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The effects of *Ginkgo biloba* on nephrotoxicity induced by cisplatin-based chemotherapy protocols in rats

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Abstract

The study was aimed at investigating the possible renoprotective effects of *Ginkgo biloba* on nephrotoxicity induced by cisplatin w/wo other antineoplastic agents (etoposide and gemcitabine) in rats. The animals were randomly divided into eight groups each consisting of six rats. Serum blood urea nitrogen (BUN) and creatinine values at baseline and after drug administration, kidney malondialdehyde (MDA), glutathione (GSH) levels, and myeloperoxidase activity (MPO) were measured, and a histopathologic examination of kidney tissues was carried out. *Ginkgo biloba* extract significantly decreased the serum creatinine and kidney MDA levels, which had increased as a result of cisplatin administration and also improved the depletion of kidney GSH levels in cisplatin administered rats ($p<0.05$). These results were confirmed by histopathologic observations of the kidney tissues. According to the results of the present study, the potential interactions between the renoprotective agents and the cisplatin-based chemotherapeutic regimens must be considered.

Keywords: Cisplatin- induced nephrotoxicity, Etoposide, Gemcitabine, *Ginkgo biloba*,
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Sıçanlarda sisplatin içeren kemoterapi rejimlerinin nefrotoksisitesi üzerine *Ginkgo biloba*'nın etkileri

Özet

Bu çalışmada, sıçanlarda sisplatin ve diğer kemoterapötik ajanların (etopozid ve gemsitabin) nefrotoksisitesi üzerine *Ginkgo biloba*'nın olası etkilerinin belirlenmesi amaçlandı. Hayvanlar, rastgele olarak ve her biri 6 adet sıçandan oluşan 10 gruba ayrıldı. Deneyin başlangıcında ve tedavi sonrasında serum BUN (kan üre azotu) ve kreatinin değerleri; tedavi sonrasında böbrek dokusu malondialdehit (MDA) seviyeleri ile glutatyon (GSH) ve miyeloperoksidaz (MPO) aktiviteleri ölçüldü. Ayrıca böbrek dokusunun

histopatolojik incelemesi yapıldı. *Ginkgo biloba* ekstresi, sisplatin tedavisinin bir sonucu olarak yükselmiş olan serum kreatinin ve böbrek MDA seviyelerini anlamlı olarak düşürdü ($p<0.05$). Aynı zamanda sisplatin tedavisi sonucu azalmış olan böbrek GSH değerlerini anlamlı olarak yükseltti ($p<0.05$). Elde edilen sonuçlar, böbrek dokusunun histopatolojik değerlendirmesiyle de paralellik gösterdi. Çalışmanın sonuçlarına göre, renoprotektif ajanların kullanılması sırasında sisplatin içeren kemoterapötik rejimlerle olası etkileşimlerinin göz önünde bulundurulması gerekmektedir.

Anahtar kelimeler: Sisplatin içeren nefrotoksisite; Etopozid, Gemsitabin*, Ginkgo biloba*

Introduction

Cisplatin is a major antineoplastic drug for the treatment of solid tumors, but it has dose-dependent renal toxicity. The mechanism(s) underlying this renal injury have been the focus of intense investigation for many years, and it has been suggested that inflammation and oxidative stress cause renal toxicity (Schrier et al. 2004). There is no specific treatment for cisplatin-induced renal dysfunction. Therefore, many studies have been designed to investigate the potential prophylactic effects of various agents on cisplatin-induced nephrotoxicity. However, regarding cases where cisplatin is combined with other antineoplastic agents, as is recommended in most chemotherapy protocols, the effect of protective agents on the potential renal injury has not been previously investigated.

Ginkgo biloba extract is well known for its antioxidant properties, which may result from its ability to scavenge free radicals (Naik et al. 2006). Previous studies have reported that the antioxidant activity of *Ginkgo biloba* extract could be helpful in the prevention and management of diseases associated with oxidative stress (Oken et al. 1998; Sener et al. 2005).

In the present study, the aim was to investigate the possible renoprotective effects of *Ginkgo biloba* on nephrotoxicity induced by cisplatin w/wo other antineoplastic agents (etoposide and gemcitabine) in rats.

