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Radioprotective effect of Malva sylvestris L. against radiation-induced liver, kidney and intestine damages in rat: A histopathological study

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ABSTRACT

Background: Ionizing radiation (IR) is widely used in the treatment of cancer in radiotherapy. One of the main concerns of patients with gastrointestinal cancers undergoing radiotherapy is the harmful side effects of IR on normal tissues. The liver, kidney, and duodenum are usually exposed to high doses of radiation in the treatment of some cancers in abdominal region radiotherapy. We aimed to assess the radioprotective effects of Malva sylvestris L. against IR damages to the abdominal region.

Materials and methods: This current study was conducted on 45 rats divided randomly into nine groups of five: A) negative control group, B) sham group, C) irradiation group, D) mallow treatment-1(200gr/kg), E) mallow treatment-2(400gr/kg), F) mallow treatment-3(600gr/kg), G) mallow treatment-4(200gr/kg) plus irradiation, H) mallow treatment-5(400gr/kg) plus irradiation, I) mallow treatment-6(600gr/kg) plus irradiation. Irradiation was performed with a 6Gy x-ray. Histopathological evaluations were performed 10 days after irradiation.

Results: The histopathological examination results confirmed that preventive therapy with the effective dose of mallow reduced the liver, kidney, and intestine damage induced by radiation. The dose of 400 mg/kg was more effective than other selected dose in improving the damage caused by irradiation in the studied tissues.

Conclusion: This study concludes that Malva sylvestris L. contributed to significant improvements in radiation-induced histological parameters of the liver and kidney and, to a lesser extent, in the intestine. These results collectively indicate that mallow is an effective radioprotective agent.

1. Introduction

One of the most important applications of IR is medical research and radiotherapy [1]. Today, with the expanding use of radiotherapy (RT) in cancer treatment, the side effects of cancer treatment are more severe than ever before [2]. Although radiation therapy is commonly used to treat a wide range of human cancers, irradiation of adjacent normal tissues and the radiation toxicities are significant, which limit the gain of radiotherapy [3]. Irradiation of normal tissue can cause both acute and chronic toxicity, which can lead to failure of intended treatment, manifestation of various symptoms, and reduced quality of life [3]. On the other hand, upgrading radiotherapy techniques and equipment may reduce the side effects of IR. Different methods with different mechanisms for protection against IR have been introduced [4–6]. Radioprotectors are always identified by radiobiologists as compounds that are used to protect normal cells from the harmful effects of radiation. Attempts have been made to identify novel, nontoxic, effective, and convenient compounds of radioprotectors to protect normal tissues against radiation damage [7]. The use of radioprotectors could improve the therapeutic gain of radiation therapy [8]. Various radioprotectors have been introduced that can be very effective and helpful in mitigating the side effects of IR [9–14]. Flavonoids are a group of natural polyphenolic compounds that have been identified in many plants in different species and can have radiation protection properties [15,16].

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Malva sylvestris L., commonly called mallow, is a compound with antioxidant and anti-inflammatory effects [17,18]. Mallow plant extracts have been shown to be non-toxic and safe for a wide range of biological activities [19]. Mallow has also been shown to have high antioxidant capacity due to its high levels of phenolic compounds [20]. It has been reported that mallow extract may have renal and hepatic protective effects against the toxic effects of gentamicin [21]. It may protect the kidney from ischemia-reperfusion injury [22] and the liver from acetaminophen injury [23]. This study surveyed the radioprotective efficacy of Malva sylvestris L. in the liver, kidney, and intestine tissue damage in a rat model.

2. Materials and methods

2.1. Extract preparation

The aqueous extract of the Malva sylvestris L. was used for this study. The flowers were approved by an herbal pharmacist at the college of pharmacy. The aqueous extract of the plant (1 kg) was extracted by soaking in distilled water with a shaker for 72 h and 3 times at room temperature (maceration method). The resulting extract was filtered using Whatman filter paper and microbial filter. Next, the extract was dried and concentrated in a vacuum at 40 °C by a rotary evaporator (Laborota4000, Heidolph Instruments, Schwabach, Germany), and stored in the refrigerator away from light until use [24].

