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Review Article

Exploring Natural Bioactive Compounds for Radiation Countermeasure Properties: A Review

Toijam Sanjeev Lyngdoh[1,3], Dollyca Ningombam[1,4], Thangal Yumnamcha[2], Maibam Damayanti Devi[2,*]

[1]Department of Life Sciences (Zoology), Manipur University, Imphal, Manipur, INDIA.
[2]Department of Life Sciences (Botany), Manipur University, Imphal, Manipur, INDIA.
[3]Department of Zoology, Don Bosco College, Tura, Meghalaya, INDIA.
[4]Department of Zoology, Jadonang Memorial College, Noney, Manipur, INDIA.

ABSTRACT

Radiation-induced toxicity poses significant challenges in radiation therapy, nuclear incidents, industrial, and other occupational applications. This review investigates the potentiality of natural bioactive compounds as defences against such toxicity. The study objectives include a comprehensive literature review, evaluation of compound efficacy, clarification of mechanisms, translational potential assessment, and identification of future research directions. Using a systematic methodology, peer-reviewed studies were carefully gathered from institutional library and databases including PubMed, ResearchGate, and Google Scholar. Qualitative analysis revealed patterns and trends in compound effectiveness. The review highlighted natural bioactive compounds like polyphenols, flavonoids, phenolic acids, ginseng, curcumin, and garlic among others, which exhibit antioxidant, anti-inflammatory, and DNA-protective effects. These compounds show promise in alleviating radiation-induced damage across different bodily tissues. Given the substantial health risks linked to ionizing radiation exposure, effective health-protective strategies are imperative to counter radiation-induced toxicities. Advancements in understanding signaling pathways and developing innovative radiation countermeasure agents offer avenues for better management of radiation toxicity. Future research directions involve robust clinical trials, clarification of molecular mechanisms, exploration of synergistic interactions, and long-term assessments of efficacy and safety.

Keywords: Bioactive compounds, Health-protective strategies, Ionizing radiation, Radiation countermeasure.

Correspondence:
Prof. Maibam Damayanti Devi
Genetics Lab., Department of Life Sciences (Botany), Manipur University, Imphal-795003, Manipur, INDIA.
Email: damayanti60.mu@gmail.com
ORCID: 0009-0006-1119-1270

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INTRODUCTION

Radiation therapy is a key component of cancer treatment, effectively targeting malignant cells. However, its clinical use is limited by damage to healthy tissues caused by oxidative stress, inflammation, and DNA damage (Baskar *et al.*, 2012). Radiotherapy efficacy may vary with cancer type (Moding *et al.*, 2013), but its associated toxicity significantly affects patients' quality of life (Joly *et al.*, 2010). Radiosensitivity refers to the susceptibility to side effects, which depends on the extent of healthy tissue exposure. Early effects occur during or shortly after treatment, typically resolving in 4-6 weeks, while late effects may appear months or years later and can be long-lasting (Berkey, 2010). Additionally, the risk of secondary malignancies, usually arising 5-15 years post-treatment, remains a serious concern (Sountoulides *et al.*, 2010).

Beyond cancer therapy, ionizing radiation is used in industrial quality control, food and medical sterilization, radiobiology, material science, nuclear physics, and nuclear power generation. Despite its utility, these applications pose risks of radiation toxicity from occupational or accidental exposure. As a result, there is growing interest in agents that can mitigate radiation-induced damage.

Research increasingly focuses on natural compounds for radiation protection. Plants, for instance, possess inherent mechanisms to survive high radiation environments, such as intense sunlight, partly due to antioxidants produced via secondary metabolism (Hall *et al.*, 2016; Altomare *et al.*, 2022). Understanding the bioactive compounds and metabolic pathways in plants is vital due to their medicinal relevance and potential in human health (Kaur *et al.*, 2019). Exploring antioxidants from natural sources requires appropriate model systems and analytical methods to evaluate their behavior during oxidative stress.

