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Protection during radiotherapy: selenium

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Abstract – The multifaceted applications of nuclear technology, especially in cancer treatment through radiotherapy, bring considerable benefits to our daily lives but also necessitate the imperative for effective strategies to effectively mitigate radiation-induced issues. While strict compliance with usage specifications is essential, ensuring proper protection against radiation-induced damages is crucial. Selenium, in its various forms including selenomethionine, Ebselen, and sodium selenite, emerges as a promising radioprotective agent with demonstrated efficacy across diverse radiation-injured organs, highlighting its significance as an effective and potent antioxidant that affordable for most patients. Abundant experiments have exhibited the capacity of selenium-containing compounds and metabolites to function as valuable radioprotective adjuvants, emphasizing their potential in safeguarding against the adverse effects of radiation exposure. To harness the full radioprotective potential of selenium, further research is needed to optimize selenium supplementation strategies, taking into account factors such as timing and dosage, particularly in the context of radiotherapy.

Keywords: Radioprotection / radiotherapy / selenium / Ebselen / sodium selenite

1 Introduction

With the evolution of society, nuclear technology has found applications in various fields including medicine, the military and nuclear power instead of one terminology. This transition from a singular application to a multifaceted usage has spurred significant progress across all walks of life. Despite the strides made and given that nuclear energy itself is still considered risky in condition of inadequate compliance of instructions, we could never underestimate its detriments. Nowadays, with the escalating global incidence of cancer worldwide, radiotherapy (RT) is introduced to cancer patients during their treatment more often, thus the likelihood of radiation damage ensue. The problems stemming from radiation have garnered heightened attention, making the prevention and treatment of the radiation-induced damage become a hot topic of discussion (Arnold, 2022).

In addition to being directly acting on DNA, ionizing radiation (IR) also leads to superfluous production of reactive oxygen species (ROS), such as hydroxyl radicals, singlet oxygen, and hydrogen peroxide, which, in turn, causes damage to pivotal cellular contents including DNA, RNA, proteins and lipids, leading to necrosis and apoptosis, ultimately resulting in cell death. Approximately two-thirds of radiation-induced damage attributes to ROS, which continues to be generated post-irradiation (Brown *et al.*, 2010).

Radiotherapy is now commonly used in the realm of cancer treatment, with roughly half of cancer patients undergoing this procedure. Higher doses of radiation within a reasonable range are frequently needed to maximize the eradication of cancer cells in the irradiated area, but high doses of RT may cause severe toxicity in adjacent tissues and organs (De Ruysscher *et al.*, 2019). Biological effects caused by radiation exposure could be divided into two categories according to the dose of radiation: relatively higher dose of radiation could cause acute radiation syndrome and the following delayed effect of acute radiation exposure, while lower dose of radiation is inclined to chronic radiation injury (Ray *et al.*, 2014). Receiving high-dose (>2 Gy) total-body irradiation (TBI) in a relatively short time may lead to acute radiation syndrome (ARS), which represents a collection of symptoms such as nausea, vomiting, fatigue, fever, diarrhea and seizures. And these symptoms typically manifest with minutes to weeks after the exposure. While the injury lingers, placing survivors of ARS at risk of delayed effect of acute radiation exposure (DEARE), which occurs months to years after radiation exposure and may cause a range of chronic illness, such as injury in pulmonary tissue, hepatic tissue, kidney tissue, cardiovascular tissue, reproductive tissue and oral cavity as well as salivary glands, giving rise to corresponding symptoms (Dainiak *et al.*, 2011; DiCarlo *et al.*, 2011; Gasperetti *et al.*, 2021; Wu and Orschell, 2023). Chronic radiation injuries may elevate the risk of cardiac toxicity, cognitive impairment, reproductive disorders, deformity and impairments to bone and teeth growth, hair loss and secondary malignancy, genetic mutations and carcinogenesis.

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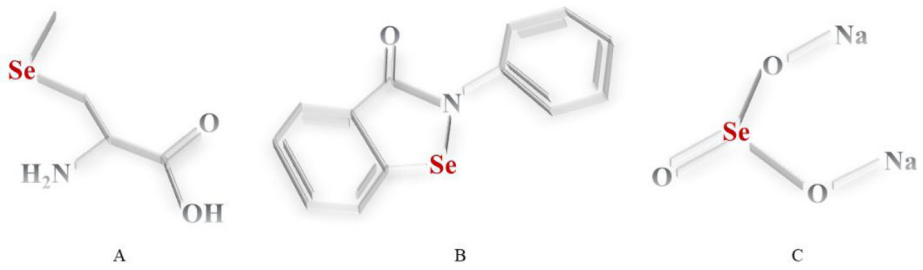

Fig. 1. Chemical structures of compounds and metabolites of selenium. (A) Selenomethionine [$C_5H_{11}NO_2Se$] (Se-Met); (B) Sodium selenite [Na_2SeO_3]; (C) Ebselen [2-phenyl- 1,2-benzisoselenazol-3(2H)-one] (Eb).

