

# Radioprotective countermeasures for radiation injury (Review)

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**Abstract.** A series of physiological and pathological changes occur after radiotherapy and accidental exposure to ionizing radiation (IR). These changes cause serious damage to human tissues and can lead to death. Radioprotective countermeasures are radioprotective agents that prevent and reduce IR injury or have therapeutic effects. Based on a good understanding of radiobiology, a number of protective agents have achieved positive results in early clinical trials. The present review grouped known radioprotective agents according to biochemical categories and potential clinical use, and reviewed radiation countermeasures, i.e., radioprotectors, radiation mitigators and radiotherapeutic agents, with an emphasis on their current status and research progress. The aim of the present review is to facilitate the selection and application of suitable radioprotectors for clinicians and researchers, to prevent or reduce IR injury.

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## 1. Introduction

Ionizing radiation (IR) refers to energy released by atoms in the form of particles (neutrons,  $\alpha$  or  $\beta$  particles) or electromagnetic waves (X- or  $\gamma$ -rays), which is sufficient to ionize atoms or molecules (1). Exposure to IR from these sources, including natural and artificial radiation, can have lethal consequences (2,3). The effects of IR are divided into deterministic effects, such as acute radiation sickness and radiation cataracts, and stochastic effects, such as radiation-induced cancer and genetic diseases (4). Even low-dose IR can cause DNA damage, and produce free radicals and reactive oxygen, causing DNA and protein damage, which can result in cell death, teratogenesis or carcinogenesis (5,6).

Exposure to IR can lead to chemical bond breaks or a variety of other chemical genetic modifications that can cause damage to biological macromolecules, particularly DNA, resulting in biochemical and biological cascade reactions. IR-induced DNA damage includes single-strand breaks and double-strand breaks (DSBs) (7-9), nucleotide base damage, glycosyl damage and DNA cross-linking, with DSBs being the most serious. DNA damage can activate a series of cellular DNA damage response signals, which control cell cycle arrest, DNA repair and cell fate. It can lead to serious consequences, such as cell death, chromosomal aberrations and genomic instability (Fig. 1). Furthermore, DNA damage followed by abnormal repair and genetic mutations is an important link in the development of tumors (8,10). Therefore, there is an urgent need to identify effective countermeasures against the harmful effects of IR.

## 2. Strategies to reduce radiation injury

IR countermeasures protect organisms against the harmful effects of IR and reduce tissue damage (11). Based on the time of administration relative to IR exposure, countermeasures against radiation injury are classified as radioprotectors, radiation mitigators or therapeutics (12-15). No radioprotective agent is both non-toxic at an effective dosage and capable of protecting normal cells from IR damage while maintaining the radiosensitivity of tumor cells.

IR-induced injury can be prevented using chemical compounds, biological agents, Chinese herbal extracts or cellular therapy (16,17). These measures reduce or improve radiation-induced tissue damage, and thus promote rehabilitation. Radioprotective countermeasures are radioprotective agents that prevent and reduce IR injury, or have therapeutic effects. The mechanism of action of radioprotective agents varies, yet the most common protective mechanism involves scavenging free radicals and enhancing DNA repair, thereby inhibiting oxidation and protecting cells.

In the present review, the radioprotective mechanisms, and clinical and preclinical applications, of radioprotectors, radiation mitigators and radiation therapeutic agents are summarized and discussed. Known radioprotective agents were grouped according to biochemical categories and potential clinical use, and radiation countermeasures, i.e., radioprotectors, radiation mitigators and radiotherapeutic agents, were described as was their probable mechanism of action (Figs. 2 and 3). These measures, and the main emerging therapies, are listed in Tables I and II.

#### *Radioprotectors in clinical use*

**Amifostine (AMF).** AMF is a United States Food and Drug Administration-approved selective normal tissue radioprotector that can be hydrolyzed and dephosphorylated to active N-(2-mercaptoethyl)-1,3-propanediamine by cell membrane-bound alkaline phosphatases, the sulfhydryl structure of which scavenges oxygen free radicals from tissue (18,19). Treatment with AMF during radiotherapy for lung cancer can reduce the incidence of severe radiation pneumonitis by 16%. AMF is mainly used to prevent radiotherapy-induced mucositis, dry mouth, dysphagia, pulmonary fibrosis and pneumonia (20-26). In previous studies, AMF selectively protected healthy cells against the harmful effects of radiotherapy, whereas cancer cells remained radiosensitive (27,28). However, AMF has a narrow therapeutic index, is administered intravenously and is toxic. AMF needs to be administered intravenously before radiotherapy; however, the drug is rapidly cleared from blood circulation, which cannot protect the gut. Furthermore, AMF is easily metabolized and sensitive to gastric acid, making direct oral administration an obstacle (19,29,30). Recently, it has been reported that a research team has produced orally available SP@AMF (31), which can prevent intestinal damage caused by radiation and prolong the survival period without affecting tumor regression in mice. Therefore, radioprotectors with oral administration, high efficacy, low toxicity and a long duration of action are needed.

**Benzydamine.** Benzydamine is a nonsteroidal anti-inflammatory drug that can inhibit the inflammatory factors TNF- $\alpha$  and IL-1 $\beta$ , and has antipyretic and analgesic effects (32-37). Radiotherapy-induced oral mucositis (RTOM) refers to inflammation of the oral mucosa caused by radiotherapy, which accounts for 80% of the complications from head and neck tumor radiotherapy. Benzydamine mouthwash has been reported to reduce RTOM pain in radioactive oral mucositis (38). In patients receiving radiotherapy, benzydamine oral rinse significantly reduced the rate of RTOM (32). Epstein *et al* (33) reported that benzydamine oral rinse

reduced the rate of RTOM triggered by a high radiotherapy dose. Thus, benzydamine is recommended for the prevention and treatment of RTOM with simple radiotherapy for head and neck tumors in moderate doses.