2.2. The procedures and animal study

In this current study, we used 45 male rats (250-300gr and 6–8 weeks), randomly assigned into nine groups (5 rats in each group). All ethical principles of working with laboratory animals were observed according to the instructions of the ethics committee of Hamadan University of Medical Sciences, and the research protocol was approved by this committee (IR.UMSHA.REC.1400.630). Animals were kept in the animal room at 22 ± 1 °C under a 12/12-h dark light. The liquid extract of mallow was administered to the animals every day for one week at doses of 200, 400, and 600 mg/kg in treatment groups and before receiving X-ray irradiation.

A: Control group: Without any intervention
B: Sham group: Normal saline (5 ml/kg).
C: Irradiation only (6Gy)
D: Treatment group [1]: only 200 mg/kg mallow extract
E: Treatment group [2]: only 400 mg/kg mallow extract
F: Treatment group [3]: only 600 mg/kg mallow extract
G: Treatment group [4]: 200 mg/kg mallow extract plus 6Gy radiation
H: Treatment group [5]: 400 mg/kg mallow extract plus 6Gy radiation
I: Treatment group [6]: 600 mg/kg mallow extract plus 6Gy radiation

On the seventh day, all rats in groups C and G-I were anesthetized with ketamine (80 mg/kg) and xylocaine (5 mg/kg). The rats were then irradiated in the supine position to their abdomen with 6Gy X-rays according to previous studies [25–27] by linear accelerator (LINAC). The source-to-skin distance (SSD) was 90 cm while the radiation dose rate was 600 cGy/min. The rats were returned to the laboratory and 10 days later rats were sacrificed whose liver, intestine, and kidney tissues were removed to evaluate the acute effects of IR. The tissues were kept in formalin (Cat No: 104402, Merck, Germany) for histological examination.

2.3. Histopathological evaluation

Ten days after irradiation, all rats were euthanized following anesthesia via intraperitoneal injection of ketamine and xylocaine. Their liver (a 1-cm piece from the margin of the left lobe of the liver), kidney, and jejunum tissues (equally, 10 cm after the pylorus) were sampled and after washing, immediately fixed within 10% neutral-buffered formalin, for 72 h. Specifically, 10-μm sections of the liver, kidney, and intestine tissues were obtained and stained with hematoxylin and eosin (H&E); (Hematoxylin: Cas N0: 517-28-2; Eosin: Cas N0: 17372-87-1, Merck, Germany) as well as Masson's trichrome (MTC); (Cat no: 25088-10, Bio Trend, Germany) while kidney and intestine tissues were only stained with H&E. H&E slides were used for evaluating general tissue characterization, and Masson's trichrome for detection of collagen accumulation. To investigate histological changes, three slides were prepared from each sample and 20 non-overlapping visual fields were randomly examined by each group under the light microscope (echo LAB cmos 16 M). Finally, the semi-quantitative scoring of parameters was performed using Image-J software under a light microscope (echo LAB CMOS 16004DSDW21) and Motic Moticam 3+ Digital Camera.

2.3.1. Hematoxylin and eosin staining

For hematoxylin and eosin staining, the following steps were performed respectively. Initially, all slides in each group were deparaffinized with xylene, dehydrated with ethanol and placed in hematoxylin solution, then washed under running water. They were differentiated by acidic alcohol for a dip, and then immediately rinsed with water, after which the slides were placed in eosin for 3 min. The next steps were dehydration in ascending ethanol and clearing in xylene, and finally mounting [28].

2.3.2. Masson's trichrome staining

This staining was done according to the instructions provided in the kit (Asia Pajohesh).

Tissue fibrosis, the number of necrotic cells, infiltration of lymphoid cells, increase in the number of Kupffer cells, congestion vacuolation and foamy cells, changes in the size and shape of the central vein as well as the arrangement of liver sinusoids were also the items used for the description of liver injury. The changes in the tubule/interstitial space, glomerular changes, endothelial changes, tubular changes were used to show kidney damages. The integrity of absorptive cells and microvilli, as well as the height and structure of finger-shaped villi and crypt were employed in the description of the jejunum injury.

