REVIEW ARTICLE IJD

Melatonin as a therapeutic adjuvant for radiation dermatitis in breast cancer: a review of mechanisms and clinical outcomes

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Radiation therapy is one of the main treatments for patients with breast cancer. Dermatitis is a common side effect of breast cancer radiation. The use of adjuvant molecules can enhance the anticancer effects of radiotherapy while reducing damage to surrounding healthy tissues by either killing tumor cells or slowing their growth. Melatonin, a natural hormone secreted by the pineal gland, has been shown to increase the therapeutic efficacy of radiation and mitigate side effects in normal tissues. It can also act as a radiosensitizer in breast cancer. These effects are likely due to reduced oxidative stress, decreased apoptosis of healthy cells, and diminished inflammation. However, few studies have explored the role of melatonin in radiation therapy for breast cancer, the optimal dosage of melatonin, and its impact on patients' quality of life. Further research suggests that higher doses of melatonin and corticosteroids may affect the efficacy of melatonin cream in preventing radiation-induced dermatitis.

This review investigated the radioprotective mechanisms of melatonin and its effects on radiation-induced dermatitis in women with breast cancer.

Keywords: melatonin, radiodermatitis, breast cancer, radiotherapy, therapeutic adjuvant

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INTRODUCTION

Radiation therapy (RT) is essential for treating breast cancer and improves overall survival rates [1]. Adjuvant breast radiation is recommended following breast-conserving surgery and, in certain cases, after mastectomy. However, RT can cause localized side effects, including skin irritation. Acute radiation dermatitis (ARD) is a common side effect during RT that develops within the first 90 days of treatment in up to 95% of patients [2-4]. Newer radiation techniques, such as partial breast irradiation [5] and intensity-modulated radiation therapy (IMRT) [6], have reduced the incidence of radiation dermatitis, including but it remains a significant concern for cancer patients [7].

The pathophysiology of ARD involves radiation-induced damage to both the dermis and epidermis, alterations in the proliferation and differentiation of epidermal keratinocytes and the basal layer, disruption of the skin barrier, and activation of proinflammatory markers [2].

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ARD causes xerosis, erythema, pruritus, dry and moist desquamation, hyperpigmentation, discomfort, and localized pain, all of which can negatively affect patient's quality of life and may lead to treatment interruption [7]. Several factors, including the radiation dose, technique and the use of a bolus, can influence the severity of ARD. In addition, patient characteristics, such as breast size, body mass index (BMI), skin color, and smoking history also impact ARD [7].

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone primarily produced in the pineal gland. Melatonin plays a crucial role in regulating circadian rhythm [8]. In addition to its interactions with G protein-coupled cell surface receptors, melatonin interacts with various receptors, including melatonin receptor 1 (MT_1) and MT_2, which play a role in regulating circadian rhythms and other physiological functions. The activation of these receptors can affect the nervous system and modulate immune responses [9,10]. It can interact with retinoid-related orphan receptors (RORs) [11], mediate inflammatory signaling through matrix metalloproteinase-9 (MMP-9) [12], and function as an antioxidant by regulating quinone reductase 2 (QR2) and phosphoprotein phosphatase 2A (PP2A). Additionally, it exhibits antiapoptotic effects by controlling the mitochondrial permeability transition pore (mtPTP) [13]. Furthermore, melatonin can cross both the plasma and mitochondrial membranes via glucose transporter 1 (GLUT1) [14] and oligopeptide transporters 1 and 2 (PEPT1/2), thereby contributing to its diverse physiological roles, particularly in cancer cells [15].

Notably, melatonin has been suggested to reduce RT toxicity by preventing inflammatory responses at multiple levels. A phase II randomized trial showed that emulsions containing melatonin can significantly reduce Grade 1--2 ARD in early-stage breast cancer patients [7].

This review examines the molecular mechanisms underlying the radioprotective and radiosensitizing effects of melatonin, as well as radiation-induced dermatitis. It also explores other potential pathways that may contribute to its effects [16].

