

Review Article

Radiomodulators enhancing and protecting against radiation – A review

Mathivadhani M.S.¹, Priya Ramani², Gayathri.P.S.³, Pravin Dhas.M⁴

^{1,4}Post Graduate, ^{2,3}Professor & Head of the Department, Department of Oral Medicine and Radiology, Thai Moogambigai Dental College and Hospital, Golden George Nagar, Mogappair, Chennai, India

ABSTRACT:

Radiotherapy also known as radiation therapy is regarded as a treatment modality by using high energy rays or radioactive substances to treat malignant lesions. With the rapid advancement in the recent times the effort has been taken to improve the therapeutic effectiveness of radiation (cellular damage, inflammation leading to fibrosis are side effects of radiation). In order to optimize the effects of radiotherapy, a radio sensitizing agent increases susceptibility to radiation, whereas radio protective agents or medications help minimize the negative effects of radiation exposure. We should aim to lessen its effect on normal tissues. In this article, we will review the functions, uses and available compounds of radio sensitizers, radio protectors and radiation mitigators.

Key words: radiotherapy, radiation protection, radio protectors, radio sensitizers, radio mitigators

Received: 10 June, 2025

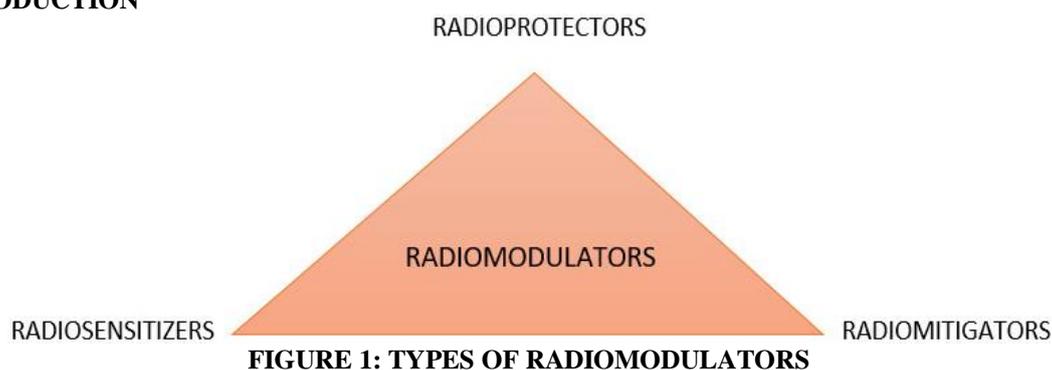
Accepted: 02 July, 2025

Published: 09 July, 2025

Corresponding author: Mathivadhani M.S, Post Graduate, Department of Oral Medicine and Radiology, Thai Moogambigai Dental College and Hospital, Golden George Nagar, Mogappair, Chennai, India

This article may be cited as: MS Mathivadhani, Ramani P, PS Gayathri, M Pravin D. Radiomodulators enhancing and protecting against radiation – A review. J Adv Med Dent Scie Res 2025; 13(7)48-54.

INTRODUCTION



The type of radiation—alpha, beta, gamma, ultra violet rays, etc.—determines the extent of harm to living cells.^[5] The first attempts to illustrate the harmful consequences of radiation date back to 1949. The goal of radiation protection is to minimize the negative effects of radiation on human health tissues while reducing needless radiation exposure.^[1] Numerous physical, biological, and clinical approaches have been studied to increase radiation's therapeutic efficacy. Radiation therapy therefore aims to minimize radiation damage to

healthy cells while increasing radiation damage to malignant cells.^[2, 3] During radiation, radio modulators help to increase the resistance of the body by adaptively shifting the effectiveness of anti-oxidative protection. They are classified into three, based on biological properties: Radio protectors, radio sensitizers and radio mitigators

RADIOPROTECTORS

Radio protectors are substances that are given before radiation therapy to prevent healthy cells from the

damaging effects of radiation.^[4, 5]Antioxidants are frequently used as chemicals or agents before to or during radiation therapy in order to avoid or lessen the immediate or delayed effects of damage to healthy tissues.^[6]Radio protecting agents can be classified into three groups: 1) radio protectors, 2) adaptogens and 3) absorbents.

