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Ameliorative Effects of the Aqueous Extract of *Allium porrum* (Wild Leek) against Cisplatin-Induced Nephrotoxicity in Rabbits

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Abstract

The aim of the present study was to investigate the nephroprotective, hypolipidemic and hypoglycemic effects of *Allium porrum* (leek) in rabbits with cisplatin nephrotoxicity. Forty adult male New Zealand rabbits were divided randomly into four groups (ten rabbits in each group) as follows: Group I: (negative control) (C) received oral daily dose of distilled water for 15 successive days. Groups II: (Leek) (L) received oral daily dose of aqueous leek extract (500mg/kg/day) for 15 successive days. Group III: (positive control) [cisplatin (CP)] received oral daily dose of distilled water for 15 successive days, and subsequently administered single dose of Cisplatin (3.5mg/kg/day) by intraperitoneal injection from day 10 for five days. Groups IV: (Leek and Cisplatin) (LCP) received oral daily dose of aqueous leek extract (500 mg/kg/day) for 15 successive days with subsequently administered single intraperitoneal dose of cisplatin (3.5 mg/kg/day) from day 10 for five days in association with aqueous leek extract. All animals were fasted overnight then sacrificed. Serum urea, creatinine, glucose, lipids, renal histology, tissues glutathione, lipid peroxidation (thiobarbituric acid reactive substance), catalase and superoxide dismutase was measured. cisplatin intoxication exhibited significant (P<0.001) elevations in serum creatinine and urea with marked renal tubular injury. Whereas, treatment of aqueous leek extract prior to cisplatin intoxication significantly caused (P<0.001) reductions of serum creatinine and urea levels with moderation of renal histology. Cisplatin intoxication also showed significant (P<0.01) reductions in renal glutathione and activities of catalase and superoxide dismutase and increased lipid peroxidation accompanied with increases in serum glucose, total cholesterol, triglycerides, low density lipoproteins cholesterol, very low density lipoproteins cholesterol and decreased high density lipoproteins cholesterol compared to controls. However, administration of aqueous leek extract prior to cisplatin intoxication showed significantly (P<0.001) elevated glutathione and activities of superoxide dismutase and catalase and significant reduction in thiobarbituric acid reactive substance, reductions in glucose, triglycerides, low density lipoproteins cholesterol, very low density lipoproteins cholesterol and increased high density lipoproteins cholesterol. Cisplatin treatment impaired the kidney function of rabbits with marked renal injury. This was accompanied with increased cortical lipid peroxidation and reduced antioxidant system. Cisplatin also induced dyslipidemia and hyperglycemia. All deranged parameters were reversed by co-administration of the leek extract.

Keywords: *Allium porrum*, Cisplatin, Dyslipidemia, Nephrotoxicity, Wild Leek

التأثيرات الوقائية للمستخلص المائي لنبات الكراث البري ضد السمية الكلوية المستحثة بعقار السيسبلاتين في الارانب

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الخلاصه

الهدف من الدراسة هو التحقق من التأثيرات الوقائية للمستخلص المائي لنبات الكراث البري ضد السمية الكلوية ونقص شحميات الدم ونقص السكر في الدم المستحث بعقار السيسبلاتين في الارانب. تم استخدام أربعون من ذكور الأرانب النيوزيلاندية البيضاء وتم تصنيفها الى اربع مجموعات تحتوي كل منها على عشر ارانب على النحو التالي: المجموعة الأولى: (المراقبة السلبية) تلقت جرعة يومية واحدة عن طريق الفم من الماء المقطر لمدة ١٥ يومًا متتاليا. المجموعة الثانية: تلقت جرعة يومية واحدة من المستخلص المائي للكراث البري (٥٠٠ ملغم / كغم / يوم) عن طريق الفم بواسطة التغذية الانبوبية لمدة ١٥ يومًا متتاليا. المجموعة

