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Advances in Radioprotectors: Enhancing Radiation Protection and Improving Treatment Outcomes

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ABSTRACT: Radiation exposure poses significant risks to human health and the environment, necessitating the development of effective strategies to mitigate its adverse effects. Radioprotectors, mitigators, and candidate agents represent promising approaches for enhancing radiation protection by either preventing or alleviating radiation-induced damage. This review paper comprehensively analyses the radioprotectors, mitigators, and candidate agents in radiation protection, covering their mechanisms of action, effectiveness, and potential applications. By synthesizing the latest research findings and technological advancements, this review elucidates the role of these agents in safeguarding human health and promoting radiation safety across various fields.

Keywords: Radiation, Radioprotector, Mitigator, Environment, Radiation-Exposure-

I. INTRODUCTION

Ionizing radiation, whether from medical procedures, nuclear accidents, or environmental sources, poses significant risks to human health and the environment [1].While traditional approaches to radiation protection focus on physical shielding and safety protocols, radioprotectors, mitigators, and candidate agents offer complementary strategies for mitigating the adverse effects of radiation exposure. Radioprotectors aim to prevent or reduce radiation-induced damage by enhancing cellular resilience and mitigating oxidative stress, DNA damage, and inflammatory responses [2]. Mitigators, however, focus on alleviating the symptoms and consequences of radiation exposure by promoting tissue repair, modulating immune responses, and reducing radiation-induced toxicities [3]. Candidate agents represent novel compounds or therapeutic interventions under investigation for their potential radioprotective or mitigative effects. This review explores the mechanisms of action, effectiveness, and potential applications of radioprotectors, mitigators, and candidate agents in radiation protection. It highlights their role in safeguarding human health and promoting radiation safety across various fields.

Radioprotectors aim to prevent or reduce the harmful effects of ionizing radiation on living organisms by enhancing cellular resilience and reducing radiation-induced damage [4]. These agents exert their effects through various mechanisms, including free radical scavenging, DNA repair enhancement, and modulation of cellular signaling pathways [5]. Notable radioprotectors include antioxidants, such as vitamins C and E, polyphenols, flavonoids, and thiols, which neutralize reactive oxygen species (ROS) and also prevent the oxidative damage to some cellular components. DNA repair enhancers, such as amifostine and dexrazoxane, facilitate the repair of radiation-induced DNA lesions and maintain genomic integrity. Furthermore, biological response modifiers, such as cytokines, growth factors, and immunomodulators, enhance immune responses and promote tissue repair and regeneration following radiation exposure [6]. Radioprotectors have shown promise in mitigating the acute and long-term effects of radiation exposure in various experimental models and clinical settings, including cancer radiotherapy, nuclear accidents, and space travel.

Radiation mitigatorsaim to alleviate the symptoms and consequences of radiation exposure by promoting tissue repair, modulating immune responses, and reducing radiation-induced toxicities [7]. These agents may act through various mechanisms, anti-inflammatory, anti-fibrotic, and anti-apoptotic effects, to mitigate the pathological changes associated with radiation-induced damage [8]. Anti-inflammatory drugs like corticosteroids & NSAIDs reduce inflammation & edema.Growth factors such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), which suppress inflammatory responses and reduce tissue inflammation and edema. Additionally, growth factors like granulocyte colony-stimulating factor (G-CSF) and keratinocyte growth factor (KGF),

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promote tissue repair and regeneration following radiation-induced injury[9]. Moreover, radio mitigators may include antioxidants, immunomodulators, and radioprotective peptides that target specific cellular pathways involved in radiation-induced damage and tissue injury.**Table 1** represents various radioprotector/mitigators and their target sites [10].Mitigators have shown promise in alleviating the acute as well as late effects or consequences of radiation exposure in different preclinical models and clinical scenarios, including acute radiation syndrome, radiation dermatitis, and radiation-induced fibrosis.

