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Review Article

Radioprotectors & mitigators in radiation therapy: Harnessing diverse pathways for optimizing clinical outcomes

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Radioprotectors are agents that protect normal tissues from the harmful effects of radiation during cancer treatment. Combining these protective agents with advanced radiotherapy techniques such as stereotactic body radiotherapy (SBRT) and proton therapy offers a promising strategy to enhance therapeutic efficacy while minimizing normal tissue toxicity. However, despite extensive research and the identification of numerous potential radioprotectors, only a few have made it into clinical practice. It is primarily because the transition from laboratory research to clinical application faces significant challenges. These include adverse side effects, lack of tissue specificity, complex regulatory requirements, and the high cost of development and implementation. Addressing these challenges requires a multifaceted approach. Streamlined regulatory pathways and increased funding for translational research can further accelerate the clinical adoption of these agents. This paper reviews the landscape of radioprotector research, examining the biological mechanisms, clinical trials, and challenges that have limited the clinical translation of many promising agents. This review underscores the critical need for continued research and innovation to bridge the gap between experimental radioprotectors and viable clinical treatments, aiming to enhance the therapeutic ratio of radiotherapy in oncology.

Key words Clinical validation - mitigators - preclinical insights - radiation-induced toxicities - radioprotectors

Radiation therapy is an essential part of cancer treatment. It uses high doses of ionizing radiation to stop tumour growth. The aim is to maximise damage to tumour cells while minimising harm to normal cells. This can be achieved by improving dose precision or using radioprotectors that selectively protect healthy tissue. Radioprotectors, often antioxidants, are given before or during exposure. They have been developed as emergency treatments for nuclear events and as radiotherapy aids to improve the patient quality of life. Early studies focused on synthetic thiol-containing compounds[1]. The most effective, amifostine (WR-2721), protects various normal tissues, including oral mucosa, salivary glands, lungs, bone marrow, heart, intestines, kidneys and reduces toxic effects of chemotherapy, such as cisplatin-induced kidney and nerve damage and cyclophosphamide-related blood cell toxicity[2]. Another FDA-approved radioprotector,

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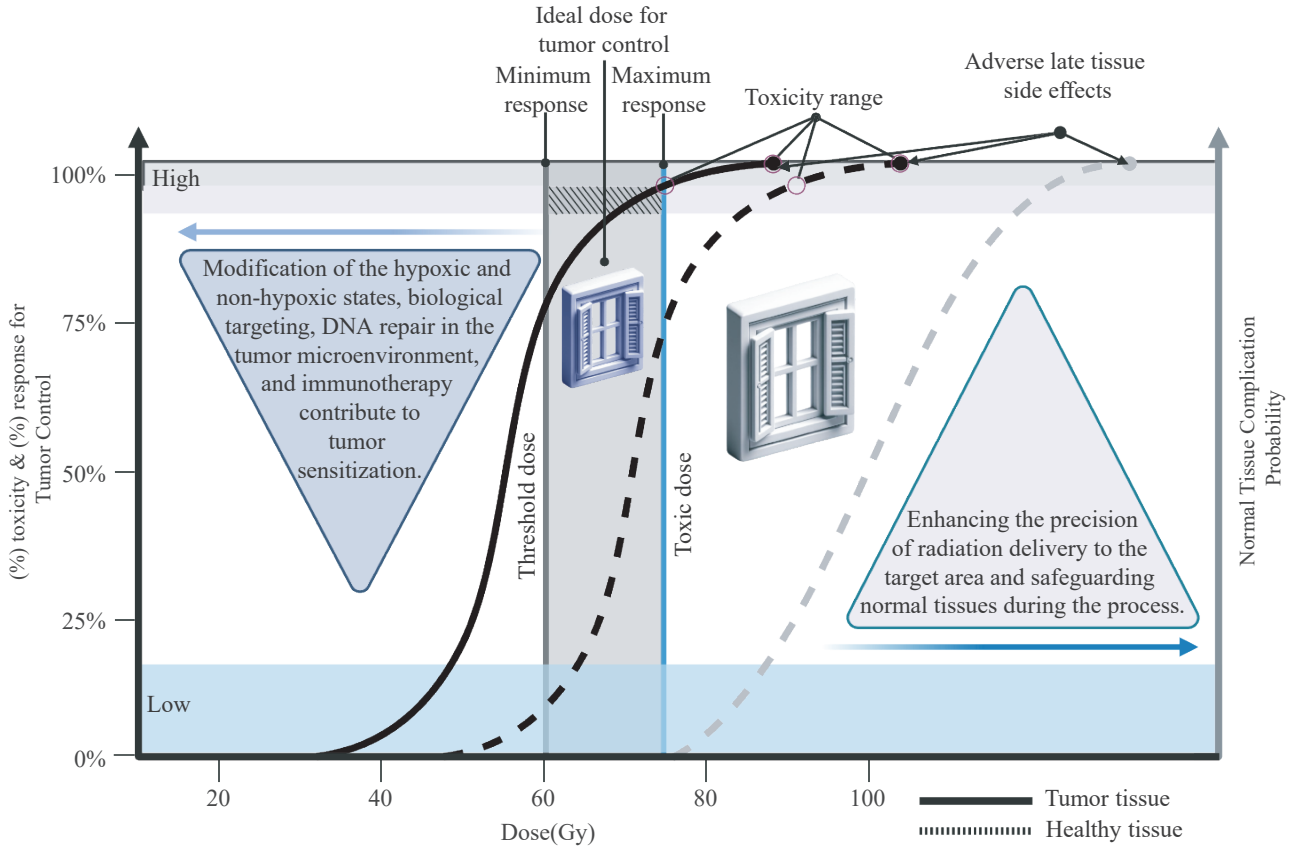

Fig. 1. Therapeutic ratio in radiotherapy. Sigmoid curves show tumour control and tissue toxicity. The gap is the therapeutic ratio. A protective agent shifts toxicity right without affecting tumour control. The figure is created by the authors using BioRender.

palifermin, a lab-made human keratinocyte growth factor (KGF) expressed by epithelial cells, promotes cell growth and repair, DNA recovery, and defence against reactive oxygen species[3]. Its anti-apoptotic and anti-inflammatory roles help reduce oral mucositis in patients undergoing total-body irradiation.

Mitigators, used after exposure, differ from radioprotectors. FDA-approved examples include filgrastim, pegfilgrastim, and sargramostim[4]. They block prolonged damage by halting cytokine activity, preventing or reducing toxicity. Therapeutic agents, like dexrazoxane, are used post-symptom onset of radiation-induced toxicity. Dexrazoxane reduces radiation- or chemo-induced heart damage by removing iron and stopping harmful free radicals, preventing long-term heart failure without affecting cancer treatment. Radioprotection strategies in oncology include physical [Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), proton therapy], and pharmacological approaches (amifostine, palifermin). Memantine, for example, reduces neurocognitive decline by blocking overactive NMDA receptors[5]. These strategies individually or in combination aim to widen the therapeutic window.

Rationale for radioprotection in clinical oncology

The overarching goal of radiation therapy is to destroy tumour cells while sparing normal tissue, maximizing the therapeutic ratio, as shown in figure 1. Tumour kill can be achieved by increasing radiation dose using conformal techniques like IMRT and stereotactic radiosurgery, or by leveraging the higher effectiveness of particle beam therapy. Tumour sensitivity can also be increased by combining radiation with chemotherapy, biological agents, hypoxic sensitizers, or anti-angiogenic agents. Protecting normal tissue involves avoiding exposure using IMRT or Image Guided Intensity Modulated Radiation Therapy IG-IMRT, or using compounds that are absorbed by healthy cells and reduce radiation damage without affecting tumours. Radiation effects are classified as acute (during or shortly after therapy) or intermediate to late (months to years). Acute toxicity mainly results from cell death, while later effects involve inflammation and fibrosis. These effects can occur with radiation alone