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الثالثة: (المراقبة.الايجابية): تلقت جرعة يومية واحدة عن طريق الفم من الماء المقطر لمدة ١٥ يومًا متتاليا وكذلك تلقت عقار السيسبلاتين (٣,٥ ملغم / كغم / يوم) عن طريق الحقن داخل الصفاق من اليوم العاشر ولمدة خمسة أيام متتالية بالتزامن مع الماء المقطر. المجموعة الرابعة: تلقت جرعة يومية واحدة من المستخلص المائي للكراث البري (٥٠٠ ملغم / كغم / يوم) عن طريق الفم بواسطة التغذية الانبوبية لمدة ١٥ يومًا متتاليا وكذلك تلقت عقار السيسبلاتين (٣,٥ ملغم / كغم / يوم) عن طريق الحقن داخل الصفاق من اليوم العاشر ولمدة خمسة أيام متتالية بالتزامن مع المستخلص المائي للكراث البري. في نهاية التجربة قتلت الحيوانات وسحب الدم منها لغرض إجراء التحاليل الكيموحيوية واخذت الكلى لغرض الفحوصات النسيجية. أظهرت النتائج التي تم الحصول عليها حدوث ارتفاع معنوي في مستوى اليوريا والكرياتنين والجلوكوز والدهون في الدم وانخفاض في تراكيز الغلوتاثيون إرتفاع مستوى البيروكسيدات وكذلك انخفاض نشاط انزيمات الcatalaseوالsuperoxide dismutase في الانسجة في المجموعة المحقونة بعقار السيسبلاتين فقط. أما المجموعة المعالجة بالمستخلص المائي للكراث البري بتركيز (٥٠٠ ملغم / كغم / يوم) وحقنت بعقار السيسبلاتين بجرعة (٣,٥ ملغم / كغم / يوم) فقد لوحظ انخفاض معنوي في مستوى اليوريا والكرياتينين والجلوكوز والدهون في الدم وتحسن مستويات الغلوتاثيون و وانخفاض مستوى البيروكسيدات وكذلك استعادة نشاط انزيمات ال catalaseوال superoxide dismutase في الانسجة مقارنة بالمجموعة الضابطة. كذلك بينت نتائج الفحص المجهري لنسيج الكلى للمجموعة المحقونة بعقار السيسبلاتين فقط حدوث تغيرات نسيجية مرضية تمثلت في وجود نزيف دموي شديد في منطقة القشرة، وحدوث انكماش وضمور بعض الكبيبات الكلوية مع تجمع الخلايا الالتهابية، وعندما جرعت المجموعات المحقونة بعقار السيسبلاتين بالمستخلص المائي للكراث البري لوحظ تحسن واضح في أنسجة الكلى من حيث شكلها وترتيبها. النتائج تشير الى ان استخدام المستخلص المائي للكراث البري كان فعالا في تقليل السمية الكلوية المستحثة بعقار السيسبلاتين في الارانب من خلال الاستفادة من اثاره الإضافية المفيدة المتعددة كمضاد للأكسدة والالتهابات

الكلمات المفتاحية : نبات الكراث، السيسبلاتين، عسر شحميات الدم، السمية الكلوية، الكراث البري.

Introduction

tableCisplatin is an anticancer drug with a high preference; commonly used as a first line therapy against solid tumors such as the head and the neck, ovarian, and testicular carcinoma. Unfortunately, the clinical use of the cisplatin is limited due to the severe renal toxicity that may accompany its therapy [(1)] which was shown to occur in about 36% of patients treated with the drug [(2)]. Due to its therapeutic efficiency as an anti-neoplastic agent, there is a pressing need for ways to prevent the renal toxicity associated with cisplatin therapy. Mechanisms of cisplatin-induced nephrotoxicity are believed to involve the generation of oxygen free radicals and oxidative stress [(3)]. This is known to induce the DNA damages and produces inflammatory cytokines that proceed into renal injury [(4)]. Thus, several antioxidant agents have been tested to alleviate the cisplatin nephrotoxicity.

Several medicinal plants are rich in potent antioxidant agents, and many have been tested as protective agents against drug-induced nephrotoxicity [(5,6).]

Allium ampeloprasum var. *porrum* (also known as *Allium porrum* Family, *Liliaceae*), and commonly named leek is a plant used as food that contains excellent amounts of polyphenols, trace minerals and phytochemicals, and the plant has hypolipidemic, hypoglycemic and antimicrobial properties[(7)]. However, from literature survey little is known about its nephroprotective activity. Therefore, the present study was planned to investigate the possible protective effects of the aqueous extract of Wild Leek against the cisplatin-induced nephrotoxicity and dyslipidemia in the rabbit.