CHARACTERISTIC OF IDEAL RADIOPROTECTORS^[7]

1. To be efficient in providing multifaceted protection
2. To avoid both acute and long-term direct as well as indirect effects on healthy tissue

3. It should be easily and comfortably administered without toxicity
4. It should cause no or minimal adverse effects on organism
5. The windowing time should be sufficiently long and effective after administration and also have a sufficiently long shelf life.
6. It should have an acceptable stability profile.
7. It should be compatible with the wide range of other drugs.
8. It shouldn't shield tumours from radiation or aid them.
9. It should be easily accessible and economical
10. Handling and transportation should be made easy.

MECHANISM OF RADIOPROTECTORS^[8,9]

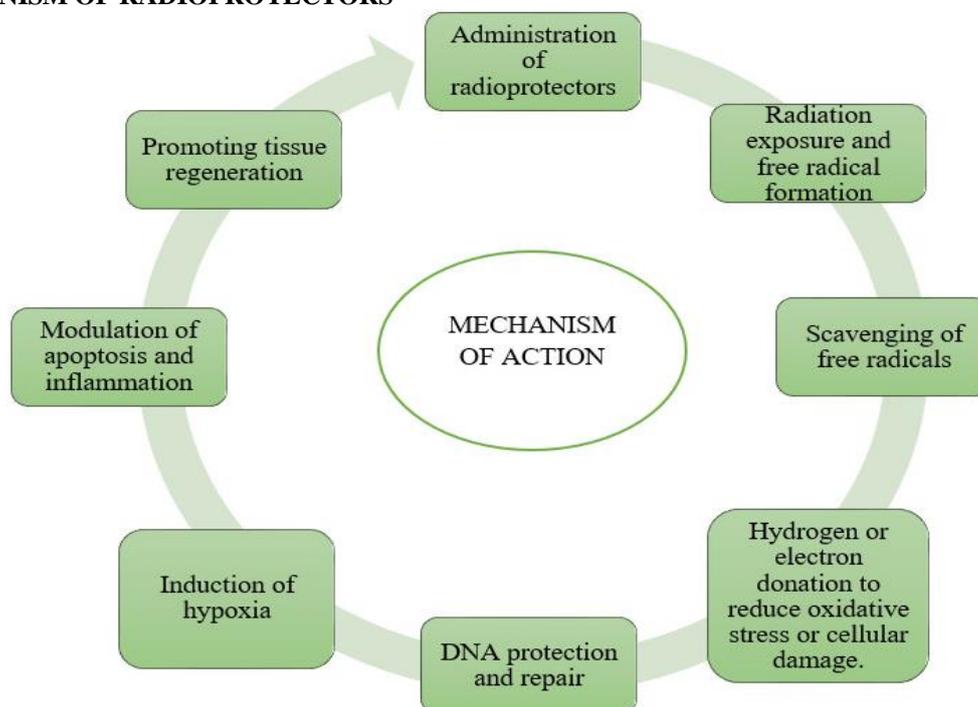


FIGURE 2: MECHANISM OF ACTION OF RADIOPROTECTORS

TABLE I. RADIOMODULATORS CATEGORIZED BY FUNCTION, MECHANISM, AND SOURCE

Category	Agent	Mechanism of Action	Source
Radioprotectors	Amifostine	Scavenges free radicals; protects normal tissues during radiotherapy	Synthetic thiol compound
	Filgrastim	Stimulates neutrophil production; mitigates hematopoietic and GI damage	Recombinant human cytokine
	Genistein	Antioxidant; scavenges free radicals; reduces oxidative stress and DNA damage	Isoflavone from soy
	Vitamin E	Reverses hematopoietic injury; modulates antioxidant response	Vitamin E isomer
	Curcumin	Anti-inflammatory; mitigates oxidative damage	Turmeric root
	EGCG	Enhances antioxidant enzymes; protects DNA; anti-apoptotic	Green tea
	Troloxerutin	Inhibits lipid peroxidation; enhances DNA repair mechanisms	Plant flavonoid

