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Research Article
Protective Role of *Juniperus phoenicea* L. Leaves Extract against Gamma-irradiation-induced Oxidative Stress

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Abstract

Background and Objective: Radiation exposure can cause several harmful effects in biological systems due to free radical production. Several antioxidants have been tested as potential hepatoprotective agents against ionizing radiation as they lower oxidative stress in normal cells induced by Reactive Oxygen Species (ROS). The present study was conducted to evaluate the possible ameliorative effects of *Juniperus phoenicea* L. **Materials and Methods:** Aqueous leaves extract on different biochemical and histopathological parameters against whole body gamma-irradiation-induced oxidative stress, organ dysfunction and metabolic disturbances in experimental Swiss Albino rats. After a single dose of gamma-radiation (6 Gy), there was a significant reduction in albumin, total protein and globulin levels and a significant increase in the liver enzymes (ALT, AST, ALP and GGT) and lipid profile parameters (cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol) in gamma-irradiated rats unlike in normal controls. **Results:** The gamma-irradiated rats pre-treated with *J. phoenicea* leaf extracts, however, showed a significant increase in albumin, total protein and globulin levels and a significant reduction in liver enzymes and lipid profile parameters as opposed to the untreated ones. The gamma-irradiated rats showed toxic changes in the liver, whereas, the rats pre-treated with *J. phoenicea* leaves extract demonstrated a protective effect. Additionally, gamma- irradiation caused myocardial degenerative changes, interstitial edema between muscle fibers, necrosis and inflammatory cells infiltration and fibrotic and cellular damages to the heart, but *J. phoenicea* leaves extract were found to ameliorate the gamma-irradiation-induced changes in the heart. **Conclusion:** The results suggested that treatment with *J. phoenicea* leaves extract is possibly safe and can ameliorate gamma-irradiation-induced oxidative damage and tissue injury in rats. The leaves of *J. phoenicea* could serve as a potential source of therapeutic antioxidants.

Key words: Gamma irradiation, *Juniperus phoenicea*, oxidative stress, globulin, albumin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Juniperus phoenicea L. (family: Cupressaceae) is a well-known medicinal plant. For centuries, each part of this plant has been used in household remedies against different diseases[1,2]. *Juniperus phoenicea* grows into trees or shrubs, locally known as "Arayar," and grows up to 8 m in height. In Saudi Arabia, this plant species is distributed from the Mediterranean region to as far as Taif[3].

In the traditional system of medicine different *Juniperus* species have been used to treat various infectious and inflammatory diseases[4]. *Juniperus* species are considered to help in maintaining good health[5]. Phytochemical examination of the methanolic leaves extract of *J. phoenicea* showed the presence of 4 flavonoid compounds, namely, quercetin, quercitrin, cosmosin, myricitrin and 2 phenolic compounds, namely, caffeic acid and ρ-coumaric acid[6-8]. Extracts of different parts of *J. phoenicea* is traditionally used as an oral drug to cure gastrointestinal related symptoms, such as; indigestion and poor appetite[9]. The oil extracted from this plant also helps in regulate the digestive system and reduce stomach cramps[10]. Parts of different *Juniperus* species are also used as antiseptic and anthelmintic agents[11]. It is also used as a diuretic and to treat common cold[12]. It is hypothesized that *J. phoenicea* extracts help in improving various enzymatic activities and protect the liver from toxins owing to the high content of flavonoids[13].

Radiotherapy is widely used for the treatment of different types of cancers. However, because of its adverse effects on non-target tissues, its effective use is often limited. Atomic disruption of the cells is caused by the ionizing radiation from radiotherapy leading to different biochemical alterations. Radiotherapy can cause radiolysis of water, thereby, producing Reactive Oxygen Species (ROS), which can cause oxidative damage to vital biomolecules, such as; DNA, proteins, lipids and lipoproteins[14,15]. The generated free radicals can induce oxidative stress in the presence of other existing comorbidities, such as; atherosclerosis, arthritis, asthma, cancers, kidney damage, liver injury, heart attack and can induce of apoptosis[16]. Radiation initiates a series of molecular and biochemical signaling alterations that result in the damage of cell repair mechanisms, resulting in permanent physiological alterations and cell death[17,18].

The present study was conducted to evaluate the possible protective effects of the aqueous extracts of *J. phoenicea* leaves on different biochemical parameters and whole-body gamma-irradiation-induced oxidative stress, organ dysfunction and metabolic disturbances in experimental Swiss Albino rats.

