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Review

Biomaterials in Radiation Dermatitis: The Role of Hydrogels, Films, and Dressings in Wound Healing

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Abstract

Radiation dermatitis (RD) remains one of the most frequent and distressing complications of radiotherapy, with manifestations ranging from mild erythema to severe ulceration that compromise both patient comfort and treatment adherence. Conventional management strategies often provide limited protection and inadequate wound healing support, highlighting the urgent need for advanced therapeutic approaches. Biomaterials including hydrogels, films, and dressings have emerged as promising solutions due to their unique physicochemical properties and ability to create an optimal wound-healing microenvironment. Hydrogels, composed of natural or synthetic polymers, provide hydration, cooling, and drug delivery capabilities, while bioactive films act as protective barriers that reduce friction, prevent infection, and regulate moisture balance. Advanced wound dressings, such as hydrocolloids, foams, and nanocomposite scaffolds, offer additional functionalities including antioxidant, antimicrobial, and pro-regenerative activity. This review summarizes the pathophysiology of RD, explores the design and therapeutic mechanisms of hydrogels, films, and dressings, and critically evaluates preclinical and clinical evidence supporting their efficacy. Furthermore, challenges related to safety, cost, and regulatory approval are discussed, alongside emerging innovations such as smart dressings and 3D bio printed biomaterials. Collectively, these insights underscore the transformative potential of biomaterials to improve wound healing and quality of life for patients undergoing radiotherapy for cancer.

Keywords: radiation dermatitis; biomaterial; hydrogels; films; wound healing

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1. Introduction

Radiation dermatitis (RD), also known as radiodermatitis or skin injury induced by radiotherapy, remains a prevalent and distressing side effect in oncology, affecting up to 95% of patients receiving external-beam radiotherapy or brachytherapy; however, this estimate primarily reflects RD of any grade, and the incidence and severity of skin reactions vary considerably depending on cancer type, treatment site, radiation dose, fractionation schedule, concurrent therapies, and patient-related factors [1–3]. These reactions not only cause pain, itching, impaired mobility, and risk of infection but may also lead to treatment interruptions or dose de-escalation, thereby potentially compromising therapeutic efficacy [2]. Although radiation delivery techniques have improved considerably, including advances such as intensity-modulated radiation therapy, prone positioning in breast cancer, and more precise targeting, substantial gaps still exist in the current treatment of RD [3]. The existing

standard of care, including moisturizers, barrier creams or films, topical corticosteroids, and general wound care, provides inconsistent clinical benefits [4]. Furthermore, the available evidence is limited by small sample sizes, "risks of bias", inconsistencies in outcome measures, and a lack of long-term studies or investigations involving severe radiation-induced skin injuries [5,6]. While most patients experience mild-to-moderate skin reactions, severe manifestations such as moist desquamation, ulceration, and necrosis occur less frequently but remain clinically significant, particularly in high-risk treatment settings involving the head and neck, breast, and pelvic regions, as well as in patients receiving bolus-based treatment, large radiation fields, higher-dose intensities, or concurrent chemotherapy [3,7]. Moreover, patient-centred outcome (pain, functional impairment, cosmesis, skin integrity after healing) are less well captured in trials, and there is limited high-quality evidence for biomaterial-based advanced dressings, films, or scaffolds specifically for RD [8]. There remain pronounced unmet needs for therapies that not only prevent skin toxicity but also accelerate healing in cases of moderate to severe injury, reduce discomfort and improve quality of life, while being cost-effective, easy to apply, and safe [9].

In recent years, biomaterials have emerged as promising interventions for addressing these unmet needs in the management of RD [10]. Novel dressings incorporating natural polymers, antimicrobial agents, and herbal extracts are currently under investigation in breast and head and neck cancer settings [11]. There is also increasing mechanistic insight into how biomaterials may address key pathological drivers of RD, including oxidative stress, inflammation, impaired epidermal stem cell renewal, and vascular damage, thereby providing not only symptomatic relief but also supporting tissue regeneration and wound healing [12,13]. Given these advances, it is timely to review and synthesize the state of the art in biomaterial-based interventions for RD management, critically evaluate the available evidence, and identify existing knowledge gaps and future directions for research and clinical translation.

2. Pathophysiology of Radiation Dermatitis

RD arises from the interaction of ionizing radiation with skin tissue through both direct and indirect mechanisms. While direct ionization can induce DNA damage (e.g., single- and double-strand breaks) and protein alterations, the indirect effects of radiation predominate in biological tissues because of their high-water content. Ionizing radiation interacts with intracellular and extracellular water molecules, resulting in water radiolysis and the generation of highly reactive species, including hydroxyl radicals (•OH), hydrogen atoms (•H), hydrated electrons (e_{aq}^-), hydrogen peroxide (H_2O_2), and other secondary reactive oxygen species (ROS). These reactive intermediates contribute substantially to oxidative damage and tissue injury associated with RD [3,14–16]. The physicochemical phase of radiation exposure begins within femtoseconds following energy deposition, during which water radiolysis generates primary reactive species such as hydroxyl radicals (•OH), hydrogen atoms (•H), and hydrated electrons (e_{aq}^-). These species subsequently participate in a cascade of secondary reactions that produce hydrogen peroxide (H_2O_2), superoxide anions ($O_2^{\bullet -}$), and other oxidants [15,17,18]. Persistent ROS overproduction overwhelms endogenous antioxidant defence, leading to lipid peroxidation, protein oxidation, mitochondrial dysfunction, and amplification of DNA damage [15]. Studies report that ROS-mediated oxidative injury suppresses cellular proliferation and impairs wound healing by affecting keratinocytes, fibroblasts, and endothelial cells through oxidative stress-dependent pathways [10,19]. Keratinocytes and dermal fibroblasts are particularly vulnerable, resulting in cell death, impaired proliferation, and disruption of the epidermal barrier [19]. Damage to basal keratinocytes compromises skin renewal, while endothelial cell apoptosis leads to microvascular dysfunction and hypoxia, further impairing wound healing [20]. The p53/Bax/Bcl-2 axis has been implicated: increased p53/Bax expression

and reduced Bcl-2 contribute to apoptosis in irradiated skin [21]. The pathogenesis of RD is initiated by a sequence of physical, physicochemical, chemical, and biological phases. The early physicochemical phase involves energy deposition and water radiolysis, followed by the generation of reactive intermediates that trigger oxidative stress, inflammation, vascular injury, and tissue remodelling. Figure 1 summarizes these interconnected processes.

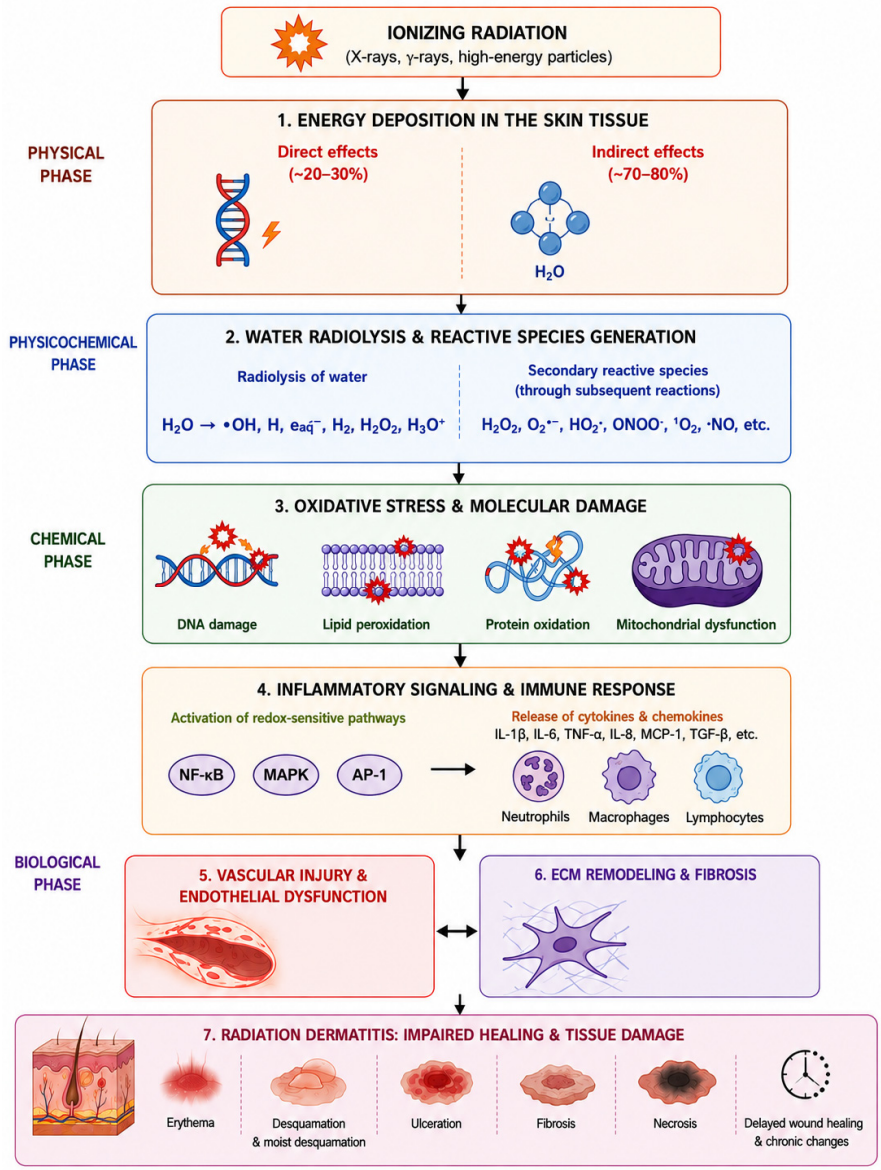

Figure 1. Mechanisms underlying radiation-induced skin injury and the development of radiation dermatitis. Following exposure to ionizing radiation, energy is deposited within skin tissue through both direct interactions with cellular biomolecules and indirect interactions with intracellular and extracellular water. Because biological tissues are predominantly composed of water, indirect effects mediated by water radiolysis constitute a major source of radiation-induced injury. Water radiolysis generates primary reactive species, which subsequently participate in secondary reactions that produce reactive oxygen and nitrogen species. These reactive intermediates induce oxidative stress, resulting in DNA damage, lipid peroxidation, protein oxidation, and mitochondrial dysfunction. The resulting molecular damage activates redox-sensitive signalling pathways, including NF-κB and MAPK, leading to cytokine release, immune-cell recruitment, and sustained inflammation. Concurrently, radiation-induced endothelial injury and microvascular dysfunction promote tissue hypoxia, while extracellular matrix remodelling and fibroblast activation contribute to fibrosis. Collectively, these interconnected physicochemical, chemical, and biological processes impair tissue repair and promote the progression of radiation dermatitis, characterized by delayed wound healing, fibrosis, and, in severe cases, tissue necrosis.