	Sesamol	Scavenges ROS; enhances DNA repair	Sesame oil
Adaptogens	Podophyllum hexandrum	Modulates DNA repair; inhibits topoisomerase	Medicinal herb
	Ocimum sanctum	Antioxidant; metal chelation; inhibits lipid peroxidation	Holy basil
	Hippophae rhamnoides	Reduces DNA damage; antioxidant activity	Sea buckthorn
	Tinospora cordifolia	Immunomodulatory; antioxidant activity	Ayurvedic herb
	Zingiber officinale	Anti-inflammatory; ROS scavenging	Ginger root
	Rhodiola rosea	Modulates stress response; reduces radiation-related fatigue	Arctic plant
Absorbents	Potassium Iodide	Stops radioactive iodine from being absorbed by the thyroid by filling it with stable iodine.	Inorganic salt
	Prussian Blue	Binds radioactive cesium and thallium; prevents GI absorption	Synthetic pigment
	Activated Charcoal	Adsorbs radioactive particles in the gastrointestinal tract	Carbon-based material
	Alginates	Binds radioactive strontium; reduces intestinal absorption	Seaweed-derived polymer

Footnotes:

ROS: Reactive Oxygen Species, **GI:** Gastrointestinal, **DNA :** Deoxyribonucleic Acid.

RADIO SENSITIZERS

Radio sensitizers are substances that make tumour cells more sensitive to radiation. At the molecular level, they encourage the fixation of radiation-induced free radicals. It also amplifies radiation's cytotoxic effects.^[10,11] Oxic cell radio sensitization, hypoxic cell radio sensitizers, and cytotoxic radio sensitizers are all considered radio sensitizing agents by this criteria.^[12,13]

CHARACTERISTICS OF IDEAL RADIO SENSITIZERS^[2]

1. Radio sensitizers should be non-toxic
2. It should increase cytotoxic effects of irradiation on cancer cells by accelerating DNA damage and producing free radicals
3. It should enlarge therapeutic window period
4. It should suppress antioxidant mechanism of defence or inhibit the repair of biomolecules
5. It should be economically affordable

MECHANISM OF ACTION^[14]