MATERIALS AND METHODS

Study area: The study was carried out at the labs of Deanship of Scientific Research, Taif University, KSA and National Center for Radiation Research and Technology, Cairo, Egypt during the period of June, 2017-September, 2019.

Experimental animals: A total of 100 male Swiss Albino rats, weighing between 110-120 g were procured from an animal farm of the Egyptian Holding Company for Biological Products and Vaccines, Egypt. The rats were acclimatized for one week before initiating the experiment. All the procedures were performed by the public health guide according to the guidelines of ethics for the Care and Use of Laboratory Animals[19] and the Animal Care Committee of the National Center for Radiation Research and Technology, Cairo, Egypt.

Radiation facility: The gamma-irradiation was given in the National Center for Radiation Research and Technology, Cairo, Egypt. The source of the radiation was a Cesium-137 Gamma cell® 40 exactor, which ensured a homogenous dose distribution all over the irradiation tray. The rats were transferred to a specially designed well-ventilated acrylic container where they were exposed to a single dose of 6 Gy radiations. The dosage rate was 0.84 Gy min^{-1} and the radiation time was 7.14 min.

Plant materials: The fresh *J. phoenicea* plants were collected from wadi Ze-Ghazal in the western slopes of the mountains of Shafa at Taif province, Saudi Arabia (Fig. 1). The plant was authenticated by the Biology Department, College of Science, Taif University, Saudi Arabia.

All the unwanted parts of the plant, such as; flowers, stems, stones and roots were detached from the leaves. The leaves were cleaned, air-dried and powdered mechanically to prepare the aqueous extracts.

Preparation of the aqueous leaves extract of *J. phoenicea*: Five hundred grams of the powdered leaves *J. phoenicea* were added to 50 mL of boiled distilled water and immersed in a closed vessel for a few minutes. A piece of gauze was used to filter the crude extracts. The filtrates were freshly obtained for administration. Each rat received orally 40 mg kg^{-1} of the extract in 0.1 mL solution/day[20].

Fig. 1(a-b): *Juniperus phoenicea* L. tree

Experimental design: One hundred rats were equally divided into 4 groups (n = 25 in each group) and received the following treatment:

- **Group I (control group):** Basal diet orally for 21 consecutive days
- **Group II:** Basal diet orally for 21 consecutive days followed by a single dose of 6 Gy gamma-irradiation
- **Group III:** Basal diet orally plus 40 mg kg^{-1} per day of *J. phoenicea* leaves extract orally for 21 consecutive days
- **Group IV:** Basal diet orally plus 40 mg kg^{-1} per day of *J. phoenicea* leaves extract orally for 21 consecutive days followed by a single dose of 6 Gy gamma-irradiation

Estimation of the biological parameters: After 48 h of gamma-irradiation and an overnight fast, the rats were anesthetized and blood samples were collected by retro orbital puncture using capillary tubes. The sera were separated immediately by centrifugation at 4000 rpm for 10 min at 4°C and were stored at -20°C for future use.

Cholesterol was measured by a previously reported method[21], triglyceride was measured according to the method described by McGowan *et al.*[22] and high-density lipoprotein HDL-cholesterol was measured by a method described previously by Burstein *et al.*[23]. The levels of Low-Density Lipoprotein (LDL)-cholesterol were estimated according to the formula[24]:

$$\text{LDL-cholesterol} = \text{Total cholesterol}-(\text{Triglyceride}/5+\text{HDL-Cholesterol})$$

The total protein was measured by the method of Burtis and Edward[25] and albumin was determined by the method of Doumas *et al.*[26]. The globulin level was obtained by subtracting the albumin level from the total protein level. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were determined using a kinetic method described by Sherwin[27]. Alkaline phosphatase (ALP) was measured using a kinetic method described by Tietz *et al.*[28] and gamma-glutamyltransferase (GGT) was estimated using the method of Tietz[29].

Histopathological studies: The hearts and livers were removed and fixed in 10% neutral formalin, Bouin's solution, Susa and Zenker formal fluids[28] for 24 h. The samples were dehydrated using graded concentrations of ethanol, cleared in xylene and embedded in paraffin wax (melting point between 56-58°C). The paraffin sections of 5-7 µm thickness were obtained by a rotary microtome (Leica RM 2125) and stained using hematoxylin and eosin (H and E) and periodic acid Schiff stains according to the method described by Bancroft and Gamble[30]. The slides were covered by Canada balsam and coverslips and were examined by an upright light microscope (Nikon Eclipse E400).

