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Effect of probiotics and melatonin on inflammatory cytokines and oxidative stress status in distant organs after local radiotherapy: An experimental study

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ABSTRACT

***Background*:** Abdominopelvic radiotherapy (RT) can lead to inflammatory and oxidative changes in non-targeted organs, such as the lungs. This study aimed to investigate the protective effect of probiotic and melatonin administration on the inflammatory and oxidative changes in the lungs after abdominopelvic RT in Wistar albino rats. ***Materials and Methods*:** Thirty female Wistar albino rats were divided into four groups: Group 1 (Control), Group 2 (RT) receiving a single dose of radiotherapy to the abdominopelvic region, Group 3 (RT + Melatonin) receiving a single dose of melatonin intraperitoneally before radiotherapy, and Group 4 (RT + Probiotic) receiving probiotic containing Lactobacillus rhamnosus GG and BB-12 (1010 CFU) via an orogastric feeding cannula before radiotherapy. After the rats were sacrificed, lung tissue samples were analyzed for the levels of Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Oxidative Stress Index (OSI), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α). ***Results*:** TAS was lower in Group 2 compared to Group 3 or 4 ($p<0.001$). TOS was higher in Group 2 compared to Group 3 ($p=0.007$). IL-1β, IL-6, OSI, and TNF-α levels were lower in Group 3 or Group 4 compared to Group 2. ***Conclusion*:** Abdominopelvic RT resulted in increased TOS and inflammatory cytokines and decreased TAS in non-targeted lung tissues. However, administration of melatonin or probiotics improved the antioxidant status and mitigated the increase in inflammatory cytokines and OSI caused by RT. Melatonin exhibited more prominent effects.

INTRODUCTION

Radiotherapy (RT) has been regarded as an important component of cancer management in recent decades. However, ionizing radiation in the abdominopelvic region can affect tissues not directly exposed to the radiation, such as the lungs, a so-called non-targeted effect [1-5]. Increased production of inflammatory and anti-inflammatory cytokines, which may result in overproduction of reactive oxygen species (ROS), and the migration of the cytokines to distant sites have been implicated in the occurrence of various changes in non-targeted lung tissue after RT [2, 6-8].

Various studies have been conducted in an attempt to decrease radiotoxicity. The protective effect of melatonin against radiotoxicity is due to its neutralizing effect on free radicals, the scavenging of free radicals, upregulation of the bcl-2/Bax ratio in lymphocytes and an increase in cell survival [9-12]. It has also been shown that melatonin can increase the expression of anti-oxidant enzymes such as glutathione transferase, superoxide dismutase (SOD) and catalase, and decrease signaling cascade genes such as TLR4, MyD88 and NF-kB [13, 14].

Lactobacillus reuteri releasing interleukin (IL) 22, a probiotic, was shown to ameliorate the intestinal damage, following abdominal irradiation, and to increase survival after whole body irradiation in experimental models [15, 16]. Probiotics were shown to decrease neuronal toxicity after whole body irradiation in mice [1]. *Lactobacillus rhamnosus* was found to be effective in decreasing radiation enteritis, following abdominopelvic radiation in mice [17].

However, studies investigating the protective role of melatonin or probiotics on non-targeted lung tissue are limited. Melatonin was shown to ameliorate the production of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and the formation of 8-hydroxydeoxyguanosine in non-

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targeted lung tissue after pelvic irradiation in rats [4]. It was also shown to increase SOD and glutathione peroxidase activity in non-targeted lung tissue in colon cancer in mice [5]. We aimed to investigate the protective effect of probiotic and melatonin administration on the inflammatory response and oxidative stress in non-targeted lung tissue, following abdominopelvic radiotherapy in Wistar albino rats.

MATERIALS AND METHODS

Study design and experimental animals

Our study was carried out with the approval of the experimental animals' ethics committee of the University of Health Sciences (Dated: 12.04.2023, with an approval number of 17495). Experimental procedures were performed in accordance with the rules of the local ethical unit for experimental animals. All experimental procedures were performed in the University of Health Sciences Hamidiye Medical Faculty. Female Wistar albino rats (3-4-month-old) with an average weight of 250±20 grams were used. The rats were housed at a constant temperature of 23±2 ^{0}C under sunlight in ventilated rooms with a humidity of 60±5% under standard laboratory conditions. The rats had ready access to food and water.