Materials and methods

All animal protocols were reviewed and approved by the Animal Care and Use Committee of The University of Marmara. Male Sprague-Dawley albino rats weighing 200–350g were obtained from Marmara University, Animal Center (DEHAMER). All the experimental animals were maintained under standard laboratory conditions, including a well aerated room with alternating light and dark cycles of 12 h each, and maintained at room temperature. During the study, all animals had access to food and water *ad libitum* and were housed in suitable and adequate conditions that fulfilled the animal house instructions.

At the beginning of the experimental period, blood samples were drawn from the tail vein of the animals under ether anesthesia.

The animals were randomly divided into eight groups each consisting of six rats as **control:** (*Serum saline-Control* [1mL/100 g i.p. normal saline], *Ginkgo biloba- Control* [150 mg/kg i.p. *Ginkgo biloba*] **toxicity:** (*Cisplatin-Toxicity* [10 mg/kg i.p. cisplatin], *Cisplatin + Gecitabine- Toxicity* [10 mg/kg i.p. cisplatin and 160 mg/kg i.p. gemcitabine], *Cisplatin + Etoposide- Toxicity* [10 mg/kg i.p. cisplatin and 40 mg/kg i.p. etoposide]) and **treatment:** (*Cisplatin + Ginkgo biloba- Treatment* [10 mg/kg i.p. cisplatin and 150 mg/kg i.p. *Ginkgo biloba* extract], *Cisplatin + Gemsitabine + Ginkgo biloba- Treatment* [10 mg/kg i.p. cisplatin, 160 mg/kg i.p. gemcitabine and 150 mg/kg *Ginkgo biloba* extract], *Cisplatin + Etoposide + Ginkgo biloba- Treatment* [10 mg/kg i.p. cisplatin, 40 mg/kg i.p. etoposide and 150 mg/mL/kg *Ginkgo biloba*]). Serum saline (1mL/100 g i.p.) and *Ginkgo biloba* extract (150 mg/kg i.p.) (EGb 761, Abdi İbrahim Pharmaceuticals)

were intraperitonally administered to all control and renal prophylaxis groups each day for 5 days. Cisplatin (10 mg/kg i.p.), gemcitabine (160 mg/kg i.p.) and etoposide (40 mg/kg i.p.) were administered on the second day of the administration period.

All the animals were sacrificed 72 h after the cisplatin dose (10 mg/kg i.p.) was administered. Blood samples were drawn by cardiac puncture under ether anesthesia, and separated for biochemical testing. Serum specimens were aliquoted into multiple fractions and stored at -20°C until they could be analyzed. The kidney tissue samples were rapidly removed, washed with physiological saline (0.9%) and divided into equal sections. The tissue samples were rapidly separated and stored at -80°C until used for enzymatic analysis. An appropriate quantity of each tissue sample was fixed in formaldehyde (%10, v/v) for histopathological examination.

Biochemical measurement

Pre and post drug administration blood urea nitrogen (BUN) and creatinine levels were measured for all groups using Architect 16200.

Measurement of malondialdehyde (MDA) and glutathione (GSH) levels

Tissue MDA and GSH levels were measured in kidney tissues (0.15–0.30 g). The tissue samples were homogenized in ice with 150 mM potassium chloride and a 10% tissue homogenate was prepared. The MDA levels were assayed for products of lipid peroxidation by monitoring thiobarbituric acid reactive substance formation as described previously (Ohkawa et al. 1979). The results were expressed as nmol/mL. GSH levels of the kidney tissue samples were evaluated using the method previously described (Ellman 1959). GSH analysis included the determination of a yellow colored product (5-5'-dithiobis 2-nitrobenzoic acid [DTNB]) produced by Ellman's reagent reduction, with sulfydryl groups in tissues using spectrophotometry. The results were expressed as μmol/g.