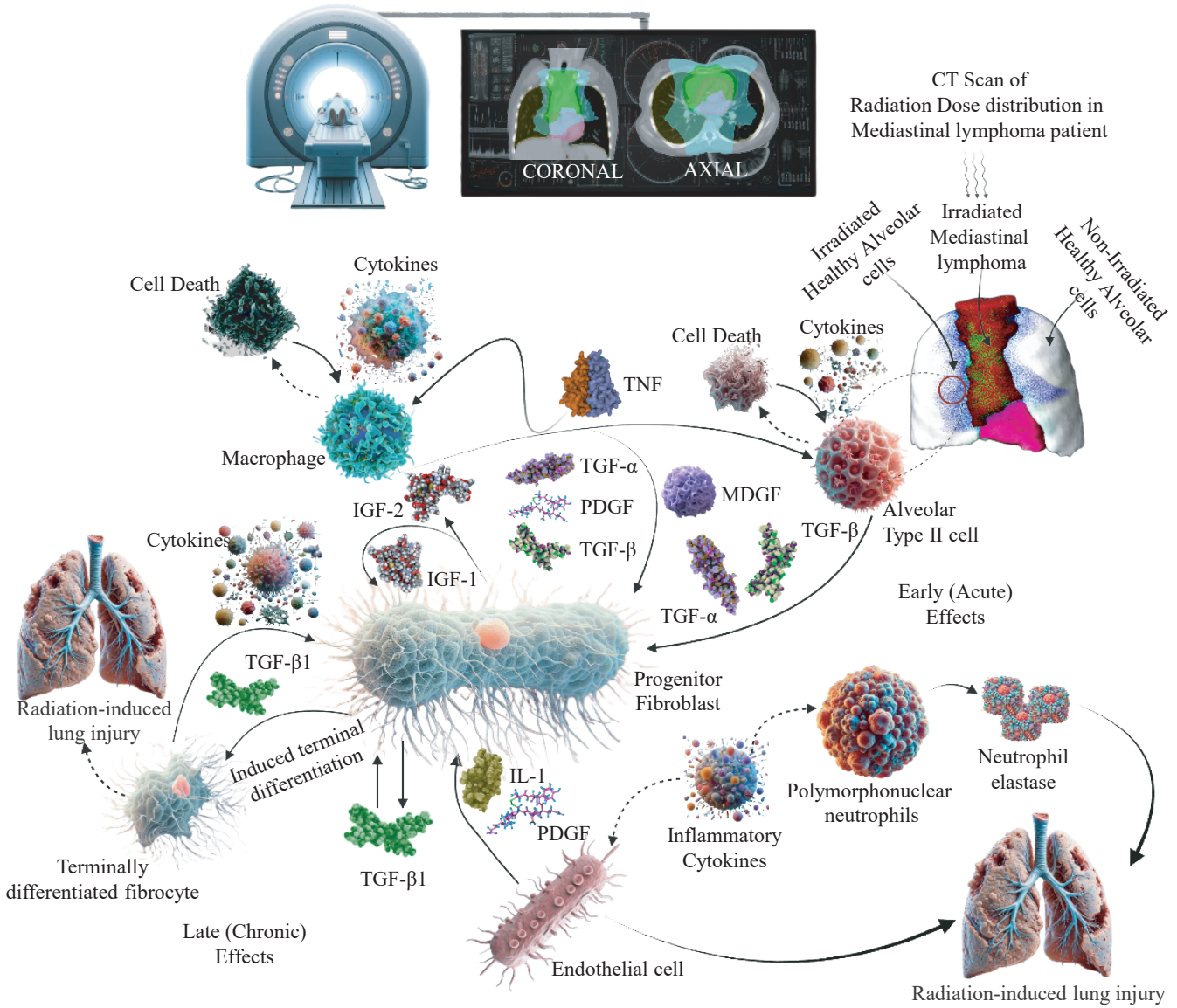

Fig. 2. Interactions and events illustrating the complex nature of Lung tissue as a model. Subtotal lung irradiation shows alveolar pneumocyte response. ROS and cytokines (IL-1, TNFα, TGFβ) trigger local and systemic inflammation. The figure is created by the authors using BioRender.

or with chemotherapy, as shown in figure 1, and often compromise quality of life. To improve outcomes, radiation toxicity must be minimised through a clear understanding of its causes.

Overview of radiation toxicities across organ includes common effects (dermatitis, mucositis) and organ-specific issues (heart, CNS, lung, liver, *etc*.). Acute effects are inflammatory; chronic effects impair function.

Tissue damage from radiation often involves shared pathways like oxidative stress, inflammation, blood vessel injury, and fibrosis. For example, in lung tissue (Fig. 2), ionizing radiation in oxygen-rich environments creates reactive oxygen species (ROS) that break DNA strands[6]. Excessive DNA damage overwhelms repair systems. Signals from damaged DNA activate stress-response proteins, leading to mitochondrial changes, cytochrome c release, and activation of caspase-3, causing cell death[7,8]. Damaged or recovering cells release ROS and cytokines such as IL-1, TNFα, and TGFβ. These spread damage beyond the radiation volumes. Cytokines can trigger apoptosis[9,10], autophagy and necrosis in nearby or distant cells. Damage severity depends on radiation dose and volume exposed. This mechanism is common

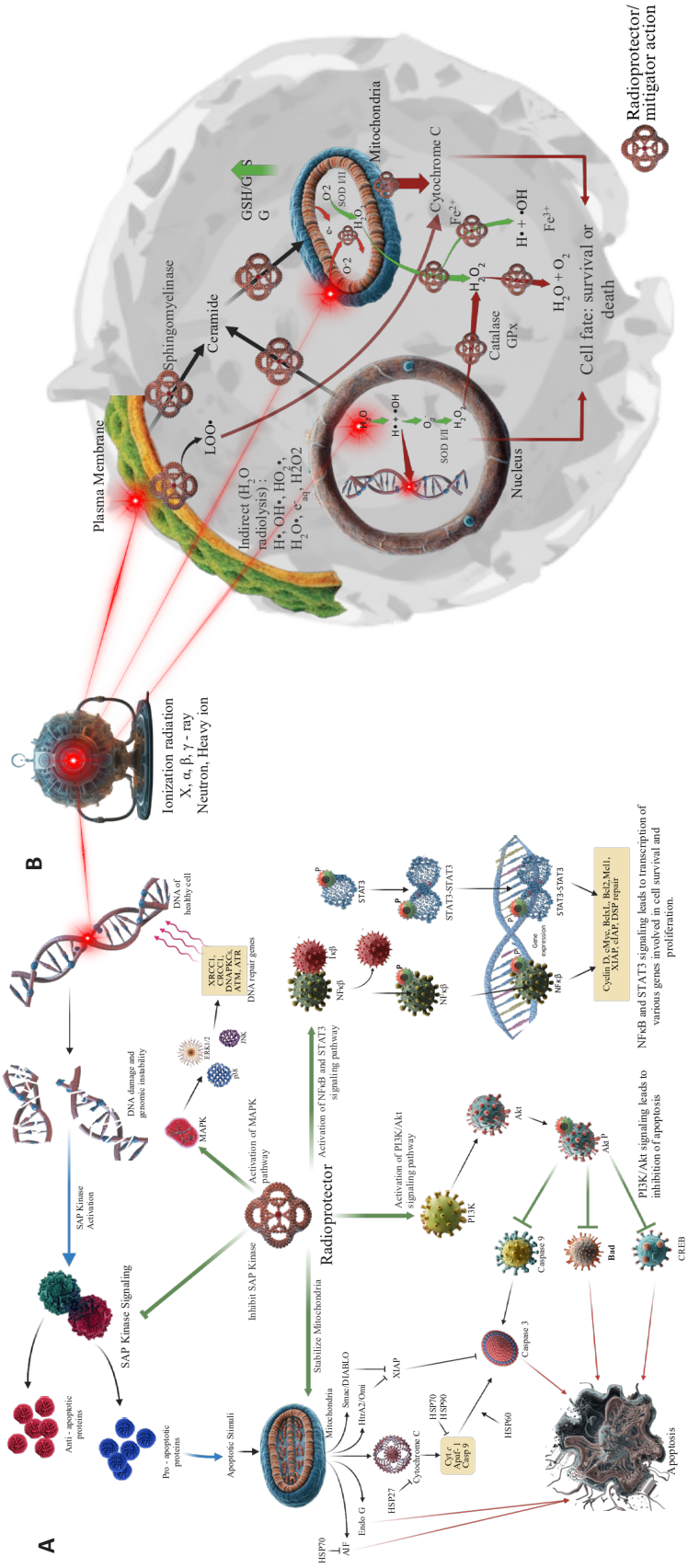

Fig. 3. (**A**) Direct targets for the development of radioprotector agents based on molecular pathways. (**B**) Indirect targets for development of radioprotectors and mitigators based on molecular pathways. The figure is created by the authors using BioRender.

across organs. In the brain, oxidative damage, barrier disruption, and inflammation lead to white matter loss and cognitive decline. In the heart, radiation causes blood vessel injury, inflammation, and fibrosis, which can lead to artery disease, pericarditis, or heart failure.

Pathways and molecular targets for the development of radioprotectors, mitigators, and therapeutic agents

The development of radioprotectors, mitigators, and therapeutic agents relies on understanding molecular pathways involved in cellular response to radiation (as illustrated in Fig. 3A and B).

