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The Hepatoprotective Effect of Omega-7 Against Paracetamol-Induced Hepatotoxicity in Male Rats

Hadeel Ali Hameed[*,1] and Ali Faris Hassan [2]

[1] Ministry of Health and Environment, Diyala Health Directorate, Diyala, Iraq.
[2] Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

Paracetamol toxicity, whether accidental or not is a worldwide issue that leads to hepatotoxicity, acute liver failure, as well as irreversible liver injury requiring liver transplantation. Omega-7 is a monounsaturated fatty acid with a number of beneficial properties. The aim of the present study was to assess the potential protective role of omega-7 fatty acid against hepatotoxicity induced by paracetamol in male rats. Thirty male Rats were separated into five groups (six rats in each group) and received the following treatment: group 1 received liquid paraffin orally via gavage tube for seven days successively, group 2 received liquid paraffin orally via gavage tube for seven days successively, and on day eight, rats received a single intraperitoneal injection of paracetamol (500 mg/kg/day), group 3 received omega-7 (300 mg/kg/day) orally via gavage tube for seven days successively, group 4 received omega-7 (100 mg/kg/day) orally via gavage tube for seven days successively, and on day eight, rats received a single intraperitoneal injection of paracetamol (500 mg/kg/day), group 5 received omega-7 (300 mg/kg/day) orally via gavage tube for seven days successively, and on day eight, rats received a single intraperitoneal injection of paracetamol (500 mg/kg/day). On day nine, rats have been sacrificed by cervical dislocation and liver homogenate samples were collected for analysis. This study showed that there was a significant decrease in hepatic superoxide dismutase, catalase, glutathione-peroxidase and glutathione levels, accompanied with significant increase in hepatic malondialdehyde level in paracetamol group compared to the negative control group. However, administration of omega-7 resulted in significant increase in hepatic superoxide dismutase, catalase and glutathione levels and significant decrease in hepatic malondialdehyde level compared to paracetamol group. In conclusion, omega-7 has a protective effect on paracetamol-induced hepatotoxicity in rats.
Keywords: Antioxidant, Hepatotoxicity, Omega-7, Oxidative stress, Paracetamol.

التاثير الوقائي للاوميكا-٧ ضد السمية الكبديه المستحثة بواسطة الباراسيتامول في ذكور الجرذان

هديل علي حميد [*،١] و علي فارس حسن [٢]

[١]وزارة الصحة والبيئة، دائرة صحة ديالى، ديالى ، العراق.
[٢] فرع الادوية والسموم، كلية الصيدلة،جامعة بغداد، بغداد، العراق.

الخلاصة

ان سمية الباراسيتامول سواء كانت عرضية او لا هي مشكلة حول العالم تؤدي الى تسمم الكبد, فشل الكبد الحاد وكذلك اصابة الكبد التي لا رجعة فيها والتي تتطلب زراعة الكبد. الاوميغا-٧ هو حمض دهني احادي غير مشبع لديه العديد من التأثيرات المفيدة.
تهدف هذه الدراسة الى تقييم الدور الوقائي المحتمل للأحماض الدهنية أوميغا ٧ ضد السمية الكبدية التي يسببها الباراسيتامول في ذكور الجرذان. تم تقسيم الجرذان الى خمس مجاميع(ستة جرذان في كل مجموعة) وتم اعطاؤها على النحو الاتي: المجوعة الاولى تلقت البارافين السائل عن طريق انبوب فموي يوميا لمدة سبعة ايام متتالية, المجموعة الثانية تلقت البارافين السائل عن طريق انبوب فموي لمدة سبعة ايام متتالية , وفي اليوم الثامن تلقت الجرذان جرعة واحدة من الباراسيتامول (٥٠٠ ملغم/كغم/اليوم) داخل الصفاق, المجموعة الثالثة تلقت الاوميكا-٧ (٣٠٠ ملغم/كغم/اليوم) عن طريق انبوب فموي لمدة سبعة ايام متتالية, المجوعة الرابعة تلقت الاوميكا-٧ (١٠٠ملغم/كغم/اليوم) عن طريق انبوب فموي لمدة سبعة ايام متتالية , وفي اليوم الثامن تلقت الجرذان جرعة واحدة من الباراسيتامول (٥٠٠ ملغم/كغم/اليوم) داخل الصفاق, المجوعة الخامسة تلقت الاوميكا-٧(٣٠٠ملغم/كغم/اليوم) عن طريق انبوب فموي لمدة سبعة ايام متتالية , وفي اليوم الثامن تلقت الجرذان جرعة واحدة من الباراسيتامول (٥٠٠ ملغم/كغم/اليوم) داخل الصفاق. في اليوم التاسع , تم اجراء القتل الرحيم للجرذان وجمع عينات النسيج الكبدي لغرض الفحص. اظهرت هذه الدراسة ان اعطاء الباراسيتامول للجراذان ادى الى انخفاض معنوي في النسيج الكبدي لكل من السوبر اكسيد ديسميوتاز, الكاتالاز, الجلوتاثيون-بيروكسيداز و الجلوتاثيون , مصحوبا بزيادة معنوية في النسيج الكبدي للمالون داي الديهايد , في حين ادى اعطاء الاوميكا-٧ الى زيادة معنوية في مستوى النسيج الكبدي لكل من السوبر اكسيد ديسميوتاز, الكاتالاز والجلوتاثيون وانخفاض معنوي في مستوى النسيج الكبدي للمالون داي الديهايد مقارنة بالجرذان التي تلقت الباراسيتامول. كاستنتاج. لدى الاوميكا-٧ تاثيرات واقية ضد التسمم الكبدي الناتج عن الباراسيتامول في الجرذان.
الكلمات المفتاحيه: مضادات الاكسدة، التسمم الكبدي،الاوميكا-٧، الاجهاد التاكسدي، باراسيتامول.

