Biochemical and Histopathological Evaluation of the Radioprotective Effects of Melatonin Against Gamma Ray-Induced Skin Damage

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Abstract: Background: Radiotherapy is one of the treatment methods for cancers using ionizing radiations. About 70% of cancer patients undergo radiotherapy. Radiation effect on the skin is one of the main complications of radiotherapy and dose limiting factor. To ameliorate this complication, we used melatonin as a radioprotective agent due to its antioxidant and anti-inflammatory effects, free radical scavenging, improving overall survival after irradiation as well as minimizing the degree of DNA damage and frequency of chromosomal abrasions.

Methods: Sixty male Wistar rats were randomly assigned to 4 groups: control (C), melatonin (M), radiation (R) and melatonin + radiation (MR). A single dose of 30 Gy gamma radiation was exposed to the right hind legs of the rats while 40 mg/ml of melatonin was administered 30 minutes before irradiation and 2 mg/ml once daily in the afternoon for one month till the date of rat’s sacrifice. Five rats from each group were sacrificed 4, 12 and 20 weeks after irradiation. Afterwards, their exposed skin tissues were examined histologically and biochemically.

Results: In biochemical analysis, we found that malondialdehyde (MDA) levels significantly increased in R group and decreased significantly in M and MR groups after 4, 12, and 20 weeks, whereas catalase (CAT) and superoxide dismutase (SOD) activities decreased in the R group and increased in M and MR groups during the same time periods compared with the C group (p<0.05). Histopathological examination found there were statistically significant differences between R group compared with the C and M groups for the three different time periods (p<0.005, p<0.004 and p<0.004) respectively, while R group differed significantly with MR group (p<0.013). No significant differences were observed between C and M compared with MR group (p>0.05) at 4 and 20 weeks except for inflammation and hair follicle atrophy, while there were significant effects at 12 weeks (p<0.05).

Conclusion: Melatonin can be successfully used for the prevention and treatment of radiation-induced skin injury. We recommend the use of melatonin in optimal and safe doses. These doses should be administered over a long period of time for effective radioprotection and amelioration of skin damages as well as improving the therapeutic ratio of radiotherapy.

Keywords: Radiation, melatonin, skin, oxidative stress, histopathology.

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radiations which are seen in radiotherapy has serious side effects on normal tissues. All parts of the body are covered with skin tissue, and are primarily affected by radiotherapy [2]. Radiation effect on the skin is one of the main complications of radiotherapy and dose limiting factor [3]. The epidermal cells, which are rapidly dividing and growing, are main target cells that are affected by ionizing radiations. Ionizing radiations, via production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) cause damages to various biomolecules as well as unfavourable changes in their structure and function, while their interaction with genomic content of cells can lead to death through apoptosis, mitotic catastrophe, etc. Massive cell deaths following exposure to radiation may lead to the disruption of normal functions of irradiated organs [4]. Antioxidant systems consist of enzymes such as SOD and CAT. They protect cells against the harmful effects of free radicals as well as neutralizing extra free radicals. Ionizing radiation can lead to excess free radical production over the antioxidant system potency, thereby causing oxidative damage to DNA, proteins and lipids. As a result, normal cell functions are inhibited and increases the risk of cancers [5]. In addition, lipid peroxidation (LP) is increased [6]. LP has the ability to change poly unsaturated fatty acids to malondialdehyde (MDA). MDA causes cellular toxicity as well as a reduction in protective enzyme and functions as co-carcinogen agents [7]. SOD is mostly found in oxygen-based organisms. Its main function is to catalyze the dismutation of O2•− to H2O2. It represents the body’s main antioxidant defence because it prevents subsequent free radical production [8]. CAT is an enzyme composed of iron. It is usually found in small membrane-enclosed cell components called peroxisomes. It detoxifies H2O2 as well as other molecules via the catalysis of two H2O2 molecules, to form H2O and O2 [9].