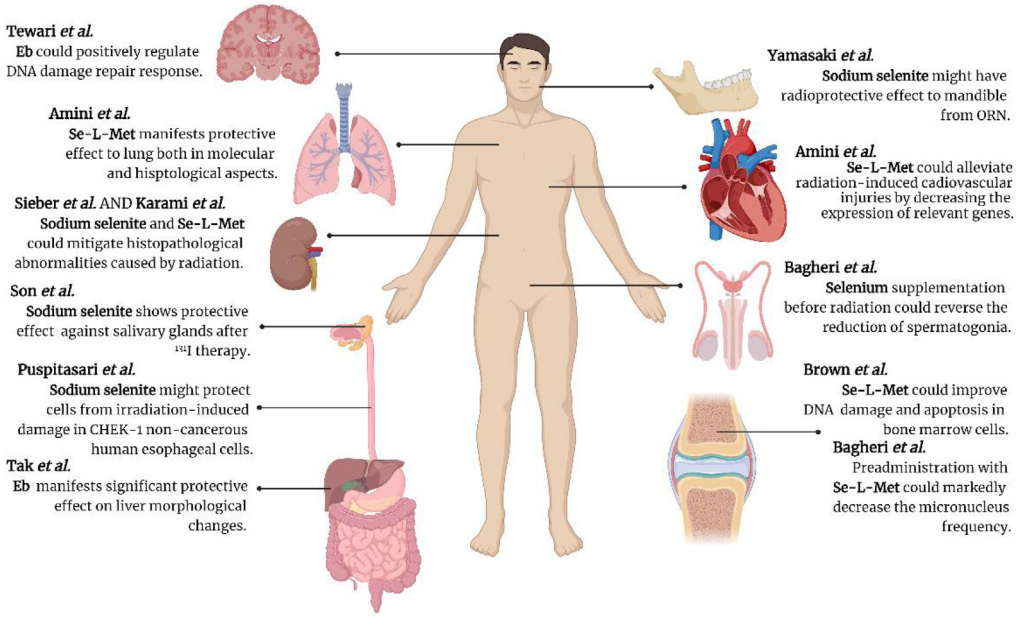

Fig. 2. Simple conclusion of Selenium and its various forms including selenomethionine, Ebselen, and sodium selenite acting as radioprotective agents to different body systems. Eb, Ebselen; Se-L-Met, Seleno-L-Methionine.

Therefore, the identification of active and effective radiation protection agents against ionizing radiation is crucial to mitigate the radiation hazard of radioactive accidents (De Ruysscher *et al.*, 2019; Tapio *et al.*, 2021).

Selenium (Se), an essential microelement, and its compounds, along with their metabolites, play vital roles in numerous of biological functions (Green, 2018). As one of the highly regulated proteins, selenoproteins are instrumental in preventing and modulating several clinical outcomes and diseases, including cancer, diabetes, Alzheimer's disease, mental disorders, cardiovascular disorders, fertility impairments, inflammation, and infections (including SARS-CoV-2) (Barchielli *et al.*, 2022). Additionally, selenium has long been considered as radiation – protective agent in the field of radiobiology since 1969 (Michalke, 2018). By upregulating the absorption and utilization of cysteine, the biosynthesis of glutathione, detoxificating reactive oxygen free radicals, and protecting of polyunsaturated fatty acids and cholesterol molecules free from peroxidation, selenium takes its role in radiation protection. In short, the antioxidation, anti-inflammatory effect and DNA stabilizing formed the protective effects of selenium against DNA damage induced by radiation (Bartolini *et al.*, 2020).

This review seeks to elucidate part of the potential abilities of selenium together with its compounds and metabolites including selenomethionine [$C_5H_{11}NO_2Se$] (Se-Met) (Fig. 1A), sodium selenite [Na_2SeO_3] (Fig. 1B) and Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one](Eb) (Fig. 1C) to act as radioprotectants, and present selenium as a reliable radioprotective agent for scientists and companies seeking effective solutions in this domain (Fig. 2, Tab. 1).