3. Biomaterial Strategies for Radiation Dermatitis

Biomaterials are natural, synthetic, or hybrid substances designed to interact with biological systems for therapeutic purposes, particularly in wound healing and tissue repair. In wound healing, these materials serve as scaffolds, dressings, or carriers for therapeutic agents that support tissue restoration [22]. Biomaterials that demonstrate efficacy in conventional wound models cannot automatically be considered effective treatments for RD. In this review, evidence derived from non-radiation wound models is therefore distinguished from studies specifically investigating radiation-induced skin injury (RISI), with greater emphasis placed on the latter when discussing therapeutic efficacy. Recent radiation-specific studies have demonstrated that multifunctional biomaterials can directly target radiation-associated pathological mechanisms [23]. Antioxidant hydrogels containing ROS-scavenging components have reduced oxidative stress and inflammatory responses in experimental RISI, while ECM-mimetic glycopeptide hydrogels have simultaneously modulated inflammation, promoted angiogenesis and improved epidermal regeneration in irradiated animals [23–25]. Biomaterials can be classified according to their origin, physical form, and composition or design. Based on origin, they may be broadly categorized as natural, synthetic, or semisynthetic materials. Natural biomaterials are derived from biological sources, whereas synthetic biomaterials are produced through chemical or polymerization processes [26]. Semisynthetic biomaterials are derived from naturally occurring materials that have been chemically modified to improve specific physicochemical or biological properties. According to physical form, biomaterials may be developed as hydrogels, foams, films, membranes, nanofibers, or other scaffold architectures. They may also be classified according to their composition or functional design as single-component systems, blends, composites, or hybrid systems, depending on the combination and organization of their constituent materials [26]. Advances in bioengineering have further expanded their application in RD management, where unique physicochemical properties are required to counter oxidative stress, inflammation, and delayed epithelialization [27]. Radiation-induced wounds present unique challenges that require biomaterials with tailored characteristics. Biocompatibility is critical for preventing immune rejection and local irritation, as shown by MoS_2-doped hydrogels that exhibited strong compatibility and reduced RD in vivo [13]. Moisture balance is equally important because it maintains a favourable wound environment by preventing desiccation while controlling exudate accumulation, which supports keratinocyte migration and granulation tissue formation. For example, hyaluronic acid-based hydrogels loaded with deferoxamine, and retinoic acid have been shown to promote angiogenesis and collagen remodelling in irradiated wounds [28]. Antimicrobial activity is also essential because irradiated skin is highly susceptible to opportunistic infections, and multifunctional hydrogels with antimicrobial properties have been investigated to reduce infection risks in RISI [2,27]. Moreover, biomaterials possessing antioxidant and anti-inflammatory properties may mitigate radiation-induced oxidative stress, while functionalized hydrogels and films incorporating nanoparticles or growth factors can further promote wound closure and tissue regeneration [29]. Recent radiation-specific studies demonstrate that biomaterials can be deliberately engineered to address these pathological mechanisms. An in situ photocrosslinkable F127/HA-based hydrogel incorporating Prussian blue nanoparticles and resveratrol reduced ROS and inflammatory responses and promoted neovascularization and wound repair in a mouse model of RISI [23]. An ECM-mimetic glycopeptide hydrogel developed specifically for RISI combined ROS scavenging and DNA double-strand-break repair with inflammatory-factor adsorption, resulting in reduced radiation injury, enhanced epidermal regeneration and angiogenesis in animal experiments [25]. Hydrogels evaluated in diabetic, excisional, or full-thickness wound models have demonstrated important general wound-healing property. These findings

provide stronger evidence for RD-directed biomaterial therapy than studies conducted solely in conventional wound models.

Natural biomaterials such as alginate, chitosan, collagen, gelatin, silk fibroin, and hyaluronic acid are valued for their biocompatibility, biodegradability, and similarity to ECM components, enabling them to promote cell adhesion, migration, and angiogenesis [30,31]. Despite these advantages, their clinical translation may be constrained by relatively poor mechanical strength, rapid or variable degradation rates, batch-to-batch variability, and challenges associated with large-scale manufacturing and long-term storage. Consequently, many contemporary biomaterial platforms employ chemical modification, crosslinking approaches, or hybridization with synthetic materials to overcome these limitations while preserving biological functionality [32–34]. Synthetic biomaterials may lack intrinsic bioactivity, they can be functionalized with peptides, growth factors, or nanoparticles to enhance their therapeutic potential [35]. Hybrid natural–synthetic systems combine components of different origins within a single material platform and are increasingly investigated to integrate the biological activity and biocompatibility of natural polymers with the mechanical strength, stability, and tunability of synthetic materials [36].

A critical distinction should be made between biomaterials evaluated in conventional wound-healing models and those investigated specifically under RISI [25]. Conventional models, including diabetic wounds and full-thickness excisional wounds, are valuable for establishing basic properties such as biocompatibility, moisture retention, cell migration, angiogenesis and antimicrobial activity [37]. However, RISI involves additional pathological processes, including persistent ROS generation, radiation-associated DNA damage, endothelial injury, cellular senescence, chronic inflammation and fibrosis [23]. Therefore, biomaterials optimized in non-radiation models may require additional functionalization to address these radiation-specific barriers. Recent studies using irradiated cellular or animal models have begun to demonstrate this distinction, with radiation-specific biomaterials incorporating antioxidant, anti-inflammatory, anti-senescence, angiogenic and DNA-protective functions [23,25,37,38].

3.1. Hydrogels in Radiation Dermatitis

3.1.1. Composition and Design of Hydrogel-Based Dressings

Hydrogels are three-dimensional, crosslinked polymeric networks capable of absorbing and retaining large amounts of water while preserving their structural integrity; these characteristics make them ideal for maintaining a moist wound environment in radiation-damaged skin [39]. They are fabricated from natural, synthetic, or semisynthetic polymers and may be formulated as composite or hybrid systems in which two or more components are combined to improve biological activity, mechanical stability, drug-delivery performance, or other functional properties [40]. Crosslinking approaches used in hydrogel design include physical, chemical, and photo-crosslinking methods. The selection of a crosslinking strategy determines swelling behaviour, adhesive strength, degradation rate, and drug-release kinetics [41]. Functionalization strategies for radiation wound management commonly involve the incorporation of antioxidant nanomaterials (e.g., MoS_2, MXene), nanozymes, antimicrobial agents (e.g., silver, antimicrobial peptides), and pro-regenerative payloads such as growth factors or small molecules including deferoxamine. These modifications are intended to address the underlying multifactorial pathology of RD [41].

3.1.2. Mechanisms of Action of Hydrogels in Radiation Dermatitis

Hydration and moisture retention: Hydrogels maintain a humid wound environment that prevents desiccation, preserves matrix proteases at physiological activity levels, and promotes keratinocyte migration and re-epithelialization, processes that are critical for

radiation-damaged skin characterized by impaired epidermal renewal [2,42]. Cooling and symptomatic relief: Owing to their high-water content, hydrogels provide an evaporative cooling effect that can reduce burning sensations, irritation, and patient discomfort associated with acute RD [2]. Barrier and infection control: Hydrogels form a semi-occlusive protective barrier that reduces friction and limits external contamination. When loaded with antimicrobial agents or nanozymes, they can additionally suppress microbial growth at the wound site [43]. Sustained local drug delivery: Hydrogels can function as localized drug delivery depots, enabling the controlled release of anti-inflammatory agents, growth factors, or angiogenic molecules such as deferoxamine. This approach supports prolonged therapeutic activity while minimizing systemic exposure [28]. ROS scavenging and immune modulation: Hydrogels incorporating ROS-scavenging materials, nanozymes, MoS_2, or MXene can reduce oxidative stress, attenuate pro-inflammatory signalling pathways, and promote macrophage polarization toward a pro-healing M2 phenotype. These mechanisms have been associated with accelerated tissue repair in preclinical radiation injury models [41]. Figure 2 provides a schematic overview of the principal mechanisms through which hydrogel dressings contribute to the management of RISI. These biomaterials maintain a moist wound environment, provide symptomatic cooling, facilitate localized therapeutic delivery, reduce oxidative stress, and promote angiogenesis and re-epithelialization, collectively supporting tissue repair and wound regeneration.

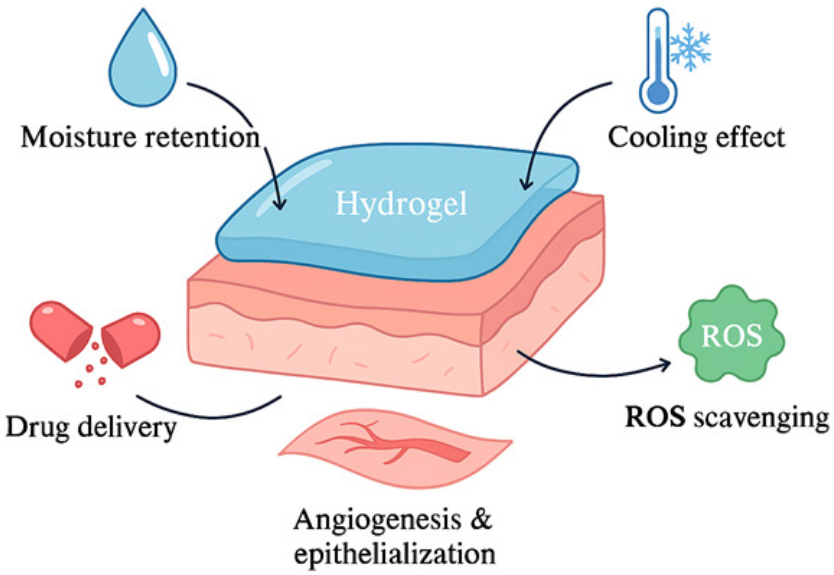

Figure 2. Hydrogel modes of action in radiation dermatitis.

3.1.3. Biopolymer-Based Hydrogels

Natural biopolymer hydrogels derived from alginate, chitosan, hyaluronic acid (HA), gelatin, and other ECM-derived materials are attractive candidates for RD management. These materials combine high water content and ECM-mimetic properties with intrinsic bioactivity, including cell-adhesive characteristics and biodegradability. In addition, they can be readily modified to enable controlled drug release or the incorporation of antioxidant and antimicrobial agents.

Alginate

Alginate is an anionic polysaccharide that forms hydrogels through ionic crosslinking, typically with calcium ions (Ca^{2+}) [44]. Calcium-crosslinked alginate hydrogels are highly hydrophilic and can absorb substantial amounts of wound exudate while maintaining a moist healing environment. Their high swelling capacity and conformability make them

particularly suitable for irregularly shaped irradiated wounds [40,44]. Owing to their effective exudate management, ease of gel formation, relatively low cost, and broad clinical acceptance, alginate-based dressings are widely used in wound care applications [45]. However, alginate possesses limited intrinsic bioactivity, exhibits poor cell adhesion unless blended or modified with other biomaterials, and may display variable mechanical properties and degradation behaviour due to ion exchange within the wound environment [46]. Despite these limitations, recent case reports and small observational studies have shown that alginate dressings, particularly when combined with hydrogels, may support autolytic debridement and help maintain a moist wound bed in patients with severe (grade 4) acute RD, although high-quality trials are still lacking. In the reported cases, treatment was associated with improvements in wound size, exudate management, patient comfort, and psychological well-being; however, the generalizability of these observations remains uncertain and further clinical validation is required [9].