Radiation burn is skin tissue damage as a result of exposure to ionizing radiation. It can also be caused by high dose of radiation during diagnostic medical imaging or radiotherapy. The latter is the most common [10, 11]. The most common side effect of radiotherapy is acute skin reaction. It has been observed that 90-95% of patients experience this side effect [12, 13]. Skin reaction to ionizing radiation is mainly due to death of proliferating cells [14]. Massive cell deaths by apoptosis, mitotic catastrophe and necrosis lead to appearance of skin reactions such as inflammation, which may occur from weeks up to years [14]. The use of radioprotectors is one of the important methods for eliminating side effects to normal tissues [15].

Melatonin (N-acetyl-5-methoxytryptamine) is a chemical substance secreted by the pineal gland and is involved in the regulation of physiological processes. It has capacities to function as an antioxidant or free radical scavenger [16-18]. The ability of melatonin to protect tissues against oxidative damage due to free radical agents have been shown in in vitro and in vivo examinations [19]. It prevents oxidative damage to the DNA, lipid and proteins via endogenous and exogenous toxins [20] [21]. It easily penetrates all cell types in the body, hence it can protect different organs from complications of radiotherapy [22]. Furthermore, melatonin improves overall survival after irradiation as well as minimizing the degree of DNA damage and frequency of chromosomal abrasions [23]. It gives better cellular function due to its ability to stabilize cellular membranes as well as changes in enzyme activities [24, 25]. It is a major contributing element to hair growth cycle, cutaneous pigmentation in addition to skin physiology and pathology [26]. Melatonin also has anti-inflammatory properties [27]. It has shown ability to attenuate the production of inflammatory cytokines, prostaglandins, etc., and offers protection against radiation injury [28-34]. Free radical scavenging is a direct action of melatonin while its stimulation of antioxidant enzymes in improving the endogenous antioxidant ability of organisms is an indirect effect [28, 35]. To further assess this drug in preventing potential radiation effects, these properties of melatonin were studied using radiation-induced skin damage in rat’s model.

2. MATERIALS AND METHODS

2.1. Animals

Sixty 8-week-old (180–210 g), male wistar rats were obtained from the animal laboratory of the School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran and kept under controlled conditions such as ambient temperature of 21 ± 1°C, 50–70% relative humidity, an air-flow rate of 15 exchanges per hour as well as a 12-hour light and dark cycle (7:00 am to 7:00 pm) was provided. Animals were housed in plexiglas cages (5 per cage), fed with standard rodent chow diet and water from sanitized bottles.

2.2. Experimental Design

The experimental design of this study was in accordance with the guidelines for the care and use of laboratory animals as adapted by the Ethical Committee, School of Medicine, Tehran University of Medical Sciences. Sixty rats were grouped according to body weight and randomly assigned to four groups (each group had fifteen rats). The grouping was specified as: C (Control + Vehicle), M (Melatonin), R (Radiation + Vehicle), MR (Radiation + Melatonin).

C group did not receive radiation or melatonin but only intraperitoneal injection of ethanol diluted with normal saline 0.9 NaCl. The total concentration of ethanol was 5% and vehicle period of four weeks. M group received an intraperitoneal injection of melatonin dissolved in ethanol and normal saline. The ethanol concentration in the final solution was 5%. The right legs of rats in R group were exposed to gamma radiation. Similarly, rats in MR group also had their right legs exposed to gamma radiation in addition to melatonin.

2.3. Irradiation Procedure

Prior to irradiation, animals were anesthetized with an intraperitoneal injection of ketamine (90 mg/Kg body weight) and xylazine (10 mg/Kg). A single dose of 30 Gy [36, 37] gamma radiation was exposed to the right hind legs of the rats with a cobalt-60 gamma ray teletherapy unit with a source-to-skin distance of 80 cm, 10 x 20 cm2 anterior field and a dose rate of 0.65 Gy/min. The dose was calculated at the depth of 0.5 cm on the right hind leg. The irradiation of the animals followed the protocol of Ohrnell et al. [38]. When a single dose of 30 Gy was compared to clinical practice, it would correspond to approximately 50-70 Gy applied in fractionated radiotherapy [38]. Using beam collimation
and lead shields to protect all other body parts, only the right hind legs were exposed.