2 Selenium

Selenium is an important microelement that exists primarily in plants and animals in two chemical forms: organic and inorganic. The selenium content in foods varies, most of which occurs in a protein-combination way, while fruits and vegetables generally contain relatively lower levels. The primary organic selenium compound is selenomethionine [$C_5H_{11}NO_2Se$] (Se-Met), a natural amino acid incorporating

Table 1. Selenium and selenium-containing compounds and metabolites to function as valuable radioprotective adjuvants. Se-L-Met, Seleno-L-Methionine; Eb, Ebselen; Se-NPs, selenium nanoparticles.

Type of Selenium Seupplementation	Dosage of Selenium	Object	Dosage of Radiation	Timing	Author
Selenium	800 IU for selenium group and 50 mg for combined group	human	2 Gy of X-rays	before radiation	Rostami *et al.* (2016)
	0.8 mg/kg body weight	mice	2 Gy of γ irradiation	before radiation	H Bagheri *et al.* (2019)
Se-L-Met	10 μM	RKO cells	UV-radiation	before radiation	Fischer *et al.* (2006)
	100 μg/kg body weight/day*30d	mice	UV-radiation	before radiation	Guo, Guo, and Liu (2020)
	4 mg/kg body weight	rats	2 Gy of γ irradiation	before radiation	H Bagheri *et al.* (2017)
	4 mg/kg body weight	rats	15 Gy of γ irradiation	1 day before and 3 consecutive days after radiation	Amini *et al.* (2018)
	4 mg/kg body weight	rats	15 Gy of γ irradiation	1 day before and 5 consecutive days after radiation	Amini *et al.* (2019)
Eb	5 μM	U937 cells	2/20 Gy of γ irradiation	before radiation	Tak and Park (2009)
	10 mg/kg body weight/day*14d	mice	8 Gy of γ irradiation	before radiation	
Sodium Selenite	50 nM	CHEK-1 cells	2 Gy of X-rays	before radiation	Puspitasari *et al.* (2017)
	0.8 mg/kg body weight	rats	15 Gy of X-rays	before radiation	Yamasaki *et al.* (2019)
	cumulative dose of 17 mg	human	Depending on the individual treatment plan	during the whole radiotherapy	Muecke *et al.* (2010,2014)
	4μg/kg body weight	mice	5/8 Gy of γ radiation	before and after radiation	Verma, Kunwar, and Indira Priyadarsini (2017)
Sodium Selenite and Se-L-Met	100 μg of (atomic) selenium/d*21w	rats	10 Gy of X-rays	after radiation	Sieber *et al.* (2009)
	150 or 200μg/d*4m				Sieber *et al.* (2011)
Sodium Selenite and Se-NPs	0.1 mg/kg body weight*14d	mice	2/8 Gy of γ irradiation	before and after radiation	Karami *et al.* (2018)

selenium, and the most common inorganic selenium supplement is inorganic salts, with sodium selenite [Na_2SeO_3] being the most widely known (Kieliszek and Błażejak, 2016; Kieliszek and Serrano Sandoval, 2023; Yang *et al.*, 2017). The predominant way for human body to intake of selenium is through daily dietary sources and integrate into selenoproteins in the form of selenocysteine. Being involved in several processes, selenoproteins are historically regarded as a primary focus of related studies. Selenium has been wildly acknowledged to contribute to the reduction of oxidative stress through different selenoproteins including thioredoxin reductase (TrxR), glutathione peroxidase (GSH-Px, GPx) and others (Sieber *et al.*, 2009). Notably, GPx is one of which has been studied in depth and extensively (Mangiapane *et al.*, 2014; Rayman, 2012). Fenech *et al.* discussed the protective role of microelements supplements from DNA damage in humans with selenium considered as a prevention of oxidative stress and inflammation. Meanwhile biological effects that are not mediated by selenoproteins have drawn the scientists' attention, specifically safeguarding of DNA by preventing damages as well as promoting repairment, which may be the main reason for why selenium is regarded as a radioprotective agent. Researchers worldwide recently have substantiated that selenium do have promising radioprotective effect in different organs (Fenech *et al.*, 2023).

Selenium and Vitamin-E are both regarded as efficient antioxidants and are affordable for most patients. Rostami *et al.* performed their study and 15 volunteers were divided into 3 different groups treated with selenium, Vitamin-E, and the combination of both, respectively. 2 whole blood samples were collected at each sampling time, one of which was used as non-irradiated control and another was irradiated with 2 Gy of 6 MV X-rays. Results indicated that both selenium and Vitamin-E effectively reduced the incidence of micronuclei

and the total micronuclei values 1 hour after finishing oral supplementation were decreased by more than 40% comparing with similarly irradiated whole blood collected at the beginning, specifically in the combined treatment group, the total micronuclei values were reduced by 50% (Rostami *et al.*, 2016).

