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Protective Effect of Tomato seed oil (TSO) against γ-radiation induced damage in male Wistar rats.

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ABSTRACT

Tomato seed oil (TSO) contains a wealth of fatty acids, vitamins, nutrients, carotenes, and phytosterols in addition to lycopene. To investigate the possible protective effects of TSO on radiation induced toxicity in rats. To evaluate the biological damage of radiation on rat tissue, liver enzymes (AST & ALT), renal function (urea & creatinine)and oxidative stress biomarkers were measured. Thirty two Wistar albino rats were divided into four subgroups: control (C), TSO alone (TSO), irradiation alone (IRR), and IRR + TSO combined. After sacrificing the rats, antioxidant enzyme superoxide dismutase (SOD) and activity and malondiadehyde (MDA)levels were evaluated in liver and kidney. Administration of TSO resulted in a decrease in the activities of AST and ALT and renal markers levels (urea & creatinine). Moreover, the activity of SOD was significantly increased accompanied by a significant depletion in MDA level in the hepatic and renal tissue compared with the irradiated group. Also, the histopathological finding supported the biochemical investigations in both liver and kidney. Therefore, the administration of TSO prior to γ-radiation exposure increased the endogenous antioxidant defense mechanism in rats and protected the animals from radiation-induced hepatic and renal toxicity. In addition, TSOis a promising radioprotective agent that can be effectively used against lethal doses of γ-radiation after further investigations in higher animal models.

Keywords: TSO, γ-radiation, liver enzymes, renal markers, MDA, SOD

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INTRODUCTION

Ionizing radiation (IR) has attracted a lot of attention due to its beneficial as well as possible harmful effects to human population [1]. Radiotherapy is one of the beneficial effects of radiation. The deleterious effects of IR are due to generation of reactive oxygen and nitrogen species (ROS/RNS) resulting in imbalance of the pro-oxidant and antioxidant in the cells [2].Radiation exposure attenuates the endogenous antioxidant enzymes, which are considered to function as part of a first line defense mechanism to maintain redox balance and normal biochemical processes. Thus, supplementation of antioxidants to improve the efficacy of radiotherapy is a current proposed strategy, as antioxidants are capable to scavenge free radicals from the radiolysis of water and to protect cells from damage [3].

A wide range of synthetic [4,5] as well as natural compounds [6] have been tested in experimental models to overcome the deleterious effects inflicted by ionizing radiation. Many naturally occurring compounds with antioxidant activity are known to protect cellular components from oxidative damage and prevent diseases [7].Dietary supplementation of fruits and vegetables like tomato has been linked to a rise in plasma antioxidant levels and to a reduction in blood pressure [8,9].Studies have also shown that the increased consumption of tomato and tomato-based products may reduce the risk of cancers [10]. A number of dietary antioxidants have been reported to decrease free radical attack on biomolecules like tomato seed, which is a byproduct of industrial processing of tomatoes into paste and canned products **[12]**.Among of these natural products, TSO which becomes a matter of choice for our investigation. In addition to lycopene, TSO contains a wealth of fatty acids, vitamins, nutrients, carotenes, and phytosterols. In particular, TSO has been reported to possess high unsaturated fatty acid content, with over 50% linoleic acid, followed by oleic acid [13]. Therefore, this study has been oriented to investigate possible protective effect of tomato seed oil against γ-radiation induced damage in liver and kidney in male Wistar rats.

MATERIALS AND METHODS

Chemicals

Tomato seed oil (TSO) was obtained from Stöger GmbH (A-2164 Neuruppersdorf 65, Austria). All other chemicals and reagents used in this study were of analytical grade and obtained from Sigma Chemical Co., Nasr City, Cairo, Egypt.

Animals

Wistar albino male rats weighing120 to 140g, were obtained from the Egyptian Organization for Biological Products and Vaccines (Abbasia, Egypt).They were housed in standard environmental conditions like, ambient temperature (25±1°C), relative humidity(55±5%) and 12/12 h light dark cycle. Animals had free access to standard pellet diet and water ad libitum. All animal experiments were carried out in accordance with the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals.

