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Original article

Role of Acacia arabica gum in reducing the impair alterations in liver tissue of irradiated Albino rats - Histopathological study

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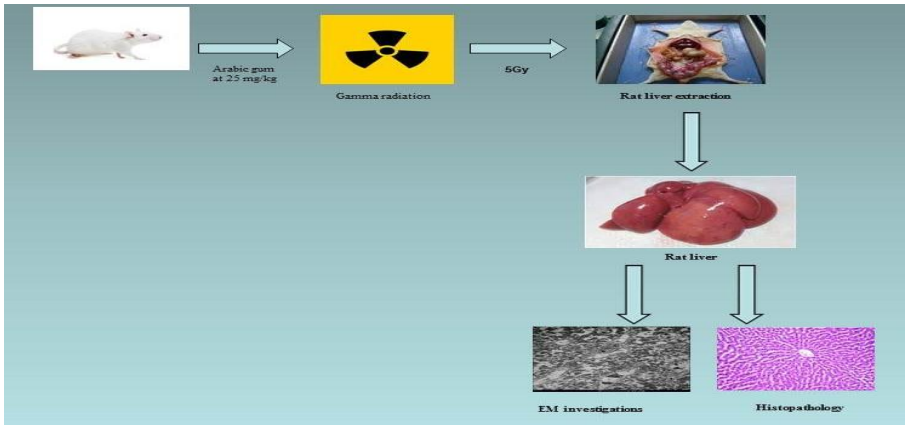
ABSTRACT

The use of ionizing radiation exposure increases oxidative stress especially for cancer patients. Therefore, there is a critical need to develop antioxidants that prevent oxidative stress damage. Arabic gum is an antioxidant and anti-inflammatory mediator. The function of Arabic gum (Acacia arabica) in protecting against injury to the liver tissue caused by 5 Gy whole-body γ-irradiation was studied using histopathological and ultrastructure techniques. Forty-eight male albino Sprague–Dawley rats were divided into four groups: control (C), irradiated (R): rats were exposed to 5 Gy gamma-radiation as a single dose for 10 min., Arabic gum (AG) : rats were treated orally with 25 mg/kg/day AG for 3 weeks and AG + R. Experimental rats were treated orally with 25 mg/kg/day AG for one week before, and three weeks after irradiation, and were sacrificed after 7 and 21 days of irradiation. Gamma radiation was observed to affect the histopathology and ultrastructure of liver tissues, such as distorting the central vein with a highly dilated and delaminated endothelial lining, lymphocytic infiltration, many vacuolated hepatocytes with increased signs of karyolysis (disintegrated and fragmented chromatin) and pyknosis in hepatocytes nuclei, faint electron outer and inner membranes of mitochondria and increases in collagen fibers. On the other hand, treatment with AG ameliorated all of the previous histological and ultrastructure changes. Arabic gum showed a radio-protective effect and improved liver structure indicating that pre-treatment with Arabic gum is effective in lowering the incidence of the hepatic histopathological changes induced by gamma-radiation with remarkable restoration of normal hepatocytes structure.

Graphical abstract



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1. Introduction

Ionizing radiation (IR) is considered as an important environmental risk factor for different cancers yet it is also a major therapeutic agent for the treatment of cancer. Current understanding of the effects of ionizing radiation on biological systems has mainly originated from experimental studies on animals and radiation accidents. These effects depend on many factors, including radiation type, radiation dose, the radio-sensitivity of tissue receiving radiation, and the volume of tissue exposed [1]. IR affects tissue either by causing cell death or by indirect action through water ionization producing reactive oxygen species (ROS). Reactive oxygen species help in promoting the oxidation of DNA, proteins, and lipids [2]. Gamma rays are a form of IR and are thus biologically hazardous [3]. Exposure to IR, whether occupational or during radiotherapy, can lead to serious damage to various cellular and sub-cellular structures and can negatively affect the biological cell membrane [4].

Exposure to IR increases the generation of ROS, such as superoxide (O_2–), the hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\cdot}$), causes lipid peroxidation in the cell membrane, and prevents cell development, leading to physiological disorders and dysfunction in cell and tissue [5]. Clear histopathological changes have been observed in the liver tissue of rats after whole-body gamma irradiation. The liver is an organ subject to frequent metabolic strains due to its central role in detoxification, the metabolism of drugs, xenobiotics, and exposure to insecticides, pesticides and other environmental pollutants [6]. Arabic gum is an edible, water-soluble dietary fibrous heteropolysaccharide, made from the dried gummy exudate obtained and cultivated as a cash crop in agroforestry systems from the stems and branches of Acacia senegal or Acacia seyal trees [7]. It is rich in Ca^{2+}, Mg^{2+} and K^{+}, and is therefore widely used as emulsifier and a stabilizer in the pharmaceutical, cosmetic and food industries [8]. Experimentally, AG has been used in Middle Eastern and North African countries in the traditional treatment of a variety of diseases, such as renal failure, hepatic and cardiac issues, anemia, and diabetes mellitus, in addition to its use as an oral hygienic substance, antidiarrheal, and anti-inflammatory for intestinal mucosa and inflamed skin. Arabic gum improves patients' digestive systems and appetite and has numerous benefits for kidney disease patients [7, 9]. In mice and rats, AG has been reported to act as a protecting agent against hepatic and renal toxicity [10]. It is a widely known safe dietary fiber and affects bacterial mass and enzyme activity; the bacteria count of the cecum may increase due to a higher dietary fiber content without altering the bacteria types present. The relative quantities of acetate and butyrate produced depend on the amount of AG fed [11].