Statistical analysis: All the experiments were performed in a minimum of 3 replicates. The obtained data were statistically analyzed. The means were compared according to the Least Significant Difference (LSD) at 5% level of significance as described previously by Gomez and Gomez[31].

RESULTS

Biochemical parameters: The rats irradiated at a dose of 6 Gy showed a significant increase in the liver enzymes ALT, AST, ALP and GGT compared to those in normal control rats

Table 1: Effects of *Juniperus phoenicea* L. and gamma-irradiation on liver enzyme activities of ALT, AST, ALP and GGT in different rat groups

Groups	ALT (U L^{-1})	AST (U L^{-1})	ALP (U L^{-1})	GGT (U L^{-1})
Group I	016.2±0.94^{c}	019.6±1.14^{c}	034.9±2.67^{c}	028.6±1.92^{c}
Group II	128.4±07.4^{a}	148.5±8.55^{a}	112.7±6.49^{a}	173.9±16.71^{a}
Group III	012.9±0.99^{c}	017.2±1.32^{c}	032.7±0.99^{c}	024.5±1.41^{c}
Group IV	045.5±4.83^{b}	053.3±5.66^{b}	049.8±4.78^{b}	047.6±5.33^{b}

Data is represented as Mean±SD (data were obtained in 4 replicates), Means marked with the same superscript letters are not significant ($p>0.05$), whereas, the means marked with the different superscript letters are significant ($p<0.05$)

Table 2: Effects of *Juniperus phoenicea* L. and gamma-irradiation on total bilirubin, albumin, total protein, globulin and albumin/globulin ratio in the different groups of rats

Groups	Total bilirubin (mg dL^{-1})	Albumin (g dL^{-1})	Total protein (g dL^{-1})	Globulin (g dL^{-1})	Albumin/Globulin ratio
Group I	0.54±0.13^{c}	3.3±0.13^{a}	5.3±0.68^{b}	2.0±0.11^{c}	0.62±0.03^{d}
Group II	1.83±0.09^{a}	1.8±0.09^{c}	3.2±0.16^{c}	1.4±0.08^{d}	1.28±0.06^{b}
Group III	0.49±0.15^{c}	3.6±0.15^{a}	6.2±0.49^{a}	2.6±0.21^{b}	1.38±0.07^{a}
Group IV	0.86±0.17^{b}	2.8±0.17^{b}	5.7±0.23^{b}	2.9±0.21^{a}	0.96±0.04^{c}

Data is represented as Mean±SD (data were obtained in 4 replicates), Means marked with the same superscript letters are not significant ($p>0.05$), whereas, the means marked with the different superscript letters are significant ($p<0.05$)

Table 3: Effects of *Juniperus phoenicea* L. and gamma-irradiation on cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol in the different groups of rats

Groups	Cholesterol (mg dL^{-1})	Triglyceride (mg dL^{-1})	HDL-cholesterol (mg dL^{-1})	LDL-cholesterol (mg dL^{-1})
Group I	142.9±08.5^{c}	098.5±05.9^{c}	045.8±2.7^{c}	77.4±3.9^{b}
Group II	279.7±13.9^{a}	226.2±18.0^{a}	145.4±9.9^{a}	89.1±4.8^{a}
Group III	112.5±09.1^{d}	081.2±05.6^{d}	041.7±2.5^{c}	54.6±2.2^{d}
Group IV	170.3±06.8^{b}	123.5±07.4^{b}	077.8±4.6^{b}	67.8±5.4^{c}

Data is represented as Mean±SD (data were obtained in 4 replicates), Means marked with the same superscript letters are not significant ($p>0.05$), whereas, the means marked with the different superscript letters are significant ($p<0.05$)

(Table 1). The gamma-irradiated rats pre-treated with *J. phoenicea*, however, showed a significant improvement in the levels of liver enzymes, which were almost near the normal control rats.

The rats irradiated at a dose of 6 Gy showed a significant reduction ($p<0.05$) in total bilirubin, albumin, total protein, globulin levels compared to those in normal control rats and Albumin/Globulin ratio (Table 2).

The levels of cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol increased significantly ($p<0.05$) in the gamma-irradiated rats compared to those in the normal controls (Table 3).