(i) Blocking nuclear DNA damage: DNA is a critical radiation target. Even one unrepaired double-strand break can trigger apoptosis. Ionizing radiation acts directly or indirectly through water radiolysis, producing ROS like hydroxyl radicals, superoxide, hydrogen peroxide, and hydroperoxyl radicals[11]. These ROS inflict oxidative damage to critical cellular components, including DNA, lipids, and proteins, contributing to genomic instability and cell death. In mitochondria, radiation disrupts the electron transport chain, causing electron leakage and more superoxide. Superoxide dismutase (SOD) converts superoxide to hydrogen peroxide, which is detoxified by catalase or glutathione peroxidise (GPx). If unchecked, hydrogen peroxide reacts with iron, forming highly reactive hydroxyl radicals that tilt the balance toward damage[12].

Antioxidants that neutralise free radicals can prevent DNA damage. Genistein (from soy) scavenges radicals and enhances DNA repair. Curcumin, derived from turmeric, exhibits strong antioxidant properties by neutralizing hydroxyl radicals and reducing oxidative stress in normal tissues. Osmium compounds, including those derived from *tulsi (Ocimum sanctum)*, are known for their ability to counteract radiation-induced damage. Additionally, glutathione and cysteine derivatives, as thiol-based compounds, protect DNA by donating electrons to neutralize ROS[13]. Enzyme mimics like SOD mimics (superoxide dismutase mimetics) and GPx mimics (selenium-based compounds) act by catalyzing the breakdown of ROS, such as superoxide anions and hydrogen peroxide, into less harmful molecules, thereby enhancing the radioprotection of normal cells. Alternatively, compounds that induce cell cycle arrest or delay can provide cells with more time to repair DNA damage before progressing to mitosis[9]. CHK1 (Checkpoint Kinase) inhibitors disrupt cell checkpoints, increasing vulnerability to radiation, while CDK (Cyclin Dependent Kinase) inhibitors like palbociclib induce G1 arrest, enhancing radioprotection. G2/M arrest can sensitize cells by trapping them during less repair-friendly phases. By refining radiation delivery and combining with such agents, normal tissue damage can be minimised[14].

(ii) Mitochondrial stabilisation: Mitochondria are vulnerable to oxidative damage induced by radiation-generated ROS. Radiation damages mitochondria, opening the mitochondrial permeability transition pore (MPTP), disrupting membrane potential, and leading to cell death[15]. MPTP inhibitors like cyclosporin A and sanglifehrin A prevent mitochondrial destabilization. Inhibitors of cyclophilin D and p53 can further stabilize mitochondria. Since excessive p53 activation leads to apoptosis, its regulation is key. Agents like sodium orthovanadate block p53 signalling, reducing cell death in sensitive tissues[16]. 3,3′-Diselenodipropionic acid (DSePA) a selenium-based compound, offers strong radioprotection. It preserves glutathione and SOD, reduces liver damage, and improves survival in irradiated mice. At 2 mg/kg, DSePA improves gastrointestinal and spleen integrity and shows high lung absorption, enhancing protection in chest radiation[17]. Pharmacokinetic studies indicate that DSePA is absorbed effectively in lung tissues, enhancing its protective effects during thoracic irradiation scenarios[18].

Radioprotectors activate MAPK, PI3K/Akt, NF-κB, and STAT3 pathways, inducing DNA repair genes (XRCC1, ATM, DNAPKCS), blocking apoptosis, and promoting survival *via* Bcl2, BclxL, and XIAP. Also shown are SAP kinase inhibition and mitochondrial stabilization.

(iii) Blocking caspase activation and poly ADP-ribosyl-polymerase (PARP) cleavage: Targets for blocking apoptotic signalling pathways to prevent cell death include (*i*) Bcl-2 family proteins (anti-apoptotic: Bcl-2, Bcl-xL) and (*ii*) Caspases[19]. Bcl-2 and Bcl-xL prevent mitochondrial membrane damage, blocking cytochrome c release. Inhibiting pro-apoptotic proteins like Bax and Bak enhances survival. Caspase inhibitors, such as Z-VAD-FMK, can block caspase activation and prevent apoptotic cell death induced by radiation[20]. ARP, a DNA repair enzyme, can worsen cell damage when overactivated by consuming too much NAD+ and ATP, leading to energy collapse and cell death[21]. Inhibiting Poly (ADP-Ribose) Polymerase (PARP)

prevents this chain reaction, preserving energy and cell function. Blocking caspase activation and PARP cleavage helps maintain cell viability during radiation exposure.

(iv) Decreasing systemic cytokine-mediated cell death & immunomodulators: Inflammatory pathways activated by radiation involve NF-κB and TNF-α, which drive cytokine production. Suppressing these can reduce systemic damage. NF-κB activates genes for cytokines like TNF-α and interleukins. Blocking NF-κB reduces inflammation and limits chronic radiation effects like lung or heart injury. TNF-α, released by immune and blood vessel cells after radiation, promotes apoptosis and tissue damage. Inhibiting TNF-α or its receptors helps minimise these outcomes[22]. Additionally, chlorophyllin, a plant-derived antioxidant, has demonstrated radioprotective effects by reducing oxidative stress and modulating the inflammatory response, further limiting tissue injury and enhancing recovery.

Ionizing radiation (X, α, β, γ rays, neutrons, heavy ions) generates lipid peroxides, ceramides, and ROS, damaging DNA, membranes, and mitochondria, leading to cytochrome C-mediated apoptosis. Growth stimulating hormones (GSH) and antioxidants detoxify ROS. $OH^{\cdot}$ forms *via* water radiolysis or Fenton's reaction. Countermeasures target these pathways and activate pro-survival signals.

Radiation activates pro-survival transcription factors such as NF-κB, Akt, MAPK, and Nrf2, which promote genes tied to repair, growth, and detoxification. Their activation in normal tissue offers protective advantages. For example, in acute radiation injury, the agent CBLB502 activates NF-κB, triggering anti-apoptotic genes like c-IAP-1 and c-FLIP, helping cells survive. Importantly, this protection does not interfere with radiation's tumour-killing effect. PI3K/Akt activation also protects cells by suppressing pro-apoptotic proteins like Bad and Bax and activating mTOR to promote DNA repair. Akt enhances survival under oxidative stress. STAT3 is another protective pathway. It regulates survival genes and works with NF-κB to amplify radioprotective responses. The TLR5 agonist CBLB502 activates both STAT3 and NF-κB, shielding normal cells while sparing tumour sensitivity. This dual-pathway support boosts cell defense and recovery. Small molecule activators like bardoxolone methyl and sulforaphane, along with Keap1 inhibitors, enhance Nrf2 activity, promoting DNA repair and reducing radiation-induced tissue injury. Nrf2 also synergizes with other pathways like NF-κB and MAPK to strengthen cellular defenses, maximizing radioprotection while maintaining redox balance[23].

Differential effects on tumour vis-a-vis normal tissue: An essential prerequisite for an ideal radioprotectors: The challenge for developing an ideal radioprotector is to protect normal tissues from radiation damage without protecting the tumour cells, which need to stay vulnerable for effective cancer treatment. By taking advantage of physiological differences such as enzyme activity, proliferation rate, oxygenation levels, and DNA repair capacities between normal and malignant tissues, selectivity can be achieved through various modes of action.

For instance, amifostine, an FDA-approved radioprotector, is selectively targeted by the enzyme alkaline phosphatase, which is abundantly present in healthy tissues than in cancerous cells. Here, the active form of amifostine scavenges radiation-induced free radicals and also supports DNA repair. On the other hand, tumour cells frequently lack the enzyme activity required to change amifostine into its active form, which leaves tumour tissues with little to no protection. Compared to normal tissues that receive adequate oxygen, tumour tissues are less vulnerable to ROS-induced oxidative damage because they frequently reside in hypoxic environments. Amifostine and other radioprotectors work mainly by scavenging ROS, which are more prevalent in situations with higher oxygen levels. As a result, tumour cells, which are already less dependent on ROS-induced oxidative damage, continue to be vulnerable, whereas normal oxygenated tissues gain from the reduction of ROS-induced damage by the radioprotector. Tumour cells are especially susceptible to radiation-induced DNA damage because they frequently have compromised DNA repair mechanisms. Normal cells, on the other hand, usually have efficient repair systems. Radiation can efficiently target and kill cancer cells because of this differential response. Moreover, without improving the tumour's ability to repair DNA damage, radioprotectors can increase the ability of healthy cells to repair radiation-induced damage by strengthening cellular antioxidant defences or DNA repair pathways. Apart from the aforementioned differential effects, HemaMax (Recombinant Human Interleukin 12), a promising radioprotective drug, reduces radiation damage to healthy tissues by utilizing the body's

immunological response[24]. IL-12 is essential for both haematopoiesis and immunological control. Especially in the hematopoietic system, *i.e*., bone marrow, which is extremely vulnerable to radiation damage, HemaMax boosts the immune system and aids in regenerating damaged tissues. The preclinical studies have shown that HemaMax treatment leads to a considerable increase in the survival rates of animals irradiated with high absorbed doses by reducing the gastrointestinal and haematological syndromes. However, IL-12 does not directly protect malignant tissues, therefore tumour cells are not protected by this immune-mediated defence, which keeps the tumour vulnerable to radiation-induced damage[24].