The present study was designed to investigate the role of AG against whole-body γ-radiation -induced histopathological and ultrastructure alterations in liver tissue of male albino rats.

2. Materials and Methods

1.1. Animals

In this study 48 male albino Sprague – Dawley rats weighing 160-180 g were used. Rats were purchased from the Egyptian Holding Company for Biological Products and Vaccines, Helwan, Cairo, Egypt and were kept in the laboratory for 2 weeks before experimental work for acclimatization, where they were housed in specially designed cages, 6 rats per cage, with controlled air, temperature, and relative humidity. The animals had been fed standard rodent pellets. Food and water were made available *ad libitum* throughout the whole experimental period. The investigation was performed in accordance with the Guide for the Care and Use of Laboratory Animals.

1.2. Radiation processing

A Canadian gamma cell-40 Cesium-137 source biological irradiator (Atomic Energy of Canada Ltd, Ottawa, Ontario, Canada), located at the National Center for Radiation Research and Technology (NCRRT), Cairo, Egypt, was used to conduct whole-body γ-irradiation of rats. The dose rate at the time of experiment was 0.6 Gy / min. Rats were exposed for 10 min in order to reach a single dose of 5 Gy (LD_{50} for an acute exposure to radiation).

1.3. Arabic gum (AG)

AG is a soluble dietary fiber naturally obtained from the stems and branches of *Acacia arabica* trees (Family: *Leguminosae*). AG powder was purchased from El-Gomhouria Company (Cairo, Egypt), freshly suspended in distilled water, and orally administered to rats at a dosage of 25 mg / kg / day using a gastric tube for 21 consecutive days according to the method of Gamal El-Din *et al*. [12].

1.4. Experimental design

Forty-eight male albino rats were divided randomly into four groups (12 rats in each group) as follows:

Group 1 (C): administrated with distilled water for 21 days and served as the control rats.

Group 2(R): subjected to 5Gy single-dose gamma radiation.

Group 3(AG): received AG at 25 mg/kg body weight as a daily oral dose for 21 days.

Group 4(AG+R): received AG at 25 mg/kg body weight as a daily oral dose for 7 days before and 21 days after irradiation.

1.5. Histopathological findings

After seven and twenty-one days post-irradiation, animals in control and treated groups were sacrificed, after which the liver was immediately excised and fixed for 24 hours in 10% neutral formalin followed by dehydration in ascending grades of alcohol, whereupon it was cleared in xylene and embedded in paraffin wax. Sections were cut at 5 µm thickness and stained using hematoxylin and eosin stain according to the method of Bancroft and Gamble [13]. Collagen fibers were stained using Mallory's trichrome stain [14]. Olympus BX-53 microscope was used for histopathological examinations with DP 80 Olympus (Japan) camera for imaging process.

1.6. Tissue preparation for electron microscopy

The liver was processed for electron microscopic examination by fixing thin pieces with 5% glutaraldehyde in 0.05 mol/L sodium cacodylate buffer for 1 h, after which the pieces were removed, sliced to a thickness of 1 mm^3 and placed in the same fixative overnight. Tissue slices were post-fixed in osmium tetraoxide for 2 h, dehydrated, and embedded in Epon [15]. One-micron thick sections were cut and stained with 0.5% toluidine blue and examined by light microscopy. Ultrathin sections were cut and stained with uranyl acetate and lead citrate for Transmission Electron Microscopic (TEM) examination using JEOL JEM-1010 TEM (Japan) at the Regional Center for Mycology and Biotechnology, Al-Azhar University (Cairo, Egypt). Digital Hamamatsu C4742-95 camera was used for imaging.