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METHODOLOGY

In this review, a systematic methodology was employed to identify relevant research concerning the role of natural bioactive compounds in mitigating radiation-induced toxicity and exploring effective health-protective measures. Searches were conducted using a combination of keywords related to radiation-induced toxicity and natural radioprotective agents across multiple sources including the institutional library repository and electronic databases such as PubMed, ResearchGate, and Google Scholar. This process enabled the identification of key themes, forming the foundation for drawing conclusion based on collective evidence in the literature.

RESULTS

Radiation-induced toxicity

Radiation is crucial in disease treatment and human welfare, yet it also poses risks to living organisms (Little, 2003). Organisms, including humans, encounter varying levels of radiation based on factors like location and intensity, with harmful effects depending on dosage and specific thresholds (Tubiana *et al.*, 2007). Studies consistently indicate that radiation exposure leads to DNA damage, cell death and premature ageing (Desouky *et al.*, 2015). Typically, radiation-induced tissue damage presents as local effects and can be categorized as acute (early) and chronic (late) side effects. Early symptoms appear shortly after starting radiotherapy and result from cell damage. Some quickly renewing tissues which may not regenerate adequately like the oral mucosa, bone marrow, skin or intestinal mucosa, struggle to regenerate sufficiently, leading to potential adverse effects such as dry or moist desquamation, oral mucositis, skin erythema, nausea, headaches, diarrhoea, or oedema (Dörr, 2009). Additionally, cellular damage triggers a local inflammatory response, contributing to these effects (Altomare *et al.*, 2022).

Late side effects involve a more complex pathogenesis and are typically gradual and irreversible. Tissues with low rates of cell turnover may experience side effects persisting for long periods after treatment (Chatterjee, 2013). These late effects can encompass radiation-induced atrophy, damage to blood vessels and fibrosis. Thus, ionizing radiation exposure results in different pathways for the two types of side effects. Nonetheless, the intensity of acute side effects can impact the degree of chronic side effects, known as consequential late effects. Understanding the mechanisms behind radiation-induced damage to normal tissues is crucial for mitigating toxicities. Disruption of finely modulated regeneration processes often necessitates supportive therapies to alleviate symptoms (Seibold *et al.*, 2020).

Biological effects stemming from radiation exposure can manifest through direct or indirect mechanisms. When energy from ionizing radiation is absorbed within biological material, there is a potential for direct interaction with vital cellular targets. This interaction may induce ionization or excitation of atoms within the target, initiating a sequence of events that ultimately lead to biological damage, i.e., the direct effect of radiation. Alternatively, radiation can interact with cellular molecules, thereby producing reactive species which are capable of damaging critical targets. This process is commonly known as the indirect effect of radiation (Kam and Banati, 2013).

During radiation exposure, ionizing radiation produces Reactive Oxygen Species (ROS) and free radicals which cause cellular DNA strand breaks, and DNA cross-linking with proteins or other DNA molecules. Typical clinical ionizing radiation doses result in about 1000 SSBs, 40 DSBs, and as many as 3000 base damage per Gray (Hall and Giaccia, 2012). The breakdown of DNA strands can contribute to long term diseases and age-dependent medical issues (Sharma and Singh, 2021; Gao *et al.*, 2014; Guleria *et al.*, 2017). Increasing doses of ionizing radiation also induce impairment of hematopoietic systems (Guo *et al.*, 2015).

Overview of natural bioactive compounds and their mechanisms in mitigating radiation-induced toxicity

Investigations by various researchers on the protective properties of natural compounds against ionizing radiation-induced damage have given us insights into alleviating radiation-induced toxicity. Sorokina and Steinbeck, (2020) explained that natural herbal remedies traditionally employed for a wide array of human ailments serve as a rich reservoir of potential radiation countermeasure agents, with recent databases reporting approximately 400,000 medicines derived from natural sources.

Pasqualetti *et al.*, (2021) studied the effect of extracts sourced from various plants, including olive mill water, pomegranate fruit mesocarp (*Punica granatum* L. cv. Wonderful), rosemary leaves (*Rosmarinus officinalis* L.), Vineatrol®30 and grape seeds (*Vitis vinifera* L. cv. Italia) against Ultraviolet-B (UV-B)-induced erythrocyte membrane lipid peroxidation. They emphasised the link between the phenolic content of plant-derived compounds and their ability to alleviate oxidative damage in biological systems.