Classification of radioprotectors, mitigators, and therapeutic agents

Understanding the distinct roles of radioprotectors, mitigators, and therapeutic agents is essential for developing effective strategies in radiation medicine. Radioprotectors, such as amifostine, are designed to shield healthy tissues from radiation damage. Mitigators, like palifermin, aim to alleviate damage after exposure, reducing the severity of radiation-induced injuries. Therapeutic agents focus on promoting tissue repair and regeneration post-radiation exposure, enhancing recovery, and improving clinical outcomes in radiation therapy and emergency scenarios.

The figure shows DNA damage progression from femtoseconds to years. Early stages involve chemical radioprotectors (Amifostine, thiols, nitroxides); later stages involve mitigators (repair enzymes, MAPK activation). Late effects like fibrosis and organ damage are shown with treatments (antifibrotics, transplants).

Radiation protectors, mitigators, and therapeutic agents utilise diverse mechanisms to safeguard cellular integrity and mitigate damage, as depicted in table I[25-58]. Sulfhydryl compounds like amifostine function as cytoprotective agents by scavenging free radicals and enhancing DNA repair. Antioxidants such as vitamin E and glutathione neutralize ROS, preventing oxidative damage to cellular components. Targeted mitochondrial agents like Mn porphyrin-based SOD mimics stabilize mitochondrial membranes and mitigate oxidative stress[25]. Immunomodulators and plant extracts, including curcumin, enhance radioprotection by modulating inflammatory responses and upregulating cellular defences. Together, these compounds provide a multi-faceted approach to radiation-induced damage, leveraging mechanisms ranging from ROS scavenging to cytokine inhibition.

Radioprotectors in clinical oncology - amifostine and palifermin as lead agents in clinical studies

Decades-long research on radioprotectors and radiomitigators persists. Radical scavengers show potential as radioprotectors by reducing cellular damage from ionizing radiation, but clinical translation faces significant challenges. Toxicity at effective doses, narrow therapeutic windows, lack of specificity for normal tissues, and variable patient responses limit widespread adoption. High development costs, context-specific efficacy, and regulatory challenges further delay clinical integration. Nevertheless, radioprotectors and radiomitigators could enhance radiation therapy's therapeutic index and improve cancer treatment outcomes by enabling higher radiation doses and reducing normal tissue damage.

Radioprotectors and radiomitigators remain under active investigation. Amifostine, extensively studied for radioprotection, was developed by the U.S. Army to mitigate ionizing radiation damage[59]. After decades of research, it became the first FDA-approved radioprotective drug, demonstrating selective protection of normal tissues against radiation and chemotherapy-induced damage. As a synthetic compound, amifostine contrasts with natural products gaining attention for radioprotective potential.

Amifostine: Amifostine, an inactive prodrug, is converted by alkaline phosphatase in normal endothelial cells into an active thiol metabolite that neutralizes reactive metabolites from platinum and alkylating agents. Its selective cytoprotection results from higher concentrations in healthy cells (~100-fold greater than in tumour cells) due to the tumour microenvironment and differential enzyme expression. Amifostine's mechanisms include scavenging secondary radicals, donating electrons for chemical repair, stabilizing DNA repair, inhibiting cell-cycle progression, and inducing hypoxia, protecting normal tissues while preserving cancer treatment efficacy[59]. This multi-faceted mechanism of action allows amifostine to protect normal tissues from the damaging effects of radiation and chemotherapy while still allowing these treatments to target cancer cells.

The U.S. FDA approved intravenous amifostine in 1996 to reduce renal toxicity from repeated cisplatin in advanced ovarian cancer and in 1999 to decrease

Table I. Radiation protectors, mitigators and therapeutic agents with their mechanistic action and their comparison in terms of efficacy

Radio-modulating agents	Model system (Cell line/Mice/ Subject)	Dose & mode of administration	Type & dose of radiation	Mechanism of action	Efficacy (DMF or % protection)	Reference
Radiation protectors						
WR-2721 (Amifostine)	Human clinical trials	500-1500 mg subcutaneous (2 injections)	Fractionated (50-70 Gy total)	Scavenges free radicals and protects DNA damage.	DMF: 1.2-3.0 (preclinical models, Amifostine); approximately 2.0-2.3 in rodent studies. Clinical DMF ~1.2 for xerostomia protection in head & neck cancer patients	25
Glutathione	C57BL/6 mice (glioma model)	100 mg/kg intraperitoneal (pre- or post-irradiation)	X-ray, single dose (not specified, typical preclinical range 4-8 Gy)	Detoxifying ROS and preventing DNA, protein and lipid from oxidative damage	DMF: Not known	26
Polycysteine (compound 5, L-configuration)	Mice (C57BL/6)	20 mg/kg intraperitoneal, 20 min before irradiation	γ-ray (whole body: 4, 7.2, 7.5, 10, 12.5 Gy at 0.99 Gy/min); abdominal: 15, 18 Gy; lung: 17 Gy X-ray at 3.23 Gy/min	Mitigating tissue injury.	Achieves an 80% 30-day survival rate at lethal radiation doses	27
Cysteine	Rat (feverish, whole-body)	30 mg/kg intraperitoneal, 30 min before irradiation	Gamma, 6.5 Gy single dose	Precursor for the synthesis of glutathione.	DMF: Not known	28
Tempol	C3H mice (RIF-1 tumour model)	275 mg/kg intraperitoneal, 10-15 min before irradiation	Tumour & normal tissue, single dose	Membrane-permeable radical scavenger and metal-independent superoxide dismutase-mimetic.	DMF: Not known	29
Vitamin E	Mice, non-human primates, human cell lines	200-400 mg/kg oral (mice); 37.5-75 mg/ kg subcutaneous (tocotrienols, mice); 50-100 mg/kg oral (non-human primates); various doses in cell culture	Whole-body gamma/X-ray, 7-9 Gy (mice); 5-7 Gy (primates); 2-4 Gy (cell lines)	Lipid-soluble antioxidant.	DMF: 1.1-1.3 (mice, α-tocopherol); up to 1.3-1.4 (tocotrienols); 60-80% survival improvement at lethal doses in mice	30
Vitamin C	Mice (*in vivo*)	1% dietary enrichment or injection (dose not specified)	Iodine-131 (chronic), acute 120 kVp X-rays	Quenching ROS, contributing to the stabilization of mitochondrial membranes.	DMF: 2.2-2.4 (spermhead survival, I-131); DMF: 1.2 (acute X-rays)	31
Nitrooxides	Mice (*in vivo*), cell lines (*in vitro*)	275 mg/kg intraperitoneal (Tempol, mice); Nanoparticles: dose not specified (*in vivo/in vitro*)	Whole-body X-ray, 8.5-9 Gy (mice); X-ray (dose not specified, *in vitro/in vivo*)	Targeting mitochondria.	DMF ≈ 1.3 (Tempol, 30-day survival, mice)	32

Contd...

