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Review

Heat Shock Protein 27 as a Candidate Mediator of Radiation-Induced Periodontitis: Mechanistic Rationale and Translational Perspectives

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Highlights

What are the main findings?

- No experimental or clinical study has directly investigated HSP27 in radiation-induced periodontitis.
- Indirect evidence suggests that HSP27 may influence oxidative stress, inflammatory signaling, epithelial barrier integrity, extracellular matrix remodeling, and alveolar bone homeostasis following radiotherapy.
- Current evidence supports HSP27 as a biologically plausible, hypothesis-generating candidate rather than a validated pathogenic mediator.

What are the implications of the main findings?

- HSP27 represents a promising candidate biomarker and potential therapeutic target for radiation-induced periodontitis, pending direct validation.
- Future periodontal cell, organoid, animal, and prospective clinical studies are required to establish its mechanistic, diagnostic, and therapeutic relevance.
- Integrating HSP27 with clinical, dosimetric, inflammatory, and microbiome-based factors may improve personalized prediction and management of radiation-induced periodontal injury.

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Abstract

Radiation-induced periodontitis represents an underrecognized and mechanistically complex toxicity of head and neck radiotherapy, arising from the interplay of oxidative stress, inflammatory dysregulation, impaired bone remodeling, and epithelial barrier disruption. Despite its clinical relevance, the molecular determinants underlying inter-individual susceptibility remain poorly defined. Heat shock protein 27 (HSP27), a stress-inducible molecular chaperone, has emerged as a candidate mediator potentially linking biological pathways relevant to radiation-induced tissue injury, including redox regulation, cytoskeletal stability, DNA repair, and apoptosis control. However, no clinical or experimental study has directly evaluated HSP27 in radiation-induced periodontitis. Therefore, the proposed

involvement of HSP27 in this setting should be interpreted as a biologically plausible, hypothesis-generating framework rather than evidence of a proven causal mechanism. Convergent but indirect evidence from periodontal biology, radiation-response models, inflammatory disease, and cellular stress systems suggests that HSP27 may plausibly influence periodontal tissue resilience and injury responses after radiotherapy. Therapeutic modulation of HSP27 may represent a potential investigational strategy to mitigate radiation-induced periodontitis, but this concept requires direct validation in periodontal cell-based, animal, organoid, and prospective clinical studies. This review synthesizes current mechanistic and translational evidence to evaluate HSP27 as a candidate mediator, biomarker, and investigational therapeutic target in radiation-induced periodontitis.

Keywords: radiation-induced periodontitis; heat-shock proteins 27; head and neck neoplasms; radiotherapy; biomarkers; oxidative stress

1. Introduction

Radiotherapy (RT) remains a key component in the management of head and neck cancers (HNCs), but it is frequently associated with collateral damage to adjacent healthy oral tissues. Among these, the periodontal apparatus—including the gingiva, periodontal ligament, cementum, and alveolar bone—is particularly susceptible to radiation-induced injury. Available basic and clinical evidence indicates that RT induces a state of periodontal fragility, characterized by either exacerbation of pre-existing periodontitis or de novo accelerated attachment loss and alveolar bone resorption [1,2]. This vulnerability likely reflects the intrinsic radiosensitivity of periodontal connective tissues and their reliance on tightly regulated vascular, immunological, and cellular homeostasis, thereby contributing to long-term oral morbidity and functional impairment in HNC survivors.

Excessive generation of reactive oxygen species (*ROS*) and the resulting oxidative stress represent central pathomechanisms underlying radiation-induced periodontal breakdown. Ionizing radiation induces water radiolysis, generating hydroxyl radicals, hydrogen peroxide, and superoxide anions at levels that overwhelm endogenous antioxidant defense systems [3]. The resulting ROS burden drives a multifaceted cascade involving DNA double-strand breaks (*DSBs*), mitochondrial dysfunction, protein misfolding, and activation of programmed cell death pathways in fibroblasts, osteoblasts, and periodontal ligament cells [4]. Radiation-induced apoptotic depletion of periodontal ligament fibroblasts is of particular pathological relevance, given their essential roles in extracellular matrix (*ECM*) remodeling, maintenance of periodontal ligament structural integrity, and post-injury tissue repair [5]. Collectively, current evidence indicates that ionizing radiation reduces fibroblast proliferative capacity and collagen biosynthesis, while upregulating matrix metalloproteinase activity, culminating in progressive and potentially irreversible connective tissue degradation.

Beyond direct cytotoxicity, RT induces profound microvascular injury, characterized by endothelial apoptosis, capillary rarefaction, and intimal fibrosis that progressively compromise tissue oxygenation and perfusion within the periodontal microenvironment [6,7]. This microcirculatory insufficiency exacerbates hypoxia-driven *ROS* generation, impairs wound healing capacity, and heightens susceptibility to plaque-mediated inflammation, collectively establishing a pathological milieu conducive to accelerated periodontal destruction. Concurrently, RT disrupts immunological homeostasis by impairing neutrophil chemotaxis, attenuating macrophage function, and compromising antigen presentation [8,9]. The resulting dysregulation undermines host defense mechanisms against oral pathogens and

promotes microbial dysbiosis, which, in turn, perpetuates periodontal inflammation and progressive alveolar bone loss. Notably, RT has been shown to shift the subgingival microbiota toward a more pathogenic and proteolytic profile, favoring species implicated in severe periodontitis [10]. These processes are likely further modulated by patient-specific factors influencing inflammatory and oxidative stress responses.

Within this pathophysiological landscape, heat shock protein 27 (*HSP27* or *HSPB1*) emerges as a particularly compelling cytoprotective mediator. As a member of the small heat shock protein family endowed with *ATP*-independent chaperone activity, *HSP27* plays a multifaceted role in maintaining redox homeostasis, cytoskeletal integrity, proteostasis, anti-apoptotic signaling, and inflammatory modulation [11,12]. At the level of oxidative defense, *HSP27* enhances cellular antioxidant capacity by stabilizing the glutathione and thioredoxin systems, thereby attenuating ROS-driven macromolecular injury [13,14]. In addition, *HSP27* preserves cytoskeletal architecture by dynamically regulating actin polymerization, a function particularly relevant to periodontal ligament fibroblasts under concurrent radiation-induced mechanical and oxidative stress [15]. Furthermore, *HSP27* exerts anti-apoptotic effects by inhibiting cytochrome c-dependent caspase activation [16], a pathway central to radiation-induced cellular attrition in periodontal tissues.

Collectively, these multidimensional cytoprotective functions position *HSP27* as a potential modulator of the principal pathological processes underlying radiation-induced periodontitis, including oxidative stress, microvascular injury, chronic inflammation, cytoskeletal destabilization, and programmed cell death. Several reviews have addressed the broader biological functions of *HSP27* in cellular stress responses, inflammation, cancer biology, and radiation resistance. In parallel, radiation-induced oral toxicities, including periodontal complications after head and neck radiotherapy, have been discussed in the supportive-care and dental oncology literature. However, to our knowledge, no prior review has specifically examined *HSP27* in the context of radiation-induced periodontitis.

This absence of direct synthesis mirrors a broader evidence gap: no experimental or clinical studies have yet directly evaluated *HSP27* in radiation-induced periodontitis. Therefore, the present review should be interpreted as a mechanistic and hypothesis-generating synthesis rather than evidence of a proven causal role. Evidence from cancer radioresistance, inflammatory diseases, and non-periodontal stress models is used only to identify biologically plausible pathways that may warrant direct validation in radiation-induced periodontitis-specific models. Notwithstanding this limitation, *HSP27's* established roles in redox regulation, extracellular matrix remodeling, and cellular stress adaptation provide a biologically plausible basis for its involvement in this process. Such mechanisms may ultimately influence clinically relevant outcomes, including the severity of periodontal breakdown, tooth loss, and long-term oral morbidity following radiotherapy.

In this context, the present review synthesizes mechanistic insights and critically examines the potential role of HSP27 as a modulator in radiation-induced periodontitis. It further aims to identify emerging translational opportunities for risk stratification and targeted intervention in patients with head and neck cancer undergoing radiotherapy.