2.4. Drug Administration

Melatonin (40 mg/ml) was dissolved in ethanol and diluted with sterile saline to give a final concentration of 0.05% and administered by intraperitoneal injection 30 minutes before irradiation then 2 mg/ml once daily in the afternoon for one month till the date of rat’s sacrifice [39-41]. The 30-minute interval between melatonin injection and irradiation was based on the previous animal studies [42, 43]. These melatonin doses had no toxic effects afterwards [26, 44-46].

2.5. Histological Examination of the Specimens

Sixty rats (5 from each group) were sacrificed 4 and 12 and 20 weeks after irradiation. Skin tissue pieces were obtained from the posterior aspect of femoral region of right hind leg of each animal. These tissues were fixed in 10% formalin, paraffin wax embedded and processed for routine histology examination (light microscopic studies).

2.6. Examination of Morphological Changes

4 μm thick slices were prepared and stained with hematoxylin and eosin (H&E) for evaluation with light microscopy. The radiation effects were evaluated using different parameters: Inflammatory infiltration, epidermal atrophy, dermal degeneration such as edema and collagen fibre loss, congestion, sweat gland atrophy and hair follicle atrophy. The semi-quantitative scoring of each variable was carried out by an experienced histopathologist using the following scale: Grade 0 = normal, Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe injury [47].

2.7. Biochemical Survey

The skin sample were cut and weighed. Afterwards, the sample was homogenized (100 mg skin tissue per 1 ml phosphate buffer (pH 7.4) (PBS). Where the PBS are 100 mM (pH 7.4) by homogenizer. It was centrifuged at 6000 RPM for 20 minutes at 4°C. The supernatants were separated and kept at -20°C for malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT) assessment.

2.8. Malondialdehyde (MDA) Measurement

MDA levels were measured using a commercially available kit purchased from ZellBio GmbH Company (ZellBio GmbH, Germany), according to the kit instructions. The assay was dependent on the measurement of the pink colour produced by the interaction of barbituric acid with MDA under high temperature and measured in acidic media and heat (90-100°C), then at room temperature using a spectrophotometer (Eon, Bio TeK, U.S.A.) at 535nm. MDA levels (expressed as μmol/mg of protein) were measured in each of the tissue samples.

2.9. Catalase (CAT) Activity Measurement

Activity of CAT was measured using a commercially available kit purchased from ZellBio GmbH Company (ZellBio GmbH, Germany). It was operated based on the manufacturer’s instructions. The products were measured at room temperature using a spectrophotometer (Eon, Bio TeK, U.S.A) at 405 nm. CAT activity was expressed as U/mL.

2.10. Superoxide Dismutase (SOD) Activity Measurement

Activity of SOD was measured using a commercially available kit purchased from ZellBio GmbH Company (ZellBio GmbH, Germany). SOD activity measurement was based on the kit instructions. The product made a chromogen to a colour which was measured at room temperature using a spectrophotometer (Eon, Bio TeK, U.S.A.) at 420 nm. SOD activity was expressed in U/mL.

2.11. Total Protein Measurement

Total protein concentration was determined using the method developed by Bradford. It is measured at room temperature using a spectrophotometer (Eon, Bio TeK, U.S.A.) at 595 nm. The protein concentration was expressed in gm/ml.

2.10. Statistical Analysis

The data are presented as mean ±SEM, and the difference between the groups for biochemical tests was analysed by using a two-way variance analysis (ANOVA) followed by Tukey’s multiple comparison tests. For histopathological results, data were analysed by Mann-Whitney test. Significance was accepted at p<0.05.

3. RESULTS

It was found that MDA levels significantly increased in R group and significantly decreased in M and MR groups after 4, 12, and 20 weeks, whereas CAT and SOD activities decreased in the R group and increased in M and MR groups during the same time periods compared with the C group (p<0.05).