Beyond the involvement of selenium in the process of spermatogenesis, previous studies have proven that it can also improve sperm motility and semen quality (Moslemi and Zargar, 2011). Given its vulnerability to environmental toxic agents, even regular therapeutic dose of radiotherapy (RT) may have detrimental impact on spermatogenesis system. Bagheri *et al.* conducted their experiments by feeding mice selenium and zinc before radiation and evaluated the radioprotective effect through histopathological results. The findings revealed that both selenium and zinc supplementation before radiation could reverse the reduction of spermatogonia. Notably, apart from the edema, selenium could reverse the damage caused by 2 Gy of γ irradiation including spermatogenic arrest, atrophy of seminiferous tubules, thickening of basal lamina, leydig cell hyperplasia, epididymis decreased sperm density and epididymis vacuolatio, meanwhile selenium showed no toxicity to spermatogenesis in comparison with the mice without radiation treatment. During the assessment of histopathological results, zinc not only exhibited less radioactive protective effect for its protective ability merely to basal lamina and epididymis but also caused damage to seminiferous tubules. And strikingly, zinc treatment without radiation induced damage in epididymis (Bagheri *et al.*, 2019).

3 Selenomethioine

Selenomethionine [$C_5H_{11}NO_2Se$] (Se-Met) is deemed to be an appropriate supplemental form of selenium for its outstanding bioavailability and low toxicity in comparison to other selenium compounds (Wang *et al.*, 2007). With the presence of both selenium and methionine, Seleno-L-Methionine (Se-L-Met) is the L-isomer of Se-Met and both of which could act as potent antioxidants and scavenge ROS.

A study designed by Fisher *et al.* explored the protective effects of selenium against DNA damages, revealing that the selenium supplementation in the form of Se-L-Met at a relatively physiological and nontoxic concentration could increase the levels of p53 and redox factor-1 (Ref-1) proteins, meanwhile p53 cysteine residues 275 and/or 277 were reduced, being consilient with former studies (Pluquet and Hainaut, 2001). P53 cysteine residues 275 and/or 277 are specifically crucial for the binding of p53 and downstream effector gene sequences, meanwhile Ref-1 was essential for selenium signal transduction to p53 (Seo *et al.*, 2002). Breast cancer susceptibility gene 1 (Brca1) is a tumor suppressor gene being involved in the repair of DNA damage (Jasin, 2002). Se-L-Met may effectively influence related processes. Their further study suggested that the protective effect of Se-L-Met did not extend to Brca1-deficient fibroblasts from UV-radiation, indicating that in addition to p53 and Ref-1, Brca1 may also be considered to take an important place in the DNA protection enhanced by Se-L-Met (Fischer *et al.*, 2006).

Previous studies have reported that Se-Met could efficiently inhibit the formation of lipid peroxy radicals, preventing lipid peroxidation (Dowlath *et al.*, 2021). Guo *et al.* had demonstrated in their research that Se-Met, composing over 90% of selenium content, acts as the primary form of selenium in Se-rich yeast peptide fractions. By scavenging the free radical and inhibiting the lipid peroxidation, Se-rich peptide fraction together with yeast extract enzyme (abbreviated as sSeP) presents its remarkable synergistic antioxidant in vitro. Experiments in vivo also manifested its significant antioxidant activity through abating malonaldehyde (MDA) as well as increasing GPx, had shown significant antioxidant activity in vivo. Furthermore, the application of sSeP on shaved dorsal skin of UVB-irridated mice could significantly alleviated morphological changes (including drier skin, redness, edema formation and increased scaly wrinkle) as well as histopathological changes (mainly epidermis thickness). Additionally, sSeP was testified to enhance the expression of aquaporin-3 and attenuate the phosphorylation of p38 MAPK in H_2O_2-treated HaCaT cells (a human epidermal keratinocytes cell line), providing a potential mechanism for sSeP to alleviate UVB-induced oxidative damages in skin of mice (Guo *et al.*, 2020).

