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In vivo antioxidant and anti-inflammatory effects of *Myrtus communis* against ionizing radiation-induced gastrointestinal injury: TROD-GROG-002 study

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ABSTRACT

OBJECTIVE: This study aimed to investigate the *in vivo* radioprotective effects of *Myrtus communis* (MC) on the gastrointestinal system.

METHODS: A total of 30 female rats were divided into four groups: i) Control; ii) irradiation (IR) only; iii) MC-pretreated; and iv) MC-treated. The rats received oral MC extract (100 mg/kg/day) for 4 days before exposure to 10 Gy IR or continued until sacrifice. On the fourth day of IR exposure, the rats were sacrificed, and histopathological and biochemical analyses were performed on the ileum, pancreas, and liver tissues.

RESULTS: Malondialdehyde and myeloperoxidase levels decreased in both MC-treated groups, while glutathione levels and Na^+-K^+-ATPase activity increased ($p<0.01$), with significant histopathological improvements compared to the IR-only group.

CONCLUSION: The results of this study demonstrate that MC significantly decreases ionizing radiation-induced oxidative and inflammatory damage in the gastrointestinal systems of rats. Therefore, it may be regarded as a new candidate with radioprotective potential for future clinical application.

Keywords: Ionizing radiation; ileum; liver; Myrtus communis; pancreas; rats.

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Radiotherapy has been a key therapeutic intervention in gastrointestinal cancer treatment, and new treatment techniques have improved its efficacy [1, 2]. Modern techniques reduce the radiation dose received and the volume of surrounding organs irradiated. However, the effectiveness of radiation therapy has been associated with harmful side effects due to the damage to healthy tissues [3–5]. Different regions of the gastrointestinal system may be directly affected by the primary tumor location or by organs at risk [4, 5]. Radiation-induced late effects such as ulcers, bleeding, enteritis, and proctitis reduce the quality of life of cancer survivors [5–7]. Moreover, the side effects of radiotherapy often negatively affect tumor control, which may lead to incomplete treatment [8]. In abdominal radiotherapy, protecting normal tissues with medical and pharmacological agents and technical advancements still require further investigation [6, 8].

Ionizing radiation directly and indirectly causes cellular damage through reactive oxygen species, leading to cellular dysfunction and triggering inflammatory responses. These effects can cause either repairable damage to essential cellular structures or permanent damage, which may result in cell death [9, 10]. Several agents and interventions have been studied to decrease normal tissue injury due to radiotherapy on gastrointestinal organs [8, 11, 12]. Preclinical studies have shown that plant-derived products and their phenolic compounds may be a potential solution for suppressing radiation-induced gastrointestinal damage. These compounds were targeted due to their antioxidant and anti-inflammatory activities [13–20]. Hence, phenolic compounds such as phenolic acids and flavonoids may be potential radioprotectors for clinical usage.

Myrtus communis (MC) is a species of flowering plant in the myrtle family, Myrtaceae, with leaves that contain phenolic acids, flavonoids, terpenoids, tannins, coumarins, and oligomeric nonprenylated acyl phloroglucinol compounds. The leaves, berries, flowers, and essential oils are already used for medicinal properties [21, 22], and the anti-inflammatory and anti-antioxidant effects of MC have been extensively studied. However, to date, no studies have investigated the effects of MC on radioprotection [23–27]. Therefore, the present study aimed to investigate the potential protective effect of MC on abdominal organ damage, including the ileum, liver, and pancreas, as a novel radioprotection intervention.

Highlight key points

- This experimental study investigates the *in vivo* antioxidant and anti-inflammatory (radioprotective) effects of *Myrtus communis* against ionizing radiation–induced gastrointestinal damage.
- MC reduced oxidative stress markers, as indicated by lower levels of malondialdehyde (MDA) and myeloperoxidase (MPO).
- MC enhances antioxidant and cellular defenses, increases glutathione levels, and Na^+-K^+-ATPase activity.
- Histopathological improvements in gastrointestinal tissues compared to the IR-only group.
- MC may be a potential new radioprotective agent for future clinical applications.