[*]Corresponding author E-mail: hadeel.ali.hameed1@gmail.com
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Introduction

Liver is a key organ that is responsible for metabolism, storage, secretion and detoxifying activity in the body, and hepatic damage is frequently associated with disruption of these functions. Drug induced liver toxicity is a major contributor of liver injury, it accounts for around half of all cases of acute liver failure. The majority of hepatotoxic drugs harm liver cells by inducing lipid peroxidation and other oxidative damage [1,2] .
Paracetamol is one of the most commonly used drugs as an analgesic and antipyretic. Even though it is safe at therapeutic doses, over doses can lead to hepatocyte damage and acute liver failure. Paracetamol hepatotoxicity include multi-stages and pathogenic mechanisms, involving formation of toxic metabolites, oxidative stress, mitochondrial malfunction and at the end hepatocyte death [3,4].
At therapeutic doses more than 90% of paracetamol is converted to non-toxic metabolites by sulfation and glucuronidation [5]. Approximately 5–10% of paracetamol is oxidized to a reactive metabolite known as N-acetyl-p-benzoquinone imine (NAPQI) [6]. NAPQI is produced in the liver by cytochrome P-450 isoform (CYP2E1) which is primarily responsible for paracetamol-induced hepatotoxicity, and it is effectively detoxified by binding to the sulfhydryl group of glutathione (GSH) and eliminated in the urine as cysteine and mercapturic acid conjugates [7].

However, at high paracetamol doses (more than 4 g/day) [8], the sulfation and glucuronidation pathways become saturated, whereas oxidation increases, resulting in an excess of NAPQI formation that depletes hepatic GSH levels [9]. Leading to the generation of oxidative stress which is defined as an imbalance between oxidants and antioxidant. This causes NAPQI to interact with mitochondrial membrane proteins. The formation of mitochondrial protein adducts with NAPQI leads to reactive oxygen species (ROS) production, which damages mitochondrial DNA, opens the mitochondrial permeability transition pore, and halts ATP production. Furthermore, the membrane protein BAX translocates, combining with Bak in the outer mitochondrial membrane to form pores that allow the release of intermembranous proteins such as cytochrome c. The leak of mitochondrial proteins as well as the cessation of ATP production together leads to cell death [10,11].