Myeloperoxidase (MPO) activity

The kidney tissue samples were homogenized in ice cold water with a potassium phosphate buffer (20 mM K_2HPO_4; pH: 7.4) which was added in a quantity of 10 fold the volume of each tissue. The homogenate was centrifuged at 10000 rpm for 20 min at 4ºC. The pellet was again homogenized with an equivalent volume of 50 mM K_2HPO_4 containing 0.5% hexadecyltrimethylammonium bromide (HETAB). MPO activity was expressed in U/g. One unit of MPO activity was defined as reduction of 1 μmol H_2O_2 at 25ºC for one minute. MPO activity was evaluated by spectrophotometry, according to dependent oxidation of o-dianisidine dihydrochloride to H_2O_2. (Bradley et al. 1982).

Histological examination

The samples of kidney were fixed in 10% buffered formalin and dehydrated by passing over elevating concentrations of ethanol. After fixation, the tissues were dehydrated with increasing concentrations of ethanol. Then, the samples were cleared/ cleaned in toluene and embedded in paraffin. Sections were stained with hemotoxylin -eosin (HE) and then evaluated by light electron microscope. The severity of tissue damage was scored according to previously determined criteria (Sener et al. 2000; Ozveri et al. 2001). Tissue toxicity was quantified using a scale (0: none; 1: mild; 2: moderate; 3: severe) for each criteria with a maximum score of nine. (Table 1). For histological scoring, at least 5 microscopic fields were examined.

Table 1. The criteria for the histological scoring of the tissues.

Tissue	Criteria
Kidney	*Deterioration in glomerulus and Bowman space* *Deterioration in proximal and distal tubule* *Vascular congestion and inflammatory cell infiltration*

Statistical analysis

All results were expressed as mean ± standard error (SEM). The significance of the difference between the pre- and post-administration values of BUN and creatinine was tested using paired t-test and Wilcoxon. Differences between all parameters were analyzed using one-way analysis of variance (ANOVA) and Kruskall-Wallis, followed by Tukey Kramer as a post-hoc test. The p value was represented as $p<0.001$, $p<0.01$ and $p<0.05$ to determine the strength of statistically significance.

Results

Biochemical measurement

Levels of serum BUN and creatinine at baseline, after drug administration, and also the percentage change calculated by the difference between pre- and post-values are shown in Table 2. A significant decrease was observed in BUN and creatinine levels after the administration of *Ginkgo biloba* alone ($p<0.05$). The administration of *Ginkgo biloba* with cisplatin + etoposide, induced significantly higher serum BUN levels ($p<0.05$). On the other hand, there was no significant increase in BUN after the cisplatin + gemcitabine + *Ginkgo biloba* administration. When changes in serum BUN levels in the cisplatin + gemcitabine + *Ginkgo biloba* group were evaluated, a lower, but non-significant percentage change in serum BUN levels was observed compared to cisplatin alone and the cisplatin + gemcitabine combinations ($p>0.05$).

Table 2. Serum BUN and creatitine levels.

Groups	BUN Pre	Post	% Change	Creatitine Pre	Post	% Change
Cisplatin+ Etoposide+ Ginkgo biloba	19.20±0.92	173.60±9.43¤	809.80**	0.57±0.02	2.34±0.37¤	311.43+
Cisplatin+ Etoposide	21.00±2.58	169.50±6.25¤	751.41**	1.09±0.48	2.72±0.10¤	258.45+
Cisplatin+ Gemcitabine+ Ginkgo biloba	26.00±3.21	113.67±34.80	368.41	0.62±0.05	3.05±0.61¤	396.68
Cisplatin+ Gemcitabine	17.50±0.50	150.50±27.73¤	769.20**	0.55±0.01	2.45±0.47¤	346.04
Cisplatin+ Ginkgo biloba	25.75±0.25	93.00±26.00	262.23+	0.70±0.04	2.10±0.41¤	208.23++
Cisplatin	20.50±1.19	204.50±47.14¤	900.66**	0.52±0.00	4.17±0.87¤	702.52**
Ginkgo biloba	24.67±1.67	16.33±0.42¤	-32.48	0.66±0.05	0.51±0.01¤	-21.77
Serum Saline	30.00±2.31	18.33±1.76	-37.60	0.75±0.09	0.48±0.01	-33.62

Pre: baseline values of the present study, Post: 72 h after the cisplatin dose.