Experimental Design:

The rats were randomly divided into four groups with eight animals per group. In all cases, rats were treated with TSO with an orogastric tube. The experimental design is described in Table 1. **Group I** corresponds to normal control rats without treatment. **Group II (TSO)**corresponds to rats treated with TSO (1ml/kg b.w.)(3 times/week for 8 weeks).**Group III (IRR)** corresponds to rats exposed to 6 Gy (single dose) whole body gamma irradiation. **Group IV (TSO+ IRR)** corresponds to rats treated with TSO (1ml/kg b.w.) (3 times/week for 8 weeks) then exposed to 6 Gy (single dose) whole body gamma irradiation. At the end of the experiment, rats were fasted overnight, anesthetized by light ether and the blood was collected by heart puncture. Blood samples were collected by cardiac puncture and allowed to clot for 45 min at room temperature. Serum was separated by centrifugation at 600xg for 15 min and analyzed for ALT, AST, Urea and creatinine. Liver and kidney were excised, homogenized and assayed for MDA and SOD and pathological histology.

Table 1 – Experimental design		
Group	**TSO**	**IRR**
I	**—**	**—**
II	**+**	**—**
III	**—**	**+**
IV	**+**	**+**

Tissue homogenate preparation

Immediately after the animals were sacrificed, liver and kidneys of each animal were quickly excised, washed with normal saline, blotted dry with filter paper and 1 g of each tissue was finely homogenized in a small volume of ice cold buffer solution (50 mMTris-HCl, 0.25 M sucrose, pH 7.4), then made up to 10 ml to obtain ultimately 10% (w/v) whole tissue homogenate. The homogenate was centrifuged at 10,000 rpm for 10 min at 4˚C and the supernatant was used to assay enzymatic markers of oxidative stress, including MDA level and SOD activity.

Irradiation

Radiation was delivered to rats from a Canadian Gamma cell 40-Cesium,137Biological sources, in the National Center for Radiation Research and Technology (NCRRT)(Cairo, Egypt)at a dose rate of 0.59 Gy/min during the experimental period. Dosimetry was carried out using Baldwin Farmer's secondary dosimeter and Fricke's chemical dosimetry method.

Determination of TSO acute toxicity

A pilot study was carried out using male Wistar rats (120-140 g) administered orally TSO (0.5-1.5 ml/kg bw). The oil was given to five animals per dose. The number of deaths and signs of clinical toxicity were recorded. The animals were observed for all physiologic signs of toxicity 48h after dosing **[14]**.Therefore, the dose (1.0ml/kg bw) was used in the current study.

Determination of oxidative stress biomarkers in the tissue homogenate

Superoxide dismutase (SOD) activity was determined according to **Minami and Yoshikawa[15].** The assay relies on the ability of the enzyme to reduce the rate of NBT-diformazan formation which was followed photometrically at540 nm. Lipid peroxidation (LPO) in terms of malondialdehyde (MDA) was measured according to the method of **Yoshioka et al. [16],** using 1,1,3,3-tetraethoxypropane (TEP) as a standard. One molecule of MDA reacts with two molecules of thiobarbituric acid (TBA) in an acidic medium with production of a pink color of TBA-MDA that is measured at 535 nm.

Determination of serum alanine aminotransferase and aspartate aminotransferase activities

The levels of serum alanine aminotransferase **(ALT)** and aspartate aminotransferase **(AST)**activities were determined by the colorimetric method of **Reitman and Frankel [17]** using a commercial assay kit (Biodiagnostic, Egypt).

Determination of serum Urea Concentration:

The concentration of urea was determined by the end point colorimetric method of **Fawcett and Soctt [18]** using a commercial assay kit (Biodiagnostic, Egypt).

Determination of serum Creatinine Concentration:

The concentration of creatinine was determined by the colorimetric method of **Bartleset al.[19]**using a commercial assay kit (Biodiagnostic, Egypt).

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Determination of serum lipid profile:

Serum total cholesterol, triacylglycerol (TAG) and high density lipoprotein cholesterol (HDL-C) concentrations were determined according to the method of **Young [20]** using commercial assay kits(N.S BIOTEC, Egypt). Low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) levels were calculated according to **Friedewald et al. [21]**, while the atherogenic index of plasma (AIP) was calculated according to **Holmes et al. [22]** [AIP =log10 (TAG/HDL-C, where TAG and HDL-C concentrations were expressed as mmol/L).

