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The Anti-Inflammatory Effect of Omega-7 Against Cisplatin in Rat Model

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A B S T R A C T

Omega-7 (palmitoleic acid, 16:1 n7) is a monounsaturated fatty acid that is found to have several beneficial effects. Cisplatin is commonly considered for the treatment of different carcinomas. Cisplatin therapy is restricted due to its nephrotoxicity. Nephrotoxicity caused by cisplatin is thought to be associated with inflammatory reactions among other mechanisms. The aim of the present study was to evaluate the possible anti-inflammatory effect of omega-7 on cisplatin in rats. Thirty adult male Wistar Albino rats were divided randomly into five equal groups, rats of group 1 received liquid paraffin solution orally for 7 consecutive days, rats of group 2 received cisplatin (7.5 mg/kg) by single intraperitoneal injection, rats of group 3 received omega-7 (50 mg/kg) by oral administration for 7 days consecutively and then followed by single cisplatin (7.5 mg/kg) intraperitoneal injection on the eighth day, rats of group 4 received omega-7 (100 mg/kg) by oral administration for 7 days consecutively followed by single intraperitoneal injection of cisplatin (7.5 mg/kg) on the eighth day, rats of group 5 received omega-7 only (100 mg/kg) orally for 7 consecutive days. On day 9, all animals were euthanized and then serum samples were utilized for assessment of tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10) and interleukin-1β (IL-1β). Treatment of rats with omega-7 had led to significant decline in the activities of the pro-inflammatory cytokines TNF-α and IL-1β, and significant reduction in the level of IL-10. Omega-7 has an anti-inflammatory effect against cisplatin adverse effects.

Keywords: cisplatin, omega-7, anti-inflammatory

INTRODUCTION

Omega-7, also known as palmitoleic acid, is a monounsaturated fatty acid present in plants such as macadamia and sea buckthorn berries and in cold water fish. Different studies have revealed that omega-7 is linked to several useful effects such as reduced cardiovascular risk and improved insulin sensitivity (1), reduced levels of highly sensitive C reactive protein in patients with hypertriglyceridemia, and reduced inflammatory activity through colonic mucosa enhanced expression of hepatocyte nuclear factor 4 gamma (HNF4γ), hepatocyte nuclear factor 4 alpha (HNF4α) and serum interleukin (IL)-6 (IL-6) in patients suffering from ulcerative colitis, whose specific regions are implicated in alterations of intestinal epithelial integrity(2). However, the effects of omega-7 on kidney are still not extensively evaluated.

Cisplatin is an efficient antineoplastic medication utilized for different solid tumors such as bladder (3), non-small cell (4) and small cell lung cancers (5). The anticancer activity of cisplatin is due to its crosslinking the purine bases within the DNA resulting in defective DNA template and arresting DNA replication and synthesis. Thus, by impairing cell division, which is cisplatin's main effect,

cisplatin shows highest efficacy in rapidly dividing cells (6). In addition to DNA damage, apoptosis, necrosis, oxidative stress and inflammation are also implicated in cisplatin mechanism of action (7, 8).

Because the kidney has the capability to operate blood filtration, it is considered as the preferred organ for pollutants and toxic agents such as cisplatin (9). The therapeutic use of cisplatin is hampered by its nephrotoxic effect which occurs within few days after treatment initiation (10). Approximately 36% of cisplatin-treated patients reported nephrotoxicity (11). The kidneys are the main route for excretion of cisplatin, for this reason the kidneys tend to accumulate higher levels of cisplatin than other organs including the liver (12). Nephrotoxicity induced by cisplatin is thought to be mediated by different mechanisms including apoptosis, necrosis and inflammation of renal tubules (13, 14). Inflammation induced by cisplatin is manifested by massive production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-1β, this enhanced production is the result of cisplatin-induced phosphorylation of nuclear factor kappa-B (NF-κB), toll-like receptors and poly ADP-ribose polymerase-1 (PARP-1) activation (15). Cisplatin-induced kidney injury is currently being managed by hydration regimens and supplementation of magnesium (because cisplatin results in hypomagnesemia) (16). In addition, mannitol-induced forced diuresis is used in patients receiving high doses of cisplatin. However, mannitol treatment results in over-diuresis and hence higher risk of dehydration (16). Therefore, the need for new safe and effective protective agent as an adjunct therapy for patients receiving cisplatin is seriously insisting. Thus, the current study aim was to evaluate the possible anti-inflammatory effect of omega-7 against cisplatin in rats.

