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REVIEW ARTICLE

Radiation Protection and Mitigation by Natural Antioxidants and Flavonoids; Implications to Radiotherapy and Radiation Disasters

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Abstract: ***Background:*** Nowadays, ionizing radiations are used for various medical and terroristic aims. These purposes involve exposure to ionizing radiations. Hence, people are at risk for acute or late effects. Annually, millions of cancer patients undergo radiotherapy during their course of treatment. Also, some radiological or nuclear events in recent years pose a threat to people, hence the need for radiation mitigation strategies. Amifostine, the first FDA approved radioprotector, has shown some toxicities that limit its usage and efficiency. Due to these side effects, scientists have researched for other agents with less toxicity for better radioprotection and possible mitigation of the lethal effects of ionizing radiations after an accidental exposure. Flavonoids have shown promising results for radioprotection and can be administered in higher doses with less toxicity. Studies for mitigation of ionizing radiation-induced toxicities have concentrated on natural antioxidants. Detoxification of free radicals, management of inflammatory responses and attenuation of apoptosis signaling pathways in radiosensitive organs are the main mechanisms for radiation protection and mitigation with flavonoids and natural antioxidants. However, several studies have proposed that a combination in the form of some antioxidants may alleviate radiation toxicities more effectively in comparison to a single form of antioxidants.

Conclusion: In this review, we focus on recent findings about natural radioprotectors and mitigators which are clinically applicable for radiotherapy patients, as well as injured people in possible radiation accidents.

Keywords: Radiation, Radioprotector, Mitigation, Flavonoids, Antioxidant.

1. INTRODUCTION

For several years, the search for development of a novel and more potent radioprotector was one of the interesting goals in radiobiology. Low toxicity and cost are important properties of an appropriate radioprotector [1]. However, a number of developed radioprotectors were avoided in wide clinical applications due to their high toxicities. In the past two decades, several experiments have revealed that herbal radioprotectors can be used in higher doses with lower toxicities. Amifostine is the first FDA approved radioprotector. Despite promising radiation protection properties, it may cause severe side effects on patients, resulting in the discontinuation of amifostine treatment [2].

In recent years, trends in the development of novel radioprotectors are drifting towards natural compounds with less toxicities [3]. They should have some properties applicable in clinical radiotherapy or radiation disaster. However, the

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characteristics of radioprotectors in these two cases are not similar. For example, in radiotherapy, it is very important that the administered agent does not cause the protection of tumor cells. Both radioprotectors and mitigators should have minimal toxicities and protect normal tissues especially radiosensitive organs such as hematopoietic and gastrointestinal [4]. Although the search for radioprotectors has been on for a long time, there has been more emphasis on the development of radiation mitigators with high efficiency. The most important focus in this issue is mitigation of radiosensitive organs such as bone marrow and gastrointestinal system [5].

Results of several experiments have shown that cell metabolism and inflammatory responses following exposure to radiation play a key role in continuous free radical production and disruption of normal organ functions [6-9]. Attenuation of oxidative damage and inflammation following exposure to ionizing radiation can alleviate damage to radiosensitive organs, leading to increased survival [10, 11]. The suppression of reactive oxygen species (ROS) derived mitochondria, NADPH oxidase enzymes and COX-2 has shown promising results [12-15]. Targeting mitochondrial ROS is one of the new strategies that has also shown promising results. Development of 4-Amino-Tempo is the best example of a mitochondrial targeted derivative [16-18]. Selenium, Selenium-L-methionine, ascorbic acid *etc*., are natural agents that have proved effective.

2. MOLECULAR MECHANISMS FOR CONTINUOUS ROS PRODUCTION FOLLOWING EXPOSURE TO IR

A large body of studies has revealed that chronic oxidative injury following exposure to IR plays a key role in radiation toxicity. A study showed that exposure of mice to IR lead to ROS production in hematopoietic bone marrow cells for 8 weeks. Also, this study showed that upregulation of NOX4 and NOX2 is responsible for continuous ROS production and genomic instability in bone marrow cells. Moreover, their results showed that inhibition of NOX4 can protect mice similar to a potent radioprotector (N-acetyl cysteine) [19, 20]. Other studies confirmed that continuous ROS production through stimulation of redox interactions plays a key role in the development of both early and late effect of IR [21-23]. Weyemi *et al*. showed that inactivation of both NOX4 and NOX5 can mitigate ROS production and oxidative DNA damage in irradiated human fibroblast cells [24]. In animal model, it has shown that upregulation of pro-oxidant enzymes such as NOX1, NOX4, COX-2, iNOS and also increased superoxide production by mitochondria are involved in the development of pneumonitis and fibrosis [25-27]. Similar results have shown for intestinal cells, vascular endothelial cells, mice brain, *etc* [28-30].

Exposure to ionizing radiation cause damages to DNA and other organelles. This is associated with cell death through some mechanisms such as mitotic catastrophe, apoptosis, necrosis, autophagy and senescence [31]. Studies have shown that apoptosis to necrosis ratio is higher following exposure to doses lower than 1 Gy. However, for doses higher than 2 Gy, necrosis is more common. Ingestion of apoptotic bodies by macrophages causes secretion of anti-inflammatory cytokines such as IL-10 and TGF-β [32]. However, the release of necrotic products such as oxidized DNA and high mobility group box 1 (HMGB1) leads to stimulation of lymphocytes to elevate the expression of transcription factors like nuclear factor-κB (NF-κB), signal transducer and activator of transcription (STAT), mitogen-activated protein kinases (MAPKs), Intercellular Adhesion Molecule 1 and vascular cell adhesion molecule 1 (VCAM-

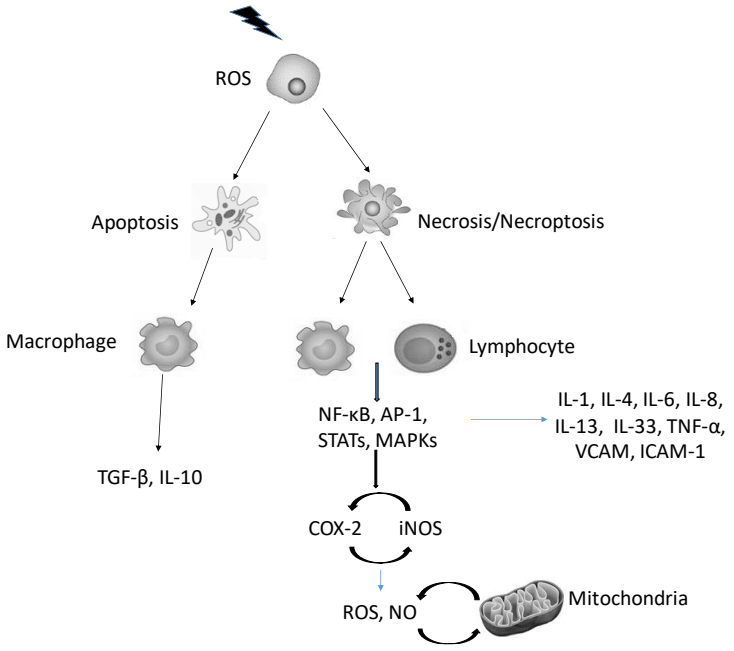

Fig. (1). Mechanisms of radiation toxicity in normal tissues. Ionizing radiation cause generation of ROS and cells death, leading to initiation of inflammatory responses and chronic free radical production. These are associated with several side effects in irradiated normal tissues such as fibrosis, pneumonitis, dermatitis, ulcer and *etc*. Suppression of oxidative damage and other factors involved in these side effects by various agents such as flavonoids can help the management of radiation toxicity.