Brown *et al.* demonstrated that antioxidant food supplementation including Se-L-Met could scavenge ROS after total-body irradiation (TBI), and improve DNA damage and apoptosis in bone marrow cells (Brown *et al.*, 2010). Bagheri *et al.* assessed chromosome damage through the micronuclei test, revealing that comparing to the control group, 2 Gy irradiated rats manifest a significant increase in micronucleus frequency, which could be markedly decreased by preadministration with Se-L-Met. And in contrast with the control group, the impact of ionizing radiation (IR) to cell proliferation could be significantly suppressed with the preconditioning of Se-L-Met. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5dione], a natural pigment with broad economic value and pharmacological effects, is widely known for its anti-inflammatory and antioxidant potential, and is also considered to be protective from DNA damage caused by radiation (Srinivasan *et al.*, 2006). By controlling the variables, Bagheri *et al.* also confirmed that the combined form of Se-L-Met and curcumin outperformed the effects of Se-L-Met or curcumin alone (Bagheri *et al.*, 2017).

Usually, RT will not result in severe damages to lung immediately but further influences including pneumonitis and fibrosis may contribute to the limited dose of RT for malignant tumors of organs in the chest area. These two pathological changes are related to the changes of inflammatory factors and cytokines caused by chronic oxidative stress. Previous studies proved that IL-4 plays an instrumental role in late effects of radiation-induced lung injuries as potent pro-fibrotic cytokines, and mainly causes the constant production of ROS after IR. Being related to the oxidation process in the body and involved in the inflammatory response, dual oxidase 1 (Duox1) and dual oxidase 2 (Duox2) are nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. IL-4 could upregulate interleukin-4 receptor subunit alpha-1 (IL4Ra1), thus stimulating Duox1 and Duox2 and ultimately mediate the continuous production of H_2O_2 (Raad, 2013). Ameziane *et al.* had demonstrated that the upregulation of IL-4 after irradiation could induce the expression of dual oxidases including Duox1 and Duox2, thus leading to the chronic production of ROS and instability of genome (Ameziane-El-Hassani *et al.*, 2015).

Amini *et al.* evaluated the regulatory effect of Se-L-Met on the aforementioned genes and the protective effect to the lungs after local irradiation to the chest of rats. Results showed that the serum level of IL-4 increased markedly as well as the expression of IL4Ra1, Duox1 and Duox2 after irradiation. The levels of IL4Ra1, Duox1 and Duox2 were significantly upregulated after exposing to 15 Gy radiation and could be reversed by supplementation of Se-L-Met. Histopathological analysis also showed that Se-L-Met could markedly attenuate the filtration of macrophages and lymphocytes together with the vascular and alveolar thickening and fibrosis, during which the JAK1-STAT6 cascade induced by IL-4 stimulation may take a leading role (Amini *et al.*, 2019).

Myriad evidences have proved that IR may lead to the increase of incidence of cardiovascular diseases (Boerma *et al.*, 2016; Najafi *et al.*, 2018), including carotid and coronary artery disorders, blood supply impairment to heart muscles, pericarditis and atherosclerosis (Stewart *et al.*, 2006). The chronic excretion of pro-fibrotic and pro-inflammatory cytokines plays an instrumental role in the aggravation of cardiovascular diseases after irradiation for the stimulation of chronic production of ROS during the progression of inflammation and fibrosis (Farhood *et al.*, 2019). Joseph L. Unthank *et al.* demonstrated that a significant reduction of the endothelial cells in coronary arteries was observed in mice 4 months after TBI at 8.53 or 8.72 Gy of γ radiation, and persisted through 18 months (Unthank *et al.*, 2019). Amini *et al.* revealed that γ radiation exposed locally to chest area of rats could lead to increased expression levels of IL4Ra1, Duox1 and Duox2, meanwhile treatment before and after 15 Gy γ local radiation with the combination of curcumin and Se-L-Met could decrease the expression all three significantly. Among which the change of Duox1 level is most obvious for its expression reduced to lower than 2-fold in treated rats (Amini *et al.*, 2018), indicating the potential of Se-L-Met together with curcumin to alleviate radiation-induced injuries (Basnet and Skalko-Basnet, 2011).

4 Ebselen

Ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one] (Eb), a synthesized multifunctional lipid-soluble selenium-containing compound, is recognized as an inhibitor of TrxRs, could functionally simulate GPx to protect cells free from ROS-induced injuries thus demonstrating its significant radioprotective effect (Briviba *et al.*, 1998; Cardoso *et al.*, 2017; Tak and Park 2009). Additionally, Eb also exhibits a broad range of biological activities, including anti-atherosclerotic, anti-inflammatory, anti-SARS-CoV-2, and anti-cancer properties (Barchielli *et al.*, 2022; Thabet *et al.*, 2023).