Epicatechin, a polyphenol present in green tea, inhibits radiation-induced cell apoptosis, membrane potential loss in mitochondria and intracellular oxidative damage in human keratinocytes (Shin *et al.*, 2013; Altomare *et al.*, 2022). Tea polyphenols' antioxidative effects include direct free radical elimination, suppression of free radical production, scavenging radical precursors, chelation of metals, and intracellular antioxidant regeneration (Altomare *et al.*, 2022).

Epigallocatechin-3-Gallate (EGCG), a flavanol catechin found in green tea, has been reported to increase the concentrations of endogenous antioxidants such as Glutamate-Cysteine Ligase (GCL, EC 6.3.2.2) and Superoxide Dismutase (SOD, EC 1.15.1.1) *in vivo* and *in vitro* (Zhu *et al.*, 2014). In their article, Zhu *et al.*,

(2014) have highlighted that EGCG enhances the survival of human skin cells subjected to X-rays, decreases apoptosis and relieves mucositis symptoms. EGCG also exhibits protective effects against ultraviolet radiation, thereby impeding skin photo aging (Zhu *et al*., 2016; Avadhani *et al*., 2017).

Ginsenosides, obtained from *Panax ginseng*, has demonstrated radiation countermeasure effects on mammalian cells in laboratory and animal studies, reducing radiation-induced damage to healthy cells (Lee *et al*., 2005; Lee *et al*., 2010). Fennel seed extract and senna (*Cassia* sp.) have also shown promise as radiation countermeasure agents, with fennel seed extract scavenging free radicals and senna in inducing cell apoptosis (Mohamad *et al*., 2011; Farid *et al*., 2020).

Curcumin, a major curcuminoid found in turmeric (*Curcuma longa*) and known for its potent antioxidant properties, mitigates injuries to normal cells caused by irradiation through its anti-inflammatory effects (Verma, 2016; Chikara *et al*., 2018; Zoi *et al*., 2022). It has exhibited a mitigative role in heart tissue and prostate cancer patients undergoing radiotherapy (Hejazi *et al*., 2013; Kolivand *et al*., 2019). In a pilot study, curcumin is also reported to be both effective and safe in treating Radiation-Induced Oral Mucositis (RIOM) when used as a mouthwash among patients undergoing radiochemotherapy (Patil *et al*., 2015).

Peppermint (*Mentha piperita* Linn.) extract and *Amaranthus paniculatus* extract have demonstrated radiation countermeasure effects attributed to their antioxidant activities (Samarth and Samarth, 2009; Krishna and Kumar, 2005). Silymarin, derived from milk thistle, is also found to protect the liver from radiation damage through its antioxidant properties (Ramadan *et al*., 2002).

Moringa (*M. oleifera* L.) is an economically important deciduous plant found in Asia, Africa and Central America which is used as traditional medicine. The leaf extract of this plant has exhibited notable radiation countermeasure as observed from the effects on the chromosome integrity of bone marrow cells and survivability after lethal dose in mice (Rao *et al*., 2001); and enhancing antioxidant levels in the blood (Elwan *et al*., 2018).

Garlic, particularly allicin, has demonstrated protective effects against radiation-induced hepato-alveolar damage; and mortality, potentially through induction of apoptosis (Park *et al*., 2005; Xu *et al*., 2014). Flaxseed reduces lung injury biomarkers Bax, p21 and TGF-β1 expression, which otherwise show proportionate injury with increased radiation; ameliorates inflammation and lung fibrosis post ionizing radiation exposure in mice (Lee *et al*., 2009).

Apigenin, a flavonoid found abundantly in numerous fruits, vegetables and beverages, has demonstrated a significant reduction in UV-B induced micronuclei formation in human dermal fibroblast cells. Pre-treatment with apigenin has been shown to protect human peripheral blood lymphocytes from DNA damage caused by UV-B exposure (Britto *et al*., 2017).

