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Role of Omega-3 in ameliorating acute liver injury- induced by D-galactose on adult male rats

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Abstract

Background and objective: Numerous morphological and functional changes in the liver are linked to aging. The two main ageing processes that can cause significant damage to mitochondrial DNA and ultimately apoptosis are now well recognised to be inflammatory reaction and oxidative stress. Because aging is a poor prognostic factor that raises the mortality rate, it may also raise the risk of developing a number of liver illnesses. In rodents, chronic D-galactose treatment accelerates aging. In addition to improving hepatic beta oxidation and decreasing endogenous lipid production, omega-3 polyunsaturated fatty acids also have a positive effect on the metabolism of lipids and insulin sensitivity. They can also lower oxidative stress and hepatic inflammation, which merely lessens the damaging aging effect of D-galactose on rats.

Methods: Four equal groups of twenty-eight (28) male *Rattus norvegicus* rats, weighing between 210 and 240 g, were randomly selected. Group T₁ animals received an intraperitoneal injection of normal saline, while group T₂ animals received an IP injection of D-galactose (150 mg/kg bwt) and were drenched 80 mg/kg (bwt) of Omega3 twice a day for 75 days. T₃ received an intraperitoneal (I/P) injection of D-galactose (150 mg/kg b.wt) for 75 days, and they were drenched omega 3 (80 mg/kg b.wt) twice a day for 21 days. D-galactose (150 mg/kg b.wt) was given intraperitoneally (I/P) into T₄ rats for 75 days. All animals have been sacrificed 24 hours after the last dose, and samples of liver tissue were obtained to look for histopathological changes, serum samples were gathered also for biochemical analysis.

Conclusion: Omega-3 supplement for 75 days cause a significant enhancement with mitigating the aging harmful properties of D-galactose on liver functions and oxidative stress marker MDA and showing liver tissue sections showing the improvement with liver architecture occurring due to Omega 3 supplementation.

Keywords: D-galactose, omega 3, rats, liver, oxidative stress

Introduction

The process of aging is defined by the slow accumulation of biological changes that eventually cause a person's functional abilities to deteriorate. According to estimates, the percentage of older individuals (those 60 and over) would almost double from 12% in 2015 to 22% by 2050 (Nations, 2015) ^[31]. In general, there are two types of aging models: those that age naturally and those that age more quickly. Because rapid aging models are easier to implement, needless study time, and have a better animal survival rate throughout the course of the experiment, they are preferred over naturally occurring aging models, which take a long time and are very expensive in vitro research uses hydroxyurea therapy and D-galactose-induced models, while in vivo studies use radiation-induced, accelerated susceptible mice, thymus-removed, and D-galactose-induced models. The D-galactose-induced ageing model is the most extensively utilised among various ageing models because of its ease, absence of adverse effects, and better survival rate during the experiment (Cebe *et al.*, 2014; Yanar *et al.*, 2011) ^[10, 42]. A reducing sugar called D-galactose is found naturally in the body and in a variety of foods, including butter, milk products, dairy products, honey, beets, and fruit like celery, plum berries, and figs in particular. (Acosta and Gross, 1995) ^[1].