**Glutamine.** Glutamine plays an important role in reducing radiotherapy side effects and improving body tolerance to radiotherapy (39-41). Radiotherapy kills cancer cells as well as normal cells in the body, especially intestinal mucosa cells, which can cause nausea, vomiting, diarrhea and other symptoms in patients receiving radiotherapy. A number of clinical studies have confirmed that glutamine is helpful in the repair of intestinal mucosa after radiotherapy and has significant effects on preventing and relieving adverse symptoms in patients with radioenteritis (41-44). An animal experiment showed that adding glutamine to feed could reduce acute radiation damage to intestinal mucosa structures and improve the antioxidant capacity of radiation-damaged animals (45). Similarly, the preventive effect of glutamine on acute radioesophagitis has been confirmed in several clinical trials (46-48). IR-induced enteritis was decreased by compound glutamine capsules. It has also been reported that the use of glutamine in patients receiving radiotherapy for breast cancer can significantly reduce the incidence of radiation injury (49). Therefore, taking compound glutamine capsules during radiotherapy can effectively prevent and improve the symptoms of radiation enteritis and esophagitis. Moreover, the combined supplementation of  $\beta$ -hydroxy- $\beta$ -methylbutyrate, L-glutamine and L-arginine improved radiation-induced acute intestinal damage (50). Therefore, glutamine has an important protective effect for patients receiving radiotherapy and can improve the immune function of the body.

**Pentoxifylline (PTX).** PTX is a methyl xanthine derivative with anti-inflammatory, immunomodulatory and vascular effects (51-53). PTX can be used for the treatment of delayed skin changes, such as skin fibrosis and necrosis caused by radiotherapy. It is usually combined with vitamin E after breast resection and reconstruction. It can also be used in the conservative treatment of radioactive bone necrosis (54). PTX can also decrease the risk of radiation-induced oral mucositis after oral administration. In an experimental pilot study, PTX suppressed TNF receptor upregulation and neuronal responsiveness in patients with RTOM (55). Similarly, radiotherapy combined with PTX and vitamin E reduced the incidence of severe oral mucositis and dysphagia after adjusting for age (56). Therefore, PTX treatment should be considered for radiodermatitis and radiation-induced mucositis.

**Statins.** Statins are used to lower lipid levels (57), and can ameliorate IR-induced inflammation and fibrotic remodeling (16,58). Statins have been found to reverse radiation-induced gene expression disorders such as p53. p53 is closely associated with radiosensitivity and radiation-induced cell death; notably, statins can target the p53-controlled mevalonate pathway, thereby reducing the risk of cancer (59,60). The IR-induced expression of proinflammatory and profibrotic marker genes was revealed to be attenuated by statins *in vitro* and *in vivo* (61-63). These effects were mediated by the attenuation of Rho signaling. Ostrau *et al* (64) reported that lovastatin

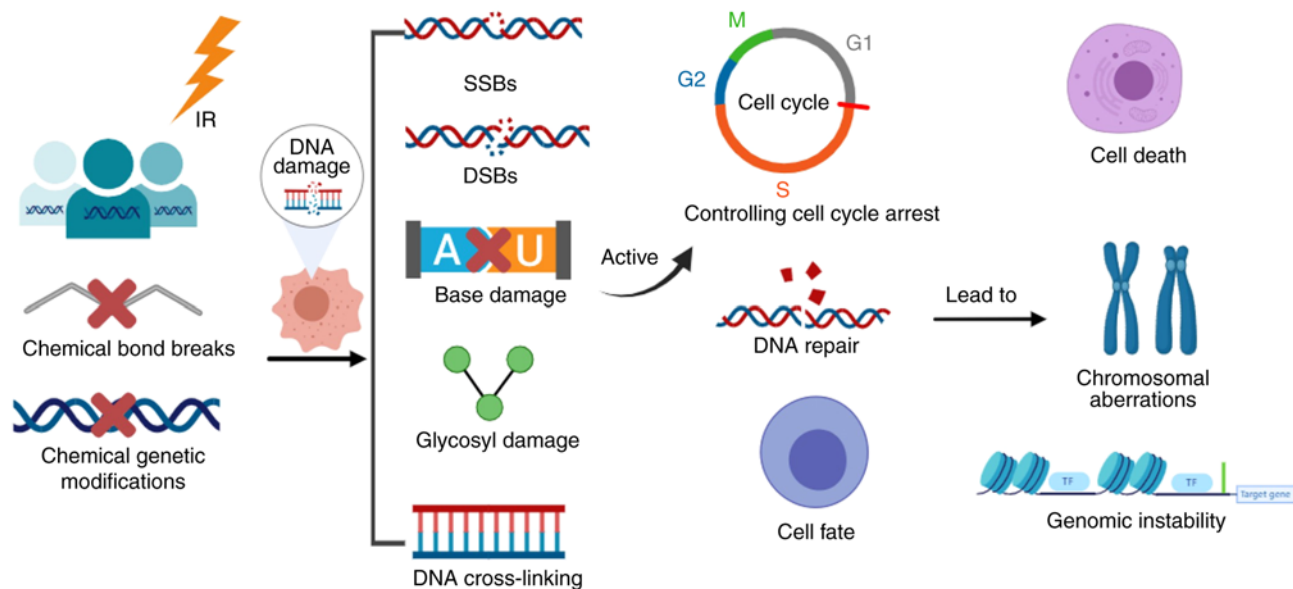


Figure 1. Pathway of radiation response. IR, ionizing radiation; SSBs, single-strand breaks; DSBs, double-strand breaks. The figure was generated using online drawing software tools (<https://www.medpeer.cn>).