MATERIALS AND METHODS

Experimental Animals

The present study received approval from the Marmara University Animal Care and Use Committee (approval no: 07.2022). A total of 30 female Rattus norvegicus rats (age, 3 months; weight, 250-300 g) were obtained from Istanbul Health Sciences University. The animals were housed at 22-24°C with a 12-hour light/dark cycle at Marmara University Experimental Animals Application and Research Center. Each cage housed four animals, and the rats received food and water regularly before and during the experiment, with no restrictions imposed during the study. An adaptation period was provided for the animals to acclimate to the environment before the experiment. Throughout the experiment, the animals were kept in a low-stress, clean, and quiet environment where they could maintain their natural behaviors and were protected from stressful factors such as noise and light. The oral gavage administration of MC and irradiation (IR) was painless during the experiment; therefore, no pain-relieving treatment was administered. This experimental study was conducted in accordance with the principles outlined in the Helsinki Declaration.

Collection of MC leaves and obtaining the extract. *Myrtus communis* L. subsp. communis leaves were collected from the Turgutlu district of Manisa province, Turkiye, by Dr. Gizem Bulut, an expert botanist. Voucher specimens were stored in the Herbarium in the Faculty of Pharmacy, Marmara University (MARE No: 13006). MC extract was prepared according to a previously described procedure [26]. Dried powdered leaves (100 g) were extracted with 96% ethanol using a Soxhlet

extractor. After filtration, the extract was dried using a rotary evaporator. The MC extract powder, with a yield of 28.56%, was kept in a dark glass bottle in a refrigerator (4°C) until subsequent use.

Experimental groups and procedures: Animals were divided into four groups: i) The control group (n=6), which received only oral saline (SF) for the duration of the experiment (8 days); ii) the IR group (n=8), which received oral SF for 4 days, commencing on the day of IR exposure; iii) the MC pretreated group (n=8), which received oral MC for 8 days, commencing 4 days before IR exposure; and iv) the MC treatment group (n=8), which received oral MC for 4 days, commencing on the day of IR exposure.

A previous study described the preparation of the MC extract, and in the present study, the same conditions were followed, demonstrating its efficacy [26]. A total of 100 mg/kg MC extract was administered daily in the morning to the MC treatment and MC pretreated groups using an oral gavage tube, as previously described [26, 27].

Anesthesia (60 mg/kg ketamine, 10 mg/kg xylazine) was injected intraperitoneally to immobilize the rats immediately before the IR procedure. After this, the anesthetized rats were positioned face down on a board with their tails and legs taped. Computed tomography images with 1-mm slices were obtained for radiotherapy planning simulation, and 3D planning was performed. Following completion of 3D planning, a single fraction of 10 Gy IR was delivered with a linear accelerator using 6 MV photons from two anteroposterior directions, at a dose rate of 500 MU/min. After administering with ether anesthesia, all animals were decapitated by guillotine on the fourth day after IR exposure. After the rats were sacrificed, appropriate methods were used to remove the ileum, pancreas, and liver tissues.

Biochemical analysis: Tissue samples were analyzed to determine malondialdehyde (MDA) and glutathione (GSH) levels, and myeloperoxidase (MPO) and Na^+-K^+-ATPase activity as previously described [28–33].

Histopathological evaluation: Histopathological analysis with hematoxylin and eosin was performed as previously described [34]. Samples were fixed in a 10% formaldehyde solution, dehydrated in an ascending alcohol series, cleared in toluene, and embedded in paraffin. For histopathological evaluation, paraffin sections (5 μm) were stained with hematoxylin and eosin and examined under a photomicroscope (Olympus BX51; Olympus Corporation). Histopathological evaluation was performed by histologists who were blind to the study groups. Both histologists evaluated and scored the samples independently, and the results were the same. In cases that were not compatible, the results were averaged after discussion between the two researchers. Modified semiquantitative histopathological criteria are summarized in Table 1. Histopathological scores were given as 0, none; 1, mild; 2, moderate; and 3, severe for each criterion. Each criterion was calculated as the sum of its scores, and in each specimen, at least 5 microscopic areas were examined. The maximum score calculated was 3 for the ileum, 6 for the liver, and 12 for the pancreas [35–37].

