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Research Article BIOCHEMISTRY

Omega-3 mitigates cardiotoxicity in male rats

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KEY WORDS

Omega-3, Doxorubicin, Cardiotoxicity, Oxidative stress, Biochemical parameters

ABSTRACT

Omega-3 is an essential biochemical constitutes that showed several biomedical potentials. Doxorubicin (DOX) is an anticancer drug that had cardiotoxic effects. This study evaluated the usefulness of omega-3 on DOX-induced cardiotoxicity in rats. Forty male rats were equally divided into G1 was the normal control group, G2 was injected i.p with DOX (4 mg/kg) once a week for a month, and G3 was administered orally with omega-3 (200 mg/kg) daily for a month. G4 was injected with DOX as in G2, and then administered with omega-3 (200 mg/kg) as in G3. All treatments were for a month. The percentage of body weight changes were determined, blood and sera were collected for hematological and biochemical analyses. Heart tissues of each group were isolated for determination of the oxidative stress biomarkers. The results showed that omega-3 treatment led to improvement of cardiotoxicity induced by DOX in male rats evidenced by significant enhancement in hematological and antioxidant as superoxide dismutase and catalase.

Introduction

Cancer diseases represent the largest cause of mortality all over the world **(Abullaev *et al*., 2000)**. Conventional chemotherapeutic drugs are not safe due to their severe side effects on the healthy tissues. Doxorubicin (DOX) is anthracycline antibiotics-derived drug as a secondary metabolite of *Streptomyces peucetius*. DOX is used against several types of cancer **(Gianni *et al*., 2007)**. Chemotherapeutic drugs used for cancer treatment, particularly anthracyclines-derived cause cardiotoxicity that leads to cardiovascular disease development **(Naiyra *et al*., 2010)**. The efficacy of DOX has been hampered by its toxicities **(Jain, 2000)**. Cardiac dysfunction, cardiomyopathy, heart failure and loss of endothelial tissues, were reported post DOX injection **(Alpsoy *et al*., 2013)**. The proposed cardiotoxic mechanisms of DOX include oxidative stress that can be reversed by antioxidants **(Wenningmann *et al*., 2019)**.

The molecular mechanisms underlying DOX-induced cardiotoxicity are multifactorial including mitochondrial dysfunction, oxidative stress, and apoptosis; furthermore, the heart is very susceptible to DOX-induced lipid peroxidation (**Kawaguchi *et al*., 2012)**. It has been reported that the toxic effect of DOX treatment led to significant increase serum levels of lactate dehydrogenase, creatine kinase iso-enzyme MB, Troponin, and cardiac malondialdehyde (**Zilinyi *et al*., 2018)**.

Omega-3 is essential fats that cannot be synthesized by mammals due to the absence of their enzymes; it plays a key role in numerous metabolic processes **(Jump *et al*., 2004)**. Previous study demonstrated that omega-3 can be benefits against Alzheimer's disease **(Johnson *et al*., 2006)**. Furthermore, omega-3 was reported to protect against cardiovascular disorders and cancer **(Leitzmann *et al*., 2004; Yokoyama *et al*., 2007)**. Omega-3 also improves endothelial function, decrease atherosclerotic growth, and reduced inflammation, furthermore the impact of omega-3 in the regulation of heart rate was reported, **(Hibbeln *et al*., 2004; Mozaffarian *et al*., 2006)**. The current study evaluated the therapeutic impact of omega-3 treatment on DOX-induced cardiotoxicity in male rats.

Materials and Methods

Chemicals and drugs

Doxorubicin and omega-3 were purchased from Al-Hekma Company. All biochemical kits were purchased from the Company of Biodiagnostic.

Experimental design

Forty male Sprague Dawley rats (120 ± 10 g) were divided into equal groups as follows; G1 was negative control. G2 was injected i.p with DOX (4 mg/kg) once a week for a month **(Warpe *et al*., 2015)**. G3 was administered with omega-3 orally (200 mg/kg) daily for a month **(Majeed and Al-Shawi, 2019)**. G4 was injected with DOX as in G2, and then administered with omega-3 as in G3. Whole blood was collected for hematological parameters assessments and serum was separated for biochemical analyses. Furthermore, heart tissues were harvested for determination of the oxidative stress biomarkers. All groups were weighted and the percentages of body weight change were calculated as follows: (final b.wt – initial b.wt / initial b.wt) × 100.