METHODOLOGY

To explore and synthesize the existing evidence on the potential role of melatonin in radiation dermatitis, we conducted a focused literature review. Searches were performed across three major electronic databases- PubMed, Scopus, and the Web of Science- to identify relevant studies published up to December 2024. The search strategy combined keywords and MeSH terms related to *melatonin*, *radiation dermatitis*, *breast cancer*, *radiotherapy*, *radioprotection*, and *radiosensitization*.

Studies were eligible for inclusion if they were original research articles, clinical trials, or experimental investigations examining the effects of melatonin on radiation-induced skin toxicity, with particular emphasis on patients with breast cancer. We excluded studies that were not published in English, review articles lacking original data, and any research unrelated to radiotherapy or radiation-induced skin reactions.

Although relatively few studies have specifically examined melatonin in the context of breast cancer–related radiation dermatitis, all relevant data were analyzed to identify consistent findings, therapeutic trends, and gaps in the literature. To strengthen the biological context of this review, we also explored studies describing the mechanistic pathways underlying melatonin's radioprotective and radiosensitizing effects. Additionally, evidence from research on other cancer types was reviewed to provide a broader understanding of melatonin's potential mechanisms and applications. (Table 1) Together, these insights allowed us to contextualize melatonin's prospective role in preventing or mitigating radiation dermatitis and to outline key directions for future investigation.

BASIC BIOLOGY

Melatonin can prevent genomic instability and reduce the incidence of cancer through various mechanisms, including neutralizing free radicals [17], suppressing the reduction/oxidation (redox) system, preserving mitochondrial function [17], inducing pro-oxidant enzymes, stimulating DNA repair responses [18], and exerting antiestrogenic effects [19,20]. It can also inhibit tumor growth by inducing cancer cell death and suppresing tumor cell proliferation [21]. Other effects of melatonin include inhibiting tumor angiogenesis and stimulating the activity of natural killer cells [19,22,23].

MELATONIN AS A RADIOPROTECTIVE AGENT

Melatonin and reactive oxygen species (ROS) in normal cells

Ionizing radiation directly ionizes H2O molecules,

Table 1. Melatonin potential mechanisms of action and efficacy in various cancers

Malignancy	Key Findings	Mechanisms of Action	Pathophysiology
Breast Cancer	- Reduces tumor progression, especially in hormone-sensitive cases.	- Modulates estrogen receptor activity, Reduces estrogen synthesis.	- Estrogen dependency, oxidative stress, and inflammation [67,68]
Prostate Cancer	- Slows tumor growth and enhances responsiveness to treatments.	- Inhibits androgen receptor signaling and promotes apoptosis. Reducing glucose uptake in prostate cancer cells.	- Androgen dependency, oxidative stress, and immune evasion [83]
Colorectal Cancer	- Decreases tumor size and metastasis in preclinical study.	- Anti-inflammatory effects, apoptosis induction, and inhibition of angiogenesis.	- Chronic inflammation and abnormal angiogenesis [84]
Lung Cancer	- Enhances chemotherapy efficacy and reduces toxicity.	- Antioxidant and anti-inflammatory properties; immune enhancement.	- High oxidative stress and immune suppression [85]
Leukemia and Lymphoma	- Improves immune response and mitigates treatment-related side effects.	- Enhances T-cell and natural killer cell activity; reduces oxidative stress.	- Immune dysfunction and chemotherapy-induced oxidative damage [86,87]
Glioblastoma	- Demonstrates antiproliferative and pro-apoptotic effects in glioblastoma cells.	- Inhibits cell cycle progression; enhances mitochondrial-mediated apoptosis by increasing methylation of the ABCG2/BCRP promoter.	- Aggressive cell proliferation and resistance to apoptosis [88]
Ovarian Cancer	- Inhibits cell proliferation and enhances chemotherapy sensitivity.	- Modulates inflammatory cytokines and induces apoptosis.	- Chronic inflammation and treatment resistance [89]
Pancreatic Cancer	- Potential role in reducing tumor growth and improving treatment outcomes.	- Inhibits angiogenesis and metastasis; promotes apoptosis.	- High metastatic potential and resistance to therapy [90]
Head and Neck Cancers	- Improves radiotherapy efficacy and protects normal tissues from damage	- Antioxidant effects; reduction of inflammatory mediators by Increasing ROS production.	- High oxidative stress and localized inflammation [91]

