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THERAPEUTIC POTENTIAL OF OMEGA-7 FATTY ACIDS IN MITIGATING DOXORUBICIN-INDUCED HEPATOTOXICITY IN ALBINO RATS

Hasan M. Hasan, Zeina A. Al-Thanoon, Marwan M. Merkhan
University of Mosul, College of Pharmacy, Department of Pharmacology and Toxicology, Mosul, Iraq

TERAPIJSKI POTENCIJAL OMEGA-7 MASNIH KISELINA U UBLAŽAVANJU HEPATOTOKSIČNOSTI IZAZVANE DOKSORUBICINOM KOD ALBINO PACOVA

Hasan M. Hasan, Zeina A. Al-Thanoon, Marwan M. Merkhan
Univerzitet u Mosulu, Farmaceutski fakultet, Katedra za farmakologiju i toksikologiju, Mosul, Irak

ABSTRACT

Objective. Omega-7 fatty acids have offered promising hepatoprotective properties in various experimental models. This study aimed to investigate the prophylactic potential of omega-7 supplementation against doxorubicin (Dox)-induced hepatic injury in albino rats.

Methods. A total of 42 rats were divided into 6 groups (7 animals each), namely control, Dox (15mg/kg, single IP dose at day 7), glycerin group, omega-7 (100mg/kg/day), omega-7 (100mg/kg/day, oral gavage) plus Dox, and omega-3 (100mg/kg/day) plus Dox. The groups were treated for 14 days with either normal saline alone, glycerin alone, omega-7 or omega-3 with intervention by Dox single dose at day-7 for omega groups only. Hepatic injury was assessed via biochemical parameters, including liver parameters, oxidative stress markers, inflammatory cytokines, and histopathological examination of liver tissues.

Results. Omega-7 pretreatment resulted in a significant reduction of mean serum hepatic enzymes (ALT: vs. Dox alone, p<0.0001; ALP: vs. Dox alone, p<0.0001; AST: vs. Dox alone, p<0.001). Omega-7 modulated oxidative stress status, indicated by reduced mean MDA (P<0.001) compared to Dox alone and increased TAS (vs. Dox alone, p<0.0001). The elevated proinflammatory markers (TNFα and IL-1β) induced by Dox were significantly (p<0.0001) mitigated by omega-7. Histological analysis revealed severe hepatocellular degeneration, necrosis, and inflammatory infiltration. Histopathological examination showed preservation of hepatic architecture with minimal inflammatory changes in the omega-7 pre-treated group.

Conclusion. Omega-7 offered prophylactic anti-inflammatory benefit against Dox-induced hepatic injury, confirmed by histological and biochemical findings.

Key words: *doxorubicin; fatty acids, monounsaturated; fatty acids, omega-3; chemical and drug induced liver injury; oxidative stress; inflammation.*

SAŽETAK

Cilj. Omega-7 masne kiseline pokazale su obećavajuća hepatoprotektivna svojstva u različitim eksperimentalnim modelima. Ova studija je imala za cilj da istraži profilaktički potencijal suplementacije omega-7 protiv hepatotoksičnosti izazvane doksorubicinom (Dox) kod albino pacova.

Metode. Ukupno 42 pacova podeljena su u šest grupa (po sedam životinja): kontrolna, Dox (15 mg/kg, jedna intraperitonealna doza 7. dana), glicerinska grupa, omega-7 (100 mg/kg/dnevno), omega-7 (100 mg/kg/dnevno, oralno) plus Dox, i omega-3 (100 mg/kg/dnevno) plus Dox. Grupe su tretirane 14 dana ili samo fiziološkim rastvorom, samo glicerolom, omega-7 ili omega-3, uz intervenciju jednom dozom Doxa 7. dana samo za grupe sa omegama. Oštećenje jetre procenjeno je pomoću biohemijskih parametara, uključujući parametre jetre, markere oksidativnog stresa, inflamatorne citokine i histopatološki pregled tkiva jetre.

Rezultati. Predtretman sa omega-7 doveo je do značajnog smanjenja srednjih vrednosti serumskih jetrenih enzima (ALT: u odnosu na samo Dox, p < 0,0001; ALP: u odnosu na samo Dox, p < 0,0001; AST: u odnosu na samo Dox, p < 0,001). Omega-7 je modulirao status oksidativnog stresa, što je pokazano smanjenom srednjom vrednošću MDA (p < 0,001) u poređenju sa samo Dox i povećanjem TAS (u odnosu na samo Dox, p < 0,0001). Povišeni proinflamatorni markeri (TNF-α i IL-1β) izazvani Doxom bili su značajno (p < 0,0001) ublaženi primenom omega-7. Histološka analiza je pokazala tešku hepatocelularnu degeneraciju, nekrozu i inflamatornu infiltraciju. Histopatološki pregled je pokazao očuvanje arhitekture jetre sa minimalnim inflamatornim promenama u grupi predtretiranoj omega-7.

Zaključak. Omega-7 je pružila profilaktičku antiinflamatornu korist protiv Doxom izazvanog oštećenja jetre, što je potvrđeno histološkim i biohemijskim nalazima.

Ključne reči: *doksorubicin; masne kiseline, mononezasićene; omega-3 masne kiseline; oštećenje jetre izazvano hemikalijama i lekovima; oksidativni stres; inflamacija.*

INTRODUCTION

Doxorubicin (Dox)-induced hepatotoxicity (DIH) represents a significant but often under-recognised complication of cancer chemotherapy, manifesting through a complex cascade of molecular and cellular disruptions that compromise liver function (1). The pathogenesis of cardiotoxicity and hepatotoxicity linked to oxidative stress, alterations in cellular metabolism, and bioenergetics serves as a fundamental mechanism driving these toxic effects (2). Liver damage initiates at the molecular level when Dox and its derivatives undergo hepatic metabolism through microsomal enzymes, potentially generating toxic or immunogenic intermediate compounds that can trigger hepatic injury (3). The molecular mechanism underlying hepatotoxicity primarily

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Marwan M. Merkhan,
University of Mosul,
Al-Majmoaa Al-Thaqafia, 41002 Mosul, Iraq,
Phone: +964 7508662343,
E-mail: marwanmerkhan@uomosul.edu.iq

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involves reactive oxygen species (ROS) generation, increased oxidative stress and inflammation, impaired mitochondrial production and function, and elevated apoptosis (1). Morphologically, Dox-treated liver tissue exhibits hepatocyte vacuolation, hepatocyte cord degeneration, bile duct hyperplasia, and focal necrosis, while hepatotoxicity can produce necrosis, fatty infiltration, fibrosis, cholestasis, and vascular damage (4). The metabolic impacts are similarly significant, with metabolomic analyses showing elevated levels of most acyl-carnitine species, high-energy phosphates, citrate, and oxidative stress markers. These changes indicate early steatohepatitis development with excessive and dysregulated fatty acid uptake and oxidation, disrupting amino acid metabolism, lipid pathways, purine metabolism, and energy production (5). Clinically, patients with cholestasis experience delayed drug clearance and increased systemic toxicity because roughly 80% of Dox is eliminated through bile. Fortunately, DIH is typically mild and resolves on its own, making hepatotoxicity a significant yet manageable factor when balancing cancer treatment effectiveness against organ protection (6).