Palmitoleic acid is a monounsaturated omega-7 fatty acid with 16 carbons. Palmitoleic acid can be obtained through diet; good sources include macadamia oil, and sea buckthorn oil. Palmitoleic acid is produced by desaturating of palmitic acid in a reaction catalyzed by stearoyl-CoA desaturase-1 (SCD1). The liver and adipose tissue are most likely the primary sites of SCD activity. Palmitoleic acid is abundant in human adipose tissue, where it accounts for more than 5% of the fatty acids present [12]. Palmitoleic acid, like other fatty acids, circulates in the bloodstream as a component of complex lipids (phospholipids, triglycerides and cholesteryl esters) within lipoproteins [13]. It has been established that palmitoleic acid is produced and released by adipocytes and serves as a lipokine that modulates several metabolic processes in other tissues [14].
Various studies have shown that palmitoleic acid has a number of beneficial effects, where it improved whole-body glucose disposal in rodents [15], reduced hepatic steatosis in diabetic mice [16], prevent pancreatic B cell from death induced by palmitic acid [17] and enhanced lipid profile in human [18].
Furthermore, supplementation with palmitoleic acid was found to reduce liver inflammation in mice with non-alcoholic fatty liver disease [19]. Additionally, palmitoleic acid reduced inflammatory gene expression and cytokine production in macrophages as well as increased differentiation to an anti-inflammatory phenotype [20,21].

Materials and Methods

Animals

A total of thirty (30) Albino male rats, weighting 180-200 gm were employed in this study, they were obtained and kept under circumstances of controlled temperature, humidity and light- dark cycle in the Animals House of the College of Pharmacy, University of Baghdad. Throughout the experiment, animals were given conventional laboratory pellets and unlimited access to water. Upon approval by the scientific committee of the college of pharmacy, university of Baghdad, this study was conducted.

Paracetamol and omega-7 fatty acid (palmitoleic acid)

Paracetamol ampoule of 600 mg/5ml was purchased from BS PHARMA (FRANCE), and omega-7 soft gel (210 mg) from SOURCE AND NATURALS (USA).

Experiment protocol

Thirty male rats were separated into five groups (six rats in each group) and received the following treatment:

Group 1 received liquid paraffin orally via gavage tube for seven days successively. This group served as negative control.

Group 2 received liquid paraffin orally via gavage tube for seven days successively, and on day eight, rats received a single intraperitoneal injection of paracetamol (500 mg/kg/day) [(22)]. This group served as positive control.

Group 3 received omega-7 (300 mg/kg/day) orally via gavage tube for seven days successively.

Group 4 received omega-7 (100 mg/kg/day) orally via gavage tube for seven days successively, and on day eight, rats received a single intraperitoneal injection of paracetamol (500 mg/kg/day) [(23)].

Group 5 received omega-7 (300 mg/kg/day) orally via gavage tube for seven days successively, and on day eight, rats received a single intraperitoneal injection of paracetamol (500 mg/kg/day) [(23)].

Twenty-four hours after the end of the treatment period (day 9), all rats were sacrificed by cervical dislocation under diethyl ether anesthesia and liver tissues were collected and processed for analysis. Briefly, the liver of each animal was rapidly excised and washed in ice-cold phosphate buffer saline (PBS) (PH 7-7.4) to remove excessive blood. The liver tissue was then weighted and cutdown into small pieces. In a tube containing 0.9 ml of phosphate buffer saline, 0.1 gm of liver tissue was placed to prepare 1 ml of liver homogenate. The liver tissues were then homogenized using a homogenizer, and then the homogenate was centrifuged at 10000 rpm for 15 minutes in a cold centrifuge. Liver tissue homogenate was taken to be used in superoxide dismutase (SOD), catalase (CAT) glutathione-peroxidase (GP-X), malondialdehyde (MDA) and glutathione (GSH) estimation [(24)].

Statistical analysis

Statistical Package for Social Science (SPSS, version 26) was used to conduct the analysis. This study presented data by mean ± standard deviation (mean ± SD). One-way Analysis of Variance was used to assess the significance of differences between various groups (ANOVA) followed by Tukey's post hoc test. The probability value (P) was considered significant when the value is < 0.05.

Results

In comparison with the negative control group, in rats intraperitoneally injected with paracetamol (500mg/kg/day) (Group 2), there were a significant decrease in the hepatic levels of superoxide dismutase (SOD), catalase (CAT) and glutathione-peroxidase (GP-X) ($p<0.05$); furthermore, there were non-significant differences of the hepatocellular level of SOD, CAT and GP-X in omega-7 treated group (Group 3) when compared to each corresponding level in the negative control (Group 1) ($p>0.05$) rats. Besides, there were a significant increase in the hepatic level of SOD, CAT and GP-X in omega-7 treated group (Group 3) when compared with each corresponding level in paracetamol group (Group 2) rats ($p<0.05$) as shown in "Table 1" and "Figure 1,2 and 3".