Determination of hematological and biochemical parameters

Red blood cells (RBCs), hemoglobin (Hb), total platelets count, total count of white blood cell (WBCs) and their differential counts were determined by the electronic

blood counter. Complete blood count was counted by the automated hood using Dirui BCC-3600, MA, USA automated hematology analyzer.

Serum creatinine kinase-MB (CK-MB), Troponin I, and Lactate dehyrogenase (LDH), aspartate aminotransferase (AST) were determined by using commercial Bio-diagnostic kits according to the manufacturers' protocols. Furthermore, in heart tissues homogenates, catalase (CAT), superoxide dismutase (SOD) activities, and malondialdehyde (MDA) levels were assessed according to the manufacturers' protocols using commercial Biodiagnostic kits.

Results

Treatment with omega-3 increase the % of the changes in the body weight in doxorubicin-intoxicated rats

The results showed that group that injected with DOX chemotherapeutic drugs (4 mg/kg/week) for a month showed a significant decrease ($p \leq 0.05$) in the % of the total body weight changes (% B.W. change) that represented 11.46% when compared to the negative control group (53.81%). Rats that injected with DOX and treatment with omega-3 (200 mg/kg) daily for a month showed significant increase ($p \leq 0.05$) in the % B.W. change (23.68%) when compared with the group of rats that treated with DOX alone (11.46%) (Table 1).

Effect of omega-3 treatment on hematological parameters

The data obtained from this study reported that there were no significant alterations in the total count of RBCs, Hb concentration, and Hct% values among all groups under the study when compared to the control group. The total platelets count was significantly increased in the group of rats that intoxicated with DOX. Treating DOX-injected rats with omega-3 led to significant decrease in platelets count (Table 2). Furthermore, the total count of WBCs and the differential counts were significantly increased in the group of rats that injected with DOX when compared to the control groups. Omega-3 treated group showed significant decrease in WBCs count and their differential counts (Table 3).

Table (1): Initial, final body weight, and % of B.W. changes

Groups	I.B.W. (g)	F.B.W. (g)	% B.W. change
Gp1 (control)	92 ± 5.53^{a}	141.5 ± 10.61^{a}	$53.81\ \%^{a}$
Gp2 (DOX)	94.2 ± 9.6^{a}	105 ± 12.43^{b}	$11.46\ \%^{b}$
Gp3 (omega-3)	96.5 ± 9.6^{a}	135 ± 12.43^{b}	$40.62\ \%^{b}$
Gp4 (DOX/omega-3)	$114 \pm 10.63^{a,b}$	140.3 ± 8.08^{c}	$23.68\ \%^{c}$

All data were represented as mean ± S.D, I.B.W.: Initial body weight, F.B.W.: Final body weight, B.W.: Body weight, DOX: Doxorubicin. Groups don't share a letter are significantly different ($p \leq 0.05$).

Table (2): Total RBCs count, Hb, Hct % values, and total platelets count

Groups	RBCs ($\times 10^6$/ul)	Hb (g/dl)	Hct (%)	Platelets ($\times 10^3$/ul)
Gp1 (control)	7.11 ± 0.29 [a]	12.90 ± 0.62 [a]	36.7 ±1.12 [a]	533.7 ± 57.4 [a]
Gp2 (DOX)	6.43 ± 0.24 [a]	12.23 ± 1.52 [a]	35.8 ±1.32 [a]	694.8 ± 68.4 [b]
Gp3 (omega-3)	6.08 ± 1.88 [a]	12.15 ± 3.9 [a]	35.2 ± 3.35 [a]	524.7 ± 48.4 [a]
Gp4 (DOX/omega-3)	7.21± 0.61 [a]	13.32 ± 1.6 [a]	39.12 ±3.21 [b]	512.2 ± 65.2 [a]

All data were represented as mean ± SD, RBCs: red blood cells, Hb: Hemoglobin, Hct: Hematocrit. DOX: Doxorubicin. Groups don't share a letter are significantly different ($p \leq 0.001$).