Given Dox's essential role in cancer therapy alongside its severe adverse effects, developing strategies to improve its safety profile represents a critical medical priority. Laboratory studies with mice and rats have shown that natural dietary supplements – including minerals, vitamins, and healthy fats – may help reduce or prevent these harmful side effects (7). Omega-3 fatty acids are a type of healthy fat with a specific chemical structure – they have a double bond located between the third and fourth carbon atoms when counted from one end of the molecule. The three main omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (8). ALA is primarily found in nuts, seeds, and plant oils, while EPA and DHA come from eating fatty fish. These healthy fats become part of cell walls, helping cells stay flexible and supporting important functions like controlling inflammation and cell communication (9).

Giving omega-3 supplements has been proven to reduce inflammation caused by Dox in heart tissue by lowering the levels of harmful inflammatory substances that the drug normally triggers (10). In animal studies, giving omega-3 supplements (400 mg per kg of body weight) for 28 days before a single Dox dose (30 mg per kg) helped reduce cell damage, boost protective antioxidant enzymes, and improve tissue damage in the liver, kidneys, and reproductive organs caused by Dox (11). This tissue protection and stimulation of development and tissue regeneration capacity have also been reported in a previous study investigating the role of omega-7 in skeletal muscle cell differentiation (12, 13). However, most Dox treatments in humans involve multiple-dose protocols because previous studies using single doses typically fail to provide a mechanistic understanding of how omega-3 fatty acids protect liver and kidney tissues. This study was designed to determine the hepatoprotective role of omega-7 against Dox-induced liver injury.

MATERIALS AND METHODS

Study setting

Approval was obtained from the Institutional Animal Care and Use Committee (College of Veterinary Medicine). Ref: UM.VET.2024.131 on 02/12/2024. The current study was conducted over a period of 29/10/2024 to 28/02/2025. All experimental procedures used and the animal sacrifice were performed in accordance with applicable EU directives - European Directive for the welfare of laboratory animals No 86/609/EEC and the principles of Good Laboratory Practice.

Animals and housing

A group of 42 male albino Wistar rats, each approximately ten weeks old and weighing around 200 grams on average, were obtained from the animal facility at the College of Veterinary Medicine, University of Mosul (Iraq), for the use in this study. These animals were kept in metal cages and given a two-week adjustment period under controlled conditions, including 12-hour light/dark cycles, temperature maintained at 25°C (plus or minus 2°C), and humidity levels between 45-50%. Throughout this period, the rats had unrestricted access to standard food and water. All animals underwent a one-month acclimatisation process prior to being used in the experimental procedures.

Experimental design

The 42 rats were subdivided into 6 groups, which include (Figure 1):

- C = Control group (7rats): received distilled water orally for 7 days and an IP normal saline dose at day 7.
- D = Dox group (7 rats): received distilled water orally for 14 days and a single IP Dox dose (15mg/kg) at day 7(12).
- G = Glycerin group (7 rats) received glycerin orally for 14 days at a dose of 100mg/kg/day.
- O7 = Omega-7 group (7 rats) received omega-7 orally for 14 days at a dose of 100mg/kg/day (12).
- O7+D = Omega-7+Dox group (7 rats): received omega-7 orally for 14 days at a dose of 100mg/kg/day and a single IP Dox dose (15mg/kg) at day 7 (12).

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- O3+D = Omega-3+Dox group (7 rats): received omega-3 orally for 14 days at a dose of 100mg/kg/day and a single IP Dox dose (15mg/kg) at day 7.

The sampling for all groups was conducted at day 0, day 10, and day 14. The day 14 sampling was done only for O7+D and O3+D groups, including blood collection and tissue harvesting after the animal was sacrificed (Figure 1).

Drug used and reconstitution

Drugs have been freshly prepared in the laboratory and given to animals orally by gavage needle. Doxorubicin vial (Doxo-cell 50 mg, STADAPHARM GmbH (Germany)) was diluted for administration using normal saline. Omega-7 softgel capsule (Provinal 420mg, Life Extension (USA)) and omega-3 softgel capsule (Fish Oil Omega-3 1000mg, Green Field (USA)) were diluted in glycerin (Scharlab S.L. (Spain)) for administration. The volumes of reconstituted drug administered were titrated for the weight of each rat upon administration.

Blood sampling

Blood samples were taken from the retro-orbital venous plexus using capillary test tubes and centrifuged at 3000 rpm for 15 minutes to analyse many biological markers. Serum was isolated and kept in a deep freeze at -20 °C until used. Approximately 5 ml of venous blood was collected in the morning from the orbital vein of rats at day 0, day 10, and day 14. Blood samples from the control group were obtained and processed using identical procedures.

Euthanasia and tissue harvesting

At the completion of the experiment, the animals were euthanised by cervical dislocation. The animals were anaesthetised with 10 mg/kg of ketamine hydrochloride (Ketalrom, Romvac company, Romania) and 3 mg/kg of xylazine hydrochloride (XylaR, Intercheime, Holland). In the laboratory setting, livers were removed from the rat carcasses and cut open along the major curve, then washed with distilled water. The liver tissues were first rinsed with normal saline solution and subsequently preserved in 10% formalin fixative. The animal health was monitored before each daily dosing, and none of the animals died during the period of the study.

Histological analysis

The process involved two sequential steps: initially, the liver tissue was extracted from the animal corpse, followed by immersion in a 10% formalin fixative to preserve and prevent decomposition of the tissues. Followed by washing, dehydration, clearing, embedding in liquid paraffin, microtome sectioning, and staining with eosin and hematoxylin. A light microscope supplied with a camera is used to capture images.

Severity grading: The pathologist assessed the severity of the lesion based on morphological features (14, 15):

- Normal/Negative: No significant pathological changes detected.
- Mild: Minimal, focal (limited to a small area), tissue architecture is intact.
- Moderate: Changes are more widespread (multifocal to diffuse) and pronounced. There is a clear disruption of normal tissue structure.
- Severe: Extensive, marked, and often diffuse changes. There may be severe architectural distortion, necrosis (cell death), or other end-stage features.

Biochemical tests

ELISA technique: A Microplate reader (BioTek 800 TS, Agilent, USA) was used, and all samples were measured based on the ELISA assay, TNFα (Cat: ELK1396), IL-1β (Cat: ELK1272), AST (Cat: ELK5635), ALT (Cat: ELK2683), and ALP (Cat: ELK5657) kits. The ELK Biotechnology Rat ELISA Kit (China) procedure follows a systematic sandwich enzyme immunoassay protocol designed to quantitatively measure these markers in various biological samples.