Radio-modulating agents	Model system (Cell line/Mice/ Subject)	Dose & mode of administration	Type & dose of radiation	Mechanism of action	Efficacy (DMF or % protection)	Reference
Mn porphyrin-based SOD mimics (*e.g.*, MnBuOE, BMX-001, MnTE-2-PyP5+)	Mice (oral mucosa, salivary gland, tumour xenograft)	MnBuOE: 0.2-1.0 mg/ kg subcutaneous, daily (timing: before and during irradiation)	Fractionated X-ray, up to 66 Gy (normal tissue); 10-30 Gy (tumour xenograft)	Targeting the organelle and exhibiting potent SOD activity	DMF (normal tissue protection): 0.77 (xerostomia); DMF (tumour radiosensitization): 1.3 (TCD50)	33
Eukaryon-134 (EUK-134, SOD mimic)	Human lymphoblastoid cells (*in vitro,* wildtype and A-T)	10-100 μM, pre-incubation (overnight)	X-ray, 5-10 Gy (acute, single dose)	Achieves mitochondrial localization & demonstrates potent SOD activity	DMF: Not known	34
DMSO	Golden hamster embryo cells (*in vitro*)	2% DMSO in medium (pre-irradiation)	γ-rays (acute external), dose not specified	Suppression of inflammatory signalling pathways (ERK1/2, p38, JNK, Akt phosphorylation)	DMF: 1.24 against lethal irradiation	35
Histamine (H2) receptor antagonist (Cimetidine, Famotidine)	Mice (liver, oxidative stress model)	Cimetidine: 50 mg/kg i.p.; Famotidine: 20 mg/kg i.p., 30 min before irradiation	Gamma, 2 and 4 Gy	Reducing clastogenic effects of radiation	DMF: Not known	36
Flagellin (*e.g.*, CBLB502, TLR5 agonist)	Mice, Rhesus monkeys	Single systemic injection (dose varies by model; *e.g.*, CBLB502 at 0.2 mg/kg, i.p. or s.c., pre-irradiation)	Total-body irradiation, lethal dose (*e.g.*, 8-13 Gy in mice, 6.5 Gy in monkeys)	Stimulates stem cells and haematopoiesis	DMF: Not known	37
Heat-killed Lactobacillus casei	Mice (C3H/He)	Pre-administration (dose not specified, systemic, before irradiation)	X-ray, lethal dose (not specified)	Eliciting innate and adaptive immune responses by the homeostatic control of inducible T regulatory cells, and modulation of pattern recognition receptors (PRR) on immune cells	DMF: Not known	38
Polysaccharides (Acanthopanax senticosus, Auricularia, Poria cocos, *etc*.)	Mice, rats, cell lines, C. elegans	Oral or intraperitoneal, doses vary by study (*e.g.*, 50-100 mg/kg or μg/mL *in vitro*)	X-ray, Gamma-ray, heavy ion, 4-8 Gy (mice/rat); 60Co-γ (cell/animal); 80 Gy X-ray (zebrafish embryos)	Modulates the mononuclear-macrophageal cell system	DMF: Not known	39
Eicosanoids	Animal models (mice, rats); *in vitro*; combination regimens	Administered before irradiation; dose varies by agent (*e.g.*, prostaglandins, leukotrienes, thromboxanes)	Gamma, X-ray, or other ionizing radiation (various doses)	Cell membrane G-protein coupled receptors influences cellular responses to radiation	DMF: Not known	40

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Radio-modulating agents	Model system (Cell line/Mice/ Subject)	Dose & mode of administration	Type & dose of radiation	Mechanism of action	Efficacy (DMF or % protection)	Reference
Curcumin	Rat (larynx, *in vivo*)	Intraperitoneal, dissolved in DMSO, 5 days before RT (dose not specified)	X-ray, single 16 Gy to neck	Reduces ROS production & upregulating antioxidants.	Statistically significant reduction in oedema, hyperaemia, necrosis, and TNF-α expression in laryngeal tissue	41
Interleukin-1 (IL-1, including IL-1α and IL-1β)	Mice (C57BL/6, B6D2F1, C3H/ HeN)	Recombinant IL-1α, single injection (dose varies by study; typically pre-irradiation)	Whole-body gamma irradiation, lethal dose (*e.g.*, 8-9 Gy)	Binds to IL-1 receptor type 1 (IL-1R1) and forms a heterodimer with IL-1 type 3 receptor (IL-1R3), also known as IL-1RAcP.	DMF: Not known.	42
Stem Cell Factor (SCF, c-kit ligand)	Human bone marrow progenitor cells (*in vitro*); mice (*in vivo*)	Recombinant human SCF, pre-irradiation (dose varies; *e.g.*, single or repeated injection)	Gamma/X-ray, lethal or sublethal dose (*e.g.,* 8-9 Gy in mice)	Modulates cellular responses by regulating of radiation-induced effects on haematopoietic progenitor cells and stem cells	DMF: Not known	43
G-CSF (Granulocyte Colony-Stimulating Factor)	Mice (CD2F1, C57BL/6), Humans (clinical)	Single or repeated injection, typically started within 2 h post-irradiation (mice); clinical dosing per neutropenia protocols (humans)	Total-body gamma irradiation, lethal dose (*e.g.*, 8-9.2 Gy in mice); fractionated or concurrent chemoradiotherapy in humans	Induces the activation of the master regulator of granulopoiesis, the transcription factor CCAAT, upon binding to G-CSFR on hematopoietic progenitors.	DMF: Not known	44
Selenium (various forms: nanoparticles, sodium selenite, dietary)	Rats, mice, human lymphocytes, cell lines, clinical (advanced cancer)	Oral, intraperitoneal, or *in vitro*; doses vary (*e.g.*, selenium 800 IU in humans, SeNPs at optimal concentrations *in vitro*/ *in vivo*)	X-ray, gamma, I-131, 2-6 Gy (preclinical); clinical radiotherapy	Scavenges ROS & protects DNA damage.	Up to 50% reduction in micronuclei in human lymphocytes	45
Zinc (salts, nanoparticles)	Rats, mice, human cell lines, clinical (cancer patients)	Oral, intraperitoneal, or *in vitro*; Zn NPs: 10-25 mg/kg (rats); zinc sulfate: dose varies	X-ray, Gamma-ray, clinical radiotherapy	Scavenges ROS & protects DNA damage.	Up to 50% reduction in radiation-induced micronuclei; improved antioxidant enzyme activity.	46
Superoxide dismutase (SOD)	Mice (*in vivo*), cell lines (*in vitro*), human tissues	Intravenous (bovine SOD, 1 h pre-irradiation); gene transfer; SOD mimetics	Total-body irradiation, 6-7 Gy (mice); Gamma-ray, X-ray (various)	SOD facilitates the dismutation of superoxide anion into hydrogen peroxide, while Catalase converts the produced hydrogen peroxide into oxygen and water.	Increased 30-day LD50 by 12% (mice); reduced lethality from 72.5% to 20.8% at 650 rads; robust reduction of radiation-induced DNA, protein, & tissue damage	47

Contd...

Radio-modulating agents	Model system (Cell line/Mice/ Subject)	Dose & mode of administration	Type & dose of radiation	Mechanism of action	Efficacy (DMF or % protection)	Reference
Catalase	Animal models, cell lines, human tissues	Exogenous (injection, gene transfer, overexpression); endogenous upregulation	Ionizing radiation (X-ray, Gamma-ray, UV, *etc*.)	SOD facilitates the dismutation of superoxide anion into hydrogen peroxide, while Catalase converts the produced hydrogen peroxide into oxygen & water.	DMF: Not known	48
Melatonin	Mice, rats, human lymphocytes, cell lines	Oral or parenteral (*e.g.*, 5-10 mg/kg in rodents; 100 mg orally in humans, 1-2 h pre-irradiation)	X-ray, Gamma-ray, I-131, 2-8 Gy (preclinical); clinical radiology	Scavenges free radicals through electron donation, inhibiting apoptosis, & protecting against radiation-induced cell death	Up to 50% reduction in γH2AX foci in human lymphocytes; robust organ protection in animals	49
Taurine	Human lymphocytes (*in vitro*), mice (*in vivo*), RPE cells	100 µg/mL (human lymphocytes); dose not specified for mice; various doses in cell models	X-ray, Gamma-ray, various doses	Reduces DNA damage, with Taurine demonstrating antioxidative & detoxification properties, while L-carnitine synergistically inhibits proliferation & osteoblastic differentiation of vascular smooth muscle cells	DMF: Not known.	50
L-carnitine	Rats, hamsters, guinea pigs, cell models	50-300 mg/kg orally or intraperitoneally (pre- and/or post-irradiation; 5-15 days)	Gamma, X-ray, total cranial, abdominal, or whole-body irradiation (various doses, *e.g.*, 8 Gy)	Reduces DNA damage, with Taurine demonstrating antioxidative & detoxification properties, while L-carnitine synergistically inhibits proliferation & osteoblastic differentiation of vascular smooth muscle cells	DMF: Not known	51
Radiation Mitigators						
Captopril	Mice, Göttingen minipigs, rats, cell lines, *in vitro*	Oral (*e.g.*, 0.96 mg/kg twice daily for 12 days in minipigs); high-dose for 30 days in mice; various *in vitro* doses	Total body irradiation (*e.g.*, 60Co, 1.79 Gy/min), X-ray, fast neutrons	Inhibition of the angiotensin II system	DMF for mitigation of lung injury: 1.07-1.13 radiolysis	52
Lisinopril	Rats (various strains, including Dahl salt-sensitive and Brown Norway), preclinical models	Oral administration, dosing varies by study (*e.g.*, started after irradiation and continued long-term)	Partial or whole-body irradiation (*e.g.*, 8 Gy × 5 fractions, 12.5-13 Gy leg-out PBI)	Prevents the conversion of angiotensin I to angiotensin II, potentially blocking cytokine release and receptor binding	Mitigates delayed radiation injuries in heart, lung, kidney, & brain	53