Table 1. Histopathological evaluation criteria

Tissue	Histopathological appearance
Ileum	• Normal • Degeneration of surface epithelium and mild inflammatory cell infiltration • Degeneration of surface and crypt epithelium, a moderate decrease in the number of goblet cells with moderate inflammatory cell infiltration • Flattened mucosal villi with a severe decrease in the number of goblet cells and severe inflammatory cell infiltration
Liver	• Hepatocyte degeneration • Congested and dilated sinusoids
Pancreas	• Acinar cell degeneration • Edema • Vascular congestion • Langerhans islet degeneration

Statistical Analysis

The statistical analysis were performed using GraphPad Prism 6.0 (GraphPad Software, San Diego, CA). Groups of data were compared using a one-way analysis of variance followed by Tukey's post hoc test. Data were presented as the mean±S.E.M. at the 95% confidence level, and $p<0.05$ was considered statistically significant. The resource equation method was used to calculate the sample size [38]. Therefore, in the present study, for the total sample size (n=30) and an effect size of 0.25, the statistical power for independent samples was calculated at 60.7% at the 5% significance level [39].

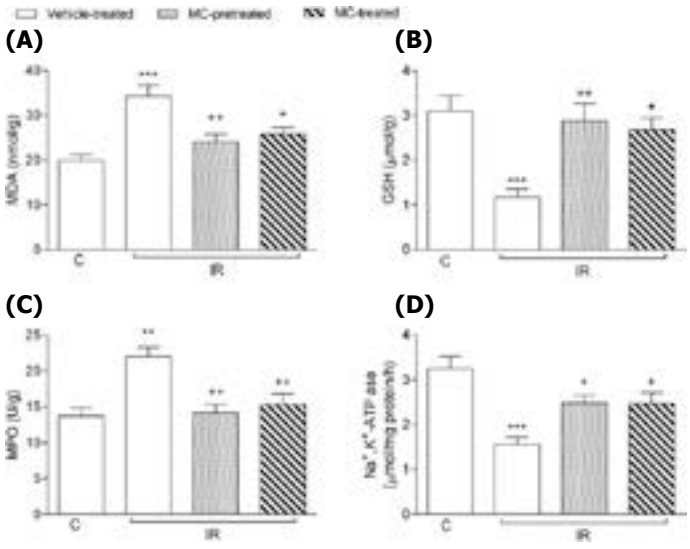

FIGURE 1. Ileum tissue: **(A)** MDA and **(B)** GSH levels, and **(C)** MPO and **(D)** Na^+-K^+-ATPase activity in ileum tissues in the control **(C)**, vehicle, MC-pretreated, and MC-treated groups.

**: P<0.01; ***: P<0.001 vs. control group; +: P<0.05; ++: P<0.01 vs. saline treated-IR group. Statistical analysis was performed using ANOVA (the mean values with 95% confidence level). MDA: Malondialdehyde; GSH: Glutathione; MPO: Myeloperoxidase; MC: *Myrtus communis*; IR: Irradiation.

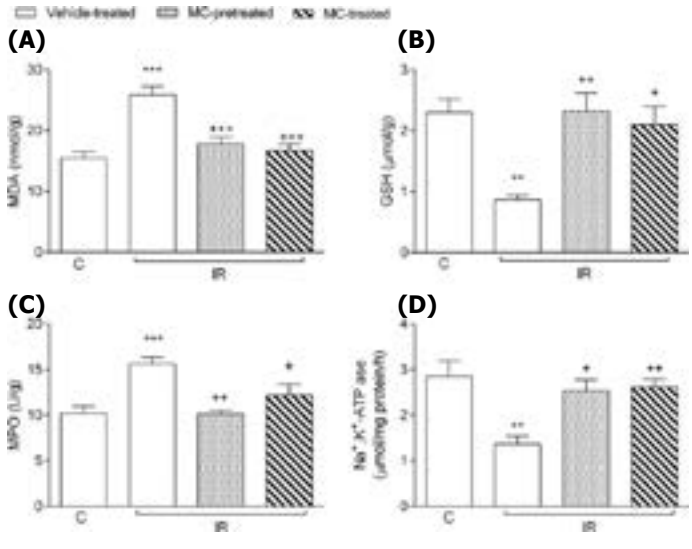

FIGURE 2. Pancreatic tissue: **(A)** MDA and **(B)** GSH levels, and **(C)** MPO and **(D)** Na^+-K^+-ATPase activity in pancreatic tissues in the control **(C)**, vehicle, MC-pretreated, and MC-treated groups.