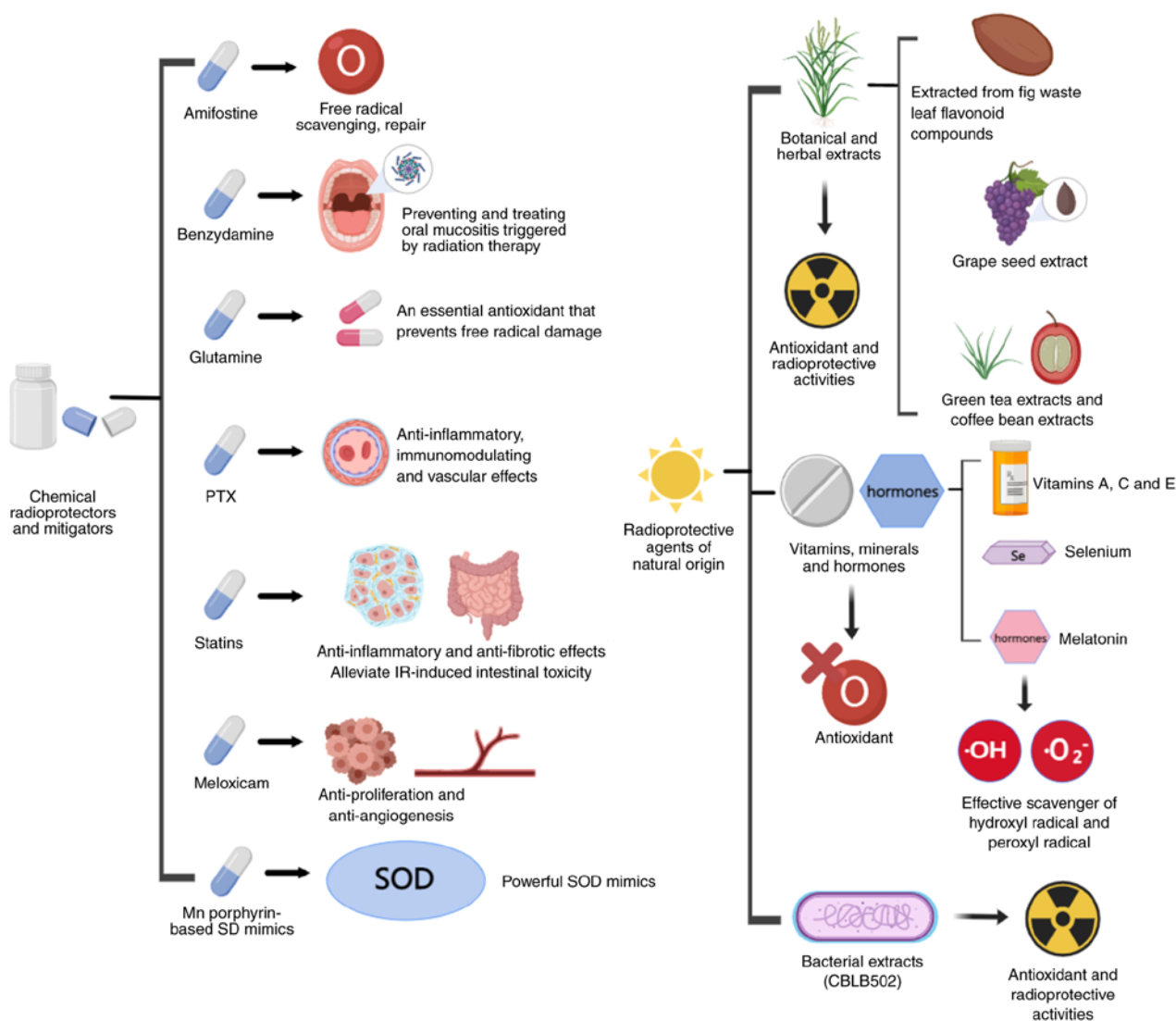


Figure 2. Main radioprotectors or mitigators, and their probable mechanism of action. PTX, pentoxifylline; SOD, superoxide dismutase; Mn, manganese. The figure was generated using online drawing software tools (<https://www.medpeer.cn>).

