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Natural Compounds with Radioprotective Properties in Radiotherapy
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ABSTRACT

Radioprotective agents are the compounds that are administered before radiation to reduce the cell damage and cell death caused by ionizing radiation. These compounds are used in the patients undergoing radiotherapy, radiation therapy staff, and other involved healthcare staff in the event of job-related incidents in radiation departments. The first category evaluated in radioprotective agents includes the synthetic compounds containing sulfur. For instance, amifostine is used to prevent the radiotherapy-induced complications that affect the oral mucosa. However, the application is limited due to the severe side-effects, such as nausea and vomiting and hypotension. Therefore, access to radioprotective agents with low complications is of paramount importance. Natural products, especially medicinal plants, could be used as an appropriate alternative in this regard. Natural plant-based products have been mainly studied in Asia. Evaluation of herbal has shown their antioxidant properties despite their role in stimulating the immune system, which affects the proliferation of the hematopoietic system. Compared to synthetic compounds (e.g., amifostine), plant-based compounds have lower protective effects, while they also cause fewer side-effects in radiotherapy patients. The present study aimed to review the studies on of the natural products with radioprotective properties and asses their advantages and disadvantages.

1. Introduction

Radioprotective Function in Radiotherapy

Ionizing radiation is frequently used in various fields, including medicine, radiotherapy, and radiopharmaceuticals for diagnostic and therapeutic purposes. Ionizing radiation penetrates the tissues of the body and transports energy to vital biological molecules, such as the cell membrane, DNA, proteins, and lipids. Ionizing radiation may lead to cell damage and cell death, and the severity of the damage caused by radiation depends on the radiosensitivity of the tissues. Radioprotective compounds are injected to humans and animals upon exposure to radiation or immediately after exposure to reduce the effects of irradiation.

Application of Radioprotective Agents in Radiotherapy

Radioprotective compounds are mainly used in the cancer patients undergoing radiation therapy. In radiation therapy, gamma radiation is employed for the treatment of various tumors. Gamma radiation generates free radicals in tumor cells, causing severe cell damage and even cell death. Despite the inhibitory effects of radiation on the growth and proliferation of tumors, it causes severe damage to normal cells as well. Due to the high rate of growth and multiplication in cells following radiation, the bone marrow and gastrointestinal cells become sensitive to the adverse effects of radiation. Therefore, use of radioprotective agents to protect normal cells by increasing the radiation beam is a major step toward the treatment of cancer patients and reducing the adverse effects of radiation on the patients.

Application of Radioprotective Agents in Nuclear Accidents

Radioprotective agents are applied in the individuals exposed to nuclear accidents. Due to the risk of radiation accidents, healthcare staff and medical team members must be protected against the lethal effects of radiation (1, 2).

Amifostine is a synthetic drug with protective effects against radiation, which is used in the patients undergoing radiotherapy. However, the application is limited due to its adverse side-effects and high cost (3). Therefore, access to cpst-efficient and safe drugs with radioprotective properties is of paramount importance.

Compounds of natural origin, such as medicinal plants, have long been used in medicine with few complications as the basis for developing safe alternative drugs with limited toxic effects. The present study aimed to review the literature of natural radiation and predominantly evaluate the products of the protective medicinal plants to enhance the knowledge of researchers regarding the development of natural radioprotective agents. In addition, we investigated the categories of the natural ingredients with radioprotective properties and discuss their advantages and disadvantages.

Radiation-Induced Damage

Ionizing radiation, such as X-rays and gamma rays, could cause damage to critical macromolecules, such as the DNA and proteins. Water is the main constituent of cells, and radiation exerts the most significant impact on water. The energy of radiation is predominantly absorbed by water, leading to the production of free radicals that are highly reactive toxic chemicals contributing to the damages caused by X-rays and gamma rays. When the water molecules in the cells are irradiated, various active molecules and ions containing hydrogen and hydroxyl radicals are formed, which are mainly responsible for the subsequent cell damage. In the presence of oxygen-reactive species, some derivatives of oxygen (e.g., oxygen and peroxide) are also produced. The density of these active agents depends on the oxygen concentration in irradiated cells and type of the tissues. Damage to macromolecules and cells leads to tissue damage and dysfunction (Figure 1).

