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Research Paper

Natural Radioprotectors For Oncology: Therapeutic and Diagnostic Prospects

Md Sadikuj Jaman*[1], Md Rokibul Hasan Bhuiyan[1], Md Maniruzzaman[2], Mst Tasnova[3], Sanjida Monira[2], Md Rakib Rased Rana[2], Md Nahid Hasan[2], Dipongkar Ray Sobuj[4], Tamanna Rashid[4], Saiful Islam Arif[5]

[1] University of Rajshahi, Bangladesh

[2] Varendra University, Bangladesh

[3] North South University, Bangladesh

[4] Lamar University, United States

[5] Jahurul Islam Medical College, Bangladesh

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Abstract

Cancer remains one of the most significant global health challenges, and radiotherapy continues to be one of the most effective treatment options. However, Patients are also exposed to low doses of ionizing radiation during diagnostic procedures such as computed tomography (CT) and magnetic resonance imaging (MRI). These exposures can induce various cellular and molecular defects in the human body. Therefore, there is an urgent need to develop safer and more reliable radioprotective agents to minimize radiation-induced damage. This review was prepared using selected keywords searched across major scientific databases, including Google Scholar, ScienceDirect, PubMed, and Scopus, covering publications from the inception of each database up to October 14, 2025. This review highlights plant-derived radioprotective agents that exhibit antioxidant, anti-inflammatory, immunomodulatory, DNA repair-enhancing, and metal-chelating actions. It outlines the key molecular pathways involved, such as antioxidant defense, DNA repair regulation, and ROS scavenging, and briefly compares natural compounds with conventional pharmaceutical radioprotectors. Radioprotective agents offer several advantages in both oncotherapy and diagnostic applications. However, many synthetic radioprotectors are associated with limitations such as high cost, short duration of action, toxicity, and adverse effects on the central nervous system. In contrast, natural radioprotectors derived from plants have shown the potential to safeguard normal cells from radiation induced damage more effectively and safely than their synthetic counterparts. This review aims to identify safer and more effective radioprotective agents for use by oncologists and radiation biologists.

Keywords: *Radioprotective Agents, Natural Antioxidants, Radiation-Induced Damage, Cancer Radiotherapy, Molecular Radioprotection*

INTRODUCTION

It is believed that cancer is a group of diseases that can arise anywhere in the body and are typified by unrestrained abnormal cell development that invades or spreads to other parts of the body. There were almost 20 million new cases and 9.7 million cancer-related deaths globally, and according to the International Agency for Research on cancers 202 global cancer statistics. Data indicate that one in five men and women will experience illness at some point in their lives, and one in nine men and one in twelve women will die from cancer (Jaman et al., 2018). According to the US National Cancer Institute, there will likely be 2001140 new cases of cancer in the US in 2024, and 611720 people will die from the disease. The majority of malignancies seem to originate from a single genetically defective cell that multiplies uncontrollably (Bhuiyan et al. 2023). One of the

Corresponding author's: sadik09bio.ru19@gmail.com

best forms of treatment for cancer patients is radiation therapy. IR such as CT scan, X-Ray are used as part of treatment for about 60% of all cancer patients. Although IR is a useful technique for getting rid of cancer cells, it also damages healthy cells and has unforeseen adverse effects. This is shown in Figure 1. Biological molecules are impacted by IR both directly and indirectly (Jaman et al., 2023). Indirect effects happen through ROS generated by molecules surrounding DNA, while direct effects are mediated by direct interaction of IR with particular DNA moieties. All of this demonstrates the complexity of oxidative stress in relation to both healthy cells and cancer (Bhuiyan et al. 2022).

The goal of radiotherapy, which affects ROS formation, is to kill cancer cells while preserving as many healthy cells as feasible. Since there is presently no way to totally stop radiation's damaging effects on healthy cells, it is crucial to create countermeasures. Radiosensitizers make tumor cells more sensitive to therapy, either damage will worsen with irradiation or making them susceptible to treatment after being harmed by the agent (Jaman et al., 2025). Substances that shield normal tissue from radiation exposure might be classified as radioprotectors, mitigators, or treatments depending on how they are administered. This is shown in Figure 2. Agents known as radioprotectors are administered either before or during radiation therapy to reduce harm to healthy cells. Even after radiation exposure, mitigators may be given (Maniruzzaman et al., 2025). Following radiation treatment is performed to repair normal tissue damage and enhance the quality of life. Beyond fundamental processes of growth, development, and reproduction, plants create a wide range of organic substances known as secondary plant metabolites. Primary metabolites that are vital to basic plant life processes and secondary metabolites serve a range of ecological roles, primarily in interactions with environmental defense mechanisms and stressor adaptation (Jaman et al., 2023). The best radioprotective substances should protest body's healthy cells from the damaging effects of infrared radiation without compromising IRs ability to target cancerous cells. According to the suggested categorization schedule, radioprotectors are utilized as a tactic to prevent chemical exposure (Jaman et al., 2025). It is used prior to radiation treatment or ionizing radiation to avoid either acute or long-term damage. IR therapy is given after symptoms appear and is used both during and after treatment to lessen chronic or adverse effects. Many compounds that have been researched as radiation protectors, modifiers, and treatments are currently pending clearance from the US Food and Drug Administration or FDA (Jaman et al., 2017). This review aims to find a radioprotectant from a plant and find a better option between natural and derived drug as radioactivity in cancer treatment or radiation-related diagnosis.

RESEARCH METHOD

A comprehensive and systematic review of literature was conducted in accordance with PRISMA 2020 guidelines to identify studies addressing radioprotective plants, radioprotective compounds, radiation-associated cellular mechanisms, and therapeutic agents used against radiation induced damage. The search included Multiple scientific databases: Google Scholar, Science Direct, PubMed, and Scopus. A broad search strategy was developed using relevant keywords and Boolean combinations to maximize retrieval. The primary search term included radioprotector, radioactivity, signaling pathway associated with radioactivity, and radioprotector, natural radioprotectant source, natural, and synthetic radioprotective drugs. These terms were applied across all databases without year limitations but restricted to English-language publications. Search strings were adapted to the indexing structure of each database. The initial search yielded more than one thousand records. These records underwent an organized screening process in accordance with PRISMA 2020. Many duplicate findings, non-English studies, only title and abstract screening, or studies unrelated to natural and pharmaceutical radioprotectors were excluded. About 80 studies focused on radioprotective plants, 50 studies addressed radioprotective

with biological importance, and 85 studies discussed signaling pathways associated with radiation. After applying all inclusion and exclusion criteria, about 72 studies met the eligibility requirements and were included in the final synthesis. The included studies are on radioprotective plants and their components, the necessity of radioprotectors in oncology and diagnostics, Natural radioprotectant associated with cellular response, and limitations of synthetic radioprotectants.

FINDINGS AND DISCUSSION

The necessity of a radioprotectant and the purpose of synthetically or naturally occurring radioprotectants.

Chemicals or medications that lessen damage done to living things when IR therapy is applied are known as radioprotective agents. For radiation oncologists and basic radiologists, determining an effective and non-toxic radiation protection strategy is a crucial objective. The most radioprotective substances to date include aminothiols and their derivatives, including systemin, amipocene (WR2721), and aminoethyl isothiouronium bromide hydrobromide. Some of these compounds have been successfully utilized to prevent radiotherapy difficulties in cancer patients and are believed to protect against radiation risks related to unintentional radiation exposure scenarios (Maniruzzaman et al., 2025). Amifostine has not been authorized for use in clinical nuclear or radiation circumstances despite its present clinical use. Amifostine's adverse effects include toxicity, restricted use, and duration expense, as well as central nervous system effects. Sulfasalazine is another drug that has been demonstrated to protect mice at 120 mg/kg without being harmful. SAZ stopped plasmid DNA from dissolving from Fenton at this dose, suggesting that free radical scavenging is one of the possible mechanisms of radioactivity, even if different degrees of toxicity have also been reported. Due to their extreme toxicity majority of synthesized chemicals still had limited practical applications (Jaman et al., 2023). The best protective agents have high levels of protection against healthy tissues and minimal protection against cancerous cells, and most importantly, nontoxicity. Researchers had to concentrate on evaluating radioprotective capabilities of natural materials, as synthetic compounds could not provide more potent and less hazardous radioprotective chemicals. Research is being conducted globally to locate radioprotective medications that have all the necessary components of a perfect radioprotective medication, including effective long-term protection, a long shelf life, and no cumulative or permanent toxicity (Jaman et al., 2017). Plant substances known as natural radioprotectors shield healthy non-cancerous cells from radiation therapy-induced harm. Natural herbal products are non-toxic, have demonstrated therapeutic benefits, and have been used to treat a wide range of ailments. Approximately 60% of 1144 new medications created in the past 25 years are derived from natural resources. In a range of in vitro and in vivo investigations and radioprotective potential of about 74 plant products has been examined to date. A few plant extracts that function as radioprotectors are among them (Jaman et al., 2017). Normal cells were shielded from radiation by the use of food and herb modulators, as well as enhanced radiation to make tumor cells more sensitive to radiation. Radiation protectors are medications or substances intended to lessen the harm that radiation does to the human body. Radiation from radionuclides like uranium, strontium90, thorium, cesium-137, radium, and radon, as well as gamma, X-ray, and cosmic rays. Oncologists and biologists must conduct research and develop pharmaceutically dynamic, effective, nontoxic, and user-friendly radiation protectors to shield humans from this dangerous and deadly infrared radiation (Jaman et al., 2018). For a radiation protector to be effective, it must have followed characteristics. (i) with minimal adverse effects in the majority of tissues and organs, and it provides total protection from the damaging effects of radiation. (ii)It should be stable and have a long shelf life; (iii) It should be easily administered orally or intramuscularly; (iii) It should be accessible and economically practical and compatible with a wide range of medications throughout

clinical therapy. (iv) It must be used in recommended dosages in a range of affordable clinical therapies that can target particular organs and cross blood brain barrier. (v) Its effects should last for a long time in case of an emergency. One could argue that a perfect radiation shield should be harmless and capable of offering normal cells a high level of protection with little defense against malignant cells (Jaman et al., 2024). Researchers worldwide have turned their attention to natural materials with the potential to provide radioactive protection due to the lack of effective, efficient, low-cost, low-toxic, or nontoxic radioprotectors. Natural herbal treatments have historically been utilized to treat a variety of human illnesses, and almost 400,000 pharmaceuticals derived from nature have been documented.