3. Results

3.1. Histological investigation

Histological examinations of sections of liver tissue from control animals revealed a normal liver tissue structure **(**Figure. 1A,1B) and a normal distribution of collagen fibers **(**Figure. 1C). Histological examination of liver tissue sections 7 days post-irradiation (5 Gy) showed many drastic changes in central and portal areas (Figure. 2A-2D). These changes included: lymphocytic infiltration around the corrugated wall of the central vein that contained hemolyzed blood cells; many vacuolated hepatocytes with increased signs of karyolysis and pyknosis in hepatocytes nuclei; highly distorted portal areas containing elongated, dilated, and fibrotic areas in and around portal areas; highly distorted bile duct walls; thickened arterial walls; and numerous degenerated areas containing debris from degenerated hepatocytes. A significant increase in collagen fibers was detected inside hepatic portal vein, in the detached endothelial linings, in the walls of the bile ducts, and in arterial walls (Figure. 2E, 2F). In the second group (21 days post-irradiation), liver tissue exhibited ruptured endothelial lining of the central vein with hemolyzed blood cells within, increased proliferation (hyperplasia) in the walls of the bile ducts, hemorrhagic areas between hepatocytes surrounded by numerous lymphocytes, vacuolated hepatocytes containing pyknotic or karyolytic nuclei, and increased Kupffer cells (Figure. 3A-3D).

A significant increase in collagen fibers was observed throughout the liver tissue, especially in and around walls of the hepatic portal veins and central veins (Figure. 3E,3F). On the other hand, liver tissue of rats administered AG showed near to normal appearance after 7 (Figure. 4A) and 21 days (Figure. 4B,4C), with a normal distribution of collagen fibers around hepatocytes, central vein and in the portal area after 7 (Figure. 4D) and 21 days (Figure. 4E) of treatment. Rats treated with AG after 7 days of irradiation (AG+R) also showed well-developed central areas with increased Kupffer cells and increased lymphocytic infiltration in and around the portal areas. Some hepatocytes showed vacuolation (Figure. 5A,5B). In the second group (after 21 days of irradiation), liver sections showed a well-developed architecture in the central and portal areas, however, the hepatic portal veins were still congested with lymphocytic infiltration in and around the portal areas (Figure. 5C, 5D) with a somewhat normal distribution of collagen fibers in these areas after 7 (Figure. 6A,6B) and 21 days (Figure. 6C,6D) of irradiation.

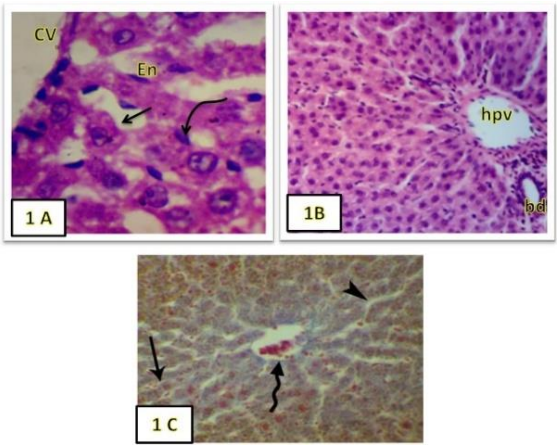

Figure 1. Photomicrographs of sections of liver tissue obtained from the control group. (1A&1B) the central vein (cv) and blood sinusoids (↗). Sinusoids are lined with endothelial cells (En) and Kupffer cells (↥). The portal area contains a branch of the hepatic portal vein (hpv), a branch of the hepatic artery, and bile ducts (bd) (H&E, A X400 & B X250); (1C) thin bundles of collagen fibers support the walls of the hepatocytes, blood sinusoids, and walls of the blood vessels (Mallory's trichrome stain X250).

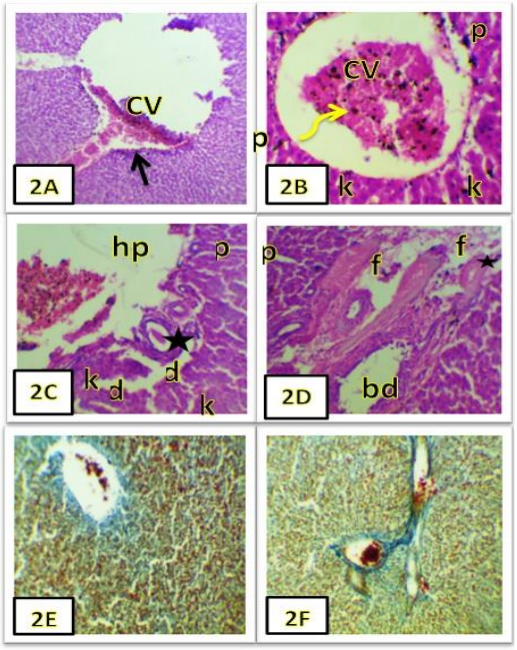

Figure 2. Photomicrographs in sections of liver tissue of irradiated rats after 7 days. (2A&2B) corrugated wall of the central vein (cv), lymphocytic infiltration (↗), hemosiderin granules (↥), nuclei of hepatocytes showing pyknosis (p) and karyolysis (k) (H&E, A X200 & B X400); (2C&2D) corrugated walls of the hepatic portal veins (hpv), fibrotic areas (f), thickened arterial wall (★), numerous pyknotic (p) or karyolytic (k) nuclei, increased proliferation (hyperplasia) in the walls of the bile duct (bd) and degenerated hepatocytes (d) (H&E X250); (2E&2F) significantly increased collagen fibers in the central and portal areas of the liver tissue (Mallory's trichrome stain X250).

