

## The Protective Effect of Omega-7 on Cisplatin-Induced Nephrotoxicity in Rat Model

Shurouq Hussam Mahmood <sup>\*,1</sup> and Ali Faris Hassan <sup>2</sup>

<sup>1</sup>Ministry of Health and Environment, Baghdad AL-Russafa Health Directorate, Baghdad, Iraq.

<sup>2</sup>Department Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq

### Abstract

Omega-7 is a monounsaturated fatty acid that has a number of beneficial effects. Cisplatin, an effective antineoplastic agent is commonly used to treat solid tumors. Cisplatin's clinical use is limited due to its nephrotoxicity. Nephrotoxicity induced by Cisplatin is thought to be linked with increased formation of reactive oxygen species. The purpose of this study was to evaluate the anti-oxidant effect of omega-7 against cisplatin-induced nephrotoxicity. Thirty male wistar rats were divided randomly into five groups (six rats in each group), group 1 rats received liquid paraffin solution orally for 7 consecutive days, group 2 rats received liquid paraffin solution orally for 7 consecutive days then received single cisplatin intraperitoneal injection (7.5 mg/ kg), group 3 rats received omega-7 (50mg/ kg) orally for 7 consecutive days and then received single cisplatin intraperitoneal injection (7.5mg/ kg) on day 8, group 4 rats received omega-7 (100 mg/ kg) orally for 7 consecutive days and then received single intraperitoneal injection of cisplatin (7.5mg/ kg) on day 8, group 5 rats received omega 7 (100mg/ kg) orally for 7 consecutive days. On day 9, all animals were sacrificed and renal tissue homogenates were used for the estimation of glutathione peroxidase-1(GPX-1), superoxide dismutase-1(SOD-1), reduced glutathione(GSH), catalase(CAT) and malondialdehyde(MDA). Treatment of rats with omega-7 showed significant ( $p < 0.05$ ) elevation in the activities of anti-oxidant enzymes (GPX-1, SOD-1, reduced GSH and CAT) and significant ( $P < 0.05$ ) reduction of MDA level when compared to Cisplatin (positive control) group. In conclusion, omega-7 has a protective effect against cisplatin-induced nephrotoxicity maybe through its anti-oxidant activity.

**Keywords:** antioxidants, cisplatin, nephrotoxicity, omega-7, oxidative stress.

### التأثير الوقائي للأوميكا ٧ ضد التسمم الكلوي المستحث بواسطة السبيلاتين في نموذج الجرذان

شروق حسام محمود<sup>\*,١</sup> و علي فارس حسن<sup>٢</sup>

<sup>١</sup>وزارة الصحة والبيئة، دائرة صحة الرصافة، بغداد، العراق  
<sup>٢</sup>أفرع الأدوية والسموم، كلية الصيدلة، جامعة بغداد، بغداد، العراق