MATERIALS AND METHODS

Animals

Thirty adults male Wistar Albino rats, weighing 150-200 g were brought from and maintained in the animal house at College of Pharmacy, University of Baghdad on normal conditions of temperature, humidity, and light/dark cycle with water and standard diet free access.

Chemicals and Drugs

Cisplatin (1 mg/mL, 50 mL vial) was purchased from Accord (United Kingdom), omega-7 was obtained from Source Naturals (USA), liquid paraffin was obtained from Riedel-de Haën AG (Germany), and normal saline 0.9% was purchased from pioneer, Iraq. ELISA kits of TNF-α, IL-1β and IL-10 were purchased from Bioassay Technology Laboratory (Zhejiang, China).

Experimental Design

Animals were randomly divided into five equal groups, (n=6) and assigned as follows : Group 1 (negative control) received liquid paraffin solution orally, Group 2 (positive control) received single dose of cisplatin (7.5 mg/kg) diluted in 0.9% normal saline by intraperitoneal injection (15), Group 3 (omega-7+cisplatin) received omega-7 (50 mg/kg) (17) by oral administration for seven consecutively days and then cisplatin (7.5 mg/kg) by single intraperitoneal injection on day eighth, Group 4 (omega-7+cisplatin) received omega-7 (100 mg/kg) (17) by oral administration for seven consecutively days followed by a single cisplatin (7.5 mg/kg) intraperitoneal injection on day eighth, Group 5 (omega-7) rats received omega-7 (100 mg/kg) (17) orally for 7 consecutive days. On the ninth day, all animals were sacrificed by cervical dislocation under diethyl ether anesthesia (18).

Blood Sampling and Biochemical Analysis

At the end of the study and before sacrifice, samples of blood were collected from the jugular vein using a needle of 25 G. The blood was withdrawn slowly to prevent blood vessels collapse, blood samples are collected into gel tubes and allowed to stand for 30 min in order to clot. Blood samples were then centrifuged for 30 min to obtain clear serum and then stored at -20 °C till the day of analysis. Stored sera were used for estimation of serum activities of TNF-α, IL-1β, and IL-10 using kits purchased from BT lab (Zhejiang, China) according to manufacture's procedures (19). The principle of this test is based on the sandwich qualitative ELISA technique.

Statistical Analysis

The values presented in this study are given as mean ± standard deviation (SD). The statistical analysis was carried out using version 25 of the Statistical Package for the Social Sciences (SPSS). A one-way analysis of variance (ANOVA) was used to determine statistical significance between groups, followed by Tukey's post hoc. A $P \leq 0.05$ was considered statistically significant.

RESULTS

The effects of omega-7 on TNF-α, IL-1β, and IL-10 are illustrated in Figure 1 a-c, respectively. Results showed that treatment with cisplatin at 7.5 mg/kg induced an acute inflammatory response, as evidenced by significantly ($P<0.05$) increased serum activities of TNF-α, IL-1β, and IL-10 compared to the negative control group. Treatment with omega-7 at a dose of 50 mg/kg prior to cisplatin injection did not show significant effect on these parameters, while treatment with omega-7 at a dose of 100 mg/kg prior to and during the injection of cisplatin significantly ($P<0.05$) reduced the activities of these cytokines, conferring a dose-dependent anti-inflammatory effect. Treatment with omega-7 at 100 mg/kg only showed significant ($P<0.05$) decline in the activities of the above-mentioned parameters when compared to cisplatin group and no significant difference from the control group ($P<0.05$) was recorded indicating that omega-7 has no adverse effect.