Treatment protocol

Rats were grouped according to treatment:

Group 1 (Control Group, n=7): No medical treatment or RT was applied. Standard rat chow and water were given. Two rats died naturally 2 days before sacrification.

Group 2 (RT Group, n=7): A single dose of 16 Gy RT was applied to the abdominopelvic region of the rats. Standard rat chow and water were given.

Group 3 (RT and Melatonin [RT+M] Group, n=8): A single dose of 50 mg/kg melatonin (Melatonin Crystalline, Sigma-Aldrich Corporation, St. Louis, MO) was administered via intraperitoneal injection 15 minutes before a single dose of 16 Gy RT.

Group 4 (RT and Probiotic [RT+P] Group, n=8): The 2 mL probiotic containing *Lactobacillus rhamnosus* GG and *BB-12* 1010 CFU (Forbiome ®, Abdi İbrahim, Türkiye) was administered orally (by dissolving freeze-dried powder in water) every day to the rats for 5 days in addition to feeding with standard rat chow and water. The probiotic solution was administered by the feeding cannula via the orogastric route. After administration of the probiotic, RT was applied.

Radiotherapy protocol

Rats in Group 2, Group 3 and Group 4 were anesthetized with 80 mg/kg ketamine (Ketaset, Fort Dodge Animal Health, Fort Dodge, USA) and 5 mg/kg xylazine (Anased, Akorn, Decatur, USA). Then, radiotherapy was applied in the prone position. The Varian Trilogy Linear Accelerator (Varian Medical Systems, Palo Alto, CA) was used to apply RT. A single dose 16Gy RT with 6 MV ionizing X-ray was applied to the abdominopelvic region of the rats at a source-skin distance (SSD) of 100 cm. In addition, the maximum point dose (Dmax) for 6 MV ionizing X-ray was calculated at a depth of 1.6 cm from the skin surface. Before the RT application, the dose efficiency of the device (dose output) was calibrated to be 1MU=1cGy. In 12-hours after the RT application, 1 rat in Group 2, 1 rat in Group 3 and 1 rat in Group 4 died.

Sacrification protocol

The rats in all groups were prepared for surgical intervention with a high-dose general anesthesia provided by the intraperitoneal administration of 80 mg/kg ketamine (Ketaset, Fort Dodge Animal Health, Fort Dodge, USA) and 5 mg/kg xylazine (Anased, Akorn, Decatur, USA). Then, the lungs were removed for biochemical analysis. Sacrification was done 24 hours after radiotherapy.

Biochemical analysis

Tissue samples taken for biochemical analyses were stored at -80°C in sterile Eppendorf tubes until analysis. Fr lung samples, Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Oxidative Stress Index (OSI), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF- α) levels were studied with commercially available ELISA (Enzyme-Linked Immunosorbent Assay) kits and calculated using a ELISA microplate reader (Thermo ScientificTM VarioskanTM Flash Multimode Reader).

At the end of the study, tissue samples taken from the rats were weighed and homogenized with 1/5 cold 1.15% M KCl solution at 14000 rpm for 30 minutes. Then, the supernatants were separated by centrifugation at 10,000 x g at +4°C for 30 minutes, and protein determination in the supernatants was made according to the Lowry protein assay.

Statistical analysis

SPSS 25 (IBM Corp, USA) was employed for data analysis. An evaluation of the quantitative data's conformity to normal distribution was conducted using the Kolmogorov-Smirnov test, while the Levene test was utilized to evaluate variance homogeneity. When comparing quantitative data from more than two independent groups according to each other, we used ANOVA and for post-hoc analysis, the Tukey-HSD test was used. Mean ± standard deviation values were used in the description of quantitative data in the tables. Where $p<0.05$ and the confidence level was 95%, statistical significance was held to have been established.