The initial preparation phase involves reconstituting the lyophilised standard with 1.0 mL of standard diluent buffer to create a stock solution of 1000 pg/mL for each measured parameter. This stock is then serially diluted across seven tubes to create a standard curve ranging from 1000 pg/mL down to 15.63 pg/mL, with an eighth tube serving as a blank (0 pg/mL). The wash buffer concentrate is diluted 25-fold with double-distilled water, and both the biotinylated antibody and streptavidin-HRP are diluted 100-fold with their respective diluent buffers to create working solutions.

The assay procedure commences by adding 100 µL of each standard working solution or sample to the appropriate wells of the pre-coated microplate with a specific capture antibody for measured parameters, which has been coated with antibodies specific to rat for each parameter. The plate is covered and incubated at 37°C for 80 minutes, allowing the target antigen to bind to the capture antibodies. Following this initial incubation, the liquid is discarded from each well, and the plate undergoes the first washing cycle using 200 µL of 1× wash buffer per well, repeated three times with complete liquid removal between washes by patting the plate dry on absorbent paper.

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The second phase involves adding 100 µL of biotinylated antibody working solution to each well, covering the plate, and incubating for 50 minutes at 37°C. This biotinylated detection antibody binds to a different epitope on the captured parameters, forming a sandwich complex. After this incubation, the plate is washed three times using the same washing procedure as before to remove unbound antibodies.

The third incubation step introduces 100 µL of streptavidin-HRP working solution to each well, followed by a 50-minute incubation at 37°C under plate cover. The streptavidin conjugated to horseradish peroxidase binds to the biotin on the detection antibody, completing the enzyme-linked detection system. This step is followed by a more thorough washing cycle, repeated five times to ensure complete removal of unbound enzyme conjugate.

The colour development phase begins with the addition of 90 µL of TMB substrate solution to each well, followed by incubation at 37°C for 20 minutes in the dark. During this critical step, wells containing the complete antigen-antibody-enzyme complex develop a blue colour as the TMB substrate is converted by the horseradish peroxidase enzyme. The reaction is carefully monitored to ensure it does not exceed 30 minutes, as over-development can compromise results.

The final step involves stopping the enzymatic reaction by adding 50 µL of stop reagent to each well, which changes the blue colour into yellow and stabilizes it for measurement. The plate is gently shaken for one minute to ensure thorough mixing, and any water droplets or fingerprints are carefully removed from the bottom of the plate before optical density measurement.

Colorimetric assays

Malondialdehyde (MDA) Colorimetric Assay: The assay procedure commenced with the preparation of plasma samples, which were processed directly without dilution. The analytical protocol involved the systematic addition of clarifying solution to precipitate interfering proteins, followed by the incorporation of an acid reagent application solution to establish the optimal pH conditions for the malondialdehyde-thiobarbituric acid reaction. The chromogenic application solution, containing thiobarbituric acid dissolved in hot distilled water and glacial acetic acid, was then introduced to initiate the colour development reaction. The reaction mixture was subjected to thermal treatment at 95-100°C for 40 minutes under controlled conditions, with tube mouths sealed with perforated plastic film to prevent evaporation while allowing pressure equilibration.

Following the incubation period, the samples were rapidly cooled to room temperature and centrifuged at 3100×g for 10 minutes to separate the coloured supernatant from any precipitated matter. The optical density of the resulting supernatant was measured spectrophotometrically at 532 nm using a 1-cm path length cuvette, with double-distilled water serving as the blank reference. The quantification of MDA concentration was achieved through comparison with a standard curve generated using a 10 nmol/mL MDA standard solution processed under identical conditions.

Total Antioxidant Capacity (T-AOC) Colorimetric Assay: The assay protocol was initiated by combining plasma samples with a buffer solution to maintain optimal pH conditions throughout the reaction process. The chromogenic working solution, prepared by dissolving the chromogenic agent in double-distilled water at elevated temperature (80-90°C), was added to provide the phenanthroline complexing agent. Subsequently, the ferric salt working solution, freshly prepared by diluting the ferric salt stock solution with the appropriate diluent, was introduced to supply the Fe^{3}□ substrate for the reduction reaction. The reaction mixture was incubated at 37°C for 30 minutes to allow complete reduction of ferric ions by the antioxidant species present in the sample and subsequent complex formation with the chromogenic agent.

The reaction was terminated by the addition of the stop solution, which halts further ferric ion reduction and stabilizes the coloured complex. Control tubes were processed simultaneously using identical conditions except for the delayed addition of the sample after the stop solution, thereby accounting for any non-specific colour development or interference. The absorbance of both sample and control tubes was measured at 520 nm using a spectrophotometer with a 1-cm quartz cuvette, with double-distilled water serving as the reference blank.

Statistical analysis

The data are presented as means ± standard errors. A GraphPad Prism application (V9, USA) was used for statistical analysis. One-way analysis of variance (ANOVA), followed by Tukey multiple comparison tests, was used. To compare data between different groups, two-way Analysis of Variance (ANOVA) with Tukey's multiple comparison tests as a post-hoc analysis was used. Paired t-test was used for comparison of before and after the intervention. A sample t-test was used to compare two groups with different interventions. When the P value $\leq$ 0.05, the difference is considered significant.

RESULTS

Omega-7 protected the liver histologically against Dox

The control group displays normal liver histoarchitecture with well-organised hepatic cords radiating from the central vein. The hepatocytes appear

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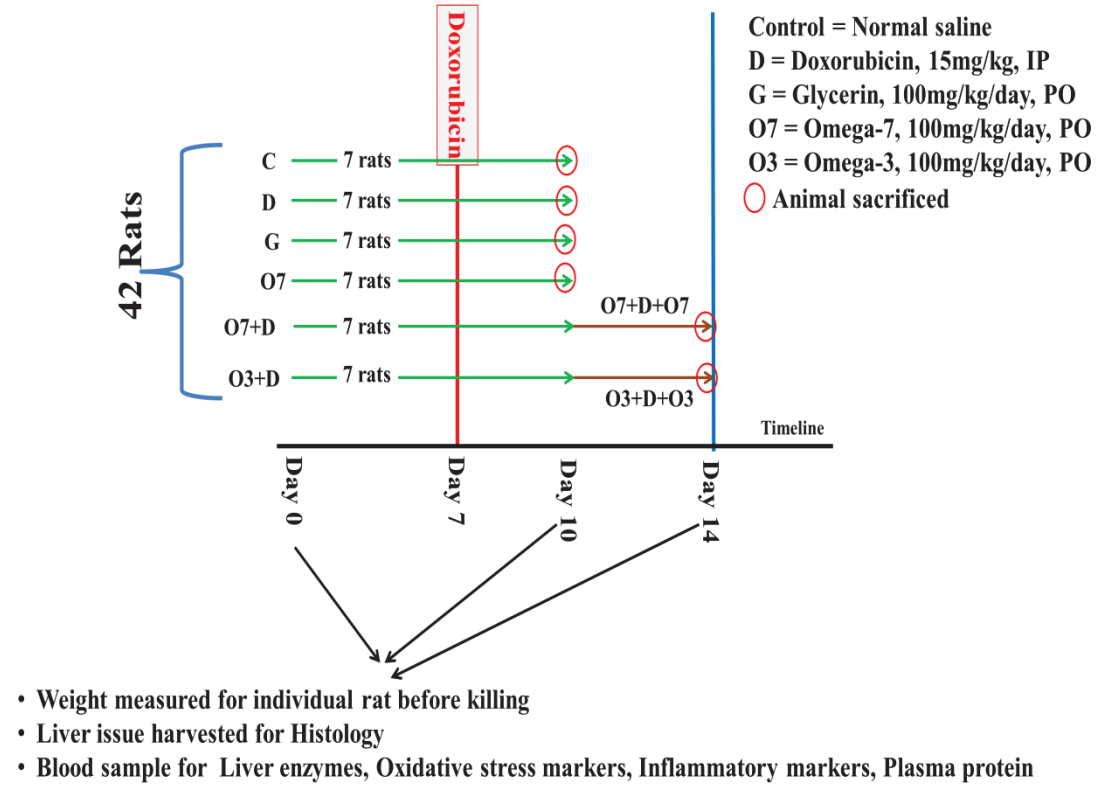