2. Literature Search Strategy

A narrative literature search was performed using PubMed/MEDLINE, Scopus, and Google Scholar databases. Search terms included combinations of "*HSP27*", "*HSPB1*", "heat shock protein 27", "periodontitis", "radiation-induced periodontitis", "head and neck cancer", "radiotherapy", "oxidative stress", "fibroblast", "osteoblast", "osteoclast", "epithelial barrier", "oral microbiome", and "radiation toxicity". Additional relevant publications were identified through manual review of reference lists. Priority was given to peer-reviewed English-language studies addressing *HSP27* biology, radiation responses,

periodontal pathophysiology, and related stress-response mechanisms. Given the absence of direct studies evaluating HSP27 in radiation-induced periodontitis, mechanistic evidence from related experimental systems was also reviewed and critically appraised.

3. Molecular and Cell-Specific Biology of *HSP27* Relevant to Periodontal Tissue Injury

HSP27 is a member of the small heat shock protein family that functions as a stress-inducible molecular chaperone, with established roles in maintaining cell survival, redox homeostasis, cytoskeletal integrity, proteostasis, and regulating apoptotic signaling cascades. Although *HSP27* has been extensively characterized in oncological and systemic inflammatory contexts, its molecular properties and broad cytoprotective repertoire support its potential role as a regulatory mediator in tissues involved in periodontal homeostasis and injury responses. Periodontal ligament fibroblasts, osteoblasts, osteoclasts, and gingival epithelial cells—each essential for maintaining periodontal structure and function—are particularly susceptible to oxidative, inflammatory, and biomechanical stress, and therefore represent plausible cellular targets for *HSP27*-mediated cytoprotection.

3.1. HSP27 in Periodontal Ligament Fibroblasts

Periodontal ligament fibroblasts are central to *ECM* synthesis, collagen turnover, and tissue repair. Experimental studies demonstrate that fibroblasts upregulate *HSP27* in response to oxidative stress, mechanical strain, and inflammatory stimuli [17]. *HSP27* may contribute to cytoskeletal stability by regulating actin polymerization, thereby preserving fibroblast adhesion, motility, and *ECM* remodeling capacity under stress conditions [15]. This function is particularly relevant in the irradiated periodontium, where oxidative stress and DNA damage impair fibroblast proliferation and accelerate matrix degradation. In addition, through its chaperone activity, *HSP27* limits protein aggregation and facilitates refolding of damaged proteins, potentially enhancing fibroblast survival under radiation-induced stress. These observations remain largely derived from non-radiation-specific models and should be interpreted as hypothesis-generating in the context of radiation-induced periodontitis.

3.2. HSP27 in Osteoblasts and Alveolar Bone Remodeling

In addition to its effects on periodontal soft tissues, *HSP27* may influence alveolar bone homeostasis by acting on osteoblasts. Osteoblasts are the principal effector cells of bone formation and alveolar bone turnover, maintaining skeletal integrity by coordinating osteogenic differentiation, matrix synthesis, and mineralization. Ionizing radiation suppresses osteoblast differentiation, impairs *ECM* mineralization, and induces apoptotic cell death—processes that collectively contribute to the progressive alveolar bone loss observed in radiation-associated periodontitis [18].

Within this context, *HSP27* has been shown to enhance osteoblast survival by attenuating oxidative injury and preserving mitochondrial membrane integrity and bioenergetic stability [16]. In addition, *HSP27*-mediated regulation of actin polymerization supports osteoblast motility and *ECM* deposition, both of which are essential for effective bone formation [15]. Given that alveolar bone homeostasis depends on the balance between osteoblast-driven bone formation and osteoclast-mediated resorption, *HSP27* may act as a modulatory factor by maintaining osteoblast viability and function under radiation-induced oxidative and genotoxic stress. These observations, however, are largely derived from non-radiation-specific models and should be interpreted as hypothesis-generating in the context of radiation-induced periodontitis.

3.3. HSP27 in Osteoclast Function and Bone Resorption

Osteoclastic bone resorption depends on dynamic cytoskeletal reorganization, particularly the formation of the filamentous actin ring, which is essential for sealing zone formation and resorptive activity. *HSP27* has been implicated in regulating actin remodeling and podosome assembly in osteoclast precursors, processes critical for osteoclast polarization and function [19].

Through phosphorylation-dependent modulation of its oligomeric state, *HSP27* influences cytoskeletal dynamics, cellular motility, and resorptive capacity. Under conditions of oxidative or pro-inflammatory stress, increased *HSP27* activity may enhance osteoclast survival and resorptive function, thereby potentially contributing to alveolar bone loss in radiation-induced periodontitis. At the same time, the net effect of *HSP27* on bone remodeling likely reflects its concurrent actions on both osteoblasts and osteoclasts, suggesting a context-dependent role in regulating bone turnover under stress conditions. However, the relationship between *HSP27* expression and osteoclast-mediated bone resorption in irradiated periodontal tissues remains incompletely defined and should be considered hypothesis-generating.

3.4. HSP27 in Gingival Epithelium

The gingival epithelium serves as the first line of defense against microbial invasion. Oxidative stress and inflammation impair epithelial integrity and junctional stability, facilitating periodontal breakdown. Gingival epithelial cells upregulate *HSP27* in response to bacterial endotoxin, cytokine exposure, and environmental oxidative stress [20]. *HSP27* strengthens epithelial resistance by stabilizing cytokeratin networks, preventing apoptosis, and downregulating pro-inflammatory signaling cascades, including *JNK* and *NF-κB* [16]. These protective effects may mitigate epithelial injury following RT, where *ROS* and inflammatory mediators compromise epithelial turnover and barrier function.

3.5. Redox Regulation and Oxidative Stress Defense

At the molecular level, one of the best-established functions of *HSP27* is maintaining redox homeostasis by modulating glutathione- and thioredoxin-dependent antioxidant systems, thereby limiting pathological intracellular ROS accumulation [11,14]. Given that oxidative stress is a principal, sustained driver of periodontal tissue injury following RT, the extent of *HSP27*-mediated *ROS* buffering may influence the survival threshold of fibroblasts and osteoblasts in the irradiated periodontal microenvironment.

In radiation-exposed tissues, excessive ROS generation induces a cascade of macromolecular damage, including lipid peroxidation, DNA strand breaks, protein misfolding, and dysregulated cytokine signaling. *HSP27* is mechanistically positioned to counteract these processes through coordinated antioxidant and chaperone functions. Beyond limiting oxidative injury, *HSP27* may also support cellular recovery by facilitating repair processes required for tissue resilience following radiation-induced damage. These effects, however, should be interpreted in light of limited radiation-specific evidence in periodontal tissues.

3.6. ECM Remodeling and Actin Dynamics

Preserving ECM integrity and dynamically regulating the actin cytoskeleton are essential for periodontal tissue repair and regeneration. *HSP27* directly interacts with actin monomers and regulates filament assembly through phosphorylation-dependent changes in its oligomeric state, enabling precise control of cytoskeletal organization [15,21].

The actin cytoskeleton underpins key mechanobiological functions, including fibroblast-generated traction forces, osteoblast motility, and epithelial cohesion. Accordingly, *HSP27*-mediated regulation of actin dynamics may influence connective tissue remodeling and

alveolar bone homeostasis, particularly under the oxidative and genotoxic stress conditions induced by ionizing radiation. In addition, emerging evidence suggests that *HSP27's* cytoskeletal regulation may intersect with pathways governing DNA repair and cell survival, although these relationships remain incompletely defined in irradiated periodontal tissues.

3.7. DNA Repair and Apoptosis Regulation in Irradiated Periodontal Cells

Ionizing radiation induces DSBs, mitochondrial dysfunction, and activation of intrinsic apoptotic pathways, collectively compromising the genomic integrity and viability of periodontal cells. HSP27 has been shown to interact with components of the DNA repair machinery, including the Ku70/Ku80 heterodimer, thereby facilitating non-homologous end-joining (NHEJ)-mediated repair of radiation-induced DNA damage [22].

In parallel, *HSP27* exerts anti-apoptotic effects by inhibiting the release of mitochondrial cytochrome c and attenuating downstream caspase activation, thereby enhancing cellular survival under stress conditions [16]. Together, these mechanisms suggest that HSP27 may prolong the survival of radiation-damaged periodontal cells. However, sustained survival in the context of unresolved damage may also contribute to persistent inflammatory signaling and altered tissue remodeling, indicating a context-dependent role that warrants further investigation (Table 1) (Figure 1).