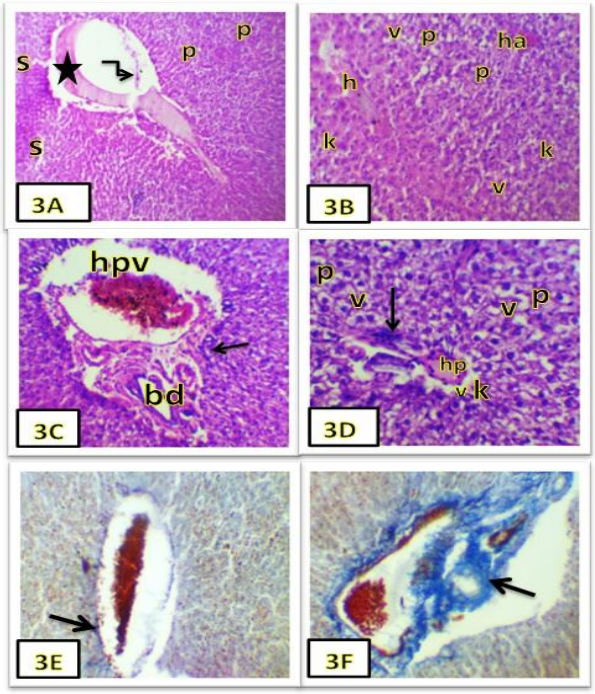

Figure 3. Photomicrographs in sections of liver tissue of irradiated rats after 21 days. (3A) delaminated endothelial lining (⮥) , dilated sinusoidal spaces(s), hemolyzed blood cells (★) and pyknotic nuclei (p). (H&E X200); (3B) hemorrhagic area (ha) and vacuolated hepatocytes (v) with pyknotic (p) or karyolytic (k) nuclei. (H&E X250); (3C&3D) congested hepatic portal veins (hpv), distorted bile ducts walls (bd), lymphocytic infiltration (↗), and vacuolated hepatocytes (V) with pyknotic (p) or karyolytic (k) nuclei (H&E, C X250 & D X400); (3E&3F) increased collagen bundles in and around the central and portal areas (↗) (Mallory's trichrome stain X 250).

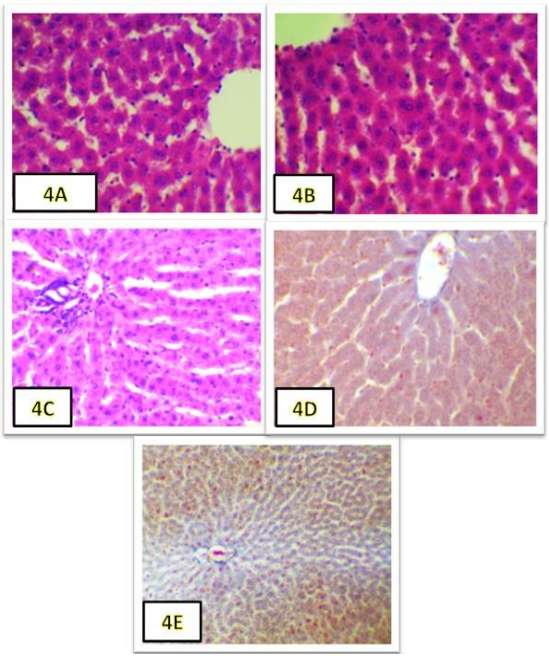

Figure 4. Photomicrographs of sections of liver tissue from the AG groups showing well-developed central and portal areas with increased lymphocytes in and around the portal areas after 7 (4A) and 21 days (4B&4C) of treatment (H&E X250) and showing a nearly normal appearance of collagen fibers after 7 (4D) and 21 days (4E) of treatment (Mallory's trichrome stain, 4D-4E X 250 & 4E X200).

