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Radiation Skin Injury: Cellular Mechanisms And Herbal Alternative Treatment Approaches For Recovery

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Abstract

Nearly 90% of patients get moderate-to-severe skin reactions as a result of radiation therapy, making radiation-induced skin damage (RSI) a common side effect. This can hinder the treatment of their illness and drastically lower the quality of life for patients. There isn't yet a gold standard for treating RSIs, despite how common they are. In addition to discussing the pathophysiology of RSI, this article gives a summary of topical drugs that are used to treat it. In modern clinical medicine, it acts as a point of reference for clinicians to direct how they manage RSI. A serious side effect of several medical procedures, including radiation therapy for cancer, is RSI. Uncertainty surrounds the exact mechanisms underlying radiation-induced skin damage. Recent developments in cellular and molecular biology have uncovered a sophisticated web of pathways that contribute to the skin's radiation response. In this study, we go over the several processes and mechanisms that lead to radiation-induced skin damage, such as DNA damage, reactive oxygen species formation, inflammatory cytokine activation, and direct skin cell damage. We also go over how crucial it is to comprehend these pathways in order to create treatment plans that lessen radiation-induced skin damage. We also look at herbal remedies as possible complementary or alternative treatments for RSI, emphasising how they might aid in skin restoration and promote healing. In order to manage RSI more effectively, this review aims to support doctors in combining conventional and herbal therapeutic alternatives in a complete strategy.

Keywords: Radiation induced skin injury, DNA damage, apoptosis, complementary treatment, Reactive oxygen species.

1. INTRODUCTION

Although radiation therapy is a successful treatment for cancerous tumours, normal tissue cells in the radiation field may also be damaged (1, 2). Radiation-induced skin pathogenesis is caused by excessive radiation exposure and is influenced by a number of variables, including radiation dose, type, energy, duration of exposure, and overall treatment plan (3) (4). The degree of skin damage that a patient experiences might vary based on their age, physical condition, skin type, exposure location, and length of time. A variety of skin damage and reactions, ranging from minor ones like sunburn to more serious ones like radiation dermatitis, may arise from this. An inflammatory response, radiation dermatitis can result in pain, swelling, itching, and redness. Additionally, it may result in more severe skin damage such blistering, ulceration, and scarring (5). More severe skin conditions like blistering, ulceration, and

scarring may also result from it (4, 5). Radiation therapy, wound care, and topical medicines are possible treatments for radiation-induced skin pathogenesis. One frequent side effect of radiation therapy for cancer is radiation-induced skin damage. It is brought on by ionising radiation's direct effects on the skin's cellular and molecular structures, such as the basement membrane, dermis, and epidermis (6). Redness, itching, swelling, and blistering are some of the signs that define radiation-induced skin damage.

Direct damage to DNA and the generation of reactive oxygen species (ROS) are the two main biological causes of radiation-induced skin damage (7). These ROS can cause senescence or cell death by harming lipids, proteins, and other cellular constituents. Furthermore, inflammatory mechanisms, including the release of inflammatory cytokines, may be activated by radiation-induced skin damage, further harming the skin cells and adjacent tissues (8). Additionally, radiation-induced skin injury can lead to the activation of inflammatory pathways, including the release of inflammatory cytokines, which can further damage the skin cells and surrounding tissues (9).

Radiation-induced skin damage can change the expression of genes involved in cellular functions like DNA repair, cell cycle regulation, and cell death at the molecular level (4, 10, 11). These changes may result in more skin damage and a higher chance of developing skin cancer. Furthermore, alterations in the expression of skin-related proteins like collagen and keratin may result from radiation-induced skin damage, which may compromise the integrity and structure of the skin (12).

2. Types of Radiation-Induced Skin Pathology

There are various types of Radiation-Induced Skin Pathology given as follows:

2.1.Acute Radiation Dermatitis: This kind of radiation-induced skin injury is typified by pain, redness, and swelling in the radiation-exposed area (13).