3. Results

3.1. Histopathology of the liver

To determine acute changes in liver tissue after RT, histopathological evaluations of the liver sections were performed in the control, radiation, mallow treatment, and mallow + radiation (A-I) groups on 10 days post-radiation (Table 1, Fig. 1, and Fig. 2). Examination of slides stained with H&E indicated that the control group (group A) and sham group (group B) had a normal tissue structure with hexagonal lobules around circular central veins and peripheral triads. The hepatocytes radiated towards the outside from the central vein, and in the space between the hepatocyte cells, dis spaces, were observed. Hepatocytes in this group had a large spherical nucleus with a distinct nucleolus distribution and peripheral chromatin.

In group C, following irradiation, the structure of the lobules was erratic with infiltration of mononuclear cells around the central vein and around the triad and irregularity in the arrangement of hepatocytes. Vacuolation and size changes of hepatocyte cells were not seen in this group. The nucleus of hepatocytes revealed an increase in chromatin density and a very compact nucleolus structure, as well as acidophilic cytoplasm, which indicates necrotic changes around the central vein.

Group D and Group E showed normal histological features, though Group F indicated irregularities in the arrangement of hepatocytes and infiltration of mononuclear cells around the central vein, as well as

Table 1
Effect of Mallow treatment on Liver index of rats exposed with X-irradiation (EGTI scoring).

Groups	Sinusoidal irregularity	Changing the size and shape of the central vein	Vacuolation and foamy cells	Congestion	Increase in the number of Kupffer cells	Infiltration of lymphoid cells	The number of necrotic cells	Tissue fibrosis	The severity of damage(sum)
A	–	–	–	–	-	–	–	–	0
B	–	–	–	–	–	–	–	–	0
C	++++	++++	+	+	–	++++	++	++++	20
D	–	–	–	–	-	–	–	–	0
E	–	–	–	–	-	–	–	–	0
F	++	++++	–	+	–	++	+	+	11
G	+++	++	–	–	–	++	+	+	9
H	+	–	–	–	–	+	+	+	4
I	++++	++++	–	+	–	++	++	+++	16