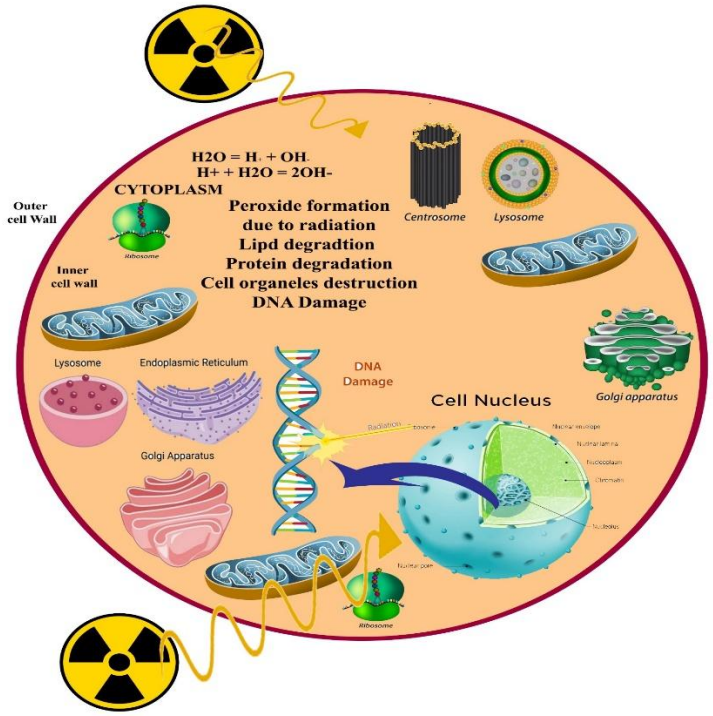


Figure 1. Radiation affects normal cells and convert into abnormal or cancer cells

Biological study of plants and herbs related to radioprotectants and their medicinal values.

Adhatodavasica (Acanthaceae): An evergreen shrub of the Acanthaceae family, Adhatoda vasica (now justicia adhatoda) has been used in traditional and folk medicine, especially in Unani and Ayurvedic medicine. Commonly referred to as vasaka or Malabar nut, it is prized for its respiratory properties and contains a radioprotectant (Manning, 1985). This is shown in Table1.

Aegle marmelos (Rutaceae): Aegle marmelos, sometimes called bael or wood apple, is a holy and therapeutic tree that is indigenous to Southeast Asia and the Indian subcontinent. It belongs to the Rutaceae family, which also includes citrus fruits, and is the only species in the genus Aegle. Because of its important medicinal qualities, the tree is highly valued in Ayurveda, the old Indian medical system (Singhal et al., 2011)

AlliumcepaLinn (Alliaceae): The scientific name for the common onion, which is grown and utilized for its culinary and therapeutic qualities all across the world, is Allium cepa L. It belongs to the genus Allium and the Alliaceae family, which is also known as the onion family (Alves-Silva et al., 2022)

Aloearborescens (Liliaceae): Candelabra aloe and krantz aloe are common names for the succulent perennial plant Aloe arborescens (Liliaceae). There are more than 250 types of aloe, and

because of its therapeutic qualities, it is frequently likened to aloe vera. Originating in southern Africa, it is grown extensively as a decorative and therapeutic plant across the world (Smith et al., 2012).

Asparagusracemosus (Liliaceae): Sharvari, also known as Asparagus racemosus (Liliaceae), is a climbing plant that is highly prized in traditional medicine, especially Ayurveda. It presently belongs to the Asparagaceae family, which was once the Liliaceae family. The plant's tuberous roots are the main source of its therapeutic qualities, and it is indigenous to tropical and subtropical areas of Africa and Australia (Afroz et al., 2022).

Centellaasiatica (Apiaceae): Centella asiatica, also referred to as Asiatic pennywort or gotu kola, is a perennial herbaceous plant that belongs to the Apiaceae family, which also includes carrots. It is renowned for its foods and therapeutic applications and is indigenous to tropical and subtropical wetlands in Asia and Australia (Rakotondralambo et al., 2012)

Curcumalonga (Zingiberaceae): This perennial plant, which belongs to the Zingiberaceae family, is grown for commercial purposes in Tamil Nadu, Andhra Pradesh, Mumbai, and Bengal, but it can be found in every state in India. Over the past ten years, many studies in rodents and cell culture have demonstrated that curcumin can make tumors more sensitive to various chemotherapeutic treatments. Similarly, there is proof that this substance can make several malignancies more sensitive to ϑ-GR, such as glicoma, neuroblastoma, cervical cancer, epidermal carcinoma, prostate cancer, and colon cancer. Numerous growth regulatory pathways and particular genetic targets, including genes for cyclooxygenase-2, Akt, NF-kB, STAT3, anti-AP, GFR, and MRP, have shown to be inhibited by it. In certain circumstances, it also acts as a radiosensitizer and chemosensitizer for cancer. It has been demonstrated that curcumin protects healthy organs from harm caused by chemotherapy and radiation therapy. Therefore, curcumin has two functions: first, it radioprotects healthy cells that are not malignant, and it radiosensitizes dangerous cells (Kim et al., 2001)

Emblica Officinalis (Euphorbiaceae): Amla or Indian gooseberry is another name for Emblica Officinalis that a deciduous tree in the Euphorbiaceous family. Because of its nutritional richness and medicinal qualities, amla is highly prized in ancient Indian medicine, including Ayurveda (Gantait et al., 2021)

Ginkgo biloba (Cycadaceae): Ginkgo biloba (Cycadaceae), a native of China, Japan, and Korea, has been demonstrated to enhance endogenous antioxidants like glutathione and lessen Oxidative stress. An extract from Ginkgo biloba that a combination of flavonoids, heterosides, and terpenes with antioxidant qualities, has been shown to prevent mitochondrial aging by reducing oxidative damage. Moreover, ginkgo biloba extract can be used to treat hypoxic and aging-related brain problems. Ascorbic acid, α-carotene, flavonoids, coumarins, catechins, and ginkgo boloba manu of which have radioprotective properties when taken separately. Ginkgo biloba extracts protected brain neurons from oxidative damage. When tested in rat cerebellar neural cell culture, at a concentration of 100µg/ml, G biloba leaf extract 30% effectively shielded neurons from death caused by hydroxyl radicals (Singh et al., 2008).

Glycyrrhiza glabra (Fabaceae): A member of fabaceae family of peas, licorice, also known as Glucyrrhiza glabra, is a perennial herbaceous plant valued for its sweet, fragrant roots. It is indigenous to West Asia, North Africa, and southern Europe, and it has been utilized for ages in Western, Ayurvedic, and traditional Chinese medicine (El-Saber et al., 2020).

Menthaarvensis (Lamiaceae): Mentha arvensis, commonly known as wild mint, corn mint, or field mint, is a perennial herb in the mint family, Lamiaceae. It is valued for its strong aromatic and medicinal properties, which are largely due to its essential oil composition (Drew et al., 2012)

Menthapiperita (Labiatae): Mentha piperita is the scientific name for peppermint, a hybrid mint species that belongs to the Lamiaceae family formerly known as Labiatae. It is a cross between

watermint (Menta aquatica) and spearmint (Mentha spicata). The use of secondary biomolecules. Monoterpenoids in essential oils and different structural types of phenolic compounds. Essential oils are known to act as antimicrobial, antispasmodic, carminative, and antiviral agents (Mimica-Dukić et al., 2008)

Moringaoleifera (Moringaceae): Northern India is home to the fast-growing, drought-resistant Moringa oleifera tree, which is a member of the Moringaceae family. Often referred to as malunggay, horseradish tree, or drumstick tree, it is prized for its remarkable therapeutic and nutritional qualities. The leaves, pods, flowers, seeds, roots, and almost every other part of the tree are edible and have long been utilized in traditional medicine. The plant Moringa oleifera, which has many therapeutic, nutritional, and economic uses, was analyzed for phytochemicals and assessed for antioxidant properties. Using established methods, phytochemical assays were used to assess the total phenol and flavonoid levels (Ndiaye et al., 2002)

Murravakienigii (Rutaceae): A tropical to subtropical tree, Murray koenigii (L) spreng belongs to the Rutaceae family of citrus trees. Often referred to as the curry tree or sweet neem, it is valued for both its important medical qualities and its fragrant culinary leaves. The common spice Murraya Koenigii (L.) Spreng (Rutaceae) has been used to treat hepatitis and inflammation. In response to paracetamol-induced liver damage in BALB/c mice and current study sought to determine antioxidant and anti-inflammatory properties, as well as control of cytochrome p450 levels produced by aqueous extracts of M koenigii leaves. An overdose of paracetamol and subsequent administration of an aqueous extract of M koenigii leaves caused liver damage (Salwe et al., 2017).