Candidate agents represent novel compounds or therapeutic interventions under investigation for their potential radioprotective or mitigative effects. These agents may include natural compounds, synthetic molecules, biologics, or combination therapies that target specific pathways involved in radiation-induced damage and tissue injury. Notable candidate agents include botanical extracts, such as ginseng, ginkgo biloba, and aloe vera, which exhibit antioxidant, anti-inflammatory, and immunomodulatory properties that may confer radioprotective or mitigative effects [11]. Furthermore, synthetic molecules, such as radioprotective peptides, radiomimetic compounds, and radiation-responsive nanoparticles, are being developed to target specific cellular pathways and mitigate the consequences of radiation exposure [12]. Moreover, combination therapies involving multiple candidate agents or synergistic combinations of natural and synthetic compounds are being investigated to enhance their efficacy and broaden their therapeutic applications [13]. Candidate agents hold promise as future therapeutics for radiation protection, pending further preclinical and clinical evaluation of their safety and effectiveness.

Mechanism of Radiation Injury and Repair

The DNA damage response (DDR) to double-strand DNA breaks (DSBs) plays a critical role in both the acute as well as late effects of radiation exposure, including acute radiation syndrome (ARS) and late tissue damage [14].

In the context of acute radiation syndrome (ARS), which manifests shortly after high-dose radiation exposure, the DDR is activated as a cellular defense mechanism against the extensive DNA damage caused by ionizing radiation. When DSBs occur, sensor proteins such as ATM (ataxia telangiectasia mutated) and DNA-PK (DNA-dependent protein kinase) are activated and initiate a signaling cascade. This cascade leads to the phosphorylation of various downstream targets, including histone H2AX (forming γ-H2AX) and checkpoint kinases (CHK1 and CHK2). These phosphorylation events serve to amplify the DDR signal and recruit repair factors to the sites of DNA damage [15].

In the acute phase of ARS, the DDR primarily aims to repair damaged DNA and maintain cellular homeostasis. If the DNA damage is severe and overwhelms the repair competence of the cell, DDR signaling pathways may trigger cell cycle arrest at checkpoints to allow time for repair or induce apoptosis if the damage is irreparable. Thus, the DDR plays a crucial role in determining cell fate following radiation exposure, influencing the severity of ARS.

In addition to its role in the acute phase, the DDR also contributes to the late effects of radiation exposure, which can manifest months to years after the initial exposure. Chronic DDR activation and incomplete or erroneous repair of DSBs can lead to genomic instability, mutations, and aberrant cellular responses, ultimately contributing to late tissue damage, fibrosis, organ dysfunction, and carcinogenesis. Persistent activation of DDR signaling pathways may also promote chronic inflammation and oxidative stress, further exacerbating tissue damage and increasing the risk of late radiation-induced complications [16].

Overall, the DDR to DSBs is a central mechanism underlying both effects of radiation exposure i.e. acute and late. Understanding the dynamics of DDR activation and its implications for cellular responses to radiation injury is essential for developing strategies to mitigate acute radiation syndrome and minimize the long-term consequences of radiation exposure on human health [17].

Table 1: List of radioprotector or mitigator agents and their target sites [18].

Target site	Agent name	Type of the agents
Lung	TGF-β3	Protein
Bone marrow; GI system	γ-Tocotrienol (GT3)	Small-molecule of vitamin E isomer
Bone marrow	Genistein	Small-molecule;soyisoflavone

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Salivary glands mucosa	Amifostine	Small-molecule; thiol
Oral and esophageal mucosa	Palifermin	Protein; keratinocyte growth factor
Bone marrow	Tetracycline	Small-molecule;antibiotic
Kidney protector, bone marrow, lung	Captopril	Small-molecule; anti-hypertensive drug
GI system	R-spondin1	Protein;intestinal cell mitogen
GI system	Bone marrow stromal cells	Cellular therapy