3.1. Skin Tissue MDA Levels

4, 12 and 20 weeks post irradiation, MDA levels in the skin tissue samples were found to be significantly higher in radiation groups than in the control (p<0.0001). Treatment with melatonin before and after irradiation reduced MDA levels significantly (p<0.001). Melatonin significantly reduced MDA levels in the skin compared to C group (p<0.05) at 4 and 20 weeks. No significant differences were observed between the levels of MDA in the skin tissues of C and M groups compared with MR group until after 4 weeks (p<0.05) as shown in Fig. (1). The melatonin as well as radiation effects were not time dependent.

3.2. Skin tissue CAT Activity

4, 12 and 20 weeks post irradiation, CAT activity in the skin tissue samples were found to be significantly lower in R group than in C (p<0.001). Treatment with melatonin before and after irradiation reversed CAT activity (p<0.001). Also, melatonin treatment significantly increased CAT activity in the skin compared to C group (p<0.05) at 12 and 20 weeks. No significant differences were observed between the levels
4.1. Skin Tissue CAT Activity

Fig. (1). Effect of irradiation pre and post treatment with melatonin on MDA level (μmol/mg of protein) at 4, 12 and 20 weeks post irradiation. a* denotes significantly different values from those obtained in R groups (P < 0.0001). b# denotes significantly different values from those obtained in MR groups (P < 0.0001).

of CAT in the skin tissues of C and M compared with MR group where (p>0.05) as shown in Fig. (2). The melatonin as well as radiation effects was also not time dependent.

3.3. Skin tissue SOD Activity

4, 12 and 20 weeks post irradiation, SOD activity in the skin tissue samples were found to be significantly lower in R groups than in the C group. Treatment with melatonin before and after irradiation reversed SOD activity (p<0.001). Also melatonin significantly increased SOD activity in the skin compared to C group (p<0.05) only after 20 weeks. There was significant difference between the levels of SOD in the skin tissues of melatonin compared with MR group (p<0.01) as showed in Fig. (3). Similarly, the melatonin as well as radiation effects were not time dependent.

3.4. Histopathological Study

4, 12 and 20 weeks post irradiation, the histopathological results (given as mean ± SD) of different variables in terms of congestion, inflammation, dermal degeneration, epidermal atrophy, hair follicle atrophy and sweat gland atrophy were evaluated (Table 1). There were statistically significant dif-

<table>
<thead>
<tr>
<th>Group</th>
<th>Congestion Mean± SD</th>
<th>Inflammatory Infiltration Mean± SD</th>
<th>Dermal Degeneration Mean± SD</th>
<th>Epidermal Atrophy Mean± SD</th>
<th>Hair Follicle Atrophy Mean± SD</th>
<th>Sweat Gland Atrophy Mean± SD</th>
</tr>
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<tbody>
<tr>
<td>C post 4 Weeks</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>M 4 W</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>R 4 W</td>
<td>2.60±0.54*</td>
<td>2.60±0.54*</td>
<td>1.80±0.44*</td>
<td>1.6±0.54*</td>
<td>1.60±0.54*</td>
<td>1.40±0.54*</td>
</tr>
<tr>
<td>MR 4 W</td>
<td>0.40±0.059</td>
<td>1.20±0.44*</td>
<td>0.0±0.0</td>
<td>0.2±0.04</td>
<td>0.20±0.04</td>
<td>0.40±0.055</td>
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<tr>
<td>C Post 12 Weeks</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>M 12 W</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>R 12 W</td>
<td>3.00±0.00*</td>
<td>2.60±0.54*</td>
<td>2.20±0.44*</td>
<td>1.80±0.44*</td>
<td>1.40±0.54*</td>
<td>1.80±0.44*</td>
</tr>
<tr>
<td>MR 12 W</td>
<td>1.200±0.44*</td>
<td>0.40±0.055</td>
<td>0.60±0.054</td>
<td>0.60±0.055</td>
<td>0.60±0.055</td>
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<tr>
<td>C post 20 Weeks</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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<tr>
<td>M 20 W</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
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</tr>
<tr>
<td>R 20 W</td>
<td>2.00±0.70*</td>
<td>2.20±0.44*</td>
<td>1.80±0.44*</td>
<td>1.60±0.54*</td>
<td>1.60±0.54*</td>
<td>1.80±0.44*</td>
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<tr>
<td>MR 20 W</td>
<td>0.60±0.54*</td>
<td>0.20±0.04*</td>
<td>0.4±0.055</td>
<td>0.20±0.04</td>
<td>0.60±0.055</td>
<td>0.80±0.045</td>
</tr>
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</table>
ferences between R group compared with the C and M groups for the three different time periods (p<0.005, p<0.004 and p<0.004) respectively, while R group differed significantly with MR group (p<0.013). No significant differences were observed between C and M compared with MR group (p>0.05) at 4 and 20 weeks except for inflammation and hair follicle atrophy, while there were significant effects at 12 weeks (p<0.05) as shown in Figs. (4, 5 and 6) in addition to Table 1. They were not time dependent, suggesting that melatonin may be an efficient protective agent in all pathological conditions.