2.2.Radiation Burns: Burns caused by radiation exposure happen when the skin receives a high radiation dose. Skin discolouration, blistering, discomfort, and swelling are some of the symptoms (14).

2.3.Radiation Induced Skin Necrosis: It describes how radiation exposure damages skin tissue, causing scarring and ulceration because it damages the cellular structure of the skin. This frequently happens as a side effect of radiation therapy, which is used to treat cancer (15).

2.4.Telangiectasias: A telangiectasia is a tiny, dilated blood artery that develops on the skin, frequently as a result of radiation exposure, ageing, or UV damage. These are frequently referred to as "spider veins," suggesting that radiation exposure can, in fact, cause skin telangiectasias (16).

2.5.Hyperpigmentation: Hyperpigmentation is the darkening of skin caused by radiation exposure(17).

2.6.Hypopigmentation: When melanin production declines, the skin becomes lighter, a condition known as hypopigmentation. By harming the melanocytes that produce melanin, radiation exposure can result in hypopigmentation, which causes lighter spots on the skin (18).

2.7.Radiation-Induced Skin Cancers: Radiation exposure can result in the development of some skin malignancies, including squamous cell carcinoma and basal cell carcinoma (19).

3. Causes of Radiation Skin Pathology

The intricate interplay of molecular pathways brought on by exposure to ionising radiation causes radiation skin disease. DNA damage, oxidative stress, inflammatory reactions, cellular death, and compromised tissue repair are the main factors behind this disorder (15). The main chemical mechanisms for radiation-induced skin damage are broken down as follows:

3.1. DNA Damage and the DNA Damage Response (DDR) Pathway

DNA lesions, especially double-strand breaks (DSBs), are one of the direct consequences of radiation exposure. The DNA Damage Response (DDR), a molecular signalling network designed to identify and fix the damaged DNA, is triggered by this damage. **Fig. 1** explains the key participants in this pathway.