Myristica fragrans (Myristicaceae): Mace (aril) and nutmeg (seed), which have long been employed as spices in culinary arts, are commercially sourced from the fragrant evergreen tree Myristica fragrans Houtt (Myristicaceae). Additionally, folk medicine has utilized different sections of M fragrans to treat a variety of illnesses. Pharmacologists and chemists have long been interested in M. fragrans because of its wide range of applications in the culinary industry and traditional medicine (Ha et al., 2020)

Ocimumsanctum (Lamiaceae): This herb, which belongs to the Lamiaceae family, is widely distributed in tropical and somewhat temperate climates. About 130 species of herbs and shrubs from Asia's tropical areas are found in the genus Ocimum. It was observed that an aqueous ethanolic extract of O sanctum has a radioprotective effect against gamma radiation in albino mice. According to reports, acute LD50 was 6 g/kg body weight, while ideal dosage for protection was 50 mg/kg body weight exposed to 2Gy of gamma radiation, Ocumum flavonoid, orientin and FDA approved amifostine were shown to have comparable radioprotection at dosages of 50 mg/kg body weight and 150 mg/kg body weight respectively but vicenin demonstrated less action. In C57BL and Swiss albino mice, Ocimum has demonstrated anti-melanoma and radioprotective qualities. Mice's survival rate, average body weight, and tumor volume were all decreased by Ocimum aqueous extract, which increased/decreased GSH levels and GST activity, which in turn controlled radiation-induced chromosomal damage. Both orientin and vicenin have been shown to have radical scavenging action, which seems to be one of the ways these flavonoids provide protection (Patil et al., 2011).

Panaxginseng (Araliaceae): Following hydrodistillation, the volatile components of Panax ginseng CA Meyer roots were examined and analyzed using a variety of analytical techniques. Besides various chemicals, three sesquiterpene hydrocarbons have been identified from the essential oil. Structure elucidation of bicyclic panaxene, as well as tricyclic panaginsene and ginsinsene was undertaken by MS and NMR (Richter et al., 2005).

Piper betle (Piperaceae): Originally from central and eastern Malaysia, this tropical perennial evergreen plant, which thrives in the shade, is a member of piparaceae family and has been

cultivated across Malaysia and tropical Asia. Two in vitro models, rat liver mitochondria and pBR322 plasmid DNA, have been used to investigate the radioprotective properties of pepper betel ethanolic extract (PE). Lipid hydroperoxide, conjugate diene, and reactive substrates of thiobarbituric acid were measured to determine how well the extract inhibited gamma-ray-induced lipid peroxidation. Similarly, it inhibited concentration-dependent DNA strand breaks caused by radiation. Pes's radioprotective action stems from both its lymphoproliferative and hydroxyl and superoxide radical scavenging capabilities (Jaramillo et al., 2004).

PiperlongumLinn (Piperaceae): Around the world, herbs are used to orchestrate revival and vegetal rebirth. Medicinal plants have always been crucial to human health growth. We can discover novel compounds for medications that target different pharmacological targets thanks to Piper longum. This family of plants includes perennial herbs recognized for their therapeutic and pharmacological properties (Gani et al., 2019).

Podophyllum hexandrum (Berberidaceae): The two stages of podophyllum's life cycle are the aerial phase, when primordia of structures within the winter bud give rise to an aerial shoot made up of a stem, two leaves, and a single flower the following spring, and the subterranean phase, when a noticeable winter mixed terminal bud forms at the end of the rhizome. The apical meristem transforms into a globoid structure around the end of July, marking a change from a vegetative to a floral apex. The floral organs are arranged along the sides of an extended floral apex during the first and second weeks of August. The floral organs are sepals, petals, stamens, gynoecium and gynoecium in sequence of initiation. Early in August, petal primordia begin to grow, but once they reach a height of around 2 mm, they stop growing (DeMaggio et al., 1986).

SaccharumofficinarumL (Gramineae): Flavonoid concentration of sugarcane (Saccharum officinarum L., Gramineae) bagasse and leaves was exmined and transgenic sugarcane (also known as "Bowman-Birk" and Kunitz) was contrasted with unmodified (Control) plants. The analyses were conducted utilizing tandem MS, high-performance liquid chromatography connected to diode array UV detection, and post-column addition of shift reagents (Chougala et al., 2024).

SpinaciaoleraceaL (Chenopodiaceae): The scientific name for spinach, a leafy green vegetable belonging to the Amaranthaceae family, is Spinacia oleracea. Though it was originally classified under the family Chenopodiaceae, contemporary botanical knowledge has integrated it into the wider Amaranthaceae family, with spinach belonging to the subfamily Chenopodioideae (Vitale et al., 1987).

Syzygium cuminii (Linn) Skeels (Myrtaceae): The tropical evergreen Syzygium cuminii (L) Skeels belongs to the Myrtaceae family of flowering plants. Often referred to as Java plum or jamun, it is valued for its wood, sweet, somewhat sour fruit, and decorative appeal. The plant is indigenous to Southeast Asia and the Indian subcontinent, although it is also found in China and Australia from Syzygium cuminii Linn. Skeels seeds in mice with a focus on their sedative and anticonvulsant properties (De Lima et al., 1998).

Terminaliaarjuna (Combretaceae): With over 250 species worldwide, Terminalia Linn is a genus of mostly medium to large trees in the Combretaceae family. It is primarily found in southern Asia, the Himalaya, Madagascar, Australia, and tropical and subtropical parts of Africa. Many ancient medical systems, such as Tibetan medicine, Indian Ayurvedic medicine, and traditional Chinese medicine, make extensive use of numerous species. About 39 species have been the subject of phytochemical research to date, and 368 compounds, including terpenoids, tannins, flavonoids, phenylpropanoids, simple phenolics, and others, have been identified as a result. In vitro or in vivo, several of the isolates demonstrated a variety of bioactivities, including analgesic, anticancer, antiHIV-1, antifungal, antibacterial, antimalarial, antioxidant, and diarrheal (Zhang et al., 2019).

Terminalia chebula (Combretaceae): Native to South Asia, Terminalia chebula (Combretaceae) is a medium to big deciduous tree that is prized for its therapeutic fruit. In

Ayurvedic medicine, it is referred to as Haritaki and is also widely termed black or chebulic myrobalan. There are more than 500 species of tropical trees, shrubs, and woody plants in the Combretaceae family (Ravi Shankara et al., 2016).

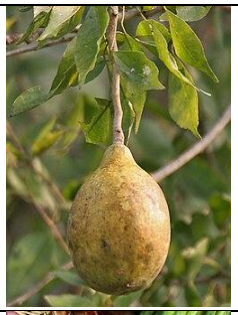
Tinosporacordifolia (Menispermaceae): The cordifolia Tinospora, the family Menispermaceae, which has comparatively fewer recognized medicinal plants than other families, is also called Guduchi, one of the most significant medicinal herbaceous vines. The menispermaceae family, which includes over 320 species and 73 genera, is indigenous to Srilanka and the tropical parts of India. Among them, Tinospora cordifolia is widely recognized for its therapeutic potential and medicinal worth. The stem and leaf sections of the plant contain a large number of alkaloids and are of medicinal worth. Because the stem and leaf sections of the plant contain a large number of alkaloids and entire plant is used in both traditional and contemporary medicine. Mostly found in India, China, Thailand, Myanmar, the Philippines, Indonesia, and Africa, T. cordifolia usually grows well in arid deciduous woods up to 1000 feet in elevation. This plant is well known for its immunomodulatory, anti-inflammatory, anti-hyperglycemic, and antioxidant qualities. Alkaloids, steroids, glycosides, diterpenoid lactones, sesquiterpenoids, and other major phytochemical compounds are found (Malavika et al., 2024)

Vitislabrusca (Vitaceae): Because it produces grapes and wine, the genus Vitis L. is the most commercially significant fruit crop. The genus's phylogenetic ties have generated a lot of debate. Here, we try to improve vitis phylogenetic resolution by using sequencing data from whole plastomes. The findings confirm the monophyletic status of new world vitis subgenus Vitis. The surviving New World subgenus Vitis is siter to V. californica within the lineage (Wen et al., 2018)

Zingiber officinale (Zingiber aceae): Originally from South China, this herbaceous perennial migrated to other regions of Asia, including spice islands and then to West Africa. Since ancient times, the rhizome of Z. officinale, sometimes referred to as ginger, has been utilized extensively as a condiment and spice in many cultures. Ginger has been shown in several preclinical studies to have anticancer and chemopreventive properties. In the past ten years, preclinical research has demonstrated that ginger and its phytochemicals, zingerone and dehydrozingerone, exhibit radioprotective properties in lab animals and cultured cells in vitro. According to mechanistic research, observed protection may be attributed to antioxidant, anti-inflammatory, anti-clastogenic, and free radical scavenging properties. Additionally, studies on tumor-bearing mice have demonstrated that zingerone specifically shields healthy tissues from radiation's tumoricidal effects (Ojewole., 2006).