### الخلاصة

الأوميكا ٧ هو حمض دهني أحادي غير مشبع لديه العديد من التأثيرات المفيدة. يعد السبيلاتين مركبا فعالا شائع الاستعمال في الامراض السرطانية المختلفة، بدأ الاستخدام العلاجي للسبيلاتين يصبح محدودا وذلك لارتباطه بالسمية الكلوية. يعتقد ان السمية الكلوية المستحثة بواسطة السبيلاتين انها مرتبطة بزيادة تكوين اصناف الاوكسجين التفاعلية الهدف من هذه الدراسة هو لتقييم التأثير المضاد للاكسدة للأوميكا ٧ ضد السمية الكلوية المستحثة بواسطة السبيلاتين في نموذج الجرذان. تم تقسيم ثلاثون جرذا ذكرا بالغا بشكل عشوائي الى خمس مجاميع (٦ جرذان في كل مجموعة) وعلى النحو التالي: المجموعة الأولى تلقت محلول البارافين السائل عن طريق الفم لمدة ٧ ايام متتالية، المجموعة الثانية تلقت جرعة واحدة من السبيلاتين عن طريق الصفاق (٧,٥ ملغم/ كغم)، المجموعة الثالثة تلقت الأوميكا ٧ عن طريق الفم بجرعة (٥٠ ملغم/ كغم) لمدة ٧ ايام متتالية ثم تلقت جرعة واحدة من السبيلاتين عن طريق الصفاق (٧,٥ ملغم/ كغم) في اليوم الثامن، المجموعة الرابعة تلقت الأوميكا ٧ عن طريق الفم بجرعة (١٠٠ ملغم/ كغم) لمدة ٧ ايام متتالية ثم تلقت جرعة واحدة من السبيلاتين عن طريق الصفاق (٧,٥ ملغم/ كغم) في اليوم الثامن، المجموعة الخامسة تلقت الأوميكا ٧ عن طريق الفم (١٠٠ ملغم/ كغم) لمدة ٧ ايام متتالية. في اليوم التاسع، تم قتل جميع الجرذان وجمع العينات (عينات الانسجة الكلوية المتجانسة) لغرض قياس المؤشرات التالية: مستويات انزيم بربوكسداز الغلوتاتايون-١ في الكلى، مستويات انزيم الغلوتاتايون المختزل في الكلى، مستويات انزيم الكتاليز في الكلى، ومستويات المالون داي الديهايد في الكلى. نتج عن اعطاء الأوميكا ٧ للجرذان تأثير وقائي تجلى بارتفاع معنوي في مستويات الانزيمات المضادة للاكسدة (انزيم بربوكسداز الغلوتاتايون-١، انزيم دسموتاز الفائق-١، انزيم الغلوتاتايون المختزل، وانزيم الكتاليز) وبتناقص معنوي في مستوى المالون داي الديهايد في كلى الجرذان المعاملة بالأوميكا ٧ مقارنة بالجرذان المعاملة بالسبيلاتين فقط. لدى الأوميكا ٧ تأثير وقائي ضد التسمم الكلوي الناتج عن السبيلاتين وذلك من خلال تأثيره المضاد للاكسدة المحتمل.

الكلمات المفتاحية: مضادات الاكسدة، السبيلاتين، التسمم الكلوي، الأوميكا-٧، الاجهاد التأكسدي

### Introduction

Omega-7, also known as palmitoleic acid (16:1, cis -9 - hexadecanoic acid), is a monounsaturated fatty acid found in plants such as macadamia and sea buckthorn berry and also in

cold water fish. Studies have reported that omega-7 has a number of beneficial effects such as improved cardiovascular risk and enhanced insulin sensitivity (1).

<sup>1</sup>Corresponding author E-mail: shurouqhussam@gmail.com

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Palmitoleic acid has also been found to have a positive correlation with body mass index and HDL cholesterol but not with LDL cholesterol levels<sup>(2)</sup>. However, the effect of omega-7 on the kidney is still unclear, therefore this study aimed to evaluate the anti-oxidant effect of omega-7 against cisplatin-induced nephrotoxicity.

Cisplatin is a potent chemotherapeutic medication considered for the treatment of many solid-organ cancers<sup>(3)</sup>. Cisplatin exhibits its anticancer effect via a number of different mechanisms mainly through DNA damage, renal vasoconstriction, apoptotic activation, and cellular damage by oxidative stress and inflammation<sup>(4,5)</sup>. Nephrotoxicity is the main drawback in cisplatin's clinical use<sup>(6)</sup>. Approximately 36% of Cisplatin-treated patients reported nephrotoxicity<sup>(7)</sup>. It has been reported that cisplatin initially enters the cell via cellular transporters mainly the human copper transport protein (Ctr 1) and the organic cation transporter 2 (OCT 2) which play an important role in cisplatin's mode of cytotoxicity but also in its nephrotoxicity<sup>(8)</sup>. Cisplatin-induced nephrotoxicity is mediated by a number of mechanisms including necrosis and apoptosis, and inflammation of the tubules<sup>(9)</sup>. Oxidative stress is also involved in cisplatin-induced nephrotoxicity in which reactive oxygen metabolites alter the structure and function of cellular membranes<sup>(10)</sup>. Endoplasmic reticulum and mitochondria are among the most severely injured cellular organelles by cisplatin<sup>(11)</sup>. Previous studies have reported that administration of cisplatin decreased the renal levels of anti-oxidant enzymes such as SOD-1, GPX-1, CAT and GSH<sup>(12)</sup>. Therefore the anti-oxidant agents can prevent cisplatin-induced nephrotoxicity.