Treatment of rats with omega-7 in a dose of 100mg/kg/day prior to a single intraperitoneal injection of paracetamol (500mg/kg/day) (Group 4), there were a significant increase in hepatic SOD level ($p<0.05$) and non-significant increase in CAT and GP-X level ($p>0.05$) compared with such level in group of rats intraperitoneally-injected with a single dose of paracetamol (500mg/kg/day) (Group 2). Moreover, treatment of rats with the dose of omega-7 300mg/kg/day prior to a single intraperitoneal injection of paracetamol (500mg/kg/day) (Group 5), the results showed that, there were a significant increase in the hepatic levels of SOD and CAT ($P<0.05$) and non-significant increase in the level of GP-X ($P>0.05$) compared to corresponding levels in Group 2 rats that intraperitoneally-injected with a single dose of paracetamol (500mg/kg/day). By comparing each of hepatic levels of superoxide dismutase (SOD), catalase(CAT) and glutathione-peroxidase (GPX)between the pretreated omega-7 Groups (4 and 5), there were non-significant differences in such hepatic enzymes levels ($P>0.05$) as shown in "Table"1 and" Figure 1, 2 and 3".

Table 1 .Effects of omega-7 pretreatment on the oxidative stress biomarkers

Groups	SOD (ng/ml)	CAT (ng/ml)	GP-X (ng/ml)
Group 1 (Liquid paraffin) (Negative control)	0.460±0.021	26.966±1.214	0.361±0.038
Group 2 Paracetamol (500 mg/kg/day) (Positive control)	0.215± 0.051*	20.516±1.132*	0.239±0.032*
Group 3 Omega-7 at dose 300 mg/kg/day	0.487±0.094#	26.666±1.512#	0.396±0.066#
Group 4 Omega-7 at dose 100 mg/kg /day+ Paracetamol (500 mg/kg/day)	0.352±0.031#a	22.65±3.107a	0.254±0.026a
Group 5 Omega-7 at dose 300 mg/kg + Paracetamol (500 mg/kg/day)	0.384±0.027#a	24.5±2.276#a	0.305±0.091a

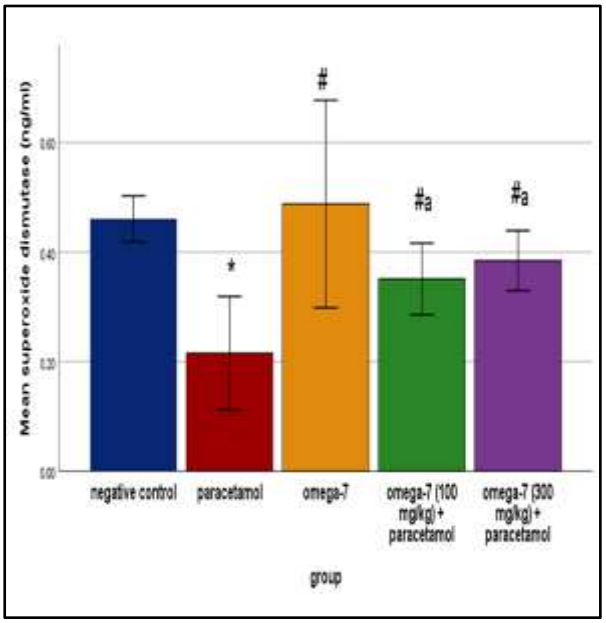

Figure 1. Effect of omega-7 on Superoxide dismutase level.

The data are expressed as mean± standard deviation, number of rats in each group =6

(*) indicate significant differences when group2 and 3 are compared to the negative control group ($p<0.05$). (#) indicate significant differences when group 3,4 and 5 are compared to the Paracetamol group ($p<0.05$).

(a) indicate no significant difference between group 4 and 5 ($p>0.05$).