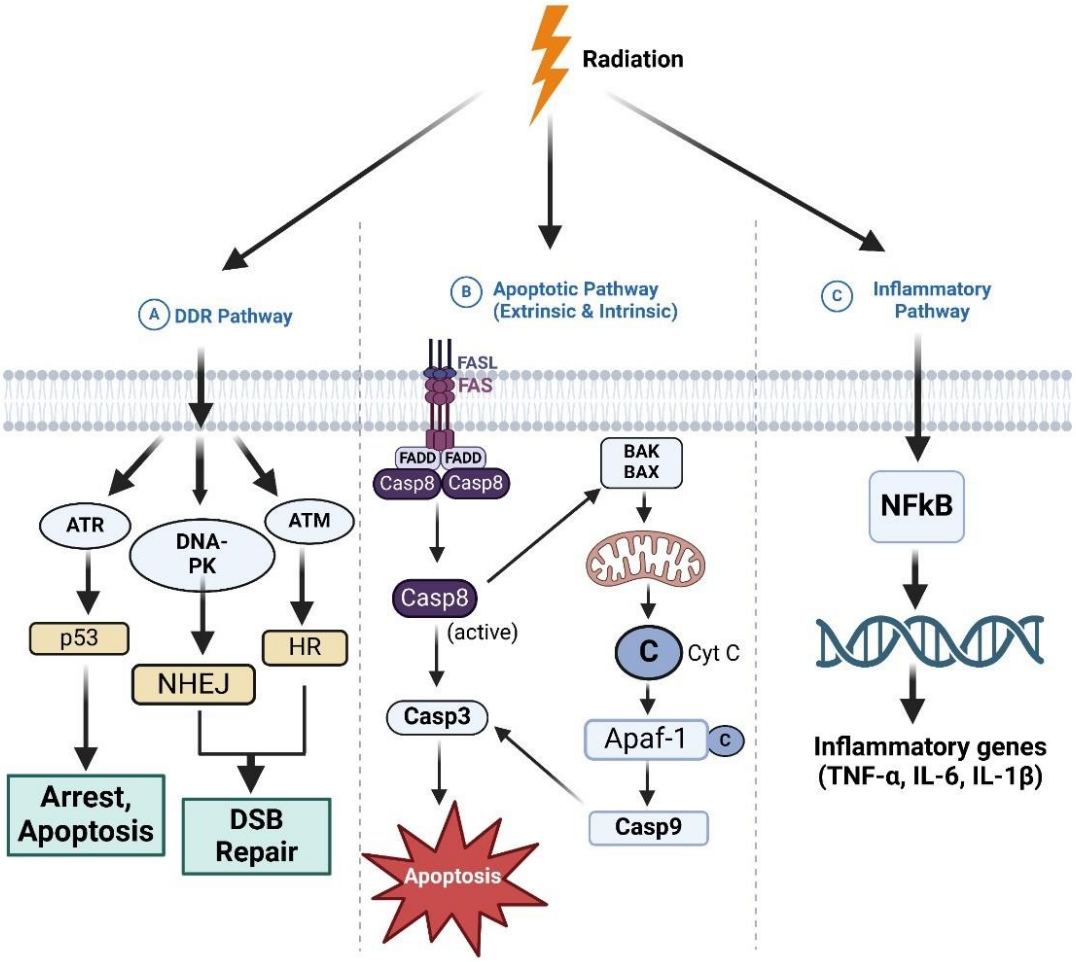

Figure.1. Radiation-induced inflammatory, apoptotic, and DNA damage response pathways. Important participants in the biological reaction to DNA damage include ATR (ATM and Rad3-related), DNA-PK (DNA-dependent Protein Kinase), and ATM (Ataxia Telangiectasia Mutated). Double-strand breaks (DSBs) are the main cause of ATM's activation. It works by phosphorylating proteins like p53, which stops the cell cycle and makes DNA repair easier. Conversely, ATR is mainly triggered by single-strand breaks (SSBs) and regulates DNA repair mechanisms while simultaneously guaranteeing cell viability. One important mechanism for repairing DSBs is the non-homologous end joining (NHEJ) pathway, of which DNA-PK is an essential part. The cell may experience apoptosis or senescence if there is significant DNA damage and these repair pathways are overloaded or inadequate. As cells accrue genetic instability, improper DNA repair can lead to long-term tissue damage, including radiation-induced skin fibrosis.)

4. Oxidative Stress and Reactive Oxygen Species (ROS) Generation

Radiation leads to the production of reactive oxygen species (ROS), which causes oxidative damage to lipids, proteins, and nucleic acids(20). Key molecular events include:

4.1.Lipid Peroxidation: The peroxidation of membrane lipids brought on by radiation-induced ROS compromises membrane integrity and results in cell death (21).

4.2.Protein Oxidation: Proteins that have undergone oxidative alteration can affect cellular processes, including those necessary for the preservation and repair of the epidermal barrier (22).

4.3.Antioxidant Pathways: Glutathione peroxidase and superoxide dismutase (SOD), two antioxidant genes that scavenge ROS, are produced in response to oxidative stress, which activates the Nrf2 (nuclear factor erythroid 2-related factor 2) signalling pathway.This antioxidant defence, however, could not be enough in situations where radiation exposure is excessive. Although its function in mitigating radiation-induced skin injury (RIS) is still unclear, Nrf2 is a well-known modulator of the cellular antioxidant response. In a recent study, Xue et al. (2021) found that adenovirus-mediated Nrf2-overexpression (ad-Nrf2) helped shield skin cells from high-dose radiation, while Nrf2-deficient (Nrf2--) animals were more susceptible to its effects. It was discovered that Nrf2 overexpression lessened the degree of skin damage brought on by high-dose electron beam irradiation. The mRNA expression profiles of Ad-Nrf2 skin cells after radiation were analysed using mRNA sequencing techniques in order to learn more about the mechanisms of Nrf2-mediated RIS. According to the analysis's findings, Nrf2 overexpression caused 127 genes to change considerably, with 55 of those genes being upregulated and 72 being downregulated. Furthermore, Nrf2 was linked to the positive regulation of genes involved in the reactive oxygen species pathway after radiation, according to GSEA. This study offers fresh perspectives on function of Nrf2 in RIS and offers viable methods for reducing its effects (23).