Materials and Methods

Experimental animals

Forty adult male New Zealand white rabbits (average body weight 1100-1300 grams), were obtained from the Animal House of the Faculty of Medicine, University of Benghazi, Benghazi-Libya. The animals were maintained under natural lighting conditions (12 h light and 12 h dark cycle) with temperature of 22-25 °C and 50% relative humidity. The animals were divided randomly into four equal groups and housed in well-ventilated stainless steel cages with free access to a standard pelleted diet and tap-water. All procedures performed in the studies involving experimental animals were in accordance with the ethical standards of the institutional Ethical committee for Experimental Animals (Institutional approval number EAAU-26/17) and in accordance with the Helsinki declaration for experimental animals. The leek (*Allium porrum*) plant was collected from its habitat in the surrounding area of Sedi-khalifa; an area located 15 km east of Benghazi, Libya, between February, 15 and March 1st 2016. The collected plants were washed, dried at room temperature, ground under liquid nitrogen and stored in a refrigerator awaiting use within one week. Weighed amounts of the powder was extracted with distilled water at the concentration of 500 mg/ml and filtered through a cloth filter.

Protocol of experiment

The experimental groups were treated as follows:

Animals of the Group I received distilled water orally by gastric intubation (1ml/kg) for 15 days, and were injected intraperitoneally (I.P) with normal saline from day 10 to the day 15; this group served as negative control (C). Group II (L) were given leek extract (500mg/kg/day) orally by gastric intubation for 15 consecutive days, and injected I.P with normal saline from day 10 to the day 15.

Animals of the Group III received distilled water orally by gastric intubation (1ml/kg) for 15 days and

dosed with single dose of cisplatin (3.5mg/kg/day) I.P from day 10 and continued for five consecutive days, and served as positive control (CP). Group IV (LCP): rabbits received oral daily dose of aqueous leek extract (500mg/kg/day) for 15 successive days with subsequently administered single intraperitoneal dose of cisplatin (3.5mg/kg/day) from day 10 for five days in association with aqueous leek extract. After 24 h of the end of the experimental period (15 days) all animals were sacrificed by decapitation under light anesthesia with diethyl ether. The animals were weighed before treatments and before killing. Blood samples were collected from the heart into plain tubes then centrifuged at 1000 g for 15 minutes and, the serum was used for biochemical analysis.

The kidneys were excised immediately and weighed. One kidney was homogenized in ice-cold saline (10 % w/v) and used for the assay of catalase (CAT) and superoxide dismutase (SOD) enzymes activities, reduced glutathione (GSH) and lipid peroxidation levels. The other kidney was fixed in 10 % (v/v) formal saline for histopathological examination.

Biochemical Analysis

The concentration of serum glucose, serum creatinine, urea, total cholesterol (TC), high density lipoprotein - cholesterol (HDL-c) and triglyceride (TG) were measured by COBAS INTEGRA 400 using commercial kits (Roche Diagnostics, IN, USA) according to the manufacturer's instructions. The very low density lipoprotein (VLDL) and low density lipoproteins (LDL) were estimated based on the Friedewald equation (LDL-c (mg/dL) = TC (mg/dL) − HDL-c (mg/dL) − TG (mg/dL)/5) [8]. The protein concentration was determined using commercial Kit from (Thermo Fisher Scientific,UK) [9]. The activities of CAT and SOD enzymes were assayed as described by Goth [10] and Spitz and Oberley [11], respectively. The renal cortical GSH was measured by the method of Sedlak and Lindsay [12] and the amount of lipid peroxidation was measured as thiobarbituric acid reactive substance (TBARS) according to the method of Walter *et al.*[13].

Histopathologic examination

The fixed kidneys were embedded in paraffin wax, cut into 5 µm sections and stained with hematoxylin and eosin. Five coded slides from each group were examined by a histopathologist unaware of the treatments under a light microscope. Intensity of the tubular injury was assessed as follows: Grade 0 (normal) no cell necrosis; Grade I (mild): rare necrotic cells (less than 1% of the outer cortical tubules involved); Grade II (moderate): necrosis involved in less than half of the cortical tubules; Grade III (marked): exhibiting total necrosis in more than half of the tubules; Grade IV: total or subtotal outer cortical tubular necrosis [14].

Statistical analyses

Data are expressed as mean±SEM. The comparison between the means was performed by the one way analysis of variance by SPSS statistical software version 21. The significance of differences between the means was assessed by the Tukey–Kramer multiple comparison test, and $P < 0.05$ was considered significant.

Results

In a pilot study the aqueous extract of *Allium porrum* was found to be nontoxic up to the dose of 3000mg/kg showing no deaths or altered kidney functions. The cisplatin-treated rabbits were less active and three of the animals died during the course of experiment.