Figure 1. The study design workflow. Dox=doxorubicin, O7=omega 7, O3=omega 3, PO=oral, IP=intraperitoneal.

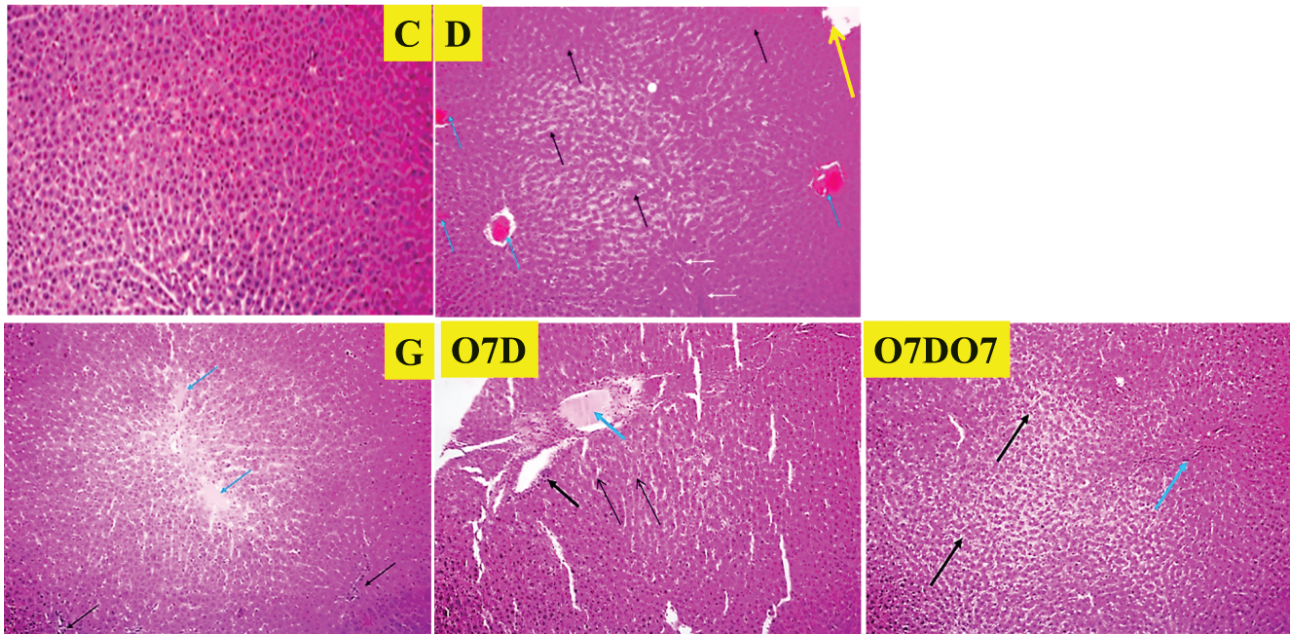

Figure 2. Histological section of the rat's liver tissue at the end of the experiment. (C) The control group showed intact architectures of liver tissues with normal immune cell distribution. (D) The doxorubicin group shows hepatic cell swelling (black arrow), congested hepatic blood vessels and central veins (blue arrow), with endothelial necrosis (yellow arrows), and mild periportal infiltration of inflammatory cells. (G) The glycerin group revealed clear hepatic cord orientations and a normal presence of inflammatory cells (black arrows), normal area of white pulp (blue arrows). (O7D) The Omega-7 and Doxorubicin group demonstrates mild periportal infiltration of inflammatory cells (black arrows), recent thrombi formation (blue arrows), and hepatic tissue architectures slightly upset. (O7DO7) The Omega-7 and Doxorubicin group demonstrates nearly normal tissue architecture with a pseudo-lobular structure, consisting of a mixture of cellular nodules (black arrow), with mild periportal infiltrations of inflammatory cells (blue arrows). H&E stain, scale-bar=100μm.

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healthy with normal morphology, and there is an appropriate distribution of immune cells throughout the tissue. The sinusoidal spaces are clearly visible and patent (Figure 2).

Dox group showed significant pathological alterations, including hepatocyte swelling (black arrows), indicating cellular damage and metabolic stress, congested hepatic blood vessels and central veins, suggesting impaired circulation, endothelial necrosis, demonstrating vascular damage, and mild periportal inflammatory cell infiltration, indicating an inflammatory response.

Glycerin group: Exhibited relatively preserved liver structure with clear hepatic cord orientations maintained, with normal presence of inflammatory cells, areas of white pulp visible, and overall architecture appears closer to normal compared to the Dox group.

Omega-7 + Dox group demonstrated intermediate pathological changes, mild periportal infiltration of inflammatory cells. Recent thrombi formation, indicating localised blood clotting. Slightly disrupted hepatic tissue architecture, though less severe than the Dox-only group. The tissue showed some protective effects compared to Dox alone. The scale bar indicates 100 micrometres of magnification.

Omega-7 + Dox + omega-7 treatment group: displayed improved tissue preservation with nearly normal tissue architecture restored, Pseudo-lobular structure formation with cellular nodules, suggesting tissue regeneration or reorganisation, and mild periportal infiltration of inflammatory cells.

Omega-7 mitigated liver enzymes against Dox

The baseline ALT measurements demonstrated approximately similar levels over groups, with the control group ranging from 33.6 to 39.8 U/L. Marked changes occurred in serum ALT levels across the groups after intervention. The Dox-alone group experienced a substantial increase from 39.2±6.9 to 122.4±22 U/L (p=0.0001), reflecting the hepatotoxic effects of Dox. The glycerin and omega-7 alone groups demonstrated no significant changes, with values remaining at 38.9±6.8 U/L (p=0.41) and 34±6.4 U/L (p=0.12), respectively (Table 1).