1) [33]. These transcription factors upregulate the expression of inflammatory mediators and pro-oxidant enzymes such as cyclooxygenase-2 (COX-2), iNOS and NADPH Oxidase [5, 34]. These pro-oxidant enzymes produce ROS and then stimulate more free radical production by mitochondria *via* a phenomenon known as ROS-induced ROS [35]. Hence, suppression of inflammatory mediators and pro-oxidant enzymes as well as mitochondrial ROS can be proposed for inhibition of these signaling pathways and more injury following exposure to ionizing radiation [36-39]. Also, it has shown that some protective effect of radioprotectors and mitigators are mediated through blunt of these pathways [40]. (Fig. **1**).

3. RADIATION TOXICITY IN RADIOTHERAPY

More than half of cancer patients undergo treatment with ionizing radiation during their course of treatment. As millions of patients go through this process each year, management of the side effects of this treatment modality has been noted in various reports [41]. Although the introduction of novel technologies in radiotherapy instruments can help the management of radiation toxicity, the risk of damage to normal functions of organs remain. These novel technologies such as conformal radiotherapy, intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), stereotactic body radiotherapy (SBRT), drug delivery techniques and using heavy ion particles facilitate normal tissue sparing during the course of treatment [42, 43]. Most of these techniques reduce the volume of irradiated organs, while heavy particle radiation reduces the dose to the normal tissue *via* an interesting property named Brag peak [44]. Despite these improvements, radiation toxicity remains an unsolved problem in radiotherapy. The features of radiation toxicity in each organ is different from others. In addition, the mechanisms of toxicity and tissue response vary [45]. According to published documents, oxidative stress and inflammatory responses are responsible for various side effects to the patients [12]. The most common consequences of exposure to clinical doses of ionizing radiation include skin burning, mucositis, xerostomia, gastrointestinal bleeding and fibrosis, lung pneumonitis and fibrosis, cardiovascular disorders, infertility *etc*. [46-48]. So far, several experiments have been conducted for the amelioration of these side effects. Hence, achieving an appropriate protocol for the clinical applications of radioprotectors requires further studies.

4. RADIATION DISASTERS; POSSIBLE ROLE OF MITIGATORS

The threats of radiological or nuclear disasters leading to exposure of a large number of people to ionizing radiation have been felt in this century. After exposure to an acute high dose of ionizing radiation, exposed people may suffer fatal damages to bone marrow or gastrointestinal organs. This is referred to as acute radiation syndrome. Moreover, exposure to sub-lethal doses of ionizing radiation results in an increased risk of various diseases such as cardiovascular and neurophysiological disorders, lung pneumonitis and fibrosis, as well as cancer [49-51]. In an accidental radiological or nuclear disaster such as a dirty bomb, nuclear explosion, and damage to nuclear plants (like Fukushima and the Chernobyl disasters), a large number of people may be affected with a need for medical care.

Several studies have been conducted to identify potent and effective radiation mitigators for the alleviation of acute and late effects of ionizing radiation in a possible radiation disaster. In studies conducted to ameliorate the dangerous effects of radiation, crucial attention must be paid to the mechanisms of radiation-induced cell death in bone marrow and gastrointestinal as two radiosensitive organs [52, 53]. However, some studies attempted to develop mitigators for the lung and heart [54-57]. It seems that continuous ROS production following exposure to ionizing radiation plays a key role in the disruption of these organs. For example, administration of some antioxidants after irradiation can help to alleviate radiation toxicity in radiosensitive organs and increase survival. However, it may be not true for all organs. For example, treatment with ROS scavenging agents following irradiation can't mitigate kidney damage.

In recent years, some agents have been developed for mitigating radiation-induced hematopoietic injury [58, 59]. JP4-039 (GS-Nitroxide) has been tested for this aim. It is a mitochondria-targeted nitroxide concentrated in the mitochondria and scavenges free radicals [60, 61]. A study showed that treatment with this agent (10 mg/kg) a day after whole body irradiation with 9 Gy can stimulate the recovery of hematopoiesis and increase survival rate in mice [62]. In addition to mitochondrial targeting, the fact that TGF-β and NADPH oxidase are other targets with the ability to cause inhibition has been proposed for mitigation of radiation-induced toxicity in hematopoietic systems [63-65].

In a study by Rabender *et al*. it has been discovered that using IPW-5371 (a small molecule TGF-β receptor 1 (TGF-βR1) inhibitor) a day after thorax irradiation with 11.5 Gy can mitigate radiation induced lung and heart fibrosis. Their result showed that inhibition of TGF- βR1 for 6 or 20 weeks following thoracic irradiation can increase survival rate compared to irradiated mice without treatment [66]. In a similar study, using small molecule antioxidant (AEOL 10150) indicated a 28% increase in survival following administration for 4 weeks [67]. Using another inhibitor of TGF-βR1 (LY2109761) 4 weeks after a single irradiation of the thorax with 20 Gy showed mitigation of lung inflammation and fibrosis [68]. Other studies have shown that targeting of pro-inflammatory and pro-fibrotic mediators can mitigate severe inflammation and fibrosis in the heart and lung, leading to an increase in survival [69-73].

5. AMIFOSTINE AND KERATINOCYTE GROWTH FACTOR (KGF) AS FDA APPROVED RADIOPROTECTORS

Amifostine, a chemical agent, is the first FDA approved radioprotector used for protection against ionizing radiation induced xerostomia in head and neck cancer patients [74]. It is a thiol compound that neutralizes free radicals and prevents DNA oxidative injury due to the presence of SH group in its structure [75]. Clinical studies have shown that amifostine is able to alleviate radiation toxicity in more than half of the patients with lung, head and neck, breast or uterus malignancies [76]. In addition to potent radioprotection of parotid gland in head and neck cancer patients, it has been reported

that amifostine administration does not interfere with therapeutic outcomes of radiotherapy or chemo/radiation therapy [77]. However, its use is limited as a result of high toxicity and little or no radioprotective effect on most organs. The high toxicity of this agent may cause discontinuation of its use and in some situations delay of radiotherapy. This may have an effect on the therapeutic ratio as well as a reduction in final efficiency of radiotherapy [78]. Keratinocyte growth factor (KGF) is another FDA approved agent that has shown radioprotective effect. KGF was proposed for ameliorating radiation-induced oral mucositis and salivary hypofunction [79, 80]. The radioprotective effect of KGF results from stimulating stem cell proliferation, leading to the expansion of progenitor and functional cells in irradiated area [81]. Application of KGF is limited to mucus cells and has a risk of carcinogenesis [82].

6. FLAVONOIDS AND NATURAL ANTIOXIDANTS

Flavonoids have a potent antioxidant effect due to their high redox potential, which allows them to act as hydrogen donors and reducing agents, metal chelating potential as well as quenchers of singlet oxygen [83]. In plants, flavonoids are the most abundant type of photochemical, which protect them against detrimental effects of ultraviolet rays, pathogens, and oxidative stress conditions [84]. A large number of studies have proposed regular consumption of flavonoids in reducing the risk of some malignancies such as the incidence of prostate and breast cancer [85, 86]. Flavonoid intake has also been discussed as potentially beneficial in terms of prevention of cardiovascular disorders as well as inflammatory diseases [87]. The radioprotective effects of some flavonoids are a result of their potent antioxidant and anti-inflammatory effects. In addition, it is believed that the radioprotective effects of flavonoids are due to the presence of phenolic hydroxyl groups in their structures [88].