Histopathological Study

Specimen from kidney of all examined groups was washed, dehydrated in ascending grades of ethyl alcohol, cleared in xylene and embedded in paraffin wax. Sections of 5–6 µm in thickness were cut out, deparaffinized and stained with Hematoxylin and Eosin (H & E) for examination under the light microscope.

Statistical Analysis:

Statistical analysis of results including the mean, standard error (SE) and p values were performed using Statistical Package for Social Science (SPSS) version 20.0 for windows. Data were analyzed using one-way analysis of variance (ANOVA) followed by Post Hoc Less significant difference (LSD) test. The data were expressed as mean ± standard error. Differences were considered statistically significant at $p \leq 0.05$.

RESULTS

To test the changes induced by administration of TSO (1 ml/kg bw) (3 times/week for 8 weeks) pre-exposure to γ-radiation (6Gy), ALT, AST, urea and creatinine have been measured in blood serum. γ-irradiation (6 Gy) induced a significant increase in the activities of serum ALT and AST and levels of urea and creatinine which amounted to 62.79, 64.49%, 143.21 and 123.68%,respectively, compared with controls as compared to the control group. However, the increases in levels of ALT, AST urea and creatinine were significantly decreased in rats pretreated with TSO (Fig. 1).

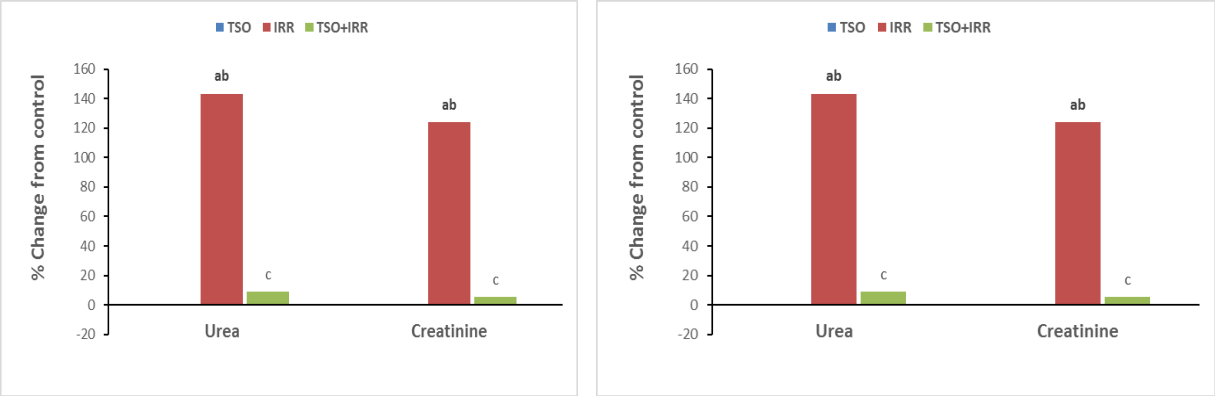

Fig 1: Percent change of ALT, AST, Urea and Creatinine levels in different treated groups compared with controls (a, b and c denote significant change atp< 0.05 versus control, TSO and IRR groups, respectively) .

To evaluate the oxidative stress biomarkers in the liver and kidney, MDA concentrations and SOD activity were measured (Table 2). IRR) induced a significant increase in the levels of MDA contents in liver and kidney tissue and caused a significant decrease in activity of SOD in liver and kidney activities. Pre-treatment with TSO reduced lipid peroxidation as demonstrated by the normalization of MDA level and also, normalized SOD activity in the aforementioned organs.

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Table 2: Effect of treatment with TSO and /or gammaradiation on the activity of superoxide dismutase (SOD) in some body organs in rats

Groups	MDA (nmol/g tissue)		SOD (U/g tissue)	
	Liver	Kidney	Liver	Kidney
Control	211.15±19	281.14±19	0.73±0.03	0.59±0.03
TSO	219.89±28^{c}	298.71±14^{c}	0.70±0.05^{c}	0.59±0.03^{c}
IRR	471.96±53^{ab}	446.79±24^{ab}	0.54±0.03^{ab}	0.49±0.01^{ab}
TSO+IRR	242.23±30^{c}	308.75±2.45^{c}	0.68±0.04^{c}	0.57±0.02^{c}

Results were expressed as Mean± SE

a, b and c denote significant change at p<0.05 versus control, TSO and IRR groups, respectively.