**: P<0.01; ***: P<0.001 vs. control group; +: P<0.05; ++: P<0.01, +++: P<0.001 vs. saline treated-IR group. Statistical analysis was performed using ANOVA (the mean values with 95% confidence level). MDA: Malondialdehyde; GSH: Glutathione; MPO: Myeloperoxidase; MC: *Myrtus communis*; IR: Irradiation.

RESULTS

Biochemical analysis. IR groups showed increased MDA and MPO levels and decreased GSH and Na^+-K^+-ATPase activity in the ileum, pancreas, and liver tissues ($p<0.001$ vs. control). MC-treated and pretreated groups showed reversed effects ($p<0.01$ vs. IR; Fig. 1–3).

Histopathological Analysis

The histological scores among tissues of the experimental groups are shown in Table 2. Regular ileum morphology of the mucosa with villus formation and normal liver and pancreas parenchyma morphologies were observed in the control group. By contrast, blunted villus damage and dilated glandular structures in the ileum were observed in the IR group. This difference was significant from the control ($p<0.001$). The damage notably decreased in the ileum tissues in the MC pretreated ($p=0.02$) and treated ($p=0.01$) groups (Fig. 4). In the pancreas, irregularities and cellular damage in pancreatic acini, as well as irregularities in cellular organization and dilatation between cells in the islets of Langerhans, were observed in the IR group ($p<0.001$). However, these effects were reduced in the pretreated and MC-treatment

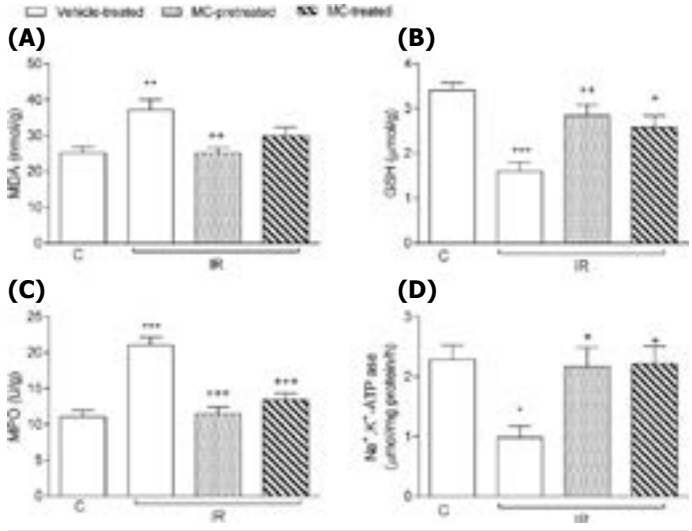

FIGURE 3. Liver tissue: **(A)** MDA and **(B)** GSH levels, and **(C)** MPO and **(D)** Na^+-K^+-ATPase activity in liver tissues in the control **(C)**, vehicle, MC-pretreated, and MC-treated groups.

*: P<0.05; **: P<0.01; ***: P<0.001 vs. control group; +: P<0.05, ++: P<0.01; +++: P<0.001 vs. saline treated-IR group. Statistical analysis was performed using ANOVA (the mean values with 95% confidence level). MDA: Malondialdehyde; GSH: Glutathione; MPO: Myeloperoxidase; MC: *Myrtus communis*; IR: Irradiation.