Body weight and kidney weight was assessed at the end of the study. As shown in Table 1, CP treated rabbits showed a significant loss in body weight when compared with control rabbits. There was no significant change in the body weight of leek treated rabbits (L) when compared with control rabbits. The co-administration of cisplatin with leek extract showed a significant gain in body weight ($p < 0.001$) as compared to CP treated rabbits. Moreover, substantial growth in kidney weight ($p < 0.001$) was observed in CP treated rabbits, as compared to control rabbits. Co-administration of cisplatin with leek extract restored the kidney weight ($p < 0.01$) to control rabbit's kidney weight.

Table 1. The changes in body weights and kidney weights in different groups of rabbits.

	C	L	CP	LCP
Change in body weight (g)	+ 62.80 ±16.70	+ 61.00 ±15.50	-120.00 ±14.70 a ‡ a‡	-31.60 ±10.40 a ‡ a ‡
Kidney. weight (g)	0.60 ± 0.03	0.63 ± 0.03	1.10 ± 0.10 a*b**	0.77 ± 0.06 a**b**

C :(negative control), L(Leek), CP: (positive control) and LCP (Leek and Cisplatin) ,n=40 (10 rabbits in each group).Data expressed as means ± SEM.** $P<0.01$ ‡ $P<0.001$ (a):Significantly different from C (b): Significantly different from L.(+): Weight gained ,(-):Weight lost

Figure 1, summarizes the changes in serum creatinine and urea levels measured as renal function parameters. The serum creatinine concentration in the CP animals showed a significant ($P<0.001$) elevation by 3.21-fold compared to control, whereas, animals of LCP exhibited a significant ($P<0.01$) reduction by 67.2% compared to CP group, but was still higher than that of group C by

40.52%. Similarly, animals of CP group showed a significant increase (P<0.001) in serum urea concentration by 10.99-fold compared to control, whereas, that of LCP had significant reduction (P<0.001) in the serum urea levels by 74.83% compared to CP group.

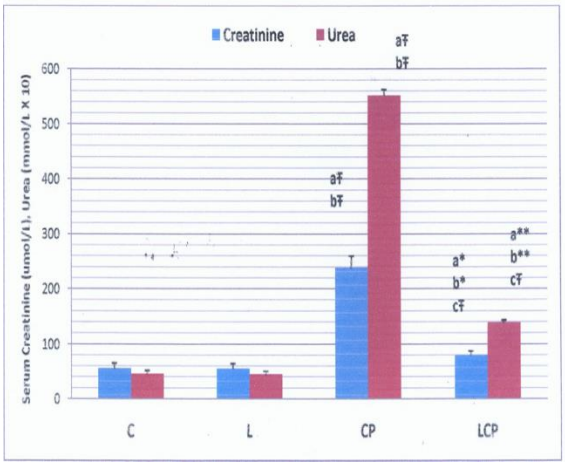

Figure 1. Serum creatinine and urea concentrations in different groups of rabbits.
C : (negative control), CP: (positive control), L (Leek) and LCP (Leek and Cisplatin)

Column and vertical bars represent means ± SEM. * P<0.05, ** P< 0.01, ₸ P<0.001, a significantly different from C; b significantly different from L; c significantly different from CP.

Antioxidant changes

Cisplatin treated group exhibited significant reductions in the renal cortical GSH content and activities of CAT and SOD by 32.20%, 73.86% and 41.82%, respectively and a significant (P<0.01) increase in the cortical lipid peroxidation by 89.64% compared to control. However, the LCP animals showed significant increases in the GSH content and the activities of CAT and SOD by 36.07%, 2.19-fold and 63.88%, respectively and a significant decrease in the TBARS by 42.43% compared to CP as shown in (table 2).

Table 2. The cortical GSH, CAT and SOD enzyme activities and TBARS in different groups of rabbits

	C	L	CP	LCP
GSH (µmol/g protein)	29.19 ± 2.018	28.84 ± 1.29	19.79 ± 1.15 $^{a**\ b**}$	26.93 ± 1.76 $^{c₸}$
CAT (U/mg protein)	13.20 ± 1.68	13.09 ± 1.07	3.45 ± 0.2 $^{a₸\ b₸}$	10.97 ± 1.7 $^{c₸}$
SOD (U/mg protein)	263.70 ± 12.01	261.00 ± 17.7	153.4 ± 22.7 $^{a**\ b**}$	251.4 ± 8.83 $^{c₸}$
TBARS (nmol/mg protein)	2.51 ± 0.53	2.62 ± 0.76	4.76 ± 1.12 $^{a**\ b**}$	2.74 ± 1.39 ^{c**}

C : (negative control), L(Leek), CP: (positive control) and LCP (Leek and Cisplatin) ,n=40 (10 rabbits in each group). Data expressed as means ± SEM.** P<0.01, ₸ P<0.001, (a): Significantly different from C ,(b): Significantly different from L(c): Significantly different from CP.