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Radio-modulating agents	Model system (Cell line/Mice/ Subject)	Dose & mode of administration	Type & dose of radiation	Mechanism of action	Efficacy (DMF or % protection)	Reference
Penicillamine	Guinea pigs, mice (*in vivo*); cell models	10 mg/kg i.p. (guinea pigs, 1 h before 9 kGy γ-rays); 3,000 mg/ kg i.p. (mice, 1 h before 6-10 Gy 60Co γ-rays); oral (in mice for radiopharmaceutical protection)	Acute gamma irradiation (up to 9 kGy), whole-body irradiation (6-10 Gy), internal radiotherapy	Acts as a chelating agent, inhibits macrophages, decreases IL-1, & prevents collagen cross-linkage	Significant protection of haematopoietic cells	54
Pentoxyphylline	Neonatal and adult rats, mice (*in vivo*)	25-100 mg/kg, i.p. or systemic, before or after injury	Brain irradiation, hypoxic-ischemic brain injury, closed head injury	Acts as a phosphodiesterase inhibitor, inhibits cytokine release by likely reducing adenosine production through the direct inhibition of 5′-nucleotidase activity.	Up to 80-84% protection (pre-treatment, 75 mg/kg); 54% protection (post-injury, 75 mg/kg)	55
Therapeutic agents						
Alfa tocoferol	Mice, cell models, human skin	Subcutaneous, oral, topical; α-TOS: 100-400 mg/kg s.c. 24 h pre- and 1 h post-irradiation (mice); topical for skin protection	Total body irradiation (gamma/X-ray), UVA/ UVB, various doses	Scavenges ROS & modulates growth factors and cytokines, thus inhibiting cytokine release and receptor binding during radiation exposure.	40% survival at 9.5 Gy TBI.	56
Pirfenidone	Mice (thoracic irradiation), rats, humans (pilot & clinical trials), cell models	Oral or systemic; dosing varies (*e.g.*, daily oral in humans; 50 Gy thoracic X-ray in mice)	X-ray, gamma, UVB, radiotherapy (various doses)	Acts as an antifibrotic agent, reducing the production of growth factors & cytokines that cause fibrosis.	DMF: Not known.	57
Nintedanib	Mouse models (radiation-induced pulmonary fibrosis), patients with fibrosing ILD and NSCLC	Oral; administered before or after thoracic irradiation; clinical dosing per antifibrotic protocols	Thoracic irradiation (preclinical); radiotherapy (clinical)	Acts as a tyrosine kinase inhibitor, blocking the signaling pathways that lead to fibrosis	DMF: Not known.	58

SAP, stress-activated protein; SOD, superoxide dismutase; ERK, extracellular signal-regulated kinases; JNK, c-Jun amino-terminal kinases; G-CSF, granulocyte-colony stimulating factor; CCAAT, cytosine-cytosine-adenine-adenosine-thymidine

moderate to severe xerostomia in head and neck cancer patients undergoing postoperative radiotherapy[59]. Indeed, amifostine holds promise for various oncologic contexts beyond its current FDA-approved indications. Ongoing research explores new administration schedules and routes to reduce side effects like nausea, vomiting, and hypotension, and to expand applications beyond current indications. However, toxicity and side effects limit its use in non-clinical radiological or nuclear scenarios, requiring further research for FDA approval in these contexts.

Palifermin: Palifermin, a recombinant human keratinocyte growth factor (KGF) developed by Amgen, is a 140-residue protein produced using *E. coli*. Initial preclinical data demonstrated that Palifermin could reduce gastrointestinal injury and mortality resulting from a variety of toxic exposures[60]. These studies also showed that palifermin has protective effects on many epithelial tissues, particularly when administered prior to the toxic radiation exposure. Toxicology studies were conducted using animal models, including mice, rats, and monkeys. The endogenous form of palifermin is expressed in the kidneys of rats. The FDA approved palifermin in 2004 for reducing severe oral mucositis in haematological malignancy patients undergoing chemoradiotherapy. However, the gain in radioprotection remains hampered with a low margin of tolerance[61]. In a phase II trial for head and neck cancer, palifermin reduced the incidence, severity, and duration of oral mucositis during concurrent chemotherapy and hyperfractionated radiotherapy[62]. Extensive preclinical research, coupled with a burgeoning field of clinical investigation, has been dedicated to the development of agents like palifermin aimed at safeguarding normal tissues from the deleterious effects of irradiation.

Palifermin prevents and treats oral mucositis by binding to KGF receptors on buccal cells, stimulating epithelial cell proliferation, differentiation, and migration in the tongue and mouth. The KGF receptor is widely distributed across various tissues, with notable concentrations observed in regions such as the tongue, oesophagus, salivary gland, and other gastrointestinal tract organs.

Table II[62-75] shows clinical trials investigating the role of amifostine and palifermin for mitigating radiation-induced toxicities in cancer patients and stem cell transplantation, particularly for hematologic conditions. Their synergistic potential is under study, but further research is needed to clarify benefits and risks. Current evidence should guide their use. Radioprotection is essential in radiation therapy to minimise normal tissue damage. Amifostine and palifermin are FDA-approved radioprotectors used in clinical settings.

The use of amifostine in preventing chemotherapy-associated neutropenia has been inconsistent across studies. However, a notable large randomized trial published since 2002 demonstrated a significantly lower frequency of grades 3 to 4 neutropenia in the amifostine arm. A large randomized trial since 2002 showed reduced grade 3-4 neutropenia with amifostine, but no benefit for thrombocytopenia, leading to recommendations against its use for thrombocytopenia prevention in chemotherapy[76]. Amifostine also reduces cisplatin-associated nephrotoxicity in ovarian cancer and acute/late xerostomia in head and neck cancer patients undergoing fractionated radiotherapy.

Palifermin effectively prevents severe oral mucositis in hematopoietic stem-cell transplant (HSCT) patients with hematologic malignancies, reducing its incidence, severity, and duration. Updated guidelines support palifermin's use for mucositis prevention in HSCT. Some studies have also shown that palifermin is associated with a decrease in the use of patient-controlled analgesia (PCA) and a subsequent reduction in severe mucositis. Additionally, it contributes to a decrease in the number of days requiring analgesics and antibiotics, further highlighting its prophylactic benefits. When comparing amifostine and palifermin, as portrayed in supplementary table I[77-99], it's important to note that they are used to prevent different types of toxicities.

Radioprotectors in clinical oncology, specifically amifostine and palifermin, have shown promising results as both agents have demonstrated significant potential in radiation protection, with their therapeutic roles being well-documented and supported by clinical trials. The comparative analysis of the effectiveness of amifostine and palifermin further underscores their potential as lead agents in clinical studies. However, it is important to note that while these findings are encouraging, further research is necessary to fully understand the long-term effects and potential side effects of these agents. As we continue to advance in the field of oncology, the role of the above radioprotectors will undoubtedly become more crucial in improving patient outcomes and quality of life.

Final destination: Challenges in adoption in clinics and opportunities to overcome the challenges in

Table II. Different clinical trials of radiotherapy with Amifostine and palifermin