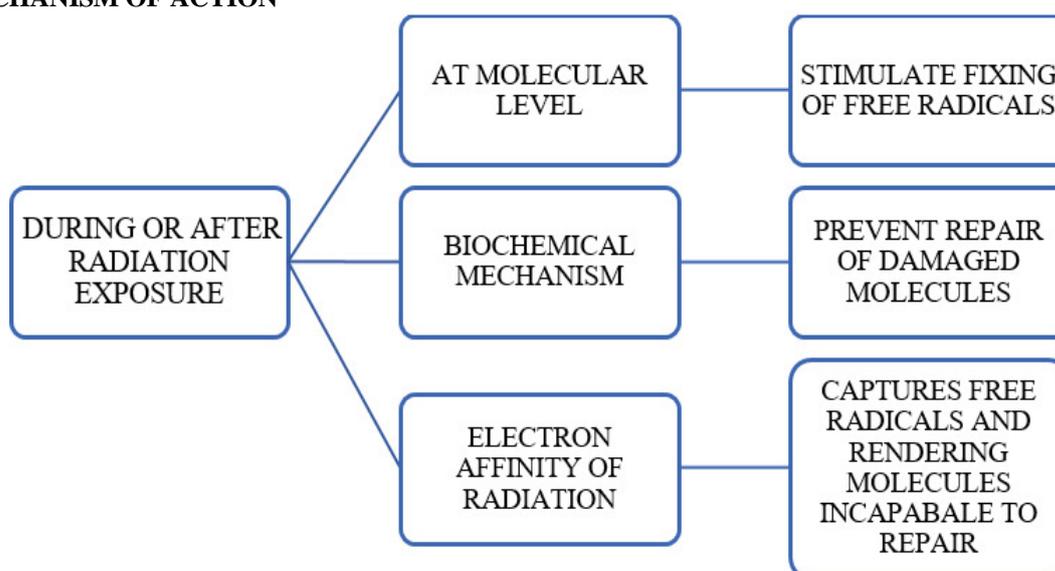


FIGURE 3: MECHANISM OF ACTION OF RADIOSENSITIZERS

CORE MECHANISM OF RADIOSENSITIZERS

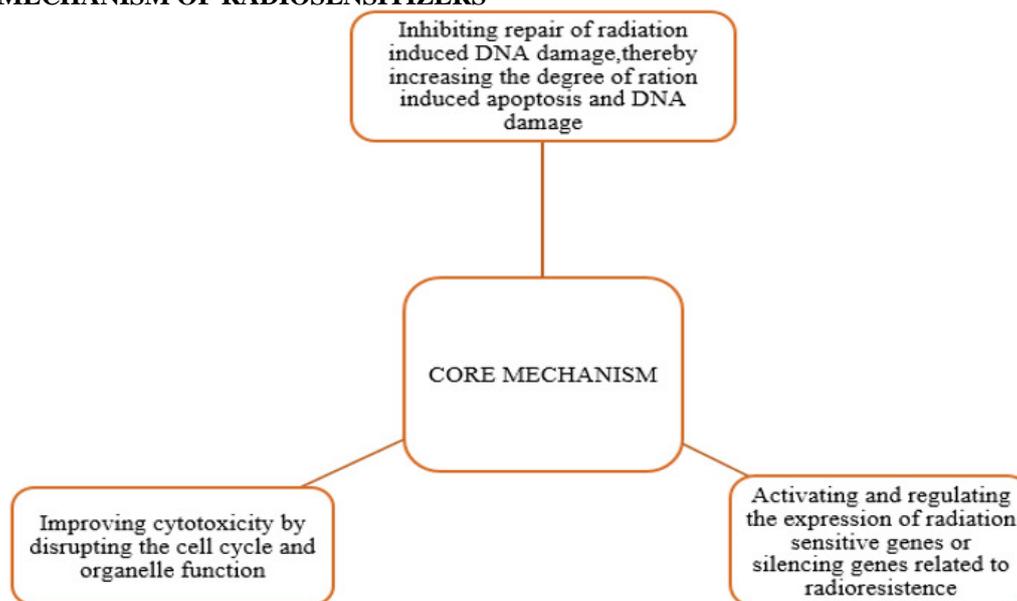


FIGURE 4: CORE MECHANISM OF ACTION OF RADIOSENSITIZERS

TABLE II: TABULATION ON VARIOUS RADIO SENSITIZERS BASED ON OXYGENATION STATUS AND MECHANISM OF ACTION

Category	Agent	Mechanism of Action
Hypoxic Radiosensitizer	Misonidazole	Mimics oxygen to stabilize radiation-induced DNA damage in hypoxic tumor environments
	Etanidazole	Electron-affinic agent; enhances ROS generation under hypoxia
	Nimorazole	Stabilizes radiation-induced DNA damage under hypoxic conditions
	RSU 1069	Bifunctional compound; causes DNA strand breaks in hypoxic cells
	Tirapazamine	Becomes selectively cytotoxic under hypoxia; amplifies radiation-induced damage
	Sanazole	Inhibits DNA repair mechanisms in hypoxic cells
Oxic Radiosensitizer	Cisplatin	Forms DNA crosslinks; augments radiation-induced DNA damage and inhibits repair
	5-Fluorouracil (5-FU)	Thymidylate synthase inhibitor; disrupts DNA synthesis and enhances radiosensitivity
	Gemcitabine	Incorporates into DNA; impairs post-radiation repair mechanisms
	Paclitaxel	Arrests cells in radiosensitive G2/M phase; stabilizes microtubules
	Docetaxel	Similar to paclitaxel; enhances mitotic arrest and radiosensitivity
	Cetuximab	Inhibits EGFR; prevents repair of radiation-induced DNA damage
Cytotoxic Radiosensitizer	Mitomycin C	DNA crosslinking agent; more effective in hypoxic environments
	Doxorubicin	Intercalates DNA; inhibits topoisomerase II; increases ROS-mediated cytotoxicity
	Actinomycin D	Binds DNA; inhibits RNA synthesis; enhances radiation response
	Bleomycin	Generates ROS; causes direct DNA strand breaks
	Vincristine	Disrupts microtubules; enhances radiation effects in some protocols