Several studies have been conducted to evaluate the possible positive effects of antioxidants for preventing radiation toxicity without a negative effect on tumor control. Some studies proposed the use of natural antioxidants such as beta carotene and vitamin E for preventing mucositis, melatonin for patients with brain cancer and a combination of some antioxidants for prostate cancer patients [89-92]. Studies concluded that with limited exceptions, administration of antioxidants does not interfere with tumor control [93]. Among the most interesting flavonoids which have been studied in recent years include curcumin, hesperidin, resveratrol, quercetin, flaxseed, ocimum sanctum, sesamol and rutin. However, some natural antioxidants such as selenium, Co-enzyme q10, α-tocopherol, cafeic acid and ascorbic acid have shown promising results. Moreover, some studies proposed that using a combinational form of these antioxidants may be more effective in comparison to a single form [94, 95]. Less toxicity of flavonoids and natural antioxidants is an interesting advantage. Hence, making it a suitable natural medicine for individuals who may be exposed to high doses of ionizing radiation in radiotherapy or a radiation accident [96].

7. CURCUMIN

Among the various herbal agents, curcumin has been studied widely for its radiation protection effects. Turmeric (curcuma) is well-known and used for medicinal purposes in Indian and Chinese traditional medicine. Curcumin was found to be a potent free radical scavenger with abilities to inhibit the development of lipid peroxidation and neutralize a variety of reactive oxygen and nitrogen species in different animal models [97, 98]. In addition to the direct suppression effect of curcumin on free radicals, it can inhibit inflammation *via* reduction of inflammatory cytokines (such as IL-1a, TNF-α) and inflammatory mediators (such as NF-κB and Smad) [99]. Its anti-inflammatory effect can help the reduction of oxidative stress induced by redox activity of inflammatory cells [100].

One of the most interesting properties of curcumin is that despite its beneficial medical features, no amount of toxicity has been traced to it. Administering 8 gm/day of curcumin for 3 months has shown no problem in voluntary individuals [101]. In a recent study on patients with breast cancer, treatment with 6 gm of curcumin during radiotherapy showed protection against radiation-induced dermatitis without any significant toxicity [102]. In addition to dermatitis, curcumin has indicated a protective effect against other side effects of radiation such as pneumonitis, fibrosis, mucositis, myelopathy, neural toxicity and others [103-107]. The anti-inflammatory effect of curcumin has a central role in radioprotection against these toxicities. Studies conducted to evaluate the effects of curcumin on radiation-induced pneumonitis revealed that it offers protection by decreasing inflammation mediators like NF-κB and its cascades such as inflammatory and fibrogenic cytokines [108]. In addition, it aids the reduction of gastrointestinal toxicities through protection of mucosal cells against ROS production and oxidative damage [109, 110].

One of the most important advantages of novel radioprotectors that should be noticed is their effects on cancer cells. Although various tumors are genetically deferent, anti-inflammatory effects of some herbal agents may be proposed for suppression of angiogenesis and tumor growth. An interesting advantage for curcumin is its anti-cancer effects. This advantage makes curcumin a suitable radiosensitizer [111-113].

8. HESPERIDIN

Hesperidin is a natural bioflavonoid. It was first extracted in 1828 by French chemist Lebreton from the spongy inner portion of orange peel. This bioflavonoid has been found in other citrus fruits. In traditional Chinese medicine, hesperidin has been used for inflammation and allergy diseases [114]. Nowadays, it is used for the treatment of a wide range of disorders such as neurological disorders, cardiovascular diseases, and others [115, 116]. Hesperidin has shown radioprotective abilities for both early and late effects in different organs.

Hosseinimehr *et al*. [117] evaluated the radioprotective effects of hesperidin on radiation-induced bone marrow cells damage. They used different doses of hesperidin ranging from 10-160 mg/Kg at 45 min prior gamma rays exposure with dose 2 Gy. Their results showed that all administered doses of hesperidin can reduce DNA damage in bone marrow cells and increase proliferation ratio. Further results showed that the most effective dose of hesperidin for reduc-

ing bone marrow DNA damage is 80 mg/kg body weight. No toxicity effect was observed at a dose of 80 mg/Kg, while a dose of 160 mg/kg showed signs of toxicity. It was confirmed that the protective effect of hesperidin could be mediated *via* inhibition of apoptosis in radiosensitive cells [118]. Moreover, hesperidin has the ability to reduce the level of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, with improved nutritional functions [119].

A study by Park *et al*. [120] indicated that hesperidin has the ability to mitigate the hepatocellular cells of Sprague–Dawley rats against oxidative damage induced by ionizing radiation. In this study, rats were irradiated with gamma rays in three different doses of 1, 3 and 5 Gy. Afterwards, the rats were treated with hesperidin for 7 days after exposure with 50 mg/kg or 100 mg/kg. The results showed that although treatment with 50 mg/kg hesperidin can protect rats against 1 Gy and 3 Gy, a higher dose of 5Gy will require a higher amount of hesperidin. In this study, it was reported that hesperidin can ameliorate the serum level of hepatic oxidative damage as well as oxidative stress in liver tissue. Oral administration of hesperidin before irradiation of mice with a dose of 100 mg/kg body weight resulted in amelioration of oxidative damage and stimulation of antioxidant enzymes, including superoxide dismutase, glutathione (GSH) and glutathione peroxidase (GSPx) in the skin [121].

A potent radioprotective and anti-inflammatory effect of hesperidin has been seen in heart tissues. Treatment of rats with hesperidin before exposure of chest area to a high dose of gamma radiation has shown improvement in survival as well as reduction of oxidative damage, vascular leakage, inflammation, fibrosis and infiltration of macrophages, lymphocytes and mast cells [122]. Moreover, treatment with hesperidin for 7 consecutive days before irradiation was effective in ameliorating serum heart disease markers [123]. These results have also been observed for lung tissues [124, 125]. The radioprotective effects of hesperidin have been revealed for other organs such as testis and kidney [123, 126].

9. RESVERATROL

Another herbal agent that has shown potent radioprotective effect is resveratrol. Resveratrol ($C_{14}H_{12}O_3$) is a natural polyphenolic compound produced by some plants such as grapes, peanuts, soy and *etc*., in response to pathogen agents. This herbal product was isolated for the first time in 1940 by Japanese scientists. Resveratrol has been observed to reduce aging and promotes cell survival by simulating sirtuin-1 (Sir1) which consequently increases genomic stability [127]. Sir1 *via* upregulation of p53 has a key role for protection against genotoxic agents [128]. In addition to immunoregulatory and epigenetic effects of resveratrol, a study proposed that it can strongly protect cells against toxic effects of free radicals [129]. Interesting properties of resveratrol as a potent antioxidant have been observed to possess other various health benefits such as radioprotective effect and neuroprotective properties [130].