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The maximum amount of galactose that is advised for a healthy adult to consume each day is 50 g, and the majority of it can be broken down and eliminated from the bloodstream within 8 hours of consumption. (Morava, 2014) [28]. However, galactose oxidase can catalyze its conversion to aldose and hydroperoxide at high concentrations, producing reactive oxygen forms. Significantly higher concentrations of reactive oxygen compounds (ROS) and malondialdehyde (MDA) and reduced levels of superoxide dismutase (SOD) and total antioxidant capacity were indicative of D-galactose-induced oxidative stress in the NSCs. D-galactose rats were showed considerably greater levels of pro-inflammatory cytokines, such as interleukin 1 beta (IL-1b), the interleukin 6 (IL-6), and TNF-a, compared to the normal group. Additionally, the expression of genes linked to cellular senescence, P53 and P21, was increased. These demonstrated that D-galactose may cause senescence through inflammatory pathways. (Azman and Zakaria, 2019) [8]. The onslaught of ROS is the primary cause of the progressive deterioration in liver functioning that occurs with aging. A surplus of D-galactose in the bloodstream can have a major impact on the liver because it is primarily processed there by raising NO, MDA and 8-hydroxy-2-deoxyguanosine, as well as decreasing the CAT, GPx, SOD, the NOS, the hormone GSH, and the overall antioxidant capacity of liver tissues. It has been shown that D Galactose treatment results in oxidative stress in the liver (Feng *et al.*, 2016; Kong *et al.*, 2018) [17, 26]. Reactive oxygen species are very reactive substances that can affect the activities of different cellular components (Al-Tamemi and Al-Okaily, 2023) [2]. Advanced glycation end products are created when D-galactose combines with unbound amines that are present in proteins via nonenzymatic glycation. Additionally, long-term D-gal treatment may increase the production of ROS through glycation end products (AGEs) and D-gal oxidative metabolism (Parameshwaran *et al.*, 2010) [33]. Regular cellular metabolism produces reactive species (ROS), which can damage lipids, proteins, and DNA. Oxidative damage contributes to ageing and cellular dysfunction over time (Andrés Juan *et al.*, 2021) [4]. Ageing can cause cirrhosis, hepatocyte necrosis, and a malfunction in the liver, which plays a part in immunity and homeostasis (Fan *et al.*, 2017) [16]. About 88% of D-Gal is absorbed in the gut and has the ability to buffer against liver retention when it is dissolved in drinking water and given to mice and rats (Homolak *et al.*, 2023) [21]. D-Gal is given intraperitoneally or subcutaneously for 6-12 weeks at a dose of 50-1200 mg/kg/day to induce liver ageing (Azman, Safdar and Zakaria, 2021) [7]. Ω -3 fatty acids' ability to prevent liver and kidney damage by controlling the inflammatory NF-KB and antioxidant Nrf2 pathways (Eraky and El-Magd, 2020). Supplementing with fish oil that is high in ω -3FA may be a natural way to prevent hepatorenal damage in people who are accidentally or professionally exposed to manganese, improving both human and veterinary medical conditions (Owumi *et al.*, 2020) [32]. Omega-3 polyunsaturated fatty acid supplementation was suggested as a therapeutic approach to lower plasma triglyceride levels by reducing hepatic lipogenesis and raising lipoprotein lipase (LPL) activity, which speeds up the breakdown of chylomicrons and VLDL (Santos *et al.*, 2013) [36]. Alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the three fatty acids that make up the omega-3 series. Some cereals, legumes, and vegetable oils contain ALA, while fish from deeper waters, such as salmon and sardines, have higher concentrations of the fatty acids EPA

and DHA (Innes and Calder, 2018). It's possible that omega-3 fatty acids can lower oxidative stress, TG levels, and the severity of hepatic steatosis (Ratziu *et al.*, 2019) [35].

Materials and Methods

Animal Ethical approval

Ethical approval was granted by the local committee of animal care and use (P.G. 584 date 3-12-2024), and the study's animal care and treatment were conducted at the College of Veterinary Medicine within Al-qasim Green University with strict compliance in the code of ethics for animal experiments.

Animals and experimental design

In this study, twenty-eight male rats (*Rattus norvegicus*), ages 4-5 months, weighing between 210-240 g, were used. The animals were housed in cages at 22-25 °C with a 12-hour light/dark cycle. During the two weeks that they were housed at the animal's house/college of veterinary medicine/Al-Qasim Green University for acclimation, the rats had complete access to water and pellets. For 75 days, the rats were divided into four equal groups at random and given daily treatments. While the animals in group T₂ received an intraperitoneal injection (I/P) of D-galactose (150 mg/kg bwt), the animals in the control group T₁ received an intraperitoneal injection of normal saline and were drenched in normal saline (Chang *et al.*, 2017) and drenched with 80 mg/kg bwt of Omega3 twice daily for 75 days. T₃ were injected I/P with D-galactose (150 mg/kg b.wt) for 75 days and drenched with omega 3 (80 mg/kg b.wt twice daily) for 21 days. T₄ rats were I/p injected with D-galactose (150 mg/kg b.wt) for 75 days. (D-galactose C₆H₁₂O₆ >99%, Lot 28899-62205, MW 180.2 soluble in water, CAS no. 59-23-4 USA, Omega-3-acid ethyl esters high purity, 90%, Uk, concentration 840 mg for each 1000 mg Omacor dissolved in 28ml of soy bean oil).