producing highly reactive hydroxyl radicals that can interact with other cellular components, including lipids and proteins, generating additional ROS [24]. The hydroxyl radical promotes DNA damage via single- and double-strand breaks as well as base modifications [25,26]. Lipid peroxidation comprises cell membrane integrity, while protein oxidation results in its degradation and malfunction [24]. Melatonin counteracts these effects by directly neutralizing free radicals; additionally, its metabolites exhibit antioxidant properties, further enhancing its protective role in normal cells [27,28]. An in vitro study demonstrated that melatonin protects human skin fibroblasts from oxidative damage and lipid peroxidation without activating the p53/p21 pathway [29]. Furthermore, a double-blind, randomized trial involving breast cancer patients revealed that, compared with the placebo, applying a melatonin-containing emulsion twice daily for two weeks after radiation treatment significantly reduced Grade 1–2 dermatitis [7]. Melatonin is more potent than classic antioxidants such as vitamin C and vitamin E [30]. This potency may contribute to reduced radiation-induced side effects [31-33].

The administration of melatonin prior to radiotherapy can increase total leukocyte and lymphocyte counts (TLC and LC), increase superoxide dismutase (SOD) activity and total antioxidant status (TAS), and reduce lipid peroxidation (LPO) and caspase-3 activity, thereby contributing to melatonin's radioprotective effects (Figure 1) [34]. Melatonin also protects the hematopoietic system and lymphoid organs from X-ray-induced cellular toxicity through its antioxidant properties. By neutralizing free radicals and enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase, it mitigates oxidative damage [35]. Furthermore, melatonin promotes the accumulation of immune cells, facilitating improved tissue recovery following radiation exposure [36].

Melatonin and apoptosis

The protective effect of melatonin against radiation-induced death in normal cells involves increasing the Bcl-2/Bax ratio [37,38]. This effect on Bcl-2/Bax is influenced by MT1/MT2 receptors and calmodulin, with the involvement of the lipoxygenase pathway [38]. Nonetheless, ROS scavenging is also known to contribute to the antiapoptotic properties