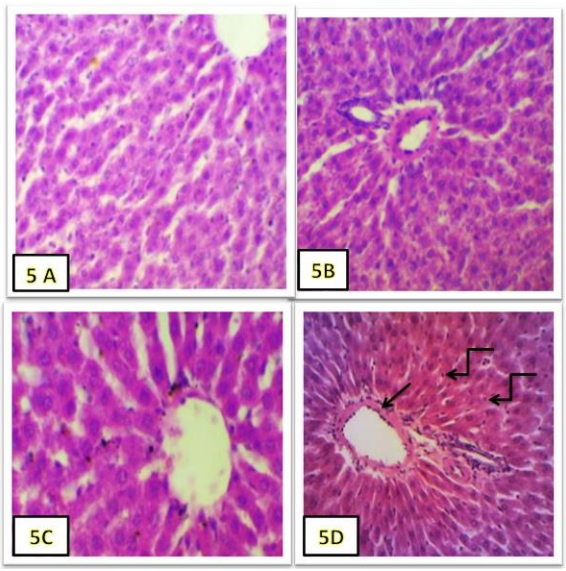

Figure 5. Photomicrographs of sections of liver tissue from the AG + R groups after 7 (5A&5B) and 21 days (5C&5D) of irradiation (5A&5B) somewhat normal architecture of the central and the portal area; (5C&5D) Well-developed architecture of the central and portal areas, however, the hepatic portal vein exhibits a thickened wall (↙) and numerous Kupffer cells were detected (⮥) (H&E X 250).

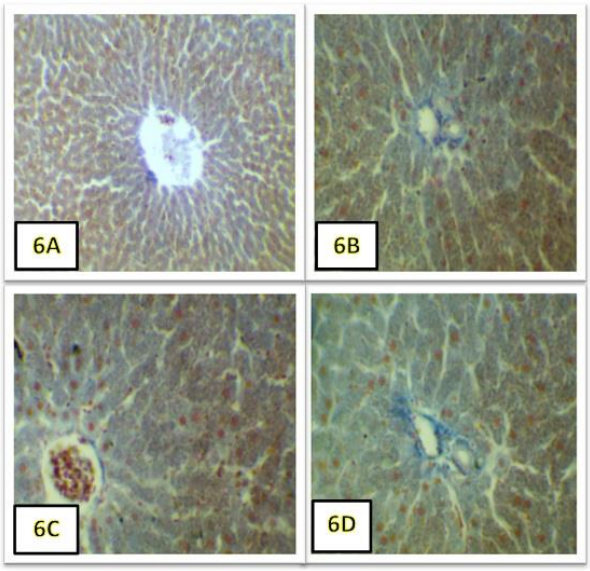

Figure 6. Photomicrographs of sections of liver tissue from the AG + R groups after 7 (6A&6B) and 21 days (6C&6D) of irradiation showing slightly increased collagen fibers in the central and portal areas of the liver tissue of the AG + R groups after 7 (6A&6B) and 21 days (6C&6D) of irradiation (Mallory's trichrome stain, 6A X200 & 6B-6D X250).

3.2. Ultrastructural results

In the control group, the fine structure of the hepatocytes shows a polyhedral shape containing large, rounded euchromatic nuclei with prominent nucleoli. The hepatocyte cytoplasm contains abundant cell organelles, mainly mitochondria of rounded or oval form, which are slightly variable in size and distributed throughout the cytoplasm in association with the endoplasmic reticulum, secondary lysosomes, and glycogen that appears as electron-dense particles dispersed within individual minute granules (Figure. 7).

The irradiated groups after 7 days showed a significant increase in collagen fibers, disintegrated and highly decreased flakes, and granules of glycogen, together with faint electron mitochondria, and poorly detected outer and inner mitochondrial membranes. The nucleus appeared malformed and distorted with disintegrated and fragmented chromatin and has poorly detectable outer and inner nuclear membranes. The undetected cisternae of the rough endoplasmic reticulum decreased the visibility of the ribosome (Figure. 8A, 8B).

Significantly widened sinusoidal spaces contained aggregated collagen fibers and leukocytes with abnormal nuclei and faint electron-dense red blood cells (Figure. 8C). An abnormal shape characterized red blood cells which contained disintegrated hemoglobin and hemosiderin granules are observed in figure 8D. The fine structure of hepatocytes from the irradiated group after 21 days showed disintegrated chromatin, increased collagen fibers, malformed and distorted red blood cells, a relatively reduced number and size of mitochondria, numerous degenerated and necrotic areas containing debris from degenerated cytoplasmic organoids, and an absence of the rough endoplasmic reticulum (Figure. 9A). The widened sinusoidal space contains distorted red and white blood cells (Figure. 9B). Lysosome appeared to be more distributed in the cytoplasm and the electron-faint cisternae increased within the Golgi apparatus (Figure. 9C, 9D). On the other hand, electron microscopy examination of sections of liver tissue from the AG groups after 7 (Figure. 10A) and 21 days (Figure. 10B) of treatment showed a normal hepatocyte structure with well-developed mitochondria, rough endoplasmic reticulum, free ribosomes, and nucleus. Furthermore, electron micrographs of sections of liver tissue from the AG + R group after seven (Figure. 11A) and 21 days (Figure. 11B) showed near to normal nucleus and mitochondria in spite of the decreased amount of glycogen present.