DNA: Deoxyribonucleic Acid, **RNA:** Ribonucleic Acid, **ROS:** Reactive Oxygen Species, **EGFR:** Epidermal Growth Factor Receptor

RADIOMITIGATORS

Radiomitigators are substances or chemicals that are used during or soon after radiation treatment or exposure to radiation in order to lessen the effects of radiation on healthy tissue before symptoms develop.^[3, 15] Concern has been raised about radiation-induced late normal tissue toxicity, which is different from radioprotectors. These may include vascular injury, tissue hypoxia, excessive extracellular matrix deposition, and mitotic cell death. The aim of radiation mitigators is to interrupt these cascades and

to intervene, prevent and reduce the expression of toxicity.

CHARACTERISTICS OF IDEAL RADIO MITIGATORS

1. Easy administration
2. It should protect normal sensitive tissues associated with toxicity.
3. It should be easily available
4. It should have no relevant toxicity.

MECHANISM OF ACTION ^[9, 16, 14]

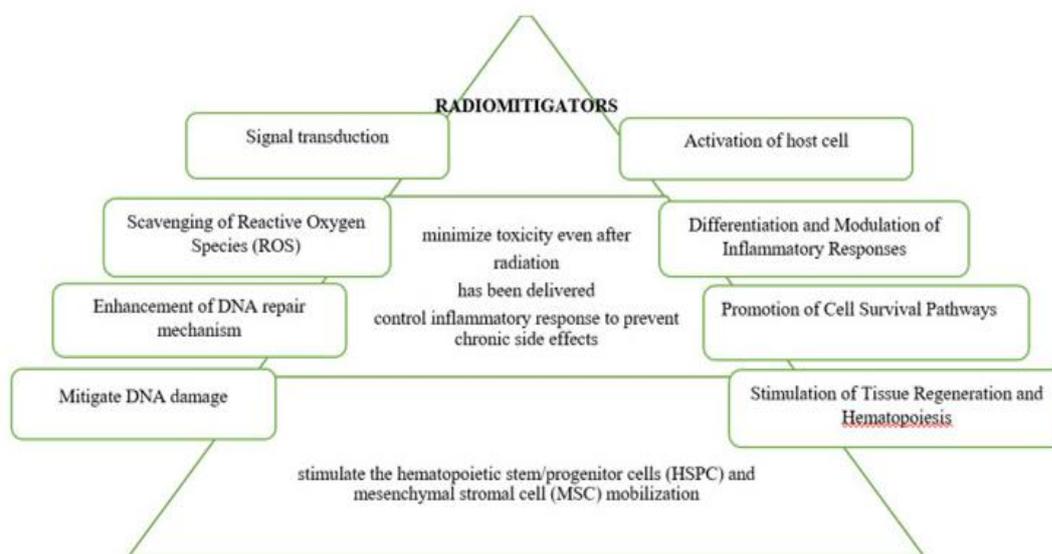
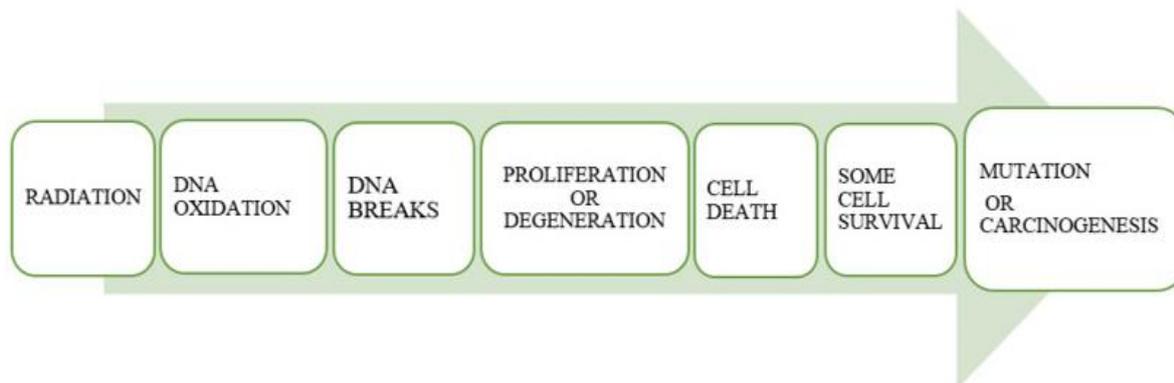