Tissue samples collection

The animals were subjected to regular weighing both prior to and throughout the duration of the experiment. This was done in order to accurately administer D-galactose and Omega 3 dosages in accordance with the rats' respective weights. Rats were subjected to anaesthesia with ketamine and xylazine according to (Veilleux-Lemieux *et al.*, 2013) [38]. Liver tissues of the sacrificed specimens were preserved in a solution of natural buffer formalin (10%) in order to facilitate further histopathological examinations. Blood samples were collected at the end of the experiment to quantify the serum malondialdehyde (MDA) content using a modified method, MDA assay kit was obtained from Solarbio Life Science /china. Operation Equipment: Spectrophotometer. Serum samples were separated for measurement of alanine transaminase (ALT), alkaline phosphatase (ALP) and bilirubin, immediately after serum samples were separated, and estimated by using the clinical chemistry analyzer Cobas c 311an open reagent system, Roche diagnostic cobas c311 automated, software-controlled analyzer.

Results

Serum AST (IU)/L: The T₄ group's serum AST levels were significantly greater ($p \leq 0.05$) than those of the other groups, as shown in Figure (1-A). A significant decrease ($p \leq 0.05$) was observed in the T₁ group when compared to the T₃ and T₄ groups. Comparing T₂ to the T₁ control group, not a noticeable rise was seen. Serum ALT (IU)/L: The T₄ group's serum ALT levels were substantially greater ($p \leq 0.05$) than

those of the other groups, as shown in Figure 1-B. When compared to the T₃ and T₄ groups, the T₁ group displayed a statistically significant decrease ($p \leq 0.05$). Comparing T₂ to the T₁ control group, no discernible increase was seen.

Total bilirubin mg/dl According to fig. (1-C) results, the T₄ group's serum bilirubin level was statistically significantly ($p \leq 0.05$) greater than that of the other groups. The results indicated a statistically significant decrease ($p \leq 0.05$) between the T₁ group and the T₃ and T₄ groups. Likewise, T₂ displayed non-significant increases in serum malondialdehyde (MDA) concentration (mmol/ml) compared to T₁: According to the blood MDA concentration measurement results in figure (2), the D-galactose exposed group (T₄) had a statistically significant ($p < 0.05$) greater level than the negative control (T₁) and the other treatment groups. T₁ and T₂ were also found to not differ statistically substantially ($P > 0.05$). But when T₁ and T₂ were contrasted with T₃ and T₄, a significant ($p < 0.05$)

decrease in serum MDA levels.

According to the results of the current study we can notice the harmful effect of 75 days of IP injection of D-galactose in T₄ rats for the above parameters, AST, ALT, total bilirubin and MDA, and we can notice the improvement effect of Omega-3 for the same parameters for group T₂ which has been drenched for 75 days as compared with those who received omega 3 for only 21 days with IP D-galactose injection for 75 days values expressed as mean $\pm$ SE. N=7 rats. T₁=Control group rats were injected with normal saline. T₂=were injected (I/P) with D-galactose (150 mg/kg bwt) and drenched with 80 mg/kg bwt of Omega3 twice daily for 75 days rat T₃= rats were injected I/P with D-galactose (150 mg/kg b.wt) for 75 days and drenched with omega 3 (80 mg/kg b.wt) twice daily for 21 days T₄=rats were I/p injected with D-galactose (150 mg/kg b.wt) for 75 days. Different letters denote significant differences between groups, ($p \leq 0.05$).