Histopathological characteristics of heart: The heart sections obtained from the normal control group and the *J. phoenicea* extracts-treated group showed normal architecture. The heart cells contained a normal amount of cytoplasm with one or two nuclei and well-defined cell boundaries. The cardiac muscle fibers appeared as short branching and anastomosing cylinders containing moderately stained eosinophilic sarcoplasm and centrally located oval nuclei (Fig. 2a, b). The gamma-radiation-induced changes were manifested as slight disruption of the striated appearances and disorganization of the myofilaments, which were appearing as discontinuous, fragmented and lysed. Structural changes in the cardiac muscle fibers, deformation of the striated appearance and areas of vacuolation (Fig. 2c) were also detected in addition to patches, necrosis of muscle fibers, pyknotic myocardial cells and myocardial damage. In the group treated with *J. phoenicea* leaves extract, amelioration of many of the radiation-induced changes was observed. The pyknotic cells were not seen and the grade of myocardial damage was less than that of the untreated groups. The interstitial edema and inflammation were less and evidence of necrosis was not markedly visible (Fig. 2d).

Histopathological characteristics of liver: Histopathological examination showed a normal architecture of the liver in both the control rats and the *J. phoenicea* extracts-treated rats (Fig. 3a, b). The livers of the gamma-irradiated rats exhibited foci of inflammatory cells in between the hepatocytes surrounding a central vein along with necrosis and degenerative changes in the hepatocytes (Fig. 3c).

The liver sections of the gamma-irradiated rats treated with *J. phoenicea*, leaves extract showed normal hepatic strands radiating from the central vein, hepatocytes with normal architecture (some were slightly vacuolated) with normal nuclei and sinusoids (Fig. 3d).

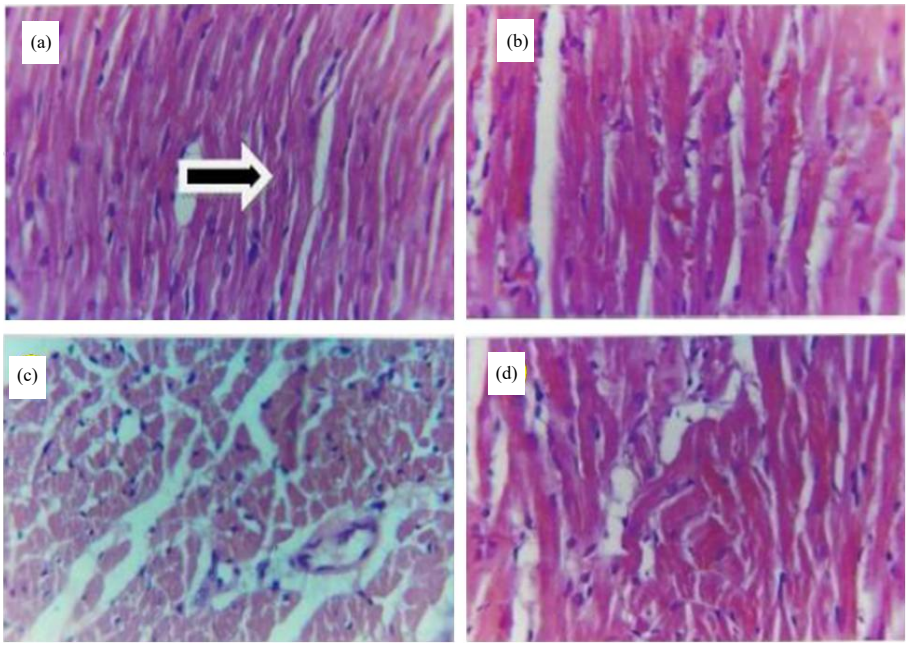

Fig. 2(a-d): Histopathological structure of a section of the heart (H and E, 400X), (a) Normal control rats showing normal structure of myocardium (arrows showing normal cardiac muscle fiber), (b) *Juniperus phoenicea* L. treated rats showing no deviation from the normal architecture, (c) Gamma-irradiated rats showing patches of necrotic of muscle fibers and (d) Gamma-irradiated rats pre-treated with *J. phoenicea* L. amelioration of radiation-induced changes