¤: $p<0.05$; when compared with baseline levels with after administration

*: $p<0.05$; **: $p<0.01$; when compared with serum saline

+: $p<0.05$; ++: $p<0.01$; when compared with cisplatin alone

When the percentage change between these groups was evaluated, the serum BUN and creatinine levels in animals receiving the cisplatin + *Ginkgo biloba* combinations were observed to be significantly lower than that of cisplatin alone ($p<0.05$). The cisplatin + etoposide +

Ginkgo biloba combinations induced significantly lower serum creatinine levels compared to cisplatin alone ($p<0.05$).

MDA and GSH levels and MPO activity

Kidney MDA, GSH and MPO levels are presented in Table 3. The administration of cisplatin alone caused significantly higher kidney MDA and MPO levels and significantly lower kidney GSH levels than serum saline ($p<0.05$). Administration of cisplatin + etoposide resulted in significantly decreased kidney MDA levels compared to cisplatin alone. On the other hand, the cisplatin + etoposide combinations appeared to increase kidney MPO levels, compared with serum saline ($p<0.05$).

Table 3. MDA, GSH, and MPO levels in kidney tissues.

Groups		Kidney Tissue		
		MDA	**GSH**	**MPO**
	Cisplatin+ Etoposide+ Ginkgo biloba	16.99±0.60	$23.48\pm2.40^{+++,\Psi}$	2.33±0.43
	Cisplatin+ Etoposide	$16.20\pm2.17^{+}$	12.98±2.09	3.65±0.43***
	Cisplatin+ Gemcitabine+ Ginkgo biloba	$14.70\pm1.65^{++}$	$20.82\pm1.52^{+++}$	2.52±0.27
	Cisplatin+ Gemcitabine	16.99±0.51	15.10±3.46	3.52±0.36**
	Cisplatin+ Ginkgo biloba	$11.60\pm0.90^{++}$	$26.80\pm2.37^{+++,\Psi\Psi,\gamma}$	$1.27\pm0.20^{+,\Psi\Psi\Psi,\gamma\gamma}$
	Cisplatin	26.77±5.09*	6.48±3.17**	2.91±0.38*
	Ginkgo biloba	13.93±0.66	21.17±1.59	0.75±0.07
	Serum Saline	14.97±1.37	22.63±1.98	1.26±0.32

*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$, when compared with serum saline

+: $p<0.05$; ++: $p<0.01$; +++: $p<0.001$, when compared with cisplatin alone

Ψ: $p<0.05$; ΨΨ: $p<0.01$; ΨΨΨ: $p<0.001$, when compared with the cisplatin plus etoposide combination

γ: $p<0.05$; γγ: $p<0.01$; γγγ: $p<0.001$, when compared with the cisplatin plus gemcitabine combination

Animals receiving the cisplatin + gemcitabine + *Ginkgo biloba* combinations demonstrated significantly decreased kidney MDA levels and increased kidney GSH levels compared to those exposed to cisplatin alone ($p<0.05$). The combinations of cisplatin + etoposide + *Ginkgo biloba* led to significantly increased kidney GSH levels compared to cisplatin alone ($p<0.05$).

Histological examination

Regarding the assessment of the severity of tissue damage, despite the addition of *Ginkgo biloba* to groups which contained cisplatin alone, cisplatin + etoposide and cisplatin + gemcitabine, significantly high kidney scores were still recorded, and significantly high kidney damage was induced when compared with serum saline administration; significantly diminished tissue damage was also observed when compared with the alone cisplatin group and the cisplatin plus etoposide combination (Fig. 1).