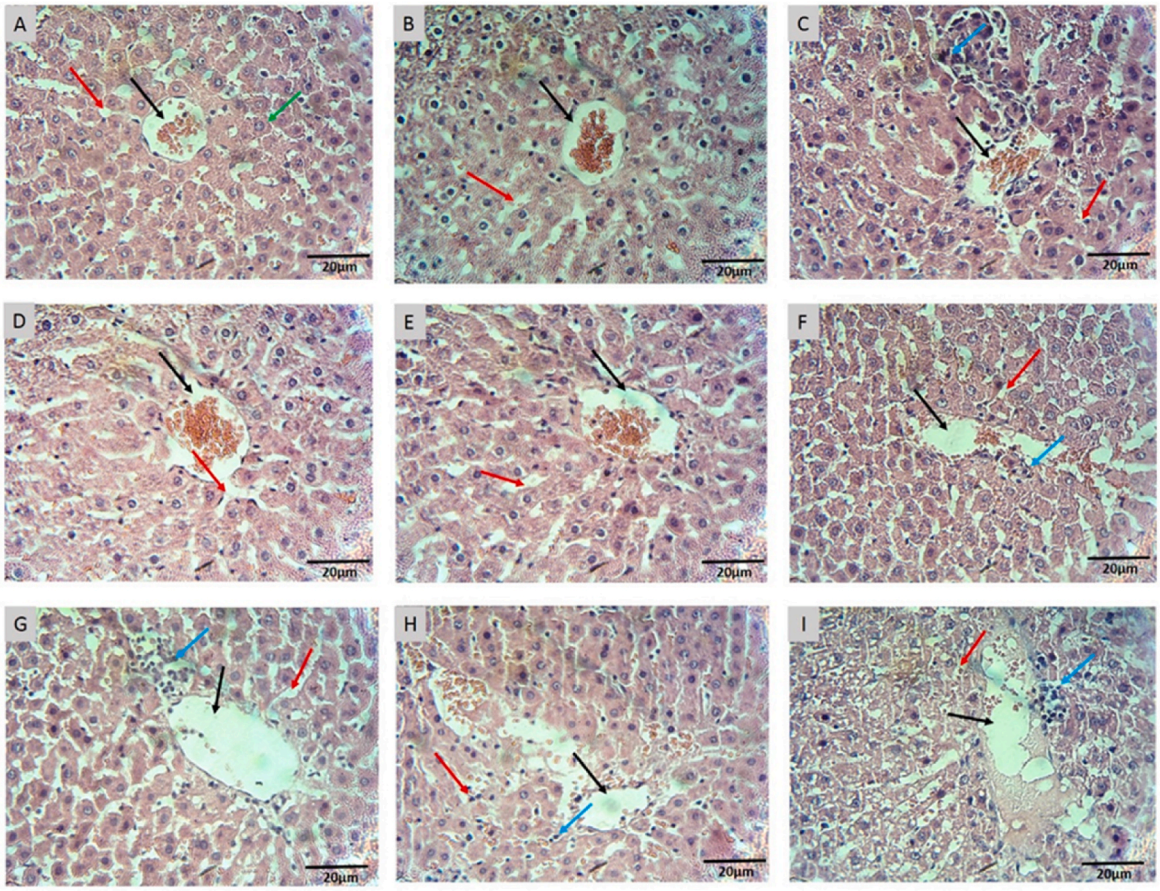

Fig. 1. Hematoxylin and Eosin staining. Histopathological changes of liver: A: Control group, B: Sham group: Receive normal saline, C: Irradiation only, D: Pretreatment with 200 mg/kg Mallow extract, E: Pretreatment with 400 mg/kg Mallow extract, F: Pretreatment with 600 mg/kg Mallow extract, G: Pretreatment with 200 mg/kg Mallow extract plus Irradiation, H: Pretreatment with 400 mg/kg Mallow extract plus Irradiation, I: Pretreatment with 600 mg/kg Mallow extract plus Irradiation. The images were selected as samples from the central vein region with 40× magnification.
Black arrow: central vein/red arrow: sinusoidal space or dic/green arrow: hepatocyte/blue arrow: mononuclear cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

changes in the size and shape of the central vein.

Group G and Group H showed improved histopathological condition of the samples so that the effectiveness of the dose of 400 mg/kg was greater than that of 200 mg/kg. Examination of different visual fields of the group I showed that this dose was not effective on improving the histopathology of the liver. Samples stained with Masson's trichrome indicated the presence of relative tissue fibrosis in the group irradiation only. The intensity of fibrosis was not high and it was more evident around the triads. The dose of 400 mg/kg was the most effective on improving fibrosis while the dose of 600 was not effective on improving fibrosis.

3.2. Histopathology of kidney

Histopathological changes in the kidney are shown in Table 2 and Fig. 3 the kidney sections were stained using the H&E staining method. From the prepared slides, the cortex and medulla were studied using an optical microscope. Some non-overlapping random fields were selected from the cortical region as well as the cortex region of each kidney and analyzed (see Fig. 4).

The qualitative analysis of the kidney sections in the cortex and medulla region shows that in groups A and B, there is a standard tissue structure in the glomerulus and tubes. On the contrary, kidney sections