## Materials and Method

### Animals

Thirty adult male wistar rats, weighing 150-200 g were obtained and kept in the animal house at College of Pharmacy / University of Baghdad under conditions of controlled temperature, humidity, and 12-12hr light-dark cycle with free access to standard diet and water. All experimental protocols related to animals were conducted in accordance with the national institute of health guide for the care and use of laboratory animals and have been approved by institutional animal care and use committee, University of Baghdad, Iraq.

### Chemicals and drugs

Cisplatin (1mg/ml, 50ml vial) was purchased from Accord (United Kingdom) and omega-7 was obtained from Source Naturals (USA). Liquid paraffin was supplied from College of Pharmacy store /University of Baghdad and normal saline 0.9% was purchased from Pioneer, Iraq. GPX-1, SOD-1, reduced GSH, CAT, and MDA

ELISA kits were purchased from BT Lab (Bioassay Technology Laboratory, Zhejiang China).

### Experimental protocol

Animals were randomly divided into five groups, six animals per group: group 1 (negative control) rats received liquid paraffin solution orally using oral gavage for 7 consecutive days, group 2 (positive control) rats received liquid paraffin solution by oral gavage for 7 consecutive days then received single intraperitoneal injection of cisplatin (7.5mg/kg) diluted in 0.9% normal saline<sup>(13)</sup> on day 8, group 3 (omega-7 + cisplatin) rats received omega-7 (50mg/kg) orally by oral gavage for 7 consecutive days and then received cisplatin (7.5mg/kg) by single intraperitoneal injection on day 8, group 4 (omega-7 + cisplatin) rats received omega-7 (100mg/kg) orally using oral gavage for 7 consecutive days followed by cisplatin (7.5mg/kg) by single intraperitoneal injection on day 8 and lastly, group 5 (omega-7) rats received omega 7 (100mg/kg) orally by oral gavage for 7 consecutive days. On day 9, all animals were sacrificed by cervical dislocation under diethyl ether anesthesia<sup>(14)</sup>. The kidney tissue homogenate was utilized for the estimation of GPX-1, SOD-1, reduced GSH, CAT, and MDA<sup>(15)</sup>.

### Biochemical analysis

Renal tissue homogenates were prepared by immediately excising the kidneys after sacrifice, cleaning the kidneys from fatty tissues and washing them with pre-cooled phosphate buffer saline (pH 7.4, 4°C) to remove any left blood. The left kidney of each rat was utilized for the preparation of tissue homogenate by taking 0.1g of tissue and adding 0.9ml of phosphate buffer saline (pH 7.4, 4°C) into a tube and homogenized for 1 minute using tissue homogenizer and kept at 4°C by immersing the tube in ice. The supernatant obtained was then centrifuged by a refrigerator centrifuge for 10 minutes at 10000 rpm and 4°C. The obtained supernatant was then rapidly collected and stored at -20°C till analysis. Stored tissue homogenates were used for estimation of GPX-1, SOD-1, reduced GSH, CAT and MDA using kits purchased from BT lab (Zhejiang, China) according to manufactures procedures<sup>(16)</sup>.

### Statistical analysis

The results of the study are expressed as mean  $\pm$  standard deviation of the mean (SD). One-way analysis of variance (ANOVA) followed by tukey's post hoc were performed for evaluating statistical significance between different groups. A p value < 0.05 was considered statistically significant.