Thabet *et.al* have demonstrated that Eb has anti-arthritic and radioprotective effects in an arthritic irradiated model (Thabet *et al.*, 2023). Eb, by abating ROS, could enhance the antioxidant system thus reducing the peroxidation of serum and synovial tissue, meanwhile inhibit the activation of NOD-like receptor protein-3 (NLRP-3), thereby impeding caspase-1/IL-1β/receptor activator of nuclear factor κB ligand (RANKL)/nuclear factor-κB (NF-κB) pathway. Arthritic irradiated rats treated with Eb exhibited a superior ability to limit ROS comparing with rats without Eb, highlighting the protection of Eb against oxidative stress. Antioxidant system also exhibited a upregulation by activities of superoxide dismutase (SOD), catalase (CAT) and GPx, along with the level of glutathione (GSH) in serum and synovial in the Eb-treated group compared to the untreated group (Thabet *et al.*, 2023). Recent experiments and studies have shown that the up-regulation of NLRP3 inflammasome has a substantial impact on radiation damage, including oral mucositis, skin, lung, intestine and other systems (Wei *et al.*, 2019). Considering the notable inhibition of the activation of NLRP3 that Eb manifests, it is possible that Eb could present a potential protective effect on different radiation-induced organ damages, however further studies both in vivo and in vitro are necessary to support this point.

Tewari *et al.* have demonstrated that Eb could positively regulate DNA damage repair response by restoring decreased expression of mismatch repair (MMR) proteins. In their study, showing no effect on either mutL homolog 1 (MLH1) or mutS homolog 2 (MSH2) expression in A172 cells, Eb could restore the decreased levels of them both in TNFα treated cells, meanwhile in T98G cells, the decreased level of MSH2 was also elevated. Knowing that Eb could abate the pro-inflammatory mediators as well as ROS from TNFα treated cells, along with its ability of increasing the expression of MMR protein, Eb may curtail the accumulation of genetic instability, indicating that Eb could act as radioprotector during glioma treatment, while further demonstration in future study is warranted (Tewari *et al.*, 2009).

The pretreatment with 5 μM Eb for 2h significantly increased the viability of U937 cells exposed to 2 Gy γ radiation comparing to the untreated cells and decreased the increased dihydroethidium (DHE) fluorescence (Tak and Park, 2009). Eb pretreatment could significantly inhibit oxidative stress by decreasing the level of MDA which was 3 times higher after 20 Gy γ radiation in untreated cells. The fluorescence probe studies, including 1,3-Bis(diphenylphosphino)propane (DPPP) for lipid peroxidation and 8-OH-dG for DNA damage in vivo and in vitro, demonstrated that Eb could protect DNA from oxidative damages induced by IR. In comparison with the untreated cells, the pretreatment of Eb could lessen the amount of apoptotic cells after 2 Gy γ radiation. The induction of the mitochondria permeability transition (MPT) is related to the opening of large pores in the membranes of mitochondria, which takes an important role in apoptosis, during which ROS act as stimuli that change MPT, thus fluorescence probe JC-1 was chosen to observe the change of MPT. Results showed that the pretreatment of Eb could markedly suppress the disruption in the mitochondrial membrane potential induced by 2 Gy γ radiation. While the oxidant-sensitive probe, DHR 123 was chosen to estimate the levels of intracellular peroxides in the mitochondria of U937 cells, and results showed that the pretreatment of 5 μM Eb could significantly reduce the mitochondrial fluorescence in comparison with the untreated cells, suggesting that Eb could protect mitochondria from oxidative damages. Male mice treated orally with Eb at 10 mg/kg per day for 2 weeks also manifested a significant protective effect on liver morphological changes after 8 Gy of TBI comparing to the control group treated with DMSO (Tak and Park, 2009).

5 Sodium selenite

Sodium selenite [Na_2SeO_3] has long been recognized as one of the most redox-active selenium compounds and exhibiting potent anticancer properties, and notably, sodium selenite is considered to generate ROS which is contrary to the consensus that selenium is an antioxidant. Its high biological activity is attributed to its ability to primarily enhance the expression of selenoproteins, thus sodium selenite may not be inherently antioxidant until incorporated into selenoproteins with oxidoreductase functions (Misra *et al.*, 2015; Spallholz, 1994).