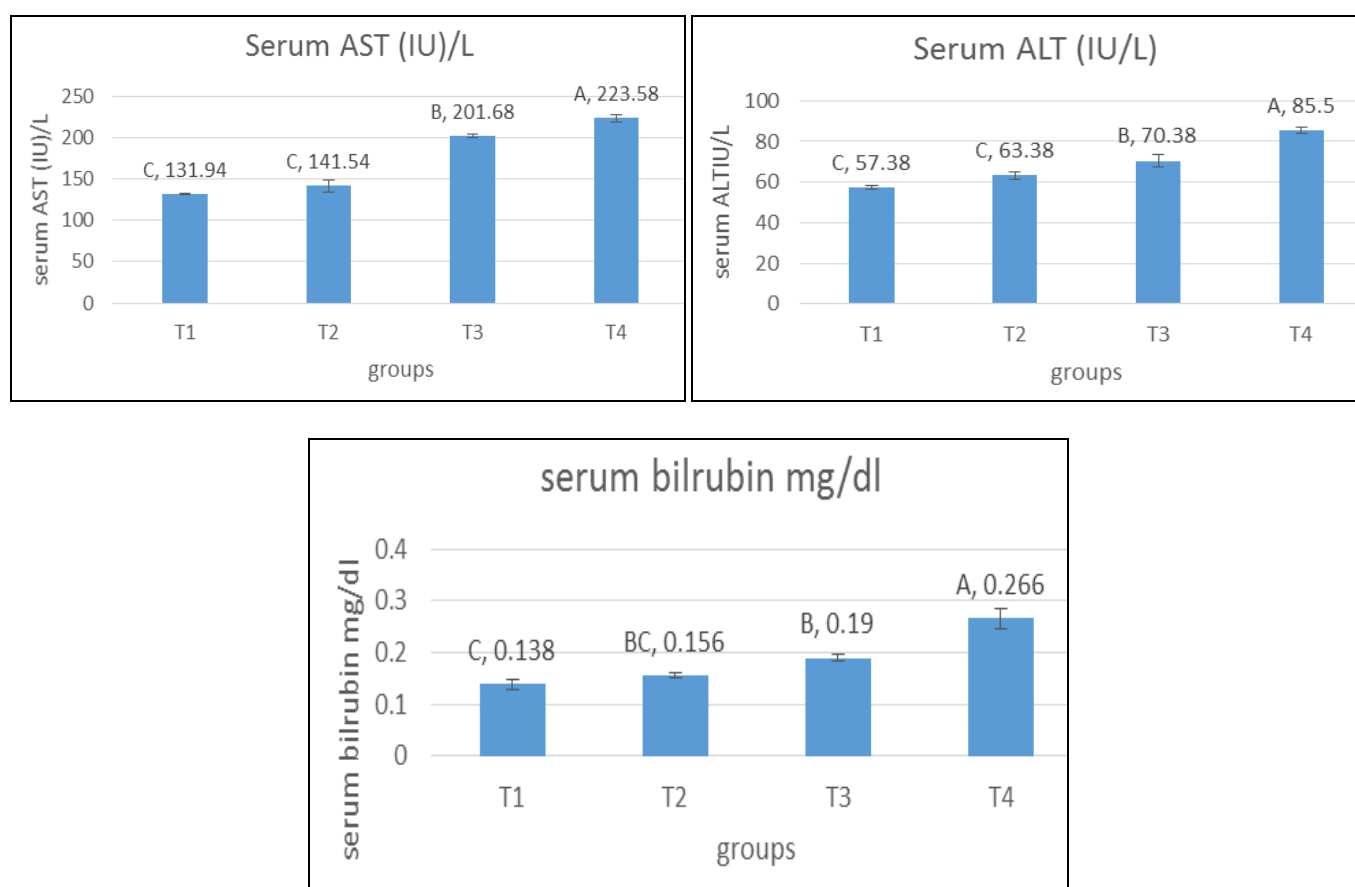


Fig 1: Effect of omega-3 and D-galactose on serum, AST (A), ALT (B) and total bilirubin (C) of adult males rats for 75 days

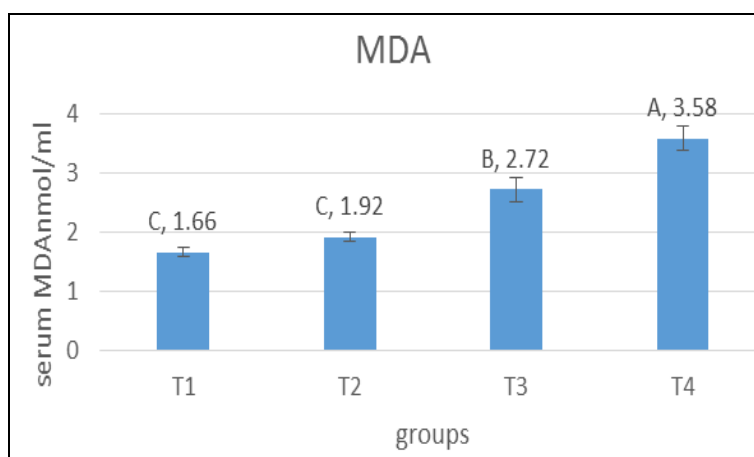


Fig 2: Effect of omega-3 and D-galactose on serum MDA of adult males rats for 75 days