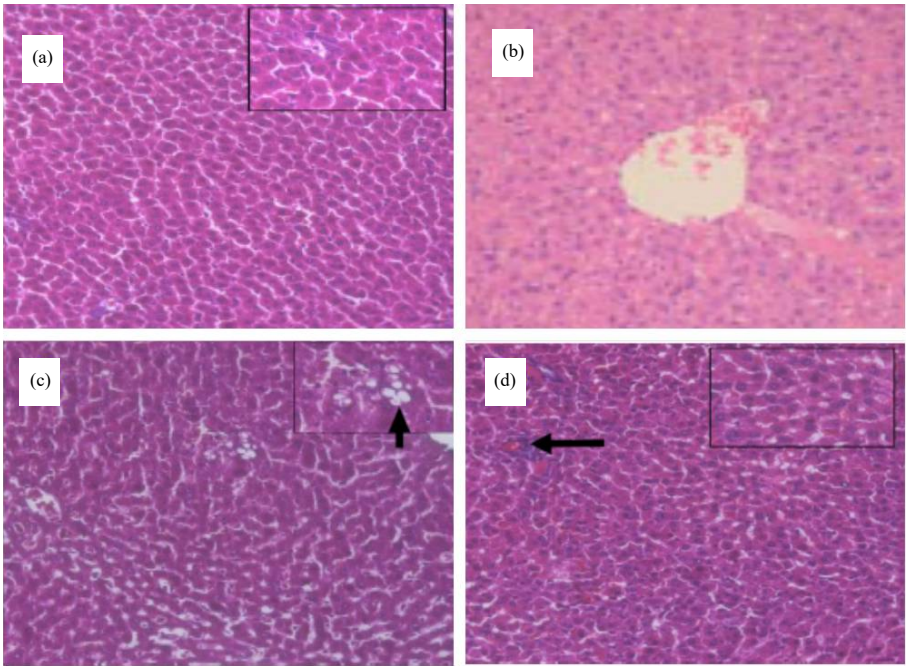

Fig. 3(a-d): Histopathological structure of a section of the liver (H and E, 200X), (a) Normal control rats showing normal hepatic lobular architecture, (b) *Juniperus phoenicea* L. treated rats showing no deviation from the normal architecture, (c) Gamma-irradiated rats showing vacuolar degeneration of hepatocytes (steatosis) (black arrow) and (d) Gamma-irradiated rats pre-treated with *J. phoenicea* L. showing normal hepatic lobular architecture, with scattered inflammatory cells (black arrow)

DISCUSSION

Ionizing radiation causes several damages in the living organisms. The different drugs obtained from the medicinal plants (natural products) can be used to reduce the harmful effects of ionizing radiation[32]. Gamma-irradiation produces liver injury[33] by the destruction of the cellular membranes of the hepatocytes, which in turn causes an increase in the membrane permeability, followed by the release of intracellular enzymes into the blood stream[34]. The high levels of these liver function markers in the irradiated rats reflect the degree of hepatocellular damage induced by the radiation[35]. The gamma-irradiated rats pre-treated with *J. phoenicea*, however, showed a significant improvement in the liver function markers which were almost near the normal control rats. The ionizing radiation causes derangement of several metabolic and physiological activities and biochemical parameters by inducing oxidative stress[36].

Moreover, gamma-irradiation causes peroxidation of the lipids present in the hepatocyte membrane, which contains a large number of fatty acids. Therefore, there is an excessive generation of free radicals leading to an increase in the permeability of the cytoplasmic membrane to organic substances and leakage of cytosolic enzymes, such as ALT, AST, ALP and GGT[37]. The significant increase in the activities of AST and ALT induced by gamma-irradiation observed in this study was similar to that reported in the previous studies of Ibrahim[38] and Mansour[39]. The rise in AST and ALT levels could be a result of the damage of the cell membranes of the hepatocytes resulting in an increased cell membrane permeability. This facilitates leakage of the cytoplasmic enzymes out of the cells causing an increase in the AST and ALT levels in the serum[40]. Hypothesized that *J. phoenicea* extracts can ameliorate the radiation-induced hepatotoxicity because of the high antioxidant activity of its constituent flavonoids[13].

It has been previously reported that *J. phoenicea* exhibit potential hepatoprotective effects[13,41]. This might be attributed to the antioxidative compounds such as flavonoids, phenolics and tannins present which can mitigate the oxidative stress[42].