Table 1. List of plant diversity which contain radioprotectants ingredients

Name of Plant	Source	Chemical associated with radioprotectant	Mode of action	Reference
Adhatodavasica (Acanthaceae)		Vesicine, vesicinone, betaine, vitamin C, b-carotene and vasakin	Decrease the irradiation effect and increase hematological parameters.	(Manning, 1985)

Name of Plant	Source	Chemical associated with radioprotectant	Mode of action	Reference
Aeglemarmelos (Rutaceae)		Skimmianine, luvangetin, psoralen, marmin, marmelide, aurapten, marmelosin, lupeol, aegelin, marmrsinin, eugenol, and coumarin	Protect against radiation-related sickness and mortality in vivo study	(Singhal et al., 2011)
AlliumcepaLinn (Alliaceae)		Allyl propyl disulfide,31,8-cineole	Effective against X-ray radiation	(Alves-Silva et al., 2022)
Aloearborescen (Liliaceae)		Campesterol, stigmasterol, β-sitosterol	Protect the mouse from soft X-rays and antioxidant activity	(Smith et al., 2012)
Asparagusracemosus (Liliaceae)		9,10-dihydro-1,5 dimehtoxy-8-methyl-2,7-phen-anthrenediol, steroidal saponins, polysaccharides	Free radical activity induced by gamma radiation	(Afroz et al., 2022)
Centellaasiatica (Apiaceae)		Triterpene, flavonoid, phenolic acid, sterols, acetylenes	It protects mice from radiation 6Gy 60 co gamma radiation	(Rakotondralambo et al., 2012)
Curcumalonga (Zingiberaceae)		Curcumin	Radioprotective effect	(Kim et al., 2001)

Name of Plant	Source	Chemical associated with radioprotectant	Mode of action	Reference
Emblica officinalis (Euphorbiaceae)		Tannins, alkaloids, quercetin, emblicanin A and B, and ellagotannin	Protect gamma radiation and induced lipid peroxidation and mitochondrial SOD	(Gantait et al., 2021)
Ginkgobiloba (Cycadaceae)		Ginkgetin and Ginkgolides (A & B)	Radioprotectant in rats induced apoptosis	(Singh et al., 2008)
Glycyrrhiza glabra (Fabaceae)		Glycyrrhizin	Ethanolic extract protect rate membrane and induces lipid peroxidation	(El-Saber Batiha et al., 2020)
Menthaarvensis (Lamiaceae)		Alkaloids, flavonoids, phenols, tannins, saponins, diterpenes, and monoterpenes	Extract good for pre-irradiation treatment of rat-induced gastrointestinal and bone death	(Drew et al., 2012)
Menthapiperita (Labiatae)		Menthol	Radioprotective activity on the testis and gastrointestinal system in rats	(Mimica-Dukić et al., 2008)
Moringaoleifera (Moringaceae)		Vitamin C	Leaf extract significantly reduced the percent aberrant cells in metaphase chromosomes	(Ndiaye et al., 2002)
Murrayakoenigii (Rutaceae)		Oxalic acid, glycosides, carbazole alkaloids, koenigin, resin,girinimbin, isomahanim- bin, koenine, koenigine, koeni- dineandkoenimbin e. Mahanim- bicine, bicyclomahanimbic ine, phebalosin, coumarine	Anti-oxidant and radioprotective effect	(Salwe et al., 2017)

Name of Plant	Source	Chemical associated with radioprotectant	Mode of action	Reference
Myristicafragrans (Myristicaceae)		Myristicin, lignanand eugenol, abinene, α-pinene and β-pinene, myrcene, 1,8-cineole, myristicin, limonene, safrole, and terpinen4- ol	Radioprotectant and induces a decline in WBC, bone marrow, and GSH	(Ha et al., 2020)
Ocimumsanctum (Lamiaceae)		Orientin, Vicenin	Radioprotective and protects against chromosomal aberration.	(Patil et al., 2011)
Panaxginseng (Araliaceae)		Ginsenosides, Polysaccharides	Best radioprotector for mice	(Richter et al., 2005)
PiperbetleLinn (Piperaceae)		Chevibetol and allylpyrocatechol	Anti-oxidant and induce DNA strand breaks from radiation	(Jaramillo et al., 2004)
PiperlongumLinn (Piperaceae)		Monoterpenes (Z) p-ocimene, a-pinene and b-pinene, E-caryophyllene and germacrene D, have the E, E-farnesyl-PP	Radioprotectant and induces a decline in WBC, bone marrow, and GSH	(Gani et al., 2019)
Podophyllumhexandrum (Berberidaceae)		Epipodophyllotoxin, podo-phyllotoxin, aryl tetrahydro naphthalene lignans	Protective for haematopoietic, gastrointestinal, reproductive, and CNS	(DeMaggio et al., 1986)
Saccharumofficinarum L (Gramineae)		Phenolics	Radioprotective and growth protective activity	(Chougala et al., 2024)
SpinaciaoleraceaL (Chenopodiaceae)		Carotenoids, Ascorbic acid, Flavonoids, and P-Coumaric acid	Antioxidants and radioprotectors induce oxidative stress	(Vitale et al., 1987)

Name of Plant	Source	Chemical associated with radioprotectant	Mode of action	Reference
Syzygiumcuminii (Linn.) Skeels (Myrtaceae)		Acetyl oleanolic acid, triterpenoids, ellagic acid, Jambolin	Reduced radiation and induced sickness	(De Lima et al., 1998)
Terminaliaarjuna (Combretaceae)		Baicalein	Anti-oxidant and radioprotective activity	(Zhang et al., 2019)
Terminaliachebula (Combretaceae)		Ascorbate, gallic acid, and ellagic acid	Induce lipid peroxidation and radioprotection, and antioxidant properties	(Ravi Shankara et al., 2016)
Tinosporacordifolia (Menispermaceae)		Cordifolioside-A, palmatine, tembetarine	Radioprotection and induce intestinal death	(Malavika et al., 2024)
Vitislabrusca (Vitaceae)		Trans-resveratrol	Radioprotective, inhibiting body weight and increasing WBC, RBC	(Wen et al., 2018)
Zingiber officinale (Zingiber- aceae)		Zingerone	Reduce radiation sickness and mortality	(Ojewole, 2006)

Study of pharmaceutical radioprotectants and their biological importance

To lower morbidity and mortality in acute damage caused by large doses of ionizing radiation, an efficient pharmaceutical countermeasure must be developed. Genistein is now produced using chemosynthetic techniques and has demonstrated bioactivity in reducing radiation damage. The therapeutic use of genistein remains a significant problem because of high expense and worries about chemical residues. Our goal in this work was to develop a productive technique for genistein extraction from fructus sophorae (Zhang et al., 2021). This is shown in Table2. One of the organs most susceptible to harm from IR is the small intestine. There aren't many ways to prevent intestinal damage brought on by IR. Salmonella flagellins TLR5 agonist CBLC502 has radioprotective effects on a variety of organs and tissues. Nevertheless, it is still unknown what molecular processes CBLC502 uses to prevent intestinal damage brought on by IR (Wang et al. 2024). Moreover, 5AED has been proposed as a potential IR defense mechanism. It is safe well tolerated and very effective both before and after IR exposure. 5AED increases the survival of bone marrow cell progenitors and quantity of circulating neutrophils and platelets, preventing radiation induced inhibition of hematopoiesis.