Carsten *et al*. [131] showed that administering resveratrol with a daily dose of 100 mg/kg for 3 days before whole-body irradiation with 3 Gy single dose of γ-rays reduces the numbers of chromosome aberrations in the bone marrow cells of mice. Also, this study reported that daily treatment with resveratrol at this dose does not lead to genotoxicity. Although resveratrol can't scavenge free radicals directly, it can upregulate the activity of antioxidants enzymes such as SOD and GPX in hematopoietic cells following exposure to ionizing radiation [132]. In addition to the antioxidant effects of resveratrol, resveratrol can suppress chronic free radical production *via* amelioration of inflammatory responses in the bone marrow stem cells of mice. Zhang *et al*. showed that treatment with resveratrol for 7 days before exposure to 7.2 Gy γ-rays (as a lethal dose of ionizing radiation) ameliorates the upregulation of NADPH oxidase 4 (NOX4) and subsequent NOX4-derived ROS production, which is involved in stem cell apoptosis and senescence. The result indicated an increase in survival from 25 to 66 % [133].

Resveratrol has also shown the radioprotective effect on the chromosome aberrations in peripheral blood lymphocyte of mice. In a study designed by Hejazi *et al*. revealed that intraperitoneal injection of resveratrol in 50 and 100 mg/kg body weight 2 hours before whole body irradiation (2Gy) resulted in a significant reduction in DNA damage. Administration of injected resveratrol doses did not show any toxicity [134].

Resveratrol can protect against the detrimental effects of ionizing radiation in the intestinal organ. It can ameliorate oxidative stress, DNA damage, apoptosis and subsequent consequences following exposure to gamma radiation in mice intestinal tissue. These radioprotective effects are mediated by acetylation of p53 and activation of Sir1, resulting in resistance of intestinal crypt cells to apoptosis [135]. Administering resveratrol before irradiation of rats' abdomen with 10 Gy could ameliorate increased level of inflammatory cytokine, regulatory T cells, and oxidative DNA damage, whereas it increased the white blood cell counts such as CD4+ T cells [136]. These results have also confirmed the long-term inflammatory effects of radiation [137].

10. QUERCETIN

Quercetin belongs to the flavonoid compounds, which are found in aerial photosynthetic plants like onions, kale, apples, French beans and others [138]. Quercetin has shown some cancer chemotherapeutic and chemopreventative properties [139]. Some studies proposed that quercetin protects normal cells *via* scavenging of free radicals, inhibition of lipoprotein oxidation, and inhibition of eicosanoid synthesis [140, 141]. Despite the beneficial effects of quercetin, some studies reported mutagenesis and carcinogenesis effects [142].

Quercetin has radioprotective properties in some organs. Benkovic *et al*. evaluated the protective effect of quercetin against ionizing radiation induced DNA damage in mice leukocytes. In this study, the radioprotective effect as well as the cytotoxicity of quercetin was evaluated using the comet assay. Quercetin was administered with a dose of 100 mg/kg body weight for 3 consecutive days before and after irradiation with 9 Gy. Results showed no toxicity for quercetin on leukocyte counts. Also, treatment with quercetin could significantly protect mice leukocytes against DNA damage [143, 144]. Devipriya *et al*. examined the radioprotective effect of quercetin in human peripheral blood lymphocytes. In this study, authors observed its ability to protect cells from the genotoxic effects of ionizing radiation in a dose-

dependent manner. Also, they found that the most protective effect can be achieved with a concentration of 24 μM. Moreover, quercetin could improve the depletion of antioxidant enzymes and non-enzymes [145]. Stimulation of antioxidant enzymes by quercetin have also been revealed in red blood cells [146]. In addition to direct and indirect antioxidant effects of quercetin, some experiments showed its capability to manage deleterious effects of ionizing radiation by suppressing inflammatory pathways. In an animal study, quercetin showed the ability to blunt mitogen-activated protein kinases (MAPKs) pathway genes such as JNK, p38 and p44/p42, as well as inhibiting NF-κB by preventing its nuclear translocation and degradation of IκB-α [147]. In addition to these, quercetin can reduce the release of inflammatory cytokines [148].

11. OCIMUM SANCTUM

Ocimum sanctum is an Indian holy basil and water-soluble flavonoid with promising effects on preventing radiation toxicity. It can scavenge different types of free radicals such as superoxide anion radical, NO, hydroxyl radical *etc* [149]. Adhvaryu *et al*. showed that treatment with ocimum sanctum before irradiation with 2 Gy of gamma rays can mitigate genotoxicity induced by ionizing radiation in bone marrow cells of mice. Their results showed that the protective effect of ocimum sanctum is less than curcumin [150]. In addition to the direct effects of ocimum sanctum on free radicals, its administration (10 mg/kg for 5 days) can stimulate antioxidant enzymes to reduce the toxicity of radiation on normal tissues [151]. Evaluating the possible effects of ocimum sanctum on melanoma and fibrosarcoma bearing mice showed that it does not cause radioresistance of these tumor cells [152]. This may be of help in the clinical applications of this agent for radiotherapy patients. However, this result needs verification in clinical trial studies.

12. RUTIN

Rutin is a flavonoid present in citrus fruits that acts as ROS scavenger as well as a chelator for metals prone to act as pro-oxidants. In addition, evidence showed that rutin had beneficial properties such as its anti-inflammatory and anti-cancer effects, as well as neuroprotective and cardioprotective effects [153, 154]. In *in vitro* studies, rutin showed an amelioration effect on DNA damage and mutation, as well as an increase in cell survival [155, 156]. Its radioprotective effect was also investigated in *in vivo* studies [157-159]. The presence of a phenolic group was suggested to be responsible for this effect [157]. Also, studies indicated that rutin stimulates the production of antioxidant peptides and enzymes including SOD, GSH, glutathione-S-transferase (GST) and catalase [159]. Treatment with 50 mg/kg before irradiation with 4 Gy significantly ameliorated the toxic effects of ionizing radiation on bone marrow cells of mice, while a lower dose of 25 mg/kg has a slight effect [160]. Further studies are necessary to explain the mechanisms and possible radioprotective effects of rutin in different organs.

13. SESAMOL

Sesamol has been purified from sesamolin. It is composed of phenolic and benzodioxole group in its structure. In addition to the antioxidant effect of phenolic, benzodioxole scavenges hydroxyl radicals. In several *in vitro* and *in vivo* studies, the various beneficial effects of sesamol such as antioxidant, anti-inflammatory and anti-microbial properties have been reported [161]. Sesamol can inhibit enzymes involved in the metabolism of fatty acids and prostaglandins, which are involved in inflammation and oxidative damages [162, 163]. The radioprotective effects of sesamol have been investigated in some studies.

In an *in vitro* study with V79 cells, Mishra *et al*. [164] identified the potent antioxidant and radioprotective effects of sesamol. Interestingly, their investigation revealed the free radical scavenging capacity of sesamol to be 20 times higher than melatonin. An *in vivo* study on bone marrow cells of mice has shown the similarity between sesamol and amifostine as regards their radioprotective effects on this organ. This study showed that injecting 20 mg/kg of sesamol 30 minutes before exposure to 2 Gy gamma rays resulted in a significant reduction of DNA damage markers including γ-H2AX and micronuclei formation. This study indicated that sesamol is a potent radioprotector agent against genotoxic effects of radiation with similarities to amifostine, although its toxicity is more tolerable [165]. This result was confirmed by Khan and colleagues [166]. They showed that administering 100 or 50 mg/kg of sesamol, 30 minutes before irradiation with 7.5 Gy resulted in a remarkable increase in survival of mice. Their results showed a significant decrease in apoptosis of bone marrow cells and gastrointestinal organ, as well as regenerating crypt cells. The protective effects of sesamol were more obvious for higher doses [166].