It was demonstrated that treatment with the methanolic extracts of *J. phoenicea* at an oral dose of 300 mg kg^{-1} 3 times per week for 45 days caused a marked improvement in liver functions in carbon tetrachloride-induced hepatotoxicity in a rat model[43]. The protective effect of the extract on the total protein level might be a result of an increased ribosome assembly in the endoplasmic reticulum that facilitates the biosynthesis of proteins[44].

The effects observed after treatment with *J. phoenicea* leaves extract can be explained by its role in inhibiting pancreatic lipase activity and delaying or inhibiting lipid absorption[45]. These inhibitory effects of the extracts may be related to the total phenolics compounds present in it[46].

The significant increase in levels of cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol ($p<0.05$) in the gamma-irradiated rats compared to those in the normal controls are in accordance with Pradeep *et al.*[47] who showed that a whole body exposure to gamma-irradiation (6.5 Gy) in rats produces biochemical alterations in the serum lipid profile. The rise in the level of serum cholesterol was possibly due to an injury to the cell membranes by gamma-irradiation leading to an extracellular release of cholesterol[48]. Moreover, gamma-irradiation may alter the metabolism of the high and low-density lipoproteins indirectly by various inflammatory cytokines[49]. The treatment of gamma-irradiated rats with *J. phoenicea* leaves extract showed a remarkable improvement in total cholesterol, total triglyceride, LDL-cholesterol and HDL-cholesterol levels. These findings are in agreement with the findings of a previous study by Banerjee *et al.*[50].

It was found that exposure of the rats to a whole body gamma-irradiation caused patchy necrosis of the cardiac muscle fibers with infiltration of chronic and acute inflammation cells. A distinct interstitial edema was also noted. These results are at par to some extent with the results of Mansour and Abu El-Nour[51], who concluded that the radiation-induced damage of the cardiac muscle may be due to the generation of oxidized reactive lipoproteins and through direct DNA damage in the arterial wall cells. In this study, gamma-irradiation induced the formation of structural changes in the aorta, degeneration of the endothelial cell layer of the tunica intima, changes in the endothelium of the intima by the persisting edema, fibrosis and increase of vascular permeability and degeneration and decrease of the number of smooth muscle cells of the tunica media of the aorta. These findings are also in agreement with the findings of a previous study by Soliman[52].

The significant protective effects of the *J. phoenicea* leaves extract might be because of the antioxidants present in the extract protecting against the damaging effect of the oxygen free radicals, thereby preserving the normal appearance of the heart tissue. Similar effects were observed by other free radical scavenging agents[52,53]. *Juniperus phoenicea* as a natural antioxidant prevents oxidative damage to DNA, decreases the generation of free radical oxygen species and protects the tissue against gamma-radiation-induced damage. It can also provide survival benefits to the animals exposed to radiation[13]. It can be

concluded that *J. phoenicea* leaves extract can protect the heart against radiation-induced oxidative stress by mitigating the ROS generation and hence, can be incorporated in the diet as a nutritional supplement.

It is anticipated that oxidative stress is associated with damage of the liver after exposure to an ionizing radiation[54]. Pre-treatment with *J. phoenicea* leaves extract before radiation exposure has led to the reduction of the free radicals-induced damages and thereby retaining the normal-like architecture of the liver tissue. Similar effects were observed by other free radical scavenging agents[52,53].

Pre-treatment with *J. phoenicea* leaves extract also revealed hepato-renal normalization characterized by a normal hepatic lobular architecture, with small numbers of scattered inflammatory cells, normal mesangial cells, a matrix of glomeruli, focal thickened arteriole and mild tubular dilatation. The data from other previous studies have suggested the use of *J. phoenicea* as a dietary supplement to promote protection against free radicals-induced damages[13].

CONCLUSION

The aqueous extracts of *J. phoenicea* leaves at a dose used in traditional medicine (40 mg kg^{-1}) for 3 weeks could be used for improving various blood biochemical parameters and ameliorating radiation-induced damages in the liver and heart. This protective effect may be attributed to the potent antioxidant constituents of this plant.

SIGNIFICANCE STATEMENT

This study discovers the amelioration effect of *J. phoenicea* leaves extract on the gamma-irradiation-induced oxidative damage and tissue injury in rats. The leaves of *J. phoenicea* could serve as a potential source of therapeutic antioxidants and this study will help the researcher to uncover the critical areas of the using the medicinal plants as antioxidative agents that many researchers were not able to explore. Thus a new theory on the important of medicinal plants as antioxidant and may be arrived at

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