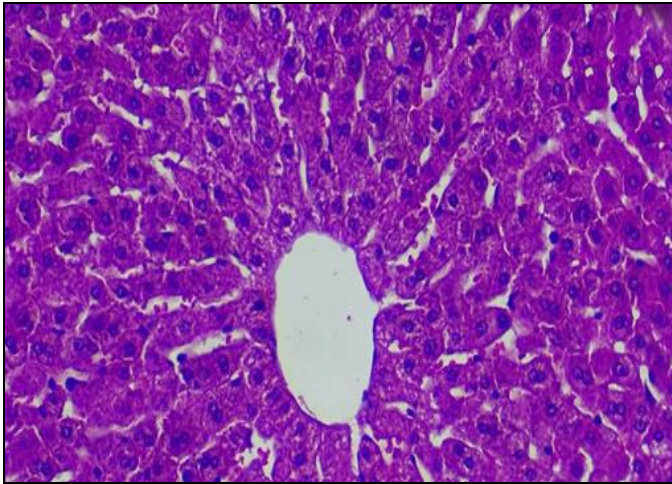


Fig (3-a): Histopathological section of rat liver for control group T₁. Showing normal histological architecture's (H&E, stains, 200x)

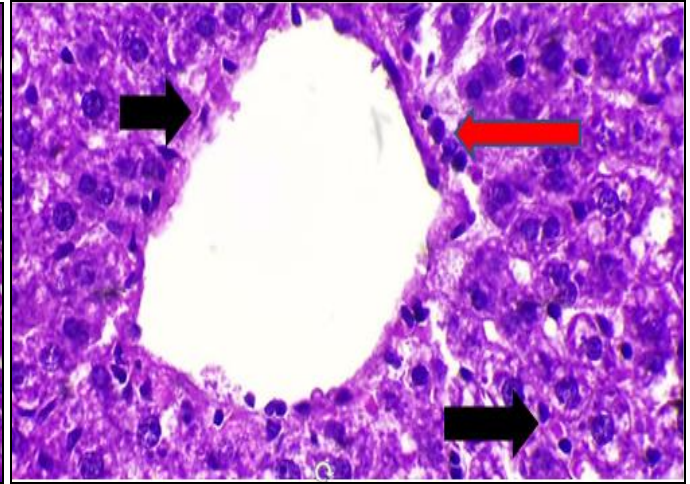


Fig (3-b): Histopathological section of rat liver for T₂ group. Showing mononuclear cells infiltration beside the central vein (red arrow), increase in the number of the Kupfer cells infiltration (black arrow), (H & E, stains, 400x)

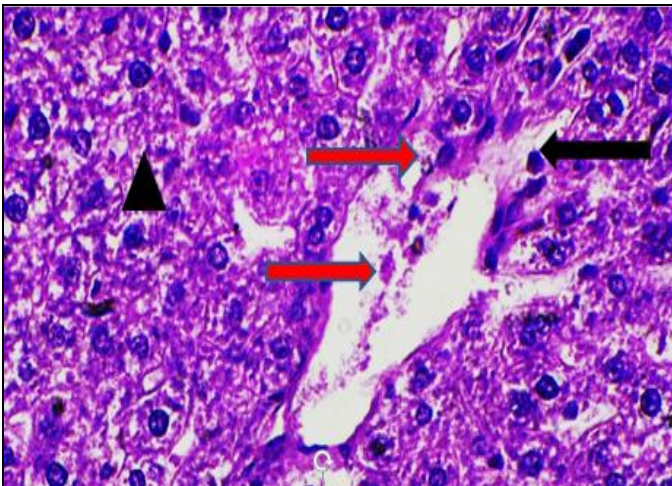


Fig (3-c): Histopathological section of rat liver for T₃ group. Showing sloughing of the central vein endothelia (red arrow), with mild inflammatory cells infiltration (black arrow), hepatocytes degeneration also seen (black head) (H&E, stains, 400x)

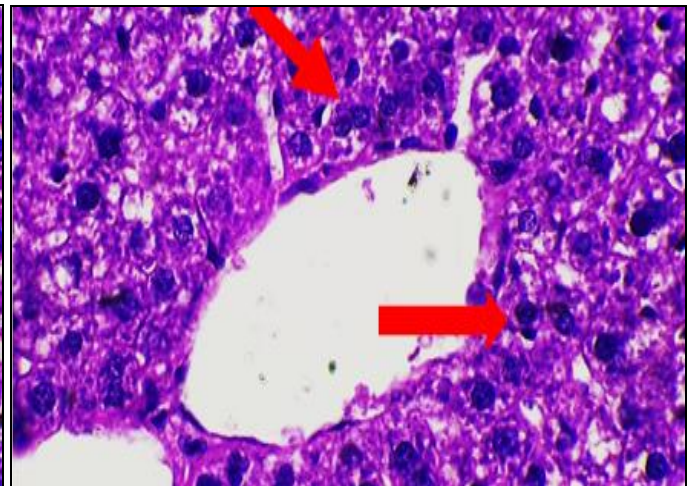


Fig (3-d): Histopathological section of rat liver for T₂ group. Showing hepatocyte regeneration by increase the nuclei mitosis (red arrow) (H&E, stains, 400x).