A study conducted by Zhao et al. developed a nanocomposite wound dressing by incorporating cerium oxide nanoparticles into an alginate hydrogel matrix, utilizing curcumin as both a reducing and capping agent. The resulting formulation exhibited strong antioxidant activity, favourable hemocompatibility and biocompatibility, and significant wound-healing efficacy in both in vitro and in vivo studies, suggesting its potential for treating RISI [47]. Luo et al. reported a study introducing a double network hydrogel doped with molybdenum disulfide (MoS_2) nanosheets, designed to prevent radiation-induced dermatitis. The composite hydrogel demonstrated strong adhesion and antioxidant properties and effectively reduced radiation-induced skin damage in animal models. These findings highlight the potential of MoS_2-functionalized hydrogels as a promising strategy for mitigating RISI; however, the evidence is currently limited to preclinical studies, and further investigations are required to establish their long-term safety, efficacy, and clinical translatability in patients undergoing radiotherapy [13]. An in-situ photo-crosslinkable hydrogel was developed by Shen et al. to treat RISI. This hydrogel demonstrated the ability to eliminate ROS and regulate inflammation, leading to improved wound healing outcomes in experimental models, indicating its efficacy in managing radiation-induced skin damage [23]. Recent radiation-specific studies increasingly support the use of polysaccharide-based biomaterials as multifunctional platforms for RISI. Zhang et al. developed an alginate/hyaluronic acid/polylysine hydrogel containing curcumin and epigallocatechin gallate. The resulting system exhibited anti-biofouling, antioxidant, anti-inflammatory and pro-angiogenic properties and accelerated healing of RISI, demonstrating that polysaccharide-based networks can simultaneously address several pathological features of RISI [48]. The combination of hydrogel and alginate-based dressings offers a promising strategy for managing RISI, particularly severe acute RD, by promoting autolytic debridement and maintaining a moist wound environment. Although in vitro, in vivo, and small observational studies indicate potential efficacy, the evidence is currently limited. Therefore, well-designed randomized controlled trials are needed to confirm their safety, efficacy, and optimal clinical use in RD management.

Chitosan

Chitosan (deacetylated chitin) is a cationic polysaccharide with intrinsic antimicrobial, hemostatic, and bioactive properties. Its positive charge enables electrostatic interactions with negatively charged microbial membranes, growth factors, and ECM components. Chitosan hydrogels can support cell attachment, promote hemostasis, and be loaded with bioactive nanoparticles or peptides [49,50]. When formulated into hydrogels, chitosan provides a moist wound-healing environment, supports cell attachment, and can be engineered to deliver bioactive agents such as nanoparticles, peptides, or platelet-rich products [49]. In

addition to its antimicrobial action, chitosan has been shown to promote collagen deposition and angiogenesis in preclinical models, and its amenability to chemical modification enables effective incorporation of growth factors or platelet-rich products (PRP) for enhanced bioactivity [49]. Despite these advantages, its application can be limited by poor solubility at neutral pH unless chemically modified, variability in the source material, and mechanical weaknesses that often necessitate blending with synthetic polymers or crosslinkers to improve stability and performance [51].

Recent in vitro studies have highlighted the regenerative potential of chitosan-based hydrogels. Ezati et al. reported that chitosan–polyethylene glycol hydrogels loaded with the mesenchymal stem cell (MSC) exosomes enhanced fibroblast proliferation, promoted keratinocyte migration, and reduced ROS-mediated oxidative stress, thereby supporting re-epithelialization processes in vitro [52]. The regenerative effects of MSC-derived secretomes have also been demonstrated in other wound-healing models. For example, exosomes derived from Wharton's jelly MSC have been shown to accelerate wound closure, promote angiogenesis, enhance collagen deposition, and modulate inflammatory responses in diabetic wound models [53]. Similarly, adipose-derived MSC conditioned media have demonstrated anti-inflammatory and regenerative properties through the regulation of cytokine production, attenuation of oxidative stress, and promotion of tissue repair [54]. Although these studies were not conducted in RD models, they provide additional mechanistic support for the incorporation of MSC-derived exosomes and conditioned media into biomaterial platforms designed to enhance healing of RISI. Additional studies further support the multifunctional role of chitosan-based systems in wound repair. A study by Kłosiński et al. reported that carboxymethyl chitosan scaffolds supported fibroblast viability, promoted proliferation, and exhibited antibacterial activity against common wound pathogens, highlighting their dual role in tissue regeneration and infection control [55]. Furthermore, composite formulations such as chitosan–hyaluronic hydrogels incorporating gold nanoparticles were shown to stimulate angiogenic pathways, as evidenced by increased endothelial tube formation and upregulation of pro-angiogenic gene expression in vitro [56]. In vivo studies further support these findings. Currently, Li et al. demonstrated that carboxymethyl chitosan–alginate hydrogels significantly accelerated wound closure in full-thickness rat skin wounds, enhanced granulation tissue formation, increased microvessel density, and reduced inflammatory cytokine expression compared with untreated wounds [57]. The incorporation of PRP into chitosan matrices has also been investigated, with studies indicating enhanced granulation tissue formation and accelerated tissue regeneration in radiation-compromised wound models, as well as pilot human reports showing reduced microbial burden and improved healing outcomes [49]. Other formulations, such as sprayable and self-healing chitosan hydrogels, have been applied in infected wound models and were shown to reduce bacterial burden, promote faster re-epithelialization, and improve collagen organization, thereby addressing both infection and impaired healing in compromised wounds [58]. A multifunctional dual-network hydrogel based on quaternized chitosan, oxidized HA and paramylon was evaluated specifically in radiation-induced wounds. The system provided antibacterial, antioxidant, anti-senescence and pro-angiogenic effects and significantly improved skin regeneration in a rat radiation-wound model [37]. These findings provide radiation-specific support for the use of chitosan- and alginate-related biomaterials beyond their established wound-healing properties in non-radiation models. Although the antioxidant, antimicrobial and regenerative properties of chitosan have been extensively demonstrated in conventional wound models, direct evidence in radiation-induced injury remains comparatively limited. Therefore, the use of chitosan for RD should currently be regarded as promising rather than clinically established. Recent radiation-specific polysaccharide-based systems nevertheless

provide encouraging evidence that chitosan-containing networks can be functionalized to address radiation-associated oxidative stress, inflammation and impaired regeneration.

Radiation-crosslinking techniques have also emerged as a promising strategy for the fabrication of chitosan hydrogels. Ionizing radiation has been used to achieve reagent-free gelation, ensuring sterility while enabling control over crosslinking density and mechanical properties [51]. Studies have demonstrated that radiation-crosslinked chitosan/carboxymethylcellulose composites exhibit improved stability and biocompatibility and have shown efficacy in preclinical wound-healing models, with potential application in RISI [55,57]. Collectively, these in vitro and in vivo findings suggest that chitosan-based hydrogels are a versatile platform with antimicrobial, pro-regenerative, and angiogenic functions, making them promising candidates for the management of RD and other chronic or hard-to-heal wounds.

Hyaluronic Acid

Hyaluronic acid (HA) is a glycosaminoglycan that is abundant within the dermal ECM, where it contributes to tissue hydration, structural integrity, and cell signalling [59]. When formulated into hydrogels, HA retains water, regulates cell migration, and interacts with receptors such as CD44 to modulate inflammation and wound healing [59]. HA-based hydrogels exhibit excellent hydration and ECM-mimetic properties, support keratinocyte and fibroblast migration, and possess a well-established safety profile in dermatological applications [28]. They can be physically or chemically crosslinked and readily loaded with therapeutic payloads, including angiogenic and anti-fibrotic agents, making them versatile platforms for regenerative medicine [28]. Despite these advantages, native HA is rapidly degraded by hyaluronidases present in wound fluid, resulting in a short residence time unless chemically modified or crosslinked. In addition, the cost of HA-based formulations is often higher than that of simpler polysaccharides, and their mechanical strength may be limited without reinforcement or blending with other polymers [59].

Recent studies suggest that HA hydrogels can facilitate the repair of radiation-compromised skin. Gao et al. reported that a physically crosslinked HA hydrogel significantly accelerated wound closure in irradiated animal models while improving cell viability and overall tissue repair compared with untreated controls [28]. These findings indicate that physically crosslinked HA systems may support healing in RISI [28]. Hong et al. developed a chlorin e6-conjugated HA (Ce6-HA) hydrogel capable of generating ROS upon exposure to LED irradiation. In vitro experiments showed that the Ce6-HA hydrogel not only produced controlled ROS but also enhanced fibroblast and keratinocyte proliferation and migration, thereby improving cellular functions critical for wound repair. These findings illustrate the potential of HA hydrogels as platforms for ROS-modulating therapeutic strategies [60]. Wu et al. developed an HA dual-network hydrogel (DNH) characterized by rapid gelation, appropriate swelling behaviour, and preserved structural integrity under mechanical stress [61]. In vivo, wounds treated with the DNH healed more rapidly than those treated with conventional gauze dressings and exhibited increased vascularization together with favourable macrophage polarization. These observations suggest that mechanical reinforcement through dual-network design can further improve the regenerative performance of HA-based hydrogels [61]. Overall, HA hydrogels demonstrate strong potential in mitigating RISI by enhancing hydration, cell migration, and angiogenesis. Preclinical evidence indicates that chemically modified HA formulations can overcome rapid degradation, supporting their application as promising therapeutic platforms for RD. Although these findings are encouraging, further translational and clinical studies are required to establish the safety, efficacy, and optimal application of HA-based hydrogels in RD management.