Parihar *et al*. evaluated the radioprotective effects of different drug doses of sesamol in albino mice. They administered sesamol in 10 to 100 mg/kg body weight before irradiation with 9.5 Gy. Their results showed that administering 50 mg/kg had a maximum effect on survival, while higher doses gave the best result for the mitotic index of bone marrow cells. In addition, treatment with sesamol in all doses could increase antioxidant capacity through activation of GSH, catalase and total thiols [167].

14. CAFFEIC ACID

Caffeic acid is a phenolic compound whose molecular formula is $C_9H_8O_4$. This compound is a natural antioxidant with potent anti-inflammatory and antimicrobial properties [168]. Various studies have revealed its inhibitory effect on cancer cell proliferation by modulating oxidative mechanisms [169-171]. However, the toxicity of caffeic acid on normal human tissues remains a subject of debate. Chen *et al*. [172] examined the protective effects of caffeic acid on radiation-induced pneumonitis. They showed that administering caffeic acid (30 mg/kg/day for 3 days) has no cytotoxicity in mice lung tissues. Furthermore, their results showed that it alleviates pneumonitis *via* amelioration of increased level of inflammatory mediators and cytokines such as NF-κB, iNOS and TNF-α after an exposure to radiation (10 Gy or 20 Gy). Caffeic acid was administered 30 minutes before exposure then 10 days after. It has the ability to increase the activities of antioxidant enzymes and glutathione [173]. These properties can help reduce ROS and nitric oxide, inducible nitric oxide synthase, and other detrimental effects of

ionizing radiation such as damage to vascular endothelial cells.

15. MELATONIN

Melatonin was first discovered in the pineal hormone in 1953 by Aaron B. Lerner, but its antioxidant effect was found 40 years later. It can be found in numerous plants such as tomatoes, olive oil, ginger, walnuts, pineapple, cereals, germinated legumes and others [174]. Melatonin has various properties such as antioxidant, anti-inflammatory as well as neuroprotective effects [175]. Its dietary administration is associated with an increase in melatonin levels of serum and tissues. Melatonin can scavenge free radicals directly, as well as *via* stimulation of antioxidant enzymes [176]. Moreover, N1-acetyl-N2-formyl-5-methoxykynuramine (AMFK), which is one of the metabolic products of melatonin, can donate two electrons to free radicals and thus scavenge ROS [177]. In addition, melatonin is a potent regulator of reduction and oxidation reactions in cells. For example, melatonin and its metabolites can inhibit upregulation and activation of COX-2 and iNOS, thus suppresses inflammation and subsequent oxidative damage [178, 179]. Since melatonin is a natural body antioxidant, its usage has less toxicity as well as appropriate penetration in various organs [180]. This makes the possibility of radioprotection of different organs with melatonin. These abilities allow its classification as a natural and photochemical agent for protection against the cytotoxic effects of radiation [181, 182].

Several *in vitro* and *in vivo* studies have investigated the radioprotective effects of melatonin. Animal studies were conducted for various organs such as lung, heart, kidney, liver, gastrointestinal system, skin, testes, lenses, spinal cord and others [183-191]. Although the clinical applications for possible radioprotection of melatonin have suffered limitations, some have shown promising results. A clinical study by Lissoni *et al*. [192] showed that treatment with melatonin (20 mg daily) for patients with glioblastoma undergoing radiotherapy resulted in better survival and minimal side effects. This study involved 30 patients who received fractionated radiotherapy with a total dose of 60 Gy. Ben *et al*. [193] in phase II, prospective, randomized clinical study evaluated the role of a melatonin-containing emulsion on the occurrence of radiation-induced dermatitis in patients who underwent radiotherapy for breast cancer. Their study showed that melatonin-containing emulsion caused the reduction of grade 1/2 dermatitis by 90%. In contrast to these studies, another research reported that administering melatonin (20 mg/day) for patients with brain metastases has no beneficial effect on their survival [90]. Further studies, especially for patients with breast and prostate cancer, may have interesting findings.

16. SECOISOLARICIRESINOL DIGLUCOSIDE (SDG)

SDG is one of the most abundant dietary lignans such as flaxseed, while numerous other herbal agents like blackberry and wheat contain a substantial concentration of SDG. Studies have reported that SDG has potent antioxidant and anti-inflammatory effects [194, 195]. SDG has the ability to scavenge free radicals generated by ionizing radiation, leading to protection of the genomic contents of cells. This effect was seen in both pre and post-irradiation treatments with different radiation doses [196, 197]. SDG can modulate apoptosis pathways *via* changes in miRNAs levels involved in cell death. Treatment with flaxseed showed a reduction in mir34 by 50%, resulting in attenuation of radiation-induced apoptosis and senescence [198]. Moreover, it can alleviate inflammatory responses through attenuation of NLRP3 inflammasome activation [199].

Lee *et al*. showed that administering flaxseed (10% (w/w) for 3 weeks before thorax irradiation with a single dose of 13.5 Gy can alleviate radiation-induced acute and chronic inflammation, as well as fibrosis [200]. Similar results were obtained from a clinical study. Treatment with dietary Flaxseed for patients with non-small cell lung carcinoma could ameliorate radiation-induced pneumonitis. This process was done daily from the start of radiotherapy to 2 weeks after treatment [201].

Treatment with flaxseed has shown a potent mitigatory effect for mice lung and heart tissues. Solomidou *et al*. evaluated the mitigatory effect of SDG on different time points after thorax irradiation with a single dose of 13.5 Gy. Treatment with SDG (10% (w/w) showed an increase in survival of mice more than twice within a period of 4 months after exposure. This was associated with decreasing pulmonary heart fibrosis as well as inflammation, resulting from suppression of inflammatory and pro-fibrotic cytokines secretion. The mitigatory effect of SDG was more obvious when administered 2 weeks after exposure [202, 203]. A similar result, although with low survival was observed for treatments 1, 2 or 3 days after exposure [204].

17. GINKGO BILOBA

Ginkgo biloba is one of the oldest species proposed for some clinical use due to its strong antioxidant properties. Extracts of Ginkgo biloba have been proposed for the improvement of some mental disorders such as dementia and Alzheimer [205-208]. In 2009, the radioprotective effect of Ginkgo biloba was detected in human and mice lymphocytes in a study by Shin *et al*. They treated mice with 500 µg/kg before irradiation with 4.5 Gy of gamma rays. Also, they observed its radioprotective after a 2-week treatment of human lymphocytes with 1 to 500 µg/kg. Results showed that Ginkgo biloba attenuates radiation-induced apoptosis in a dose-dependent manner. Moreover, it could reverse the effects of ionizing radiation on the decreased size of mice spleen [209]. A study by Okumus *et al*. showed the protective effect of Ginkgo biloba on radiation-induced oxidative injury in rat's lens. They used 40 mg/kg/day for 3 days before irradiation to ten consecutive days after irradiation with 5 Gy. Afterward, the antioxidant levels of the lenses were evaluated. Results indicated that treatment with Ginkgo biloba caused a significant improvement in the total content of antioxidant enzymes and non-enzymes such as glutathione reductase and glutathione-Stransferases, as well as a reduction of xanthine oxidase content. These changes were associated with a reduction of cataract appearance in rat's lenses [210]. A similar study revealed that it can alleviate the increased level of oxidative stress and augment the activity of SOD and GSH in rat's lens [211]. Şener *et al*. showed that in addition to the enhancement of antioxidant capacity,

Ginkgo biloba has the ability to ameliorate the upregulation of TNF-α and Lactate dehydrogenase in rat's serum and tissues following irradiation [212].