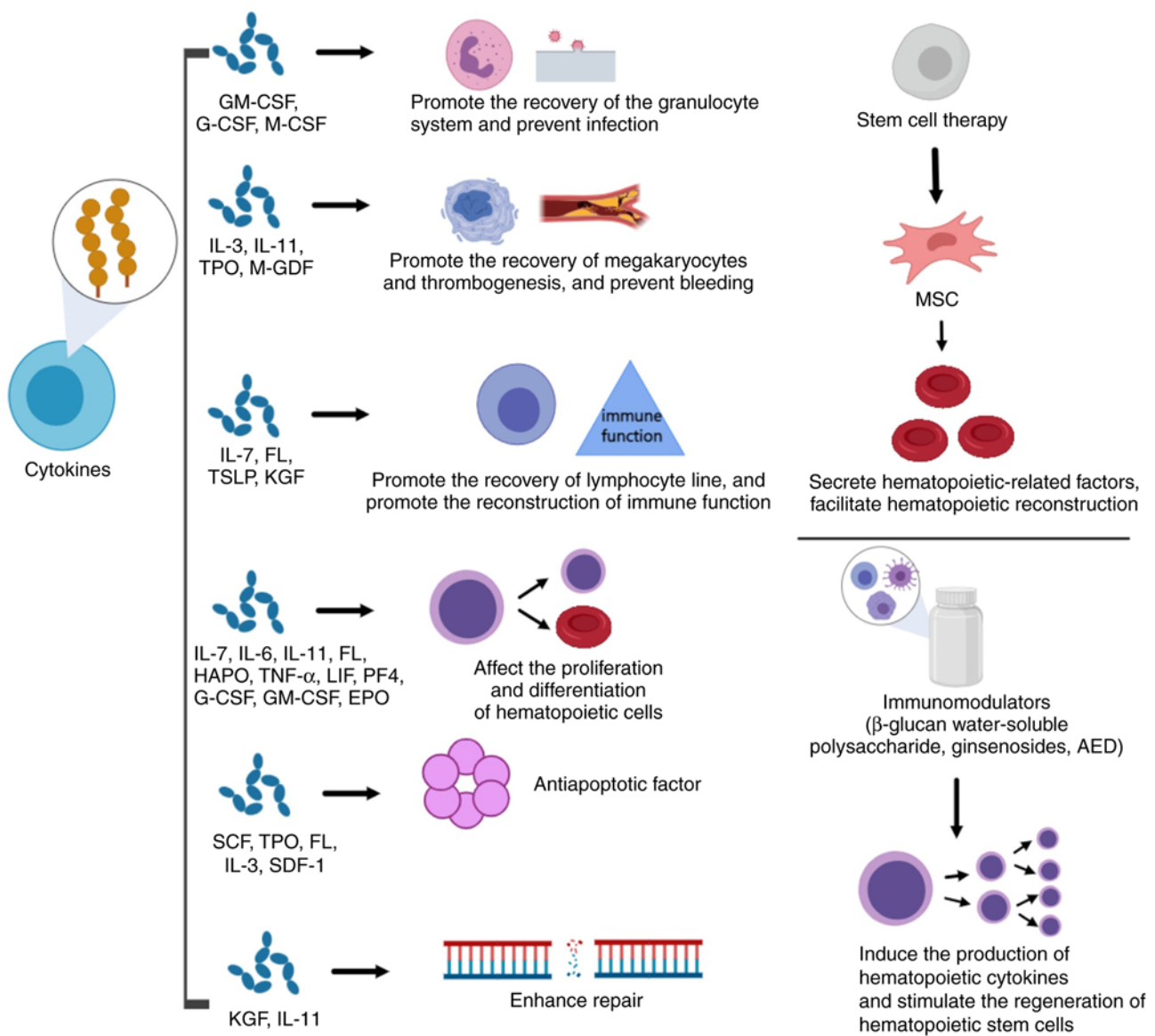


Figure 3. Main radiation treatment agents, along with their probable mechanism of action. GM-CSF, granulocyte-macrophage colony stimulating factor; G-CSF, granulocyte colony stimulating factor; M-CSF, macrophage colony stimulating factor; IL, interleukin; TPO, thrombopoietin; M-GDF, megakaryocyte growth development factor; FL, Flt-3 ligand; TSLP, thymic stromal lymphopoietin; KGF, keratinocyte growth factor; HAPO, hemangiopoietin; LIF, leukemia inhibitory factor; PF4, platelet factor 4; EPO, erythropoietin; SCF, stem cell factor; SDF-1, stromal cell-derived factor-1; MSC, mesenchymal stem cell; AED, 5-androstenone. The figure was generated using online drawing software tools (<https://www.medpeer.cn>).

showed tissue-specific anti-inflammatory and anti-fibrotic effects *in vivo*. Furthermore, simvastatin and pravastatin alleviated IR-induced intestinal toxicity by inhibiting Rho-ROCK signaling (65,66). Wedlake *et al* (67) demonstrated that statins reduced IR-induced acute gastrointestinal symptoms in a group of patients receiving pelvic radiotherapy, and showed long-term protective effects. However, while oral administration of simvastatin was shown to improve hematopoietic damage and gastrointestinal dysfunction caused by radiation in male mice, it worsened radiation-induced symptoms in female mice, which was related to sex-specific differences in gut flora (68). This suggests that using statins for treatment may be sex-specific. Based on these pleiotropic effects, especially on IR-induced intestinal toxicity, statins have potential as radioprotectors and mitigators for IR-induced injuries. In addition, statins can prevent radiation-induced heart disease. It

was found that statins can inhibit activation of the transcription factor NF-κB during the acute response period after normal tissue exposure to radiation, and can significantly reduce TGF-β1, ROCK I and phosphorylated-Akt expression, thereby ameliorating radiation-induced cardiac fibrosis (69).

**Carbamazepine (CBZ).** CBZ is an inducer of autophagy, which has been approved for the clinical treatment of bipolar disorder, trigeminal neuralgia and epilepsy (70). The safety of CBZ for patients with a variety of diseases has led to it being considered for radiation protection in humans. CBZ administration prior to radiation has been shown to increase hematopoietic cell survival and autophagy (71). However, despite its radioprotective and mitigative effects in normal murine tissue *in vitro* and *in vivo*, CBZ did not exert such effects in human cells *in vitro*. In addition, no reduction in side effects was observed

Table I. List of main radioprotectors or mitigators along with the probable mechanism of action.