4. DISCUSSION

Skin is one of the most radiosensitive organs of the body. Skin cancer is mostly due to early skin reactions to ionising radiations, which are absorbed by the epidermis to induce skin tissue damage [48]. The interaction of ionizing radiation with living tissue leads to different cytotoxic effects, production of reactive oxygen species (ROS) and oxidative stress which cause inflammatory reactions and cell death in exposed regions [49, 50]. The biological effects of ionizing radiation depend on the radiation dose as well as the time after irradiation [51]. In the present study, we investigated the protective effects of melatonin using biochemical and histological changes at different times of 4, 12 and 20 weeks after irradiation with a single dose of 30 Gy gamma radiations to the normal skin tissues of rats. Different studies used single doses of ionizing radiation (1–50 Gy) and then observed the effects of irradiation on the skin [52]. A study by Jourdan et al administered single doses of 10, 20, 30 and 40 Gy to the dermal layer, while maintaining a steep dose gradient between the surface dose and the dose delivered to critical internal organs [36]. Another study by Jang et al used single doses of 20, 30 and 40 Gy for early stage skin injury [37]. Results of a study found that a single dose of 35 Gy led to acute skin damage 4 days after irradiation and time dependent in treatment groups [53]. Another study found that 34 days after exposure to a single dose of 40 Gy to rats brought about the formation of dermatitis to moist desquamation [54]. Our results have shown that 4, 12 and 20 weeks after exposure to a single dose of 30 Gy gamma radiations, there was induced biochemical and histological changes in normal rat skin tissues. In our histological examinations, we determined the level of congestion, inflammation, dermal degeneration, epidermal atrophy, hair follicle atrophy and sweat gland atrophy in skin. There were statistically significant differences between R group compared with the C, M, and MR groups.

Proliferating cells are mostly affected by irradiation [55]. Hence, irradiation could lead to damage of proliferating stem cells as well as further development of ischemic and fibrous tissue via reduction of resident and recruited stem cells in the vascularized tissue [56]. Radiation-induced-oxidative damage leads to the variations in both lipid bilayer fluidity and permeability properties. Hence, reactive oxygen species (ROS) cause structural and functional damages to membrane lipids. In addition, cell membrane permeability as well as changes in tissue ionic contents are affected [57, 58]. Our results were in agreement with other studies by Waghmare, Balter et al. and Najafi et al. [10, 11]. However, the mean
values of these parameters were significantly decreased when rats were treated with melatonin. These were associated with significant amelioration of pathological damages in skin. It has capacities to function as an antioxidant or free radical scavenger [16, 17]). The ability of melatonin to protect tissues against oxidative damage due to free radical agents have been shown in in vitro and in vivo examinations [19]. It prevents oxidative damage to the DNA, lipid and proteins via endogenous and exogenous toxins [20, 21]. It easily penetrates all cell types in the body, hence it can protect different organs from complications of radiotherapy [22]. Furthermore, melatonin improves overall survival after irradiation as well as minimizing the degree of DNA damage and frequency of chromosomal abrasions [23]. It gives better cellular function due to its ability to stabilize cellular membranes as well as changes in enzyme activities [24, 25]. It is a major contributing element skin physiology and pathology [26]. It has anti-inflammatory properties [27]. Direct free radical scavenging and indirect antioxidant abilities. Hence, it is a favourable agent for reducing injury due to secondary injury, anti-apoptotic capability and preventing inflammatory cell infiltration [59]. These properties of melatonin play key role in serious consequences of exposure to high dose of ionizing radiation.