FIGURE 5: MECHANISM OF ACTION OF RADIO MITIGATORS

TABLE: 3 TABULATION ON VARIOUS RADIOMITIGATORS

Radiomitigator	Mechanism of Action	Source / Type
Filgrastim (G-CSF)	Stimulates granulocyte production; supports bone marrow recovery	Recombinant cytokine (biologic)
Pegfilgrastim	Long-acting G-CSF; enhances neutrophil regeneration	Recombinant biologic
Sargramostim (GM-CSF)	Stimulates macrophage and neutrophil recovery	Recombinant cytokine
Romiplostim	Thrombopoietin receptor agonist; promotes platelet formation	Peptibody biologic

Eltrombopag	increases the formation of platelets through TPO receptor agonism	Oral small molecule
5-Androstenediol (5-AED)	Stimulates hematopoiesis; boosts immune response	Endogenous steroid hormone
Meloxicam	Inhibits COX-2; reduces inflammatory and GI injury post-radiation	NSAID
N-Acetylcysteine (NAC)	Replenishes glutathione; neutralizes reactive oxygen species (ROS)	Synthetic cysteine derivative
Captopril	Inhibits ACE; protects against renal fibrosis and vascular injury	Synthetic drug
Angiotensin 1–7	Alters the renin-angiotensin system and guards against kidney and lung damage.	Endogenous peptide hormone
Metformin	Activates AMPK; reduces fibrosis and cellular senescence	Antidiabetic biguanide
Tempol	ROS is scavenged by the antioxidant nitroxide.	Synthetic free radical scavenger
Celecoxib	Selective COX-2 inhibitor; reduces radiation-induced inflammation	NSAID
MnSOD (Manganese Superoxide Dismutase)	Detoxifies superoxide radicals; preserves mitochondrial integrity	Recombinant enzyme or mimetic
JP4-039	Targets mitochondria; neutralizes ROS; enhances cell survival	Synthetic small molecule
Tocotrienols (γ, δ)	Vitamin E isomers; protect GI tract and hematopoietic system	Natural (palm oil, rice bran)
Glutamine	Fuels enterocytes; promotes mucosal regeneration	Dietary amino acid supplement
Genistein	Isoflavone; scavenges radicals, arrests cell cycle, aids DNA repair	Natural (soy-derived)
Entolimod (CBLB502)	Activates TLR-5; stimulates NF- κ B; induces anti-apoptotic and antioxidant responses	Recombinant bacterial flagellin
Melatonin	Scavenges ROS; modulates antioxidant enzymes and circadian protection	Endogenous hormone; also available synthetically
Statins (e.g., Lovastatin)	Anti-inflammatory; anti-fibrotic; mitigate GI radiation damage	Synthetic HMG-CoA reductase inhibitors
Pentoxifylline	Enhances microcirculation; immunomodulatory; reduces fibrosis	Synthetic methyl xanthine derivative
Redox nanoparticles	Neutralize oxidative stress via ROS scavenging; protect cellular structure	Engineered from polymers or metal oxides
Sphingosine-1-phosphate (S1P)	Supports cell survival; modulates immune and endothelial responses	Bioactive lipid mediator

Foot notes

GI: Gastrointestinal; **COX:** Cyclooxygenase; **ROS:** Reactive Oxygen Species; **TLR:** Toll-Like Receptor; **ACE:** Angiotensin-Converting Enzyme; **AMPK:** AMP-activated protein kinase; **HMG-CoA** Hydroxy-Methylglutaryl-Coenzyme A.