5. Apoptosis Pathways

Apoptosis, or programmed cell death, is a defence mechanism used by cells exposed to high radiation doses to stop injured cells from proliferating. The two main mechanisms by which radiation causes apoptosis are:

5.1.Intrinsic Pathway: Radiation-induced mitochondrial damage sets it off. Important proteins like Bak and Bax encourage the permeabilization of the mitochondrial membrane, which releases cytochrome c and activates caspases (like caspase-9), which trigger apoptosis(24).The skin reacts strongly to radiation by becoming inflamed. Damaged skin cells start this by generating pro-inflammatory cytokines, which draw immune cells to the injury site, including neutrophils, lymphocytes, and macrophages. Important molecular actors consist of:

5.2.Extrinsic Pathway: It is started when death receptors (like Fas) on the cell surface are activated, which triggers caspase-8 and apoptosis.The loss of skin cells caused by apoptosis causes the epidermis to shrink and wounds to heal more slowly (25).

6. Inflammatory Pathways

6.1.NF-κB (Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells): The expression of inflammatory mediators such as TNF-α, IL-6, and IL-1β is mostly driven by this transcription factor, which is triggered by ROS and cytokines(26).

6.2. Cyclooxygenase-2 (COX-2): When COX-2 is activated by radiation, more prostaglandins are produced, which exacerbates pain and inflammation. Prolonged inflammation makes skin damage worse

and can cause fibrosis, which is defined by an overabundance of extracellular matrix components (27).

7. TGF-β Pathway and Fibrosis

Long-term tissue fibrosis brought on by radiation damage is mostly caused by the TGF-β pathway. The cytokine TGF-β, which is released in reaction to tissue damage, is essential for encouraging fibroblasts to proliferate and differentiate into myofibroblasts, which generate collagen and other extracellular matrix components (28).

7.1.Smad Proteins: The Smad family of proteins mediates TGF-β signalling. They go into the nucleus to control the transcription of fibrotic genes once they are activated. The structure and function of the skin are compromised by excessive fibrosis caused by persistent activation of this system(29).

8. Stem Cell Exhaustion and Impaired Regeneration

Epidermal stem cells and mesenchymal stem cells (MSCs), which are crucial for preserving skin homeostasis and promoting skin regeneration following injury, are specifically harmed by radiation. Important molecular features include:

8.1.p53 Pathway: Stem cell fatigue can result via p53-driven stem cell differentiation or death in response to DNA damage. This eventually reduces the skin's capacity to renew, which causes wounds to heal more slowly and makes the skin more vulnerable to additional harm(30).

8.2.Wnt/β-catenin Signaling: The regeneration of skin depends on this mechanism. Wnt signalling can be inhibited by radiation, which hinders skin stem cell proliferation and differentiation (31).

9. Endothelial Dysfunction and Vascular Damage

Additionally, radiation damages the skin's vascular, which results in dysfunctional endothelial cells. This includes the activation of mechanisms that encourage endothelial apoptosis and vascular leakage in addition to DNA damage and oxidative stress (32).

9.1.VEGF (Vascular Endothelial Growth Factor): Radiation-induced damage often reduces the production of VEGF, impairing angiogenesis and contributing to poor blood supply and delayed wound healing (33).

9.2.Endothelial Nitric Oxide Synthase (eNOS): Vascular constriction and decreased skin perfusion can result from eNOS dysfunction, which lowers nitric oxide levels(34).