Caffeine, recognized for its antioxidant and anti-inflammatory properties, scavenges hydroxyl radicals and peroxides with activity comparable to glutathione (Hall *et al*., 2015; Vieira *et al*., 2020). Furthermore, it facilitates the restoration of normal cell cycle progression following G2 phase arrest induced by ionizing radiation exposure and reduces UV-induced proteins in melanoma cells (Grinfeld and Jacquet, 1987; Ravi *et al*., 2008).

Delphinidin, an anthocyanin, demonstrates potent antioxidant properties due to its numerous hydroxyl radicals (Watson and Schönlau, 2015). Additionally, delphinidin safeguards normal tissue high energy radiation, indicating its efficacy as a radioprotector (Kim *et al*., 2018).

Hesperidin, a flavone glycoside abundant in lemons and sweet oranges, possesses radiation countermeasure properties due to its anti-inflammatory and antioxidant characteristics. A study reported that hesperidin protects peripheral lymphocytes from oxidative stress damage induced by gamma-irradiated in rats (Fardid *et al*., 2016). Moreover, hesperidin demonstrates antioxidant and anti-apoptotic activity and alleviates gamma-radiation lung tissue and testes injury in Sprague-Dawley albino rats (Rezaeyan *et al*., 2016; Shaban *et al*., 2017).

Lutein, found in various sources including green leafy vegetables, serves as a potent antioxidant and blue light filter in the macula and lens of the human eye. Pre-radiation treatment with lutein has been shown to mitigate radiation-induced effects while maintaining hematological parameters and antioxidant levels in Swiss albino mice and decreasing lipid peroxidation, thus indicating protection against oxidative stress (Vasudeva *et al*., 2017).

Cinnamic acid, a phenolic phytocompound, and cinnamaldehyde found in cinnamon (*Cinnamomum* spp.) have been shown to exhibit protective effects against ionizing radiation-induced mucositis (Molania *et al*., 2012) and oxidative stress-induced splenotoxicity in rats (Abd El-Raouf *et al*., 2015), thus displaying potentiality as a radiation mitigating agents.

Lycopene, a carotenoid abundant in fruits and vegetables with red hues, offers substantial chromosomal damage protection from gamma irradiation of human lymphocytes (Cavusoglu and Yalcin, 2009). Studies indicate lycopene's capacity to mitigate radiation damage by scavenging ROS and reducing intact oxygen, thereby decreasing micronuclei and abnormalities in irradiated human lymphocytes. Lycopene pretreatment also lowers lipid peroxidation by radiation and enhances the metabolism of endogenous antioxidant enzyme activities (Gajowik and Dobrzyńska, 2017). Motallebnejad *et al*., (2020) found that lycopene reduced mucositis severity in irradiated rats' oral

mucosa, potentially preventing complications in radiotherapy, such as those in head and neck cancers.

Sesamol, a natural phenolic antioxidant found in sesame and sesame oil, exhibits potent ROS absorption and antioxidant properties, shielding human neurons from H_2O_2-induced DNA damage (Ruankham *et al.*, 2021). Sesamol significantly reduces gamma radiation-induced DNA damage in the mouse hematopoietic system and bone marrow cells (Kumar *et al.*, 2015).

N-Acetyl-Tryptophan Glycoside (NATG), derived from *Bacillus* sp. INM-1, shows promise in radiation protection. NATG pretreatment enhances the production of cytoprotective cytokines like IL-12, IL-17A, and interferon-c, thus inhibiting radiation-induced apoptosis (Malhotra *et al.*, 2015). Furthermore, NATG inhibition safeguards J774A.1 macrophages and augments antioxidant activity against radiation-induced damage in murine macrophages (Malhotra *et al.*, 2016; 2018).