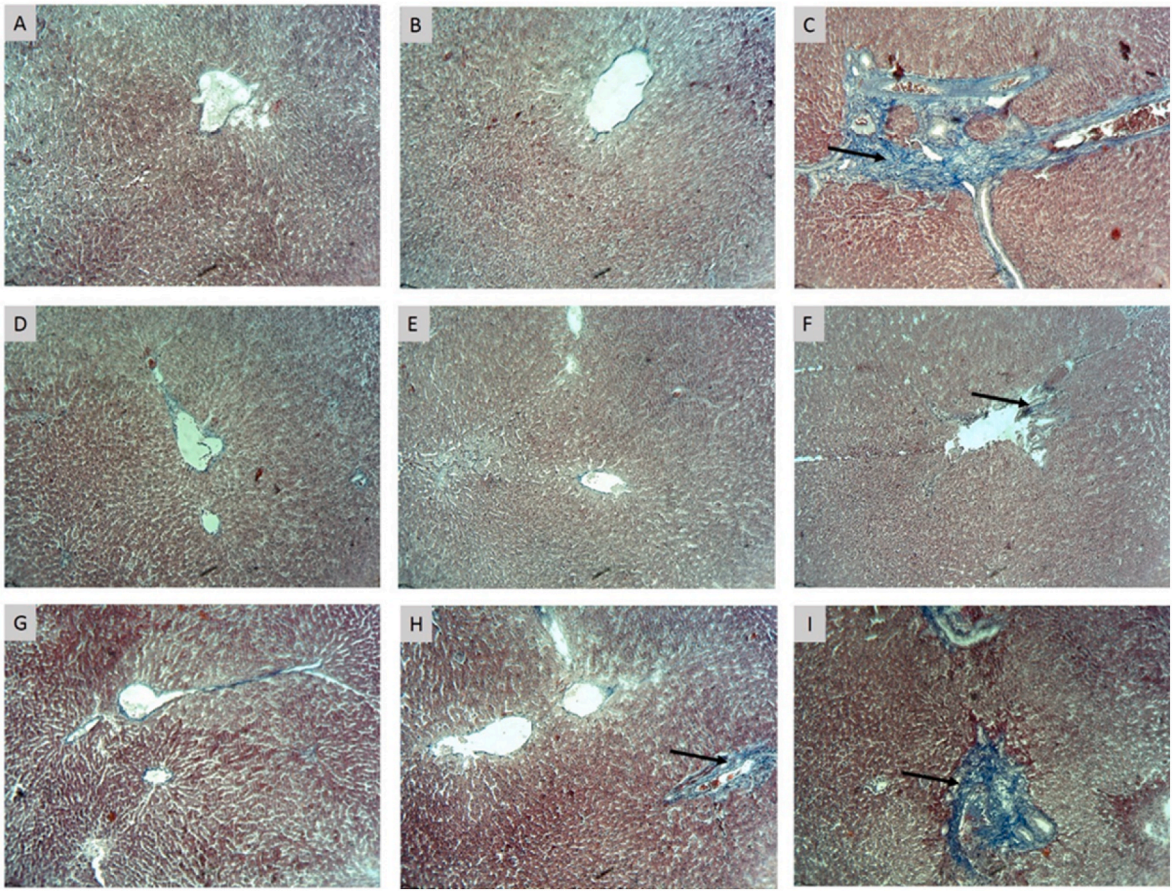

Fig. 2. Masson's trichrome staining. Staining of collagen fibers in liver groups: A: Control group, B: Sham group: Receive normal saline, C: Irradiation only, D: Pretreatment with 200 mg/kg Mallow extract, E: Pretreatment with 400 mg/kg Mallow extract, F: Pretreatment with 600 mg/kg Mallow extract, G: Pretreatment with 200 mg/kg Mallow extract plus Irradiation, H: Pretreatment with 400 mg/kg Mallow extract plus Irradiation, I: Pretreatment with 600 mg/kg Mallow extract plus Irradiation. The images were selected as samples from the central vein region with 20× magnification.
Black arrow: collagen fibers.

Table 2
Effect of Mallow treatment on kidney index of rats exposed with X-irradiation.

Groups	Tubular changes	Endothelial changes	Glomerular changes	Changes in the Tubulo/ Interstitial space	The severity of damage (sum)
A	–	–	–	–	0
B	–	–	–	–	0
C	+++	++	++++	+++	12
D	–	–	–	–	0
E	–	–	–	–	0
F	+	–	+++	+	5
G	++	+	+++	++	8
H	+	–	+	+	3
I	++	++	+++	++	9

in group C show severe tissue damage mainly in the form of inflammation. Infiltration of mononuclear cells was seen mostly in the kidney cortex area. In some region, the glomerulus does not have a clear boundary, and the parietal layer of Bowman's capsule has become very thick so the renal space has disappeared.

Also, the cytoplasm of the cells in the tubes was very acidophilic, the brush border of the proximal curved tube was shortened, and in several tubes, degeneration and cell death were observed in the epithelium of the proximal and distal convoluted tubes. There was cell necrosis in the tubes and the nuclei were seen in a pyknotic state. Hemorrhage was not observed in the space between the cortex and medulla tubes.