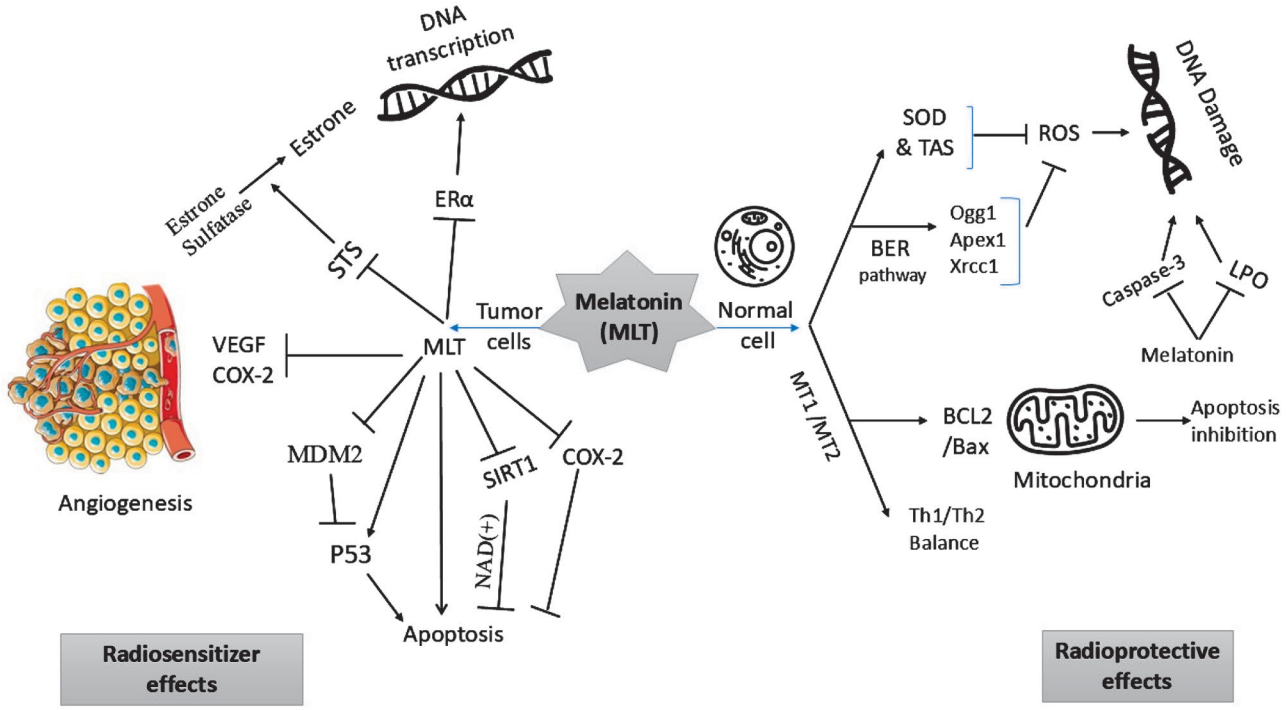

Figure 1. Radioprotective effects of melatonin on normal cells and radiosensitizing effects on tumor cells via different mechanisms. Reactive oxygen species (ROS), superoxide dismutase (SOD) [35], total antioxidant status (TAS), lipid peroxidation (LPO) [34], melatonin receptor MT1/MT2 [38,39], base excision repair (BER), estradiol sulfatase (STS) [57], vascular endothelial growth factor (VEGF), murine double minute 2 (MDM2), nicotinamide adenine dinucleotide (NAD (+)), and estrogen receptor alpha (ERα) [16,19].

of melatonin. Melatonin also affects lymphocyte apoptosis by activating caspase-3, a key enzyme in this process. Administration of melatonin prior to radiation exposure prevents caspase-3 activation. These findings highlights the anti-apoptotic properties of melatonin that protect normal cells from radiation-induced death [39].

Melatonin and the immune system

Research has highlighted the immune-modulatory effects of melatonin, including its proinflammatory effects, which enhance the activity of immune cells such as B and T lymphocytes, as well as natural killer (NK) cells. These effects result from multiple mechanisms, including the stimulation of T lymphocyte proliferation, prolongation of their survival, and enhancement of antigen presentation by macrophages. Together, these processes strengthen both innate and adaptive immunity [40,41]. This activation can lead to increased production of proinflammatory cytokines, such as TNF-α and IL-6, which contribute to inflammation. These cytokines play key roles in mediating immune responses and inflammation, potentially influencing various disease processes [42].

As an immune-modulatory agent, it can increase the production of anti-inflammatory cytokines such as IL-10 while reducing the production of proinflammatory cytokines, including interleukin-1 (IL-1), IL-6, TNF-α, and IFN-γ [42], thereby modulating the balance between Th1 and Th2 responses [43,44]. It can also affect endothelial cells, which play a key role in inflammation. Specifically, it can increase the expression of adhesion molecules in endothelial cells, contributing to leukocyte infiltration and promoting inflammation [42]. Moreover, it has been shown to reduce oxidative damage and inflammation in various experimental models, suggesting its potential as a treatment for inflammatory conditions [45].

DNA and Melatonin

In the context of radiation exposure, DNA damage repair is crucial for preventing normal cell death and protecting cells from further mutations that can lead to secondary malignancies [26]. Ogg1, Apex1, and Xrcc1 play essential roles in repairing oxidative DNA damage [46-48]. Radiation exposure can alter the expression of repair genes, while melatonin has been shown to stimulate anti-inflammatory and

antioxidative pathways [49-51].

The findings revealed that radiation exposure led to the downregulation of Ogg1, Apex1, and Xrcc1 gene expression [26]. Ogg1, in particular, is a vital repair enzyme in the base excision repair (BER) pathway, responsible for repairing 8-hydroxyguanine in damaged DNA. It plays a key role in promoting cell survival and activating the BER pathway. Xrcc1, meanwhile, is involved in rejoining DNA strand breaks, further facilitating the repair process [52,53]. Melatonin exerts a protective effect against radiation-induced DNA damage by upregulation of these genes [26].