18. SELENIUM

Selenium is a trace element which is required for the formation of several selenoproteins with key roles in important metabolic processes. In the human body, selenoenzymes and selenoproteins are considered as vital components of the antioxidant enzymes including glutathione peroxidase (GSH-Px) [213]. In addition, selenium has the ability to cooperate with other natural antioxidants like vitamins C and E for protecting the normal cells against oxidative damage. Seleno-L-methionine and N-acetylcysteine (NAC) are two main natural sources of selenium that have shown potent antioxidant and radioprotective properties [214, 215].

Selenium has potent radioprotective and mitigatory properties in terms of radiation toxicity. Clinical studies of selenium adjuvant for radioprotection have focused on patients with brain tumor. A study by Buentzel *et al*. [216] revealed its ability to reduce side effects of radiation therapy on head and neck cancer therapy including xerostomia, mucositis and dysphagia. They used 1 mg/day for patients undergoing radiochemotherapy and 0.5 mg/day for radiotherapy patients. A total of 39 patients were involved. The results of this study indicated that treatment with selenium resulted in a significant reduction of acute xerostomia and mucositis. In addition, the incidences of xerostomia and mucositis have no difference with results obtained from amifostine. However, the efficiency of selenium for ageusia and dysphagia reported was very limited [217]. Another study by Max *et al*. [218] didn't show radioprotection for these side effects after administering Seleno-L-methionine (dose of 3600 μg/m^2, twice daily for 7 days before radiotherapy). Despite protective effect of selenium, it has not shown any improvement in survival of patients with glioblastoma multiforme [219]. However, no study has shown the disadvantages of its effects such as reduction in tumor response to radiotherapy [220].

The results of mitigatory effects of selenium are very interesting. *In-vitro* studies revealed that incubating irradiated cells with selenium leads to reduced DNA damage and expression of genes involved in oxidative damage [221, 222]. The mitigatory effects were confirmed in *in vivo* studies as well. An animal study by Sieber *et al*. showed that treatment of rats with seleno-L-methionine or sodium selenite after exposure to 10 Gy radiation resulted in a reduction of damage to kidney functions. This was followed by treatment with 100 μg/day of selenium compounds for 21 weeks after irradiation [52]. In another follow-up study, these authors showed that supplementing with 200 μg of selenium per day is more effective in mitigating radiation toxicity on the nephrophysiological functions compared to higher or lower doses. The results showed a reduction in serum levels of blood urea nitrogen (BUN) from 115 mg/dl to lower than 80 mg/dl as well as ameliorating pathological damages [223].

19. TOCOPHEROLS

The α-tocopherol which is named "vitamin E", is the strongest form of tocopherol elements found in varieties of foods such as wheat germ, vegetable oils like olive and sunflower oils *etc*. [224]. The α-tocopherol is one of the most abundant fat-soluble antioxidants in tissues and plasma with a high biological activity [225]. This antioxidant has a hydroxyl group, with the ability to donate a hydrogen atom in order to reduce free radicals [226]. These properties of α-tocopherol make it one of the most interesting agents for radiation protection and mitigation.

The radioprotective effects of α-tocopherol have been confirmed years ago. It can protect sensitive organs such as bone marrow and intestinal against toxic effects of radiation [227]. Some studies proposed that α-tocopherol ameliorates toxic effects of radiation on bone marrow stem cells through stimulation of some cytokines and growth factors such as IL-6, granulocyte-colony stimulating factor (G-CSF), and certain chemokines which augment hematological cellular recovery [228-232]. These properties of α-tocopherol associated with potent radical scavenging effect make it a promising agent for radiation mitigation as well. Anzai *et al*. proposed gamma-tocopherol-N and N-dimethylglycine ester, which is a water-soluble derivative of vitamin E as a potent radioprotector and mitigator. They showed that treatment with this derivative can mitigate the detrimental effects of an exposure to 7.5 Gy x-rays. Their results indicated that gamma-tocopherol-N,N-dimethylglycine ester stimulates the recovery of bone marrow cells following exposure [233].

20. ASCORBIC ACID

Ascorbic acid (Vitamin C) is a potent antioxidant that effectively scavenges superoxide and ROS. Moreover, it has an important role in the regulation of intracellular redox state and neutralizes endogenous radical species by suppressing excess superoxide generation by mitochondrial metabolism and ROS/NO producing enzymes such as xanthine oxidase, NADPH oxidase, and nitric oxide synthase [234, 235]. The potent antioxidant properties of ascorbic acid can reduce oxidative damage resulting from exposure to radiation. On the other hand, its redox modulatory effect makes it a potential radiation mitigator [236].

Ascorbic acid has shown the ability to reduce radiation toxicity in various organs such as testes, intestine, bone marrow, skin and others [237-240]. The administered dose of ascorbic acid in these studies was different from 10 mg/kg to 300 mg/kg. However, it has no reported toxicity for any of these drug doses. Sato *et al*. showed that treatment of irradiated mice with a single dose of 3 g/kg ascorbic acid can mitigate lethal effect and other hematological damages after exposure to a 7 to 8 Gy gamma rays. However, higher doses of ascorbic acid may lead to cytotoxicity. They showed significant improvements in survival following treatment with ascorbic acid 24 hours after exposure, while 36 hours after irradiation did not show mitigatory effect. Furthermore, their results revealed that its post-irradiation treatment suppresses inflammatory cytokines such as IL-1 and IL-6, as well as radiation-induced apoptosis [241].

21. BETA-CAROTENE

Beta-carotene ($C_{40}H_{56}$) is the most abundant form of vitamin A found naturally in fruits and vegetables. It is a hydrogen-rich compound, with considerable interest due to

its antioxidant properties [242]. Epidemiological studies have reported that dietary intake of Beta-carotene is associated with a reduced risk of several diseases such as cancer [243, 244]. Beta-carotene acts by suppressing the oxidative action of ROS and singlet oxygen. In addition, Beta-carotene suppresses redox based inflammation activation *via* suppression of ROS producing enzymes such as iNOS and COX-2, and downregulates inflammatory mediators such as NF-κB [245]. However, in high dose supplements, it may act as a pro-oxidant and reduces antioxidants in the cell, leading to oxidative DNA damage [246, 247]. Treatment with Beta-carotene has been tested for clinical radiotherapy applications as well as Chernobyl survivors. These studies have found interesting results without significant toxicity or other side effects.

In 1988, a study by Mills [248] showed that administering beta-carotene to radiotherapy and chemotherapy patients result in a decrease of oral mucositis. Patients included 20 individuals with advanced squamous carcinoma of the mouth. Each of them received 60 Gy of ^{60}Co gamma rays in 30 fractions. In addition, patients received chemotherapy drugs such as bleomycin, vincristine and methotrexate. On the other hand, a randomized clinical trial study by Margalit *et al*. showed that treatment with beta-carotene for prostate cancer patients who have undergone radiotherapy had no impact on the therapeutic effect of radiation as well as the treatment outcome. However, these results cannot be extrapolated to all cancers [92].