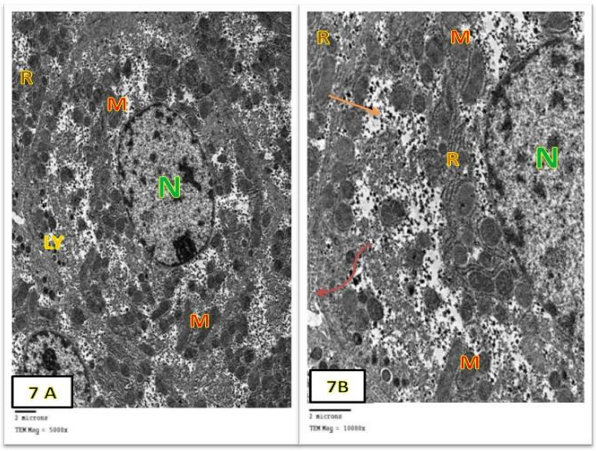

Figure 7. Electron micrographs in sections of liver tissue from the control group. (A) mitochondria (M), flakes and granules of glycogen (↗), rough endoplasmic reticulum (R) with numerous ribosome, lysosome (LY) and nucleus (N) (7AX 5000); (B) magnified portion of hepatocyte, Disse space (↵), basement membrane, and mitochondria with cristae (7BX 10000).

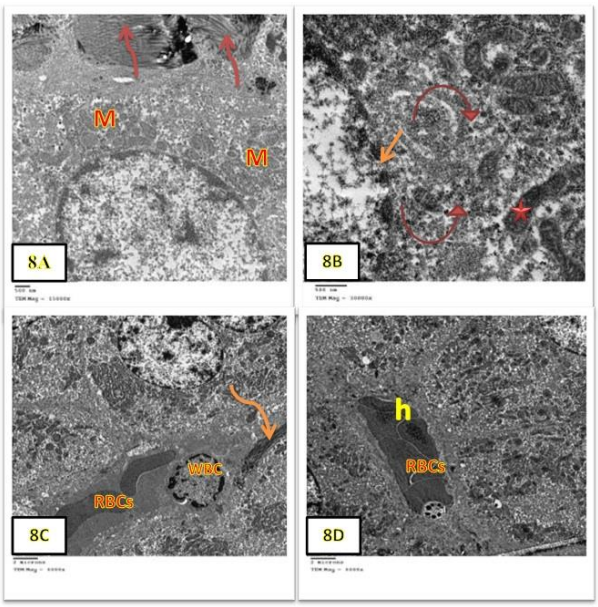

Figure 8. Electron micrographs in sections of liver tissue from the irradiated group after 7 days. (8A,8B) increased collagen fibers (↵), disintegrated flakes and granules of glycogen (↶) and faint electron mitochondria (M). Some mitochondria are malformed (★), and distorted nuclear membranes are present (↘) (8AX 15000 & 8BX 30000) ; (8C,8D) aggregated collagen fibers (↵), leukocytes (WBCs) with abnormal nuclei, and faint electron red blood cells (RBCs) containing hemosiderin granules (h) (8C,8DX 6000).

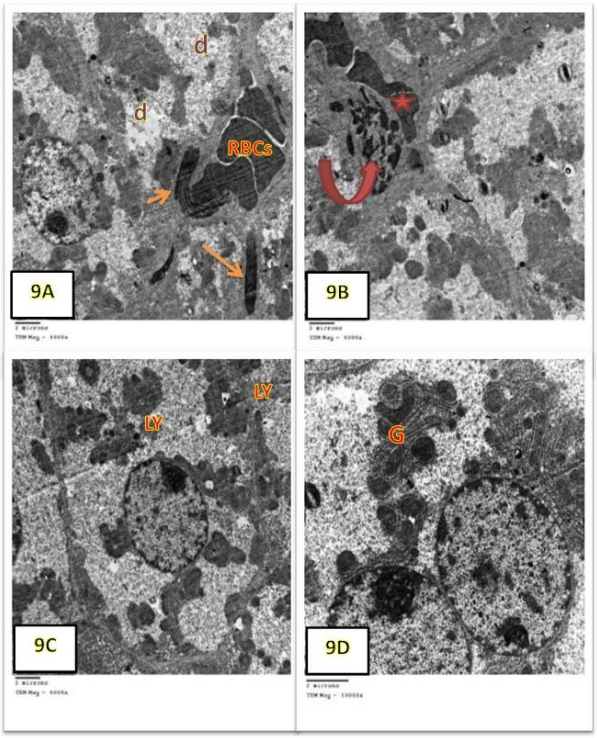

Figure 9. Electron micrographs in sections of the liver tissue from the irradiated group after 21 days. (9A) increased collagen fibers (↘), malformed red blood cells (RBCs), and numerous degenerated (d) and necrotic areas; (9B) widened sinusoidal space containing distorted red (★) and white blood cells (↺) (9A,9B X 6000); (9C,9D) increased number of lysosomes (LY) and electron-faint cisternae within the Golgi apparatus (G) (9C X 6000 & 9D X 10000) .