The prophylactic administration of both omega fatty acids demonstrated significant protective effects against DIH. The omega-7 prophylaxis group maintained ALT levels at 68.3±8.4 U/L (p=0.0001), representing a moderate elevation compared to the increase seen in the Dox-only group (122.4±22 U/L). Similarly, the omega-3 prophylaxis group showed ALT levels of 117.8±16.9 U/L (p=0.0001), indicating hepatoprotective activity, though the protection appeared less pronounced than that observed with omega-7 (Table 1).

The omega-7 treatment group showed ALT levels of 58.4±7.9 U/L (p=0.021), representing a significant reduction compared to the prophylaxis group and suggesting effective hepatic recovery. The omega-3 treatment group demonstrated ALT levels of 75.4±6.7 U/L (p=0.0001), also indicating therapeutic benefit compared to the prophylaxis group; however, the final levels were higher than those achieved with omega-7 treatment (p=0.0001) for both prophylaxis and treatment groups (Table 1).

In the control baseline, all groups demonstrated relatively similar ALP levels ranging from 43.3 to 56.4 U/L across groups. The Dox-only group demonstrated a substantial elevation to 310±28 U/L, with a highly significant p-value of 0.0001. The control group remained stable at 51.6±14 U/L with no significant change (p=0.27), while the glycerin group showed a modest increase to 64.1±14 U/L (p=0.017). The omega-7 alone group maintained relatively stable levels at 59.6±14 U/L (p=0.29), indicating minimal hepatotoxic effects from the fatty acid itself. The prophylaxis groups demonstrated varying degrees of protection against Dox-induced ALP elevation. The omega-7 prophylaxis group showed ALP levels of 55±15 U/L with a borderline significant p-value of 0.057, suggesting modest but not statistically significant protection. In contrast, the omega-3 prophylaxis group exhibited markedly elevated levels at 115.8±15 U/L with high statistical significance (p=0.0001), indicating that omega-3 alone provided insufficient protection and may have contributed to hepatic stress. The combined prophylaxis and treatment approach showed different outcomes, with omega-7 demonstrating excellent protection at 52.2±14 U/L (p=0.36, non-significant change compared to the prophylaxis only group), while omega-3 continued to show elevated levels at 69.2±13 U/L with high significance (p=0.0001) (Table 1).

In the prophylaxis group, where protective interventions were administered before Dox exposure, omega-7 demonstrated superior hepatoprotection with ALP levels of 55±15 U/L compared to omega-3, which showed substantially elevated levels at 115.8±15 U/L. This marked difference between the two fatty acids yielded a highly significant p-value of 0.0001 (Table 1).

The combined prophylaxis and treatment group, which received interventions both before and during Dox administration, showed improved outcomes for both fatty acid types compared to prophylaxis alone, though omega-7 maintained its protective advantage. Omega-7 demonstrated excellent hepatoprotection with ALP levels of 52.2±14 U/L, while omega-3 showed considerable improvement to 69.2±13 U/L. The statistical comparison between these two fatty acids in the combined approach yielded a significant p-value of 0.036, confirming that

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Table 1. Serum liver enzyme changes of rats exposed to different interventional agents.

Studied groups	ALT (U/l)			ALP (U/l)			AST (U/l)		
	Before	After	p	Before	After	p	Before	After	p
C	39±4.6	38.2±5.8	0.39	56.4±15	51.6±14	0.27	103.9±16	110.4±10	0.19
Dox	39.2±6.9	122.4±22	<0.01	46.6±12	310±28	<0.01	111±11	213.8±22	<0.01
Gly	39.8±8.2	38.9±6.8	0.41	46.7±13	64.1±14	0.017	94.2±12	113.1±14	<0.01
O7	38.4±6.9	34±6.4	0.12	55.6±12	59.6±14	0.29	95.7±15	98.8±7	0.31
O7+Dox	33.6±6.1	68.3±8.4	<0.01	43.3±10.3	55±15	0.06	111.1±9	86.4±11	<0.01
O3+Dox	36.9±5.9	117.8±16.9	<0.01	56±13.7	115.8±15	<0.01	116.5±18	161.7±14	<0.01
O7+ Dox+O7	68.3±8.4	58.4±7.9	0.02	55±15	52.2±14	0.36	86.4±11	89.3±12	0.32
O3+Dox+O3	117.8±16.9	75.4±6.7	<0.01	115.8±15	69.2±13	<0.01	161.7±14	87.9±13	<0.01
P value	<0.001	<0.001		<0.001	0.036		<0.001	0.840	

data expressed as mean±SD for each group. A value less than 0.05 is considered significant using t-tests to find the different groups. C=control group, D=doxorubicin group, G=glycerin group, O7=omega-7 group, O7+D=prophylaxis (omega-7+doxorubicin) group, O3+D=prophylaxis (omega-3+doxorubicin) group, O7+Dox+O7= treatment group (omega-7+doxorubicin+omega-7), O3+Dox+O3= treatment group (omega-3+doxorubicin+omega-3)

Table 2. Serum changes in oxidative stress markers of rats exposed to different interventional agents.

Studied groups	TAS (U/l)			MDA (nmol/ml)		
	Before	After	p value	Before	After	p value
C	16.7±2.7	16.9±2	0.4400	20.4±2.3	20.1±2.7	0.4133
Dox	17.2±2.1	3.6±1.2	0.0001	19.6±2.1	52.8±4.8	0.0001
Gly	17.1±2.5	15.9±1.9	0.1660	21.1±1.9	27.3±2.9	0.0002
O7	17.1±1.8	21.5±2.9	0.0026	19.7±1.9	20.5±2.5	0.2565
O7+Dox	16.8±1.9	15.9±2.1	0.2084	21.6±2.7	46.3±5.1	0.0001
O3+Dox	16.9±1.9	18.2±2.5	0.1474	21.3±2.1	40.8±3.9	0.0001
O7+ Dox+O7	15.9±2.1	15.5±2.1	0.3639	46.3±5.1	27.6±2.5	0.0001
O3+Dox+O3	18.2±2.5	16.1±2.8	0.0823	40.8±3.9	26.9±2.5	0.0001
P value	0.087	0.658		0.043	0.610	

data expressed as mean±SD for each group. A p-value less than 0.05 is considered significant using t-tests to find the different groups. C=control group, D=doxorubicin group, G=glycerin group, O7=omega-7 group, O7+D=prophylaxis (omega-7+doxorubicin) group, O3+D=prophylaxis (omega-3+doxorubicin) group, O7+ Dox+ O7= treatment group (omega-7+doxorubicin+omega-7), O3+ Dox+ O3= treatment group (omega-3+doxorubicin+omega-3).

Table 3. Serum IL1B and TNFα changes of rats exposed to different interventional agents.