Iodine-131 (^{131}I) is an effective treatment against thyroid cancer which is considered as one of the most common tumors of the endocrine system. Beyond the intake of the thyroid tissue, salivary glands could also accumulate radioiodine through the sodium iodide symporter (NIS). Due to the high proportion of radio-sensitive serous acinar cells, parotid glands are especially vulnerable to radiation (Choi *et al.*, 2013; De La Vieja *et al.*, 2000). Individuals undergoing high-dose treatment of ^{131}I may suffer temporary or permanent dysfunction of salivary glands accompanied by symptomatic sialadenitis, thus leading to severe impact to quality of life (An *et al.*, 2013). Selenium has been demonstrated to be radioprotective on parotid glands against γ radiation and on the blood cells against ^{131}I radiation in animal studies (Tuji *et al.*, 2010). Son *et al.* performed a prospective study that contains 2 groups of thyroid cancer patients post-total thyroidectomy, 8 patients were divided in each group for ^{131}I treatment. Both serum amylase level and salivary gland scintigraphy manifested the protective effect of sodium selenite against salivary glands after ^{131}I therapy (Son *et al.*, 2017.).

Puspitasari *et al.* proved that the sodium selenite could increase GPx-1 activity in a dose- and time-dependent manner. The administration of a 50nM sodium selenite solution to checkpoint kinase 1 (CHECK-1) non-cancerous human esophageal cells for 72 h could induce the highest activity of GPx-1. With the supplementation of 50 nM sodium selenite, cell viability at 72 h after irradiation significantly increased, and the percentage of sub-G1 phase cells markedly reduced comparing to the group treated with 2 Gy X-ray irradiation alone. These findings suggest that sodium selenite supplementation before irradiation could protect cells from irradiation-induced damage and reduce the percentage of apoptotic cells. Poly ADP-Ribose Polymerase (PARP) protein was chosen for further experiments as a principal biomarker for apoptosis. 2 Gy irradiated cells with supplementation of 50 nM sodium selenite showed increased expression levels of cleaved PARP proteins comparing to cells treated with irradiation only, although not statically significant. This indicates that sodium selenite may have the potential to inhibit irradiation-induced apoptosis in non-cancerous cells (Puspitasari *et al.*, 2017).

The concept of osteoradionecrosis (ORN) was first described by Regaud in 1922, referring to the late effect observed in individuals under RT for head and neck cancers (O'Dell and Sinha, 2011). In addition to the impact on appearance, ORN severely affects the deglutition and linguistic function. Although the perception of the pathogenesis of ORN is not yet unified, most researchers attribute it to the fibroatrophic process featuring in early inflammation and subsequent fibrosis and remodeling caused by radiation (Frankart *et al.*, 2021). Yamasaki *et al.* reported that 40 days after the 15 Gy X-ray radiation in head and neck region, all rats were anaesthetized and underwent bilateral extraction of mandibular first molars. Bone microarchitecture parameters, including total volume, bone volume, bone volume fraction (bone volume/total volume), trabecular number, trabecular thickness and trabecular separation were assessed 15 days and 30 days after surgery, respectively. Statistically higher trabecular separation was observed in rats treated with radiation, while a statistically higher value of the trabecular number evaluation was displayed in irradiated rats intraperitoneally administrated with sodium selenite (0.8 mg/kg) 15 days after the tooth extraction. However, sodium selenite did not manifest a significant radioprotective effect in the assessment of bone microarchitecture 30 days after surgery in this experiment. Therefore, it might be fair to indicate that sodium selenite could be considered as a potential radioprotective adjuvant during locally radiation therapy with further confirmatory experiments (Yamasaki *et al.*, 2019).

Sieber *et al.* found that with the supplementation of 100 μg/day of selenium in the form of sodium selenite or Se-L-Met, blood urea nitrogen (BUN) level of rats significantly decreased. 21 weeks after TBI, irradiated rats on sodium selenite-supplemented water showed no interstitial fibrosis and only minimal mesangiolysis in histopathological analysis while irradiated rats on standard drinking water showed severe histological abnormalities aforementioned (Sieber *et al.*, 2009). 2 years later, they conducted further experiments and demonstrated that 2 months after TBI, BUN level of rats with supplementation of drinking water with selenium at 150 or 200 μg/d significantly decreased comparing to rats with standard drinking water. 4 months after TBI, there's no difference in serum BUN level between irradiated rats with supplement of sodium selenium (200 μg/d) and normal controls. Interestingly, with the supplement of 200 μg/d for 4 months, sodium selenite acted better as a kidney protective adjuvant than Se-L-Met due to its superior activity in reducing BUN level. Sodium selenite also manifested better protective effect than Se-L-Met, as it could mitigate histopathological abnormalities including cysts, sclerosed glomeruli, interstitial fibrosis, and glomerular mesangiolysis in the kidneys (Sieber *et al.*, 2011).