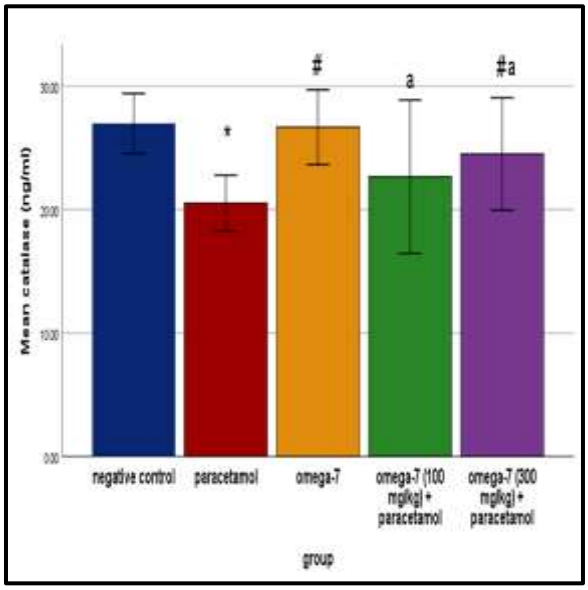

Figure 2. Effect of omega-7 on Catalase level.

The data are expressed as mean± standard deviation, number of rats in each group =6

(*) indicate significant differences when group2 and 3 are compared to the negative control group ($p<0.05$). (#) indicate significant differences when group 3,4 and 5 are compared to the Paracetamol group ($p<0.05$).

(a) indicate no significant difference between group 4 and 5 ($p>0.05$).

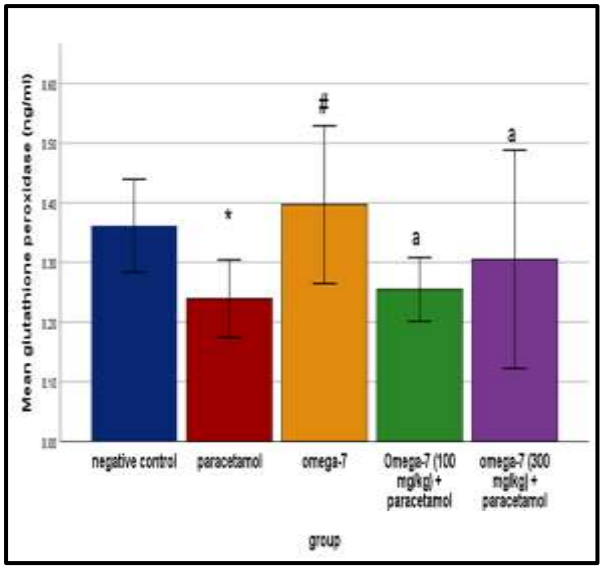

Figure 3. Effect of omega-7 on Glutathione-peroxidase level.

The data are expressed as mean± standard deviation, number of rats in each group =6

(*) indicate significant differences when group2 and 3 are compared to the negative control group ($p<0.05$). (#) indicate significant differences when group 3,4 and 5 are compared to the Paracetamol group ($p<0.05$).

(a) indicate no significant difference between group 4 and 5 ($p>0.05$).

Table 2 and "Figures 4 and 5" revealed that injection of a single dose of paracetamol intraperitoneally (500mg/kg/day) (Group 2) resulted in a significant increase in the hepatic (MD)A level, coupled with a significant decrease in GSH level ($p<0.05$) compared to the negative control group (Group 1). Moreover, there were no significant differences in the level of MDA and GSH in the omega-7 treated group (300mg/kg/day) (Group 3) rats compared to such levels in the negative control (Group 1) ($p>0.05$). Besides comparing MDA and GSH levels of omega-7 treated group (group 3) and paracetamol group (group 2) revealed significant decrease in MDA level and significant increase in glutathione level in omega-7 group (Group 3) ($p<0.05$).

Moreover, in rats treated with omega-7 (100mg/kg/day) for 7 days prior to a single intraperitoneal injection of paracetamol (500mg/kg/day) (Group 4), there were significant decrease in hepatic MDA level and significant increase in GSH level ($p<0.05$) compared to each of the corresponding levels in Group 2 rats [(intraperitoneally-injected with a single dose of paracetamol (500mg/kg/day)]. Also, treatment of rats with [omega-7 (300mg/kg/day for 7 days) prior to a single intraperitoneal injection of paracetamol (500mg/kg/day)] produced significant decrease in MDA level and significant increase in GSH hepatic level ($p<0.05$) compared to such hepatic levels in Group 2 rats [(intraperitoneally-injected with a single dose of paracetamol (500mg/kg)]. The same table also showed that, there were no significant differences in the hepatic MDA level between Group 4 and 5 rats ($p>0.05$), and there was a significant increase in GSH level in Group 5 rats compared to such hepatic level in Group 4 ($p<0.05$) rats. Table 2 and Figures 4 and 5.