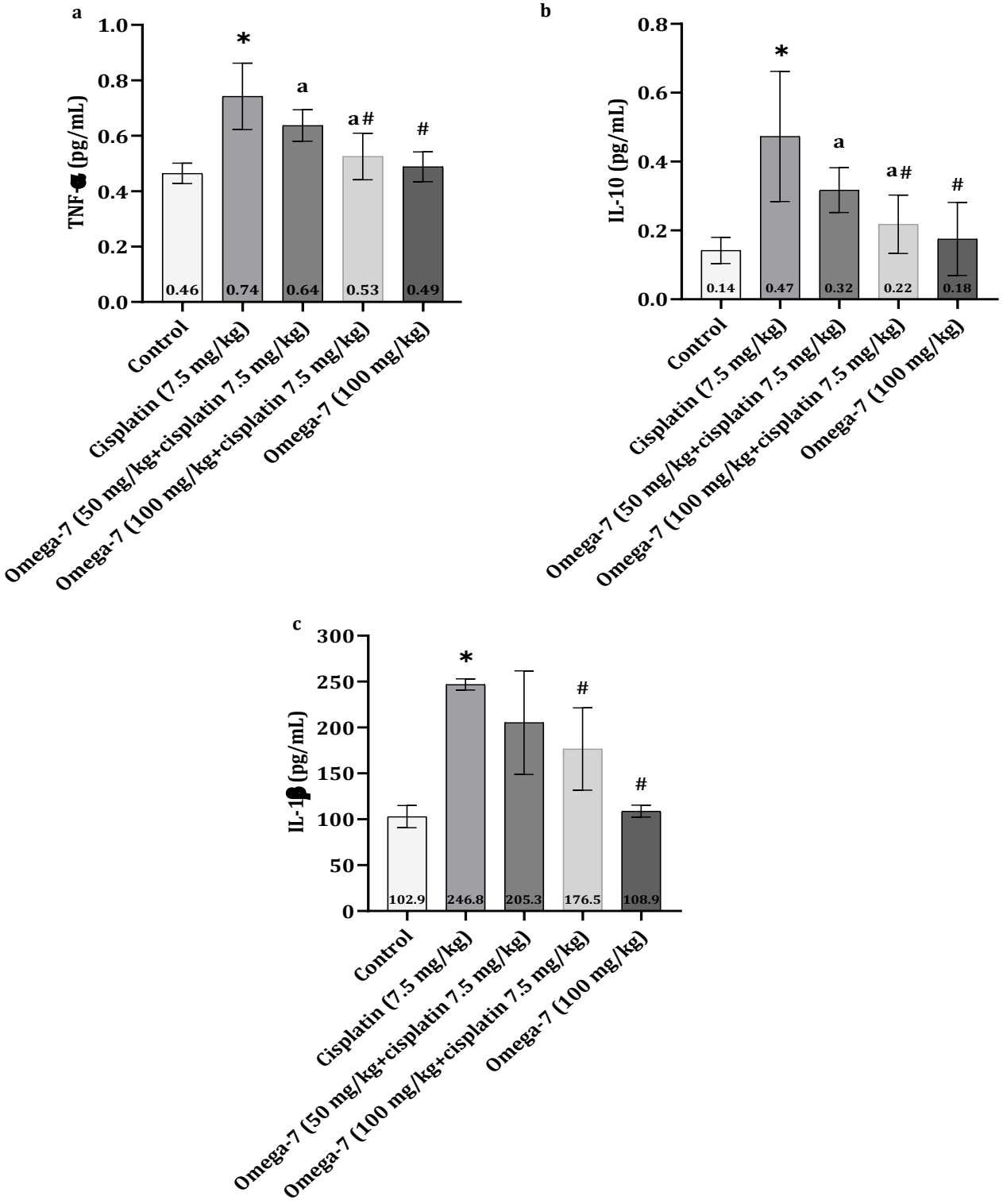

Figure 1. Effects of omega-7 on the activities of (**a**) serum tumor necrosis factor-alpha (TNF-α) pg/mL (**b**) interleuke (IL)-1β (IL-1β), and (**c**) IL-10. The data are Mean±SD,n=6. *Indicates a significant difference when compared to the negative control group (P<0.05). #Indicates a significant difference when compared to the positive control (cisplatin group) (P<0.05)