In groups D and E, Extract doses did not cause changes in tissue structure, and these groups did not have significant changes from the control group, and it is noteworthy that the dose of 600 in group F acted as a toxin and caused glomeruli degeneration.

In groups G and H, the tissue damage was less, and the dose of 400 was more effective than the dose of 200, and the dose of 600 (group I) could not cause tissue improvement.

Based on the EGTI scoring, the changes can be quantitatively expressed in Table 1.

3.3. Histopathology of intestine

A specific area of the jejunum was sampled from all groups. Slides were stained by H&E. The structure of finger-shaped villi with normal absorptive cells and striated borders as well as normal crypts of Lieberkühn was observed in Groups A and B. In Group C, after irradiation, only the shape of the villi had become irregular and their length was far shorter. In Groups D and E, as well as F, the tissue profiles were normal and there was no significant difference from the control group. Groups G and I showed improved histopathological condition of the samples to a relatively small extent, and although there was no difference between these two prescription doses, the dose of 400 mg/kg (group H) was more effective than the other doses.

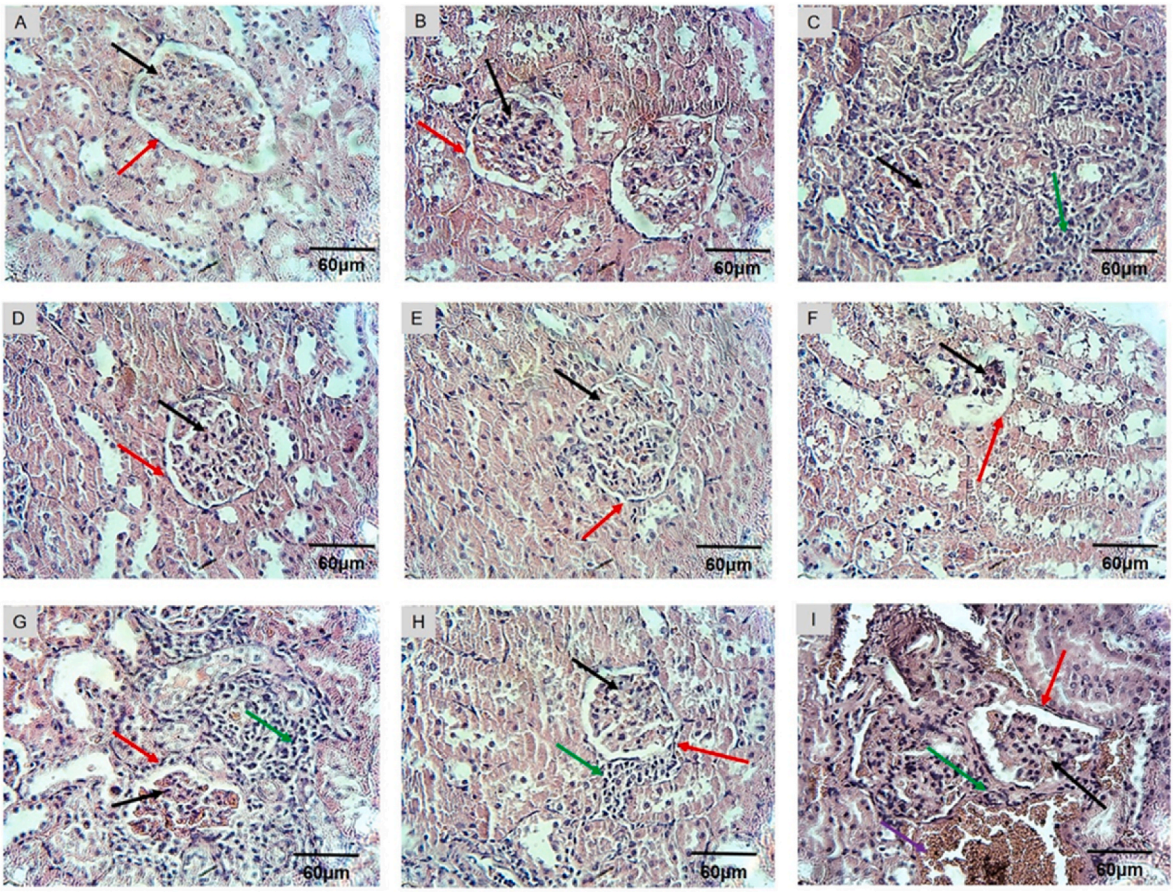

Fig. 3. Hematoxylin and Eosin staining. Histopathological changes of kidney: A: Control group, B: Sham group: Receive normal saline, C: Irradiation only, D: Pretreatment with 200 mg/kg Mallow extract, E: Pretreatment with 400 mg/kg Mallow extract, F: Pretreatment with 600 mg/kg Mallow extract, G: Pretreatment with 200 mg/kg Mallow extract plus Irradiation, H: Pretreatment with 400 mg/kg Mallow extract plus Irradiation, I: Pretreatment with 600 mg/kg Mallow extract plus Irradiation. The images were selected as samples from the cortex of kidney with 40× magnification.
Black arrow: glomerulus; Red arrow: parietal layer of Bowman's capsule; Green arrow: mononuclear lymphoid cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

To treat cancer in radiotherapy, normal tissue irradiation is one of the important challenges. These damages caused by radiation can lead to various side effects in different organs, which can be seen in different ways, including oxidative stress, fibrosis, inflammation, or loss of their function.