10. Potential Treatments

Herbal potential treatments for radiation-induced skin injury include aloe vera, comfrey, calendula, and chamomile, lavender, and rosemary essential oils. Aloe vera can be applied topically to reduce inflammation, redness, and itching (35). Comfrey can be used to treat radiation-induced skin damage because of its anti-inflammatory and wound-healing qualities (36). Calendula has antifungal and anti-inflammatory properties which can be used to treat skin irritation and inflammation caused by radiation. Chamomile is a soothing and calming herb that can reduce skin inflammation and redness(37). Lavender oil is a natural antiseptic and can be used to help reduce the risk of infection. According to a study by Kwiatkowski et al., essential oils work in concert with antiseptics and antibiotics. In light of this, the current study set out to investigate how lavender essential oil (LEO) affected the effectiveness of octenidine dihydrochloride (OCT) against strains of methicillin-resistant Staphylococcus aureus (MRSA). The findings showed that LEO increased MRSA strains' vulnerability to OCT. Additional

FTIR research showed that when MRSA was cultivated on media treated with either OCT or a combination of LEO and OCT, the cell wall underwent changes. To sum up, LEO exhibits promise as a strong supplement to traditional antiseptics(38). Rosemary essential oil has antimicrobial and antioxidant properties and can help to reduce the severity of radiation-induced skin injury(39, 40).

10.1.Calendula officinalis: Radiation-induced skin damage can be treated with this herbal treatment, which contains anti-inflammatory, anti-fungal, anti-viral, and antibacterial qualities . It can be consumed as a tea or tincture or applied topically as an ointment. For wound healing, its extract has been utilised. (41, 42).

10.2. Aloe vera: In recent decades, a number of research have concentrated on the It has traditionally been used to treat burns and is also known as the burn tree and the first aid plant. Burn wounds heal more quickly thanks to aloe vera's anti-inflammatory, immune-boosting, antibacterial, antiviral, and reduced histamine activity properties. This herb aids in the healing of injured skin cells and the reduction of inflammation. It can be applied topically as an ointment or ingested as a drink, and it cools the skin (42).

10.3. Centella asiatica: For thousands of years, people in China, India, and Indonesia have utilised Centella asiatica, used to treat a variety of illnesses. It was used to cure wounds, improve mental clarity, and treat skin conditions including psoriasis and leprosy(43). It is believed to help improve circulation, reduce inflammation, and promote the healing of skin cells.

10.4. Licorice root: This herb has anti-inflammatory and antioxidant properties that can help to reduce the effects of radiation-induced skin injury(44). It can be taken as a tea or tincture.

10.5. Chamomile: This plant can help soothe and repair damaged skin because of its anti-inflammatory and antibacterial qualities (45). It can be taken as a tea or applied topically as an ointment(46).

10.6. Romarinus officinalis L. is a member of Lamiaceae family, well-known due to its intriguing medicinal qualities. With an emphasis on its anti-inflammatory, antibacterial, wound-healing, and anticancer properties, this study assesses its antioxidant effects and bioactive components on the skin. In vitro and in vivo research support antioxidant function and point to its potential for skin problem treatment of R. officinalis. To completely determine its clinical impact, more extensive clinical trials are necessary(39).

11. Future Directions

The preventive effects of sulforaphane (SFN) on RIS in an animal model (C57/BL6 mice)
were examined by Wei et al. in 2021. The RIS model was established by irradiating the left thigh under intravenous anaesthesia. The mice were divided into four groups: Control (CON), SFN, Irradiation (IR), and Irradiation plus SFN (IR/SFN). At eight weeks post-irradiation, the morphological changes in skin tissues were analysed by H&E staining. Additionally, oxidative stress and inflammatory response levels, as well as the expression of Nrf2 and its downstream antioxidant genes, were assessed by ELISA, real-time PCR, and Western blotting. The results showed that SFN treatment significantly reduced the RISI-induced morphological changes of mouse skin, such as hyperkeratosis and hyperplasia. Furthermore, SFN treatment also inhibited the RISI-induced oxidative stress and inflammation, as evidenced by the decreased levels of malondialdehyde, nitric oxide, and tumor necrosis factor-α. Moreover, SFN treatment upregulated the expression of Nrf2 and its downstream antioxidant genes, including HO-1, NQO1, GCLC, and GCLM. These findings suggest that SFN can protect against RISI by suppressing oxidative stress and inflammation and upregulating the expression of Nrf2 and its downstream

antioxidant genes. Thus, SFN may be a promising therapeutic agent for the treatment of RIS (47).