Amifostine as a radioprotector: Amifostine, also known as ethyol or WR-2721, is a cytoprotective agent that has been extensively studied for its radioprotective properties [19]. It is the sole radioprotective drug endorsed by the U.S. Food and Drug Administration (FDA) for specific clinical applications. Radiation therapy is a standard treatment modality for cancer, but it can be responsible for damage in healthy tissues surrounding the tumor site, leading to acute and late toxicities [20]. Amifostine, a thiol compound, has been investigated as a radioprotector to reduce the side effects of radiation therapy by selectively protecting normal tissues from radiation-induced damage. Amifostine exerts its radioprotective effects through multiple mechanisms, including scavenging free radicals, enhancing DNA repair, and modulating cellular signaling pathways[21].Amifostine is converted to its active form, WR-1065, by alkaline phosphatase, WR-1065 acts as a potent scavenger of free radicals [22]. WR-1065 can neutralize reactive oxygen species (ROS) generated by ionizing radiation and by reducing the oxidative stress as well as in DNA damage in normal tissues[23]. Amifostine can efficiently repair radiation-induced DNA lesions by stimulating DNA repair mechanisms like base excision repair (BER) as well as non-homologous end joining (NHEJ). Furthermore, Amifostine may modulate the pathways of cellular signaling, i.e. nuclear factor kappa B (NF-κB) pathway, to suppress inflammation and apoptosis in irradiated tissues.Clinical studies have shown that Amifostine reduces acute and late toxicities associated with radiation therapy in various cancer types. Common acute toxicities, such as mucositis, xerostomia, and dermatitis, can be significantly reduced by the administration of Amifostine prior to radiation treatment [24]. Moreover, long-term follow-up studies have shown that Amifostine can mitigate late toxicities by protecting normal tissues from chronic radiation damage, such as fibrosis, necrosis, and secondary malignancies. Amifostine has been particularly beneficial in those patients who undergoes the radiation therapy for head and for neck cancer, where preserving salivary gland function and oral mucosa integrity is critical for maintaining quality of life [25].

The FDA has approved Amifostine for use as a radioprotector in certain clinical settings, such as head and neck cancer and ovarian cancer, where radiation-induced toxicities can significantly impact treatment outcomes[26].However, its use is associated with potential side effects, including hypotension, nausea, and vomiting, which may limit its tolerability and compliance. Furthermore, the optimal dosing and administration schedule of Amifostine remains under investigation, as well as its efficacy in combination with the modern radiation techniques, i.e. intensity-modulated radiation therapy (IMRT) and proton therapy [27]. Further research efforts should focus on the optimization use of amifostine as a radioprotector, to explore its potential in other types of cancer, and developing novel bioformulations or some delivery methods to enhance its efficacy and to reduce side effects.

Palifermin, is a type ofrecombinant human keratinocyte growth factor (KGF), has emerged as a potential radioprotector in radiation therapy [28]. Its cytoprotective properties, have sparked interest in using it to reduce radiation therapy side effects, notably in patients undergoing cancer treatment, including hematopoietic stem cell transplantation. Palifermin exerts its radioprotective effects primarily through activating the KGF receptor (KGFR) on epithelial cells, particularly in mucosal tissues[29]. Upon binding to KGFR, palifermin stimulates proliferation, differentiation, and migration of epithelial cells, leading to the regeneration and repair of damaged mucosal surfaces. Additionally, palifermin has been shown to modulate inflammatory responses and promote the production of mucin, a protective barrier against radiation-induced damage. By enhancing the resilience of mucosal tissues to radiation, palifermin mitigates the severity as well as duration of radiation-induced mucositis and improves patient tolerance to treatment.

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Palifermin has been studied extensively in clinical trials as a radioprotector in patients undergoing hematopoietic stem cell transplantation and high-dose chemotherapy with total body irradiation (TBI) for treating the hematologic malignancies[30]. Clinical studies have demonstrated that palifermin administration before conditioning regimens can significantly reduce the incidence or severity of oral mucositis and esophagitis, improving patient outcomes and reducing treatment-related morbidity. Moreover, palifermin has shown promise in reducing the duration of hospitalization, the need for parenteral nutrition, and the risk of infectious complications in transplant recipients.