During radiotherapy of tumors in the abdomen region, irradiation can damage the normal tissues adjacent to the tumor [29]. The liver, kidney, and intestine are the most important tissues located in the abdominal area and may be exposed to a high dose of radiation during treatment. In addition, people exposed to high doses of IR in nuclear accidents or terrorist attacks need some readily available, non-toxic agents to reduce the lethal effects of IR [30]. Herbal supplements due to their safety and lower side effect profile can protect as well as treat certain diseases. The protective effect of mallow has been reported in several reports which could be attributed to the interaction of antioxidant components [20,31,32].

Mallow contains several compounds, including flavonoids, vitamins C and E, β-carotene, omega-3, and omega-6 essential fatty acids, enzymes such as sulfite oxidase and catalase, and polysaccharides [33,34], all conferring antioxidant and free radical scavenging properties to this herb [35].

Protection of normal tissues against radiation exposure in the abdominal area by radiation radioprotective agents may also be useful for patients. In the present study, we aimed to define whether mallow can establish a good radiation protection effect against IR in the abdominal area.

The liver is a very important organ of the body which participates in various physiological functions. While exposed to radiation due to radiotherapy or nuclear accident, as a radiosensitive organ, the liver may suffer from radiation-induced liver injury. Sinusoidal obstruction, perivenular fibrosis, and damage to Kupffer cells as well as hepatocytes are typical pathological manifestations of IR [36].

The results of this study on the liver demonstrated that radiation leads to a significant mess in the structure of the lobules and change in lymph cells as well as irregularity in the arrangement of the hepatocytes with necrotic changes observed around the central vein.

Also, in the kidney, radiation caused severe tissue damage, mainly in the form of inflammation, infiltration of mononuclear cells in the cortex area, and thickening of Bowman's capsule parietal layer. In the jejunum, radiation induced shape irregularity and reduction of villi length.

In this study, the results showed that pre-treatment with mallow can be most effective on improving fibrosis in the liver, and kidney damage caused by radiation. The histopathological condition of jejunum samples relatively improved after administration of the mallow extract, though the differences were not significant. It seems that mallow was less effective for jejunum compared to the liver and kidney. The exact mechanisms of the radioprotective effect of mallow should be further investigated using biochemical and molecular studies.