Some studies have delved into understanding the various intracellular pathways that lead to apoptosis in ionizing radiation-induced damage as well as to identify late events in these pathways as post-irradiation intervention targets. Following irradiation, it has been noted that ATM/ATR, as a checkpoint protein and p53 tumor suppressor, modulates DNA damage pathways and initiates cell death by upregulating pro-apoptotic proteins like Apaf-1, Bax and Noxa (Mun *et al.*, 2018). Conversely, Pifithrin-μ, a p53 inhibitor, safeguards thymocytes from undergoing apoptosis following ionizing irradiation; it also significantly reduces death in mice when administered prior to ionizing irradiation (Strom *et al.*, 2006). Likewise, Bcl-2 overexpression in transgenic mice increased survivability by safeguarding hematopoietic cells from ionizing radiation-induced apoptosis (Erlacher *et al.*, 2005). Studies also suggest that CBLB502, a STAT3 activator, and enhanced STAT3 activation protect against ionizing radiation-induced damage (Xu *et al.*, 2016; Wang *et al.*, 2024). Heat shock proteins (Hsp70) mediate cell and tissue repair by alleviating post ionizing radiation G2/M block (Lee *et al.*, 2001); their overexpression or small molecule enhancers offer promise for ionizing radiation symptom treatment. Knatko *et al.*, (2015) has reported that the nuclear factor-erythroid 2-related factor 2 (Nrf_2) upregulation in SKH-1 hairless mice protects against solar-simulated UV-B-induced skin damage. Agonists of Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) impede collagen deposition and ionizing radiation-induced survival signals while enhancing apoptosis signaling. PPAR-γ ligands are potential therapeutic agents for ionizing radiation-induced fibrotic lung diseases as well as intestinal toxicity (Milam *et al.*, 2008; Mangoni *et al.*, 2017).

Notably, bioactive compounds in polyphenols have been found to upregulate the mRNA expression of various enzymes, including glutathione peroxidase, catalase, superoxide dismutase and apoptotic pathway enzymes, thereby counteracting oxidative stress induced by ionizing radiation (Adnan *et al.*, 2022).

Radiation countermeasure agents mitigate ionizing radiation-induced effects by scavenging free radicals or inhibiting their formation. Pro-inflammatory cytokines like IL-1, IL-6, TNFα, and TGF-β are produced post-ionizing radiation exposure (Di Maggio *et al.*, 2015). A study indicated that TGF-β modulates the development of lung fibrosis following irradiation (Straub *et al.*, 2015). Since oxidative free radical's damage DNA through SSBs, DSBs and base lesions, preventing cellular damage is crucial. Radiation countermeasure agents act to enhance the cellular recovery pathways and DNA repair processes. Studies suggest that the absence of Glutathione (GSH) synthesis impairs DNA SSB repair, indicating the involvement of thiols like GSH in the repair process (Chatterjee, 2013).

DISCUSSION

Health protective strategies

An optimal radiation countermeasure agent should possess several essential characteristics: (i) Comprehensive shielding of tissues and organs from radiation-induced damage, (ii) Long shelf life and ease of administration, (iii) Accessibility, affordability, and compatibility with various clinical treatments, (iv) Effective recommended doses that can reach target organs (v) Long-lasting effects during emergencies. Therefore, an ideal radiation countermeasure agent ought to be non-toxic, providing robust protection to normal cells while minimally affecting tumor cells.

A study has indicated that ionizing radiation exposure induces dose-dependent changes in the lymphoid and hematopoietic systems, leading to hematopoietic syndrome, septicemia, and potential fatality (Guo *et al.*, 2015). Therefore, enhancing hematopoietic cell regeneration and immune system stimulation, such as increasing spleen colony-forming units, are vital therapeutic approaches to ionizing radiation-induced damage. By stimulating the stem cells and supporting the regeneration of hematopoietic bone marrow, immune modulators like IL-1, TNF-α, G-CSF, SCF, EPO, and GM-CSF, have shown promise as radioprotectors (Dumont *et al.*, 2010; Schaue *et al.*, 2012). Upregulation of these immune modulators offers a potential avenue for radioprotection.

Studies of Dutta *et al.*, (2021) have reported that the natural products extracted from plants show promise as protecting agents against ionizing radiation. Brown *et al.*, (2010), through their research, have reported that initiating an antioxidant-rich diet 24 hr after radiation exposure effectively decreased the radiation-induced mortality by preserving bone marrow cells in murine models. Furthermore, their study indicated that a diet with higher antioxidant content was more successful in counteracting lethality when administered 24 hr post-exposure, surpassing the

efficacy observed with immediate post-exposure administration. This phenomenon is attributed to natural products acting as scavengers of ROS generated post-radiation exposure.