Table (3): Total WBCs and the percentage of differential leucocytes

Groups	WBCs ($\times 10^3$/ul)	Lymph. (%)	Neut. (%)	Mono. (%)
Gp1 (control)	10.1 ± 1.4 [a]	87.25 ± 2.22 [a]	5.5 ± 1.6 [a]	7.5 ± 1.01 [a]
Gp2 (DOX)	15.7 ± 1.2 [b]	94.75 ± 6.18 [a]	3.5 ± 3.7 [b]	5.0 ± 5.35 [b]
Gp3 (omega-3)	11.4 ± 1.7 [a]	85.25 ± 2.35 [a]	6.3 ± 1.5 [a]	8.9 ± 0.81 [a]
Gp4 (DOX/omega-3)	13.0 ± 2.3 [c]	90.5 ± 2.52 [a]	3.1 ±1.41 [a]	6.5 ± 1.29 [a]

All data were represented as mean ± SD. W.B.Cs: White blood cells. DOX: Doxorubicin. Groups don't share a letter are significantly different ($p \leq 0.001$).

Effect of omega-3 treatment on creatine kinase and troponin I

By determining the cardiac function test including creatine kinase MB (CKMB) and troponin I, results showed significant increasing in the CKMB activity and troponin I levels in the DOX-intoxicated group when compared to the control group (Fig. 1). Treatment of DOX-injected rats with omega-3 led to significant decrease in the CKMB activity and troponin I levels when compared to the DOX-intoxicated group (Fig. 1).

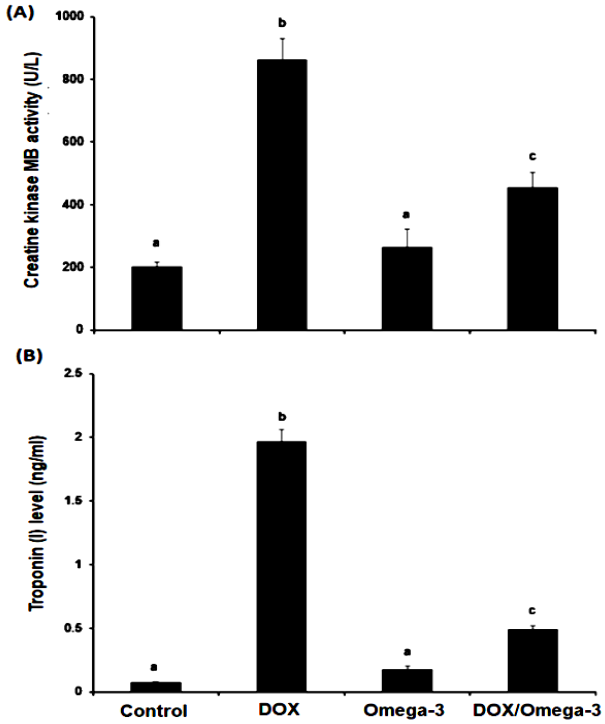

Fig. (1): Creatine kinase MB activity and troponin (I) level. All data were represented as mean ± SD. Groups don't share a letter are significantly different ($p \leq 0.05$).

Effect of omega-3 treatment on lactate dehydrogenase and aspartate transaminase activities

Regarding lactate dehydrogenase (LDH) and aspartate transaminase (AST) activities, the data revealed that the group which injected with DOX showed significant increase in the LDH and AST activities when compared to the negative control group. Treatment with omega-3 after DOX injection in rats led to significant decrease in the activities of LDH and AST (Fig. 2).

