] In the current study, pretreatment with OT ameliorated the decrease in the GST induced by CP. Moreover, OT prevented both oxidative renal injury and tissue neutrophil accumulation. A possible mediator behind the decrease in MPO activity in response to OT could be NO.[41] It has been reported that CP-induced nephrotoxicity is associated with higher kidney NO levels due to overexpression of inducible nitric oxide synthase activity.[42] Inhibition of NO was reported to decrease CP-induced lipid peroxidation and organ toxicity.[43] In the current study, OT reduced the elevation of NO and the lipid peroxidation marker TBARS, which was increased by CP.

Some studies confirmed the antioxidant property of OT in colitis,[44] pyelonephritis,[45] and sepsis-induced inflammatory models.[46] It was also shown that in brain membranes, OT displayed antioxidant properties in aqueous medium, scavenging free peroxyl radicals, preventing LDL oxidation and inhibiting lipid peroxidation.[16] OT has a protective effect against CP-induced renal toxicity in rats. This protective effect is probably mediated, at least in part, through its antioxidant effect.

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REFERENCES

1. Lebwohl D, Canetta R. Clinical development of platinum complexes in cancer therapy: an historical perspective and an update. Eur J Cancer 1998; 34:1522–34.
2. Atessahin A, Yilmaz S, Karahan I, Ceribasi AO, Karaoglu A. Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats. Toxicol 2005; 212:116–23.
3. Razzaque MS. Cisplatin nephropathy: is cytotoxicity avoidable? Nephrol Dial Transplant 2007; 22:2112–6.
4. Chang BJ, Nishikawa M, Sato E, Utsumi K, Inouea M. L-Carnitine inhibits cisplatin-induced injury of the kidney and small intestine. Arch Biochem Biophys 2002; 405:55–64.
5. Safirstein R, Miller P, Dikman S, Lyman N, Shapiro C. Cisplatin nephrotoxicity in rats: defect in papillary hypertonicity. Am J Physiol 1981; 241:F175–F185.
6. Zhong LF, Zhang JG, Zhang M, Ma SL, Xia YX. Protection against cisplatin-induced lipid peroxidation and kidney damage by procaine in rats. Arch Toxicol 1990; 64:599–600.
7. Badary OA, Abdel-Maksoud S, Ahmed WA, Owieda GH. Naringenin attenuates cisplatin nephrotoxicity in rats. Life Sci 2005; 76:2125–35.
8. Ajith TA, Usha S, Nivitha V. Ascorbic acid and ?-tocopherol protect anticancer drug cisplatin-induced nephrotoxicity in mice. A comparative study. Clin Chem Acta 2007; 375:82–6.
9. Hanigen MH, Devarajan P. Cisplatin nephrotoxicity: Molecular mechanisms. Cancer Ther 2003; 1:47–61.
10. Barberis C, Mouillac B, Durroux T. Structural bases of vasopressin/oxytocin receptor function. J Endocrinol 1998; 156:223–9.
11. Olson BR, Hoffman GE, Sved AF, Stricker EM, Verbalis JG. Cholecystokinin induces c-fos expression in hypothalamic oxytocinergic neurons projecting to the dorsal vagal complex. Brain Res 1992; 569:238–48.
12. Jankowski M, Wang D, Hajjar F, Mukaddam-Daher S, McCann SM, Gutkowska J. Oxytocin and its receptors are synthesized in the rat vasculature. Proc Natl Acad Sci USA 2000; 97:6207–11.
13. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function and regulation. Physiol Rev 2001; 81:629–33.
14. Houshmand F, Faghihi M, Zahediasl S. Biphasic protective effect of oxytocin on cardiac ischemia/reperfusion injury in anaesthetized rats. Peptides 2009; 30:2301–8.
15. Moosman B, Behl C. Secretory peptide hormones are biochemical antioxidants; structure–activity relationship. Mol Pharmacol 2002; 61:260–8.
16. Rashed LA, Hashem RM, Soliman HM. Oxytocin inhibits NADPH oxidase and P38 MAPK in cisplatin-induced nephrotoxicity. Biomed Pharmacother 2011; 65: 474-480.
17. Dü?ünceli F, Iseri S, Ercan F, Gedik N, Yegen C, Yegen B. Oxytocin alleviates hepatic ischemia-reperfusion injury in rats. Peptides 2008; 29:1216-22.
18. Doumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromocresol green. Clin Chim Acta 1971; 31:87–96.
19. Martinek RG. A rapid ultraviolent spectrophotometric lactic dehydrogenase assay. Clin Chem Acta 1972; 40:91–9.
20. Talke H, Schubert GE Enzymatic urea determination in the blood and serum in the Warburg optical test. Klin Wochenschr 1965; 43:174–5.
21. Slot C. Plasma creatinine determination. A new and specific Jaffe reaction method. Scand J Clin Lab Invest 1965; 17: 381–7.