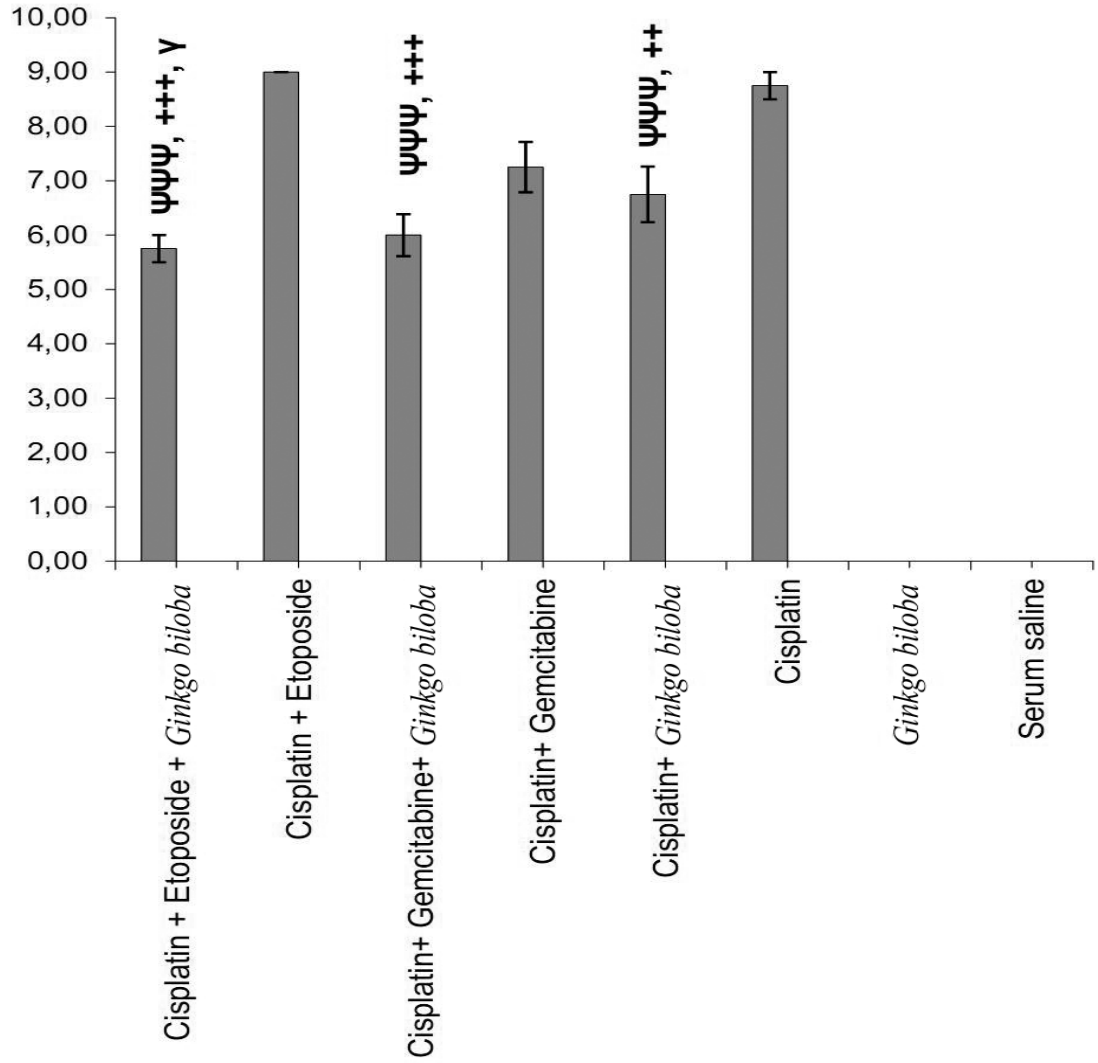

Figure 1. The severity of kidney tissue damage**.**
+: $p<0.05$; ++: $p<0.01$; +++: $p<0.001$, when compared with cisplatin alone Ψ: $p<0.05$; ΨΨ: $p<0.01$; ΨΨΨ: $p<0.001$, when compared with the cisplatin + etoposide combination γ: $p<0.05$; γγ: $p<0.01$; γγγ: $p<0.001$, when compared with the cisplatin + gemcitabine combination

Nevertheless, significantly diminished scores were observed in comparison to scores from animals receiving cisplatin + gemcitabine and the cisplatin + etoposide + *Ginkgo biloba* combinations ($p<0.05$). The photomicrographs from kidney sections belonging to each group are presented in Figure 2.