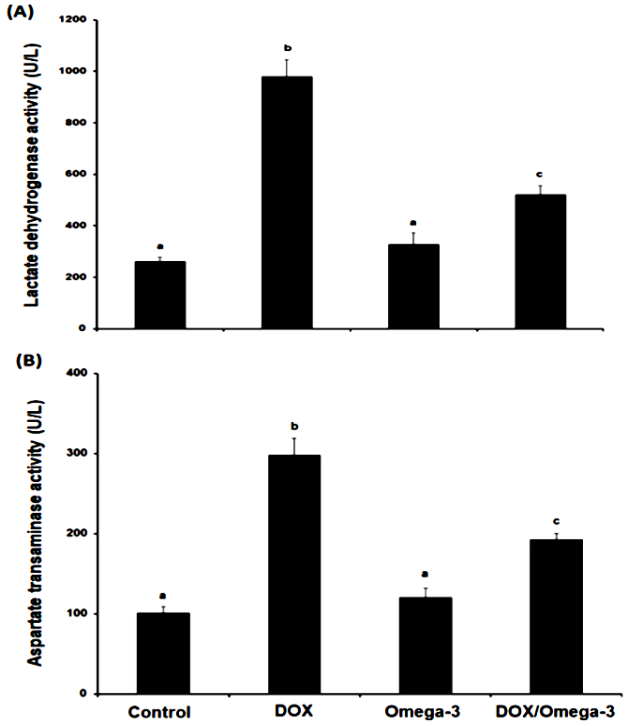

Fig. (2): Lactate dehydrogenase and aspartate transaminase activities. All data were represented as mean ± S.D. Groups don't share a letter are significantly different ($p \leq 0.001$)

Effect of omega-3 treatment on antioxidants/oxidants biomarkers

Antioxidants enzymes and lipids peroxidation parameters were determined; the results showed that there were no changes in the omega-3-administered group when compared with the negative control group. Group of rat that injected with DOX showed significant decrease in the activities of SOD and CAT, along with significant increase in the MDA levels. Rats that injected with DOX and treated with omega-3 showed significant improvement in oxidative stress biomarkers by increasing SOD and CAT activities, decreasing MDA level when compared to DOX-intoxicated rats (Table 4).

Table (4): Activities of SOD, CAT, and MDA level in the heart tissues

Groups	SOD (U/ g tissue)	CAT (U/ g tissue)	MDA (nmol/g tissue)
Gp1 (control)	32.34 ± 1.87^{a}	9.65 ± 0.87^{a}	58.87 ± 1.87^{a}
Gp2 (DOX)	7.87 ± 0.39^{b}	2.07 ± 0.13^{b}	179.24 ± 3.12^{b}
Gp3 (omega-3)	30.54 ± 1.57^{a}	8.32 ± 0.95^{a}	62.31 ± 1.57^{a}
Gp4 (DOX/omega-3)	16.78 ± 1.01^{c}	5.71 ± 0.27^{c}	107.76 ± 2.98^{c}

All data were represented as mean ± S.D. SOD: Superoxide dismutase; CAT: Catalase. MDA: Malondialdehyde. Groups don't share a letter are significantly different ($p \leq 0.05$).

Discussion

During the treatment of cancer by using anticancer therapeutic agents, most of biochemical and physiological homoeostasis were destructed. DOX antitumor drug showed wide applications for treating several malignancies, however, its uses are limited by cardiotoxicities development; therefore, much efforts have been focused on the preventive impacts of natural agents against DOX-induced cardiotoxicity **(Yagmurca *et al*., 2003)**.

Omega-3 is rich in fish oil that is important for nerve tissues and regulating the inflammation **(Schuchardt *et al*., 2010)**. It contains alpha-linolenic acid and eicosapentaenoic acid that showed prophylactic impacts on cardiovascular diseases **(Ruzickowa *et al*., 2004; Fabian *et al*., 2015)**. Omega-3 had a powerful antioxidant and anticancer properties **(Moussa *et al*., 2020)**. Previous studies have revealed the beneficial effects of antioxidant agents against DOX-induced cardiotoxicity **(Yagmurca *et al*., 2003; Alpsoy *et al*., 2013)**. This study addressed the preventive effect of omega-3 against cardiotoxicity induced by DOX injection in rats.