Table 1. Cell-specific *HSP27*-related functions potentially relevant to radiation-induced periodontal injury.

Cell Type	Radiation-Relevant Stressors	Main HSP27-Related Functions	Potential Periodontal Consequences
Periodontal ligament fibroblasts	ROS, DSBs, ECM degradation, mechanical stress	Redox buffering; actin stabilization; protein chaperoning; apoptosis modulation	May support fibroblast survival, ECM remodeling, and periodontal ligament integrity after RT
Osteoblasts	Oxidative injury, mitochondrial dysfunction, impaired mineralization	Protection against oxidative apoptosis; mitochondrial stabilization; actin regulation	May preserve osteoblast viability but does not necessarily ensure effective bone formation
Osteoclasts	Cytoskeletal stress, inflammatory cytokines, and altered RANKL/OPG signaling	Regulation of actin organization, motility, and resorptive activity	May influence osteoclast survival, bone resorption, and alveolar bone loss after RT
Gingival epithelial cells	ROS, microbial challenge, cytokine-driven inflammation	Cytoskeletal stabilization; apoptosis modulation; regulation of JNK/NF-κB signaling	May influence epithelial survival, barrier integrity, microbial ingress, and inflammatory responses

Abbreviations: DSBs, DNA double-strand breaks; ECM, extracellular matrix; HSP27, heat shock protein 27; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa B; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κB ligand; ROS, reactive oxygen species; RT, radiotherapy.

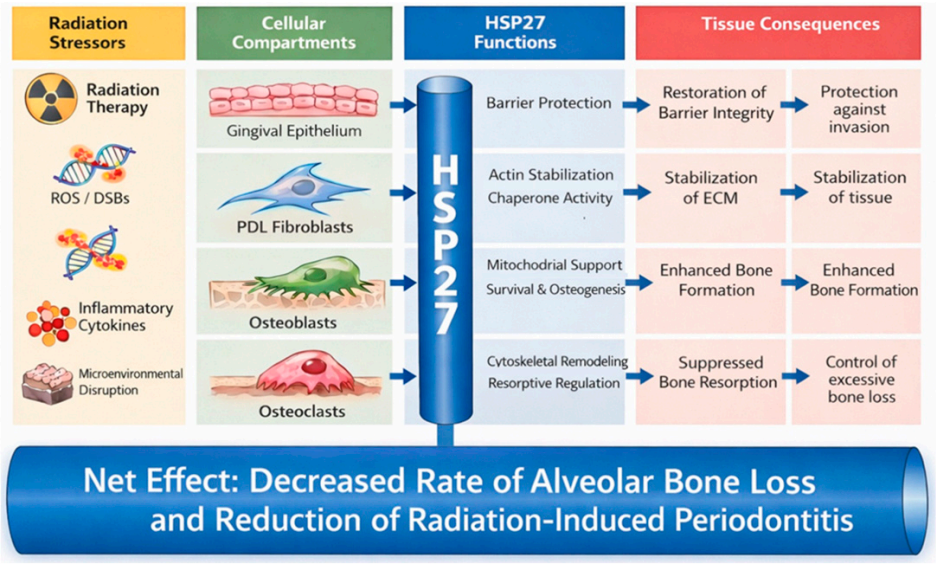

Figure 1. Cell-specific roles of *HSP27* in radiation-induced periodontal tissue responses. **Note:** Schematic representation of the proposed cell-specific functions of heat shock protein 27 (*HSP27*) in irradiated periodontal tissues. Ionizing radiation induces oxidative stress, DNA damage, inflammatory signaling, and microenvironmental disruption, affecting key periodontal cell compartments, including the gingival epithelium, periodontal ligament fibroblasts, osteoblasts, and osteoclasts. *HSP27* exerts cytoprotective effects through multiple mechanisms, including preservation of epithelial barrier integrity, stabilization of the actin cytoskeleton and extracellular matrix, attenuation of oxidative and mitochondrial injury, and regulation of bone remodeling dynamics. Through these coordinated but context-dependent actions across different cell types, *HSP27* may influence tissue homeostasis, alveolar bone integrity, and susceptibility to radiation-induced periodontal damage. **Abbreviations:** HSP27, heat shock protein 27; ROS, reactive oxygen species; DSBs, DNA double-strand breaks; ECM, extracellular matrix; PDL, periodontal ligament.

4. Mechanistic Rationale for a Hypothesized Link Between *HSP27* and Radiation-Induced Periodontitis

Radiation-induced periodontitis arises from the convergence of oxidative injury, microvascular compromise, immunological dysregulation, and impaired tissue remodeling, collectively driving progressive periodontal destruction. Rather than revisiting the cell-specific biology of *HSP27* described in Section 3, this section focuses on how these functions may intersect with the principal pathogenic mechanisms underlying radiation-induced periodontitis. Although *HSP27* has not been directly investigated in radiation-induced periodontitis, its established roles in redox regulation, cytoskeletal stabilization, DNA damage response, and inflammatory signaling align with several biological processes implicated in radiation-associated periodontal injury. Accordingly, these observations provide a hypothesis-generating rationale for further investigation of *HSP27* in this setting. The proposed interactions among radiation-induced stress responses, *HSP27* activation, downstream signaling pathways, and periodontal tissue injury are summarized schematically in Figure 2.