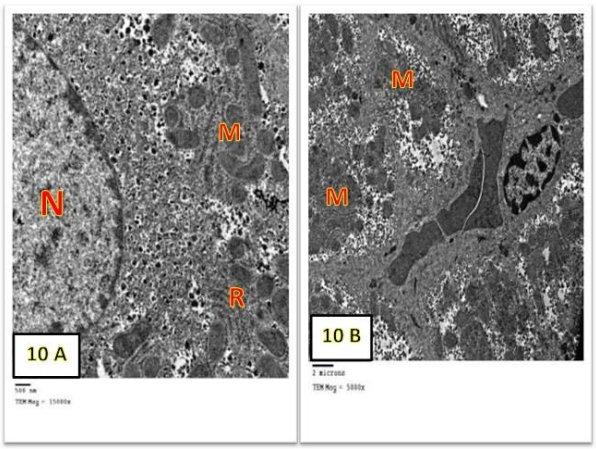

Figure 10. Electron micrographs in sections of liver tissue from the AG groups showing well-developed mitochondria (M), the rough endoplasmic reticulum (R), free ribosomes, and the nucleus (N) after 7 (10A) and twenty-one days (10B) of treatment (10A X 15000& 10B X 5000).

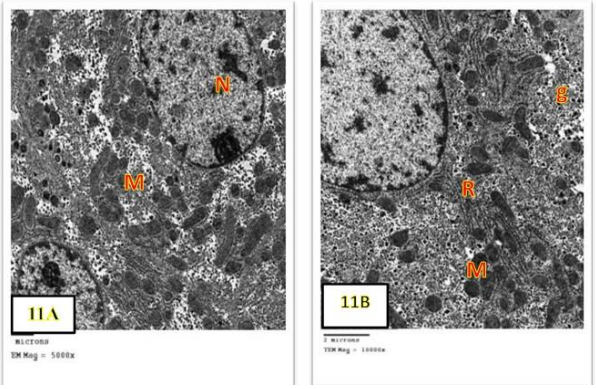

Figure 11. Electron micrographs of sections of liver tissue from the AG + R group after 7 (11A) and 21 days (11B) showing the normal appearance of nucleus (N), mitochondria (M), flakes, and granules of glycogen (g) and rough endoplasmic reticulum (R) (11A X 5000 & 11B X 10000).

4. Discussion

Ionizing radiation is known to cause oxidative stress through the generation of ROS leading to cell unbalance in prooxidant and antioxidant states [16]. When a living cell absorbs radiation, damage is primarily caused by ionization and excitation of that cell's atoms and molecules, resulting in changes in cell structure, damage to essential components and observable biological injury [17]. In the present study, light and electron microscopic investigation of sections of liver tissue from irradiated rats showed many drastic changes in the central and portal areas. These changes included lymphocytic infiltration, numerous vacuolated hepatocytes with increased signs of karyolysis and pyknosis in hepatocytes nuclei, highly distorted portal areas containing congested and corrugated walls of the hepatic portal veins, increased proliferation of bile ducts in the portal areas, and a relatively increased collagen fibers in the wall of hepatic portal veins ,the arterial walls and bile ducts, with many scattered collagen fibers in between hepatocytes of the exposed groups.

These results are in agreement with those of Hodhod et al. [18] who revealed partial loss of hepatic architecture in areas of liver from rats exposed to gamma radiation at dose level 5 Gy, with moderate hydropic degeneration of hepatocytes, congested central veins, and sinusoids. Mahgoup et al. [19] detected severe histological changes in hepatic and renal tissues post-irradiation. It was observed that radiation-induced extended necrosis, dilatation and congestion of the central veins, and sinusoids. Increased collagen following exposure to radiation has been detected in different tissues by several authors [20, 21, 22]. The presence of collagen in the sinusoidal spaces could affect blood supply to liver cells and thus reduce metabolite exchange, thus it might induce hepatocellular dysfunctions and necrosis [23]. George et al. [24] indicated that diminished collagenolytic enzyme synthesis by impaired hepatocytes could lead to further collagen accumulation. Epidermal growth factor (EDF) is one of the key hepatocyte cell proliferation factors and promotes DNA synthesis [25]. EDF has also been shown to promote the proliferation of the hepatic stellate cells (HSC) [26]. The hepatic stellate cells and liver fibroblasts have modulatory roles in inflammatory conditions as a result of their capability for cytokine and chemokine production. It store vitamin A, but produce extra-cellular matrix and collagen when activated. They are located in the space of Disse between hepatocytes and endothelial cells [27]. Hepatic stellate cells plays a main role in fibrogenesis through the synthesis of increased amounts of collagen when activated by profibrogenic factors such as oxidant stress [28].