Muecke *et al.* initiated their phase III clinical trials and one purpose of which was to estimate the radioprotective effect of sodium selenite. 81 patients suffering from uterine or cervical cancer were admitted into the trial and 39 patients were administrated sodium selenite supplementation during their RT process. During the trial, radiation-induced diarrhea, being regarded as one of the most relevant side-effects of aforementioned cancers that partly impact the quality of life, was assessed to determine whether it could be reduced by the supplementation of sodium selenite. Studies revealed that the levels of selenium were elevated both in whole blood and in serum, and the incidence of common toxicity criteria (CTC) Grade 2 diarrhea was significantly reduced in patients treated with sodium selenite comparing to the control group without supplementation. Notably, there was a tendency that the patients with higher Se status tolerated the radiotherapy better

than the ones with relative Se deficiency (Muecke *et al.*, 2010, 2014, 2018).

Verma *et al.* conducted their experiments to assess the protection of low-dose sodium selenite, administrated multiple times, against TBI in mice. 4 groups were designed: sham control, sodium selenite control, radiation control, and combined treatment group. The irradiated groups received 4 μg/kg PBS (for control group) or sodium selenite through intraperitoneal administration for 5 consecutive days before and 3 times/week after TBI till the end of experiment. Results indicated that although low-dose of sodium selenite did not exhibit significant protective function from the destruction of shortening of villi in the intestinal lumen induced by 8 Gy γ radiation comparing to the untreated mice, the level of lipid peroxidation was significantly decreased. Comet assays in peripheral leukocytes were conducted and results showed that lose-dose of sodium selenite could significantly mitigate the DNA damage induced by 5 Gy γ radiation at both early and later time points (Verma *et al.*, 2017).

The kidneys are particularly vulnerable to radiation and even moderate dose of radiation whether locally or whole-bodily radiated, resulting in the deterioration of renal function (El-Ghazaly *et al.*, 2017). And selenium has been reported to have protective effects against cadmium-induced nephropathy (Bagheri *et al.*, 2019). A previous study has proved that selenium nanoparticles (Se-NPs) possess potential anti-inflammatory effects in radiated mice. Increased levels of renal function biomarkers in the serum of 8 Gy radiated mice including creatinine, urea, cystatin-c and beta-2-microglobulin (β_2M) were all significantly decreased after intraperitoneal injection of sodium selenite and Se-NPs, meanwhile activities of SOD and GPx were both normalized. Among which Se-NPs manifested higher ability than sodium selenite. Renal selenium content decreased after γ radiation dose-dependently. Notably, both the supplementation of Se-NPs and sodium selenite showed an equivalent ability to tremendously suppress the extent of histopathologic changes to 8 Gy radiated mice including glomerular sclerosis, focal glomerular necrosis and tublar epithelium necrosis to almost normal range. Additionally, both Se-NPs and sodium selenite have almost the same protective potential against pathologic changes (Karami *et al.*, 2018).

6 Conclusion

Nuclear technology has profoundly impacted our daily lives, which provides convenience while also poses potential hazards that, if mishandled, can lead to irrevocable consequences. To wield this double-edged sword responsibly requires thoughtful consideration of the risks involved and the implementation of corresponding solutions. Although radiotherapy has offered a renewed hope for individuals once suffered from cancer, it brings along challenges associated with radiation-induced problems that need to be addressed. Both acute radiation syndrome and delayed effect of acute radiation exposure are far-reaching and may significantly impact various of organs and ultimately diminishing the overall quality of life. The mechanisms underlying radiation-induced injury encompass direct and indirect impacts, with the recognized hazards of ROS are widely recognized. Consequently, the antioxidants are being investigated and used as radioprotective adjuvants. Selenium, along with its compounds and metabolites, has long been considered as an affordable and potent antioxidant, and researchers worldwide have conducted myriad experiments to demonstrate the radioprotective effect of selenium in various forms, and the results are quite affirmative. It is not arbitrary to indicate that selenium-containing compounds and metabolites could be recommended as radioprotective adjuvants for individuals undergoing radiotherapy, given their remarkable protective effects on different organs and cells.

Most studies in this review, which include research on various types of cells, animals, and humans, added Se (in the form of selenium and its compounds and metabolites) before radiation, while only one study used Se as a remedial supplement (Table 1). It is well established that Se can act as a radioprotective adjuvant, however, the appropriate dosage and optimal timing for supplementation, along with the most effective type of Se supplementation still require further rigorous comparative studies.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability statement

All relevant data are within the paper.

Author contribution statement

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