MELATONIN AS A RADIOSENSITIZER

Melatonin exhibits both radioprotective and radiosensitizing effects. It enhances the radiosensitivity of breast cancer cells through multiple mechanisms. Melatonin can inhibit cell proliferation, induce cell cycle arrest, suppress proteins involved in DNA repair -such as RAD51 and DNA-PKcs- and increase p53 mRNA expression, thereby reducing cell proliferation [8]. Additionally, it regulates enzymes involved in estradiol biosynthesis, which can be benefit patients with estrogen receptor-positive breast cancer [16,54].

Melatonin and apoptosis

In addition to its role in protecting normal cells from apoptosis, melatonin has been shown to induce apoptosis in cancer cells by upregulating the p53 gene, primarily through the inhibition of murine double minute 2 MDM2. The p53 protein is essential for initiating apoptosis in cancerous cells. However, because p53 is mutated in most cancers, these cells can evade apoptosis, leading to tumor development. A study by Cucina *et al.* identified two distinct apoptotic pathways in MCF-7 cells, a commonly used breast cancer cell line [55]: an initial p53/MDM2-dependent pathway and a subsequent TGF-β-dependent pathway. Notably, melatonin can trigger apoptosis via both mechanisms at various melatonin concentrations (1 mM, 10 μM, and 1 nM) [56]. Although all melatonin doses increased p53 expression more than irradiation alone, 1 nM was the most effective in reducing tumor cell survival [57]. In addition to its effect on p53, melatonin promotes to apoptosis by inhibiting COX-2. Radiation exposure enhances the expression of COX-2 and other antiapoptotic genes, such as iNOS and NF-κB. By inhibiting these inflammatory genes, melatonin increases the sensitivity of tumor cells to radiotherapy [58,59].

Additionally, melatonin suppresses SIRT1, providing an alternative pathway to induce apoptosis in cancer cells. SIRT1, a conserved nicotinamide adenine dinucleotide (NAD(+))-dependent deacetylase, has been associated with transcriptional silencing and cell survival and plays a crucial role in cancer development by deacetylating key regulatory proteins [60,61]. Consequently, melatonin enhances apoptosis induction in cancer cells when used in combination with radiosensitizing chemotherapy drugs such as doxorubicin, docetaxel, 5-fluorouracil (5-FU) [62], and cisplatin) and non-radiosensitizing chemotherapy agents like cyclophosphamide [63,64].

Regulation of estrogen biosynthesis

Estrogen biosynthesis plays a crucial role in the progression of estrogen receptor-positive breast cancer, as estrogen stimulates cancer cell proliferation through its receptors and induces genomic instability by enhancing cellular metabolism [65]. These changes contribute significantly to breast cancer development [66]. Melatonin has been shown to modulate various aspects of endocrine physiology, particularly in hormone-dependent cancers such as breast cancer. Notably, melatonin can influence the estrogen signaling pathway, by interfering with estrogen receptor alpha (ERα) activation through upregulation of the melatonin receptor MT1 and regulation enzymes involved in local estrogen synthesis, such as Estrone Sulfatase [8]. These mechanisms suggest that melatonin may sensitize breast cancer cells to chemo- and radiation therapy [67,68]. Estrogen biosynthesis and the regulation of estrogen receptors are intrinsically linked to the body's circadian rhythm. Disruption of this natural circadian cycle has been associated with an increased risk of breast cancer. Alterations in estrogen metabolism and the modulation of estrogen receptor activity may contribute to the relationship between circadian rhythm disruption and carcinogenesis [69]. These findings indicate a correlation between diminished melatonin levels in women and an elevated risk of breast cancer incidence [70]. Furthermore, melatonin has been proposed as a potential effective agent for preventing and slowing the progression of breast cancer [71].