Type	Example	Mechanism of action	Limitations	(Refs.)
Chemical radioprotectors and mitigators			Most of them have low potency, short time of action, high toxicity and severe side effects (hypotension, vomiting, flushing)	
	Amifostine	Free radical scavenging, DNA repair		(18-31)
	Benzydamine	Preventing and treating oral mucositis triggered by radiation therapy		(32-37)
	Glutamine	An essential antioxidant that prevents free radical damage		(39-50)
	Pentoxifylline (PTX)	Anti-inflammatory, immunomodulating and vascular effects		(51-56)
	Statins			
	Lovastatin	Anti-inflammatory and anti-fibrotic effects		(64)
	Simvastatin and pravastatin	Alleviate IR-induced intestinal toxicity		(65-66)
	Carbamazepine (CBZ)	Further research is needed		(70-73)
	Meloxicam	Anti-proliferation and anti-angiogenesis		(74-78)
	Metformin	Reducing tumor stem cells, and suppressing proliferation and hypoxia		(79-85)
	Mn porphyrin-based SD mimics	Powerful SOD mimics		(86)
	Redox nanoparticles	Free radical scavenging		(87-89)
	Toll-like receptors	Inhibits apoptosis and improves cell survival		(90-102)
	S1P	Promotes survival		(100,103-106)
Radioprotective agents of natural origin			Only <i>in vitro</i> and animal experiments have been performed, no clinical validation	
Botanical and herbal extracts	Extracted from fig waste leaf flavonoid compounds	Strong antioxidant activity		(111,112)
	Grape seed extract	High antioxidant and free radical-scavenging capabilities		(107)
	Green tea extracts and coffee bean extracts	Certain radioprotective effects		(108,113)

Table I. Continued.

Type	Example	Mechanism of action	Limitations	(Refs.)
Vitamins, minerals and hormones	Vitamins A, C and E, and selenium	Antioxidant		(114-119)
	Melatonin	Effective scavenger of hydroxyl radical and peroxy radical		(120,121)
Bacterial extracts	Recombinant polypeptide derived from <i>Salmonella flagellin</i> (CBLB502)	Antioxidant and radioprotective activities		(92,122-125)

GM-CSF, granulocyte-macrophage colony stimulating factor; G-CSF, granulocyte colony stimulating factor; M-CSF, macrophage colony stimulating factor; IL, interleukin; TPO, thrombopoietin; M-GDF, megakaryocyte growth development factor; FL, Flt-3 ligand; TSLP, thymic stromal lymphopoietin; KGF, keratinocyte growth factor; HAPO, hemangiopoietin; LIF, leukemia inhibitory factor; PF4, platelet factor 4; EPO, erythropoietin; SCF, stem cell factor; SDF-1, stromal cell-derived factor-1; MSC, mesenchymal stem cell; AED, 5-androstenone.

in patients on CBZ for radiotherapy of trigeminal neuralgia, head-and-neck cancer or lung cancer (72,73).

**Meloxicam.** Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). It is a selective inhibitor of cyclooxygenase-2 (COX-2), with anti-proliferative and anti-angiogenic effects, and is beneficial in alleviating gastrointestinal toxicity and improving radiation tolerability (74-76). Meloxicam can be used as a radioprotector in the mandible of irradiated rats. In addition, a single dose of meloxicam administered 1 h after a lethal radiation dose can achieve an increased survival rate of 30 days; however, it has been reported to be ineffective to administer meloxicam 24 h after lethal exposure (75). Intercellular adhesion molecule-1 (ICAM-1) and COX-2 are known factors involved in causing myocardial infarction after radiation exposure and were previously reported to be elevated after radiation exposure (77). According to Uehara *et al* (78), meloxicam somewhat upregulated radiation-induced expression of ICAM-1 and COX-2, i.e., the synergistic effect of NSAIDs with radiation was found, which would be a limitation of the clinical application of meloxicam.

**Metformin.** Metformin is a biguanide used for the treatment of type II diabetes. Previously, it has been report that metformin can exert radiosensitivity and radioprotective effects, and it can enhance the radiation response by reducing tumor stem cells, and suppressing proliferation and hypoxia (79-82). Additionally, metformin may prevent IR-induced esophageal carcinoma invasion and metastasis (83).

*In vitro* studies have shown, when administered 2 h before irradiation, metformin increased the expression of the BCL2 gene, and reduced the expression of BAX and CASP3 genes, thereby suppressing IR-induced apoptosis (84,85). Therefore, metformin has potential as a novel radioprotector against IR-induced apoptosis.

#### Emerging radioprotectors

**Manganese (Mn) porphyrin-based superoxide dismutase (SOD) mimics.** Mn porphyrins are powerful SOD mimics

that have radioprotective effects in the lung, prostate and brain (86). Lead Mn porphyrins, namely MnTE-2-PyP5+ (BMX-010, AEOL10113), MnTnBuOE-2-PyP5+ (BMX-001) and MnTnHex-2-PyP5+, have entered clinical trials for glioma, head and neck cancer, anal cancer and multiple brain metastases, as well as for radioprotection of normal tissues during cancer radiotherapy (86).

**Redox nanoparticles.** Low-molecular-weight (LMW) nitroxide compounds have potential as radioprotectors or mitigators. Among the various nitroxide radicals, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl (4-amino-TEMPO, also known as tempamine or NH2-TEMPO), had the highest radioprotective efficacy *in vitro* (87,88). Feliciano *et al* (89) reported that a novel nanoparticle-based radioprotective agent, NH2-TEMPO-containing redox nanoparticles, had good bioavailability and low toxicity. Most LMW compounds have extremely poor bioavailability, impairing their therapeutic efficacy and limiting their clinical use; therefore, their conversion into redox nanoparticles can effectively remove radiation-induced reactive oxygen species (ROS), with characteristic long-term bioavailability and extended tissue residence time.