Table 2 .Effects of omega-7 on the hepatic malondialdehyde **(MDA)and** glutathione **(GSH) levels.**

Groups	**MDA (nmol/ml)**	**GSH (ng/ml)**
Group 1 (Liquid paraffin) (Negative control)	0.360±0.027	55.261±6.575
Group 2 Paracetamol (500 mg/kg/day) (Positive control)	$0.712\pm0.054^{*}$	$26.583\pm4.752^{*}$
Group 3 Omega-7 at dose 300 mg/kg/day	$0.337\pm0.026^{\#}$	$57.21\pm4.987^{\#}$
Group 4 Omega-7 at dose 100 mg/kg +Paracetamol (500 mg/kg/day)	$0.486\pm0.052^{\#a}$	$38.25\pm8.156^{\#b}$
Group 5 Omega -7 at dose 300 mg/kg +Paracetamol (500 mg/kg/day)	$0.466\pm0.122^{\#a}$	$48.25\pm6.109^{\#b}$

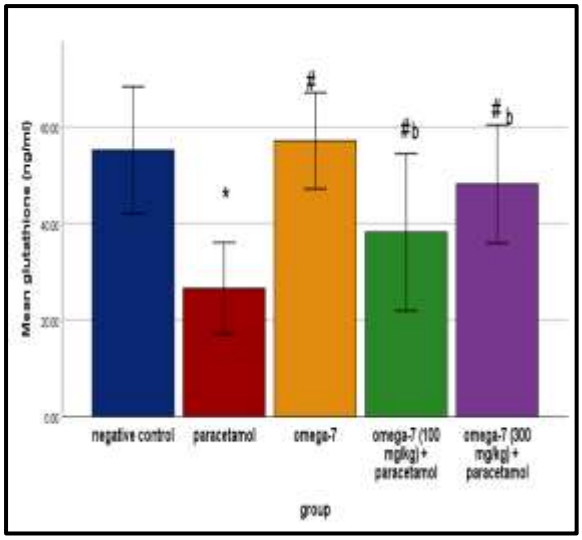

Figure 4. Effect of omega-7 on Malondialdehyde level.

The data are expressed as mean± standard deviation, number of rats in each group =6

(*) indicate significant differences when group2 and 3 are compared to the negative control group ($p<0.05$). (#) indicate significant differences when group 3,4 and 5 are compared to the Paracetamol group ($p<0.05$).

(a) indicate no significant difference between group 4 and 5 ($p>0.05$).

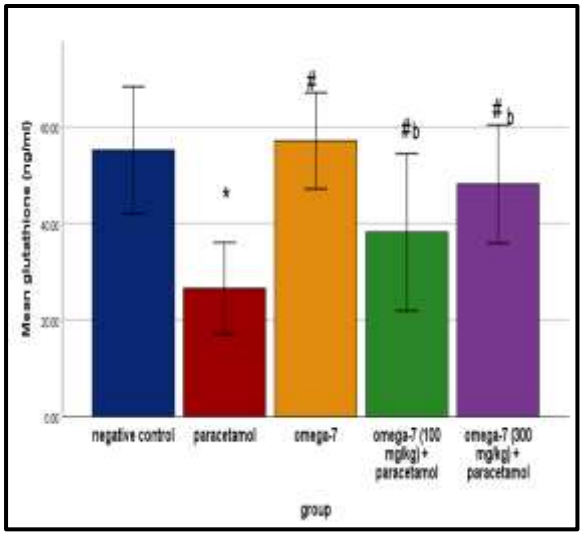

Figure 5. Effect of omega-7 on Glutathione level.

The data are expressed as mean± standard deviation, number of rats in each group =6

(*) indicate significant differences when group2 and 3 are compared to the negative control group ($p<0.05$).

(#) indicate significant differences when group 3,4 and 5 are compared to the Paracetamol group ($p<0.05$).

(b) indicate significant difference between group 4 and group 5 ($p<0.05$).

Discussion

Among the most common poisoning throughout the world is due to paracetamol toxicity. Globally it is the second leading cause of liver transplantation; moreover, paracetamol toxicity is accountable for 56000 visits to the emergency department, hospitalization of 2600 and deaths of 500 person yearly in the United States [25].