## Results

### Effects of omega 7 on anti-oxidant enzymes

The results showed that treatment with cisplatin significantly ( $P < 0.05$ ) decreased the

activities of GPX-1, SOD-1, reduced GSH, and CAT when compared to the negative control group as shown in table1. Treatment with omega-7 prior to the injection of cisplatin at doses of (50mg/kg, and 100mg/kg) significantly ( $P < 0.05$ ) increased the activities of these enzymes to reach the normal level as shown in Table1. Furthermore, the dose of

(100mg/kg) was more effective in amelioration the activities of these parameters. Treatment with omega-7 (100mg/kg) increased the levels of GPX-1, SOD-1, reduced GSH, and CAT Table1. The effects of omega-7 on kidney GPX-1, SOD-1, reduced GSH, and CAT activities measured in cisplatin-received rats are presented in Figure 1.

Table 1. Effect of omega-7 on anti-oxidant enzymes.

Group	GPX-1 (ng/ml)	SOD-1 (ng/ml)	GSH (ng/ml)	CAT (ng/ml)
Group I (control)	0.8498 ± .0817	0.9223 ± .1067	92.8933 ± 1.2031	2.3933 ± 0.4236
Group II Cisplatin (7.5mg/kg)	0.5332 ± 0.0522*	0.4298 ± .1118*	40.3298 ± 0.0281*	0.3298 ± 0.0281*
Group III omega7 (50mg/kg)+Cisplatin (7.5mg/kg)	0.6042 ± 0.1017 <sup>a</sup>	0.6372 ± 0.0418 <sup>#a</sup>	55.2909 ± 4.4469 <sup>#a</sup>	0.9576 ± 0.0217 <sup>#a</sup>
Group IV omega7 (100mg/kg)+Cisplatin (7.5mg/kg)	0.785 ± 0.0571 <sup>#a</sup>	0.8777 ± 0.1875 <sup>#a</sup>	66.5443 ± 3.2366 <sup>#a</sup>	1.5443 ± 0.4719 <sup>#a</sup>
Group V omega7 (100mg/kg)	0.8135± 0.2069 <sup>#</sup>	1.0288 ± 0.1078 <sup>#</sup>	93.8622 ± 1.5921 <sup>#</sup>	3.3622 ± 0.4396 <sup>#</sup>

The data are expressed as mean ± SD (n=6); one-way ANOVA followed by Tukey's post hoc test; were used for statistical analysis. \* denotes significant difference from negative control; # denotes significant difference when compared to cisplatin group; a denotes significant difference between combination groups III and IV;  $P < 0.05$ .