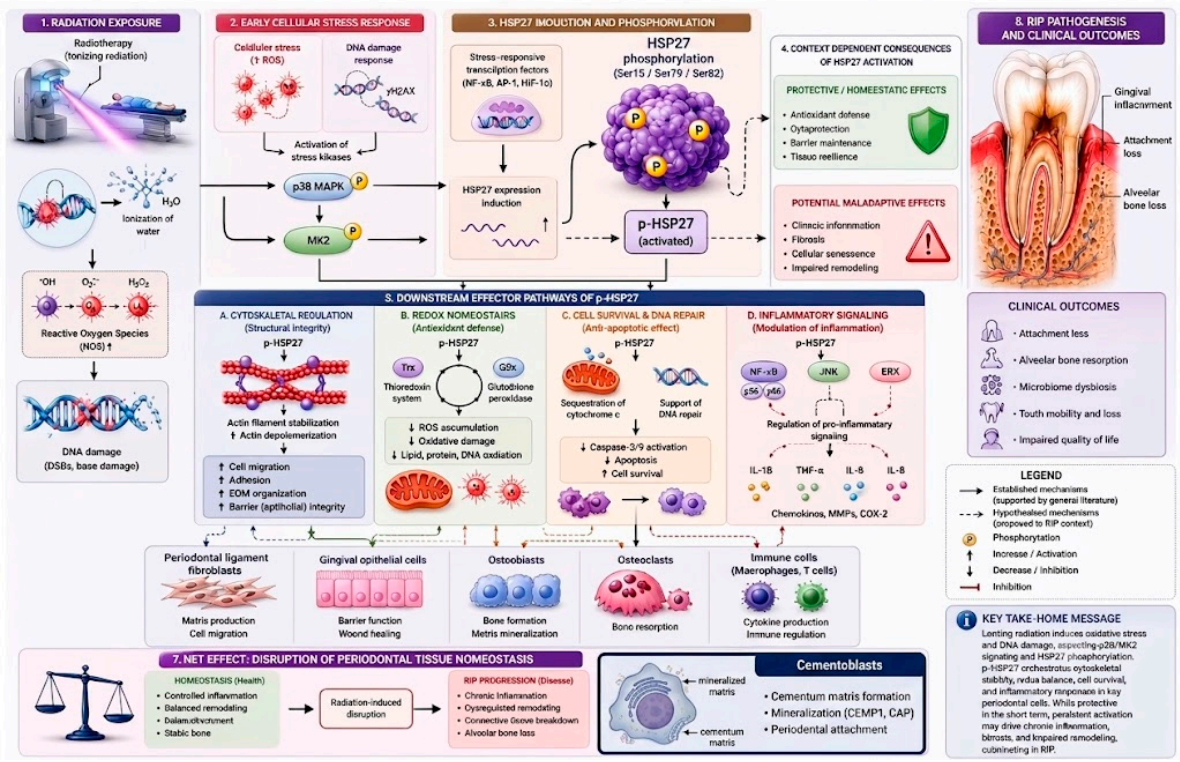

Figure 2. Proposed molecular pathway linking radiation-induced stress, *HSP27* activation, and radiation-induced periodontitis progression. **Note:** Ionizing radiation induces water radiolysis, reactive oxygen species generation, and DNA damage, activating stress-kinase signaling pathways including *p38 MAPK* and *MK2*. These pathways may promote *HSP27* induction and phosphorylation at *Ser15*, *Ser78*, and *Ser82*, leading to context-dependent downstream effects on cytoskeletal regulation, redox homeostasis, cell survival, DNA repair, and inflammatory signaling. In periodontal tissues, these processes may influence periodontal ligament fibroblast function, epithelial barrier integrity, osteoblast–osteoclast balance, immune-cell activation, extracellular matrix remodeling, microbiome dysbiosis, and ultimately RIP progression. Solid arrows indicate mechanisms supported by general biological literature, whereas dashed arrows indicate hypothesized radiation-induced periodontitis-specific relationships requiring direct validation. **Abbreviations:** COX-2, cyclooxygenase-2; DSBs, DNA double-strand breaks; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; GPx, glutathione peroxidase; HSP27, heat shock protein 27; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MK2, MAPK-activated protein kinase 2; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa B; p-HSP27, phosphorylated HSP27; RIP, radiation-induced periodontitis; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; Trx, thioredoxin.

4.1. Oxidative Stress and Periodontal Breakdown

Ionizing radiation induces an immediate and sustained increase in *ROS* through water radiolysis, mitochondrial dysfunction, and persistent inflammatory activation [3]. Periodontal cells—particularly periodontal ligament fibroblasts and osteoblasts—are highly susceptible to *ROS*-mediated injury, including apoptotic cell death, oxidative protein modification, and *ECM* degradation, all of which compromise the structural integrity of the periodontium [18]. Clinically, this cumulative oxidative burden has been linked to accelerated alveolar bone resorption and progressive attachment loss in patients undergoing head-and-neck RT [23,24].

Building on the redox-regulatory functions outlined in Section 3, *HSP27* may influence how periodontal tissues respond to radiation-induced oxidative stress. By supporting antioxidant defense systems, including glutathione peroxidase- and thioredoxin-dependent pathways [11,14], *HSP27* may limit intracellular *ROS* accumulation and attenuate down-

stream injury responses. In this context, variation in *HSP27* expression or function may influence both the extent of cellular injury and the persistence of inflammatory signaling within irradiated periodontal tissues, thereby contributing to inter-individual differences in susceptibility to radiation-induced periodontitis.

4.2. Fibroblast Apoptosis and ECM Degradation

Periodontal ligament fibroblasts are central regulators of *ECM* turnover, collagen biosynthesis, and periodontal tissue repair. Exposure to ionizing radiation induces *DSBs*, mitochondrial cytochrome c release, and activation of caspase-dependent apoptotic pathways in periodontal ligament fibroblasts, culminating in fibroblast depletion and progressive loss of connective tissue integrity [24].

As discussed in Section 3, *HSP27* modulates several stress-response and apoptosis-related pathways, including cytochrome c-dependent signaling, caspase activation, cytoskeletal stabilization, and protein quality control mechanisms [16,21]. Within the irradiated periodontium, these functions may influence fibroblast survival and the capacity for post-radiation tissue remodeling.

The consequences of these effects are inherently context-dependent. Maintenance of fibroblast viability may facilitate early extracellular matrix homeostasis and mitigate acute tissue disruption. Conversely, sustained survival of sublethally irradiated fibroblasts may promote dysregulated matrix remodeling, aberrant cytokine production, and persistence of a low-grade inflammatory microenvironment, collectively influencing the progression of periodontal breakdown. Persistent activation of cytoprotective and anti-apoptotic pathways may further promote the retention of dysfunctional yet viable irradiated fibroblasts, potentially contributing to aberrant wound-healing responses, fibrotic tissue remodeling, or cellular senescence. Taken together, these considerations indicate that HSP27-mediated modulation of fibroblast responses may reshape post-radiation tissue remodeling dynamics and contribute to the pathogenesis of radiation-induced periodontitis.

4.3. Osteoblast/Osteoclast Dynamics and Alveolar Bone Resorption

Radiotherapy profoundly perturbs alveolar bone homeostasis by suppressing osteoblast proliferation and matrix mineralization while promoting osteoclast recruitment through pro-inflammatory cytokine signaling and oxidative stress [24–26]. This disruption results in pathological uncoupling of the bone remodeling unit, shifting the anabolic–catabolic equilibrium toward net resorption and contributing directly to progressive alveolar bone loss—a defining feature of radiation-induced periodontitis.

As discussed in Sections 3.2 and 3.3, *HSP27* may influence both osteoblast and osteoclast biology through its effects on cellular stress responses and cytoskeletal regulation [15,19,26]. Within the irradiated alveolar bone microenvironment, these functions may modulate the balance between bone formation and bone resorption. Preservation of osteoblast viability may not necessarily translate into effective bone formation if surviving cells remain metabolically or genomically compromised following radiation exposure. Conversely, sustained osteoclast survival or resorptive activity may perpetuate remodeling imbalance.

Collectively, these considerations support a model in which *HSP27* may function as a context-dependent modulator of uncoupled bone remodeling in response to radiation-induced stress, potentially linking cellular stress responses to progressive alveolar bone loss in radiation-induced periodontitis.

4.4. Inflammatory Cytokine Signaling: A Shared Pathway in Periodontitis and Radiation-Induced Toxicity

Both chronic periodontitis and radiation-induced tissue injury share a convergent pathophysiological substrate characterized by sustained upregulation of pro-inflammatory cytokine signaling, with interleukin *(IL)-1β*, tumor necrosis factor (*TNF)-α*, and *IL-6* serving as central effectors. These mediators amplify ROS generation, upregulate matrix metalloproteinase (*MMP*) expression via *NF-κB-* and *AP-1*-dependent transcriptional programs, and drive *ECM* degradation, collectively contributing to progressive periodontal tissue destruction [27].

As discussed in Section 3, *HSP27* has been implicated in the regulation of multiple inflammatory signaling pathways, including *NF-κB-*, *JNK-*, and *MAPK*-associated responses [21,28]. Within irradiated periodontal tissues, these functions may influence both the magnitude and persistence of inflammatory activation. The *HSP27*–cytokine axis may therefore represent a mechanistic interface linking radiation-induced cellular stress to sustained inflammatory activation and tissue breakdown. However, the directionality of this modulation is likely context-dependent and influenced by factors such as *HSP27* expression level, phosphorylation status, oligomeric state, and local microenvironmental conditions.

Collectively, these considerations support a model in which *HSP27* functions as a context-dependent regulator of inflammation-driven periodontal injury, integrating cellular stress-response pathways with the immunological mechanisms underlying the progression of radiation-induced periodontitis.

4.5. Microbiome Shifts and Epithelial Barrier Dysfunction

Radiotherapy induces substantial and clinically relevant alterations in the oral microbiome, characterized by the depletion of commensal species and the expansion of pathogenic anaerobes associated with severe periodontitis [29]. In parallel, radiation-induced epithelial atrophy and disruption of intercellular junctional complexes compromise the mucosal barrier, facilitating microbial translocation into the subepithelial compartment and amplifying local inflammatory responses [30].

As discussed in Section 3.4, *HSP27* contributes to epithelial stress responses through its effects on cytoskeletal stability, regulation of apoptosis, and inflammatory signaling [31]. Within the irradiated gingival epithelium, these functions may influence susceptibility to barrier disruption and subsequent microbial translocation.

Within this framework, the role of *HSP27* in the irradiated epithelial compartment is likely to be context-dependent and temporally dynamic. Increased *HSP27* expression during the acute phase of radiation injury may help preserve barrier integrity and limit early microbial translocation. In contrast, sustained or dysregulated *HSP27* expression in chronically stressed tissues may reflect an adaptive response to ongoing inflammatory and microbial challenges, potentially marking more advanced barrier dysfunction and dysbiosis.

Collectively, these considerations suggest that interactions among *HSP27* expression, epithelial barrier integrity, and microbiome dynamics may contribute to radiation-induced periodontitis (Figure 3). This underexplored axis warrants focused experimental and translational investigation.