Gelatin

Gelatin, a denatured form of collagen, provides Arg-Gly-Asp (RGD) motifs that promote cell adhesion and is inherently biodegradable [62]. Gelatin hydrogels are widely utilized for the controlled release of growth factors and for ROS-responsive drug delivery owing to their tunable crosslinking chemistry [39,62]. They exhibit excellent cell-adhesion properties, support re-epithelialization and ECM deposition, and are highly adaptable. Photo-crosslinkable gelatin derivatives are increasingly used to improve stability and enable "smart" functionalities, including stimuli-responsive drug release and biosensing applications [62]. However, gelatin hydrogels remain susceptible to rapid enzymatic degradation and may present immunogenicity risks if not adequately purified. In addition, their mechanical strength is often insufficient unless reinforced through crosslinking or incorporation into composite systems [63]. Evidence from non-radiation wound models has demonstrated that GelMA can promote fibroblast proliferation, keratinocyte migration, angiogenesis and tissue regeneration [64]. GelMA hydrogels loaded with hypoxia-preconditioned adipose-derived stem cell conditioned medium exhibited increased cell migration, enhanced endothelial tube formation, and upregulated expression of angiogenic markers in vitro [64]. Jaberi et al. reported that GelMA granular hydrogel scaffolds increased granulation tissue thickness, promoted macrophage polarization toward pro-healing phenotypes, and improved wound-healing outcomes in murine full-thickness skin injury models compared with conventional bulk GelMA scaffolds [65]. These findings provide useful mechanistic evidence for the regenerative potential of gelatin-based biomaterials but should not be interpreted as direct evidence of efficacy against RD. Importantly, recent studies have begun to establish radiation-specific evidence for gelatin-based systems. Zhao et al. developed a GelMA hydrogel patch incorporating ginsenoside-Rh2/tannic-acid nanoparticles for RISI. The composite demonstrated strong ROS-scavenging activity, promoted M2 macrophage polarization and showed protective and reparative effects in cellular models of RISI [66]. In addition, a multifunctional dual-network hydrogel containing quaternized chitosan, oxidized hyaluronic acid, paramylon and a parathyroid-hormone-related peptide was evaluated in a rat model of radiation-induced wounds and was shown to reduce oxidative damage, inflammation and cellular senescence while promoting angiogenesis and skin regeneration [37]. These radiation-specific studies provide stronger evidence for the application of functionalized gelatin and polysaccharide-based hydrogels to radiation-associated wounds than evidence derived solely from conventional skin-defect models.

Multifunctional gelatin/acrylamide-based hydrogels have been developed specifically for radiation-induced wound repair. These systems, composed of gelatin-grafted dopamine, acrylamide, nanoclay, and curcumin-loaded nanoparticles, exhibited improved tissue adhesion, antioxidant activity, and wound-healing performance in breast cancer RD models, including accelerated re-epithelialization and reduced inflammatory responses [67]. The antioxidant and regenerative potential of nanoparticle-functionalized biomaterials have also been demonstrated in other wound-healing models. For example, magnetite nanoparticle-containing biomaterials have been reported to enhance tissue regeneration through antioxidant and pro-healing mechanisms [68]. Similarly, antioxidant-loaded wound dressings incorporating lipoic acid have been shown to modulate inflammatory responses, reduce oxidative stress, and improve wound repair outcomes through immunomodulatory mechanisms [69]. Although these studies were not conducted in RD models, they provide additional mechanistic support for incorporating antioxidant and immunomodulatory components into biomaterial platforms designed for RISI. Collectively, available preclinical evidence indicates that gelatin hydrogels combine biocompatibility with functional versatility, making them attractive candidates for the design of advanced biomaterials

tailored to RISI. Gelatin-based hydrogels demonstrate promising regenerative potential in RD, enhancing re-epithelialization while reducing inflammation and fibrosis. Their tunable chemistry and capacity for smart drug delivery position them as versatile platforms for future clinical translation. Nevertheless, most evidence remains preclinical, and further translational and clinical studies are required to establish their long-term safety, efficacy, and therapeutic value in patients undergoing radiotherapy for cancer.

3.2. Films and Membranes

3.2.1. Characteristics and Fabrication of Bioactive Films

Bioactive films and membranes are thin polymeric layers engineered to interact beneficially with the wound surface by providing a protective interface while allowing controlled mass transfer and, where required, local drug delivery [70]. They are produced from natural polymers (chitosan, collagen, silk fibroin and modified hyaluronic acid) or synthetic polymers (polyurethane, polyvinyl alcohol, silicone, polyethylene glycol), or as hybrids that combine bioactivity and mechanical robustness [71–73]. Film microstructure (dense vs. microporous, single vs. multilayer) and thickness determine water vapour transmission rate (WVTR), oxygen permeability and conformability key parameters that must be tuned for radiation wounds with variable exudation levels [74]. Common fabrication methods include solvent casting, layer-by-layer deposition, plasma or surface functionalization, electrospinning to form nanofiber membranes, and roll-to-roll/continuous coating processes for scalable manufacture [75–77]. Surface functionalization is widely used to impart specific activity: for example, antimicrobial coatings (silver ions, chlorhexidine, antimicrobial peptides), antioxidant coatings or embedded nano agents, and drug-eluting layers for corticosteroids, analgesics, or growth factors [78,79]. Adhesive chemistry (silicone vs. acrylate adhesives) is a critical design decision for radiated skin because adhesives must balance secure fixation with atraumatic removal to avoid further epidermal injury [70,80].

3.2.2. Occlusive vs. Semi-Permeable Films

Occlusive films create an essentially impermeable barrier to water vapour and gas and thus strongly conserve wound moisture; they can be useful in prophylaxis for intact skin but risk maceration if exudate is not effectively managed [74]. Semi-permeable films (thin polyurethane or silicone films) provide controlled WVTR and gas exchange while protecting against shear; these are the most used films in clinical RD prophylaxis and management because they maintain moist healing without excessive exudate trapping [72]. The ideal film for a given RD scenario should therefore be chosen according to objective metrics (WVTR, oxygen permeability), wound exudate category, and anatomical considerations (contour, friction) [74]. Several clinical protocols now recommend semi-permeable films as prophylaxis in breast and head-and-neck radiotherapy, while advising removal or substitution where moderate-to-heavy exudate develops [70,81].

Figure 3 below illustrates structural organization and functional mechanisms of bioactive films and membranes used in RD management. These systems typically consist of a top protective layer that limits microbial invasion and water loss, and a bioactive matrix loaded with therapeutic agents. Semi-permeable films allow controlled oxygen and moisture exchange, while occlusive membranes provide enhanced barrier protection. Together, these materials maintain a moist wound environment, reduce friction, and support tissue regeneration through sustained drug release.

3.2.3. Role in Preventing Infection, Reducing Friction, and Maintaining the Wound Environment

As a physical barrier, films reduce environmental contamination and lower the risk of superficial colonization, a particularly valuable property when epidermal integrity is com-

promised after radiotherapy [73,74]. Active antimicrobial films such as silver-impregnated, chlorhexidine-coated, or nanoparticle-functionalized films have demonstrated in vitro and burn-wound efficacy against common pathogens and are used experimentally or clinically for infected or highly colonized radiation wounds, although concerns about cytotoxicity and resistance require cautious use [82]. Films that incorporate low-friction silicone surfaces reduce mechanical shear and friction on skin folds and high-movement areas (axilla, inframammary fold), thereby limiting exacerbation of desquamation and improving patient comfort during treatment [72,73]. By maintaining moisture balance, semi-permeable films support keratinocyte migration and granulation while permitting visual inspection of the wound in transparent variants, which aids clinical monitoring and reduces dressing-change frequency [74,75]. Some composite films combine an outer semi-permeable backing with an inner hydrogel or drug-eluting layer, thereby providing both symptomatic cooling and the potential for sustained local delivery of anti-inflammatory or analgesic agents [78,79].

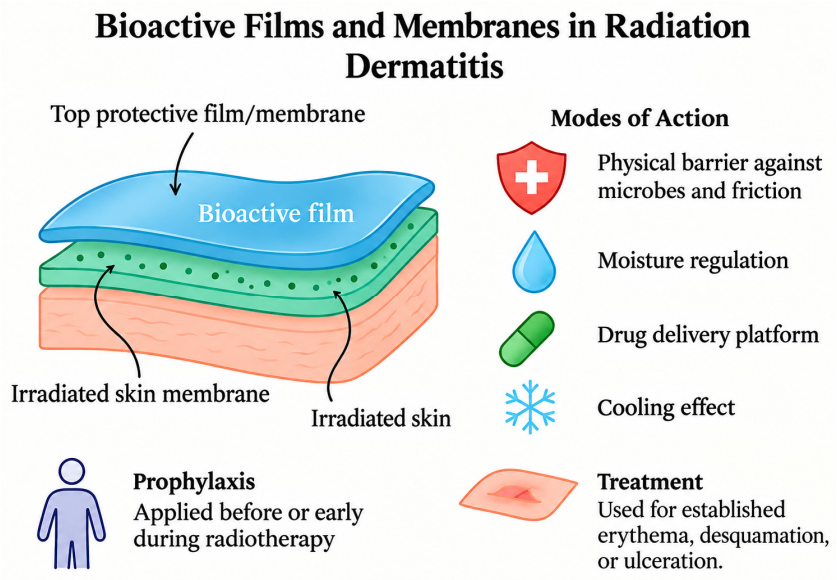

Figure 3. Schematic representation of bioactive films and membranes for radiation dermatitis.

Silver-based contact dressings, including Silverlon® and silver-leaf nylon, possess antimicrobial properties and have been used in the management of contaminated or infected wounds, including some RISI. However, their clinical use should not be interpreted as evidence of established efficacy for RD. Current evidence specific to RD remains limited and inconsistent, with some studies reporting potential benefits in symptom control and wound management, whereas others have found minimal or no significant improvement compared with standard care approaches [83,84]. Furthermore, concerns regarding silver-associated cytotoxicity and potential effects on normal tissue repair warrant careful patient selection and clinical monitoring. Therefore, while silver-containing dressings may have a role in selected cases where microbial burden is a concern, their routine use for RD cannot currently be recommended based on the available evidence [70].

Electrospun nanofiber membranes and nanofiber-based films that mimic ECM architecture and enable drug loading to have been the subject of extensive preclinical and translational research in the past 2–3 years and are promising platforms for future RD applications, but clinical data are still emerging [78,79]. Table 1 below shows a comparative summary of film types and their functional properties, highlighting representative preclinical and clinical evidence in RD. This table illustrates the therapeutic roles, benefits, and limitations of different film-based dressings in managing RD.

Table 1. Comparative Summary of Film Types and Representative Radiation Dermatitis Evidence.