DISCUSSION

Cisplatin is an efficient antineoplastic medication used for different types of solid tumors (20). Nephrotoxicity exacerbated by cisplatin is the chief dose-limiting factor in its clinical application in cancer chemotherapy (21). This process is manifested by destruction of renal tubules and stimulation of acute inflammatory response as one of several mechanisms involved in cisplatin nephrotoxicity (22). The development of cisplatin-induced inflammatory response is regulated by a complex interplay of inflammatory and immunosuppressive cytokines such as TNF-α, IL-1β and IL-10 (6). TNF-α is a pro-inflammatory cytokine that has a central role in the inflammatory process exacerbated by cisplatin, in which it stimulates the activation of other inflammatory cytokines like IL-1β and enhances the mobilization of inflammatory cells in cisplatin-injured kidneys (23). IL-10 on the other hand, is an anti-inflammatory cytokine, it efficiently suppresses TNF-α and IL-1 inflammatory response thereby reducing cisplatin-induced inflammation and nephrotoxicity (24). In the current study the acute inflammatory response triggered by significant elevation of the cisplatin in serum activities of TNF-α, IL-10 and IL-1β after cisplatin injection in comparison to the negative control. Consistent with the rise of these markers are previous studies one of which reporting that the activities of TNF-α, IL-1β and others are increased after cisplatin treatment (25), another study found that cisplatin increased of TNF-α and IL-1 activities (26). IL-10 level is also increased after cisplatin treatment to prevent production of inflammatory cytokines and protects against cisplatin induced nephrotoxicity (27). Treatment with omega-7 (50 mg/kg) showed no significant difference in cisplatin group while treatment with omega-7 (at high dose of 100mg/kg) showed significant decrease in serum activities of TNF-α, IL-10 and IL-1β, suggesting its dose-dependent anti-inflammatory activity since the inflammation induced by cisplatin is regulated and controlled by these cytokines. In the present results, the line of changes came with a previous study that reported palmitoleic acid treatment may reduce hepatic activities of TNF-α, and IL-1β (28). Previous studies have reported that monounsaturated fatty acid diets may be associated with anti-inflammatory activity in inflammatory bowel disease. Some studies have suggested functional activities of certain lipid constituents on the inflammation of intestines (29, 30).

In conclusion, omega-7 has an anti-inflammatory effect against cisplatin adverse effects manifested by reduction in TNF-α, IL-10 and IL-1β activities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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التأثير المضاد للالتهابات للأوميكا ٧ ضد السسبلاتين في نموذج الفئران

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الخلاصة

الاوميكا ٧ هو من الاحماض الدهنية الاحادية غير المشبعة والذي وجد انه يمتلك العديد من التأثيرات المفيدة. السسبلاتين هو مركب بلاتيني شائع الاستعمال لعلاج العديد من الاورام الصلبة. العلاج بالسسبلاتين تقيد بسبب السمية الكلوية. يعتقد ارتباط السمية الكلوية المحفزة بالسسبلاتين بالالتهاب ضمن العديد من الاليات. هذه الدراسة هدفت لتقييم التأثير المضاد للالتهاب المحتمل للاوميكا ٧ ضد السسبلاتين في الجرذان تم تقسيم ثلاثين جرذا من الذكور البالغين بشكل عشوائي الى خمس مجاميع متساوية على وفق ما يأتي: المجموعة الاولى اعطيت البارافين السائل عن طريق الفم لمدة سبعة ايام متتالية، المجموعة الثانية من الجرذان تلقت جرعة واحدة من السسبلاتين (ملغم\كغم) عن طريق الصفاق, المجموعة الثالثة من الجرذان تلقت الاوميكا ٧ (٥٠ ملغم\كغم) عن طريق الفم لمدة سبعة ايام متتالية ثم تلقت جرعة واحدة من السسبلاتين (٧.٥ ملغم\كغم) عن طرق الصفاق في اليوم الثامن , المجموعة الرابعة من الجرذان تلقت الاوميكا ٧ (١٠٠ملغم\كغم) عن طريق الفم لمدة سبعة ايام متتالية ثم تلقت جرعة واحدة من السسبلاتين (٧.٥ ملغم/كغم) عن طريق الصفاق في اليوم الثامن, المجموعة الخامسة من الجرذان تلقت الاوميكا ٧ (١٠٠ [ملغم\كغم) لمدة سبعة ايام متتالية. في اليوم التاسع, تم قتل جميع الجرذان وجمع العينات (عينات المصل) لغرض قياس المؤشرات الآتية:عامل نخر الورم-الفا، انترلوكين- [بيتا، انترلوكين-١٠. نتج عن اعطاء الاوميكا ٧ للجرذان انخفاض معنوي في مستويات السايتوكينات المؤيدة للالتهاب: عامل نخر الورم-الفا, انترلوكين- [بيتا, وانخفاض معنوي في مستوى السايتوكين المضاد للالتهاب:انترلوكين-١٠.نستنتج من هذه الدراسة لدى الاوميكا ٧ تأثير مضاد للالتهاب.

الكلمات المفتاحية: جرذ مضاد للالتهابات، السسبلاتين، التهاب، الاوميكا-٧