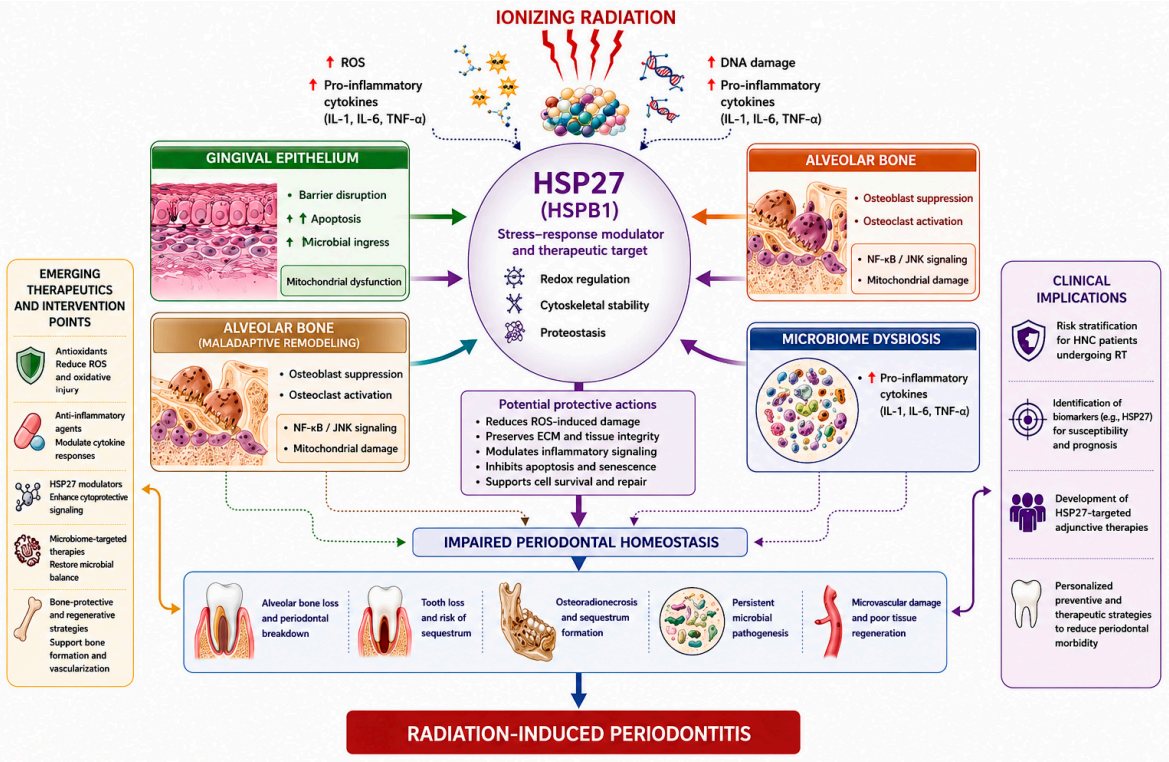

Figure 3. Mechanistic framework of radiation-induced periodontitis and the central modulatory role of HSP27. **Note:** Ionizing radiation to the oral cavity induces the generation of reactive oxygen species, DNA damage, and pro-inflammatory cytokine release, thereby initiating tissue injury within the periodontium. These processes disrupt epithelial barrier integrity, promote apoptosis and microbial ingress, impair extracellular matrix integrity, and contribute to fibroblast dysfunction, cellular senescence, osteoblast suppression, osteoclast activation, and microbiome dysbiosis. Within this integrated stress-response network, heat shock protein 27 (HSP27/HSPB1) may act as a central modulator influencing redox regulation, cytoskeletal stability, proteostasis, inflammatory signaling, and apoptosis-related pathways across multiple periodontal cell types. The cumulative effect is impaired periodontal homeostasis, progressive radiation-induced periodontitis, and, in severe cases, downstream complications such as tooth loss and osteoradionecrosis. **Abbreviations:** DSBs, DNA double-strand breaks; ECM, extracellular matrix; HNC, head and neck cancer; HSP27, heat shock protein 27; IL, interleukin; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; RT, radiotherapy; TNF-α, tumor necrosis factor-alpha.

5. Clinical and Experimental Evidence

To date, no clinical or preclinical investigation has directly evaluated the role of *HSP27* in radiation-induced periodontitis, representing a substantive gap in the current body of knowledge and highlighting the novelty of this line of inquiry. Nonetheless, a convergent array of indirect evidence—spanning periodontal biology, radiation toxicology, and molecular stress-response research—provides a biological rationale for considering *HSP27* as a plausible modulator of the pathogenesis of radiation-induced periodontitis. It is important to acknowledge, however, that much of this evidence derives from malignant, ischemic, systemic inflammatory, or otherwise non-periodontal models, limiting its direct applicability to irradiated periodontal tissues. Accordingly, the evidence synthesized in this section should be regarded as hypothesis-generating, warranting rigorous empirical evaluation before causal or translational conclusions can be drawn.

5.1. Evidence from Non-Irradiated Periodontal and Periapical Inflammatory Models

Although *HSP27* has not yet been directly investigated in radiation-induced periodontitis, evidence from periodontal and periapical inflammatory conditions supports its

potential involvement in periodontal stress responses. In a clinical study of periodontitis, circulating *HSP27* levels varied by disease phenotype and were associated with inflammatory mediators, including *TNF-α* and *HSP60*, supporting a relationship between *HSP27* and periodontal inflammatory activity [32]. In addition, proteomic analyses of apical periodontitis lesions demonstrated differential expression of *HSP27* in inflamed tissues, further suggesting the involvement of *HSP27*-associated stress-response pathways in oral inflammatory diseases [33].

Experimental studies using human periodontal ligament fibroblasts provide additional mechanistic support. Under mechanical loading conditions, phosphorylation of *HSP27* has been associated with alterations in *IL6*, *PTGS2*, *COL1A2*, and *RANKL/OPG*-related pathways, as well as osteoclastogenesis-associated responses [17]. These observations are particularly relevant because periodontal ligament fibroblasts represent key mechanosensitive and immunomodulatory cells that contribute to periodontal tissue adaptation and remodeling.

Nevertheless, these findings originate from non-irradiated inflammatory or mechanical-stress models and therefore do not fully recapitulate the multifactorial environment of radiation-induced periodontitis. Specifically, they do not account for the combined effects of ionizing radiation, microvascular injury, epithelial barrier disruption, microbiome alterations, and heterogeneous radiation dose distributions. Consequently, while the available periodontal literature strengthens the biological plausibility of *HSP27* involvement in periodontal stress biology, it does not provide direct evidence for a causal role in radiation-induced periodontitis.

5.2. Evidence from Periodontal Cell Biology

HSP27 is expressed across the principal cellular components of the periodontium, including periodontal ligament fibroblasts, osteoblasts, gingival epithelial cells, and immune cells. These cell populations are consistently shown to be highly susceptible to radiation-induced oxidative stress, DNA damage, and apoptotic signaling [4,24].

Functionally, *HSP27* may contribute to cellular stress adaptation through several complementary mechanisms. It enhances antioxidant capacity via glutathione- and thioredoxin-dependent systems, preserves cytoskeletal integrity under oxidative stress, suppresses apoptosis by inhibiting cytochrome c-dependent caspase activation, and facilitates refolding of damaged proteins through its chaperone activity [11,16,21]. Through these integrated effects, *HSP27* is positioned to influence cellular survival, *ECM* remodeling, and stress tolerance within the irradiated periodontal microenvironment.

Taken together, these observations support a biologically plausible framework in which *HSP27* functions as a context-dependent modulator of the cellular response to radiation-induced injury in periodontal tissues, linking stress-response pathways to the development of radiation-induced periodontitis.

5.3. Evidence from Osteoblast and Bone Remodeling Studies

Experimental evidence indicates that osteoblasts upregulate heat shock proteins in response to oxidative, genotoxic, and biomechanical stress. This response reflects activation of heat shock factor 1 (*HSF1*)-mediated transcriptional programs within the broader cellular proteostatic stress response [16,26].