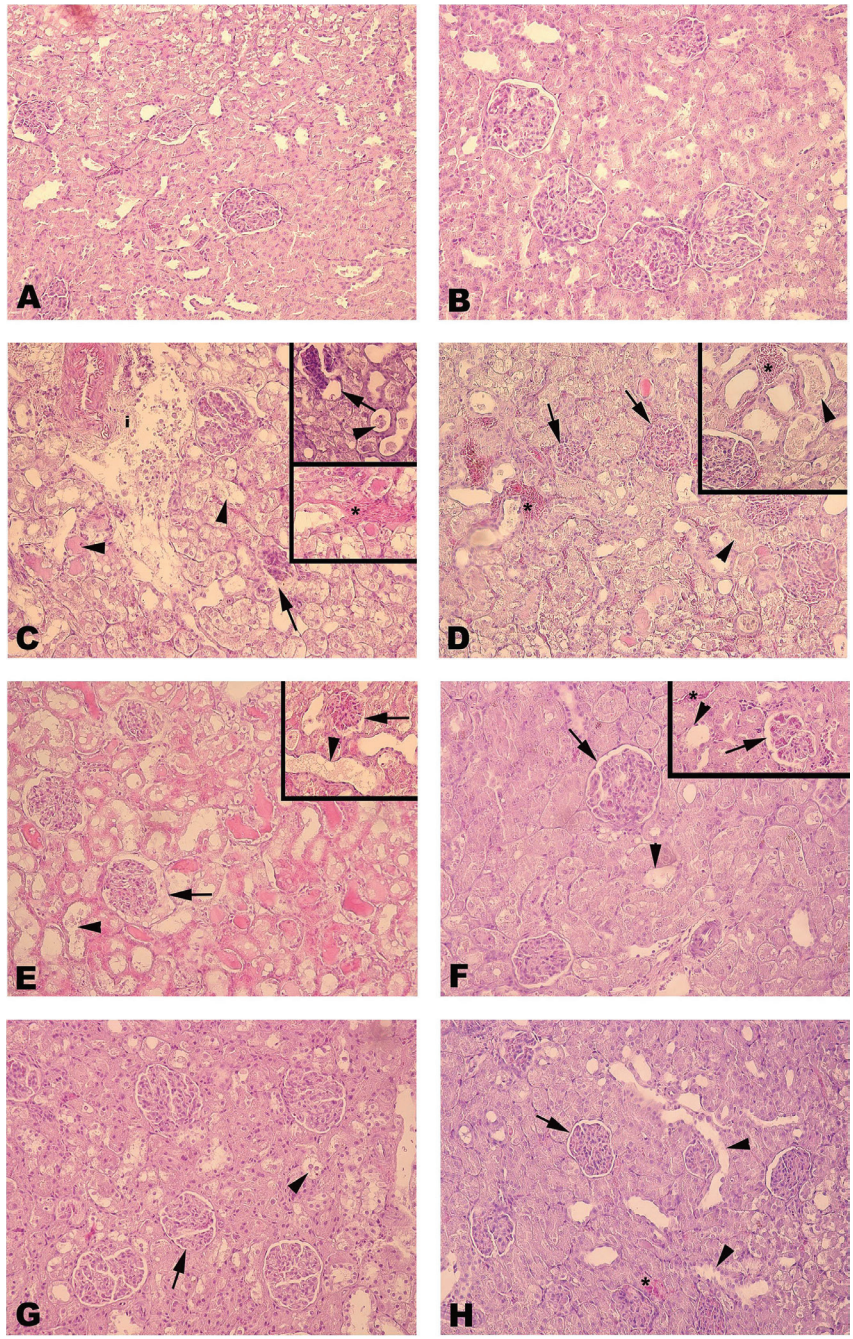

Figure 2. Serum saline (A), and ***Ginkgo biloba*** (B): Kidney cortex structure with regular morphology. **Cisplatin** (C): Atrophic glomerulus (arrow), vascular congestion (*), interstistial edema and inflammatory cell infiltration (i), injury in proximal and distal tubule (arrow head).**Cisplatin + gemcitabine** (D): Glomerulus congestion (arrow), vascular congestion (*), injury in proximal and distal tubule and cell casts in tubular lumen (arrow head). **Cisplatin + etoposide** (E): Glomerulus injury and cell casts in Bowman space (arrow), injury in proximal and distal tubule and cell casts in tubular lumen (arrow head). **Cisplatin + *Ginkgo biloba*** (F): Mild glomerular congestion (arrow), reduced vascular congestion (*), a few number of injury in proximal and distal tubule (arrow head). **Cisplatin + etoposide + *Ginkgo biloba*** (G): Regular glomerulus structure (arrow), a few number of distention in proximal and distal tubule (arrow head). **Cisplatin + gemcitabine + *Ginkgo biloba*** (H): Well regular glomerulus structure (arrow), mild vascular congestion (*), some distention and injury in proximal and distal tubule (arrow head). Hematoxylin&Eosin, orginal magnification, 200X.

Discussion

In our study, we investigated the possible protective effects of *Ginkgo biloba* extract on cisplatin-induced nephrotoxicity in rats. *Ginkgo biloba* is a natural antioxidant which contains flavonoids, including ginkgo-flavone glycosides and terpene lactones (Diamond et al. 2000). Flavonoids seem to be responsible for the antioxidant activity that is considered one of the main mechanisms involved in the pharmacological efects of the extract. Accumulating evidence showed that *Ginkgo biloba* extract can scavenge reactive oxygen species (ROS) (Wang et al. 2006; Lu et al. 2007). Moreover, *Ginkgo biloba* extract (EGb 761; 100 mg/kg oral gavage) has been demonstrated to significantly improve serum lipid profile, total protein, urea and creatinine clearance in adriamycin-induced hyperlipidaemic nephrotoxicity investigations in rats. It was also observed that *Ginkgo biloba* extract prevented adriamycin-induced hyperlipidaemic nephrotoxicity by decreasing oxidative stress and nitric oxide levels in renal tissues (Abd-Ellah et al. 2007). Additionally, the protective effect of *Ginkgo biloba* extract (200 mg/kg EGb ip) on cisplatin induced ototoxicity has been shown in rats (Huang et al. 2007).