Radiosensitivity of Tissues

High doses of ionizing radiation damage the gastrointestinal cells, hematopoietic system, and central nervous system. Furthermore, the bone marrow is susceptible to low doses of radiation, which could reduce and even suppress these tissues due to high reproduction and high mitotic rate (4). Decreased number of progenitor blood cells leads to the reduction of the white blood, platelet, and red blood cell counts (5, 6). Infections and hemorrhage are the most important causes of death due to bone marrow damage.

Although gastrointestinal and epithelial cells are among the radiosensitive tissues against radiation damage, these systems require higher radiation doses compared to the hematopoietic system (7). High doses of radiation may lead to acute and chronic damage to critical tissues, thereby causing various syndromes. On the other hand, exposure to low doses of radiation causes

damage to DNA strands, thereby creating abnormal chromosomes and causing severe diseases (e.g., cancer) in the long run.

Mechanism of Radioprotective Agents

Radioprotective compounds reduce the adverse effects of radiation on the body tissues through the following mechanisms:

1. Entrapment of the free radicals;
2. Donating hydrogen to damaged molecules;
3. Induction of hypoxia and decreased production of active species with molecular and atomic oxygen;
4. Stimulating the proliferation and differentiation of stem cells in the hematopoietic system;
5. Increasing the activities of antioxidant enzymes in the organs;
6. DNA binding and sustaining

Radioprotective agents reduce cell damage based on one or more of the mentioned mechanisms. Moreover, they exert antioxidant effects by using compounds such as sulfur, vitamins C and E, and flavonoids. These compounds could entrap free radicals and remove the active molecules that cause damage to critical macromolecules, such as the DNA and proteins (8). Considering the short half-life of free radicals, it is essential to produce radioprotective compounds within cells and adjacent to vital molecules before the formation of free radicals.

Another category of radioprotective agents has been shown to stimulate the proliferation of hematopoietic cells in the bone marrow. This class consists of immune stimulants such as cytokines, which bind to their activate receptors via intracellular routes. The media stimulate cell growth, proliferation, and differentiation. Recent studies have discovered the activate compounds that release the responsible cytokines for the proliferation and differentiation of hematopoietic cells, which increase the blood cells in the peripheral circulation, thereby diminishing the impact of the diseases caused by radiation (e.g., infections and hemorrhage) (9, 10).

Features of Radioprotective Agents

Several features must be considered in the development of effective radioprotective agents, including the ability of the media to reduce the adverse effects of radiation, protection of the major tissues, appropriate mode of administration (oral or injective), low toxicity and high efficacy, optimal stability, and compatibility with the drugs used in patients or healthy subjects. Discovery of optimal radioprotective agents with all the mentioned criteria is rather difficult. For instance, amifostine has been approved by the Food and Drug

Administration (FDA) for protection against radiation and chemotherapy in humans. However, the application of this agent is limited due to the associated side-effects (e.g., hypotension and vomiting) and its low effectiveness (11).

Radioprotective agents with adequate, long-term efficacy could be used before irradiation. These agents have been evaluated with peritoneal administration in cell culture media and animals. They cannot be used for human administration unless the effectiveness of intraperitoneal injection is ensured; therefore, they are often applied via subcutaneous injection and oral administration in animals in order for further assessment.

Evaluation of Radioprotective Compounds

Radiation-induced damages in cells and tissues are of various types, which could be mitigated using radioprotective agents. There are several tests to evaluate the effectiveness of radioprotective compounds, which are classified into two categories of *in-vitro* and *in-vivo*. Various animals and cell lines are used in these tests. For instance, rats are commonly subjected to *in-vivo* tests as experimental (drug administration) and control groups. In the studies in this regard, animals are exposed to lethal doses of radiation.

Another standard *in-vivo* test in animal models involves the dose reduction factor (DRF), which is an amount equal to the lethal dose of radiation in 50% of drug-treated animals divided by the animals in the control group. The method is used to determine the survival rate, which requires fewer animals and verifies DRF easily. As a result, survival rate is considered to be a broad assessment used for radioprotective agents. DRF is a preferred method in the fundamental comparative studies aiming to determine the actual effectiveness of these medications. To determine the DRF, test and control groups of animals are exposed to various radiation doses, and the survival rate is recorded after 30 days. LD_{50} is defined as the lethal dose in 50% of the population, which is measured in the control group (injection only), as well as the and protected group. DRF is calculated based on the following formula (4):

$$DRF = \frac{LD50/30 \text{ of protected animals}}{LD50/30 \text{ of control animals}}$$

Several methods are used in *in-vitro* tests, including the micronucleus test, comet assay, and metaphase analysis. Other tests in this regard involve the intestinal epithelial cell count, cell survival, and *in-vitro* colony count (12-16).