Studied groups	IL1B (nmol/ml)			TNFα (nmol/ml)		
	Before	After	p value	Before	After	p
C	68±7	74±5	0.045	15.6±1.2	16.5±2	0.1637
Dox	70±5	133±11	0.0001	16.2±1.8	27.9±2.3	0.0001
Gly	72±8	73±7	0.400	17.1±1.7	17.5±1.3	0.3149
O7	65±6	69±5	0.100	17.0±1.8	17.2±1.6	0.4149
O7+Dox	66±5	81±8	0.0006	16.9±1.5	22.7±1.9	0.0001
O3+Dox	65±6	78±7	0.0014	15.6±1.5	20.9±1.9	0.0001
O7+ Dox+O7	81±8	71±7	0.0142	22.7±1.9	22.6±1.5	0.4574
O3+Dox+O3	78±7	68±5	0.0048	20.9±1.9	20.8±1.8	0.4606
P value	0.470	0.380		0.102	0.065	

data expressed as mean±SD for each group. A p-value less than 0.05 is considered significant using t-tests to find the different groups. C=control group, D=doxorubicin group, G=glycerin group, O7=omega-7 group, O7+D=prophylaxis (omega-7+doxorubicin) group, O3+D=prophylaxis (omega-3+doxorubicin) group, O7+ Dox+ O7= treatment group (omega-7+doxorubicin+omega-7), O3+ Dox+ O3= treatment group (omega-3+doxorubicin+omega-3)

omega-7 continues to outperform omega-3, though the difference is less pronounced than in the prophylaxis-only group.

At baseline, all groups revealed relatively comparable AST levels ranging from 94.2 to 116.5U/L across the different experimental groups. Following the interventions, significant changes occurred in serum AST levels across the different treatment groups, reflecting the hepatotoxic effects of Dox and the varying protective capacities of the different fatty acid interventions. The

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Dox-only group experienced severe hepatotoxicity with AST levels rising dramatically to 213.8±22 U/L, representing a highly significant change with a p-value of 0.0001. The control group remained stable at 110.4±10 U/L with no significant change (p=0.19), while the glycerin group showed a modest increase to 113.1±14 U/L (p=0.094). Notably, the omega-7 alone group demonstrated a slight increase to 98.8±7 U/L but remained non-significant (p=0.31), suggesting minimal hepatotoxic effects from the fatty acid itself.

The prophylaxis and treatment groups revealed significant differences in the hepatoprotective efficacy of omega-7 versus omega-3 fatty acids. In the prophylaxis-only groups, omega-7 showed AST levels of 86.4±11 U/L with a significant p-value of 0.0003, while omega-3 demonstrated elevated levels at 161.7±14 U/L with high significance (p=0.0001), indicating that omega-3 prophylaxis alone provided insufficient protection and may have contributed to hepatic stress. The combined prophylaxis and treatment approach showed markedly different outcomes between the two fatty acids. Omega-7 demonstrated excellent hepatoprotection with AST levels of 89.3±12 U/L and a non-significant p-value of 0.32, suggesting effective prevention of Dox-induced AST elevation. In contrast, omega-3 in the combined approach still showed concerning AST levels of 87.9±13 U/L with high significance (p=0.0001), indicating that even with dual intervention, omega-3 was associated with significant hepatic enzyme elevation.

In the prophylaxis group, where protective interventions were administered before Dox exposure, omega-7 demonstrated markedly superior hepatoprotection with AST levels of 86.4±11 U/L compared to omega-3, which showed substantially elevated levels at 161.7±14 U/L. This dramatic difference between the two fatty acids yielded a highly significant p-value of 0.0001. Omega-7 maintained consistent hepatoprotection with AST levels of 89.3±12 U/L, showing minimal change from the prophylaxis-only approach. More notably, omega-3 demonstrated dramatic improvement to 87.9±13 U/L, achieving levels nearly identical to omega-7. The statistical comparison between omega-7 and omega-3 in this combined approach yielded a non-significant p-value of 0.84.

Omega-7 reduced oxidative stress against Dox

At baseline, all experimental groups revealed relatively similar TAS levels, ranging from 16.7 to 17.2 U/L across the different cohorts. The Dox-only group, TAS levels dropping dramatically to 3.6±1.2 U/L, with a p-value of 0.0001. Interestingly, the omega-7 alone group demonstrated an increase in antioxidant capacity to 21.5±2.9 U/L with significant improvement (p=0.026), suggesting that omega-7 itself possesses inherent antioxidant properties that enhance overall antioxidant status. In the prophylaxis-only groups, omega-7 maintained TAS levels at 15.9±2.1 U/L (p=0.2084), while omega-3 showed levels of 18.2±2.5 U/L (p=0.1474), with neither showing statistically significant changes. The combined prophylaxis and treatment approach showed similar patterns, with omega-7 maintaining TAS levels at 15.5±2.1 U/L (p=0.3639) and omega-3 at 16.1±2.8 U/L (p=0.0823). The non-significant p-values across all protective intervention groups indicate that both omega-7 and omega-3 fatty acids successfully preserved antioxidant capacity and prevented the dramatic oxidative stress depletion caused by Dox alone, though omega-7 demonstrated additional antioxidant-enhancing properties when used independently of Dox exposure (Table 2).

In the prophylaxis group, where protective interventions were administered before Dox exposure, omega-7 demonstrated TAS levels of 15.9±2.1 U/L compared to omega-3, which showed slightly higher levels at 18.2±2.5 U/L. The statistical comparison between these two fatty acids in the prophylaxis group yielded a p-value of 0.087, indicating a trend toward significance but not reaching statistical significance. This suggests that while omega-3 may provide marginally better antioxidant capacity preservation when used prophylactically, the difference between the two fatty acids is not definitively established. Both fatty acids appear to maintain reasonable antioxidant status compared to what would be expected with Dox-induced oxidative stress alone.

The combined prophylaxis and treatment group, which received interventions both before and during Dox administration, showed more comparable antioxidant outcomes between the two fatty acids. Omega-7 maintained TAS levels of 15.5±2.1 U/L, while omega-3 showed levels of 16.1±2.8 U/L. The statistical comparison between omega-7 and omega-3 in this combined approach yielded a non-significant p-value of 0.658, indicating that both fatty acids achieved essentially equivalent antioxidant protective efficacy when used in the dual intervention strategy. This convergence suggests that the combined treatment approach may optimise the antioxidant protective capabilities of both fatty acids.

At baseline, the experimental groups demonstrated relatively similar MDA levels ranging from 19.6 to 21.6 nmol/ml across the groups. The Dox-only group experienced severe lipid peroxidation with MDA levels rising dramatically (p=0.0001) from 19.6±2.1 to 52.8±4.8 nmol/ml. The control group remained stable with minimal change from 20.4±2.3 to 20.1±2.7 nmol/ml (p=0.4133), while the glycerin group showed a modest but significant increase from 21.1±1.9 to 27.3±2.9 nmol/ml (p=0.002).

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Remarkably, the omega-7 alone group maintained stable MDA levels with minimal change from 19.7±1.9 to 20.5±2.5 nmol/ml (p=0.2565), demonstrating that omega-7 itself does not contribute to lipid peroxidation and may provide inherent antioxidant protection.