The antioxidant potential of bioactive molecules in mitigating the adverse effects of ionizing radiation is significant. Mills *et al.*, (1988) have observed, despite a small sample size, the protective effect of a beta-carotene-enriched diet against oral mucositis among patients of mouth carcinoma undergoing radiation and chemotherapy. The effect is attributed to antioxidants' ability to neutralize free radicals generated by radiation interacting with water molecules.

Firouzi *et al.*, (2015) has suggested resveratrol as a promising agent for treating ROS-mediated and cell cycle related diseases with the possibility extending to radiation-induced damage after observing resveratrol's effects on cell colony death and DNA damage in glioblastoma cells. Fernando *et al.*, (2016) demonstrated rosmarinic acid's potential in mitigating UV-B radiation-induced skin diseases by modulating cellular antioxidant systems. Arivalagan *et al.*, (2015) found that pre-treating lymphocytes with carvacrol before X-ray irradiation reduced DNA damage. Additionally, luteolin-7-*O*-(2-apiosyl)-glucoside showed significant superoxide radical scavenging capabilities, indicating potential for radiation countermeasure (Materska *et al.*, 2015). Jin *et al.*, (2015) suggest that pretreatment with caffeic acid effectively treats radiation-induced intestinal damage in murine models by reducing intestinal mucosal apoptosis and oxidative stress following 72 hr of radiation exposure. Gallic acid, found in various fruits, acts as a radiation mitigating agent due to its antioxidant and pro-oxidant properties. Its ability to chelate transition metal ions reduces mortality in rats after γ-irradiation by inhibiting membrane lipid peroxidation (Fischer *et al.*, 2018). Das *et al.*, (2017) demonstrated ferulic acid's protective effect against radiation-induced intestinal injury in animal models.

A study by Yong *et al.*, (2009) examined the relationship between specific carotenoid intake and translocation frequency of DNA in pilots subjected to cosmic radiation, suggesting that a diet rich in zeaxanthin, vitamins, and lutein could help mitigate DNA damage caused by radiation. Nejatinamini *et al.*, (2018) focused on vitamins A, B12, D, E, and folate, revealing that patients with low plasma levels of these vitamins are more prone to development of mucositis while undergoing cancer treatment. Gamma-Tocotrienol, a form of vitamin E, showed promise as a gastrointestinal radioprotector, exhibiting protection against intestinal injury induced by ionizing radiation (Lu *et al.*, 2019). Sayed *et al.*, (2019) investigated the therapeutic effects of pentoxifylline combined with vitamin E in the treatment of RIOM among selected patients with head and neck cancer, concluding that this treatment regime reduced the aggravation of RIOM.

Challenges and future directions

Current challenges and future directions include limited clinical evidence, variable compound bioavailability, and the lack of standardized protocols. Literature gaps stem from unclear mechanisms, inconsistent study designs, and limited long-term data. Future research should prioritize clinical trials to confirm efficacy, elucidate molecular pathways, and explore compound synergy. Standardized methodologies, large-scale studies, and long-term outcome assessments are vital for advancing the field and integrating findings into clinical practice.

While the oxygen effect underpins radiotherapy's effectiveness, antioxidants used to reduce radiation toxicities do not diminish its impact. Polyphenols and vitamins have recently gained attention as natural protectors against radiation-induced toxicity (Dutta *et al.*, 2021). The use of antioxidants in cancer patients undergoing chemotherapy or radiotherapy is debated. Proponents argue that antioxidants protect healthy cells by promoting apoptosis and cell-cycle arrest, thus reducing adverse effects (Drisko *et al.*, 2003; Simone *et al.*, 2007; Merlin *et al.*, 2021). Hosseinimehr, (2007) reported that low-dose herbal preparations show superior radioprotective effects compared to toxic levels of synthetic agents. Reviews suggest dietary antioxidants can protect healthy tissue and tumor cells from oxidative damage during chemotherapy (Conklin, 2000) and radiation (Ladas *et al.*, 2004).