RESULTS

Total antioxidant status was highest in Group 1 and lowest in Group 2. TAS was lower in Group 2 than

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in Group 3 or Group 4 ($p<0.001$ and $p<0.001$, respectively). TAS was higher in Group 3 than in Group 4 ($p<0.001$). TOS was lower in the control group than in the other groups. TOS was higher in Group 2 than in Group 3 ($p=0.007$). No significant difference in TOS was found between Group 2 and Group 4 ($p=0.158$). IL-1β, IL-6, OSI, TNF-α levels were lower in Group 3 and Group 4 than those in Group 2, and were higher in Group 4 than those in Group 3 (table 1 and figure 1).

DISCUSSION

TOS and inflammatory cytokines levels increased and TAS decreased in non-targeted lung tissues after radiotherapy. Melatonin or probiotic administration improved antioxidant status in rats undergoing radiotherapy. The rate of increase in inflammatory cytokines and OSI after radiotherapy was not as high due to the effect of the melatonin or probiotic. A comparison of probiotics showed that melatonin resulted in more marked effects.

Various factors have been implicated in DNA damage after RT in non-targeted tissues, including reactive oxygen species, reactive nitrogen species, cytokines, lysosomal enzymes, and mitochondria-originated free radicals [2]. We showed that abdominopelvic RT was associated with elevated levels of oxidative and inflammatory markers in non-targeted lung tissues. In an animal study, the by-stander effect of cranial irradiation on the lungs was analyzed, and an increase in malondialdehyde levels and a decrease in glutathione peroxidase levels were found [18]. Moreover, the by-stander changes in non-targeted tissues might be associated with the emergence of secondary cancers, such as lung cancer [4, 19, 20]. Hence, possible interventions to decrease inflammatory and oxidative responses both in targeted and non-targeted tissues, following irradiation, have been investigated. Melatonin was shown to decrease radiation-induced lung injury via the miR-21/TGF-β1/Smad3 or miR-30e/NLRP3 axis pathway [21, 22]. It was also shown that melatonin did exert a protective effect against RT in the thyroid gland in rats [23]. Melatonin was shown to decrease malondialdehyde, TGF-β and TNF-α levels, and hence decrease radiation-induced lung injury [24, 14]. Studies regarding the protective effect of melatonin against radiotherapy-induced changes in non-targeted organs are scant. We showed that melatonin was protective against radiotherapy-induced oxidative stress in non-targeted lung tissue and associated with amelioration in levels of inflammatory cytokines elevated after RT. If clinical studies provide support, the melatonin-associated enhancement of the oxidative/inflammatory response in lung tissue, occurring after radiation therapy, could potentially serve as a clinical basis in the prevention of lung injury and potential malignancy. Melatonin was shown to decrease malondialdehyde levels and to improve superoxide dismutase and glutathione peroxidase activities in non-targeted lung and heart tissues after irradiation in xenograft mice colon cancer [5]. In that study, melatonin was also found to decrease the level of enzymes in tumor tissue, and melatonin was seen to have differential effects on tumor and non-targeted cells. In the current study, the experimental design did not include rats with cancer.

In an experimental study, it was demonstrated that melatonin alone, without radiation therapy (RT), resulted in reduced inflammation in lung tissues upon pathological examination and led to decreased levels of MDA (malondialdehyde) and TOS (total oxidant status) when compared to the control group [25]. Furthermore, melatonin was found to improve oxidative status and to reduce inflammation in those rats undergoing RT.

This observation suggests that melatonin could potentially exert effects on inflammatory markers even in the absence of an inflammatory trigger, such as RT. However, due to limitations, we were unable to conduct a pathological analysis or include a group of rats receiving melatonin administration without RT in the study.

The anti-inflammatory effects of probiotics have been reported in some previous studies investigating radiation-induced enteritis or neuronal toxicity in rats [1, 17]. Probiotics were shown to be effective in the context of protection against radiation-induced enteritis or mucositis [26]. In an experimental model of radiation-induced enteritis, *Lactobacillus rhamnosus GG* resulted in a decrease TNF-α, IL-1α, IL-1β, and IL-6 tissue levels [17]. To our knowledge, no studies have investigated the effect of probiotics on inflammatory or oxidative changes in non-targeted lung tissue, following RT.