At the molecular level, *HSP27* may enhance cellular survival by attenuating mitochondrial membrane permeabilization and suppressing cytochrome c translocation into the cytosol. It may also inhibit downstream caspase-3 and caspase-9 activation, thereby helping preserve viability under sustained oxidative and genotoxic stress [16,21]. These cytoprotective mechanisms, while not yet directly demonstrated in irradiated osteoblasts,

are consistently observed across multiple stressed cell systems and provide a biologically plausible basis for similar effects within the bone microenvironment.

Ionizing radiation suppresses osteoblast lineage commitment and terminal differentiation. It impairs Runx2-dependent osteogenic transcriptional programs, reduces alkaline phosphatase activity, and diminishes extracellular matrix mineralization capacity. In parallel, radiation may promote *RANKL*-mediated osteoclast recruitment and activation [7]. This radiation-induced pathological uncoupling of the bone multicellular unit (BMU) shifts the anabolic–catabolic equilibrium decisively toward net bone resorption.

Within this context, *HSP27*-driven modulation of cellular stress responses may exert a substantive, bidirectional regulatory influence on bone remodeling dynamics. On the one hand, *HSP27*-mediated cytoprotection may preserve osteoblast viability under radiation stress; on the other hand, such survival does not necessarily translate into preserved osteogenic function in sublethally damaged cells. *HSP27* also regulates actin cytoskeletal organization and cellular motility [15]. Therefore, it may influence osteoclast structural dynamics and resorptive activity, although this remains to be directly demonstrated in irradiated bone tissue.

Collectively, these observations suggest that *HSP27* may act as a context-dependent modulator of stress-adaptive processes within the bone multicellular unit. This framework may help explain dysregulated remodeling and progressive alveolar bone loss in radiation-induced periodontitis, but it requires direct experimental validation.

5.4. Evidence from Gingival Epithelium and Barrier Function

The gingival epithelium constitutes a critical structural and immunological interface that is highly susceptible to radiation-induced oxidative injury and inflammatory activation. Ionizing radiation disrupts epithelial homeostasis by inducing *ROS*, DNA damage, and cytokine-driven signaling cascades, resulting in epithelial atrophy, junctional instability, and compromised barrier integrity, thereby facilitating microbial translocation and amplifying local inflammatory responses [30].

HSP27 is mechanistically positioned to modulate epithelial resilience under these conditions. At the cellular level, *HSP27* has been shown to promote survival of oral epithelial cells through anti-apoptotic signaling and stress-response pathways, including attenuation of mitochondrial apoptotic cascades and enhancement of cellular resistance to oxidative injury [20]. More broadly, *HSP27* is mechanistically positioned to influence radiation-induced periodontitis-related pathways in cytoskeletal stability and inflammatory signaling by modulating *NF-κB-* and *JNK*-dependent pathways, both of which are central to epithelial injury and repair processes [28].

Through these integrated functions, *HSP27* may influence epithelial barrier integrity in the irradiated periodontium. In particular, its ability to preserve epithelial cell viability and modulate stress-responsive signaling suggests a potential role in limiting early barrier disruption. However, sustained or dysregulated *HSP27* activation under chronic radiation-induced stress may alternatively reflect a maladaptive response within an already compromised epithelial microenvironment.

Accordingly, alterations in *HSP27* expression or activity may have downstream consequences for host–microbial interactions and inflammatory amplification within the periodontium. While direct evidence for radiation-induced periodontitis remains lacking, the convergence of epithelial injury, barrier dysfunction, and stress-response signaling provides a biologically coherent framework that supports *HSP27* as a context-dependent modulator of epithelial integrity in radiation-associated periodontal disease.

5.5. Evidence from Head and Neck Cancer, Nasopharyngeal Carcinoma, and Radiation-Resistance Studies

In nasopharyngeal carcinoma and other HNCs, *HSP27* upregulation has been associated with multiple cellular adaptations relevant to radiation response. Mechanistically, HSP27 has been implicated in regulating DNA damage repair pathways. This includes interactions with components of the non-homologous end-joining machinery, as well as broader stress-response processes involving cytoskeletal stabilization, anti-apoptotic signaling, and inflammatory modulation [17,28].

Through these functions, *HSP27* may contribute to enhanced cellular tolerance to genotoxic and oxidative stress, a phenotype that, in oncologic contexts, has been linked to reduced apoptotic susceptibility and adaptive resistance to cytotoxic therapies. Although most evidence derives from malignant cell systems, the underlying mechanisms—namely DNA repair facilitation, cytoskeletal preservation, and stress-response signaling—are not tumor-specific and are likely operative in normal tissues exposed to radiation.

Accordingly, these oncologic observations provide indirect but biologically relevant evidence that *HSP27* may similarly influence radiation responses in non-malignant periodontal tissues. The convergence of these mechanisms with established pathways in radiation-induced periodontitis—including oxidative injury, impaired cellular turnover, and dysregulated inflammatory signaling—supports a coherent conceptual framework in which *HSP27* functions as a context-dependent modulator of tissue response to irradiation.

5.6. Evidence from Organoid and In Vitro Stress Models

Epithelial, fibroblast-derived, and salivary gland organoid systems consistently demonstrate robust, often dose-dependent induction of *HSP27* at both transcriptional and protein levels in response to oxidative, genotoxic, and inflammatory stress, reflecting activation of conserved *HSF1*-mediated stress-response pathways. In radiation-based three-dimensional models, increased *HSP27* expression has been associated with altered morphogenesis, enhanced clonogenic survival, phosphorylation-dependent cytoskeletal reorganization, and attenuation of apoptosis, supporting a functional role in cellular adaptation to ionizing radiation [14]. Although periodontal-specific organoid systems remain underdeveloped, convergent findings across structurally and functionally related oral tissue models provide biologically coherent support for a role of *HSP27* in modulating tissue responses to radiation-induced injury within the periodontium.

Collectively, these complementary lines of indirect evidence provide a mechanistically grounded rationale for investigating *HSP27* as a potential mediator of radiation-induced periodontitis. The absence of direct experimental or clinical studies, when considered alongside consistent signals across multiple biological platforms, further supports prioritizing *HSP27* as a candidate biomarker of susceptibility and a potential therapeutic target in radiation-associated periodontal injury. A summary of the indirect mechanistic and experimental evidence supporting the involvement of *HSP27* in radiation-induced periodontitis is presented in Table 2.

Table 2. Mechanistic domains through which HSP27 may influence radiation-induced periodontal injury.

Mechanistic Domain	Key HSP27-Related Mechanism	Potential Relevance to Radiation-Induced Periodontal Injury
Periodontal ligament fibroblast response	Redox buffering, cytoskeletal regulation, and apoptosis modulation	May influence fibroblast survival, extracellular matrix remodeling, and periodontal ligament integrity after radiotherapy

Table 2. *Cont.*

Mechanistic Domain	Key HSP27-Related Mechanism	Potential Relevance to Radiation-Induced Periodontal Injury
Bone remodeling	Osteoblast stress adaptation and osteoclast actin-dependent resorptive function	May affect the balance between bone formation and bone resorption in irradiated alveolar bone
Epithelial barrier integrity	Cytoskeletal stabilization, apoptosis regulation, and inflammatory signaling modulation	May influence epithelial survival, barrier disruption, and microbial ingress
Oxidative stress response	Support of glutathione- and thioredoxin-dependent antioxidant systems	May attenuate ROS accumulation and oxidative cellular injury
Inflammatory signaling	Modulation of NF-κB-, JNK-, and MAPK-associated pathways	May influence cytokine persistence, matrix degradation, and chronic periodontal inflammation
Organoid and radiation-stress models	HSP27 induction under oxidative, genotoxic, and inflammatory stress	Provides biological rationale for testing HSP27 in radiation-induced periodontitis-specific models

Abbreviations: HSP27, heat shock protein 27; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species. **Note:** Table 2 summarizes biological plausibility, whereas Table 3 critically appraises the strength and limitations of the supporting evidence.

Table 3. Direct and indirect evidence informing the proposed HSP27–radiation-induced periodontitis framework.