**Toll-like receptors (TLRs).** TLRs are pattern recognition receptors, which have been studied extensively in radiation protection in recent years (90-98). TLR2, TLR5 or TLR9 agonists have been shown to inhibit radiation-induced apoptosis and improve cell survival (91-93). The TLR4 agonist lipopolysaccharide has been reported to protect IR-induced bone marrow damage and reduce the mortality of mice after irradiation (94). The TLR5 ligand CBLB502 has been shown to serve a radioprotective role in mouse and rhesus monkey models of bone marrow, gut and reproductive damage (95,96). A novel TLR9 agonist containing synthetic immunomodulatory CpR (R=2'-deoxy-7-dezaguanosine) dinucleotide and 3'-3'-attached novel structures can also protect mice from radiation-induced gastrointestinal syndrome (97). There is growing clinical evidence that radiotherapy combined with



Table II. List of main radiation treatment agents along with the probable mechanism of action.

Type	Example	Mechanism of action	Limitations	(Refs.)
Stem cell therapy	MSC	Secrete hematopoietic-related factors, facilitate hematopoietic reconstruction	Occurrence of severe GvHD	(127-152)
Cytokines		Regulate immune, nerve and endocrine function; participate in inflammation; promote wound healing; regulate hematopoiesis	Combination of cytokines needs further study	
	GM-CSF, G-CSF, M-CSF	Promote the recovery of the granulocyte system and prevent infection		(129)
	IL-3, IL-11, TPO, M-GDF	Promote the recovery of megakaryocytes and thrombogenesis, and prevent bleeding		(129)
	IL-7, FL, TSLP, KGF	Promote the recovery of the lymphocyte line, and promote the reconstruction of immune function		(129)
	IL-3, IL-6, IL-11, FL, HAPO, TNF- $\alpha$ , LIF, PF4, G-CSF, GM-CSF, EPO	Affect the proliferation and differentiation of hematopoietic cells		(153)
	SCF, TPO, FL, IL-3, SDF-1	Antiapoptotic factor		(153)
Immuno-modulators	KGF, IL-11	Enhance repair		(154)
	$\beta$ -glucan water-soluble polysaccharide, ginsenosides, AED	Induce the production of hematopoietic cytokines and stimulate the regeneration of hematopoietic stem cells	Proinflammatory response and immunogenicity; long-term use may cause allergies and organ damage	(159-161)

GvHD, graft-vs. -host disease; GM-CSF, granulocyte-macrophage colony stimulating factor; G-CSF, granulocyte colony stimulating factor; M-CSF, macrophage colony stimulating factor; IL, interleukin; TPO, thrombopoietin; M-GDF, megakaryocyte growth development factor; FL, Flt-3 ligand; TSLP, thymic stromal lymphopoietin; KGF, keratinocyte growth factor; HAPO, hemangiopoietin; LIF, leukemia inhibitory factor; PF4, platelet factor 4; EPO, erythropoietin; SCF, stem cell factor; SDF-1, stromal cell-derived factor-1; MSC, mesenchymal stem cell; AED, 5-androstenone.

new TLR agonists targeting TLR3, TLR7/8 or TLR9, in addition to protecting normal tissues from radiation and sensitizing cancer cells to ionizing radiation, may enhance antitumor immunity. Mechanistic studies have shown that TLR agonists can enhance dendritic cell-mediated T-cell initiation after radiotherapy, in some cases leading to the production of systemic antitumor immunity and immune memory (98-102). Additionally, it has been reported that one of the protective mechanisms of gut flora against radioactive intestinal injury is resistance through the TLR signaling pathway. Bacterial

DNA binding TLR9 act as radiation protection by activating the transcription factor NF- $\kappa$ B. In addition to gut flora, this mechanism is also applicable to oral microorganisms (90), which supports the protection against radiotherapy-induced oral mucositis. Furthermore, activation of the TLR9 pathway protected against IR-induced intestinal injury (90,99). These findings suggested that activating the TLR signaling pathway may have significant radioprotective effects, indicating that TLRs have great advantages as a new target for radiation protection.

*Sphingosine 1-phosphate (S1P)*. S1P increases the likelihood of human cell survival by activating the phosphoinositide 3-kinase/AKT and mitochondrion-dependent pathways (100,103). Nitzsche *et al* (104) showed that S1P can maintain blood perfusion and microvascular patency in ischemic penumbra. Moreover, S1P and its analogs (FTY720/fingolimod) preserved testicular and ovarian function and fertility in IR-exposed animals and humans (105,106).

*Radioprotective agents of natural origin*. Some of the aforementioned chemical radioprotective agents are unsuitable for clinical use because of their toxicity and adverse side effects. Therefore, effective radioprotective agents with low toxicity have become a focus of research.

*Botanical and herbal extracts*. Some botanical and herbal plants, such as black tea extract, have radioprotective properties (107-110). Flavonoid compounds extracted from fig leaf exert strong antioxidant effects by removing superoxide anion and hydroxyl free radicals (111,112). Moreover, they significantly reduced the levels of ROS and malondialdehyde, and increased catalase, SOD and glutathione peroxidase activities in MC3T3-E1 mouse calvaria-derived preosteoblast cells. In another study (107), the blood samples of subjects who received 100, 300, 600 or 1,000 mg grape-seed extract were subjected to 1.5 Gy of X-ray radiation. The grape-seed extract reduced IR-induced DNA damage, exhibiting high antioxidant and free radical-scavenging effects. Furthermore, green tea and coffee bean extracts are reported to exert radioprotective effects (108,113).