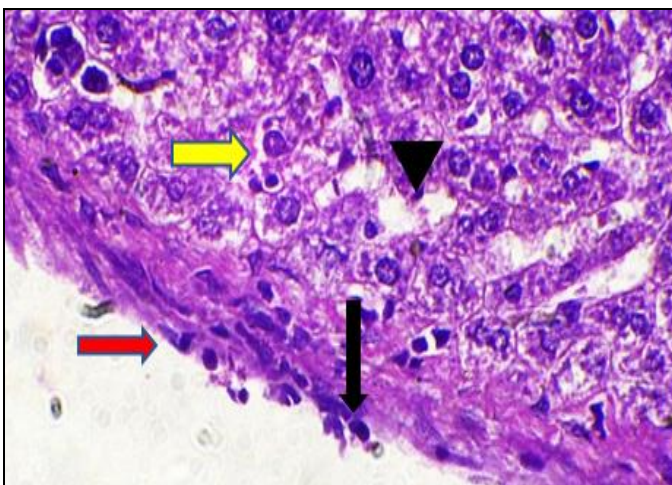


Fig (3-e): Histopathological section of rat liver for T₃ Group. Showing thickening in the hepatic capsule due to deposition of the collagen fiber (red arrow) with mononuclear cells infiltration (black arrow), dilation of the hepatic sinusoids (head), also seen apoptosis (yellow arrow)

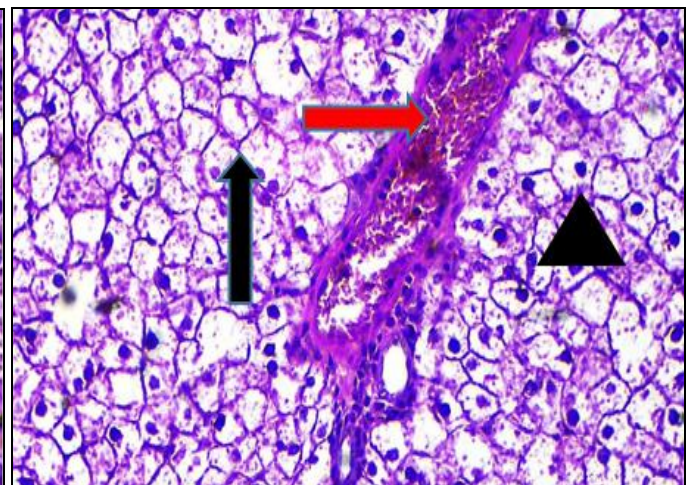


Fig (3-f): Histopathological section of rat liver for T₄ group. Showing severe thickening and congestion of the portal vein (red arrow), single cell necrosis (black), severe vacuolation of hepatocytes (head arrow), (H & E, stains, 200x)

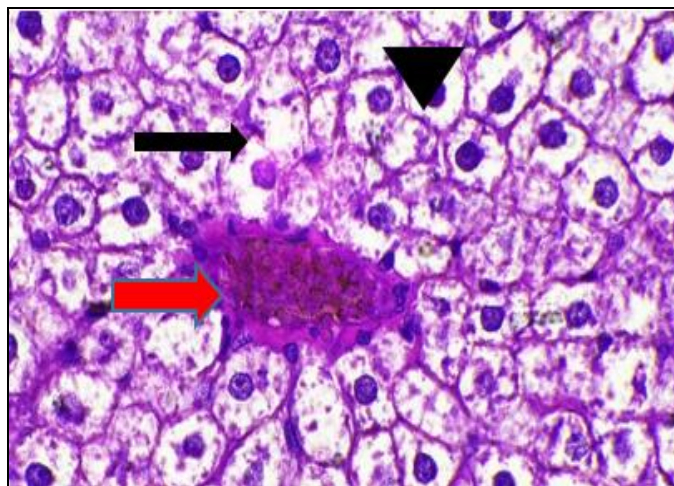


Fig (3-g): Histopathological section of rat liver for T₄ group. Showing occluded thrombus in the central vein (red arrow), single cell necrosis (black arrow), severe vacuolation of hepatocytes (head), with hypertrophy of their nuclei (H&E, stains, 200x).