Changes in fasting serum glucose and lipid profiles

Fasting serum glucose concentration in CP animals was significantly elevated by 2.35-fold as compared to negative control (C) animals; whereas, that of LCP group there was a significant (P<0.001) reduction in fasting serum glucose by 50.85% compared to that of CP group, but was still higher than that of control (C) by 49.90% (Table 3). On the other hand, serum levels of TC, TG, LDL-c and VLDL-c in the CP group exhibited significant elevations by 1.91-fold, 1.25-fold, 3.36-fold and 2.21-fold, respectively; and a significant (P<0.01) decrease in the HDL-c by 41.97% compared to that in (C) group of animals. Whereas, in the LCP animals there were significant (P<0.001) reductions in the serum TC by 48.8%, TG by 45.7%, LDL-c by 57.5%, VLDL-c by 45.6% , and a significant increase in HDL-c by 45.6%, respectively compared to corresponding concentrations in group (CP) rabbits. However, in LCP group animals, the serum TC was still higher than that in control (C) by 48.8%, the TG by 21.1%, and LDL by 50.4%, whereas, the HDL-c and VLDL-c were not significantly different (P>0.05) compared to that of control group (C) rabbits.

Table 3. The fasting serum glucose and lipid profiles in different groups of rabbits

	C	L	CP	LCP
Serum glucose (mmol/l)	5.23 ± 0.28	5.18 ± 0.29	17.76 ± 0.22 $^{a₸\ b₸}$	7.84 ± 0.17 $^{a₸\ b₸\ c₸}$
Serum Total cholesterol (TC) (mmol/l)	2.82 ± 0.17	2.65 ± 0.11	8.21 ± 0.15 $^{a₸\ b₸}$	4.20 ± 0.06 $^{a₸\ b₸\ c₸}$
Serum Triglycerides (TG) (mmol/l)	1.02 ± 0.06	1.03 ± 0.06	2.30 ± 0.03 $^{a₸\ b₸}$	1.24 ± 0.05 $^{a*\ b*\ c₸}$
Serum Low density lipoprotein cholesterol (LDL-C) (mmol/l)	1.81± 0.08	1.61± 0.11	7.28 ± 0.37 $^{a₸\ b₸}$	3.09 ± 0.13 $^{a₸\ b₸\ c₸}$
Serum High density lipoprotein cholesterol HDL-C (mmol/l)	0.81± 0.02	0.84 ± 0.04	0.47 ± 0.07 $^{a₸\ b₸}$	0.86 ± 0.03 $^{c₸}$
Serum Very low density lipoprotein cholesterol VLDL-C (mmol/l)	0.20 ± 0.01	0.20 ± 0.02	0.46 ± 0.01 $^{a₸\ b₸}$	0.25± 0.01 $^{c₸}$

C :(negative control), L(Leek), CP: (positive control) and LCP (Leek and Cisplatin) , n=40 (10 rabbits in each group). Data expressed as means ± SEM. * P<0.05 ₸ P<0.001 (a): Significantly different from C (b): Significantly different from L (c): Significantly different from CP

Histopathologic changes

Kidney sections of groups (C) and group (L) animals had a normal morphology (Grade 0), whereas, kidney sections from group (CP) animals showed a grade III histology with widespread degeneration of tubular architecture and tubular necrosis as shown in (Figure 2). However, kidney sections from group (LCP) had moderate kidney injury with sparse tubular injury (Grade I).