Table 2. Histological scores among tissues of the experimental groups

	Control	IR	MC-Ptx	MC-tx
Ileum	0	2.87±0.12*	2.33±0.33•**	1.37±0.23¶***
	*p<0.001, •p=0.002 and ¶p=0.01 compared to control; **p=0.02 compared to IR; ***p=0.01 compared to MC-Ptx			
Pancreas	0	8.16±0.16*	5.66±0.33•**	4.25±0.25¶±
	*p<0.001, •p<0.001 and ¶p<0.001 compared to control; **p=0.002 and ±p=0.002 compared to IR			
Liver	0	5.83±0.16*	4.5±0.22•**	4.0±0.36¶±
	*p<0.001, •p<0.001 and ¶p<0.001 compared to control; **p=0.001 and ±p=0.002 compared to IR			

IR: Irradiation; MC-PTx: MC-pretreatment; MC-tx: MC treatment.

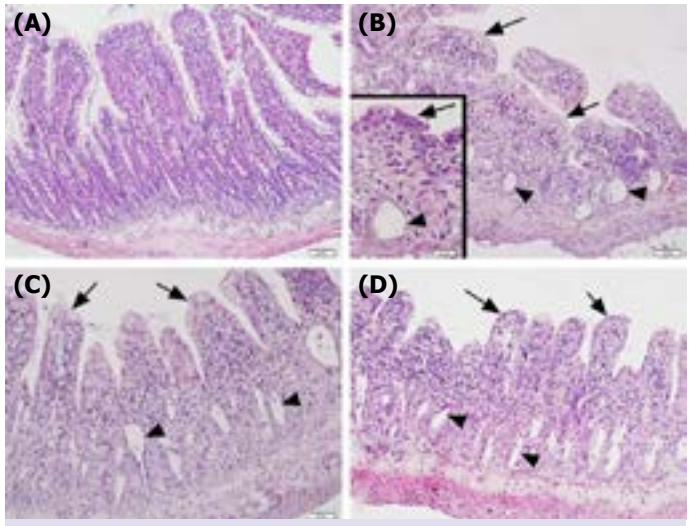

Figure 4. Histopathological results for ileum samples: Representative photomicrographs of the ileum samples in the control, IR, MC-pretreated, and MC-treated groups. **(A)** Regular villus morphology in the control group; **(B)** blunted villus morphology (arrow) and highly dilated glandular structures (arrowhead) in the IR group; **(C)** lengthened villus structures (arrow) and a small number of dilated mucosal glands (arrowhead) in the MC-pretreated and **(D)** MC-treated groups were observed through hematoxylin and eosin staining (scale bar, 50 μm; inset in B, 20 μm).

MC: *Myrtus communis*; IR: Irradiation.

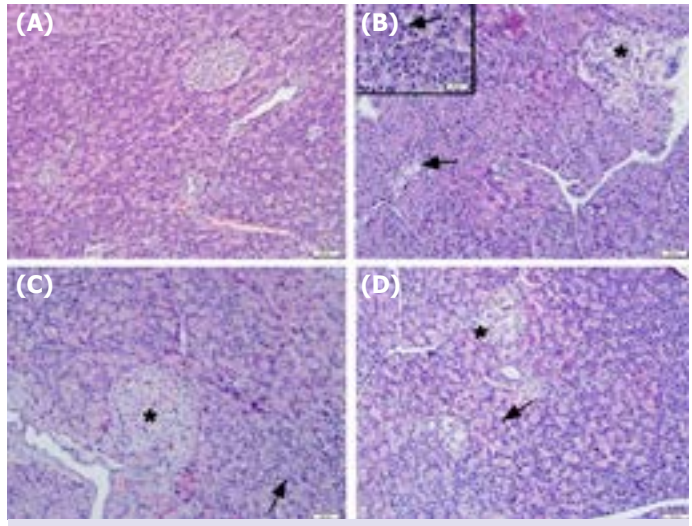

Figure 5. Histopathological results for pancreas samples: Representative photomicrographs of the pancreas samples in the control, IR, MC-pretreated, and MC-treated groups. **(A)** Regular pancreas parenchyma in the control group; **(B)** irregularity and cellular degeneration in the pancreatic acini (arrowhead) and irregularity and cellular dilatation in the Langerhans islet (*) in the IR group; **(C)** cellular degeneration in the pancreatic acini (arrowhead) in some areas and regular morphology of the Langerhans islets in the MC-pretreated and **(D)** MC-treated groups were observed through hematoxylin and eosin staining (scale bar, 50 μm; inset in B, 20 μm).