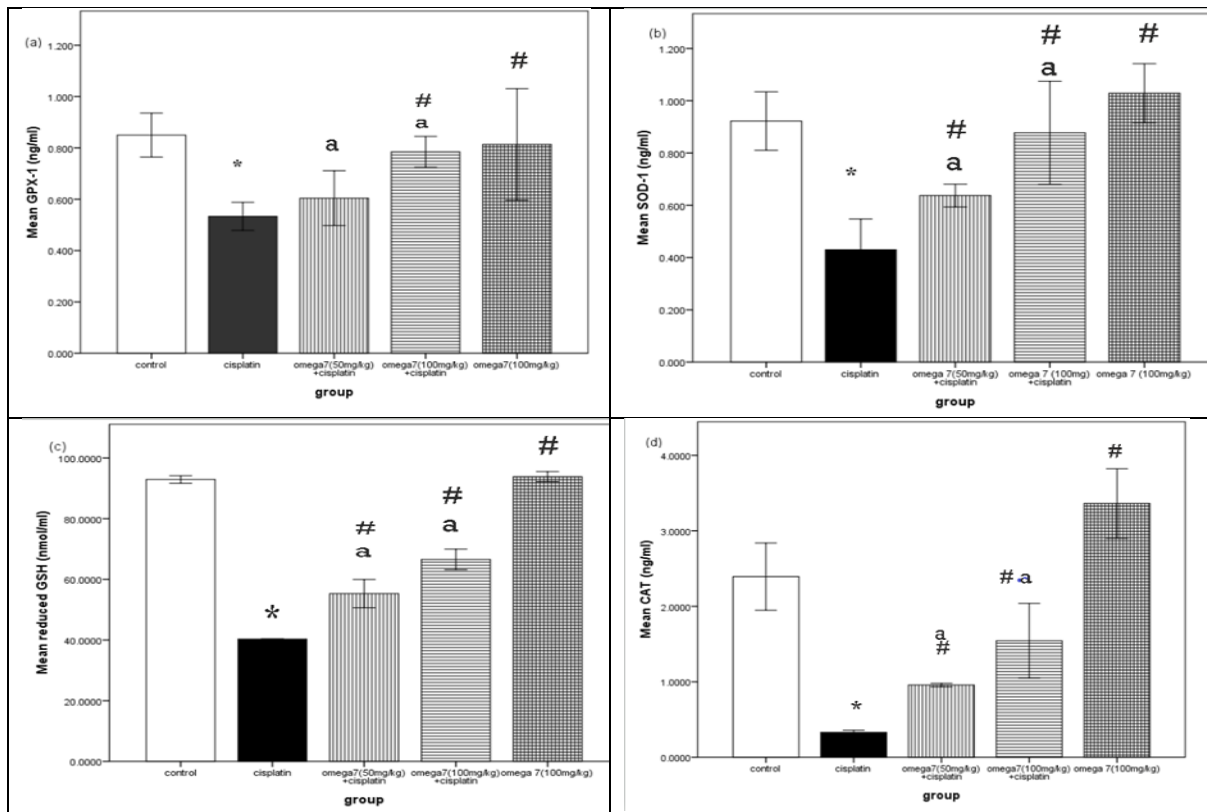


Figure1. Effects of omega 7 on the activities of (a) GPX-1 (b) SOD-1 (c) reduced GSH and (d) CAT. Results are presented as mean ± SD (n= 6); One way ANOVA followed by Tukey's post hoc test; were used for the statistical analysis. \* denotes significant difference form negative control; # denotes significant difference when compared to cisplatin group; a denotes significant difference between combination groups III and IV;  $P < 0.05$ .

### Effects of omega 7 on oxidative stress parameter MDA

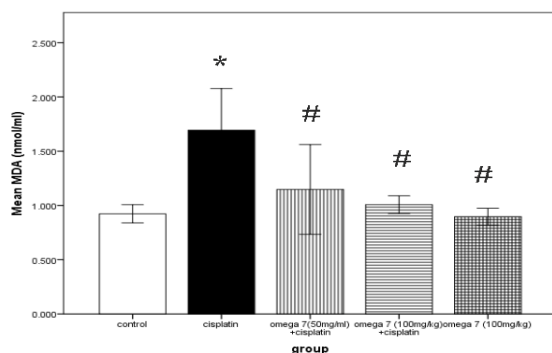
The activity of MDA in cisplatin treated rats was significantly ( $P < 0.05$ ) elevated compared to the negative control group reflecting renal impairment as shown in table2. Treatment with omega-7 at doses of (50mg/kg and 100mg/kg) significantly ( $P < 0.05$ ) decreased MDA activity to return to the normal level (Table2). The higher dose of omega-7 (100mg/kg) showed similar reduction in MDA level to the lower dose (50mg/kg) and there was no difference in the two doses. Treatment with omega-7 (100mg/kg) alone significantly ( $P < 0.05$ ) reduced the activity of MDA to return to the normal level (Table2).

The effects of omega-7 on the activity of MDA are shown in (Figure 2).