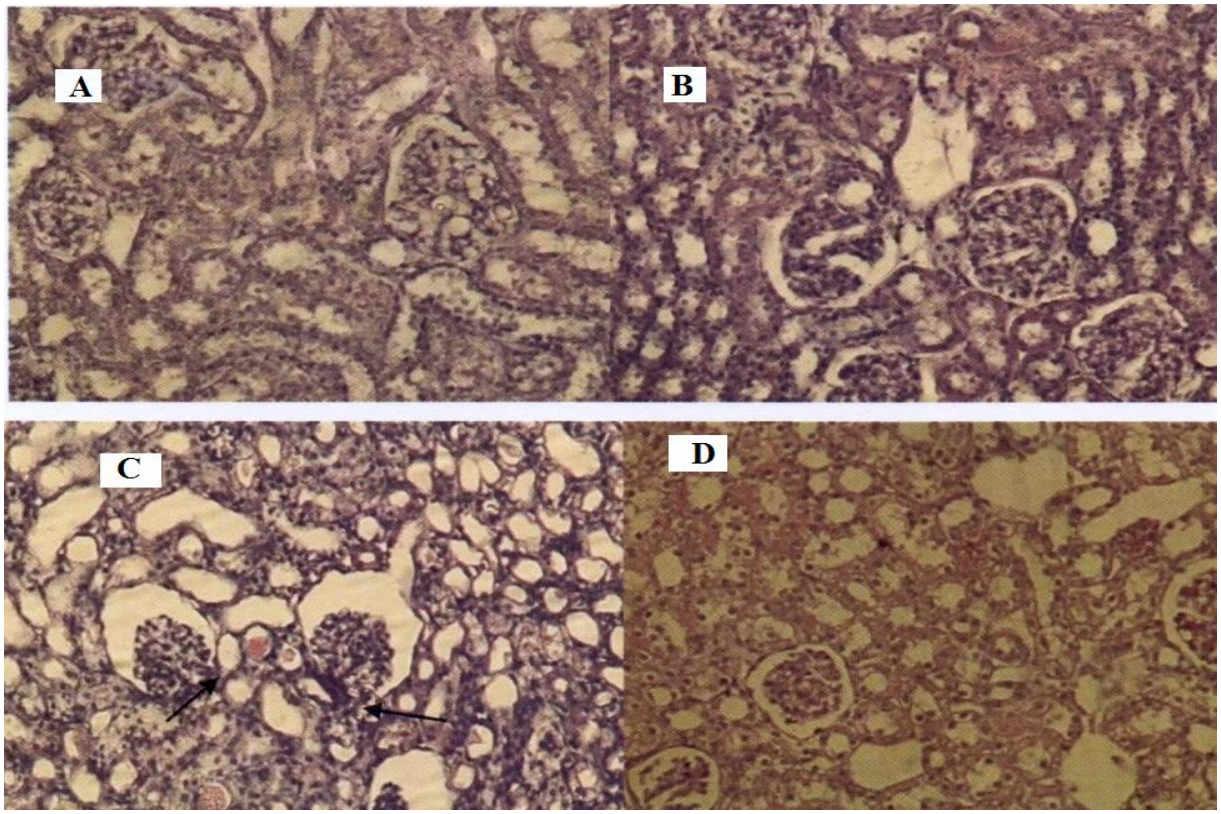

Figure 2. The histopathology of renal cortex from different groups of rabbits (A) negative control, (B) Leek (500 mg/kg/ day) orally for 15 days, (C) cisplatin (3.5 mg/kg) injected i.p., (D) Leek +cisplatin. Observe the normal renal glomeruli and normal tubules in both (A) and (B), shrinkage and atrophy of some renal glomerular with disappearance of Bowman's space and intensive tubular necrosis in (c) and improvement in the kidney tissues was showed in (d)The slides were stained with hematoxylin and eosin. (×40 mm).