In vivo studies have revealed that treatment with beta-carotene is effective in amelioration of radiation toxicities in different tissues such as liver, thyroid gland, gastrointestinal system, bone marrow and blood [249-253]. However, for parotid glands, no radioprotective effect was observed [254]. These studies indicated that beta-carotene protects cells against ionizing radiation *via* scavenging of ROS and stimulation of SOD and catalase. Also, it is able to reduce apoptosis in radiosensitive cells like human T cells [255]. Although beta-carotene may reduce oxidative damage *via* regulation of redox based enzymes, further studies are needed to confirm the effect of beta-carotene on ROS producing enzymes such as NADPH oxidase, COX-2, iNOS, lipoxygenases, and others.

Ben-Amotz and colleagues evaluated the effects of treatment with beta-carotene on serum blood oxidative stress markers in children who had exposed to radiation for a long time following the Chernobyl accident. They evaluated 709 children comprising 385 girls and 324 boys from the contaminated areas. Primary results showed an increased level of oxidation markers in serum blood of children, especially for girls. Furthermore, supplementing with a 40 mg natural mixture including beta-carotene for 3 months resulted in a remarkable reduction of oxidation markers [256]. This study is a good example of the mitigatory effects of beta-carotene in reducing the risk of carcinogenesis among irradiated people in a radiation disaster.

22. COENZYME Q10

Coenzyme Q10 (CoQ_{10}) or ubiquinone is a fat-soluble compound that is synthesized in most mammalian cells. It has been identified as an important co-factor in numerous biological processes [257]. The most crucial role of this co-factor is in mitochondria, which acts as an electron carrier in the respiratory chain [258]. The reduced form of CoQ_{10} has potent antioxidant effects in cellular organelles especially mitochondria and lipid membranes [259]. In addition, Q10 has the ability to stimulate expression of antioxidant enzymes including SOD and catalase [260]. Furthermore, it can complement the antioxidant activity of alpha-tocopherol [261].

Q10 showed a radioprotective role in some organs. Ki *et al*. [262] showed that daily administering of 10 mg/kg CoQ_{10} to rats for 24 weeks after irradiating the abdomen resulted in a significant improvement in kidney function. In addition, Q10 reduced glomerulosclerosis and tubulointerstitial fibrosis caused by radiation. Treatment with a similar dose of Q10 has shown the ability to ameliorate oxidative damage in rats' brain [263]. In animal studies, administering Q10 in higher doses like 100 mg/kg have shown protection against other side effects of ionizing radiation such as fatigue [264]. Although human studies are very limited, it has shown amelioration of pneumonitis in patients with lung cancer. Treatment was continued for 6 months after radiotherapy [265].

23. α-LIPOIC ACID (ALA)

ALA ($C_8H_{14}O_2S_2$) was discovered in 1930 while its antioxidant properties were observed in 1980. It is a natural coenzyme found in mitochondrial complexes. It catalyzes the oxidative decarboxylation of α-keto acids such as pyruvate and branched-chain α-keto acid [266]. Various experiments have revealed the ability of ALA to combat oxidative damage *via* quenching a variety of intracellular free radicals [267]. In addition, ALA is involved in the recycling of some other natural cellular ROS scavengers such as ascorbic acid, α-tocopherol, and GSH [268]. These properties make ALA a potent antioxidant for preventing pathologies involving oxidative damage.

In an *in vitro* study, ALA has shown amelioration of oxidative damage induced by NO and ROS, reduces inflammatory markers, and also restores antioxidant enzymes such as SOD and GSH [269]. Kang *et al*. [270] investigated the radioprotective effect of ALA on the small intestine of mice. The mice were treated with 100 mg/kg of ALA for 3 days before irradiation. Results showed that its administration had no effect on food intake as well as the small intestinal villus. Treatment before irradiation led to a reversal of reducing villus numbers and height. Moreover, pre-treatment with ALA caused decreased inflammatory markers, apoptosis and oxidative damage, while restoring the GSH content of intestinal cells. It has the ability to ameliorate radiation-induced fibrosis. Ryu *et al*. in a mice model showed that p65 acetylation is necessary for the activation of pro-fibrotic genes after exposure to radiation. ALA inhibition of Ac-p65 and p300 can reduce p65 acetylation and histone acetyltransferase activity during fibrosis, resulting in down regulation of fibrotic mediators such as MMP-2, PAI-1, and also NF-κB transcription. As NF-κB has a role in enhancing MMP-2 and PAI-1 *via* binding to their promoters, suppressing NF-κB by ALA has a central role in ameliorating radiation-induced fibrosis [271].

It has been shown that ALA has the ability for protection against high-energy particle radiation in mice brain. Exposure to HZE is very important in deep space missions as well as in hadron therapy. Treatment of mice with 200 mg/kg ALA 30 minutes before irradiation (1.5 Gy) showed attenuated oxidative damage and apoptosis in the cerebellum as well as memory dysfunction [272]. ALA (200 mg/kg) has shown a reversal in decreased sulfhydryl content of cerebellum and plasma after localized brain exposure to ionizing radiation (6 Gy X-rays) [273]. In addition, it has a mitigatory effect among children that has been exposed to the Chernobyl disaster. Treatment with ALA for 28 days among inhabitant children in the contaminated area resulted in a reduction of oxidative stress [274] (Table **1**).

24. COMBINATION FORM OF ANTIOXIDANTS

Some researchers have proposed that using a combination of two or more different antioxidants may be more effective in reducing radiation toxicity. So far, various combinations have been tested for this aim [278, 279]. A combination of α-tocopherol acetate and ascorbic acid, likewise a combination of some other antioxidants like selenium and Q10 with other antioxidants have been studied in several experiments [280, 281].

A combination of α-tocopherol acetate and ascorbic acid may have some synergic effects on radiation toxicity as well as reduction of radioactive particles that may be absorbed after a radiation accident [282]. Administering this combination (10mg/kg each) before and after irradiation of rats showed effective treatment when applied before exposure. It is interesting to note that individual treatment with either α-tocopherol acetate or ascorbic acid before or after irradiation had no remarkable effect on reduction of chromosome aberrations in the plasma and bone marrow [283]. This effect was also observed in the plasma level of DNA fragments. Treatment with single vitamin E (10mg/kg) or C (20mg/kg) did not show any radioprotection, while their combination could protect cells from radiation-induced chromosomal aberrations [284].

Some studies have shown promising results for radioprotection and mitigation using a combination of natural antioxidants such as Selenium-L-Methionine, N-acetyl cysteine, a-lipoic acid, Q10, and others. Guan *et al.* [285, 286] showed that a combination of these agents associated with ascorbic acid and alpha-tocopherol can reverse the reduction of serum levels of total antioxidants after exposure of rats to high LET radiation. Administering a combination of these agents showed a reversal in the reduction of total white blood cells and neutrophil counts, as well as inhibiting apoptotic genes in bone marrow cells of mice after exposure to gamma rays [287]. These results have been investigated for total body exposure to proton radiation as well [288]. Brown *et al.* showed that a combination of Selenium-L-Methionine, N-acetyl cysteine, a-lipoic acid, Q10, sodium ascorbate can mitigate total body exposure to 8 Gy gamma rays. They showed that administering a diet comprising these agents 24 hours after irradiation of mice was more effective in comparison to sooner or later times. Furthermore, their results revealed the ability of this combination to protect bone marrow cells against chronic oxidative damage, and also attenuate the upregulation of genes involved in the apoptosis pathway [289].