CONCLUSION

In conclusion, radio protectors, radio sensitizers, radiomitigators plays an important role in treating malignancies by radiation therapy. Each one of the agents has its own mode of action, application, and adverse effects^[12,14]. In most cases, the success of radiotherapy is directly related to radio sensitizers and the patient quality is dependent of radio protectors and radiomitigators

REFERENCES

1. Wardman PJ. Chemical radiosensitizers for use in radiotherapy. *Clinical oncology*. 2007 Aug 1;19(6):397-417.
2. Spalding AC, Lawrence TS. New and emerging radiosensitizers and radioprotectors. *Cancer investigation*. 2006 Jan 1;24(4):444-56.
3. Citrin D, Cotrim AP, Hyodo F, Baum BJ, Krishna MC, Mitchell JB. Radioprotectors and mitigators of radiation-induced normal tissue injury. *The oncologist*. 2010 Apr 1;15(4):360-71
4. Nair CK, Parida DK, Nomura T. Radioprotectors in radiotherapy. *Journal of radiation research*. 2001;42(1):21-37.
5. Kuntić VS, Stanković MB, Vujić ZB, Brborić JS, Uskoković-Marković SM. Radioprotectors—the evergreen topic. *Chemistry & biodiversity*. 2013 Oct;10(10):1791-803.

6. Rosen EM, Day R, Singh VK. New approaches to radiation protection. *Frontiers in oncology*. 2015 Jan 20;4:381.
7. Reiter RJ, Tan DX, Herman TS, Thomas Jr CR. Melatonin as a radioprotective agent: a review. *International Journal of Radiation Oncology* Biology* Physics*. 2004 Jul 1;59(3):639-53.
8. Hosseinimehr SJ. Trends in the development of radioprotective agents. *Drug discovery today*. 2007 Oct 1;12(19-20):794-805
9. Kamran MZ, Ranjan A, Kaur N, Sur S, Tandon V. Radioprotective agents: strategies and translational advances. *Medicinal research reviews*. 2016 Apr;36(3):461-93.
10. Candelaria M, Garcia-Arias A, Cetina L, Dueñas-Gonzalez A. Radiosensitizers in cervical cancer. Cisplatin and beyond. *Radiation oncology*. 2006 Dec;1:1-7.
11. Wang H, Mu X, He H, Zhang XD. Cancer radiosensitizers. *Trends in pharmacological sciences*. 2018 Jan 1;39(1):24-48.
12. Weinmann M, Welz S, Bamberg M. Hypoxic radiosensitizers and hypoxic cytotoxins in radiation oncology. *Current Medicinal Chemistry-Anti-Cancer Agents*. 2003 Sep 1;3(5):364-74.
13. Gill MR, Vallis KA. Transition metal compounds as cancer radiosensitizers. *Chemical Society Reviews*. 2019;48(2):540-57.
14. Baatout S, editor. *Radiobiology textbook*. Cham, Switzerland: Springer International Publishing; 2023 Sep 23
15. Malik A, Sultana M, Qazi A, Qazi MH, Parveen G, Waqar S, Ashraf AB, Rasool M. Role of natural radiosensitizers and cancer cell radioresistance: an update. *Analytical Cellular Pathology*. 2016;2016(1):6146595
16. Mun GI, Kim S, Choi E, Kim CS, Lee YS. Pharmacology of natural radioprotectors. *Archives of pharmacal research*. 2018 Nov;41:1033-50.