Clinical trials of radiotherapy with Amifostine								
Clinical trial number/ Study site	Cancer type & conditions	Interventions	Phase of clinical study/sample size	Study design	Efficacy	Toxicity/ Mortality (%)	Remarks	Reference
NCT00274937 (2022) Children's Oncology Group - National Cancer Institute (NCI)	Nasopharyngeal Squamous Cell Carcinoma	• Drug: Amifostine, Cisplatin, Fluorouracil • Radiation: Radiation Therapy	Phase 3 N: 111	• Allocation: Non-Randomized • Intervention Model: Parallel	EFS: 2 yr	AE: 32.43% SAE: 71.17% Mortality: 0%	Various serious adverse events were reported. Higher doses of Amifostine failed to improve outcome	62
NCT01288625 (2021) Sun Pharmaceutical Industries Limited	• Oral Mucositis • Stomatitis	• Drug: Amifostine • Radiation: 1.8-2.0 Gy/day × 30-35 times	Phase 4 N: NR	• Allocation: Randomized • Intervention Model: Parallel	NR	NR	The study involved in comparing the incidence of stomatitis when treating with amifostine before radiation treatment. Study results have not been reported.	63
NCT00217438 (2015) Fred Hutchinson Cancer Center - National Cancer Institute (NCI)	Multiple Myeloma	• Drug: Melphalan, Amifostine trihydrate • Genetic: Fluorescence in situ hybridization • Procedure: Peripheral blood stem cell transplantation • Procedure: Bone marrow ablation with stem cell support	Phase 3 N: 130 Arm A (High Dose Melphalan, Amifostine Trihydrate, Transplant) - N:66 Arm B (Low Dose Melphalan, Amifostine Trihydrate, Transplant) - N:64	• Allocation: Randomized • Intervention Model: Parallel	Arm A: CR or nCR: 39% Arm B: CR or nCR: 22%	Arm A: AE: 21.21% SAE: 0% Mortality: 0% Arm B: AE: 10.94% SAE: 0% Mortality: 0%	The study has shown that amifostine has the potential to mitigate the toxicities linked with melphalan administration at a dosage of 280 mg/m².	64
NCT00003313 (2014) Radiation Therapy Oncology Group - National Cancer Institute (NCI); NRG Oncology	Lung Cancer	• Biological: Filgrastim • Drug: Amifostine trihydrate, Carboplatin, Paclitaxel • Radiation: Concurrent weekly PC and hyperfractionated radiation (to 69.6 Gy at 1.2Gy bid)	Phase 3 N: 243 Arm A (Amifostine) - N:120 Arm B (No Amifostine) - N:123	• Allocation: Randomized • Intervention Model: Parallel	Arm A: MST - 27.1 months OS - 5-year survival Arm B: MST - 15.4 months OS - 5-year survival	Arm A: AE: 90.00% SAE: 31.4% Mortality: 0% Arm B: AE: 93.00% SAE: 34.00% Mortality: 0.41%	Amifostine, administered at various doses and schedules, has been observed to diminish the frequency or severity of esophagitis in this context. Nonetheless, it did not notably decrease the incidence of grade 3 or 4 esophagitis.	65

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Clinical trial number/ Study site	Cancer type & conditions	Interventions	Phase of clinical study/sample size	Study design	Efficacy	Toxicity/ Mortality (%)	Remarks	Reference
NCT00058071 (2013) Gynaecologic Oncology Group - National Cancer Institute (NCI)	Gestational Trophoblastic Tumour	Drug: Amifostine trihydrate	Phase 3 N: 100	• Allocation: Randomized • Intervention Model: NR	NR	NR	The study focused on investigating the efficacy of Amifostine in treating peripheral neuropathy in patients who have received chemotherapy for cancer. Study results have not been reported.	66
NCT00003994 (2013) Children's Oncology Group - National Cancer Institute (NCI)	• Recurrent Childhood Liver Cancer • Childhood Hepatoblastoma • Stage I Childhood Liver Cancer	• Drug: Cisplatin, Vincristine sulfate, Fluorouracil, Amifostine trihydrate, Carboplatin • Procedure: Therapeutic conventional surgery	Phase 3 N: 277	• Allocation: Randomized • Intervention Model: Parallel	NR	NR	The study focused on evaluating the effectiveness of combination chemotherapy with and without Amifostine in treating young patients with liver cancer. Study results have not been reported.	67
NCT00003252 (2013) Rush North Shore Medical Center	Unspecified Adult Solid Tumour	• Drug: Amifostine trihydrate	Phase 4 N: 20	• Allocation: NR • Intervention Model: NR	NR	NR	The study aims to evaluate the effectiveness of amifostine in managing neurological changes induced by chemotherapy in patients with cancer. Study results have not been reported.	68
NCT00004166 (2012) Northwestern University - National Cancer Institute (NCI)	Ovarian Cancer	• Drug: Amifostine trihydrate • Procedure: Quality-of-life assessment	Phase 3 N: 60	• Allocation: Randomized • Intervention Model: NR	NR	NR	The study aims to assess the efficacy of amifostine in treating patients diagnosed with ovarian epithelial cancer undergoing chemotherapy. Study results have not been reported.	69

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Clinical trial number/ Study site	Cancer type & conditions	Interventions	Phase of clinical study/sample size	Study design	Efficacy	Toxicity/ Mortality (%)	Remarks	Reference
NCT00158691 (2005) Groupe Oncologie Radiotherapie Tete et Cou ; Schering-Plough	Head and Neck Cancer	Drug: Ethyol, Amifostine-administered subcutaneously Radiation: 50 to 70 Gy delivered by standard fractionation of 1.8 to 2 Gy per fraction.	Phase 3 N: 296	• Allocation: Randomized • Intervention Model: Parallel	NR	Arm A: AE: 60.00% SAE: 23.00% Mortality: 0% Arm B: AE: 48.00% SAE: 19.00% Mortality: 0%	Administration of amifostine subcutaneously in head and neck cancer patients undergoing radiotherapy shows better efficacy, evidenced by reduced hypotension, higher compliance, and reduced rates of acute xerostomia, however, long-term efficacy on xerostomia have not been studied.	70
NCT00158041(2005) Mt. Sinai Medical Center, Miami	• Head and Neck Cancer • Lung Cancer • Lymphoma	• Drug: Amifostine administered subcutaneously	Phase 4 N: 452	• Allocation: Non-Randomized • Intervention Model: Single-Group	NR	NR	The study assessed the safety of subcutaneously administered amifostine, focusing on four specific toxicities: nausea/ vomiting, hypotension, generalized skin rash, and injection-site skin reactions. Study results have not been reported.	71
Clinical trials of radiotherapy with Palifermin								
NCT01085617 (2024) University College, London	• Mucositis • Leukaemia	• Biological: Palifermin; Rituximab • Procedure: Allogeneic hematopoietic stem cell transplantation • Drug: Vincristine sulfate, Cytarabine, Fludarabine phosphate, Daunorubicin hydrochloride, Melphalan, Pegaspargase, Imatinib mesylate,	Phase 3 N: 1033 Arm A (Standard of care) - N:292 Arm B (Standard of care plus palifermin & rituximab) - N:294	• Allocation: Randomized • Intervention Model: Parallel	Arm A: OS: 40·1 months EFS at 3years: 43·7% Arm B: OS: 81·5 months EFS at 3years: 51·4%	Arm A: AE: 100.00% SAE: 53.00% Mortality: 23·7% Arm B: AE: 100.00% SAE: 55.00% Mortality: 20·6%	The addition of four doses of palifermin and rituximab to standard care did not result in a significant improvement in event-free survival compared to standard care alone. While rituximab has demonstrated benefits in acute lymphoblastic leukaemia, administering only four doses during induction is likely insufficient for optimal efficacy.	72

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Clinical trial number/ Study site	Cancer type & conditions	Interventions	Phase of clinical study/sample size	Study design	Efficacy	Toxicity/ Mortality (%)	Remarks	Reference
		Methotrexate, Mercaptopurine, Etoposide, Cyclophosphamide, Nelarabine. • Radiation: Total-body irradiation						
NCT00360971 (2017) Radiation Therapy Oncology Group - National Cancer Institute (NCI)	• Mucositis • Head & Neck Cancer	• Drug: Cisplatin • Procedure: Neck dissection • Biological: Palifermin • Radiation: Radiation therapy	Phase 3 N: 21 Arm A (Placebo) - N:10 Arm B (Palifermin) - N:11	• Allocation: Randomized • Intervention Model: Parallel	Arm A: OS: 75.00% PFS: 75.00% Arm B: OS: 100.00% PFS: 100.00%	Arm A: AE: 90.00% SAE: 80.00% Mortality: 0% Arm B: AE: 100.00% SAE: 45.45% Mortality: 0%	The study was terminated prematurely after accruing 21 subjects out of the planned 298, resulting in no statistical testing being conducted. The decision to terminate the study was made based on positive preliminary results from other palifermin studies.	73
NCT00101582 (2016) Swedish Orphan Biovitrum Amgen	• Squamous Cell Carcinoma • Mucositis • Stomatitis • Head & Neck Cancer • Solid Tumours	• Drug: Palifermin, Cisplatin • Radiation: Radiotherapy	Phase 3 N: 188 Arm A (Placebo) - N:94 Arm B (Palifermin) - N:94	• Allocation: Randomized • Intervention Model: Parallel	Number of Participants Without Severe Oral Mucositis (WHO Grade 3 and 4): Arm A: Efficacy: 30.85% Arm B: Efficacy: 84.31%	Arm A: AE: 89.01% SAE: 27.47% Mortality: 0% Arm B: AE: 94.68% SAE: 37.23% Mortality: 0%	The study found more adverse events in the palifermin group, including serious issues related to various systems such as blood, cardiac, gastrointestinal, immune, infections, injuries, investigations, metabolism, musculoskeletal, neoplasms, nervous system, psychiatric, renal, respiratory, and vascular disorders	74
NCT00131638 (2016) Amgen	Head & Neck Cancer	• Drug: Palifermin • Radiation: 60 or 66 Gy respectively, at 2 Gy/fraction and five fractions per week	Phase 3 N: 241 Arm A (Placebo) - N:92 Arm B (Palifermin) - N:63	• Allocation: Randomized • Intervention Model: Parallel	Arm A: LTS: 34.5 months Arm B: LTS: 24.7 months	Arm A: AE: 97.00% SAE: 42.00% Mortality: 25% Arm B: AE: 97.00% SAE: 50.00% Mortality: 25%	Palifermin exhibited an acceptable safety profile in this study. However, innovative administration schedules of Palifermin and its integration into modern radiation treatment techniques could further elucidate the clinical relevance of these findings.	75