Data presented in Table (3) shows that exposure of rats to gamma radiation induced hyperlipidemia as evidenced by the significant increase in serum TAG, cholesterol, LDL-C and VLDL-C, along with a significant increase in AIP level (26.06, 82.21, 360.05, 26.01 and 157.14%, respectively), accompanied with a significant decrease in serum HDL-C level (20.55%), compared with controls. Oral administration of TSO before exposure to gamma radiation, normalized serum TAG, HDL-C and VLDL-C levels as well as AIP. On the other hand, treatment of rats with TSO before exposure to gamma radiation reduced significantly serum cholesterol and LDL-C levels, as well as AIP level for gamma irradiated rats followed by TSO treatment, compared with gamma-irradiated rats.

Table 3: Effect of treatment with TSO and/or gamma radiation on serum lipid profile in rats

	TAG (mg/dL)	Cholesterol (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	AIP
Control	67.84±1.42	56.48±2.60	31.63±1.07	13.19±2.34	0.07±0.01
TSO	64.24±2.83^{c}	58.75±2.27^{c}	30.25±1.78^{c}	13.04±1.10^{c}	0.07±0.01^{c}
IRR	85.52±3.07^{ab}	102.91±8.01^{ab}	25.13±0.95^{ab}	60.68±8.23^{ab}	0.18±0.01 ^{ab}
TSO+IRR	63.80±4.38^{c}	81.56±1.98^{abc}	30.50±1.93^{c}	38.30±2.17 ^{abc}	0.08±0.01^{c}

Results were expressed as Mean± SE

a, b and c denote significant change at p<0.05 versus control, TSO and IRR groups, respectively.

Histological study

The histopathological changes observed in the liver of different groups of rats are shown in Fig. 2. The results indicated that during radiation treatment, there was infiltration of inflammatory cells around the portal vein and some of the hepatocytes showed nuclear disintegration and some had pyknotic nuclei. In the TSO pre-administered group, most of the hepatocytes were within normal limits with the normal lobular pattern of the liver with a centrilobular vein. The drug control group did not show any change in the hepatocytes indicating the protective nature of the drug.

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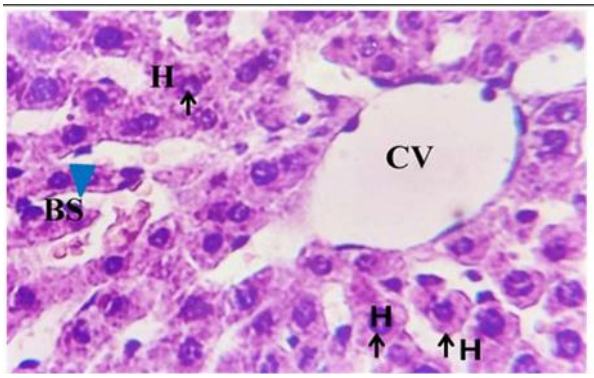
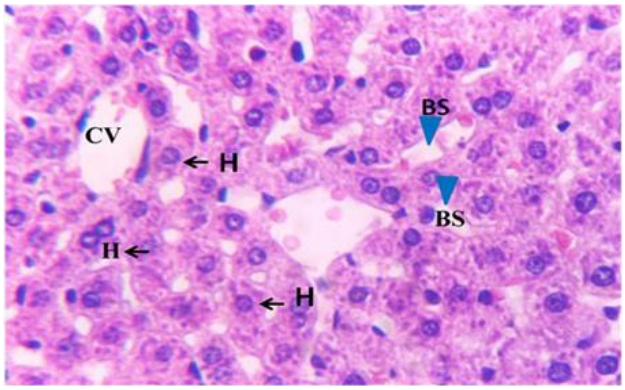
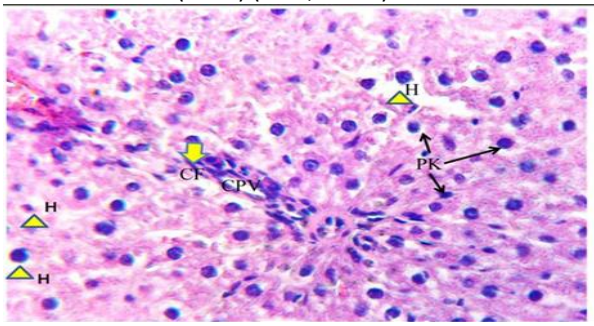