Discussion

Ageing makes the liver more susceptible to progressive structural and functional changes. As the liver ages, its mitochondrial count decreases, oxidative stress-related genes like cytochrome c are expressed less frequently, and hepatocyte telomere length decreases, which lowers cell proliferation and apoptosis (Azman, Safdar and Zakaria, 2021) ^[7]. Preservation of mitochondrial function has been found to be crucial in the restoration of organ function after severe injury. Age-related progressive organ failure, an elevated inflammatory response, and accelerated cellular senescence all contribute to the liver's diminished ability to fight injury. It has been demonstrated that aging-related mitochondrial function reduction increases the susceptibility of the heart, lungs, liver, and kidney to ischemia/reperfusion injury (Poulouse and Raju, 2014) ^[34]. Aging decreases the ability of liver to withstand trauma (Hoare, Das and Alexander, 2010) ^[20].

Receiving IP injections of D-galactose for 75 days as shown in figures (1-A, B, C) causing a significant ($p < 0.05$) increase in rats serum AST, ALT and bilirubin as compared with control and treated Omega-3 groups, these results were in agree with many studies, a study which has results were in agree with the present study confirmed that when compared to normal rats, D-Gal dramatically raises the liver enzyme indicators ALT, AST, TBIL, and DBIL. It has previously been documented that D-Gal-induced liver ageing causes an increase in liver aminotransferases, which are early, sensitive indicators of liver damage (Chen, Chen and Zhou, 2018) ^[12].

Because D-gal is a reducing sugar and an essential nutrient, It creates advancing substance related to glycosylation when it joins with amino acids, as a result, when it is injected in large quantities, it causes reactive oxygen species to be produced through the metabolism of hydrogen peroxide by galactose-oxidase. Additionally, D-Gal has been demonstrated to dramatically increase serum total and direct bilirubin in rat sera, according to another investigation that supported findings comparable to ours. Since liver function is necessary for bilirubin catabolism, increased bilirubin levels are indicative of hepatocytes destruction (Boland *et al.*, 2014) ^[9]. Bilirubin is a sensitive biomarker of liver disorders and one of the three markers used to evaluate the model for the end-stage liver disease score (Kamath and Kim, 2007) ^[25]. Additionally, hepatic dysfunction and impaired intrahepatic excretion of conjugated bilirubin from bile duct hepatocytes are indicated by increased direct bilirubin in rats administered D-galactose

(Astegiano *et al.*, 2004) ^[5]. One of the mediators of cytoprotection for inflammation and cellular homeostasis balance against oxidation processes is bilirubin (Gomes *et al.*, 2010) ^[19]. This may reveal the reason why bilirubin levels increased in serum of group exposed to D-Gal. and other oxidative stress stimuli. Intraperitoneal D-Gal, at 150 mg/kg for 75 days, induced significant increase in liver function markers compared to control and treated groups with omega-3. In addition, serum bilirubin levels also elevated significantly in d-galactose treated group T₄ as compared with control and treated group with omega 3, significantly help in restore liver function markers to normal levels compared to D-Gal treated group.

A byproduct of lipid peroxidation of polyunsaturated fatty acids, malondialdehyde (MDA) includes Moving around One of the most popular and extensively utilised indicators of oxidative stress is MDA

(Al-Tamemi and Al-Okaily, 2023) ^[2]. Some studies found that MDA plasma levels dropped following n-3 PUFA intake (Véricel *et al.*, 2015) ^[39]. It has been hypothesised that immunomodulation and a decrease in leukocyte activation may be the mechanisms by which n-3 PUFA supplementation could lessen oxidative stress which were in agree with present study according to Figure 2 showing a significant decrease in omega-3 exposed rats. Another study confirmed that omega-3 fatty acids supplementation had beneficial effects, Omega-3 fatty acids increased activity of SOD and decreased lipid peroxidation, changes in oxidative/antioxidative balance are a result of effects on lipids and enzymes of antioxidative system (Avramovic *et al.*, 2012) ^[6].