Our study demonstrated that probiotics containing Lactobacillus rhamnosus GG and BB-12 exhibited a beneficial impact on the oxidative and inflammatory response in non-targeted lung tissues induced by abdominopelvic radiation therapy in rats. From a clinical perspective, the findings could be important, particularly concerning secondary damage associated with oxidative and inflammatory responses, such as malignant transformation. Oral probiotics were shown to ameliorate non-alcoholic fatty liver disease and benzene-induced hematopoietic toxicity [27, 28]. In a murine model, *Lactobacillus rhamnosus* administered via gavage resulted in diminished levels of TNF-α, IL-1β, and IL-6 and chemokines in bronchoalveolar lavage fluid, which were induced by lipopolysaccharide of Escherichia coli [29]. Hence, systemic administration of *Lactobacillus rhamnosus* may provide an alleviation of inflammation in the lungs. We administered probiotics using the orogastric route, which could potentially have a systemic effect on the lungs. We

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could not analyze the sole effect of probiotics on the markers in lung tissue in rats not exposed to RT. We also analyzed the effect of melatonin via intraperitoneal injection. In a previous study, intraperitoneal injection of melatonin was also used to observe the effect of melatonin on non-targeted lung tissue after irradiation in mice [5]. We could suggest that intraperitoneal injection of melatonin was effective in reducing oxidant and inflammatory status in non-targeted lung tissue following irradiation.

Oral administration of Lacticaseibacillus rhamnosus CRL1505 was shown to induce antiviral respiratory immunity in mice, and macrophages were shown to have a key role in this [30]. The abundance of macrophages in lung tissue could render the lungs susceptible to the non-targeted effects of irradiation, [4, 31]. Probiotic administration in our study did ameliorate the inflammatory and oxidative response in lungs following abdominopelvic RT, and macrophages might be effective at the tissue level. Distinguishing whether the inflammatory cytokines measured in lung tissues originated from systemic circulation, tissue-resident macrophages, or a combination of both is challenging.

We showed that anti-oxidant status was higher in the melatonin group than in the probiotic group, and vice versa for inflammatory cytokines. No study has been conducted comparing the effects of melatonin or probiotics on oxidative and inflammatory status in non-targeted tissues after RT. We did not include a group of rats treated both with melatonin and probiotic. Although we investigated the same biochemical analyses in the melatonin and probiotic groups, various mechanisms in non-targeted organs following RT might be affected by melatonin or probiotics. The combined effect of melatonin and probiotics remains to be elucidated.

Table 1. Comparison of biochemical results among the groups.

		TAS	TOS	IL-1β	IL-6	OSI	TNF-α
		mean±SD.					
Group 1	**(Control) (n=7)**	0.54±0.06	3.72±0.51	459.85±31.54	344.48±30.90	6.73±0.40	264.56±19.18
Group 2	**(RT) (n=7)**	0.21±0.02	6.81±0.88	808.23±73.55	690.48±52.84	31.79±3.78	616.46±91.87
Group 3	**(RT+M) (n=8)**	0.45±0.04	5.14±1.07	564.68±52.85	491.75±74.32	11.57±2.37	393.62±30.40
Group 4	**(RT+P) (n=8)**	0.34±0.04	5.81±0.63	675.11±55.99	590.99±14.41	17.32±2.37	502.67±40.73
p value		**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Pairwise comparison	**Control *vs.* RT**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Control *vs.* RT+M	0.004	0.036	0.022	<0.001	0.038	0.002
	Control *vs.* RT+P	<0.001	0.001	<0.001	<0.001	<0.001	<0.001
	RT *vs.* RT+M	<0.001	0.007	<0.001	<0.001	<0.001	<0.001
	RT *vs.* RT+P	<0.001	0.158	0.002	0.009	<0.001	0.005
	RT+M *vs.* RT+P	<0.001	0.436	0.007	0.006	0.003	0.005

One Way ANOVA test; Post-hoc Tukey HSD Analysis of comparison of biochemical results among the groups. RT: Radiotherapy RT+M: Radiotherapy + Melatonin RT+P: Radiotherapy + Probiotic. TAS: Total Antioxidant Status TOS: Total Oxidant Status OSI: Oxidative Stress Index.