In the prophylaxis-only groups, both fatty acids showed significant changes from baseline, with omega-7 maintaining levels at 46.3±5.1 nmol/ml (p=0.0001) and omega-3 showing levels of 40.8±3.9 nmol/ml (p=0.0001). The combined prophylaxis and treatment approach demonstrated improved outcomes for both fatty acids, with omega-7 showing reduced MDA levels at 27.6±2.5 nmol/ml (p=0.0001) and omega-3 achieving levels of 26.9±2.5 nmol/ml (p=0.0001). In the prophylaxis group, where protective interventions were administered before Dox exposure, omega-7 demonstrated MDA levels of 46.3±5.1 nmol/ml compared to omega-3, which showed lower levels at 40.8±3.9 nmol/ml. The statistical comparison between these two fatty acids in the prophylaxis group yielded a significant p-value of 0.043, indicating that omega-3 provided statistically superior protection against lipid peroxidation when used prophylactically.

Omega-7 achieved substantially reduced MDA levels of 27.6±2.5 nmol/ml, while omega-3 showed comparable levels at 26.9±2.5 nmol/ml. The statistical comparison between omega-7 and omega-3 in this combined approach yielded a non-significant p-value of 0.61, indicating that both fatty acids achieved essentially equivalent protection against lipid peroxidation when used in the dual intervention strategy.

Omega-7 reduced inflammatory markers against Dox

At baseline, all experimental groups demonstrated relatively similar IL-1β levels ranging from 65 to 72 nmol/ml across the different cohorts. The Dox-only group experienced severe inflammatory activation with IL-1β levels rising dramatically from 70±5 to 133±11 nmol/ml, p=0.0001 (Table 3). Notably, the omega-7 alone group maintained stable IL-1β levels with minimal change from 65±6 to 69±5 nmol/ml (p=0.1). In the prophylaxis-only groups, both fatty acids showed significant inflammatory responses, with omega-7 levels increasing from 66±5 to 81±8 nmol/ml (p=0.0006) and omega-3 showing similar elevation from 65±6 to 78±7 nmol/ml (p=0.0014). While both showed significant increases from baseline, these levels remained substantially lower than the severe inflammatory response seen in the Dox-only group (133 nmol/ml). The combined prophylaxis and treatment approach demonstrated improved outcomes for both fatty acids, with omega-7 showing reduced IL-1β levels from 81±8 to 71±7 nmol/ml (p=0.0142) and omega-3 achieving levels of 68±5 nmol/ml from 78±7 nmol/ml (p=0.0048).

In the prophylaxis group, omega-7 demonstrated IL-1β levels of 81±8 nmol/ml compared to omega-3, which showed slightly lower levels at 78±7 nmol/ml. The statistical comparison between these two fatty acids in the prophylaxis group yielded a non-significant p-value of 0.47, indicating that both fatty acids achieved essentially equivalent anti-inflammatory protection when used prophylactically. The combined prophylaxis and treatment group showed improved anti-inflammatory outcomes for both fatty acids compared to prophylaxis alone. Omega-7 achieved reduced IL-1β levels of 71±7 nmol/ml, while omega-3 showed slightly lower levels at 68±5 nmol/ml. The statistical comparison between omega-7 and omega-3 in this combined approach yielded a non-significant p-value of 0.38, indicating that both fatty acids maintained essentially equivalent anti-inflammatory efficacy when used in the dual intervention strategy.

The baseline TNFα levels were relatively similar across all groups, ranging from 15.6 nmol/ml to 17.1nmol/ml. Following treatment interventions, dramatic differences emerged between the groups (Table 3). The Dox-only group showed a substantial increase in TNFα levels from 16.2 nmol/ml to 27.9 nmol/ml, representing a significant inflammatory response with a p-value of 0.0001. In contrast, the control group remained essentially unchanged (15.6 to 16.5 nmol/ml), while the glycerin and omega-7 groups showed minimal changes with non-significant p-values of 0.3149 and 0.4149, respectively.

The prophylaxis groups demonstrated interesting patterns, with both omega-7 and omega-3 prophylaxis groups (receiving fatty acids before Dox) showing significant increases in TNFα levels with p-values of 0.0001. However, the treatment groups that received the combination of omega fatty acids with Dox showed no significant changes in TNFα levels, with p-values of 0.4574 for omega-7 and 0.4606 for omega-3, suggesting these combinations may have provided protective effects against the inflammatory response typically induced by Dox alone. In the prophylaxis groups, where omega fatty acids were administered before Dox exposure, omega-7 resulted in TNFα levels of 22.7 ± 1.9 nmol/ml, while omega-3 produced slightly (p=0.102) lower levels at 20.9 ± 1.9 nmol/ml, indicating that both fatty acids performed similarly when used as prophylactic agents, though neither completely prevented the inflammatory response to Dox.

The prophylaxis and treatment combination groups showed remarkably similar patterns, with omega-7 producing TNFα levels of 22.6 ± 1.5 nmol/ml and omega-3 achieving 20.8 ± 1.8 nmol/ml. Interestingly, the p-value of 0.065 suggests a trend toward statistical significance, with omega-3 showing numerical advantage in reducing inflammatory markers, though this difference remains just above the conventional significance threshold.

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DISCUSSION

The present study demonstrated that omega-3 and omega-7 have provided hepatoprotection against Dox-induced tissue damage, confirmed by histological and biochemical parameters. Both drugs have mitigated the liver tissue damage against DIH, with superiority of omega-7 over omega-3 in tackling the provoked immune response, protection of liver architecture and enzyme contents, and modulating the oxidative stress parameters.

Based on the histological findings presented, both omega-3 and omega-7 fatty acids demonstrate hepatoprotective properties against DIH, though with notable differences in their protective efficacy and mechanisms. The combined prophylaxis and treatment approach with omega-3 yielded mixed results, with moderate inflammatory infiltration and continued vascular complications, suggesting incomplete protection (16–18).

In contrast, omega-7 fatty acids exhibited superior hepatoprotective capabilities, particularly in the combined treatment protocol. While omega-7 prophylaxis alone showed intermediate protection similar to omega-3, the combination of pre- and post-treatment with omega-7 resulted in remarkable tissue preservation, with nearly normal liver architecture restoration and the formation of pseudo-lobular structures that suggest active tissue regeneration. These histological differences suggest that omega-7 fatty acids may possess enhanced anti-inflammatory properties and potentially unique regenerative mechanisms that make them more effective than omega-3 in protecting against and reversing DIH, though both fatty acids offer valuable protective benefits over no treatment (16, 18). This tissue protection and stimulation of development and tissue regeneration capacity have also been reported in a previous study that investigated the role of omega-7 in skeletal muscle cell differentiation (19).