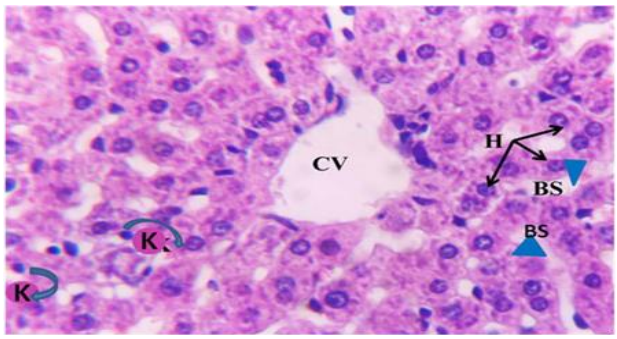
A liver section from a control rat showing the normal lobular pattern of the liver with a centrilobular vein (CV) and radiating irregular anatomising plates of hepatocytes (H↑) with their nuclei and intervening blood sinusoids (BS▼) (H&E, X 400).



A liver section from a rat treated with TSO showing the normal appearance of hepatocytes (H↑) radiating from the central vein (CV) and blood sinusoids (BS ▼) (H&E, X 400).



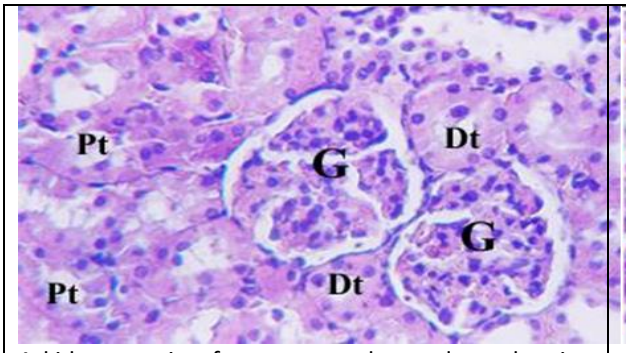
A liver section from a ratexposed to 6 Gy gamma radiation showing infiltration of inflammatory cells (CF ⇩) around the portal vein (CPV). The appearance of pyknotic nuclei (PK ↑) represents degeneration in hepatocytes (H △) (H&E, X 400).



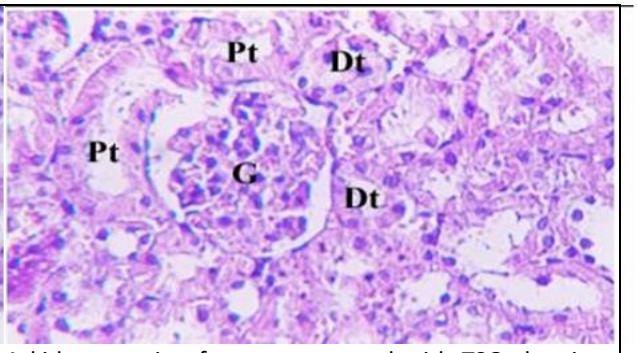
A liver section from a rat treated with TSO and exposed to 6 Gy gamma radiation showing the normal lobular pattern of the liver with a centrilobular vein (CV), normal hepatocytes (H↑), Kupffer cells (K curved arrow) and intervening blood sinusoids (BS▼) (H&E, X 400).

Fig 2: A light photomicrograph of liver sections of all studied groups

The histopathological changes observed in the kidney of different groups of rats are shown in Fig. 3. The results showed that during radiation treatment, there was decrease of the normal shape of renal corpuscles, intertubular inflammation and most of the glomeruli were atrophied. In the TSO pre-administered group, there was appreciable improvement after treatment with TSO and there were no adverse effects observed in the group treated with TSO.