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Clinical trial number/ Study site	Cancer type & conditions	Interventions	Phase of clinical study/sample size	Study design	Efficacy	Toxicity/ Mortality (%)	Remarks	Reference
NCT00041665 (2013) Amgen	• Stomatitis • Oral mucositis	• Drug: Recombinant Human Keratinocyte Growth Factor • Radiation: Total-body irradiation was administered in 6, 8, or 10 fractions over a period of 3 or 4 days, commencing on day 8. The total dose delivered was 12 Gy.	Phase 3 N: 212 Arm A (Placebo) - N:106 Arm B (Palifermin) - N:106	• Allocation: Randomized • Intervention Model: Parallel	Arm A: PFS at 12 months: 0.73 (95 per cent confidence interval, 0.64 to 0.82) Arm B: PFS at 12 months: 0.69 (95 per cent confidence interval, 0.60 to 0.78)	Arm A: AE: 100.00% SAE: 98.00% Mortality: 0% Arm B: AE: 100.00% SAE: 63.00% Mortality: 0%	The administration of 60 µg of palifermin per kilogram per day was correlated with reductions in both the duration and severity of debilitating oral mucositis. However, assessing this risk necessitates ongoing long-term follow-up. Notably, palifermin and placebo demonstrated nearly identical progression-free survival rates at 12 months.	75
NCT00109031(2013) Swedish Orphan Biovitrum, Amgen	Lymphoma & leukaemia	• Drug: Palifermin; Cyclophosphamide Etoposide; • Others: Placebo • Radiation: Total Body Irradiation	Phase 3 N: 47 Arm A (Palifermin 60 µg/kg for 3 Days) - N:11 Arm B (Palifermin 180 µg/kg on Day -1) - N:10 Arm C (Palifermin 180 µg/kg on Day -2) - N:14 Arm D (Palifermin 180 µg/kg on Day -3) - N:12	• Allocation: Randomized • Intervention Model: Parallel	Number of Participants Without Severe Oral Mucositis (WHO Grade 3 and 4): Arm A: Efficacy: 18.18% Arm B: Efficacy: 30.00% Arm C: Efficacy: 69.23% Arm D: Efficacy: 25.00%	Arm A: AE: 90.00% SAE: 10.00% Mortality: 0% Arm B: AE: 90.91% SAE: 27.27% Mortality: 0% Arm C: AE: 92.31% SAE: 30.77% Mortality: 0% Arm D: AE: 100.00% SAE: 8.33% Mortality: 0%	In the palifermin group, the incidence of oral mucositis of World Health Organization (WHO) grade 3 or 4 was 63 per cent. The median duration of oral mucositis of WHO grade 3 or 4 in this group was 3 days, with a range from 0 to 22 days.	75

PFS, progression-free survival; OS, overall survival; CR, complete response; nCR, near complete response; MST- median survival time; EFS, event free survival; LTS, long term survival; AE, adverse event; SAE, serious adverse event; NR, not Reported

bringing these agents to clinics: Incorporating new therapeutic approaches, such as radioprotectors, into clinical practice presents a host of challenges that necessitate strategic navigation. While radioprotectors hold promise in mitigating the adverse effects of radiation therapy and improving treatment outcomes, their adoption in clinics faces numerous hurdles, from concerns surrounding safety and efficacy to regulatory complexities and market dynamics; the path to integrating radioprotective agents into routine clinical care is fraught with obstacles. To ensure the successful translation of research innovations into real-world clinical applications, healthcare providers and researchers can work together to address various challenges in effectively utilizing these agents along with advanced and precision-based radiation therapies.

The figure shows how combining advanced techniques (proton therapy, CIRT, IMRT, SRS) with radioprotectors (amifostine, BIO 300, entolimod) improves tumour targeting, reduces toxicity, enhances radiosensitivity, and minimises side effects for better patient-centred care.

To expedite the translation of radioprotectors and mitigators, the Radiation Research Program and SBIR Development Center within the National Cancer Institute issued four requests for proposals (RFPs) from 2010 to 2013[100]. Through the SBIR programme, four contracts and 11 grants were funded for the development of novel radioprotectors. Overall, 50 per cent of the companies (6 out of 12) successfully advanced their investigational drugs into prospective clinical trials in cancer patients[100]. Therefore, their development and application in clinical settings are of great importance and continue to be the subject of ongoing research.

Many radioprotectors require intravenous administration, which is less convenient and more invasive compared to oral administration. This limits patient compliance and ease of use in outpatient settings. The interaction between radioprotectors and the tumour microenvironment, as well as the immune niche, is not well understood. Without robust data, clinicians are hesitant to adopt these agents widely. Additionally, contemporary radiotherapy practice involves using altered fractionation strategies like extreme hypofractionation (SRS and SBRT). These approaches are at a higher risk of causing severe toxicities. The role of radioprotectors in these settings is crucial, but their effectiveness in reducing toxicity in these high-risk scenarios is not well established. This uncertainty hampers their adoption in clinical protocols involving extreme fractionation schedules. Radioprotectors have not shown effectiveness in protecting against the most severe radiation-induced toxicities, particularly in serial organs such as the brain and spinal cord. These organs are highly sensitive to radiation, and damage can lead to serious and often irreversible complications. The inability of radioprotectors to mitigate these severe toxicities limits their perceived value in clinical practice. A few challenges are briefly described below for better understanding.

The integration of radioprotectors into clinical radiotherapy offers significant potential to mitigate normal tissue damage and enhance patient outcomes, yet their adoption faces substantial challenges, including safety concerns, limited efficacy in modern radiotherapy techniques, clinician skepticism, and regulatory and commercial barriers. These hurdles necessitate strategic approaches to facilitate the translation of radioprotective agents into routine clinical practice. Collaborative efforts among researchers, clinicians, regulatory agencies, and industry partners, supported by increased research funding, public-private partnerships, robust clinical trials, regulatory guidance, education, and market incentives, can address these challenges. Supplementary table II[101-111] summarizes key challenges in radioprotector use in cancer radiotherapy and corresponding strategies to overcome them, providing a framework for advancing their clinical integration.

Radioprotective agents hold immense promise in improving the therapeutic ratio of radiotherapy by minimizing normal tissue toxicity without compromising tumour control. By implementing these strategies and fostering collaboration among radiobiologists and clinical radiation oncologists, it is possible to overcome the challenges associated with translating radioprotectors and mitigators to clinics. Through collective efforts and commitment to advancing radiation safety and patient care, radioprotectors can become valuable platforms in enhancing the effectiveness and safety of radiation therapy for cancer patients. A key concern among clinicians is the potential for radioprotectors to inadvertently shield tumour tissue from radiation, thereby compromising treatment efficacy. However, clinical evidence supports that the use of radioprotectors such as amifostine does not compromise tumour control in patients undergoing radiotherapy. For example, a pivotal phase III randomized trial in head and neck cancer demonstrated

that while amifostine significantly reduced acute and chronic xerostomia, there was no significant difference in local-regional control, disease-free survival, or overall survival between patients receiving amifostine and those who did not, indicating preservation of antitumourefficacy[104]. Meta-analyses of randomized controlled trials further confirm that amifostine does not confer a tumour protective effect, as no significant differences were observed in complete or partial tumour response rates when compared to placebo or observation groups. Additionally, multiple clinical studies have concluded that amifostine does not reduce the efficacy of radiotherapy against tumours, although the statistical power of individual studies may limit the ability to detect very small differences in tumour control. These findings collectively provide reassurance that, when used appropriately, amifostine selectively protects normal tissues without shielding tumour cells from the effects of radiation.

Radioprotective agents through ongoing research, clinical validation, and responsible integration hold immense promise in improving the therapeutic ratio of radiotherapy. By minimising normal tissue toxicity without compromising tumour control, they represent a critical step towards more effective, personalized, and patient centred cancer care.

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