Evidence Domain	Main Model/System	Directly Tested in Radiation-Induced Periodontitis?	Strength of Extrapolation to Radiation-Induced Periodontitis	Relevance to Radiation-Induced Periodontitis	Principal Limitation/Reason for Caution
Periodontal cell biology	Periodontal ligament fibroblasts, osteoblasts, gingival epithelial cells, and periodontal inflammatory models	No	Moderate–high	Supports biological plausibility because these cells are directly involved in periodontal homeostasis, extracellular matrix remodeling, epithelial integrity, and alveolar bone turnover	Mostly derived from non-irradiated or non-radiation-induced periodontal models; does not capture combined radiation injury, microbiome disruption, vascular damage, and dosimetric heterogeneity
Radiation biology	Irradiated normal and malignant cell systems	No	Moderate	Provides mechanistic relevance for oxidative stress, DNA damage response, apoptosis regulation, cytoskeletal injury, and stress-response activation after ionizing radiation	Radiation responses may differ between tumor cells, normal tissues, and periodontal compartments; models often lack biofilm exposure, periodontal stem/progenitor niches, and alveolar bone remodeling endpoints

Table 3. *Cont.*

Evidence Domain	Main Model/System	Directly Tested in Radiation-Induced Periodontitis?	Strength of Extrapolation to Radiation-Induced Periodontitis	Relevance to Radiation-Induced Periodontitis	Principal Limitation/Reason for Caution
Cancer radioresistance	Head and neck cancer, nasopharyngeal carcinoma, and other malignant-cell models	No	Low–moderate	Demonstrates that HSP27 can participate in stress tolerance, DNA repair, anti-apoptotic signaling, and treatment resistance under genotoxic stress	Malignant-cell survival mechanisms may not translate directly to normal periodontal tissue injury; cancer models may overrepresent cytoprotective and proliferative signaling
Bone remodeling biology	Osteoblast and osteoclast stress-response models	No	Moderate–high	Relevant to radiation-associated alveolar bone loss because HSP27-related pathways may influence osteoblast viability, osteoclast cytoskeletal organization, and remodeling balance	Limited evidence in irradiated alveolar bone or periodontal bone remodeling; effects may differ according to osteoblast–osteoclast coupling, RANKL/OPG balance, radiation dose, and inflammatory milieu
Systemic inflammatory or ischemic injury models	Cardiac ischemia, neuronal injury, autoimmune, or systemic inflammatory disease contexts	No	Low	Provides general insight into HSP27-related cytoprotection, inflammatory modulation, and stress adaptation	Disease-context mismatch is substantial; these models often lack periodontal tissue architecture, microbial challenge, epithelial barrier disruption, and alveolar bone turnover
Organoid and in vitro stress models	Oral epithelial, salivary gland, fibroblast-derived, or other three-dimensional stress models	No	Moderate	Biologically informative for tissue-level stress responses, epithelial resilience, morphogenesis, and radiation-associated cellular adaptation	Models are not periodontal- or radiation-induced periodontitis-specific; most do not reproduce the biofilm-exposed periodontal niche, mechanical loading, vascular injury, or integrated immune–bone remodeling environment
Prospective clinical biomarker evidence	Saliva, gingival crevicular fluid, tissue, or longitudinal clinical cohorts	No	Not available	Would be directly relevant for validating HSP27 as a biomarker of radiation-induced periodontal injury, risk stratification, or treatment response	Currently absent; analytical validity, reproducibility, predictive performance, calibration, and incremental clinical utility remain untested

Abbreviations: HSP27, heat shock protein 27; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κB ligand. **Note:** The strength of extrapolation reflects biological proximity to irradiated periodontal tissues rather than proof of causality. No evidence domain currently provides direct validation of HSP27 in radiation-induced periodontitis.

5.7. Level of Evidence and Critical Appraisal of the Available Evidence

The evidentiary foundation for implicating *HSP27* in radiation-induced periodontitis is predominantly indirect and should be interpreted with caution. Most mechanistic insights are extrapolated from non-periodontal systems, malignant cell models, or broader investigations of cellular stress responses. Although these studies elucidate fundamental processes such as redox regulation, cytoskeletal stabilization, apoptosis modulation, and DNA repair [11,14–16,21,22,28,34], they do not provide definitive evidence that *HSP27* exerts analogous effects within irradiated periodontal tissues. Furthermore, *HSP27* function is context-dependent and may vary according to cell type, radiation dose, post-irradiation interval, phosphorylation status, and inflammatory milieu. Consequently, the proposed involvement of *HSP27* in radiation-induced periodontitis should be regarded as a biologically plausible, testable hypothesis rather than an established pathogenic mechanism, and should be validated through periodontal cell-based, animal, organoid, and prospective clinical investigations.

A further limitation of extrapolating *HSP27* biology to radiation-induced periodontitis is the distinctive structure and biology of periodontal tissues. Unlike many tumor, ischemic, or neuronal injury models, the periodontium is a compartmentalized and continuously challenged tissue complex composed of gingival epithelium, periodontal ligament fibroblasts, cementum, alveolar bone, vascular elements, immune cells, and resident progenitor populations. These compartments differ substantially in cellular turnover, regenerative capacity, extracellular matrix composition, mechanical loading, and dependence on periodontal ligament-derived stem/progenitor cells. In addition, periodontal tissues are continuously exposed to a polymicrobial biofilm, and radiation-induced disruption of the epithelial barrier may alter host–microbiome interactions in ways not captured by sterile ischemic, neuronal, or malignant-cell systems. Therefore, *HSP27*-mediated cytoprotection, apoptosis-related signaling, inflammatory modulation, or cytoskeletal stabilization may have distinct biological consequences in irradiated periodontal tissues compared with non-periodontal models. These differences reinforce the need for radiation-induced periodontitis-specific validation using periodontal cell-based systems, animal models, organoids, and prospective clinical cohorts.

6. Translational Biomarker Considerations

Although *HSP27* has not yet been evaluated as a biomarker for radiation-induced periodontitis, its established biological position within cellular stress-response pathways provides a rationale for considering it as an investigational biomarker candidate. Conceptually, *HSP27* expression, phosphorylation status, or subcellular localization could serve as tissue-level indicators of radiation-induced oxidative stress, cytoskeletal perturbation, apoptosis-related signaling, and inflammatory activation within periodontal tissues. However, this proposition remains hypothetical and should not be interpreted as evidence of validated biomarker utility in radiation-induced periodontitis.

Future biomarker investigations should prioritize longitudinal assessment of *HSP27* in irradiated periodontal tissues or accessible oral biofluids, such as saliva or gingival crevicular fluid, in parallel with clinical periodontal endpoints, mandibular dosimetry, inflammatory markers, and microbiome profiling. Such integrative studies would help determine whether *HSP27* provides incremental predictive information beyond established clinical and dosimetric risk factors. Before clinical translation, any candidate *HSP27*-based biomarker must undergo rigorous evaluation for analytical validity, biological reproducibility, predictive performance, calibration, and clinical utility.

Accordingly, *HSP27* should presently be regarded not as an established clinical biomarker but as an investigational molecular indicator of periodontal tissue stress re-

sponses that warrants systematic investigation in radiation-induced periodontitis-specific prospective translational research.

7. Therapeutic Targeting of *HSP27* for Prevention of or Reduction in Radiation-Induced Periodontitis

Therapeutic modulation of *HSP27* represents a potential strategy for influencing the severity of radiation-induced periodontitis, given its central role in regulating oxidative stress responses, cytoskeletal stability, and apoptosis. Evidence from oncology research indicates that *HSP27* may contribute to cellular radioresistance through mechanisms including stabilization of cytoskeletal architecture, facilitation of DNA repair pathways, and attenuation of apoptotic signaling [28]. These processes are not tumor-specific and may also operate in normal periodontal tissues exposed to ionizing radiation, although this extrapolation remains hypothesis-generating and requires validation in tissue-specific preclinical models.

However, the therapeutic implications of targeting *HSP27* in this context are inherently complex. In cancer, pharmacological inhibition of *HSP27* has been explored to enhance radiosensitivity and promote tumor cell death. Investigated approaches include antisense oligonucleotides, such as *Apatorsen (OGX-427*), kinase pathway modulators, including *MK2* inhibitors [35], and small-molecule disruptors of *HSP27* oligomerization. In contrast, within normal tissues, *HSP27*-mediated stress-response pathways may serve a protective function by preserving cellular integrity and limiting radiation-induced damage. This context-dependent duality raises the possibility that inhibition of *HSP27* could exacerbate normal tissue injury, whereas preservation or augmentation of *HSP27* activity might confer radioprotection [36].