A kidney section from a normalcontrol rat showing the normal appearance of the glomerulus (G), proximal (Pt) and distal (Dt) convoluted tubules (H&E, X 400).



A kidney section from a rattreated with TSO showing the normal configuration of proximal (PT) or distal (DT) convoluted tubules and the normal glomerulus structure (G) (H&E, X 400).

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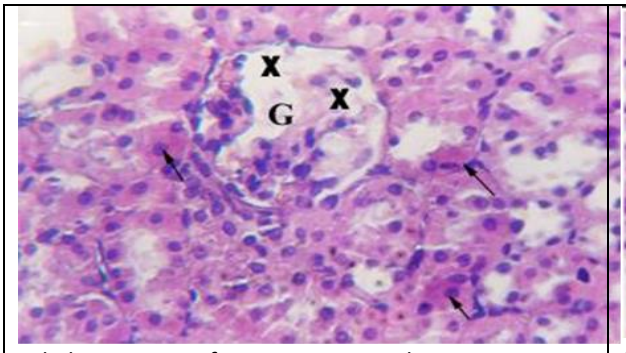
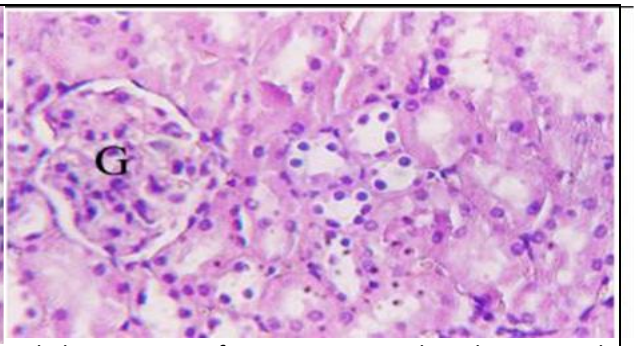


A kidney section from a ratexposed to 6 Gy gamma radiation showing decrease of the normal shape of renal corpuscles, degeneration of glomeruli (G ✱) and the presence of inflammatory cells lining the convoluted tubules (↑) (H&E, X 400).



A kidney section from a rattreated with TSO and exposed to 6 Gy gamma radiation showing the normal structure of the renal component (H&E, X 400).

Fig 3: A light photomicrograph of kidney sections of all studied groups

DISCUSSION

Ionizing radiation is an important environmental risk factor known to produce various types of reactive oxygen species in biological systems provoking oxidative damage, organ dysfunction and metabolic disturbances **[23]**.Exposure of male rats to whole body gamma irradiation induced damage to major body organs including liver (increased serum ALT AST activities), kidney (elevated serum urea and creatinine concentrations), compared with intact rats. This damage was also accompanied with by increased oxidative stress biomarkers, as manifested by increased tissue MDA level, and suppression of tissue SOD activity, as well as histopathologically.

The leakage of hepatic enzymes such as AST and ALT into blood is routinely used as a reliable biochemical index for hepatocellular damage **[24]**. In agreement with the findings reported by **El-Deeb et al. [25] & Osman and Hamza [26]**, the present investigation showed a significant increase in serum AST and ALT activities in response to whole body γ-irradiation exposure of male rats, compared with intact animals. This increase could be due to the damage of cellular membranes of hepatocytes, which was supported by the histopathological finding. This hepatic damage leads to an increase in the permeability of cell membranes and facilitates the passage of cytoplasmic enzymes outside the cells leading to the increase in transaminase activities in blood serum.

In accordance with the results of Rezk and Darwish [27] & Abd El Kader [28], the present work showed a significant increase in the levels of serum urea and creatinine after irradiation, along with altered renal histopathology, which reflected renal damage and might result from a reduction in the effective renal blood flow and glomerular filtration rate, or impairment of the kidney function. Also, the increased urea level might be due to increased protein breakdown after exposure to ionizing radiation, as urea is the end product of protein catabolism[29]. Furthermore, ionizing radiation induces extensive retention in daily excreted urine that leads to increased creatinine and urea levels in the blood[30] and increased production of ROS and oxidative stress [31].