(Fenton *et al.*, 2013) ^[18], through lipid synthesis and oxidation, dietary LCn-3 PUFAs impact hepatic lipid homeostasis. Research is being done on how these fatty acids interfere with nuclear processes that are not dependent on eicosanoid formation and regulate the expression of genes related to lipid metabolism (Molendi-Coste, Legry and Leclercq, 2011) ^[27]. When administered to animals in conjunction with DOX, omega-3 fatty acids improved the histological and biochemical changes brought on by DOX, significantly reduced the amount of MDA, and increased the activity of antioxidant enzymes. Because of its antioxidant properties, omega-3 fatty acids protected against liver damage caused by doxorubicin; they also improved the levels of AST and ALT and, because of their anti-inflammatory properties, reduced the generation of pro-inflammatory cytokines (Moussa *et al.*, 2020) ^[29].

In Figure (3-a) Hepatic architecture was normal in sections of the control liver T₁ group. When omega-3 and D-galactose were administered together as in figures (3-b, c, d, e) the liver architecture significantly improved. Histopathological results for liver sections T₂ revealed that the sections improved by boosting nuclear mitosis and hepatocyte regeneration. Liver sections Figures (3-f, g) from rats given D-galactose T₄ showed evidence of damage, including significant thickening and portal vein congestion with necrosis, as well as disturbed histological architecture.

The present study results were in agreeable with many previous studies which confirm that, the histological image changed dramatically with age, displaying apoptosis and cytoplasmic vacuolations of hepatocytes, obliterated sinusoids, central vein dilatation, and crowded inflammatory cellular infiltration at different locations the three hepatic zones exhibited modest cytoplasmic vacuolations, a dilated, clogged central vein, fatty infiltration of the liver, and slight inflammatory cellular infiltration in H. pluvialis tissue and its fractions (El-Baz *et al.*, 2018) [14]. Studies evaluating the effect of dietary ω 3 PUFA on NAFLD show that changes in hepatic PUFA impact NAFLD indicators, such as steatosis, inflammation, and fibrosis (Jump *et al.*, 2018) [23]. Excess D-galactose administration contributes to the increased formation of ROS, which subsequently leads to oxidative stress and hepatocyte damage (Azman, Safdar and Zakaria, 2021) [7]. When the antioxidant system's function declines or significant amounts of free radicals are produced, tissues and cells are vulnerable to damage caused by oxidation. Hepatocellular necrosis and cytoplasm vacuolar degradation in the D-gal group showed changes to the typical lobular architecture and structure of the liver cells in the control group (Xiao *et al.*, 2018) [41]. Elevated expression amounts of oxygen-derived free radicals in mouse hepatocytes are linked to hepatic ageing and necrosis brought on by high D-gal levels (Timchenko, 2009) [37]. Free radicals are playing important role in damage a number of cellular components including DNA, proteins and lipids (Das and Vasudevan, 2007) [13].

The benefits of administering omega-3 in reducing DOX hepatotoxicity and the efficacy of omega-3 in preventing it were demonstrated. The rat liver treated with omega-3 maintained its normal architecture and was also able to reduce congestion, hepatocyte vacuolation, and degeneration (Moussa *et al.*, 2020) [29]. Pretreatment with omega-3 FAs and concurrent treatment with Gifosfamide reduced the liver damage caused by Gifosfamide, demonstrating its hepatoprotective properties (El Kalawy *et al.*, 2017) [24]. The present study histopathological examination were in agree with (Ali and Rifaai, 2019), who confirmed that when liver sections from the control and omega-3 groups were examined under a microscope, the cords of hepatocytes radiating from the central vein revealed a typical histologic pattern. Hepatocytes had acidophilic cytoplasm and central vesicular nuclei, giving them a polyhedral appearance. Blood sinusoids were used to divide the cords. Hepatic artery, portal vein, and bile duct branches were found in the portal tract.

Conclusion

A current study found that Omega-3 caused an improvement in oxidative stress biomarkers and biochemical liver function biomarkers which were affected by the harmful effect of D-galactose treatment for 75 days also results suggest that Omega 3 mitigates histological changes induced by D-

galactose due to its properties as an antioxidant, antiaging, anti-inflammatory, antiapoptotic properties.

Authors' contribution

The completed manuscript was reviewed and approved by all authors. Conflicting interests No conflict of interest exists.

Ethical consideration

Authors has examined the manuscripts for ethical issues, including redundancy, multiple publishing and/or submission, misconduct, data fabrication and/or falsification, plagiarism, and permission to publish.

Conflicts of Interest: No conflict of interests.

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