Our biochemical results showed that the level of MDA increased in radiation group. Ionizing radiation can lead to excess free radical production over the antioxidant system potency, thereby causing oxidative damage to DNA, proteins and lipids. As a result, normal cell functions are inhibited [5]. In addition, lipid peroxidation (LP) is increased [6]. LP has the ability to change poly unsaturated fatty acids to malondialdehyde (MDA). Lipid peroxidation is a major cause of damage to the cell membrane, possibly leading to radiation-induced tissue damage [60], [61]. An indicator of lipid peroxidation increases in MDA levels [62]. Similar findings were obtained in a previous study by Naveena et al [63]. Irradiating rats’ skin using 30 Gy gamma radiation resulted to a decrease in both CAT and SOD activities. The reductions in CAT and SOD activities post irradiation may be a result of its consumption in peroxide removal. Radiation induces the formation of free radicals as well as lipid peroxidation. SOD changes O$_2^-$ into H$_2$O$_2$ in an attempt to inhibit the creation of OH while the subsequent H$_2$O$_2$ is later removed by CAT by converting it to H$_2$O and O$_2$ [64]. On the other hand, a reduction in CAT activity could be as a result of feedback inhibition or oxidative inactivation of enzyme protein caused by ROS generation [65], while a decrease in antioxidant’s enzymatic activity may be as a result of increased utilization of this antioxidant to avert lipid peroxidation [66]. Radiation-induced damage to cell membrane with variations in the dynamic permeability of membranes due to peroxidation precedes the release of intracellular enzymes to
the blood stream [67]. This could also be ascribed to the utilization of antioxidant enzymes utilization by the increased production of ROS [68]. In the present study, we found out that melatonin can inhibit the MDA level while increasing the SOD and CAT activities in irradiated skin. Because it has the ability to neutralize free radicals, upregulate antioxidant enzymes and defeat pro-oxidant enzymes. Melatonin is a potent stimulator of DNA repair [69]. Our results are in agreement with another study which revealed that melatonin can inhibit dermatitis in breast cancer radiotherapy [70]. During radiotherapy, melatonin administration significantly decreases MDA levels and elevates antioxidant enzymes' activities in the ovaries as well as plasma [71]. Studies have shown that melatonin can ameliorate radiation-induced damage by the repair system. Finally, we recommend the use of melatonin in optimal and safe doses. These doses should be administered over a long period of time for effective radioprotection and amelioration of skin damages as well as improving the therapeutic ratio of radiotherapy.

CONCLUSION

Our results have shown that exposure to gamma radiation induced the formation of ROS in the skin as well as a decrease in both CAT and SOD activities. We suggest that ROS was responsible for damages to components of connective tissue of dermis, which likely has an impact on the behaviour of cells through cell–matrix interactions. Hence, the skin properties were altered. We also suggest that the therapeutic use of melatonin may be useful because it supports the reduction in the levels of free radical in patients undergoing radiotherapy. We have also shown from our results that melatonin can be successfully used for the prevention and treatment of radiation-induced skin injury via delaying the saturation of repair enzymes, leading to the repair of more radiation-induced damage by the repair system. Finally, we recommend the use of melatonin in optimal and safe doses. These doses should be administered over a long period of time for effective radioprotection and amelioration of skin damages as well as improving the therapeutic ratio of radiotherapy.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Tehran University of Medical Sciences, with approval number: IR.TUMS.VCR.REC.1396.3354.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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