Melatonin significantly influences the estrogen signaling pathway by disrupting the binding of the ERα-calmodulin complex to DNA, thereby inhibiting ERα transcription in MCF-7 cells [20,72]. Notably, a study by González *et al.* revealed that melatonin can sensitize human MCF-7 breast cancer cells to ionizing radiation by modulating estrogen biosynthesis. In this study, MCF-7 cells were incubated with varying concentrations of melatonin for seven days before irradiation, after which the subsequent effect of melatonin on aromatase regulation was assessed. The findings revealed that melatonin administration reduced aromatase activity following irradiation and functioned as a radiosensitizer [73].

Additionally, a synergistic effect was observed when the cells were pretreated with either 1 mM or 1 nM melatonin prior to radiation exposure, resulting in a 70% suppression of aromatase activity. Although treatment with 10 μM melatonin also produced a synergistic effect, it was less effective than the effects observed at the higher and lower concentrations. This study highlighted melatonin's ability to inhibit other key sources of estrogen in breast cancer, such as estrone sulfatase (STS), which catalyzes the hydrolysis of estrone sulfate (E1S) to estrone (E1), a potent estrogen, and 17β-hydroxysteroid dehydrogenase 1. Greater suppression of these enzymes is associated with reduced cell survival [57]. Melatonin may suppress aromatase activity through modulation of the cyclooxygenase-2 signaling pathway [74], which can sensitize various types of cancers while mitigating normal tissues [16,75].

Inhibiting angiogenesis in the tumor:

Inflammation plays a crucial role in resistant tumors by triggering the release of angiogenesis-promoting factors as COX-2 and growth factors like vascular endothelial growth factor (VEGF) while also increasing the accumulation of macrophages and regulatory T cells (Tregs) [26]. Studies have shown that melatonin can effectively inhibit tumor cell growth by suppressing key growth factors, including VEGF, endothelin-1, hypoxia-inducible factor-1α, epidermal growth factor receptor, and insulin-like growth factor 1 (IGF-1) [76,77]. Since high doses of ionizing radiation (IR) are associated with increased inflammatory cells and angiogeneic factors, controlling this response has been proposed as a strategy to enhance tumor sensitivity to radiotherapy [78].

THERAPEUTIC EFFECTS OF MELATONIN IN MALIGNANCIES

Melatonin has shown promising effects in managing post-radiation dermatitis in breast cancer patients. A phase II randomized trial demonstrated that a melatonin-containing cream significantly reduced the incidence of acute radiation dermatitis (ARD) compared with a placebo in women undergoing radiation therapy for breast cancer [7]. The application of 1 g of topical melatonin twice daily to the irradiated area during the course of radiation therapy improved patients' quality of life. Fatigue is a common concern for patients undergoing radiotherapy, significantly impacting their quality of life [79]. Melatonin has shown potential in reducing side effects associated with radio-chemotherapy, including fatigue. For example, melatonin has been noted for its potential to improve the quality of life of patients with breast cancer by alleviating symptoms related to treatment [80], particularly in the most prevalent subtype of hormone-positive breast cancer [81]. Conversely, another study reported that melatonin was not effective in reducing fatigue in early-stage breast cancer patients undergoing radiotherapy. Mukhopadhyay *et al.* reported no statistically significant difference between the melatonin and placebo groups for most symptoms, including fatigue, vertigo, and dermatitis—with the exception of depression, which worsened. This led to the early termination of the trial following an interim analysis [82].

CONCLUSION

Melatonin shows promise as both a radioprotective agent and a potentially radiosensitizing agent, playing dual roles in protecting normal tissues and modulating cancer cell behavior. Although research in this area is ongoing, the findings discussed in this paper underscore the potential value of melatonin in improving therapeutic outcomes, particularly in estrogen receptor-positive patients, as well as in alleviating post-radiation dermatitis. Its potential as a safe and effective adjunct therapy warrants further investigation through well-designed clinical studies.

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Author Contributions

M M: Contributed to data acquisition, writing the draft of the manuscript, writing and editing the final version, conceptualizing and designing the study and supervising the project. **A J:** Edited and reviewed the manuscript from a hematology--oncology perspective, focusing on radiotherapy-induced skin toxicity and its clinical implications. **M A:** Supervision and final editing of the manuscript.

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