Film Type	Typical Material/Design	Best RD Use Case	Advantages	Limitations	Representative Evidence	References
Semi-permeable film (Mepitel®, Mölnlycke Health Care AB, Gothenburg, Sweden; Hydrofilm®, PAUL HARTMANN AG, Heidenheim, Germany)	Thin polyurethane or silicone film; low-moderate WVTR	Prophylaxis in breast and head and neck radiotherapy; grade 1–2 RD	Breathable, conformable, low-friction, transparent for inspection	Limited absorbency: adhesive trauma if wrong adhesive used	RAREST/Mepitel randomized trials; Hydrofilm meta-analyses showing reduced grade $\geq$2 RD.	[71,72,80]
Occlusive film	Thick silicone or dense film	Low-exudate prophylaxis; temporary protection	Strong moisture retention, barrier function	Maceration risk may alter superficial dose; not for exudative wounds	Protocols advise cautious use; limited clinical RD data supporting occlusive over semi-permeable.	[74,81]
Hydrogel-composite film	Film backing + inner hydrogel pad or drug layer	Symptomatic relief (cooling) and local drug delivery for low–moderate exudate	Cooling, analgesic delivery, local drug depot	Thicker profile; may need secondary dressing for heavy exudate	Emerging clinical reports and preclinical studies demonstrating analgesia and drug release.	[78,79]
Antimicrobial film (silver, CHX)	Silver-impregnated or peptide/coated films	Adjunct for colonized/infected wounds (short term)	Active reduction in surface bioburden	Cytotoxicity, resistance concerns; limited deep action	Silverlon FDA clearance for radiation dermatitis; mixed clinical evidence.	[77,83]
Electrospun nanofiber membrane	Electrospun collagen/PU/PLGA nanofibers (drug-loaded)	Scaffold role + drug delivery for complex wounds (research stage)	ECM mimicry, high loading capacity, customizable release	Manufacturing complexity; limited clinical RD data	Growing preclinical literature and translational studies; clinical translation ongoing.	[75,78]

Bioactive films and membranes represent a valuable class of wound dressings for the management of RD, offering multifunctional benefits beyond simple skin coverage. Their ability to provide a protective barrier against infection, regulate moisture balance, reduce friction, and serve as platforms for the sustained release of therapeutic agents makes them particularly suited to the fragile, irradiated skin microenvironment. Preclinical advances are focusing on incorporating nanomaterials, antioxidants, and growth factors to enhance regenerative outcomes. Despite these promising findings, challenges remain, including variability in film adherence on highly contoured skin surfaces, potential for maceration in high-exudate wounds, and the limited number of large-scale randomized controlled trials. Moving forward, the integration of smart biomaterials with responsive drug release and improved patient comfort may help establish films and membranes as first-line strategies for both prophylaxis and treatment of RD.

3.3. Advanced Wound Dressings for Radiation Dermatitis

Various advanced wound dressings have been investigated for the prevention and management of RD, each leveraging distinct materials and mechanisms to promote skin repair, reduce inflammation, and prevent secondary infection. Table 2 summarizes the key types of dressings, their functional compositions, preclinical or clinical models, mechanisms of action, and observed outcomes in RD management. This overview highlights the translational potential of hydrocolloids, foams, nanofibers, and composite systems in mitigating radiation-induced skin injury.

Table 2. Representative Advanced Wound Dressings Evaluated for Radiation Dermatitis.

Type of Dressing	Material/ Functionalization	Model/Study Type	Mechanism of Action	Key Outcome	Reference
Hydrocolloid	Gelatin–pectin–CMC, ECM-functionalized	Preclinical (mouse) and Clinical (breast cancer)	Moisture retention, barrier protection, enhanced cell adhesion and migration	↓ RD grade, faster re-epithelialization, improved tissue remodelling	[85]
Foam	Silver-impregnated polyurethane, silicone-contact	Clinical (thoracic and head/neck irradiation)	Absorption, antimicrobial protection, friction/ shear reduction	↓ Infection, reduced pain, shorter healing time	[86]
Nanofiber	PCL–chitosan + curcumin NPs	Preclinical (murine RD/wound model)	ROS scavenging, ECM mimicry, controlled bioactive release	↑ Collagen deposition, faster healing, enhanced fibroblast proliferation	[87–91]
Nanofiber	Chitosan-based nanofibers	Preclinical (animal wound model)	Antimicrobial, hemostatic, regenerative	↓ Infection, ↓ inflammation, accelerated re-epithelialization	[92]
Composite	Chitosan–alginate–silver or antioxidant-doped hydrogel/film	Preclinical (rat/murine RD model) and Early clinical	Anti-inflammatory, antimicrobial, sustained drug delivery	↓ Inflammation, enhanced angiogenesis, faster healing, reduced RD severity	[93–96]

3.3.1. Hydrocolloid Dressings

Hydrocolloids are occlusive or semi-occlusive dressings composed of hydrophilic polymers such as gelatin, pectin, and carboxymethylcellulose that form a cohesive gel upon contact with wound exudate. They maintain a moist wound environment, enhance autolytic debridement, and protect against secondary infection [97]. In RD, hydrocolloid dressings have been reported to reduce erythema and desquamation severity in some studies, potentially through promotion of epidermal barrier repair and reduction in transepidermal water loss [98]. However, their occlusive nature may cause maceration in heavily exudative wounds or discomfort in sensitive, irradiated skin. Functional modification of hydrocolloid matrices such as incorporation of ECM components can enhance cell adhesion and migration, thereby accelerating re-epithelialization [85]. Such functionalized hydrocolloid films have demonstrated improved wound closure, enhanced tissue remodelling, and better histological outcomes in preclinical models [85]. However, while these modifications

improve therapeutic efficacy, they may also increase production costs and compromise mechanical integrity or shelf stability [85]. Despite their advantages, moisture retention, protection from friction, and ease of application hydrocolloids have limitations in RD management. Their occlusive nature may trap excessive moisture in heavily exudative lesions, causing exudate accumulation, maceration, and delayed healing if dressings are not changed frequently [98]. Furthermore, evidence for their use in RD remains limited, as few randomized controlled trials have been conducted exclusively on hydrocolloids; most available data are derived from small observational studies or combination protocols involving hydrogel or alginate dressings [85].

Recent evidence provides preliminary but not definitive support for the use of hydrocolloid dressings in radiation-affected wounds. In a preclinical study, ECM-functionalized hydrocolloid films composed of Na-CMC/pectin/gelatin and human placental ECM achieved significantly improved wound closure, more rapid re-epithelialization, and greater hair follicle formation in mouse models compared with non-functionalized controls [85]. However, direct clinical evidence in RD remains scarce. While quasi-controlled studies, retrospective analyses, and case reports have suggested potential benefits in symptom reduction and wound healing, these findings require confirmation through larger randomized controlled trials [97,99]. A successful case report using a combination of hydrogel, alginate, and hydrocolloid dressings for grade 3 RD also suggests the utility of moisture-retentive occlusive dressings in accelerating healing. Hydrocolloid dressings provide a moist, protective barrier that promotes autolytic debridement and supports epidermal repair in RD. Available evidence suggests potential benefits in reducing erythema, desquamation, and pain, particularly in mild-to-moderate cases; however, these findings are primarily derived from limited clinical studies and supportive preclinical evidence. Their occlusive nature may contribute to maceration in heavily exudative wounds, necessitating careful patient selection and monitoring. Consequently, although hydrocolloid dressings remain a promising option for RD management, high-quality randomized clinical trials are needed before definitive conclusions regarding their efficacy can be established.

3.3.2. Foam Dressings

Foam dressings, typically made from polyurethane, provide cushioning, high absorbency, and vapour permeability, making them well suited to manage moderate-to-high exudate wounds by maintaining a moist wound environment while protecting against mechanical irritation from clothing or medical devices [100]. Foam constructions with silicone contact layers or soft, conformable backings reduce friction and shear on fragile irradiated skin, improving patient comfort and reducing pain during the healing phase [97]. Foams impregnated or coated with active agents such as ionic silver, honey, or hyaluronic acid deliver additional antimicrobial and pro-regenerative effects, with preclinical and clinical reports demonstrating reduced bioburden, lower infection rates, and improved granulation in difficult wounds [101,102].

Clinical evidence in radiotherapy settings is encouraging but heterogeneous: systematic and narrative reviews note that foam dressings (including silicone-contact foams and silver-impregnated foams) are effective treatments for established acute RD and can shorten healing time, reduce exudate, and lower pain scores in observational and single-center studies [103]. Practical considerations include excellent exudate control, cushioning, and breathability, balanced against drawbacks: some polyurethane foams may adhere to fragile peri-wound skin if not appropriately used (requiring moistening or use of a contact layer), and advanced foam dressings (e.g., silver-impregnated or bioactive foams) are typically more costly than simple gauze or basic dressings [100]. Current guidelines and expert consensus suggest foam dressings as a valuable option for managing moderate-to-severe

RD when used according to exudate level and skin condition, while calling for randomized controlled trials to define optimal dressing selection and change frequency [70,104].

Haesler conducted a randomized controlled trial (RCT) involving 88 patients with head and neck cancer undergoing radiotherapy, comparing foam dressings to standard saline wound care. The study demonstrated that patients treated with foam dressings had a significantly shorter median healing time of 16 days, compared to 23 days in the standard care group ($p = 0.009$). Moreover, the foam dressing group experienced lower severity of radiation-induced skin reactions, reduced wound pain, and fewer sleep disturbances [86]. In a separate RCT involving 80 women receiving radiotherapy for breast cancer, foam dressings were compared with aqueous cream. Although the average healing time did not differ significantly between the groups (11 $\pm$ 2 days for foam vs. 13 $\pm$ 2 days for aqueous cream, $p = 0.49$), the foam dressing group showed a lower incidence of progression to moist desquamation (15% vs. 19%) and a shorter overall duration of moist desquamation (18 weeks vs. 25 weeks) [86]. Taken together, these findings suggest that the clinical benefits of foam dressings may vary according to patient population and treatment setting. While improvements in healing time were observed in patients with head and neck cancer, similar benefits were not consistently demonstrated in breast cancer cohorts. Nevertheless, foam dressings may contribute to improved symptom management and reduction in the severity or duration of moist desquamation. Therefore, current evidence supports a potential role for foam dressings in RD management, although larger, well-designed studies are needed to clarify their effectiveness across different cancer populations and clinical contexts [86,97].

3.3.3. Electrospun Nanofiber Mats

Electrospun nanofiber mats have emerged as promising therapeutic platforms for managing RD due to their biomimetic structure, high surface area, and tunable release profiles [105]. These mats, often fabricated from biopolymers such as polycaprolactone (PCL), chitosan, and gelatin, can be loaded with bioactive agents like curcumin to address oxidative stress, inflammation, and impaired wound healing associated with RD [87]. Electrospun nanofiber mats exert therapeutic effects in RD primarily through their antioxidant delivery, controlled release properties, and biomimetic structure [88]. Curcumin, a potent antioxidant, can be encapsulated within these nanofibers to mitigate oxidative damage by scavenging ROS, reducing inflammation, and promoting re-epithelialization, thereby accelerating wound healing [88]. The electrospinning process also allows precise control over fiber porosity and surface area, enabling sustained release of therapeutic agents that maintain effective concentrations at the wound site over prolonged periods [89]. Additionally, the nanofibrous architecture closely mimics the native ECM, providing a supportive microenvironment that facilitates cell adhesion, proliferation, and migration, which are essential for efficient tissue regeneration and repair [76].

Kyritsi et al. developed electrospun nanofibrous patches incorporating *Pinus halepensis* bark extract (PHBE) and evaluated their therapeutic efficacy in patients with acute RD undergoing radiotherapy for non-melanoma skin cancer. The PHBE-loaded nanofiber patches were applied daily and compared to a standard reference cream over a 60-day period [90]. Patients treated with the PHBE patch exhibited markedly reduced erythema, transepidermal water loss, and hemoglobin concentration changes, alongside improved skin hydration and faster recovery of barrier function. Clinical grading RTOG and patient-reported scores indicated milder RD severity, less pain and itching, and greater overall comfort in the PHBE group [90]. Importantly, no adverse reactions were observed, confirming the patch's biocompatibility and tolerability. These findings suggest that sustained topical delivery of antioxidant-rich PHBE through electrospun nanofibers effectively mitigates RISI, supporting its potential as a targeted, non-invasive intervention for RD [90].