The results of the current study showed that the treatment with omega-3 increase the percentage of the total body weight change in doxorubicin-intoxicated rats. **Teng *et al*., (2010)** demonstrated that specific dose of fish oil mitigates DOX-induced cardiac malfunctions. Platelets number was significantly increased in the DOX-intoxicated rats. Treating DOX-injected rats with omega-3 led to significant decrease in the total count of platelets. Furthermore, the total count of WBCs and the differential counts were significantly increased in the group of rats that injected with DOX when compared to the control groups. Omega-3 treated group showed significant decrease in the total count of WBCs and their differential counts. Previous studies showed the ameliorative effect of fish oil on the DOX-induced toxicities **(Barakaat *et al*., 2018; Ahmed *et al*., 2021).**

The current study was extended to evaluate Biochemical cardiac parameters including CK-MB activity, troponin I level, lactate dehydrogenase and aspartate transaminase activities. Our findings showed that CKMB activity and troponin I levels were significantly increased in the in the DOX-intoxicated group. Treatment with omega-3 led to significant decrease in the CKMB activity and troponin I levels. Furthermore, lactate dehydrogenase (LDH) and aspartate transaminase (AST) activities were increased in rats that injected with DOX; omega-3 treatment post DOX injection caused the activities of LDH and AST to be decreased in rats. These findings agreed with several studies demonstrated the ameliorating effects of natural agents against DOX cardiotoxicity **(Alimoradian *et al*., 2018; Moussa *et al*., 2020; Saleh *et al*., 2020; Raskovic *et al*., 2011)** demonstrated an increase in the LDH activity in rats treated with a single cumulative dose of DOX. The increase of LDH concentration may be due to excessive ROS. The data obtained from the present study showed that group of rat that injected with DOX showed significant decrease in the activities of SOD and CAT, along with significant increase in the MDA levels. Rats that injected with DOX and treated with omega-3 showed significant improvement in oxidative stress biomarkers by increasing SOD and CAT activities, decreasing MDA level. Several studies addressed the harmful effect of DOX on the antioxidants/oxidants hemostasis and the beneficial role of other natural agents including omega-3 in experimental animals

(Moussa *et al*., 2020; Saleh *et al*., 2020; Hamza *et al*., 2021).

Conclusion

DOX chemotherapeutic drug has cardiotoxicity adverse effects. In the present study, omega-3 showed potential ameliorative effect against cardiotoxicity-induced by DOX treatment in rats by improving cardiac function biomarkers, decreasing serum CK-MB, LDH, troponin, and AST levels and enhancing antioxidants/oxidants status that evidenced by increasing SOD, CAT activities, accompanied with decreasing MDA levels in cardiac tissues.

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يخفف الأوميجا ٣ من السمية القلبية في ذكور الجرذان

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يعتبر أوميجا ٣ عنصر بيوكيميائي أساسي والذي أظهر العديد من الإمكانات الطبية الحيوية و يعد عقار الدوكسوريبسين دواء مضاد للسرطان وله تأثيرات سامة للقلب. قيمت هذه الدراسة فائدة أوميجا ٣ على السمية القلبية التي يسببها الدوكسوريبسين فى الجرذان. حيث تم تقسيم أربعين من ذكورالجرذان بالتساوي إلى اربعة مجموعات. المجموعة الأولى كانت المجموعة الضابطة ، والمجموعة الثانية حُقنت بعقار الدوكسوريبسين (٤ مجم / كجم) مرة واحدة في الأسبوع لمدة شهر ، وتم إعطاء المجموعة الثالثة الأوميجا- ٣ (٢٠٠ مجم / كجم). وتم حقن المجموعة الرابعة بعقار الدوكسوريبسين كما في المجموعة الثانية، ثم تم الأوميجا- ٣ كما في المجموعة الثالثة. وكانت جميع العلاجات لمدة شهر. تم تحديد النسبة المئوية لتغيرات وزن الجسم ، وجمع الدم والأمصال لتحليل الدم والدلائل الكيميائية الحيوية. تم عزل أنسجة القلب لكل مجموعة لتحديد المؤشرات الحيوية للإجهاد التأكسدي.

أظهرت النتائج أن العلاج باستخدام الأوميجا ٣ أدى إلى تحسين السمية القلبية التي يسببها عقار الدوكسوريبسين في ذكور الجرذان بدليل التحسين الكبير في الدم ومضادات الأكسدة مثل انزيم السوبر أكسيد ديسميوتيز و الكاتاليز وأيضا تحسن واضح في ظائف القلب مثل اللاكتات ديهيدروجينيز والكرياتين كيناز الدلائل الحيوية للأكسدة.