The effectiveness of palifermin as a radioprotector has been supported by multiple randomized controlled trials and meta-analyses, which have consistently shown its ability to lower the severity and duration of radiation-induced mucositis in various clinical settings. Moreover, palifermin has been well-tolerated with minimal adverse effects, including transient skin rash, pruritus, and erythema, which are generally mild and self-limiting [31]. However, caution should be exercised in patients with a history of malignant transformation in the target tissues or pre-existing inflammatory conditions, as palifermin may exacerbate tumor growth or inflammation.

Superoxide dismutase (SOD), a key enzyme in antioxidant defense systems, has emerged as a promising candidate for mitigating radiation-induced damage [32]. SOD reduces the level of reactive oxygen species (ROS) generated by ionizing radiation by catalyzing the dismutation of superoxide radicals (O2-) into oxygen (O2) and hydrogen peroxide (H2O2). By scavenging superoxide radicals, SOD prevents the formation of highly reactive hydroxyl radicals (OH-) through the Fenton reaction, which are potent mediators of DNA damage, lipid peroxidation, and protein oxidation[33]. Additionally, SOD may modulate cellular signaling pathways involved in radiation-induced inflammation, apoptosis, and tissue repair, further contributing to its radioprotective effects. Various preclinical studies have demonstrated theradioprotective efficacy of SOD, including cultured cells, animal models, and ex vivo tissues. Administration of exogenous SOD or overexpression of endogenous SOD has been shown to attenuate radiation-induced DNA damage, lipid peroxidation, and pro-inflammatory cytokine production, leading to enhanced cell survival and tissue regeneration. Moreover, SOD has been effective in mitigating acute and late radiation toxicities in multiple organ systems i.e. skin, lungs, GI tract, and central nervous system.

Although the clinical translation of SOD-based radioprotection has been limited, preliminary studies have shown promising results in specific clinical settings. Topical application of SOD-containing formulations has been used to mitigate radiation-induced skin reactions in cancer patients undergoing radiotherapy, reducing erythema, desquamation, and pain. Moreover, SOD supplementation has been investigated as a supportive therapy to mitigate radiation-induced oral mucositis, lung injury, and neurotoxicity in cancer patients [34]. However, well-designed clinical trials are required to determine the safety, efficacy as well as optimal dosing regimens of SOD-based radioprotection in clinical practice.

Genistein, a naturally occurring isoflavone found in soybeans and other legumes, has attracted attention for its potential radioprotective properties. Genistein has multiple mechanisms of radioprotection, including scavenging ROS, modulating inflammatory responses, and enhancing DNA repair. As a potent antioxidant, genistein can neutralize free radicals generated by ionizing radiation, that reduces oxidative stress and DNA damage in irradiated tissues [35]. Moreover, genistein may inhibit the activation of pro-inflammatory cytokines, transcription factors involved in radiation-induced inflammation and tissue injury. Additionally, genistein has been shown to enhance the activity of DNA repair enzymes, such as poly(ADP-ribose) polymerase (PARP) and also ataxia telangiectasia mutated (ATM), leading to the efficient repair of radiation-induced DNA lesions. Various preclinical models have demonstrated genistein's efficacy as a radioprotector, including cultured cells, animal models, and ex vivo tissues [36]. Administration of genistein before or following irradiation has been shown to lower the severity and duration of radiation-induced toxicities, such as mucositis, dermatitis, pneumonitis, and gastrointestinal injury.

Genistein supplementation has been investigated as a supportive therapy to mitigate radiation-induced toxicities in cancer patients undergoing radiotherapy or hematopoietic stem cell transplantation. Moreover, genistein-containing formulations, such as topical creams or oral supplements, have been evaluated for their efficacy in reducing radiation-induced skin reactions and oral mucositis [37]. Additionally, well-designed clinical trials are necessary to establish the efficacy,

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safety and appropriate dosing regimens of genistein-based radioprotection in clinical practice.