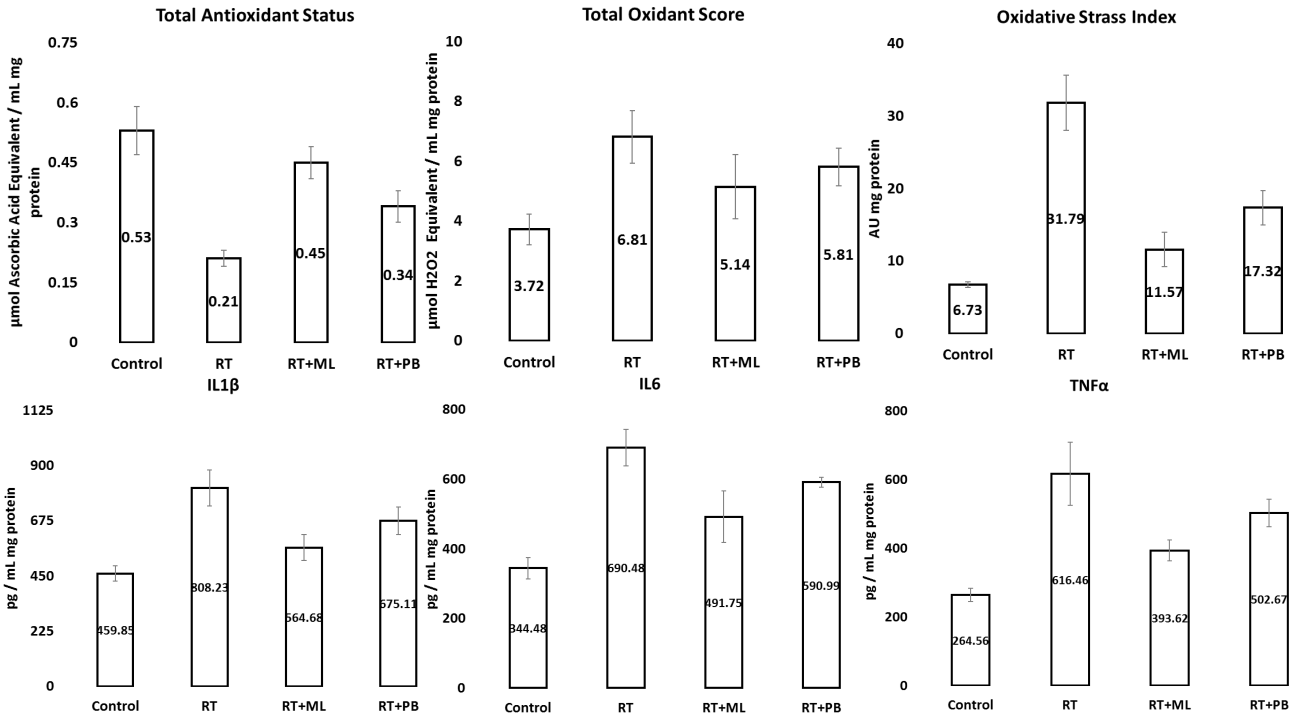


Figure 1. Comparison of biochemical results among the groups.

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CONCLUSION

Following radiation therapy (RT), non-targeted lung tissues exhibited an increase in total oxidative status and inflammatory cytokines, accompanied by a decrease in total antioxidant status. Melatonin or probiotic administration improved oxidative and inflammatory changes in the lung tissue of rats following RT. To our knowledge, studies investigating the effect of melatonin or probiotics on inflammatory or oxidative changes in non-targeted lung tissue are scant. If substantiated by clinical studies, the melatonin or probiotic-related enhancement of the oxidative/inflammatory response in the lungs, occurring after radiation therapy (RT), could potentially serve as a clinical basis in the prevention of lung injury and potential malignancy.

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***Conflict of interest*:** The authors declare that they have no competing interests.

***Author contributions statement*:** C.Ş. and S.A. wrote the main manuscript text, S.M., C.G. and M.A. prepared the figures, B.N.A., H.B. and E.M.G. analyzed biochemical data. A.K. prepared the tables. All authors reviewed and approved the manuscript.

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