Radiation-induced skin injury (RISI), which has a major negative impact on patients' quality of life, is a major problem for nuclear accidents and cancer therapies (48). Due to poor healing and a higher risk of recurrence, this injury is not like standard wounds. It is classified into acute and chronic phases based on the duration of the injury. Regretfully, there aren't many efficient treatments available to stop or lessen this harm. Over the past few decades, a large number studies have examined the effects of stem cell-based therapies to address the tissue repair and regeneration of irradiated skin. These stem cells control inflammation and start tissue repair by releasing paracrine proteins or differentiating into specific cell types. Examples of stem cell-based treatments that have been demonstrated to encourage wound healing after radiation exposure include adipose-derived stem cells (ADSCs), stromal vascular fraction (SVF), and bone marrow-derived stem cells (BMSCs) (49). Furthermore, exosomes made from stem cells have now been proposed as a successful, cell-free method of promoting skin regeneration, avoiding the issues with direct stem cell administration. We summarise the properties of various stem cells, discuss their most recent clinical and animal uses, and discuss possible pathways based on the literature on stem cell-based treatments for radiation-induced skin damage. The potential of stem-cell-based treatments to prevent radiation-induced skin damage helps us respond to nuclear events and ensures that cancer radiation therapy proceeds smoothly(50).

Skin damage brought on by radiation is a complicated biological reaction that involves many different molecular and cellular processes. Comprehending these pathways is essential for creating efficacious treatment plans to avoid or lessen radiation exposure-related harm, whether from accidental exposure or medical procedures like radiotherapy (39).

The field of research is always changing, and a number of exciting avenues for further study into the mechanisms underlying radiation-induced skin damage have surfaced.

11.1.Role of Non-Coding RNAs and Epigenetic Modifications

Non-coding RNAs (ncRNAs), such as circular RNAs (circRNAs), long non-coding RNAs (lncRNAs), and microRNAs (miRNAs), are becoming more and more interested in their function in radiation-induced skin damage. These chemicals can alter cellular reactions including apoptosis, inflammation, and DNA repair in skin cells exposed to radiation. They are also important post-transcriptional regulators of gene expression(51, 52).

Particular miRNAs or lncRNAs that are either elevated or downregulated in response to radiation will probably be the subject of future research. Using inhibitors or mimics to target these ncRNAs may be a therapeutic strategy to reduce skin damage. Furthermore, knowing how epigenetic modifications like DNA methylation and histone modification function may help explain how radiation affects skin homeostasis and regeneration over the long run (53, 54).

11.2.Oxidative Stress and Antioxidant Pathways

High levels of reactive oxygen species (ROS) produced by radiation exposure cause oxidative stress and harm to cellular constituents such proteins, DNA, and lipids (55, 56). Although oxidative stress plays a well-established role, more research might focus on the exact control of antioxidant mechanisms, such the Nrf2 (nuclear factor erythroid 2–related factor 2) signalling pathway, that prevent ROS damage (57).

Future directions could focus on identifying novel small molecules or natural compounds that enhance the skin's antioxidant defense, particularly through upregulation of Nrf2 or related pathways(58). Exploring how skin cells adapt to repeated low-dose radiation through enhanced antioxidant responses could also reveal novel insights(59).

11.3.DNA Damage Response (DDR) Pathways

DNA damage, especially double-strand breaks (DSBs), is a key mechanism behind radiation-induced skin damage. A complex network of signalling proteins, including ATM (ataxia-telangiectasia mutated), ATR (ATM- and Rad3-related), and DNA-PK (DNA-dependent protein kinase), are involved in the cellular response to such damage, which is known as the DNA Damage Response (DDR). These proteins start repair processes like homologous recombination (HR) and non-homologous end joining (NHEJ)(60, 61).