Jirofti et al. fabricated hybrid electrospun nanofiber mats composed of chitosan, polyethylene oxide (PEO), and collagen, loaded with curcumin to exploit its potent antioxidant and anti-inflammatory properties. The nanofibers exhibited uniform morphology, high porosity, and favourable mechanical strength, ensuring structural stability and controlled curcumin release [91]. In vitro, assays revealed significantly enhanced fibroblast adhesion, proliferation, and migration compared to unloaded mats, indicating the material's excellent cytocompatibility and wound-healing potential. The curcumin-loaded nanofibers also demonstrated strong free radical scavenging activity and inhibition of pro-inflammatory mediators, effectively mitigating oxidative stress in the wound microenvironment [91]. In vivo studies using full-thickness excision wound models showed accelerated wound contraction, increased collagen deposition, and earlier re-epithelialization in treated groups, confirming superior tissue regeneration and reduced inflammatory infiltration [91]. Overall, the chitosan/PEO/collagen–curcumin nanofibrous scaffold offers a multifunctional wound dressing platform combining antioxidant delivery, structural support, and bioactivity that could be translated to alleviate radiation-induced skin injury by counteracting reactive oxygen species and promoting dermal repair. Sánchez-Machado et al. investigated the therapeutic potential of electrospun chitosan-based nanofiber mats in promoting wound healing and preventing infection in animal models. The fabricated nanofibers exhibited a uniform, porous morphology with high surface area and moisture-retention capacity features favourable for exudate absorption and oxygen permeability [92]. In vitro characterization demonstrated notable antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli*, attributed to the intrinsic cationic nature of chitosan, which disrupts microbial membranes. The nanofibers also supported the attachment and proliferation of fibroblasts and keratinocytes, suggesting strong cytocompatibility and potential to enhance tissue regeneration [92]. The electrospun chitosan nanofibers serve as a multifunctional wound dressing combining antimicrobial, hemostatic, and regenerative properties that can be effectively translated to the management of RISI by preventing secondary infection, reducing inflammation, and promoting rapid tissue repair. In contrast to hydrogels, direct evidence for electrospun nanofibrous biomaterials in RISI remains limited. Most nanofiber studies have focused on conventional full-thickness, diabetic, infected or burn wounds, where the materials have demonstrated advantages related to ECM mimicry, high surface area, cellular adhesion and controlled drug release. These properties provide a strong rationale for investigating nanofibrous systems in RD, but their effectiveness against radiation-specific oxidative stress, endothelial injury, cellular senescence and fibrosis remains insufficiently established. Accordingly, nanofibers should currently be considered an emerging rather than established biomaterial platform for RD.

3.3.4. Composite Dressings

Composite dressings integrate two or more functional layers, typically a hydrogel, foam, film, or nanofiber component into a single dressing system designed to synergistically enhance wound healing outcomes. These multifunctional platforms combine the moisture-retentive environment of hydrogels or hydrocolloids with the structural integrity, exudate absorption, and barrier protection of foams or nanofibers [93,94]. For RD, composite dressings offer tailored therapeutic advantages such as sustained drug delivery, mechanical resilience, antimicrobial protection, and improved patient comfort. Preclinical studies report that adhesive, antioxidant-doped composite hydrogels can prevent or reduce RD by scavenging ROS, suppressing pro-inflammatory cytokines, and promoting epithelial regeneration in irradiated skin models [13].

Clinical and prospective studies of advanced dressings that combine barrier/film or antimicrobial layers with bioactive hydrogels also show benefit: hydrogel dressings

reduced healing time for moist desquamation in randomized trials and prospective series, and silver-containing composite/film dressings have been associated with lower severity of RD and acceptable safety/tolerability in patients [95]. Safety/feasibility trials report high compliance and few treatment-related adverse events, supporting clinical tolerability of antimicrobial composite dressings in the radiotherapy setting. However, most translational biomaterial work remains preclinical or early-phase; high-quality randomized trials comparing well-characterized composite systems against standard care are still limited and required to define optimal platforms and evidence-based protocols for RD management [96]. Composite dressings that combine antioxidant/anti-inflammatory payloads with protective/antimicrobial outer layers (foam, film, silver-coated fabrics or nanofibers) address multiple pathophysiologic drivers of RD and therefore represent a rational translational strategy; early preclinical and clinical data are encouraging but insufficient [13].

4. Mechanisms of Biomaterial-Mediated Healing in Radiation Dermatitis

Radiation-induced skin injury is characterized by interconnected pathological processes involving oxidative stress, inflammation, vascular dysfunction, impaired tissue regeneration, microbial susceptibility, and abnormal ECM remodeling. Persistent ROS production, initiated by water radiolysis and sustained by mitochondrial dysfunction, activates redox-sensitive signaling pathways such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), resulting in the release of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) [106]. Radiation-induced endothelial injury further contributes to capillary rarefaction, increased vascular permeability, impaired tissue perfusion and hypoxia, while persistent activation of transforming growth factor-β (TGF-β)/Smad signaling promotes fibroblast activation, myofibroblast differentiation and excessive ECM deposition [10,107]. Persistent DNA damage, oxidative stress and inflammatory signaling can additionally induce cellular senescence in keratinocytes and fibroblasts, thereby reducing their proliferative and regenerative capacity. Altered Wnt, bone morphogenetic protein (BMP) and Smad signaling may further contribute to the imbalance between tissue repair and fibrosis during the chronic phase of radiation injury [106].

These pathological processes provide specific biological targets for biomaterial-based intervention. Rather than functioning solely as passive wound coverings, contemporary biomaterials are increasingly designed as multifunctional therapeutic platforms capable of simultaneously regulating oxidative stress, inflammation, vascular dysfunction, impaired regeneration and pathological tissue remodeling. The following subsections therefore consider the major mechanisms through which biomaterial-based systems may promote healing in radiation-injured skin. The interconnected mechanisms through which biomaterial-based interventions address the major pathological features of radiation-induced skin injury are summarized in Figure 4. These mechanisms include restoration of the skin barrier, modulation of the wound microenvironment, regulation of oxidative and inflammatory responses, promotion of vascular and tissue regeneration, and antimicrobial and immunomodulatory activity.

4.1. Radiation-Induced Oxidative Stress and Biomaterial-Mediated Redox Regulation

Oxidative stress represents one of the earliest and most persistent pathological features of RISI. Radiation-generated ROS can damage DNA, lipids and proteins while impairing the function of keratinocytes, fibroblasts and endothelial cells. Excessive ROS also activates redox-sensitive inflammatory pathways, thereby establishing a self-perpetuating ROS–inflammation cycle [106]. Consequently, biomaterials designed for radiation-injured skin increasingly incorporate antioxidant functionality rather than serving solely as passive phys-

ical barriers. Relevant strategies include the incorporation of ROS-scavenging nanoparticles, antioxidant polyphenols, redox-active polymers, nanozymes and antioxidant-rich natural compounds into hydrated polymeric networks [107,108]. Desirable material characteristics include high antioxidant capacity, sustained local retention, biocompatibility, controlled release and, where possible, responsiveness to the oxidative wound microenvironment [108]. Recent radiation-specific evidence demonstrates the therapeutic potential of this approach. Shen et al. developed an injectable photocrosslinkable F127/hyaluronic acid (HA)-based hydrogel containing polyvinylpyrrolidone (PVP)-modified Prussian blue nanoparticles and resveratrol. The resulting system exhibited free-radical-scavenging and enzyme-mimetic antioxidant activities, reduced intracellular ROS and improved wound healing in a RISI model. Treatment was also associated with reduced inflammatory responses, enhanced neovascularization and improved collagen deposition, demonstrating the integration of antioxidant and regenerative functions within a single biomaterial platform [23].

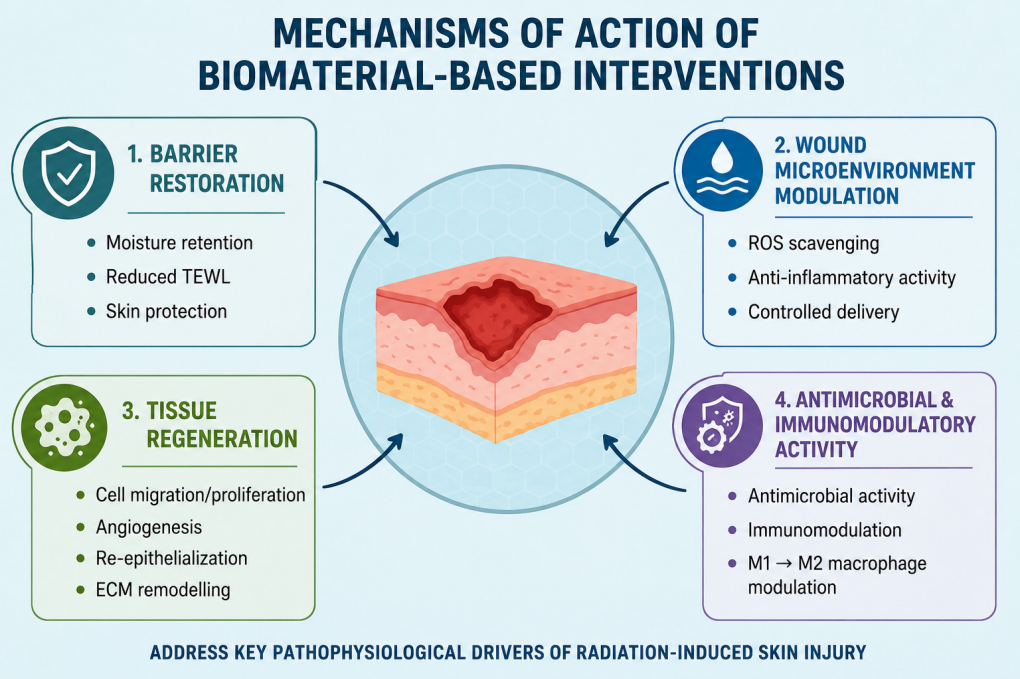

Figure 4. Schematic illustration of the mechanisms of action of biomaterial-based interventions in radiation dermatitis. Biomaterial dressings act through four interrelated mechanisms: restoring the skin barrier and preventing microbial invasion; modulating the wound microenvironment by maintaining moisture, scavenging ROS, and reducing inflammation; promoting cellular proliferation, angiogenesis, and collagen deposition to accelerate tissue regeneration; and providing antimicrobial and immunomodulatory effects that support healing of irradiated skin.