**Table 2. Effects of omega 7 on MDA activity.**

Group	MDA (nmol/ml)
Group I (control)	0.9227 ± 0.0800
Group II Cisplatin (7.5mg/kg)	1.694 ± 0.3658*
Group III omega7 (50mg/kg)+Cisplatin (7.5mg/kg)	1.1477 ± 0.3937 <sup>#</sup>
Group IV omega7 (100mg/kg)+Cisplatin (7.5mg/kg)	1.007 ± 0.0779 <sup>#</sup>
Group V omega7 (100mg/kg)	0.8963 ± 0.0743 <sup>#</sup>

The data are expressed as mean ± SD (n=6); one-way ANOVA followed by Tukey's post hoc test; were used for statistical analysis. \* denotes significant difference from negative control; # denotes significant difference from cisplatin group;  $P < 0.05$ .



**Figure2. The effects of omega 7 on the activity of MDA. The results are expressed as mean± SD (n=6); one way ANOVA followed by Tukey's post hoc were used for the statistical analysis. \* denotes significant difference from negative control; # denotes significant difference from cisplatin group;  $P < 0.05$ .**

## Discussion

Cisplatin is an effective anti-cancer drug used in the treatment of various types of solid tumors such as bladder<sup>(17)</sup>, breast<sup>(18)</sup>, non-small<sup>(19)</sup> and small-cell lung cancer<sup>(20)</sup>. Cisplatin-induced nephrotoxicity is the main dose-limiting factor in its clinical use<sup>(21,22)</sup>. Oxidative stress which involves the formation of reactive oxygen metabolites, the buildup of products of lipid peroxidation and the suppressed anti-oxidant enzymes is considered to be one of the important mechanisms of cisplatin-induced nephrotoxicity<sup>(23)</sup>. The current study sheds light on the protective effect of omega-7 as an anti-oxidant agent against cisplatin-induced nephrotoxicity. Several studies suggested that cisplatin-induced nephrotoxicity is manifested by decreased renal GSH levels and impaired activity of GPX-1, SOD-1, and CAT enzymes as well as increased MDA levels and enhanced lipid peroxidation<sup>(24)</sup> which are consistent with the current study results in which GPX-1, SOD-1, reduced GSH and CAT levels decreased while MDA levels increased in cisplatin treated group compared with the control group reflecting renal impairment. Interestingly, treatment with omega-7 significantly increased the levels of GPX-1, SOD-1, reduced GSH, and CAT and decreased MDA level, these study results correspond with previous study reporting that oral administration of oleic acid (which is also a monounsaturated fatty acid) in adult rats prevented oxidative stress by decreasing lipid peroxidation and enhancing anti-oxidant enzyme activities<sup>(25)</sup>. Earlier study about the anti-oxidant effect of mono-unsaturated fatty acid (MUFA) suggested that HDL rich in oleic acid was less liable to oxidation<sup>(26)</sup>. Another study demonstrated that omega 3 (poly unsaturated fatty acid) provided protection against renal toxicity induced by sodium nitroprusside by decreasing oxidative damage in rat kidneys<sup>(27)</sup>. However, it should be noted that the anti-oxidant effect of palmitoleic acid in the kidney has not yet been investigated and there are no previous studies about its anti-oxidant effect on the kidney, thus this study is considered as the first study on the kidney.

## Conclusion

It could be concluded that omega-7 has the ability to counter the nephrotoxic effect of cisplatin by acting as an antioxidant enhancing anti-oxidant enzyme activities and reducing MDA level, and thus providing a potential protective effect against cisplatin-induced nephrotoxicity.

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## Conflicts of Interest

The authors declare that there is no conflict of interest

## Ethics Statements

This study was approved by the scientific and ethical committees of the College of Pharmacy, University of Baghdad according to decision (2049) on 16/2/ 2022.

## Author Contribution

Shuroq Hussam Mahmood; contributed to data gathering, analysis, practical (follow the procedure) and written parts of the study. Ali Faris Hassan gave final approval and agreement for all aspects of the study, supervision, revision and rearrangement.

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