It has also been reported that *Ginkgo biloba* extract (100 mg orally) significantly increased xanthine oxidase activities in control and cisplatin groups, and also significantly decreased adenosine deaminase and MPO activities (Gulec et al. 2006). In the same study, administration of *Ginkgo biloba* extract caused elevation of BUN levels and decreased creatinine and kidney MDA levels when compared with a group which received cisplatin alone; but these conflicting data were not found statistically significant (Gulec et al. 2006). On the other hand, *Ginkgo biloba* extract (150 mg/kg i.p.) administration with cisplatin significantly diminished levels of BUN, serum creatinine, kidney MDA and MPO, and significantly elevated kidney GSH levels in the present study ($p<0.05$). The different results between these studies may result from the different administration dosage, period, and route.

In animals receiving the cisplatin + etoposide + *Ginkgo biloba* extract combinations, the serum creatinine level and GSH levels were significantly different when compared with cisplatin alone ($p<0.05$). These observations were confirmed with light microscopic evaluation**.** The severity of kidney tissue damage of the animals which were administered *Ginkgo biloba* extract + cisplatin + gemcitabine or etoposide combinations, was significantly diminished when compared with cisplatin alone, and the cisplatin + etoposide combinations ($p<0.05$). This data was corroborated by previous studies which investigated cisplatin-induced and ischemia reperfusion induced renal nephrotoxicity (Sener et al. 2005; Appenroth et al. 1997).

In conclusion, nephrotoxicity was observed in this study after the administration of cisplatin alone. The combination of cisplatin w/ wo etoposide and gemcitabine induced less nephrotoxicity, compared to the administration of cisplatin alone. As renoprotective agent, *Ginkgo biloba* extract was found to be effective in cisplatin-induced nephrotoxicity. Further clinical and in-vivo studies are needed to determine the potential beneficial effects of this renoprotective agent either with cisplatin alone or with cisplatin-based chemotherapy regimens.

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