A combination of α-tocopherol and ALA also showed mitigatory effect. A study on children exposed to Chernobyl contaminated area showed that a combination of these antioxidants is more effective in comparison to each of the individual agents [274]. In addition to natural antioxidants, the combination forms of flavonoids have been investigated for radioprotection too. Two studies by Gupta *et al.* [290] revealed that a combination of podophyllotoxin and rutin can protect mice against ionizing radiation. They showed that this compound stimulates nuclear factor erythroid-derived like-2 factor (Nrf-2) that act as an activator of GSH and other antioxidant enzymes. Also, it can induce anti-apoptotic genes (Bcl-2 and Bcl-xL) in bone marrow cells, suppress inflammatory mediators and cytokines in gastrointestinal. Administering a diet containing several types of antioxidants can significantly improve the survival rate after mice irradiation. Epperly *et al.* showed that an antioxidant diet administered with mnSOD can reduce a 30-day mortality from 45% to 17.5% [291].

CONCLUSION

After approval of amifostine as radioprotectors, several experiments have been conducted to identify novel radioprotectors with less toxicity. Moreover, amifostine offers limited protection against radiation to some organs. Radioprotection with herbal and phytochemical agents has been of high interest in the recent decade. Although curcumin is the most famous herbal agent which has been studied for its anti-inflammatory and antioxidant effects, several studies have shown promising results for some other agents. Other herbal agents such as hesperidin, melatonin, quercetin, and sesamol have shown interesting radioprotective results, while in recent years some studies proposed resveratrol as a new radioprotector. Although herbal agents have been studied for radioprotection, using these agents for mitigation may show interesting results. A potent effect of herbal radioprotectors is a result of their anti-inflammatory effects. The aforementioned agents have shown the ability to attenuate inflammation mediators such as NF-κB and SMAD, leading to amelioration of inflammatory cells recruitment and reduced level of inflammatory cytokines. The direct antioxidative effects of herbal agents or stimulation of antioxidant enzymes also contribute to their radioprotective effects. Although these effects are different for various agents. For example, sesamol has a potent direct antioxidant, curcumin inhibit inflammatory mediators, and resveratrol scavenges free radicals *via* stimulation of antioxidant enzymes, while it can't scavenge ROS and NO directly.

Natural antioxidants have shown some limited radioprotection, while a combination of two or more different antioxidants may have better radioprotective effects in comparison to a single agent. This is an area of high interest in the development of radiation mitigators for the safety of people exposed to nuclear or radiological disasters. A combination of antioxidants or radioprotectors with different radioprotective mechanisms can offer protection in a synergic manner. For example, a combination of ascorbic acid as a hydrophilic agent with alpha-tocopherol as a lipophilic agent can protect

Table 1. Different herbal and natural antioxidants for radioprotection.

Agent	Structure	In-vitro/in-vivo route	Dose range	Dose reduction factor (DRF)	Mechanisms of action	Ref
Curcumin	$C_{21}H_{20}O_6$	In-vitro/in-vivo, Human	Up to 8 gm/day for human	1.15	Targeting of NF-κB and inflammatory cytokines, scavenging of ROS and NO	[99, 101]
Hesperidin	$C_{28}H_{34}O_{15}$	Mice, Rat	No toxicity up to 100 mg/kg	-	Preventing of immune cell recruitment, stimulation antioxidant enzymes,	[117]
Resveratrol	$C_{14}H_{12}O_3$	Mice	No toxicity up to 100 mg/kg	40% increase in survival	Suppression of NOX4, simulation of Sirt-1, stimulation of antioxidant enzymes	[131]
Quercetin	$C_{15}H_{10}O_7$	Mice	No toxicity up to 100 mg/kg	1.11	Inhibition of NF-κB and MAPKs, stimulation of antioxidant enzymes, scavenging of ROS	[143, 144, 275]
Ocimum Sanctum	-	Mice	200 mg/kg	-	Scavenging of ROS, stimulation of antioxidant enzymes	[150]
Rutin	$C_{27}H_{30}O_{16}$	In vitro, Mice	50 mg/kg	1.15	Scavenging of ROS, stimulation of antioxidant enzymes	[160, 275]
Caffeic Acid	$C_9H_8O_4$	Mice	30 mg/kg	1.1-1.2	Scavenging of ROS, recycle of GSH, suppression of inflammatory cytokines	[172]
Sesamol	$C_7H_6O_3$	Mice	No toxicity up to 100 mg/kg	70% survival in 50mg/kg	Scavenging of ROS, activation of GSH and catalase	[167]
Melatonin	$C_{13}H_{16}N_2O_2$	In-vitro/in-vivo, Human	No toxicity up to 100 mg/kg. for clinical studies has tested to 20mg/kg	1.53	Scavenging of ROS and NO, stimulation of antioxidant enzymes, Suppression of Redox system activity, inhibition of inflammatory responses	[192, 276]
SDG	$C_{32}H_{46}O_{16}$	In-vitro/in-vivo, Human	No toxicity up to 3g/kg. for clinical studies has tested to	-	Inhibition of NLRP3 inflammasome,	[199]
Ginkgo biloba	Containing several chemical compositions	In-vitro/in-vivo	1 µg/kg to 50mg/kg	-	Stimulation of antioxidant enzymes, suppression of TNF-α	[212]
Selenium	Se	Human, Rat	1 mg per day	80% survival for selenium-L-Methionine	Scavenging of ROS, activation of natural antioxidants like vitamin C and E, and also antioxidant enzymes	[217, 277]
α-tocopherol	$C_{29}H_{50}O_2$	Mice	100 mg/kg	-	Scavenging of ROS, stimulation of growth factors such as IL-6 and G-CSF	[233]
Ascorbic Acid	$C_6H_8O_6$	Mice	No toxicity up to 3 gr/kg	20% survival for post exposure treatment and 80% survival for pre-	Scavenging of ROS, inhibition of Redox system	[241]

Agent	Structure	In-vitro/in-vivo route	Dose range	Dose reduction factor (DRF)	Mechanisms of action	Ref
				treatment (8Gy x-rays)		
Beta-carotene	$C_{40}H_{56}$	In-vitro/in-vivo, Human	40 mg daily for human	1.26	Inhibition of redox-based enzymes such as iNOS and COX-2, downregulating NF-κB, Stimulation of SOD and CAT	[255]
Q10	$C_{59}H_{90}O_4$	Rats, human	No toxicity up to 100 mg/kg	-	Stimulation of SOD and CAT	[264]
A-lipoic acid	$C_8H_{14}O_2S_2$	Mice	No toxicity up to 100 mg/kg	1.26	Inhibition of NF-κB, Scav-enging of ROS, restore of GSH, recycling of ascorbic acid and α-tocopherol	[270, 271]

both the fat and hydrophilic environments within the cells. This result was investigated for a combination of ALA with alpha-tocopherol. ALA can recycle ascorbic acid and alpha-tocopherol, as well as stimulate GSH. Hence, it is predicted that a combination of ALA with these agents may have synergic effects on radioprotection. The combination of different agents for radioprotection and mitigation have attracted more attention in recent years. Therefore, immunomodulatory agents such as anti-inflammatory, anti-apoptosis, and redox modulatory compounds are most promising for the development of radiation mitigators.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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