Antioxidant biomaterials may additionally influence downstream redox-sensitive signaling. Suppression of excessive ROS can reduce activation of NF-κB and MAPK and consequently decrease the production of inflammatory mediators such as TNF-α, IL-1β and IL-6 [109]. Preservation or activation of endogenous antioxidant defense mechanisms, particularly the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, represents another potential strategy because Nrf2 regulates cellular antioxidant and cytoprotective responses [110]. Future radiation-specific biomaterials should therefore be evaluated not only according to total ROS reduction but also according to their effects on Nrf2-related antioxidant defense, NF-κB/MAPK activation, mitochondrial integrity, lipid peroxidation and oxidative cell death. A further approach involves targeting iron-dependent oxidative injury. Radiation-induced alterations in iron homeostasis may contribute to lipid peroxidation

and ferroptotic cell death [111]. Tian et al. developed silk-fibroin hydrogel microneedles loaded with deferoxamine (DFO), an iron-chelating agent, for RISI. The DFO-loaded system reduced free Fe^{2+} availability, ROS generation and lipid peroxidation while promoting neovascularization and reducing fibrosis in irradiated skin [112]. This study illustrates how biomaterial-mediated local delivery can target a specific molecular source of oxidative injury rather than providing nonspecific antioxidant activity.

4.2. Inflammation and Immunomodulation

Persistent inflammation is a major contributor to delayed healing following radiation exposure. Irradiated wounds may remain in a prolonged inflammatory state, with dysregulated macrophage activity and sustained cytokine production contributing to tissue damage and impaired regeneration. Biomaterials can address this process by modifying the local wound microenvironment and providing immunomodulatory cues in addition to delivering conventional anti-inflammatory agents. An ECM-inspired glycopeptide hydrogel developed for chronic RISI combined ROS-scavenging activity with mannose-receptor-mediated modulation of macrophage behavior. The hydrogel promoted macrophage polarization towards a reparative M2 phenotype, reduced pro-inflammatory cytokine expression and enhanced angiogenesis and tissue regeneration in irradiated skin [25]. Similarly, multifunctional antioxidant hydrogels have demonstrated that simultaneous reduction in oxidative stress and inflammatory signaling may interrupt the self-perpetuating ROS–inflammation cycle [113]. This approach is particularly relevant because inflammatory signaling, oxidative stress and macrophage dysfunction are mechanistically interconnected. Accordingly, biomaterials with combined antioxidants and immunomodulatory properties may provide greater therapeutic benefit than systems targeting either pathway independently. Material composition, degradation behavior, surface chemistry and controlled release characteristics can be tailored to regulate the local inflammatory environment while supporting transition towards a reparative phase.

4.3. Vascular Dysfunction, Hypoxia and Angiogenesis

Radiation-induced endothelial cell injury and microvascular dysfunction reduce tissue perfusion and oxygen availability, generating a hypoxic microenvironment that further compromises keratinocyte and fibroblast activity, angiogenesis and tissue regeneration [10]. Biomaterials may address this pathology through promotion of angiogenesis, controlled delivery of pro-angiogenic or hypoxia-modulating agents, enhancement of endothelial-cell migration and modulation of the inflammatory microenvironment. Material properties such as interconnected porosity, appropriate water content, ECM-mimetic architecture and controlled release kinetics are particularly important because they influence cell migration, nutrient transport and vascular ingrowth. In a rat model of RISI, acellular dermal matrix hydrogel promoted angiogenesis and vascular maturation, increased M2 macrophage polarization, reduced IL-1β and IL-6 expression and increased the anti-inflammatory cytokine IL-10 [1]. These effects were accompanied by reduced wound area, improved epithelial thickness and enhanced hair-follicle regeneration. These findings demonstrate that biomaterial scaffolds may improve vascular repair through coordinated regulation of inflammation, macrophage phenotype and neovascularization rather than through a single angiogenic stimulus [1]. The glycopeptide-based hydrogel developed by Guo et al. provides additional radiation-specific evidence. This ECM-mimetic system combined ROS scavenging, DNA double-strand-break repair and inflammatory-factor modulation and promoted epidermal regeneration and angiogenesis while reducing pro-inflammatory cytokine expression in an animal model of radiation-induced skin injury [25]. Similarly, the ROS-scavenging F127/HA hydrogel described above promoted neovascularization,

suggesting that reduction in oxidative and inflammatory stress can indirectly improve the vascular microenvironment [23]. Biomaterials may also be used for the localized delivery of angiogenic or hypoxia-modulating agents. Deferoxamine, for example, can influence hypoxia-inducible signaling and promote angiogenic responses, making controlled local delivery through biomaterial systems attractive where vascular insufficiency contributes to delayed healing. Future studies should therefore evaluate vascular-specific outcomes, including endothelial-cell survival, capillary density, vessel maturation, tissue perfusion, HIF-1α/VEGF signaling and tissue oxygenation, rather than relying exclusively on wound-closure measurements [114,115].

4.4. Barrier Restoration, Moisture Regulation and Protection

Radiation-induced damage to the epidermal and dermal layers compromises the skin barrier and increases susceptibility to transepidermal water loss, mechanical irritation and microbial invasion [116]. Biomaterial dressings can provide a temporary physical barrier while maintaining a favorable moisture environment and protecting fragile irradiated tissue. Hydrogels, films and other hydrated biomaterial systems can retain water, reduce excessive moisture loss and provide cooling or soothing effects [107]. Depending on their composition and architecture, they can also absorb wound exudate and reduce mechanical friction between the wound and external surfaces. These properties are particularly relevant to RD because the clinical presentation may progress from erythema and dry desquamation to moist desquamation and more extensive tissue damage. The therapeutic value of barrier restoration therefore extends beyond simple wound coverage. An appropriately designed biomaterial can simultaneously protect damaged tissue, regulate moisture and create a microenvironment that supports cellular migration and re-epithelialization. However, material selection should be matched to wound characteristics because excessive occlusion in heavily exudative wounds may contribute to maceration, whereas insufficient moisture retention may be detrimental to dry or fragile irradiated skin.

4.5. Cellular Regeneration and Extracellular Matrix Remodeling

Successful repair of radiation-injured skin requires coordinated keratinocyte and fibroblast migration, proliferation, re-epithelialization, ECM deposition and remodeling. Radiation-induced cellular senescence, oxidative stress and inflammatory signaling can compromise these processes, resulting in delayed wound closure and defective tissue regeneration [106]. Biomaterials can support regeneration by providing ECM-mimetic architectures, cell-adhesive motifs, appropriate mechanical properties and controlled presentation of bioactive molecules. Three-dimensional porous networks can provide temporary structural support while facilitating cellular migration, nutrient transport and tissue ingrowth. In addition, localized delivery of growth factors, antioxidants or other regenerative molecules can enhance the biological activity of the material [117,118]. Radiation-specific studies demonstrate that multifunctional systems can promote regeneration while simultaneously addressing upstream pathological mechanisms. The F127/HA hydrogel containing Prussian blue nanoparticles and resveratrol promoted tissue regeneration and neovascularization while reducing oxidative and inflammatory injury [23]. The glycopeptide hydrogel developed by Guo et al. similarly promoted epidermal regeneration and angiogenesis while modulating oxidative and inflammatory responses [25]. These findings indicate that improved re-epithelialization may result not simply from physical support but from coordinated modification of the irradiated wound microenvironment.

4.6. Multifunctional and Stage-Responsive Biomaterial Strategies

The interconnected nature of RISI provides a strong rationale for multifunctional biomaterial design. ROS generation, inflammation, vascular dysfunction, impaired re-

generation and fibrosis do not occur as isolated events; instead, they influence one another throughout the progression of injury. Biomaterials capable of addressing several pathological processes simultaneously may therefore provide greater therapeutic potential than single-function systems [119]. Recent studies illustrate this emerging approach. A dual-network GelMA/sodium alginate hydrogel containing MXene nanosheets was designed to address persistent oxidative stress and immune dysregulation following radiation exposure. The optimized hydrogel reduced oxidative stress, promoted macrophage polarization towards the M2 phenotype and interrupted the chronic inflammatory cycle, thereby improving radiation-associated wound healing [120]. Similarly, alginate/HA/polylysine-based hydrogels incorporating curcumin and epigallocatechin gallate have been developed to combine antibiofouling, antioxidant, anti-inflammatory and pro-angiogenic functions, thereby addressing interconnected problems of ROS accumulation, inflammation, microbial colonization and impaired vascularization [48,121]. Stage-responsive systems may be particularly relevant to radiation injury because the dominant pathological processes change over time. Acute injury is strongly associated with oxidative stress, DNA damage and inflammation, whereas established or chronic injury may be dominated by persistent inflammation, vascular dysfunction, fibrosis and abnormal ECM remodeling. Accordingly, future biomaterials could incorporate sequential or stimuli-responsive release mechanisms in which therapeutic agents are delivered according to the evolving wound microenvironment.

Overall, biomaterial-mediated healing in RD represents a transition from passive wound coverage towards mechanism-informed therapeutic design. Hydrogels, ECM-derived matrices, films, nanofibers and nanocomposite systems can provide physical protection and moisture regulation while simultaneously targeting ROS, inflammatory signaling, macrophage dysfunction, vascular impairment, microbial colonization and pathological tissue remodeling. Nevertheless, the strength of evidence varies considerably according to the experimental model. Barrier restoration, moisture management, cellular migration and angiogenesis are supported by substantial evidence across conventional wound models, whereas direct modulation of radiation-specific processes such as persistent ROS generation, radiation-induced senescence, ferroptosis and chronic vascular injury remain supported by a smaller number of radiation-specific studies. Therefore, findings from non-radiation wound models should be considered supportive rather than definitive evidence for RD. Most mechanistically sophisticated systems also remain at the preclinical stage, highlighting the need for clinically relevant radiation models, long-term safety assessment, manufacturing reproducibility, stability studies and evaluation of interactions with ongoing radiotherapy and standard oncological treatment.

5. Comparative Analysis of Biomaterial Platforms for Radiation Dermatitis Management

The management of RD remains challenging due to the multifactorial nature of RISI, which involves oxidative stress, inflammation, vascular dysfunction, ECM remodelling, and impaired tissue regeneration [116]. Consequently, no single biomaterial platform can fully address all aspects of the wound-healing process. Over the past decade, diverse biomaterial-based strategies, including hydrogels, films, foam dressings, nanofiber systems, and bioengineered scaffolds, have been developed to provide physical protection, maintain a moist wound environment, modulate inflammation, deliver therapeutic agents, and promote tissue repair [122,123]. Each biomaterial platform possesses unique physicochemical and biological properties that influence its therapeutic performance and clinical applicability. For example, hydrogels are highly effective in maintaining hydration and enabling controlled drug delivery, whereas polymeric films offer excellent barrier protection and ease of clinical use [124]. Foam dressings are particularly valuable for managing exudative

lesions and moist desquamation, while electrospun nanofiber systems mimic the ECM and provide advanced drug delivery capabilities [125]. Furthermore, the translational readiness of these platforms varies considerably, with some technologies already incorporated into routine clinical practice and others remaining at the preclinical stage.