Paracetamol-induced hepatotoxicity has been proposed to be related to oxidative stress, where the excessive generation of NAPQI resulted in a lower glutathione concentration in the liver, leading to glutathione depletion and consequently antioxidant enzymes inactivation, mitochondrial malfunction, and apoptosis, which all contribute to cell death [26,27]. Additionally, during oxidative stress, lipids in the cell membranes are peroxidized, resulting in membrane disruption. Peroxidation of lipids produces reactive lipid aldehydes, such as malondialdehyde [28].

This study clarified a significant reduction in the hepatic level of SOD, CAT and GP-X in paracetamol treated group compared to the negative control group "Table 1" and "Figures 1,2 and 3" and these results were consistent with previous studies [29-34]; since, excessive reactive oxygen species that were generated upon exposure to paracetamol result in significant reduction in hepatic level of these antioxidant enzymes, as a result of ROS detoxification. SOD, CAT and GP-X are important antioxidant enzymes, SOD promote transformation of superoxide anion free radical(O2-) into molecular oxygen(O2) and hydrogen peroxide (H2O2) [35], subsequently, CAT enzyme decomposes hydrogen peroxide (H2O2) into water and oxygen [36]; furthermore, the GP-X enzyme has a crucial role in regulating redox-state balance during oxidative stress, thus protecting proteins and lipids from oxidative stress [37].

In addition, this study illustrated a significant elevation in hepatic level of MDA and significant reduction in hepatic GSH among paracetamol treated rats when compared to the negative control group "Table 2" and "Figures 4 and 5",these results are in consistence with previous studies demonstrated that excessive free radical generation in paracetamol overdose leads to glutathione depletion in conjugation reactions with metabolites and lipid peroxidation [38-40] .MDA is the result of lipid peroxidation that can cause a serious cellular membrane damage and potentially lead to cell death [41] . Additionally, hepatic glutathione is the master antioxidant regulator that maintains the redox environment of the liver [42], it protects cells from toxicity, and glutathione depletion increases susceptibility to oxidative stress and liver disease [43].

Importantly, the current study demonstrated that omega-7 has a protective effect against liver damage caused by paracetamol which evidenced by significant increase in the hepatic level of SOD, CAT and GSH with significant reduction in hepatic MDA level in omega-7 pretreated groups, reflecting a restoration of the cellular redox of the liver "Tables 1 and 2" and "Figures 1,2,4 and 5".

These results are consistent with previous research on the antioxidant effects of monounsaturated fatty acids (MUFAs) demonstrated that oleic acid-rich diets were less susceptible to oxidative damage [44]. Besides, the MUFAs significantly reduced almost all of the cellular insults that caused by saturated fatty acids, including oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation in both human and rat hepatocytes [45]. In addition, it was found that diets rich with MUFAs protected against paracetamol hepatotoxicity by affecting the composition of membrane phospholipid, thereby reducing susceptibility to free radical's damage [46]. Furthermore, it was found that human keratinocyte cells that were treated with omega-7 prior to being exposed to hydrogen peroxide showed a significant decrease in the generation of reactive oxygen species as well as a significant increase in the level of SOD and GSH when compared with cells that were exposed to hydrogen peroxide alone [47]. Also, an earlier study illustrated that, in omega-7 treated rats, there was a significant reduction in MDA level and a significant elevation in total antioxidant capacity value in cardiomyocytes, in comparison to such levels in saturated fatty acids treated cells [48].

In the present study, the pretreatment of rats with different doses of omega-7 resulted in significant decrease in MDA level, enhanced SOD and CAT level and an improvement in glutathione level in hepatic tissue of rats "Tables 1 and 2 and "Figures 1,2,4 and 5.

Conclusion

In this study, new therapeutic strategies are proposed to alleviate liver damage caused by paracetamol. Our findings show that omega-7 can protect against paracetamol-induced hepatotoxicity by increasing antioxidant enzymes [superoxide dismutase (SOD) and catalase (CAT)] and glutathione levels and decreasing malondialdehyde production. As a result, omega-7 supplementation may be a promising therapy for paracetamol-induced hepatotoxicity, with positive effects on oxidative stress.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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Ethics Statements

This study was approved by the scientific and ethical committees of the College of Pharmacy University of Baghdad.

Author Contribution

Hadeel Ali Hameed; 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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