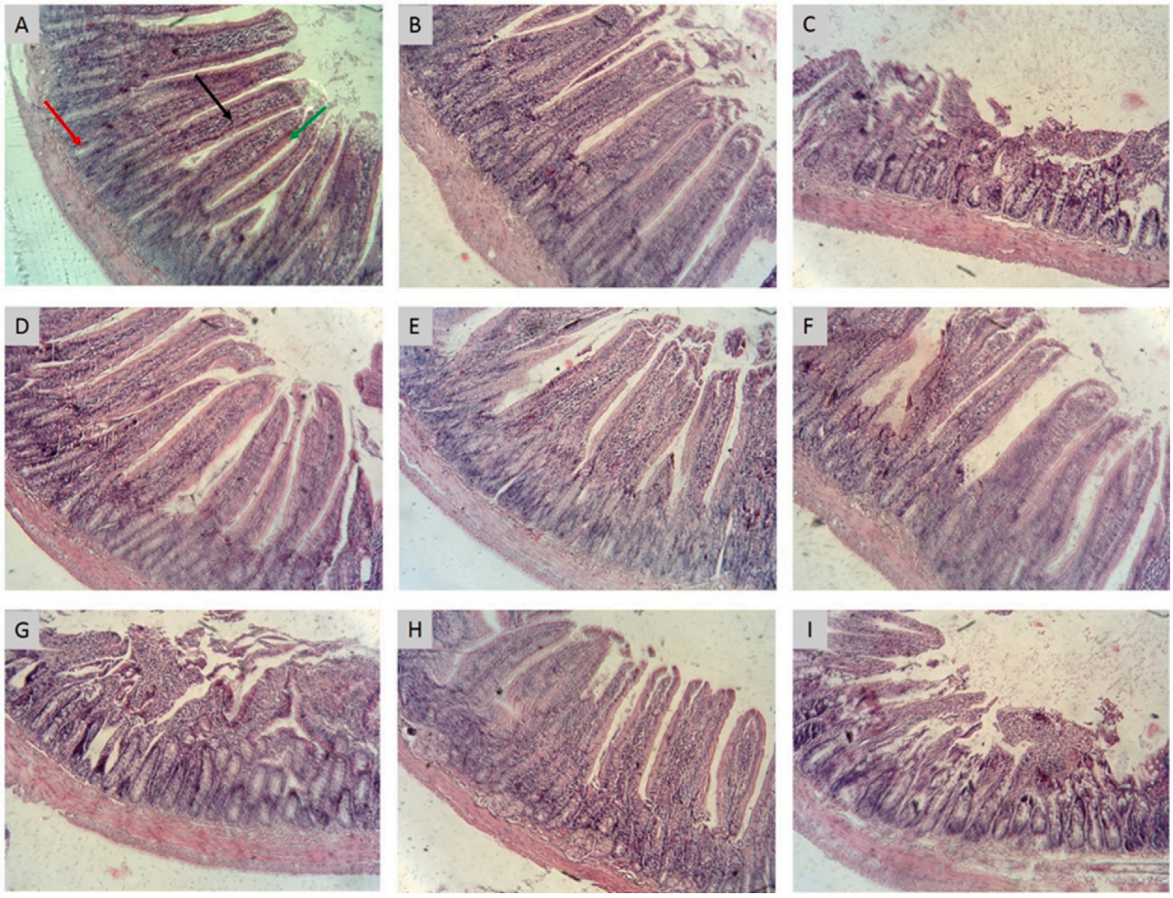

Fig. 4. Hematoxylin and Eosin staining: Histopathological changes of jejunum: A: Control group, B: Sham group: Receive normal saline, C: Irradiation only, D: Pretreatment with 200 mg/kg Mallow extract, E: Pretreatment with 400 mg/kg Mallow extract, F: Pretreatment with 600 mg/kg Mallow extract, G: Pretreatment with 200 mg/kg Mallow extract plus Irradiation, H: Pretreatment with 400 mg/kg Mallow extract plus Irradiation, I: Pretreatment with 600 mg/kg Mallow extract plus Irradiation. The images were selected as samples from the jejunum with 20× magnification.
Black arrow: Willi; Red arrow: Lieberkühn crypt; Green arrow: absorptive cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

5. Conclusion

This study has been conducted to investigate the radioprotective effect of mallow extract in the liver, kidney, and intestine. The irradiation of the abdomen area of the rats with 6 Gy was due to pathological changes in these tissues. The results revealed that administering mallow was a more effective radioprotector for the liver and kidney. Mallow may be able to prevent radiation toxicity.

6. Limitation

Our study conclusions were completely based on histopathological observations only. Functional analysis (LFT & KFT) and molecular mechanism studies required to further warrant the current findings.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Data availability

The data that has been used is confidential.

Acknowledgments

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