22. Moron MA, Depicrre JW, Mannervick K. Levels of glutathione and glutathione-S-transferase activities in rat liver. Biochem Biophys Acta 1979; 582:67–8.
23. Uchiyama M, Mihara M. Determination of malonaldehyde precursor in tissues by thiobarbituric acid test. Anal Biochem 1978; 86:271–8
24. Stuehr DJ, Know NS, Gross SS. Synthesis of nitrogen oxides from L-arginine by macrophage cytosol: requirement for inducible and constitutive components. Biochem Biophys Res Commun 1989; 161:420–6.
25. Habig WH, Pabst MJ, Jakoby WB. Glutathione S-transferases. The first enzymatic step in mercapturic acid formation. J Biol Chem 1974; 249:7130–39.
26. Aebi H. Catalase in vitro. In: Packer L, Orlando FL (Eds.), Methods in Enzymology. 3rd ed. Academic Press, New York, 1984; pp. 121–6.
27. Kakkar P, Das B, Viswanatham PN. A modified spectrophotometric assay of superoxide dismutase. Indian J Biochem Biophys 1984; 21:130–2.
28. Hafeman DG, Sundae RA, Hoekstra WG. Effect of dietary selenium on erythrocyte and liver glutathione peroxidase in the rat. J Nutr 1974; 104:580–7.
29. Wei H, Frenkel K. In vivo formation of oxidized DNA bases in tumor promoter-treated mouse skin. Cancer Res 1991; 51:4443-9
30. Lowry OH, Rosenbrough NJ, Farr AL, Randall R. Protein determination using Folin–Cicocalteu reagent. J Biol Chem 1951; 193: 265–78.
31. Daugaard G, Abildgaard U. Cisplatin nephrotoxicity. A review. Cancer Chemother Pharmacol 1989; 25:1–9.
32. Townsend DM, Tew KD, He L, King JB, Hanigan MH. Role of glutathione S-transferase Pi in cisplatin-induced nephrotoxicity. Biomed Pharmacother 2009; 63:79–85.
33. Atessahin A, Ceribasi AO, Yuce A, Bulmus O, Cikim G. Role of ellagic acid against cisplatin-induced nephrotoxicity and oxidative stress in rats. Basic Clin Pharmacol Toxicol 2006; 100:121–6.
34. Partibha R, Sameer R, Rataboli PV, Bhiwgade DA, Dhume CY. Enzymatic studies of cisplatin-induced oxidative stress in hepatic tissue of rats. Eur J Pharmacol 2006; 532:290–93.
35. Mansour HH, Hafez HF, Fahmy NM. Silymarin modulates cisplatin-induced oxidative stress and hepatotoxicity in rats. J Biochem Mol Biol 2006; 39:656–61.
36. Mansour MA, Mostafa AM, Nagi MN, Khattab MM, Al-Shabanah OA. Protective effect of aminoguanidine against nephrotoxicity induced by cisplatin in normal rats. Comp Biochem Physiol Toxicol Pharmacol 2002; 2:123–28.
37. Al-Majed AA, Sayed-Ahmed A A, Al-Yahya AA, Aleisa AM, Al-Rejaie SS, Al- Shabanah OA. Propionyl-L-carnitine prevents the progression of cisplatin-induced cardiomyopathy in a carnitine-depleted rat model. Pharmacol Res 2006; 53:278–86.
38. Cetinel S, Hancio?lu S, Sener E, Uner C, Kiliç M, Sener G, et al. Oxytocin treatment alleviates stress-aggravated colitis by a receptor-dependent mechanism. Regul Pept 2010; 160:146-52.
39. Zhang L, Hanigan M.H. Role of cysteine S-conjugate ?-lyase in the metabolism of cisplatin. J Pharmacol Exp Ther 2003; 306:988–994.
40. Sadzuka Y, Shimizu Y, Takino Y, Hirota S. Protection against cisplatin-induced nephrotoxicity in the rat by inducers and an inhibitor of glutathione S-transferase. Biochem Pharmacol 1994; 48:453–459.
41. Rhoden EL, Pereira-Lima L, Rhoden CR, Lucas ML, Teloken C, Bell- Klein A. Role of L-arginine/nitric oxide pathway in renal ischemia–reperfusion in rats. Eur J Surg 2001; 167:224–8.
42. Srivastava RC, Farookh A, Ahmad N, Misra M, Hasan SK, Husain MM. Evidence for the involvement of nitric oxide in cisplatin-induced toxicity in rats. Biometals 1996; 9:139–42.
43. Saleh S, El-Demerdash E. Protective effects of L-arginine against cisplatininduced renal oxidative stress and toxicity: role of nitric oxide. Basic Clin Pharmacol Toxicol 2005; 97:91–7.
44. Iseri SÖ, Sener G, Saglam B, Gedik N, Ercan F, Yegen BC. Oxytocin ameliorates oxidative colonic inflammation by a neutrophil-dependent mechanism. Peptides 2005; 26:483–91.
45. Biyikli NK, Tu?tepe H, Sener G, Velio?lu-O?ünç A, Cetinel S, Midillio?lu S, et al. Oxytocin alleviates oxidative renal injury in pyelonephritic rats via a neutrophil-dependent mechanism. Peptides 2006; 27:2249–57.
46. Iseri SÖ, Sener G, Saglam B, Gedik N, Ercan F, Yegen BC. Oxytocin protects against sepsis-induced multiple organ damage: role of neutrophils. J Surg Res 2005; 126:73–81.