Gamma-tocotrienol, a potent antioxidant and anti-inflammatory compound, has emerged as a promising candidate for protecting healthy tissues from radiation-induced damage [38]. Gamma-tocotrienol exerts its radioprotective effects through multiple mechanisms, including antioxidant, anti-inflammatory, and anti-apoptotic actions. As a potent antioxidant, gamma-tocotrienol scavenges free radicals generated by ionizing radiation, thereby reducing oxidative stress and DNA damage in irradiated tissues. Additionally, gamma-tocotrienol modulates inflammatory pathways and inhibits the production of pro-inflammatory cytokines, leading to the suppression of radiation-induced inflammation and tissue injury [39]. Moreover, gamma-tocotrienol has been shown to prevent radiation-induced apoptosis and promote cell survival through the activation of survival signaling pathways.

Various preclinical models have shown that gamma-tocotrienol is effective as a radioprotector, including cultured cells, animal models, and ex vivo tissues.

R-Spondin1 (RSPO1), is a type of secrete proteins that belongs to the R- Spondin family, has recently appeared as a potential radioprotector against the damaging effects of ionizing radiation [40]. RSPO1 exerts its radioprotective effects through multiple mechanisms, including stem cell activation, tissue regeneration, and modulation of inflammatory responses. As a potent activator of the Wnt/β-catenin signaling pathway, RSPO1 promotes the proliferation and survival of tissue-resident stem cells, thereby enhancing the regenerative capacity of irradiated tissues. Moreover, RSPO1 has been shown to modulate gene expression involved in DNA repair, antioxidant defense, and immune regulation, suppressing radiation-induced inflammation and tissue injury [41].

Preclinical studies have shown that RSPO1 is effective in protecting against radiation in different experimental models such as cultured cells, animal models, and ex vivo tissues. Administration of RSPO1 before or after irradiation has been shown to reduce the severity and duration of radiation-induced toxicities, such as mucositis, dermatitis, pneumonitis, and gastrointestinal injury. Moreover, RSPO1 has effectively enhanced the therapeutic index of radiation therapy by safeguarding normal tissues while sensitizing the tumor cells to radiation-induced cytotoxicity.

δ-Tocotrienol, with its potent antioxidant and anti-inflammatory properties, has emerged as a promising candidate for protecting normal tissues from radiation-induced damage. δ-Tocotrienol exerts its radioprotective effects through multiple mechanisms, including antioxidant scavenging, anti-inflammatory modulation, and DNA repair enhancement [42]. As a potent antioxidant, δ-tocotrienol scavenges free radicals generated by ionizing radiation, thereby reducing oxidative stress and DNA damage in irradiated tissues. Moreover, δ-tocotrienol modulates inflammatory pathways and inhibits the production of pro-inflammatory cytokines, suppressing radiation-induced inflammation and tissue injury. Additionally, δ-tocotrienol has been shown to enhance the DNA repair enzymes activity, poly(ADP-ribose) polymerase (PARP) and ATM kinase, facilitating the repair of radiation-induced DNA lesions [43].

Various experimental models have shown that δ-tocotrienol is effective as a radioprotector, including cultured cells, animal models, and ex vivo tissues. Administration of δ-tocotrienol before or after irradiation has been shown to reduce the severity and duration of radiation-induced toxicities, such as mucositis, dermatitis, pneumonitis, and gastrointestinal injury.

Radiation exposure poses significant risks to human health and the environment, necessitating the development of effective radiation protection strategies. Traditional approaches to radiation protection include shielding, time management, and distance from radiation sources. However, recent advancements in science and technology have led to new methodsoffering enhanced safety and mitigating radiation-induced damage.

II. CONCLUSION:

Radioprotectors, mitigators, and candidate agents represent promising approaches for enhancing radiation protection by either preventing or alleviating radiation-induced damage. These agents exert their effects through various mechanisms, including free radical scavenging, DNA repair enhancement, and modulation of cellular signaling pathways. While radioprotectors aim to prevent or reduce radiation-induced damage, mitigators focus on alleviating the symptoms and consequences of radiation exposure. Candidate agents represent novel compounds or therapeutic interventions under investigation for their potential

radioprotective or mitigative effects. By synthesizing the latest research findings and technological advancements, this review elucidates the role of radioprotectors, mitigators, and candidate agents in safeguarding human health and promoting radiation safety across various fields. Continued research, collaboration, and innovation in this area are essential for realizing the full potential of these agents and advancing the field of radiation protection.

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