By enabling DNA repair and encouraging production of inducible NO-synthase genes and activation of the NF-kB pathway in conjunction with suppression of apoptosis and pyroptosis that enhances the efficacy of 5AEDs in preventing radiation damage (Grace et al., 2012). However,

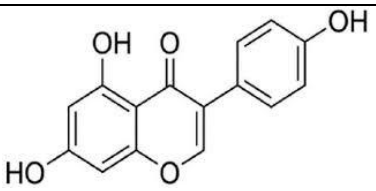
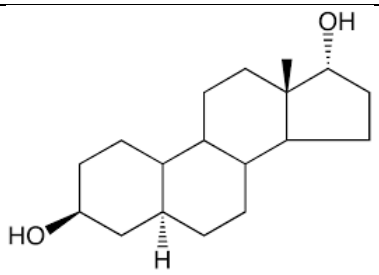
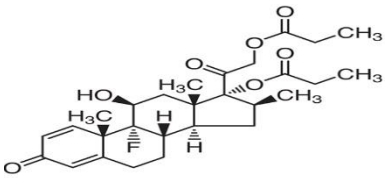
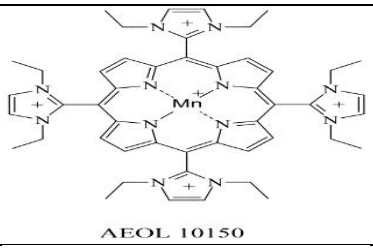
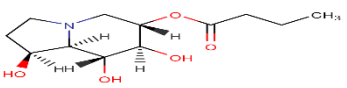
following traumatic brain damage and pathophysiological reaction, the brain releases brain-specific proteins called GFAP and BDP into the serum. Combined with other clinical data, GFAP-BDP reduced the number of needless confirmations required to rule out the diagnosis of radiographically detectable intracranial injury across the spectrum of traumatic brain injury by 12-30% (McMahon et al., 2015). Therefore, when given following 11.5Gy of whole thorax lung irradiation in a non-human primate model, AEOL 10150 may lessen radiation induced lung damage and increase OS. 6MV photons were administered to 13 animals at a dosage of 0.8Gy per min and assigned to the midplane and exposed to 11.5 Gy of radiation in a single exposure. Four weeks starting 24 hrs after radiation AEOL 10150 group received daily subcutaneous injections of catalytic antioxidant at a dosage of 5 mg per kg. Serial plasma sample analysis revealed that in comparison with control animals, AEOL 10150 therapy resulted in decreased relative transforming growth factor beta 1 levels (Garofalo et al., 2014). Additionally, Granulocytopenia and thrombocytopenia are side effects of chemotherapy and radiation treatment.

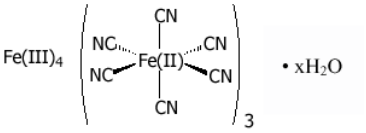
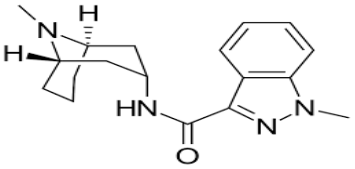
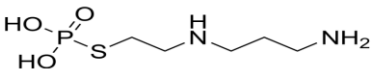
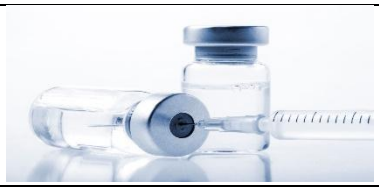
However, long-term consequences of stimulating the hematopoietic system with G-CSF in vivo during radiation treatment, different blood smears revealed that group B had a considerably lower lymphocyte count than those in group A. Following G-CSF stimulation, 3/5 patients in group A experienced an overshooting response. Circulating CD3 superse+ progenitor cells decreased in arm B. There were five out of five patients in Arm A who experienced an initial overshoot reaction, but group B experienced none. There were significant differences between CFU and cluster (Pape et al., 2006). Furthermore, in a mouse model of hepatoma, a combination of radiation and IL-12 inhibited tumor development and metastasis. Irradiation reduced IL-12 expression in the spleens and tumors of tumor-bearing animals. Nevertheless, many dendritic cells entered tumors while IL-12 expression remained unchanged. We looked at IL-12- and IL-16-associated molecules in both irradiated tumors and BMDCs after LPS-stimulated bone marrow-derived dendritic cells were exposed to irradiation to better understand intricate processes underlying the observed drop in IL-12 (Lee et al., 2016). Consequently, effective treatments that can lessen harm to the hematopoietic system caused by radiation exposure are desperately needed in medicine. Strong antioxidant nanozymes may be used therapeutically to lessen hematopoietic damage brought on by radiation. Enhancing the recruitment of nanozymes to wounded tissues in vivo while preserving their catalytic function is still very difficult (Zhang et al., 2023). However, both mucosal damage and changes in intestinal motility are implicated in radiation-induced diarrhea. Three and seven rats experienced diarrhea along with elevated 5-hydroxytryptamine levels and mitigated decreased intestinal motility and avoided diarrhea on day 3; however, fluid absorption was only marginally enhanced (Picard et al., 2002).

Additionally, as of right now, amifostine is the only FDA-approved chemical medication that can shield cancer patients from the harmful effects of radiation. Amifostine, a free-radical scavenger, is a chemical radioprotectant and organic thiol phosphate precursor, just like thiols, aminothiols, and benzothiazoles. However, because of their high toxicity and related adverse effects, these chemical radioprotectors are limited (Cassatt et al., 2002). Whereas a painful ulceration of the oropharynx is known as oral mucositis. Significant morbidity, such as prolonged hospital admissions, elevated bacteremia, and discomfort that disrupts speech, eating, and sleep, is linked to the development of mucositis. Palifermin, a recombinant humanized keratinocyte growth factor, is the first medication approved by the FDA to reduce the incidence and duration of mucositis in patients with hematologic cancers undergoing chemotherapy and needing assistance for hematopoietic stem cell transplantation (Beaven et al., 2007). From the above study, many researchers and clinicians who have studied synthetic radioprotective agents have observed that these compounds often cause unwanted side effects, which can range from mild nausea or fatigue to severe organ toxicity or immune suppression. These adverse effects can limit the clinical

usefulness of synthetic radioprotectors despite their ability to protect healthy tissues from radiation damage.

Table 2. List of pharmaceutically derived radioprotectants with chemical structure.

Name of radioprotectant	Chemical Name	Chemical Structure	Result	Reference
Genistein	405,7 trihydroxy-isoflavonoid; Bio 300TM)		Effective for radiation-related damage	(Zhang et al., 2021)
CBLB502	bioengineered truncated Salmonella sp. flagellin; EntolimodTM		Protect the small intestine from IR	(Wang et al., 2024)
5-AED	androst-5-ene-3b, 17b-diol; Neumune		Reduce radiation and induce DNA damage	(Grace et al., 2012)
BDP/SGX201	Corticosteroid-beclomethasone 17,21-dipropionate; OrbeShieldTM		Radioprotective and induces brain injury	(McMahon et al., 2015)
AEOL 10150	Mn prophyrin SOD mimic	 AEOL 10150	Antioxidant and radioprotection and induced lung injury	(Garofal et al., 2014)
rhu G-CSF	filgrastim; Neupogen		Radioprotective and prognosis for blood improvement	(Pape et al., 2006)
Rhu IL-12	HemaMaxTM		radioprotectant	(Lee et al., 2016)

Name of radioprotectant	Chemical Name	Chemical Structure	Result	Reference
Prussian Blue	(Radiogardase) KI		Radioprotectant and induce hematopoietic damage	(Zhang et al., 2023)
Granisetron	Kytril		Radioprotectant and prevent dysentery	(Picard et al., 2002)
Amifostine	WR2721 (2-(3-aminopropyl) aminoethylphosphorothioate; EthyolTM)		radioprotectant	(Cassat et al., 2002)
Palifermin	Kepivance		radoprotectant	(Beave et al., 2007)

Study of natural radioprotectant as essential and safe treatment

Apigenin (15 mg/kg body weight) was given via intraperitoneal injection to Swiss albino mice for six consecutive days before they were exposed to 7 Gy whole-body irradiation on the seventh day. Apigenin controls the expression of seven apoptotic markers generated by Gy radiation, such as p53, p21, Bax, caspase-3, and caspase-9 (Begum et al., 2021). This is shown in Table 3. Moreover, two extracts designated E1 and E2 were produced by extracting the dried root of the plant *Caesalpinia digyna* using solvents with varying polarity. The extracts underwent in vitro radioprotection tests and free radical scavenging activities after being standardized in relation to the polyphenol bergenin. A comparison of the results with those for bergenin showed that in vitro radioprotection and free radical scavenging capacity are not due to bergenin alone (Singh et al., 2009).

However, researchers investigated the effects of coffee administered both before and after whole-body gamma radiation in mice. It was discovered that while acute caffeine pre-treatment greatly decreased the rate of chromosomal aberrations brought on by radiation exposure, long-term pre-treatment provided noticeably greater protection against radiation. Immediately after whole-body gamma radiation, the mice received an intraperitoneal injection of caffeine as a post-treatment. It is shown that the frequency of chromosomal abnormalities brought on by gamma rays was likewise considerably decreased by both post-treatment caffeine dosages (Farooqi et al., 1992). Therefore, two phytochemicals, quinic acid and chlorogenic acid, have a radioprotective effect on non-tumorigenic human blood cells against genomic instability brought on by X-ray irradiation.

The alkaline comet assay was performed to evaluate the effects of two phenolic acids against radiation-induced DNA damage using human blood cells obtained from two healthy donors. Quinic acid reduced radiation-induced DNA damage by 5.99–53.57%, and chlorogenic acid by 4.49–

48.15%, according to the alkaline comet test (Cinkilic et al., 2013). Furthermore, CA was discovered to be an inducer of HSF1 after we previously evaluated natural chemicals. Through phosphorylation at Ser326 and subsequent upregulation of HSP27 and HSP70 production, CA enhanced the stability of the HSF1 protein. Phosphorylation patterns at HSF1's Ser326 were indicative of protective effects in typical cells when CA was administered concurrently with IR or taxol. Due to IR, CA also considerably reduced the proliferation of dUTP nick-end labeling–positive bone marrow cells in mice, resulting in a 30.6% and 56.0% decrease in bone marrow cellularity (Kim et al., 2015).