MC: *Myrtus communis*; IR: Irradiation.

groups (p=0.002) (Fig. 5). In the liver, sinusoidal congestion, deterioration in the organization of the hepatic cords, and hepatocyte damage were observed in the IR group (p<0.001). A reduction in sinusoidal congestion and a decreased number of damaged hepatocytes were observed in the MC-pretreatment (p=0.001) and MC-treatment (p=0.002) groups (Fig. 6).

DISCUSSION

Ionizing radiation generates free radicals, causes cellular damage through oxidizing molecules, and disrupts antioxidant balance, increasing oxidative and inflammatory markers [9, 10]. MC is a medicinal plant that has been used

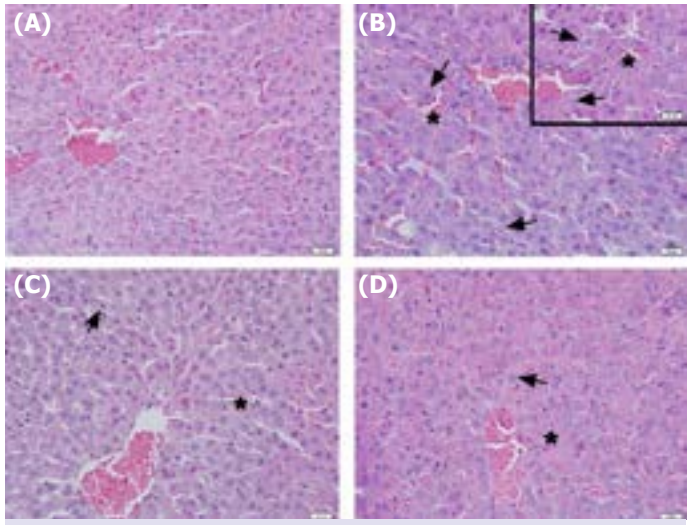

FIGURE 6. Histopathological results for liver samples: Representative photomicrographs of the liver samples in the control, IR, MC-pretreated, and MC-treated groups. **(A)** Regular liver parenchyma in the control group; **(B)** sinusoidal congestion (*) and hepatocyte damage (arrowhead) in the IR group; **(C)** decreased sinusoidal congestion (*) and hepatocyte damage (arrow) in MC-pretreated and **(D)** MC-treated groups were observed through hematoxylin and eosin staining (scale bar, 20 μm).

MC: *Myrtus communis*; IR: Irradiation.

for centuries due to its antioxidant and anti-inflammatory properties, which protect against several toxins [21–27]. Previous studies have shown that MC contains high levels of phenolics (368.68 mg/g) and flavonoids (111.35 mg/g), including caffeic acid derivatives, ellagic acid, and various forms of myricetin and quercetin [24, 26]. Its antioxidant and anti-inflammatory effects have been confirmed by *in vitro* and *in vivo* studies [24–27, 37]. In the present study, both the pretreated and treated groups of MC decreased ionizing radiation-induced early injury in gastrointestinal tissues in the experimental model. It was hypothesized that MC may protect against radiation-induced oxidative damage by reducing lipid peroxidation and boosting tissue GSH levels through its phenolic compounds.

MPO is a product of an increased inflammatory response and is synthesized in neutrophils and macrophages. It is an essential enzyme for normal neutrophil function, released from stimulated neutrophils and other tissue-damaging substances [30]. MPO is released by activated neutrophils in irradiated tissues, as previously described [40, 41]. In the present study, MC reduced MPO activity, especially in the pretreatment group, suggesting its anti-inflammatory and radioprotective effects. Previous experimental studies have also demonstrated that MC reduces serum IL-6 and TNF-α, which play a role in inflammation and MPO activity [23].

Na^+-K^+-ATPase is an enzyme that maintains the homeostasis of sodium and potassium ions in cells and operates energy-dependently. Na^+-K^+-ATPase also demonstrates intracellular catabolism due to its energy-dependent nature [42]. Following IR exposure in rats, there is impairment in the function of the Na^+-K^+-ATPase enzyme, manifested as decreased sodium binding capacity and a reduced number of active enzyme molecules [43]. In the present study, IR was shown to decrease Na^+-K^+-ATPase activity. In both the MC pretreated and treated groups, there was a similar increase in Na^+-K^+-ATPase activity in all tissues compared with the control group. In addition, decreased Na^+-K^+-ATPase activity is associated with endothelial damage, and MC plant extract is protective [44].