However, critics argue antioxidants may reduce the effectiveness of cancer therapy by lowering oxidative stress (D'Andrea, 2005). Some studies show that N-acetyl cysteine, vitamin E, and Trolox may promote carcinogenesis in mice (Sayin *et al.*, 2014; Zou *et al.*, 2021). Bairati *et al.*, (2005) found no improvement in quality of life and potential compromise in treatment efficacy from high-dose antioxidants in 540 head and neck cancer patients. Concerns remain about antioxidant supplements shielding tumor cells and affecting survival outcomes (Lawenda *et al.*, 2008). More clinical trials are essential to determine their therapeutic value (Nakayama *et al.*, 2011).

CONCLUSION

The pursuit of efficient, cost-effective and low-toxicity radiation countermeasures has fuelled global interest in natural products. Various compounds such as polyphenols, flavonoids, and phenolic acids have emerged for their radiation countermeasure properties, exhibiting antioxidant, anti-inflammatory, and DNA-protective effects. These compounds show promise in reducing radiation-induced damage across diverse tissues and organs. Additionally, natural products like ginseng, curcumin, and garlic's allicin display notable radiation countermeasure effects, hinting at their possible clinical applications. Understanding the underlying mechanisms of radiation-induced toxicity and the therapeutic actions of bioactive compounds is crucial, as emphasized in the review.

Future research should tackle existing challenges, including limited clinical evidence and variations in compound bioavailability, through rigorous clinical trials and standardized protocols. Unravelling the molecular mechanisms behind the radiation countermeasure effects of natural compounds and exploring potential synergies among them are imperative. Large-scale studies are necessary to evaluate the long-term efficacy and safety profiles of these compounds in clinical settings. Furthermore, advancements in understanding the signaling pathways implicated in radiation-induced damage; and the development of innovative radioprotectors, radiomitigators and therapeutic agents hold promise for enhancing the management of radiation toxicity and improving patient outcomes. Integrating natural bioactive compounds into health protective strategies offers a hopeful perspective for alleviating ionizing radiation-induced toxicity and bolstering the palliative care of individuals undergoing radiation therapy.

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ABBREVIATIONS

Apaf-1: Apoptotic protease-activating factor 1; **ATM/ATR:** Ataxia-telangiectasia mutated/ and Rad3-related; **Bax:** Bcl-2 associated X protein; **Bcl-2:** B-cell lymphoma 2 protein; **DSBs:** Double-Strand Breaks; **EGCG:** Epigallocatechin-3-Gallate; **EPO:** Erythropoietin; **GCL:** Glutamate-Cysteine Ligase; **G-CSF:** Granulocyte-Colony Stimulating Factor; **GM-CSF:** Granulocyte-Macrophage Colony-Stimulating Factor; **GSH:** Glutathione; **Hsp70:** Heat Shock Proteins (70 kDa); **IL:** Interleukin; **NATG:** N-Acetyl-Tryptophan Glycoside; **Nrf_2:** Nuclear factor-erythroid 2-related factor 2; **PPAR-γ:** Peroxisome Proliferator-Activated Receptor-γ; RIOM: Radiation-Induced Oral Mucositis; **ROS:** Reactive Oxygen Species; **SCF:** Stem Cell Factor; **SOD:** Superoxide Dismutase; **SSBs:** Single-Strand Breaks; **STAT3:** Signal Transducer and Activator of Transcription 3; **TGF-β:** Transforming Growth Factor beta; **TGF-β1:** Transforming Growth Factor beta 1; **TNFα:** Tumor Necrosis Factor alpha; **UV-B:** Ultraviolet-B.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTIONS

T S Lyngdoh: Conceptualization, Methodology, Investigation, Writing-Original draft, Reviewing and Editing, References.

Ningombam D: Investigation, Writing-Reviewing and Editing, References.

Yumnamcha T: Writing-Reviewing and Editing.

Maibam DD: Conceptualization, Supervision, Writing-Reviewing and Editing.

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