Additionally, for ages, humans have used a yellow pigment called curcumin, which is found in Indian saffron, as a nutritional supplement and to treat a number of proinflammatory conditions. It blocks several pathways involved in growth regulation and specific genetic targets, such as genes related to growth factor receptors and proteins that prevent apoptosis, including NF-κB, STAT3, COX2, AKT, and multidrug resistance proteins. Curcumin has been demonstrated to shield healthy organs, including the liver, kidney, heart, and oral mucosa, from the toxicity of chemotherapy and radiation, even if it occasionally serves as a chemosensitizer and radiosensitizer for malignancies. Curcumin's ability to activate and promote the synthesis of antioxidant enzymes, directly suppress free radicals, and limit p300 HAT activity appears to be the mechanism behind its protective qualities (Goel et al., 2010).

Consequently, when administered during cancer radiation therapy, radioprotectors may shield patients from adverse consequences brought on by radiation damage to healthy tissue. By scavenging radiation-induced ROS, delphinidins act as potent antioxidant enzymes that raise pro-survival protein levels and lower pro-apoptosis protein levels (Kim et al., 2018).

Although radiation-induced intestinal damage is a deadly condition that needs effective treatments and can be brought on by medical and accidental radiation exposure, the primary component of green tea, EGCG, has shown significant anti-inflammatory effects and remarkable biological activity. EGCG suppresses inflammation, which was probably the cause of EGCG's radioprotective action. EGCG offers a fresh approach to reducing RIII and enhancing patients' outcomes following radiation treatment (Gu et al., 2022).

In addition to this, rice bran, green tea, and coffee beans are among plant products that contain FA, a monophenolic phenylpropanoid. Numerous studies have demonstrated its strong antioxidant properties. The quantity of DNA strand breaks in bone marrow cells and murine peripheral blood leukocytes, as evaluated by the comet assay, was diminished when the same dose of FA was given immediately following 4 Gy of γ-irradiation. At a dosage of 6 Gy γ-radiation, FA increased mice's survival by a factor of 2.5 (Maurya et al., 2013). Whereas one of the primary isoflavone components of soy, genistein, has garnered a lot of interest due to its potential to mitigate radiation damage. By inhibiting apoptosis, reducing DNA damage and chromosomal aberrations, downregulating GRP78, and upregulating HERP, HUS1, and hHR23A, a modest concentration of GEN shielded L-02 cells against radiation damage.

A high level of GEN exhibited radiosensitizing properties by enhancing apoptosis and causing chromosomal abnormalities, hindering DNA repair and increasing the expression of GRP78 while decreasing the levels of HUS1, SIRT1, RAD17, and RNF8 (Song et al., 2015). Furthermore, HES protects male rats' lungs against radiation-induced damage. In comparison to G1, histopathological findings within 24 hours revealed radiation-induced inflammation and an increase in inflammatory cells. Delivery of HES in G2 considerably reduced this impact in contrast to G1, and when comparing G2 to G1 after 8 weeks, histological analysis revealed a significant increase in mast cells, inflammation, inflammatory cell presence, alveolar thickness, pulmonary edema, and fibrosis (Haddadi et al., 2017). Besides, by scavenging free radicals, lycopene shields healthy tissues and cells. It may be possible to reduce the negative effects of radiation by-products by treating cells with lycopene before they are exposed to oxidative stress, oxidative chemicals, or IR (Pirayesh Islamian

et al., 2015).

Therefore, J774A.1 murine macrophages were used to assess the potential radioprotective effects of NATG, a bacterial secondary metabolite, on the immune system. Compared to merely irradiated cells, irradiated macrophages pretreated with NATG showed a considerable drop in IL-10 and IL-2 levels. Compared to merely irradiated cells, irradiated macrophages pretreated with NATG showed a notable improvement in IL-12 and IL-17A. IFN-γ, IL-17A, and IL-12 expression were increased by NATG pretreatment of irradiated macrophages, whereas TNF-α, IL-10, and IL-12 expression were suppressed (Malhotra et al., 2016).

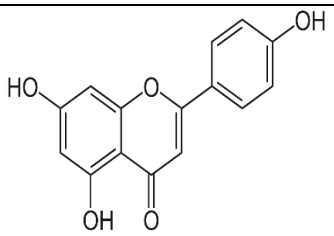
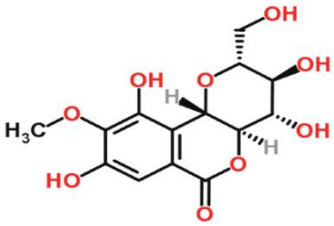
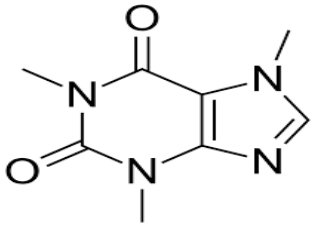
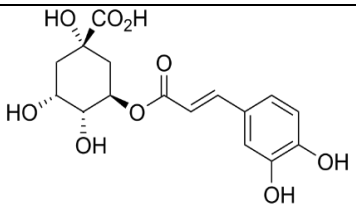
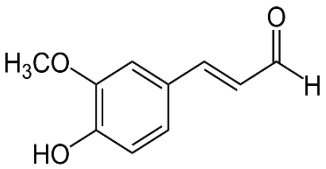
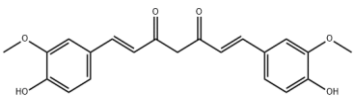
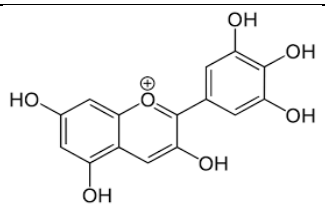
However, psoralidin, a coumestan derivative extracted from *Psoralea corylifolia* seeds, has been investigated for its antibacterial and anticancer qualities. In HFL-1 and MRC-5 cells, IR-induced ROS triggered cyclooxygenase-2 (COX-2) and the 5-LOX pathway. Psoralidin's direct interaction with the 5-LOX pathway prevented IR-induced LTB4 synthesis (Yang et al., 2011). On the other hand, different dosages of γ-radiation were applied to lymphocytes that had been pretreated with sesamol. In a dose-dependent manner, radiation dramatically raised MN and DC frequencies and TBARS levels while lowering GSH and antioxidant enzyme levels (Prasad et al., 2005).

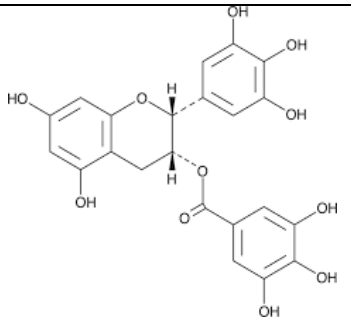
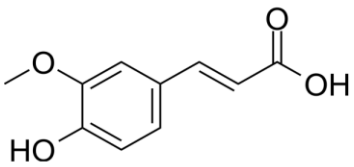
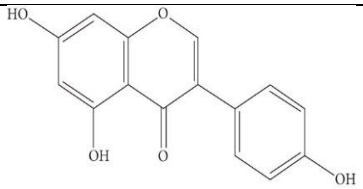
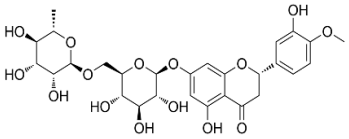
Additionally, 1 mM troxerutin treatment dramatically reduced the induction of micronuclei in human cells. Peripheral blood leukocytes were shielded from radiation-induced DNA strand breaks under ex vivo radiation conditions by troxerutin in a concentration-dependent manner. Mice given troxerutin intraperitoneally both before and after being exposed to whole-body radiation showed a considerable inhibition of micronuclei production in blood reticulocytes. When mice were given 175 mg/kg body weight of the medication intraperitoneally either one hour before or just after whole-body irradiation, the study revealed that the reduction in strand breakage was dependent on the post-irradiation interval (Maurya et al., 2005).

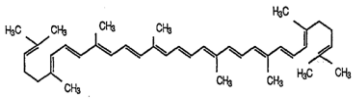
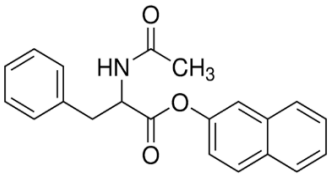
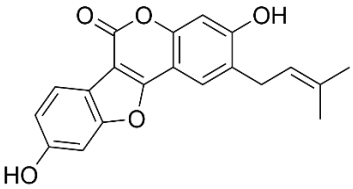
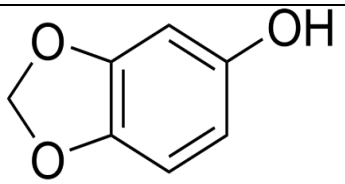
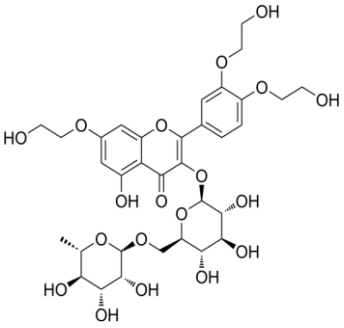
Accordingly, it has been shown that the anticlastogen vanillin prevents gene alterations in both human and bacterial cells. Inhibition tests showed that adding 100 mg/ml of VA significantly reduced the proportion of MNBN induced by X-rays at 1, 2, and 4 Gy, and at 5 and 50 mg/ml VA, the percentage of MNBN slightly dropped (Keshava et al., 1998). Whereas zingerone's radiation antagonistic potential was assessed using alkaline comet, cytokinesis-block micronucleus, apoptosis, and reactive oxygen species inhibition assays. The frequency of micronuclei was much lower in lymphocytes treated with zingerone (10 μg/ml) before exposure to 2 Gy γ-radiation than in the control group of cells, as determined by the cytokinesis-block micronucleus test. Before irradiation, zingerone (10 μg/ml) therapy dramatically reduced the proportion of apoptotic cells, as shown by DNA ladder assays and microscopical analysis. Zingerone also dramatically reduced quantities of ROS induced by radiation (Rao et al., 2011).