*Vitamins, minerals and hormones*. Vitamins A, C and E, and selenium, are antioxidants that act as radioprotective agents (114). Dietary vitamin A in soybean oil can prevent the internal radiation-induced biological effects of radionuclides in mice (115). Vitamins C and E can reduce chromosome breakage in human lymphocytes by scavenging ROS, thus protecting against internal radiation damage caused by the radionuclide iodine-131 (116-118). Vitamin E, alone or in combination with WR-3689 [S-2((3-methylaminopropyl)amino)ethylphosphorothioic acid], increased the survival rate of IR-exposed mice (118). Selenium can also protect against free radical-induced damage. Selenium reversed the effects of IR on spermatogenesis in mice, thereby reducing damage to the testicles (119). Melatonin, a hormone produced by the pineal gland can scavenge hydroxyl radicals and peroxy radicals to exert a radioprotective effect (120,121).

*Bacterial extracts*. Some bacterial species are resistant to radiation (122). A recombinant polypeptide from *Salmonella flagellin* (CBLB502) exhibited high radioprotective efficacy in mice and primates (92). In addition, an extracellular polysaccharide from the radiation-resistant bacterium *Deinococcus* showed antioxidant and radioprotective activities *in vitro* (123). *Lactobacillus rhamnoides GG* has been reported to protect the intestinal epithelium from radiation damage by releasing lipophosphate, promoting macrophage activation and the migration of mesenchymal stem cells (124). Furthermore, another study (125) reported that intestinal microorganisms are the primary regulators against radiation

damage and protect the hematopoietic and gastrointestinal systems, among which *Psilocytilae* and *Enterococcaceae* and their downstream metabolites (propionate and tryptophan) have the greatest defense. The study suggests that microbial metabolites can protect against radiation damage; therefore, bacterial extracts have potential as radioprotective agents.

*Radiation therapeutic agents*. IR affects hematopoietic tissues, and significantly reduces the number of neutrophils and platelets. The resulting decrease in the number of peripheral blood cells can cause sepsis, bleeding, anemia and, in some cases, death (126). Therefore, radiation therapeutics aim to promote the recovery of hematopoietic function. At present, acute radiation sickness is treated clinically using biological agents, such as cytokines and mesenchymal stem cells (MSCs), modulate normal immune system function (127) and the secretion of hematopoietic growth factors, and promote reconstruction of the hematopoietic microenvironment (128). Biological agents have advantages such as low immunogenicity, and ease of transfection and expression of exogenous genes. Therefore, they are used to treat IR-induced injury (129). Table II lists the main radiation therapeutic agents along with the probable mechanism of action.

*Stem cells*. MSCs originate in the embryonic mesoderm and are the most important stem cells in the bone marrow matrix. MSCs are capable of multidirectional differentiation and immune regulation (127). MSCs secrete a variety of hematopoiesis-related factors, such as interleukin (IL)-6, Flt-3 ligand (FL), stem cell factor (SCF), granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF), making up for IR-induced deficiencies in cytokines. Therefore, MSCs can repair IR-induced damage to bone marrow stromal cells and the hematopoietic microenvironment. In addition, MSCs have hematopoietic support functions in bone marrow. The described characteristics of MSCs render them important therapeutics for IR-induced injury (130-132).

Liu *et al* (133) reported that MSCs promote recovery of hematopoietic function. Additionally, MSCs can inhibit T-cell activation and proliferation by secreting cytokines, growth factors and receptors. Co-transplantation of MSCs and hematopoietic stem cells into recipient bone marrow has been shown to prevent and reduce graft-versus-host disease (GvHD) (134). MSCs exhibit ectopic differentiation and block distal microvessels and other inherent defects (135). Further research will likely lead to the development of more effective and safer MSC-based therapeutics for IR-induced injuries.

Numerous studies and clinical trials have shown that MSCs have a significant effect on wound recovery from radiation burns (136-138). For the first time, stem cells were transplanted into a patient with deep skin burns and it was revealed that the patient exhibited faster healing. In addition, paracrine factors from stem cells used to treat local radiation burns in rats, can lead to increased skin regeneration and decreased leukocyte infiltration. Furthermore, Wharton's jelly-derived-MSC-derived conditioned medium (MSC-CM) (139) was revealed to be effective for the treatment of IR-induced skin wounds in rats, suggesting that MSC-CM could serve as the basis of novel cell-free treatments for radiation dermatitis.



For radiation-shock trauma, stem cells have been shown to enhance the response of the body to infection and improve chronic diseases, such as osteomyelitis and osteoarthritis that radiation-shock trauma can induce (140). In addition, compartment syndrome and segmental bone defects can also be treated with stem cell transplantation (141,142).

For treating acute radiation syndrome, hematopoietic stem cell transplantation can be used to rebuild hematopoietic functions, which attracted attention after the 1999 Tokaimura nuclear accident in Japan. Furthermore, MSCs can promote the implantation of hematopoietic stem cells and prevent the occurrence of GvHD (143), thus improving patient survival. In addition, a number of studies have shown that MSCs have a good tissue repair effect on the gastrointestinal tract, lung injury and burn-burn complex injury caused by radiation (144-146).