The liver is the chief organ concerned with regulation of total body contents of lipids and lipoproteins. Most lipids circulate through the bloodstream as lipoproteins. In the present results showed disturbances in serum lipid profiles in gamma-irradiated rats. The hyperlipidemic state observed in the serum of irradiated rats was probably due to the release of cholesterol fractions from tissues, destruction of cell membranes and increase rate of cholesterol biosynthesis in the liver and other tissues to preserve the biomembranes. Furthermore, Nagiub et al. [32] reported that the increased level of triacylglycerols in serum maybe related to the inactivation of lipoprotein lipase enzyme, which reduces the uptake of lipids by adipose cells. In addition, Hamzaa et al**. [33]** suggested that the radiation-induced oxidative stress might be an important determinant of altered hepatic lipid metabolism and serum lipoproteins.

The major forms of cellular damage induced by radiation are DNA damage, lipid peroxidation and protein oxidation. In agreement with the findings reported by Mansour [34] and Shirazi et al. [35], the present study demonstrated a significant increase in MDA concentration (one of the lipid peroxide indices) and a significant decrease in SOD activity in liver and kidney tissue. This can be attributed to the interaction of the excess •OH, produced from the radiolysis of water upon exposure to ionizing radiation, with polyunsaturated fatty acids in the phospholipids portion of cellular membranes and the enhancement of lipid peroxidation.

Natural antioxidants play a source of protection against γ-radiation. The appropriate antioxidant may inhibit or reduce free radical toxicity and offer protection against radiation damage [36].A number of dietary antioxidants have been reported to decrease free radical attack on biomolecules such as tomato seed, a byproduct of industrial processing of tomatoes, which contains an oil of a high nutritional quality [37, 12].The data of the present study revealed that pretreatment with tomato seed oil (TSO) protect male rats form harmful effects of exposure to γ-radiation. To the best of the authors' knowledge, this is the first *in vivo* study demonstrating the radioprotective effect of TSO. Such protection was demonstrated by the significant reduction of hepatocellular damage (as manifested by the normalization of serum ALT activity as well as hepatic MDA concentration and SOD activity), renal damage (as evidenced by the normalization of serum urea and creatinine concentrations, as well as kidney MDA concentration and SOD activity). The prophylactic effects of TSO against gamma radiation exposure were also demonstrated histopathologically in the both liver and kidny tissues. The protective effect of TSO can be explained in part by the antioxidant sparing action of lycopene. During singlet oxygen ($^1O_2$) quenching, energy is transferred from $^1O_2$ to the lycopene molecule; the lycopene molecule is converted into energy rich triplet state. The energy richlycopene molecule scavenges other ROS, such as hydroxyl, nitric oxide or peroxynitrite radicals. This might be one of the antioxidant mechanisms for protecting the cells from lipid peroxidation and oxidative stress, with an ultimate improvement in the integrity of tissues [38].

Moreover, in the present investigation TSO markedly lowering the serum levels of cholesterol, TAG and LDL in rats exposed to gamma radiation. Shao et al. [39] ascribed the hypolipidimc effect of TSO to the fact that TSO was high in lycopene content, which is reported to have antioxidant activity and singlet oxygen quenching ability and its bioavailability is higher when accompanied by dietary fat, indicating that TSO may be a better more bioavailable source for lycopene and a good source of polyunsaturated fat for human consumption without the risk of hypercholesterolemia and obesity. Similarly, Silva et al. [40] evaluated the hypocholesterolemic activity of dietary β-carotene for 2 weeks in female Fisher rats fed a hypercholesterolemic diet. The authors reported that supplementation of β-carotene into the hyper cholesterolemic diet reduced serum total cholesterol, atherogenic index-1, hepatic totallipids & cholesterol levels and increased fecal total lipid and cholesterol levels. The authors suggested that β-carotene administration maydecrease cholesterol absorption in the intestine.

CONCLUSION

In conclusion, the current investigation demonstrates a radioprotective potential of TSO against whole body gamma irradiationin adult male rats. Such protection is attributed to the high antioxidants content of TSO, enhance the antioxidant defense and suppress lipid peroxidation therefore cell membranes integrity.

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