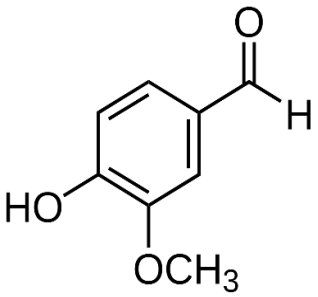
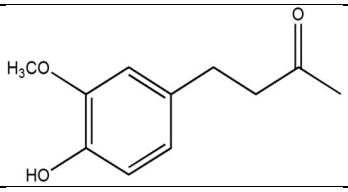
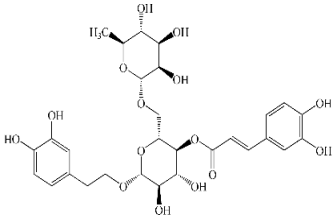
Therefore, radiation frequently causes significant harm to the hematological system, which is susceptible to ionizing radiation. Toll-like receptor 2 is one of the molecules influencing radioresistance. Zymosan-A reduced radiation-induced hematopoietic system damage and shielded mice from radiation-induced mortality. Additionally, zymosan in vivo elevated levels of IL-6, IL-11, IL-12, and TNF-α, decreased radiation-induced cell death, and generated radioprotective effects via TLR2 (Du et al., 2017). Studies have shown that natural radioprotectants exhibit minimal or no side effects. With the increased use of diagnostic and therapeutic radiation, physicians and oncologists are encouraged to consider the use of natural radioprotectants. These agents are generally safe, and their radioprotective efficacy can be further enhanced when used in combination with other compounds. Therefore, natural radioprotectants are considered promising candidates for both standalone and combination therapy to mitigate radiation-induced damage.

Table 3. List of naturally occurring radioprotectants with chemical structure.

Name of radioprotectant	Chemical Name	Chemical Structure	Result	Reference
Apigenin	5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one		The suppression of NF-κB signaling modulates the apoptotic pathway	(Begum et al., 2021)
Bergenin	1,3,7-trimethylpurine-2,6-dione		chemical-detoxification, antioxidant defense, ROS Scavenging, NF-κB, apoptosis regulators, stress kinases.	(Singh et al., 2009)
Caffeine	1,3,7-trimethylpurine-2,6-dione		modulation of DNA damage signaling, enhanced ROS homeostasis	(Farooq et al., 1992)
Chlorogenic acid/ quinic acid	(1S,3R,4R,5R)-3-{[(2E)-3-(3, 4-dihydroxyphenyl) prop-2-enoyl]oxy}-1,4,5-trihydroxycyclohexane-1-carboxylic acid		free-radical scavenging activity, Nrf2-mediated antioxidant defense	(Cinkilet al., 2013)
Coniferyl aldehyde	(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enal		ERK1/2 activation, increased HSP expression, and ROS Scavenging	(Kim et al., 2015)
Curcumin	(1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione		Inhibition of pro-survival signaling, Generation of ROS, and activation of stress-kinase pathways	(Goel et al., 2010)
Delphinidin	2-(3,4,5-trihydroxyphenyl) chromenylium-3,5,7-triol		ROS scavenging, enhancement of endogenous antioxidant enzyme activity, and modulation of	(Kim et al., 2018)

Name of radioprotectant	Chemical Name	Chemical Structure	Result	Reference
			apoptosis-related signaling	
Epigallocatechin-3-gallate	(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate		Activation of antioxidant, cytoprotective signaling via Nrf2, Suppression of radiation-induced cell death, Modulation of immune, inflammatory response & microbiota homeostasis	(Gu et al., 2022)
Ferulic acid	(2E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid		Nrf2–ARE antioxidant signaling, direct ROS scavenging, Anti-apoptotic Signaling	(Maurya et al., 2013)
Genistein	5,7-dihydroxy-3-(4-hydroxyphenyl) chromen-4-one		PI3K/Akt pathway activation, inhibition of mitochondrial apoptosis, reduction of radiation-induced DNA damage	(Song et al., 2015)
Hesperidin	(2S)-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl] oxymethyl] oxan-2-yl] oxy-2,3-dihydrochromen-4-one		NF-κB mediated anti-inflammatory protection, antioxidant enzyme activation	(Haddadi et al., 2017)

Name of radioprotectant	Chemical Name	Chemical Structure	Result	Reference
Lycopene	(all-E)-2,6,10,14,19,23,27,31-octamethyl-2,6,8,10,12,14,16,18,20,22,24,26,30-dotriacontatridecaene		Anti-apoptotic & DNA Damage–Response Regulation (ATM/ATR–p53 Axis + Bcl-2/Bax), Anti-inflammatory & Oxidative-Stress Regulation	(Pirayesh Islamian et al., 2015)
N-Acetyl tryptophan glucopyranoside (NATG)	(2S)-2-acetamido-3-(1-β-D-glucopyranosyl-1H-indol-3-yl) propanoic acid		Mitochondrial anti-apoptotic, ROS-scavenging, immune-restorative signaling	(Malhotra et al., 2016)
Psoralidin	3,9-dihydroxy-2-(3-methylbut-2-enyl)-[1]benzofuro[3,2-c]chromen-6-one		COX-2/5-LOX inhibition, ↓ prostaglandins & leukotrienes, ↓ NF-κB activation, reduced pulmonary inflammation	(Yang et al., 2011)
Sesamol	1,3-benzodioxol-5-ol		direct ROS scavenging, ↑ antioxidant enzymes, ↓ DNA & lipid damage, reduced apoptosis	(Prasad et al., 2005)
Troxerutin	2-[3,4-bis(2-hydroxyethoxy) phenyl]-5-hydroxy-7-(2-hydroxyethoxy) -3-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one		ROS scavenging, antioxidant, reduced apoptosis	(Maurya et al., 2005)

Name of radioprotectant	Chemical Name	Chemical Structure	Result	Reference
Vanillin	4-Hydroxy-3-methoxybenzaldehyde		ROS scavenging, ↑ antioxidant defense, ↓ DNA strand breaks & chromosomal aberrations, reduced apoptosis	(Keshava et al., 1998)
Zingerone	4-(4-hydroxy-3-methoxyphenyl)butan-2-one		ROS scavenging, antioxidant defense activation, induce oxidative stress	(Rao et al., 2011)
Zymosan A	crude preparation derived from the cell walls of brewer's yeast, Saccharomyces cerevisiae		TLR2 activation, NF-κB / MAPK, ↑ hematopoietic growth factors & anti-apoptotic proteins, protection of bone marrow	(Du Cheng et al., 2017)

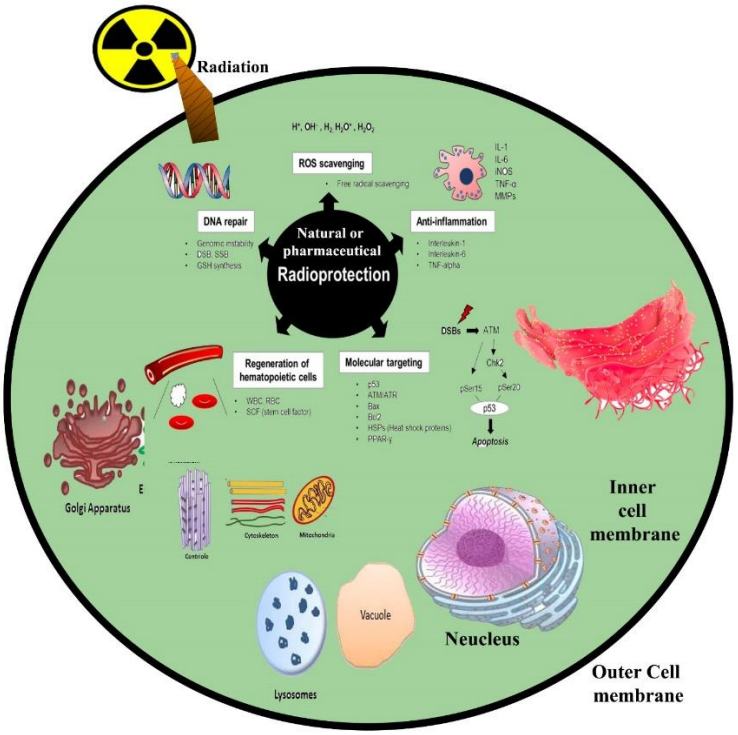


Figure 2. Activity of Radioprotectant during therapy and diagnosis.