Importantly, the broad functional repertoire of *HSP27* also complicates its therapeutic targeting. Because *HSP27* participates in redox regulation, cytoskeletal maintenance, proteostasis, control of apoptosis, inflammatory signaling, and tumor radioresistance, nonselective inhibition or activation may lead to unintended effects. In the context of radiation-induced periodontitis, therapeutic strategies should therefore not aim simply to suppress or enhance *HSP27* globally, but rather to define when, where, and in which cell populations *HSP27* modulation is protective or maladaptive. Such considerations underscore the need for radiation-induced periodontitis-specific preclinical models before HSP27-directed interventions can be considered clinically actionable.

Accordingly, therapeutic strategies targeting *HSP27* in radiation-induced periodontitis should be approached with careful consideration of tissue-specific effects and therapeutic directionality. Rather than direct inhibition, approaches that modulate *HSP27* function in a context-dependent manner—or enhance downstream protective pathways such as redox buffering and cytoskeletal stabilization—may be more appropriate for mitigating periodontal injury following RT. These considerations highlight the need for preclinical models specifically designed to evaluate *HSP27* modulation in normal oral tissues under irradiation conditions [11,22].

Given the important role of oxidative stress in radiation-induced tissue injury, antioxidant-based interventions may offer a rational adjunctive strategy to mitigate periodontal damage following radiotherapy. By reducing excessive ROS accumulation and limiting oxidative cellular injury, antioxidants could theoretically attenuate some biological processes implicated in radiation-induced periodontitis. Nevertheless, oxidative stress is only one component of a complex, multifactorial pathogenic network encompassing DNA damage, inflammatory dysregulation, microbiome perturbations, and impaired tissue remodeling. Thus, antioxidant therapies alone are unlikely to fully prevent or reverse

radiation-induced periodontal injury and should be considered as part of an integrated, multimodal protective strategy.

From a translational perspective, *HSP27* may also have value as a molecular indicator of radiation-induced tissue stress. Future studies should investigate whether HSP27 expression, phosphorylation status, or subcellular localization provides clinically meaningful information regarding susceptibility to radiation-induced periodontitis, treatment-related periodontal injury, or response to preventive interventions. Integration of such molecular markers with established clinical, dosimetric, inflammatory, and microbiome-based risk factors may ultimately support more refined approaches to toxicity prediction and personalized supportive care.

8. Future Directions

Despite increasing recognition of *HSP27* as a stress-inducible molecular chaperone involved in cellular stress-response pathways [28], its role in radiation-induced periodontitis remains largely unexplored. Future research should prioritize direct evaluation of *HSP27* within irradiated periodontal tissues using cell-based, organoid, animal, and prospective clinical models. Such investigations are needed to clarify whether *HSP27* functions primarily as a protective mediator of tissue resilience, a marker of ongoing cellular stress, or a context-dependent contributor to maladaptive remodeling responses following irradiation.

Several mechanistically grounded and clinically translatable research priorities can be identified. Experimental models incorporating periodontal cell systems and organoid platforms may help define tissue-specific *HSP27* responses to irradiation, including its regulation at transcriptional and post-translational levels. The potential role of *HSP27* as a biomarker warrants evaluation in prospective clinical cohorts, with particular attention to its incremental value beyond established clinical, dosimetric, inflammatory, and microbiome-related predictors. Integrative studies combining molecular profiling with clinical and dosimetric risk characterization may help refine risk stratification, although such approaches will require rigorous statistical validation.

In parallel, further investigation into the role of *HSP27* in modulating inflammatory and immune responses within irradiated periodontal tissues may provide additional insight into its contribution to tissue injury and repair (Table 4). Given the overlapping biological features of radiation-induced soft-tissue and bone injury, exploring whether *HSP27* participates in shared pathways across related radiation toxicities may also be informative.

Table 4. Priority research directions and representative experimental approaches for evaluating the role of HSP27 in radiation-induced periodontitis.

Research Question	Representative Experimental Approach	Primary Outcomes
Does irradiation alter HSP27 expression or activation in periodontal tissues?	Serial assessment of irradiated periodontal tissues in preclinical mandibular irradiation models	Temporal changes in HSP27 expression, phosphorylation status, and subcellular localization
Does HSP27 protect periodontal ligament fibroblasts from radiation-induced injury?	Irradiated periodontal ligament fibroblast cultures with HSP27 knockdown, overexpression, or pharmacological modulation	Cell survival, ROS accumulation, apoptosis, ECM remodeling markers, senescence-associated changes

Table 4. *Cont.*

Research Question	Representative Experimental Approach	Primary Outcomes
Does HSP27 influence radiation-induced alveolar bone remodeling?	Osteoblast/osteoclast coculture systems or mandibular irradiation models with HSP27 modulation	Osteoblast differentiation, osteoclast activity, bone formation/resorption markers, alveolar bone loss
Does HSP27 regulate epithelial barrier responses after irradiation?	Irradiated gingival epithelial or oral organoid models	Junctional integrity, epithelial apoptosis, inflammatory signaling, microbial translocation
Does HSP27 affect radiation-induced periodontitis severity in vivo?	HSP27-deficient, HSP27-overexpressing, or HSP27-modulated animal models exposed to mandibular irradiation	Periodontal attachment loss, alveolar bone loss, inflammatory infiltrates, fibrotic remodeling
Can HSP27 serve as a biomarker of radiation-induced periodontitis susceptibility or severity?	Prospective clinical studies assessing HSP27-related measures in periodontal tissues, saliva, or gingival crevicular fluid	Association with radiation-induced periodontitis incidence, severity, progression, discrimination, calibration, and incremental predictive value
Can HSP27-targeted modulation reduce radiation-induced periodontal injury?	Preclinical therapeutic intervention studies evaluating context-dependent HSP27 modulation or downstream protective pathways	Reduction in oxidative injury, apoptosis, inflammation, attachment loss, and alveolar bone resorption

Abbreviations: ECM, extracellular matrix; HSP27, heat shock protein 27; ROS, reactive oxygen species.

Overall, these directions emphasize the need for stepwise validation—from mechanistic studies to prospective clinical investigation—before HSP27 can be incorporated into predictive or therapeutic strategies for radiation-induced periodontitis. Such efforts may ultimately clarify whether HSP27 represents a viable target for risk stratification and therapeutic modulation in radiation-induced periodontal injury.

9. Conclusions

Radiation-induced periodontitis represents a complex, insufficiently characterized toxicity arising from the interplay among oxidative stress, impaired bone remodeling, inflammatory dysregulation, and epithelial barrier disruption. Integrating periodontal biology with radiotherapy-induced tissue injury highlights the potential role of HSP27 as a candidate modulator within these interconnected processes. Positioned at the intersection of redox regulation, cytoskeletal stability, DNA repair, and control of apoptosis, HSP27 represents a biologically plausible link between core radiation-response pathways and the clinical manifestation of periodontal tissue injury.

This review identifies the periodontitis–radiotherapy–HSP27 axis as an emerging area of translational interest. The current absence of direct investigations into HSP27 in radiation-induced periodontitis underscores both the novelty of this field and the need for targeted research. Advances in experimental modeling, molecular targeting strategies, and quantitative toxicity prediction may facilitate further exploration of HSP27-centered mechanisms. Future translational studies should evaluate whether HSP27 expression, phosphorylation status, or subcellular localization can provide clinically meaningful information regarding

susceptibility to radiation-induced periodontal injury. Such investigations may ultimately support the development of more refined molecular approaches to risk stratification and toxicity prediction in radiation-induced periodontitis.

Collectively, these observations support a hypothesis-generating conceptual framework in which HSP27 may plausibly connect tissue-level stress responses, periodontal injury mechanisms, and clinical outcomes. As precision radiation oncology continues to evolve, direct evaluation of the proposed HSP27–radiation-induced periodontitis axis may help determine whether HSP27 has value for risk assessment, targeted interventions, or supportive care strategies in patients with HNC. However, while the available evidence supports biological plausibility, the proposed HSP27–radiation-induced periodontitis relationship remains unproven and requires direct experimental and clinical validation before definitive mechanistic, biomarker, or therapeutic conclusions can be drawn.

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