Radiation cataracts are also a serious complication caused by IR, and Maleki *et al* (147) showed that umbilical cord MSCs can be induced by the vitreous to differentiate into lens fibroblasts, thus providing the possibility for treatment of cataracts. In 2016, the Zhongshan University Eye Hospital used endogenous stem cells to regenerate new lenses *in situ*, successfully restoring complete vision to children with congenital cataracts (148).

Radiation exposure can also cause IR-induced xerostomia, which is a permanent side effect of radiotherapy for head and neck cancer that damages the large salivary glands (149-151). A clinical trial (152) of 33 patients with xerostomia caused by radiotherapy for oropharyngeal squamous cell carcinoma evaluated the long-term safety of injecting autologous adipose tissue-derived MSCs/stromal cells into the mandibular glands. The results showed that this therapy was safe and beneficial for IR-induced dry mouth-related symptoms.

In summary, MSC-based stem cell therapy has been used in a variety of radiation-induced diseases as an effective post-radiation disease treatment strategy and has played an important role in clinical practice.

**Cytokines and immunomodulators.** Cytokines regulate immune, nerve and endocrine function; participate in inflammation; promote wound healing; and regulate hematopoiesis. Some cytokines have marked effects on IR-induced injuries (129). Several cytokines promote recovery of granulocytes and prevent infection (129), such as GM-CSF, G-CSF and macrophage colony-stimulating factor, whereas others promote recovery of megakaryocytes and thrombogenesis, and prevent bleeding, such as IL-3, IL-11, thrombopoietin (TPO) and megakaryocyte growth development factor. Other cytokines promote lymphocyte-mediated recovery of immune function, such as IL-7, FL, thymic stromal lymphopoietin and keratinocyte growth factor (KGF). Some cytokines are involved in early differentiation, namely IL-3, IL-6, IL-11, FL, hemoangiopoietin, TNF- $\alpha$ , leukemia inhibitory factor and platelet factor 4, whereas others act on the anaphase of differentiation (e.g., G-CSF, GM-CSF and erythropoietin). Cytokines with antiapoptotic effects include SCF, TPO, FL, IL-3 and stromal cell-derived factor-1 (153). Finally, some cytokines promote tissue repair and ameliorate multiple organ dysfunction syndrome, such as KGF and IL-11 (154). However, cytokines are pleiotropic, i.e., they exert varying biological effects

on different target cells; for example, IL-11 can effectively promote the recovery of gastrointestinal mucosa (153). Certain cytokines interact with other cytokines, forming a complex cytokine network *in vivo*. Therefore, blocking or promoting one cytokine may affect the activities of other cytokines. Some cytokines increase sensitivity to IR when used alone, such as tumor growth factor- $\beta$ , IL-6 and TNF- $\alpha$  (155-157). These cytokines must be used in combination with other cytokines. Therefore, further research is needed to identify the optimum combinations of cytokines for the treatment of IR injury.

Immunomodulators are not cytokines but induce the production of hematopoietic cytokines and stimulate the regeneration of hematopoietic stem cells. Cytokine release stimulates the growth, differentiation and proliferation of hematopoietic progenitor cells and stem cells. Therefore, immunomodulators are important therapeutics for IR-induced injury. Based on its immunopharmacological effect,  $\beta$ -glucan water-soluble polysaccharide has been used to modulate the host immune response (158). Glucan can increase the number of endogenous multifunctional hematopoietic stem cells in irradiated mice (159). Ginsenosides have also been shown to stimulate the production of IL-1 and IL-6. Administration of 100 mg/kg ginsenoside 24 h before  $\gamma$ -ray irradiation significantly increased the survival rate of mice, as well as the numbers of bone marrow cells, spleen cells, peripheral blood neutrophils, lymphocytes and platelets, and the GM-CFC level (160). The dehydroepiandrosterone derivative 5-androstenone has been reported to stimulate the synthesis of IL-1, IL-3 and IL-6 to promote recovery of the irradiated hematopoietic system in mice (161).

**Gene therapy.** There is much interest in gene therapy for radiation protection (162,163). At present, gene therapy for IR-induced injury typically involves growth factor and free radical inhibitor genes, to inhibit apoptosis and enhance damage repair (163). In addition, gene transfer vectors, multiple gene combinations and targeted specific gene therapy can be used to prevent harmful effects of IR. SOD, CAT, snail homolog 2, multidrug resistant gene 1, IL-3, KGF and erythropoietin have been evaluated in preclinical models regarding their radioprotective potential (164). Zhang *et al* (165) reported that IR-induced SOD2 overexpression increased the radiosensitivity of HT-29 colon cancer cells and prevented IR induced damage to normal colon (CCD841) cells.

### 3. Conclusion

Radiation exposure events occur occasionally, yet increasing numbers of patients are undergoing radiotherapy for tumors, which can have severe side effects. The present review discussed the clinical potential of radioprotectors, radiation mitigators and radiation therapeutic agents.

The ideal radioprotective agent would exert a protective effect when administered before or after IR exposure, prevent or repair IR-induced tissue damage, have a rapid onset of action and long half-life, be administered orally, and be resistant to the deleterious effects of IR and high temperatures. However, at present, most radioprotective agents with marketing approval or in clinical trials are administered intravenously. Accidental radiation exposure occur occasionally, yet increasing numbers

of patients are undergoing radiotherapy for tumors, which can have severe side effects. The present review discussed the clinical potential of radioprotectors, radiation mitigators and radiation therapeutic agents. This review may help to provide improved ideas and application value for clinical radiological protection.

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## Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

LCL prepared and drafted the manuscript. LCL, ZZL and SMM searched the relevant literature and revised the manuscript. LL and XDL critically reviewed the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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