Limitations of radioprotection study and in vivo and cell line study with natural compounds turn into drug discovery and treatment:

A new era in cancer genomic medicine is dawning. In a therapeutic environment, radioprotectants are the ultimate aim as new medicine candidates, and the most important concern is ensuring that they are safe and effective. Numerous barriers still stand in the way of tumor development being utilized beyond the bench, even with significant progress in chemotherapies. First, the effectiveness of administration: currently used radioprotectant delivery methods are chemically manufactured and have subpar cellular absorption properties. The second is the radioprotectants' specificity and off-target effects. It could have unforeseen repercussions, even though it might treat radioactivity. Targeting becomes more difficult because off-target impact requires only partial complementary binding of the radioprotectant. Third, radioprotectant-induced toxicity, since radioprotectants can transcriptionally regulate the synthesis of drug-degrading enzymes (Greenberger et al., 2012). The fourth obstacle is resolving the rapid clearance issue in blood systems. Last but not least, the primary barriers to the in vivo function of nucleotide-based medications are their rapid nuclease breakdown and endocytosis-induced drug escape.

However, experts worldwide are now using natural ingredients to treat cancer after the heyday of antibiotics. Due to the complex structures of natural products, conventional extraction methods have led to the continuous identification of previously isolated molecules that necessitate synthesis and modification. Due to the difficulties this intricacy presents from an economic and synthetic standpoint, many pharmaceutical corporations have sold off their extract collections. And lastly, there is the issue of supply.

Therefore, molecular target-based drug development has essentially supplanted the use of natural products, whereas cell line models provide several advantages, including the possibility of high sample numbers because of their cost-effectiveness. Second, by using research methods such as clinical trials offers a chance to investigate the pharmacogenomics problem, which was previously unsolvable. In contrast to cell line applications, it is simple to gather drug application results that require large sample sizes. It also encourages new research that aids scientists in selecting cell line findings for drug discovery.

Future Perspectives

In radiobiology and medicine, shielding people and animals from the effects of infrared radiation is a crucial concern. According to the research presented here, there are several possible radiation protectors with various functions and mechanisms of action (Johnke et al., 2014). By neutralizing or eliminating free radicals, activating enzymes involved in DNA repair, boosting immune and hematopoietic systems, or interacting with proteins involved in signaling and apoptotic processes, radioprotective drugs may mitigate radiation-induced damage and/or radiation-related disorders. Both natural and man-made substances are included in this group of radiation protectants.

Natural substances provide a number of benefits when it comes to radiation protection. Utilizing naturally occurring molecules has the primary benefit of being safer than synthesized ones. Additionally, radiation syndrome–like symptoms can be effectively treated with natural products. The effectiveness of herbal compounds has been demonstrated by studies investigating them as a unique radiation protection strategy (Oliai et al., 2014).

While cellular and animal model research shows that radioprotective agents can reduce DNA damage through a variety of mechanisms, the majority of the literature highlights the free radical–scavenging and free radical–induction roles of natural radioprotectants. Future studies should concentrate on the following areas, given the evidence of current limitations. The goal of derivative development is to make natural compounds more effective and bioavailable. Tailored drug

development requires determining precise active-ingredient targets to create customized treatments, which necessitates extensive research and substantial financial investment. Preclinical and clinical translation aims to assist cancer patients in the transition into clinical practice by confirming the efficacy and safety of promising natural drug-based treatments. The most difficult aspect remains mechanistic studies (Bhuiyan et al., 2022).

Future studies must investigate more sophisticated and compelling evidence of molecular pathways and the connections between pharmaceutical and natural radioprotectants. Enhancing collaboration among academics, physicians, and pharmaceutical corporations to expedite the discovery and translation of promising natural drugs and combination-based radiation therapies is referred to as collaborative research.

CONCLUSIONS

Since IR is frequently present in many facets of human life, including cancer radiation treatment, food preservation, agriculture, industry, and energy generation, the development of dependable and efficient radioprotectors is crucial. As a result, the growing use of nuclear radiation for human welfare calls for the creation of innovative, reasonably priced, and secure radioprotectors for both the general public and laboratory staff responsible for radiation handling and testing. Understanding the complex interactions and biological impacts of these natural chemicals is essential. Future studies should focus on fully understanding the ways in which these compounds might support anticancer treatment and shield healthy cells. With this approach, it will be possible to tailor treatments for each patient and maximize therapeutic strategies. Although the variety of natural substances makes them difficult to comprehend, it also offers an opportunity to identify effective treatments that may possess both anticancer and radioprotective effects. It is challenging to utilize these drugs in a regulated manner without appropriate controls and established procedures. Improved methods are required for evaluating plant extracts, ensuring their quality, and maintaining uniformity among various plant species in order to overcome these obstacles. Guidelines for the therapeutic use of these plant-derived substances might be established through collaboration among researchers, physicians, and regulators. By overcoming these challenges, the potential of plant-derived compounds to enhance current cancer therapies can be maximized, providing patients with safer and more effective ways to manage their illness.

Abbreviations:

CT, computed tomography; ROS, reactive oxygen species; SSBs , single stranded DNA breaks, DSBs, double stranded DNA breaks; IR, Ionizing radiation; UV, Ultra violet; RNS , reactive nitrogen species; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; NAC, N-acetyl cysteine; U.S. FDA, QOL, quality of life; GI , gastrointestinal; DNA, Deoxy ribo nucleic acid; RNA, Ribonucleic acid; AHH-1, Human lymphocyte; LDH, Lactate Dehydrogenase; GSH, non-enzymatic antioxidant, SOD, enzymatic antioxidants; DNA-PK, DNA-activated protein kinase, Chk, Checkpoint kinase; Cdk1, Cyclin-dependent kinase; Cdc, Cell division control protein; NBS1, Nijmegen breakage syndrome 1; NHEJ, non-homologous end-joining repair; HR, homologous recombination; DDR, DNA damage response; APE1, apurinic endonuclease 1; EGFR, Epidermal Growth Factor Receptor; RTKs, receptor tyrosine kinases; AKT, protein kinase B; PTEN, phosphatase and tensin homolog; mTOR, mammalian target of rapamycin; PI3K, Phosphoinisitide 3-kinases; Apaf-1, apoptotic protease activating factor 1; AIF, apoptosis inducing factor; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2 associated X; Bad, Bcl-2 associated agonist of cell death; CDK4, cyclin-dependent kinase 4; CDC2, cell division cycle2; COX-2, cyclooxygenase-2; CYP19/1A1/1A2, cytochrome P45019/1A1/1A2; DNMT1/3a, DNA (cytosine-5)-methyltransferase 1/3a; DMBA, 9,10-dimethyl-1,2-benzanthracene; ER-α, estrogen receptor- α; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor;

FoxM1, forkhead box M1; GSTA1, glutathione S-transferase A1; HER2/3, human epidermal growth factor receptor 2/3; hTERT, human telomerase reverse transcriptase; JNK, jun N-terminal kinase; LC3, microtubule-associated protein light chain 3; MMP-2, matrix metalloproteinase-2; UTR, 3-Untranslated Region; MDM2, Mouse Double Minute 2 Homolog; CCR6, C-C chemoattractant Cytokine Receptor 6; ATF2, Activating Transcription Factor-2; RSU1, Ras Suppressor-1; PINCH1, Protein Containing Five LIM Domains; PIP2/3, Phosphatidylinositol 4,5-bisphosphate 2/3; VGFA, Vascular Endothelial Growth Factor A; HIF1, Hypoxia Inducible Factor-1; LNM, Lymph Node Metastasis; CDH1, Cadherin protein-1; PIK3CA, Phosphatidylinositol-4-5, Bisphosphate 3-kinase Catalytic Subunit Alpha; PINK-1, PTEN Induced Kinase-1; MFN2, Mitofusin-2; CXCR4, C-X-C chemokine receptor type 4; SOD2, Superoxide Dismutase 2, mitochondrial; HUVEC, Human Umbilical Vein Endothelial Cells; STX3, Shiga Toxin 3; KLF16, Kruppel Like Factor-16; PARP, Poly ADP ribose polymerase; 4EBP1, Eukaryotic translation Initiation Factor 4E-binding Protein1 Phosphorylated; MAPK, mitogen-activated protein kinases; NQO1, NAD(P)H quinone dehydrogenase 1; STAT3, signal transducer and activator of transcription 3; TrxR1, thioredoxin reductase 1; VEGFR-2, vascular endothelial growth factor-2; Mcl-1, Myeloid cell leukemia; FLIP, c-FLICE inhibitory protein; Forkhead box O3, transcription factor FOXO3a; GSK3, glycogen synthase kinase 3; ODDD, oxygen-dependent degradation domain; CBP, CREB-binding protein; CSCs, Cancer stem cells; EMT, Epithelial-mesenchymal transition; Glut1, glucose transporter 1; YAP, Yes-associated protein; TEAD, Transcriptional Enhanced Associate Domain; CAT, catalase; GPx, glutathione peroxidase;

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