In the present study, radiation-induced damage to villus and glandular structures was observed in the ileum, as previously described [35, 40, 41]. Treatment with MC decreased oxidative damage and histopathological alterations via its strong antioxidative and anti-inflammatory effects. The radioprotective effect of MC may be due to its high content of phenolic compounds, which confer significant antioxidant and anti-inflammatory properties. Furthermore, as a photochemical, the mechanisms underlying MC's effects may involve direct interactions with the MAPK and PI-3K pathways [45].

The cerulein-induced pancreatitis model is the most commonly used experimental model for acute pancreatitis. Ceruelin increases inflammatory factors and cellular and oxidative damage in the pancreas [37]. In the present study, radiation-induced irregularities and cell damage in the exocrine pancreatic acinar structures are similar to those in previous inflammatory models. The pathogenesis of radiation-induced pancreas damage involves endothelial cell injury in the microcirculation supplying acinar cells, and ischemia contributes to this injury, in addition to radiation-induced cell injury [46]. In the present study, MC demonstrated anti-inflammatory and protective effects against histopathological damage in the irradiated pancreatic tissue.

In the present study, IR induced morphological and histopathological changes in the liver. Furthermore, previous studies have indicated that a liver biopsy may reveal endothelial damage, sinusoidal congestion, and parenchymal atrophy due to IR [47]. It has been shown that MC is protective against damage induced by toxins such

as aflatoxin and carbon tetrachloride toxicity [48]. The results of the present study have also demonstrated that MC applications may exhibit hepatoprotective effects against oxidative stress.

Modern techniques allow for reducing side effects by limiting the in-field tissues that receive doses during radiotherapy. Despite that, new agents with radioprotective properties still need to be investigated. Our research group is currently studying potential radioprotective agents for this purpose. A previous report from our group showed that MC ameliorates ionizing radiation-induced oxidative and inflammatory effects in brain tissue, as assessed biochemically and histopathologically [49]. Hence, these are the suggestions that MC may be a suitable candidate for the radioprotection clinic of radiotherapy.

Limitations

The authors chose a single large-fraction model, which researchers have long preferred for *in vivo* studies to investigate radiation-induced normal tissue injury. This unfractionated procedure offers several advantages, including easy set-up, shorter commitment, lower maintenance and housing costs, and the avoidance of anesthesia requirements before each fraction. However, this model may not fully mimic fractionated radiotherapy. Another limitation of the present study was its preclinical nature; the drug development process must be completed before MC can enter radiotherapy practice.

Conclusion

The present study demonstrated that MC has radioprotective potential for prophylactic or therapeutic purposes against damage caused by the inflammatory effects of ionizing radiation in different gastrointestinal tissues. The results may provide key information regarding the clinical use of MC as a novel radioprotective agent in the future.

No study has examined the *in vitro* effects of MC on irradiated gastrointestinal cells. Similarly, the effects of MC on critical intracellular molecules in irradiated cells warrant exploration. Moreover, investigating chronic effects that require several weeks for procedure via fractionated models may be another subject. The study includes only a few biochemical markers, so it could also be expanded to include additional inflammatory markers such as TNF-α, IL-6, IL-1β, and CCL4. Extending the studies to other critical tissues affected by radiation injury, such as bone marrow, lungs, or skin, may help find the potential protective effects of MC.

The study does not explore the effects of different doses of *Myrtus communis* extract, which is critical for establishing a dose-response relationship. Since this is the first study of the protective effects of MC against ionizing radiation, the main previous dose reported in the literature was used. Future studies may examine the radioprotective effects of using MC at different doses. Our study can be a reference for these studies.

Ethics Committee Approval: This experimental study was approved by the Marmara University Animal Experiments Local Ethics Committee (date: 11.01.2022, number: 07.2022).

Conflict of Interest: The authors declare no conflicts of interest.

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