Importantly, the optimal biomaterial selection may depend on the severity and stage of RD. While barrier films are commonly employed prophylactically to reduce friction and radiation-induced skin damage, hydrogels and advanced bioactive scaffolds may be more suitable for promoting tissue regeneration and managing established skin injury [27,126]. Therefore, understanding the comparative performance of available biomaterial platforms is critical for guiding both clinical decision-making and future biomaterial development. Given these differences, a comparative assessment is essential to identify the strengths, limitations, and clinical suitability of each biomaterial category. Table 3 summarizes the major biomaterial platforms investigated for RD management, highlighting their advantages, limitations, mechanical characteristics, biocompatibility, antimicrobial potential and drug delivery potential.

Table 3. Comparative analysis of biomaterial platforms for the prevention and management of radiation dermatitis.

Biomaterial Platform	Advantages	Limitations	Mechanical Properties	Biocompatibility	Antimicrobial Activity	Drug Delivery Potential	Suitability for Radiation Dermatitis
Hydrogels	Maintain moist wound environment; absorb exudate; cooling effect; support cell migration and tissue regeneration [127]	Limited mechanical strength; dehydration during prolonged use; some formulations require crosslinking optimization [128]	Soft, elastic, highly hydrated [129]	Excellent [130]	Moderate; enhanced when loaded with antimicrobial agents (e.g., silver, chitosan) [131]	Excellent; suitable for controlled and sustained local delivery of drugs, antioxidants, growth factors, and other bioactive agents. Nanoparticle incorporation can further enable controlled or responsive release [132]	Excellent; particularly suitable for maintaining moisture, reducing discomfort, supporting re-epithelialization, and managing dry and moist desquamation. Can be engineered to provide antioxidant, anti-inflammatory, antimicrobial, and regenerative functions [9]
Films	Transparent; allow wound visualization; barrier against microbial contamination; easy application [133]	Limited exudate absorption; may adhere to fragile skin [134]	Flexible, thin, conformable [135]	Excellent [136]	Moderate depending on composition [137]	Good; suitable for incorporation and localized delivery of topical drugs, analgesics, anti-inflammatory agents, antioxidants, and antimicrobial compounds. Composite films can provide sustained release [71,78,79]	Good to excellent for prophylaxis and mild-to-moderate RD, particularly where barrier protection, friction reduction, moisture regulation, and visual monitoring are required. Less suitable for heavily exudative wounds [3,71–74]
Foam Dressings	High exudate absorption; cushioning effect; suitable for moist desquamation [138]	Limited bioactivity; may require frequent replacement [138]	Good mechanical stability and absorbency [139]	Excellent [138]	Generally passive unless functionalized [140]	Limited to moderate; primarily designed for exudate management and protection, but may be functionalized or combined with antimicrobial, anti-inflammatory, or other therapeutic agents for localized delivery [86]	Good to excellent for moderate-to-heavy exudate and moist desquamation because of their absorbency and cushioning properties. More appropriate for established moist RD than for prophylactic use [90]
Nanofiber Systems	ECM-mimicking architecture; high surface area; enhanced cellular interactions; tunable drug release [76]	Manufacturing complexity; scalability challenges; limited clinical validation [91]	High porosity; tunable mechanical properties [91]	Excellent [91]	High when loaded with antimicrobial agents [91]	Excellent; high surface area and porous architecture provide substantial capacity for loading and controlled delivery of drugs, antioxidants, antimicrobial agents, nanoparticles, and other bioactive molecules [76,91]	Promising/emerging platform for advanced RD therapy, particularly where regeneration, ECM mimicry, controlled therapeutic delivery, and multifunctionality are required. However, clinical evidence specific to RD remains limited [91]

6. Challenges and Limitations

Despite the promising therapeutic potential of biomaterial-based dressings for RD, several challenges hinder their widespread clinical translation. Safety and biocompatibility remain paramount concerns, especially for formulations incorporating nanoparticles, growth factors, or bioactive compounds, which may trigger unexpected immune responses or degrade into harmful byproducts over time [141]. Nanoparticle-based biomaterials require careful safety evaluation, as their small size and high surface area may increase cellular uptake and tissue accumulation. While nanoparticles can enhance antimicrobial activity, antioxidant effects, and targeted drug delivery, they may also induce oxidative stress, cytotoxicity, genotoxicity, and unintended interactions with healthy tissues. The toxicity profile of nanoparticles is influenced by factors such as particle size, concentration, surface charge, chemical composition, and degradation products, highlighting the importance of comprehensive long-term toxicological studies prior to clinical implementation [102,141,142]. Immunogenicity represents an additional challenge for both natural and synthetic biomaterials. Although polymers such as chitosan, collagen, gelatin, alginate, and hyaluronic acid generally exhibit excellent biocompatibility, variations in source materials, purification processes, and chemical modifications may influence host immune responses. In some cases, biomaterials may trigger inflammatory reactions, foreign-body responses, fibrosis, or altered tissue remodelling, potentially compromising therapeutic outcomes. Therefore, rigorous biocompatibility and immunological assessments are required during biomaterial development and preclinical evaluation [22,30,143,144]. Cost and accessibility present further limitations, such as manufacturing functionalized hydrogels, nanofiber mats or composite dressings which often require advanced facilities and sterile processing, resulting in higher unit costs that may restrict use in lower-resource settings [145].

Sterilization also remains a critical manufacturing challenge for advanced biomaterial dressings. Clinical-grade products must undergo sterilization without compromising their structural integrity, mechanical performance, drug-loading efficiency, or biological activity. Common sterilization techniques, including gamma irradiation, ethylene oxide treatment, steam sterilization, and electron-beam irradiation, may alter polymer crosslinking density, porosity, swelling behaviour, degradation rates, and the stability of incorporated bioactive molecules. These effects are particularly important for hydrogels and electrospun nanofiber systems, where subtle structural changes can significantly influence therapeutic performance and reproducibility [141,143,145]. Manufacturing consistency is also a challenge, as small variations in polymer composition, cross-linking or sterilization can significantly alter dressing performance (porosity, drug release kinetics), thereby limiting translation from lab to clinic [146].

Nanoparticle-functionalized biomaterials introduce additional translational challenges because their therapeutic performance is governed not only by the properties of the bulk biomaterial but also by the physicochemical characteristics and biological behavior of the incorporated nanoparticles. Critical quality attributes may include nanoparticle size and size distribution, morphology, surface charge, surface chemistry, composition, aggregation state, loading efficiency, nanoparticle distribution within the biomaterial matrix, release kinetics, degradation behavior, and the stability of the nanoparticle–polymer interface [147,148]. Small variations in these parameters can alter cellular uptake, tissue penetration, ROS-scavenging or antimicrobial activity, drug release, and toxicity, making reproducible characterization essential for clinical translation. Standardized analytical approaches are therefore required to establish relationships between nanoparticle properties, manufacturing parameters, biological performance, and safety [147,148]. For radiation dermatitis, an additional consideration is the need to demonstrate that nanoparticle-functionalized biomaterials remain safe and effective in the context of radiotherapy. Preclinical evaluation should there-

fore consider clinically relevant radiation doses and fractionation schedules, the timing of dressing application relative to irradiation, interactions with concurrently administered cancer therapies, and whether nanoparticle exposure modifies the response of irradiated and non-irradiated tissues. Where nanoparticles are intended to scavenge radiation-induced ROS, studies should also distinguish beneficial reduction in pathological oxidative stress from unintended interference with the desired antitumor effects of radiotherapy. Such considerations highlight the importance of radiation-specific efficacy and safety studies rather than relying exclusively on conventional wound-healing models.

Furthermore, achieving batch-to-batch reproducibility at industrial scale remains challenging, particularly for multifunctional biomaterials that incorporate nanoparticles, growth factors, antimicrobial agents, or other bioactive compounds. Such variability may complicate regulatory approval and increase manufacturing costs [146,149]. Moreover, clinical evidence in the radiotherapy context remains heterogeneous and often limited to small series or early-phase trials, so adoption into guideline-driven practice is still premature despite strong mechanistic rationale. Although preclinical findings are encouraging, additional large-scale randomized clinical trials are needed to establish long-term safety, efficacy, cost-effectiveness, and optimal treatment protocols before widespread clinical adoption can be achieved [3,8,104].

7. Future Perspectives and Conclusions

Future research should prioritize combination therapies that integrate biomaterials with bioactive agents such as growth factors, stem cells, and nanoparticles to enhance wound healing through synergistic mechanisms. The emergence of 3D bioprinting offers an exciting opportunity for the development of personalized wound dressings with patient-specific geometry, controlled drug release, and tailored mechanical properties [146,150]. Moreover, the integration of digital health technologies such as smart wound dressings embedded with sensors for real-time monitoring of pH, temperature, and exudate levels holds promise for improving clinical decision-making and reducing infection risks through data-driven interventions [151,152]. In addition, future studies should focus on establishing standardized preclinical models and outcome measures to enable meaningful comparisons among biomaterial platforms and facilitate regulatory approval. More attention should also be given to long-term safety evaluations, including assessments of biocompatibility, immunogenicity, biodegradation, and potential nanoparticle-associated toxicity. Furthermore, scalable manufacturing processes, batch-to-batch reproducibility, sterilization compatibility, and cost-effectiveness must be addressed to ensure successful translation from laboratory research to clinical practice. Collectively, these innovations have the potential to advance RD management by enabling precision, adaptability, and enhanced therapeutic efficacy, although further clinical validation is required before their benefits can be fully established.

Hydrogels, films, and advanced wound dressings have demonstrated promising potential for alleviating the severity of RD through their ability to maintain a moist environment, modulate inflammation, and support tissue regeneration. Although current clinical evidence remains heterogeneous and often limited to small cohorts, preclinical and mechanistic studies provide encouraging support for biomaterial-based interventions; however, additional high-quality clinical evidence is required to confirm their effectiveness and long-term safety. Future clinical research should prioritize well-designed multicenter randomized controlled trials with standardized endpoints to establish efficacy, safety, and comparative effectiveness across different biomaterial platforms. In parallel, closer collaboration among researchers, clinicians, industry partners, and regulatory agencies will be essential to accelerate clinical translation and facilitate the incorporation of biomaterial-based therapies into evidence-based treatment guidelines. Continued interdisciplinary

collaboration among material scientists, clinicians, and bioengineers is essential to standardize testing protocols, ensure regulatory compliance, and validate efficacy through large-scale randomized trials. In the long term, successful clinical validation and translation may enable biomaterials to become important components of evidence-based RD management, with the potential to improve patient outcomes and quality of life. Importantly, the therapeutic evidence for biomaterials in RD remains heterogeneous. While conventional wound models provide substantial evidence for biocompatibility, moisture management, antioxidant activity, angiogenic potential and regenerative properties of hydrogels, chitosan, gelatin and nanofibers, only a subset of these systems has been directly evaluated in radiation-induced skin injury models. Recent radiation-specific studies nevertheless demonstrate a transition toward multifunctional biomaterials designed to target ROS accumulation, persistent inflammation, impaired angiogenesis, cellular senescence and tissue remodeling.

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