Electron microscopic examination of hepatocytes from irradiated groups showed disintegrated and fragmented chromatin and limited outer and inner mitochondrial membranes. Some mitochondria were malformed and distorted undetected cisternae of the rough endoplasmic reticulum and decreased ribosomes. Similar results have previously been detected by several authors [19, 29, 30]. Tekın et al. [31] exhibited significant ultrastructural changes in liver cells of rats exposed to ultraviolet radiation (UV R) for 7, 14, and 21 days. These changes included a decrement of cytoplasmic organelles, dilatation of the rough endoplasmic reticulum, impairment of the nuclear membrane, expanded and vacuolated cytoplasmic mitochondria .IR-induced tissue damage activates both local and systemic inflammation processes resulting in increased plaque cell turnover and oxidative stress [32]. These effects can favor the generation of lipid droplets by activating protein complexes and producing ROS, which oxidizes lipids in the liver and promotes extra ROS generation [33]. The oxidation of lipids and proteins caused damage to membrane structures, which in turn produced more changes such as membrane potential, permeability and the release of digestion enzymes into the intercellular matrix. Mitochondria are the cellular structures that are most sensitive to ROS and might lead unspecific pores to form in the inner mitochondrial membrane resulting in an imbalance between the intermembrane space and the mitochondrial matrix [34]. The erroneous functioning of the respiratory chain leads to increased ROS production and, as a result, further impairment of both the

mitochondria and the entire cell [35, 36]. Most disease processes arise from or result in cellular energy balance disturbances; therefore, mitochondrial swelling is one of the most common early ultrastructural characteristics of the affected cells [35, 37].

In the current study, hepatocyte-damaged mitochondria were detected in irradiated rat livers. Antioxidants appear to improve the condition of the blood vessels by helping to neutralize free radical molecules or ROS that may inhibit blood vessel-lining endothelial cells from liberating nitric oxide, which is responsible for blood vessel dilatation [38]. Al-Doaiss and Al-Shehri [39] interpreted the antioxidant effects of AG by its ability to trigger endogenous glutathione levels and to suppress lipid peroxidation in rats' blood, liver and kidney tissues. Pal et al. [40] indicated that the hydro-alcoholic extract of Acacia senegal had significant hepatoprotective activity, probably due to its high flavonoid content.

Our results showed that supplementation of Arabic gum to rats induces well-developed central and portal areas in liver tissue with increased lymphocytes in and around the portal areas. Also, this study has shown that supplementation of AG in the AG + R groups results in a trend toward lowering the incidence of hepatic pathological changes induced by γ-radiation and a remarkable restoration of normal cell structure. Cells restored their regularity and sizes, including a normal homogenous cytoplasm with rounded nuclei and a normal distribution of collagen fibers in the central and portal areas of liver tissue sections from the AG & AG+R groups. The present study is thus in agreement with previously described results by El-shama et al. [41], who observed both normal hepatic architecture and collagen fiber distribution in the central and portal areas of liver tissue sections from rats receiving 10 mg/kg/day of Arabic gum only. This indicates the radio-protective effect of AG and its ability to scavenge free radicals arising from γ-radiation.

Electron microscopy examination in sections of liver tissue from the AG & AG + R groups showed a near to normal hepatocyte structure with well-developed mitochondria, rough endoplasmic reticulum, free ribosomes, and nuclei. The positive role of AG in alleviating the histopathological damage caused by glycerol has been previously reported [42]. Arabic gum has several hepatic protective factors including amino acids (e.g., methionine, arginine, and isoleucine) capable of chelating trace minerals and potent antioxidants, such as phycocyanins and superoxide dismutase [43]. Arabic gum is thus a promising functional food with potential hepatoprotective effects in non-alcoholic fatty liver disease [44]. The role of AG in the improvement of radiation-induced kidney and liver dysfunction might be attributed to its antioxidant, anti-inflammatory and cytoprotective properties [45] in addition to down-regulation of the levels of hepatic caspase-3, interleukin -β1, interleukin -6 and tumor necrosis factor -α (TNF- α) genes[46] and immunomodulatory effects[47],through scavenging superoxide anions [48] and inhibiting lipid peroxidation [49] AG protects the cell membrane from radiation-induced oxidative damage. This is supported by the fact that AG has high affinity to free radicals [39]. Published reports showed the numerous biological activities of Acacia species such as hypoglycemic, antitumor, anti-inflammatory [11], anti-hepatitis C virus, spasmogenic and vasoconstrictor, antiplatelet aggregation, antihypertensive [49], and antioxidant potential [50], together with wound healing [51].

5. Conclusion

The current study shows that the histopathological and ultrastructural alterations produced by γ-rays were attenuated by pre-treatment with Arabic gum. This could be due to the radio-protective effect of AG and its ability to scavenge free radicals arising from γ-radiation. The results of this study imply that pre-treatment with AG is effective in lowering the incidence of the hepatic pathological changes induced by γ-radiation and a remarkable restoration of normal cell structure.

Acknowledgements

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Conflicts of interest

Declared none.

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