When investigating the hepatic enzyme, omega-7 demonstrated superior protective effects compared to omega-3, particularly in a prophylactic approach. In the prophylactic approach, omega-7 preserved ALT, ALP, and AST, representing substantial protection against Dox hepatotoxic attack. The fatty acid protective efficacy was enhanced when used therapeutically, suggesting not only protective but potentially regenerative properties (16–18). Most remarkably, omega-7 therapeutic application appeared to enhance hepatic recovery, confirmed by the reduction in enzyme levels compared to prophylaxis alone, indicating that this fatty acid may support both cellular protection and tissue repair mechanisms (16, 18). In contrast, the omega-3 hepatoprotective profile revealed a more complex and less favourable pattern, particularly in prophylactic applications where it appeared to demonstrate limited efficacy. This finding suggests that omega-3 fatty acids may interfere with hepatic metabolic processes when used prophylactically against Dox injury (20, 21). However, omega-3 therapeutic application has shown significant improvements in hepatic enzyme levels, achieving near-equivalence with omega-7 therapeutic effects.

When administered alone, omega-7 significantly elevated TAS levels compared to baseline values, suggesting that this fatty acid possesses intrinsic antioxidant properties that extend beyond simple cytoprotection. This enhancement of basal antioxidant capacity indicates that omega-7 may upregulate endogenous antioxidant systems (22) or provide direct free radical scavenging activity that contributes to overall hepatic resilience (23). In the context of the Dox challenge, omega-7 prophylactic application and treatment approach yielded similar protective outcomes, suggesting consistent antioxidant preservation regardless of intervention timing.

However, omega-7 performance in preventing lipid peroxidation revealed a more complex protective profile, particularly in prophylactic applications where MDA levels rose, indicating substantial oxidative lipid damage despite maintained antioxidant capacity. The dramatic improvement observed in the combined intervention approach indicates that omega-7 therapeutic application may be crucial for optimising its anti-lipid peroxidation properties, possibly through enhanced membrane incorporation or improved timing of antioxidant delivery relative to oxidative stress initiation (24).

Omega-3 antioxidant protective profile presented a contrasting pattern that highlighted its particular strengths in preventing oxidative lipid damage while maintaining comparable overall antioxidant capacity preservation. In prophylactic applications, omega-3 maintained TAS slightly at a slightly higher value in comparison to omega-7, though this difference did not reach statistical significance. More remarkably, omega-3 demonstrated superior protection against lipid peroxidation in prophylactic use, favouring omega-3 anti-peroxidative properties. This finding suggests that omega-3 fatty acids may possess enhanced membrane-protective mechanisms or more effective integration into cellular lipid bilayers (25, 26), providing superior resistance to Dox-induced lipid oxidation when administered prophylactically.

The results of the present study are in line with previous study on rat model conducted by Fadhel et al. (2023) that used oral omega-7 at both 100mg and 300mg/kg over 8 days and resulted in a significant decrease in ROS levels compared to the positive control group against Dox (I.P 15mg/kg) administered at day 9 and sample collection at day 10. However, Fadhel et al. (2023) found that superoxide dismutase levels showed no significant improvement. The study highlighted that

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glutathione peroxidase was significantly decreased in the Dox group but showed improvement with omega-7 treatment, particularly at the higher dose. Similarly, catalase was significantly restored by omega-7 treatment at both doses. Moreover, the study confirmed that while Dox caused a significant elevation of MDA, co-treatment with omega-7 produced a dose-dependent decrease in MDA levels (12).

When administered alone, omega-7 maintained stable IL-1β levels, indicating that this fatty acid possesses intrinsic anti-inflammatory properties that prevent baseline inflammatory activation (26, 27). This maintenance of inflammatory homeostasis suggests that omega-7 may modulate key inflammatory signalling pathways or cytokine production mechanisms that contribute to hepatic resilience against inflammatory insults (28, 29). In the context of the Dox challenge, omega-7 prophylactic application offered substantial protection against the severe inflammatory response observed in untreated animals, though still reflecting significant inflammatory activation compared to baseline values.

In a previous study, seven days of oral 100 mg/kg/day omega-7 has provided cytoprotection against a single IP injection dose 7.5 mg/kg cisplatin-induced nephrotoxicity indicated by tackling the inflammatory response provoked by cisplatin, the Omega-7 has reduced the immune response confirmed by reduced TNF-α, IL-1β, and IL-10 serum levels in treated versus positive and negative groups (30).

In contrast, another study conducted on humans found that three weeks of supplementation with 688 mg/day of omega-7 fatty acids failed to produce statistically detectable anti-inflammatory changes compared to placebo in a small randomized crossover trial and even omega-7 showed an increased inflammatory cytokines TNFα and IL-6. Perhaps the used supplement was the concern and cofounding variation in the research outcome due to significant discrepancies in the supplement composition – the actual palmitoleate content was 344 mg per capsule rather than the 227 mg stated in the certificate of analysis, and the supplement also contained substantial amounts of palmitate (199 mg per capsule) (27).

The present study revealed that omega-7 fatty acids have a positive hepatoprotective potential against Dox-related liver damage. The multi-modal mode of action suggests these fatty acids operate through complementary pathways rather than a single protective route. By simultaneously boosting antioxidant defences, mitigating inflammatory cytokine production, and maintaining structural hepatocellular integrity, omega-7 fatty acids address the primary mechanisms underlying Dox-induced liver toxicity. This manner could potentially reduce the need for dose modifications or treatment delays due to hepatic complications, thereby maintaining therapeutic efficacy while minimising adverse effects.

Several limitations should be acknowledged, including the reliance on a single animal rat model, which raises the question of the translatability of results to human populations, as well as species differences. The relatively short duration of study may not capture the full spectrum of chronic protective effects of omega-7 supplementation. Future research should prioritise defining the role of omega-7 fatty acids in the modulation of mitochondrial markers in the Dox-induced animal model. Comparative hepatoprotective efficacy of omega-3, omega-6, omega-7, and omega-9 fatty acids against Dox-induced liver injury. Investigating comprehensive multi-organ protective effects of omega-7 against Dox-induced toxicity: heart, liver, and kidney assessment.

In conclusion, the findings of this investigation provide compelling evidence for the prophylactic anti-inflammatory properties of omega-7 fatty acids in mitigating Dox-induced hepatic injury in albino rats. The comprehensive assessment of hepatic function, structural integrity, and some inflammatory markers demonstrates that omega-7 supplementation offers significant protection against the well-documented hepatotoxic effects of Dox chemotherapy. The histological examination of liver tissue demonstrated that omega-7 pretreatment substantially preserved hepatic architecture and reduced the characteristic cellular damage typically associated with Dox exposure. This structural protection was corroborated by the biochemical analysis of liver enzymes, which showed marked improvement in hepatic function markers among omega-7-treated animals.

ABBREVIATIONS

ALA - Alpha-linolenic acid
ALP - Alkaline phosphatase
ALT - Alanine aminotransferase
ANOVA - One-way analysis of variance
AST - Aspartate aminotransferase
DHA - Docosahexaenoic acid (DHA)
DIH - Doxorubicin-induced hepatotoxicity
Dox - Doxorubicin
ELISA - Enzyme-linked immunosorbent assay
EPA - Eicosapentaenoic acid
IL-1β - Interleukin-1 beta
MDA - Malondialdehyde
ROS - Reactive oxygen species
T-AOC - Total antioxidant capacity
TNFα - Tumor necrosis factor alpha

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