Future research will likely explore how modulation of DDR components can protect skin from radiation damage. Inhibitors of specific DDR pathways could potentially protect normal skin during radiation therapy by selectively sensitizing cancer cells to radiation, while protecting normal tissue(62, 63).

11.4Inflammatory Mediators and Immune Response

Radiation induces a robust inflammatory response in the skin, driven by cytokines, chemokines, and immune cells such as macrophages and T-cells(64). Chronic inflammation can exacerbate skin injury and lead to long-term fibrosis or non-healing wounds. The role of immune checkpoints, immune cell recruitment, and the crosstalk between resident skin cells and immune cells is a key area of future investigation(65).

Targeting inflammatory mediators like NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) or modulating the immune microenvironment in irradiated skin may offer novel strategies to reduce inflammation and enhance tissue repair(66).

11.5Stem Cell Regeneration and Tissue Repair Pathways

The activity of stem cells, especially mesenchymal stem cells (MSCs) and epidermal stem cells, is crucial for skin regeneration after radiation damage. The signalling pathways that regulate stem cell activation, proliferation, and differentiation following radiation damage are probably the main focus of future studies (67).

Growth factors, such as fibroblast growth factor (FGF), epidermal growth factor (EGF), and transforming growth factor-beta (TGF-β), which are critical for tissue repair, could be modulated to enhance stem cell-based regeneration. Additionally, advances in tissue engineering and cell therapy using exogenous stem cells or induced pluripotent stem cells (iPSCs) could be explored as a way to replace damaged skin tissues.

11.6Targeting Mitochondrial Dysfunction

Radiation-induced injury often leads to mitochondrial dysfunction, which contributes to cellular energy deficits and amplifies oxidative stress. Emerging research suggests that targeting mitochondrial biogenesis and function could mitigate radiation-induced skin damage(68, 69).

Investigating molecules that enhance mitochondrial resilience or modulate mitochondrial dynamics (fusion and fission processes) could provide new avenues for protecting skin cells from radiation damage. The role of mitophagy, a process by which damaged mitochondria are selectively degraded, is another promising direction that could be explored in this context(70, 71).

11.7Crosstalk Between Skin Microbiome and Radiation Injury

The skin microbiome plays a crucial role in maintaining skin health and modulating immune responses. Recent studies suggest that the composition of the skin microbiome can influence the severity of radiation-induced skin injury. Understanding how radiation affects the skin microbiome and how microbial dysbiosis contributes to injury progression is an emerging area of interest(72).

In order to improve skin health and resilience, especially in reaction to radiation exposure, future study

may look into modifying the skin microbiome using probiotics, prebiotics, or microbial transplantation (73).

11.8Exosome-Mediated Communication

Exosomes are tiny extracellular vesicles that facilitate communication between cells and are becoming more well acknowledged for their function in tissue damage and healing. Exosome composition, which affects inflammation, immunological response, and tissue regeneration, may change as a result of radiation-induced skin damage, according to research(74, 75).

Future research is anticipated to examine the possibilities of exosome-based treatments, in which therapeutic chemicals could be delivered to injured skin via exosomes made from stem cells or other advantageous cells, promoting healing and reducing harm.

12. Conclusion

Future investigations into the cellular and molecular processes behind radiation-induced skin damage could take many different forms and result in the creation of novel therapeutic strategies. Researchers are in a position to discover novel pathways that may result in the creation of more potent remedies for radiation-induced skin damage because to developments in epigenetics, stem cell biology, and molecular signalling. Future treatments may improve skin protection and regeneration after radiation exposure by addressing oxidative stress, DNA damage, inflammation, and mitochondrial dysfunction as well as by investigating the function of the skin microbiome and exosome-mediated communication.

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