Discussion

Cisplatin treatment is known to be associated with depletion of the renal antioxidant defense system which is implicated as the main causes of cisplatin induced nephrotoxicity [15]. *Allium porrum* is a medicinal plant rich in polyphenols, flavonoids and contains significant amounts of carotenoids and has been studied for its antioxidative and anti-inflammatory effects [7]. In the present study, injection of the rabbits with cisplatin (3.5 mg/kg) for five days resulted in severe nephrotoxicity that is evidenced by the marked reduction in body weights, elevation of serum urea and creatinine concentrations and the necrotic appearance of the renal cortices Figures (1 and 2); and these were in accordance with reports from several studies [1-4]. Reduction in body weights in animals treated with cisplatin could be due to the drug-induced gastrointestinal (GI) toxicity and decrease in food intake or due to direct renal toxicity causing reduction in renal tubular water reabsorption that can lead to dehydration and body weight loss [16]. Cisplatin-treated animals also exhibited significant increase in the kidney to body weight ratio compared to the controls. This finding is also consistent with reports from previous studies [1-4, 16]. These changes were suggested to be due to edema of renal parenchyma caused by cisplatin-induced renal tissue inflammations [17]. Moreover, all animals exposed to cisplatin exhibited significantly depleted cellular GSH, elevated TBARS and diminished activities of CAT and SOD. It has been shown that cisplatin accumulates in the proximal tubular epithelial cells and is transformed into toxic metabolites [18-20]. Cellular GSH provides the first line of defense against oxidative damage and toxic compounds beside its role in several metabolic processes. Thus, depletion of the cellular GSH is believed to be the first step in the process of drug toxicity [18-20]. The oxidative stress develops as a result of an imbalance between cellular generation of free radicals and its antioxidant defense system [19]. Cisplatin is believed to produce oxidative stress through reduction in the activities of the antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismutase leading to failure of the antioxidant defense system against the free radical challenge [20]. The overwhelming cellular oxidative stress causes per oxidation of vital macromolecules such as membrane lipids, proteins, and nucleic acids ending up in cellular damage [21]. The observed decrease in SOD activity following the cisplatin exposure may be attributed to the depletion of the enzyme`s essential cofactors, copper and zinc, known to be wasted during cisplatin treatment [22].

Interestingly however, the co-administration of the leek extract caused a significant increase in the cellular antioxidant status and alleviated lipid peroxidation. The nephroprotective property of the leek extract seems to be due to its potent antioxidant activity due to the high polyphenols and flavonoid contents [7]. The polyphenols are potent reducing agents and have a strong free radical scavenging activity. This probably explains the potent ameliorative effects of leek against the cisplatin nephrotoxicity. On the other hand, supplementation of the animals with the leek extract reversed the body weight loss caused by cisplatin alone and reduced the kidney to body weight ratio back to the control levels. This could be attributed to the anti-inflammatory effects of leek [23]. Taken together, *Allium porrum* could be a promising candidate for clinical use in protecting the kidneys against cisplatin toxicity in patients undergoing cisplatin chemotherapy.

In the present study, animals administered cisplatin alone (group III) developed significant fasting hyperglycemia. This was in congruence with findings of previous studies in animals [24]. The cisplatin- induced hyperglycemia is believed to be due to the associated impaired insulin action [25]. Szilvassy and coworkers [26] observed that guinea pigs treated with cisplatin developed insulin resistance with hyperinulinemia and produced a significant decrease in the insulin-stimulated cellular glucose uptake. However, co-administration of leek extract reversed the cisplatin-induced hyperglycemia back to the control levels. The hypoglycemic activity of leek is believed to be attributed to the presence of several sulfur-containing compounds and flavonoids that are believed to reduce the rates of glycogenolysis and gluconeogenesis and delay the intestinal glucose absorption [7]. On the other hand, the cisplatin treated animals exhibited marked elevations in the serum levels of total cholesterol, triglyceride, LDL, and VLDL-c fractions with reduced HDL-c particles. Those results of the current study were in agreement with those of previous reports [27 and 28]. Furthermore, results of this study indicated that about 80% of the circulating cholesterol was associated with LDL particles. This is probably the result of the LDL oxidation triggered by the increased cellular free radicals produced by cisplatin. The oxidative modification of LDL particles is believed not to be recognized by the LDL receptors causing impairment of their cellular engulfment by endocytosis [29]. Cisplatin is believed to reduce the expression and activity of lipoprotein lipase enzyme, which is responsible for the clearance of VLDL-triglyceride [26, 29]; this could probably explain the elevated serum TG levels in the cisplatin treated animals (Table 3). However, the co-administration of leek extract (group IV) reversed the altered levels of TC, TG, LDL and HDL by cisplatin back to the control levels (Table 3). These results were consistent with those of previous study [23]. The hypolipidemic effects of leek was suggested to be due to the high contents of flavonoids [30, 31] and the organic sulfur compounds known to inhibit the

hydroxy methyl glutaryl-CoA (HMG-CoA) reductase enzyme (HMG-CoA reductase), which is the regulatory enzyme in hepatic cholesterol biosynthesis [30, 31]. Also, Leek is rich in ferulic acid, which was shown to decrease the fatty acid synthesis by suppressing the gene expression of fatty acid synthase enzyme complex and reduce the hepatic TG accumulation [30].

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