Changes in biochemical parameters (e.g., reduction of glutathione, malondialdehyde, and endogenous enzymes) could be the criterion for the evaluation of radioprotective agents (17-20). In some of these tests, radioprotective compounds are administered to animals, tissues or cells specifically under *in-vitro* conditions in order to reduce cell damage using these agents. Currently, use of molecular techniques and proprietary compounds has been reported to detect the inhibition or activation of specific intracellular proteins and intracellular mechanism of radioprotective agents (21).

Several clinical trials have been conducted on healthy volunteers and patients for the assessment and recognition of radioprotective agents, proposing significant limitations in these tests since the irradiation of healthy subjects is unethical. Furthermore, there are certain limitations in testing human volunteers in terms of radiation protection.

In a research in this regard, a technique was developed by the author, encompassing the findings of *in-vitro* and *in-vivo* studies regarding the effectiveness of radioprotective agents in healthy humans. A radioprotective composition was administered to healthy humans, and blood samples were collected at different intervals, which were exposed to gamma radiation *in-vitro* in order to assess genetic damage and efficacy of the radioprotective composition (22).

Herbal Compounds with Antioxidant Properties

Synthetic compounds are the first generation of radioprotective agents, which contain thiol. These compounds have been extensively investigated, the results of which have suggested significant antioxidant effects. In addition, these compounds could reduce cell damage and cell death with contents such as sulfhydryl (free thiol) and entrapment of free radicals (1, 2). Several studies in this regard have also explored the effectiveness of natural herbal medicines and vitamins.

2. Materials and Methods

This systematic review aimed to evaluate the studies focusing on the status of radiation biology and radioprotective agents across the world. Literature search was conducted with no time constraints via searching in databases such as Google Scholar, Medline, Embase, PubMed, Irandoc, IranMedex, Magiran, and SID using MeSH keywords, including radiation protection, radiation biology, herbs, radioprotective agents, and radiotherapy. The keywords were determined by two specialists in the field of radiation biology

and radioprotective agents according to the MeSH in PubMed.

One researcher reviewed the resources in the mentioned databases in order to certify that the related data and articles were searched adequately. The reference lists were also reviewed manually for related studies, and 40 articles published during 1994-2017 were retrieved for further assessment.

Inclusion Criteria

The studies focusing on radiation biology and radioprotective agents that were published in prestigious journals were selected for the current review.

Quality Assessment of the Articles

The extracted resources were studied by two researchers independently. In the first step, the abstracts of the retrieved articles were reviewed, and the full texts of the papers were further studied if necessary. For a comprehensive review, the full texts of the related articles were reviewed, and the final articles were selected. Moreover, the reference lists of the selected articles were searched manually. Finally, all the articles were approved by an expert of radioprotective agents.

Data Extraction

The required data were extracted from the selected articles, including the title, author(s), year of the study, methodology, research objectives, results, and conclusions.

3. Results and Discussion

Vitamin E Alone and Combination of Vitamin E with Other Agents

Vitamin E and its derivatives have antioxidant properties and reduce the production of free radicals by oxidative stress agents. Intake of vitamin E before gamma radiation has been shown to decrease the mortality caused by the lethal doses of gamma radiation, so that the intraperitoneal injection of vitamin E (400 mg/kg) 24 hours before radiation has resulted in 80% survival in animal models (23).

Studies have denoted the protective effects of vitamin E against the acute reactions associated with radiation. For instance, Felemovicius et al. conducted a research regarding the radiation protection of intestine with vitamin E in the Unites States, stating that vitamin E exerts protective effects against severe radiation reactions, such as diarrhea (24).

Although the most important mechanism of vitamin E and its derivatives is the reduction of oxidative damage, other

mechanisms have been reported as well. Alpha-tocopheryl succinate, interleukin-1, interleukin-6, and G-CSF are the cytokines that increase the proliferation and differentiation of blood cells. These compounds are effectively administered within 48 hours before radiation and have long-term efficacy (25).

Anticlastogenic effects of vitamins A and E before and after radiation have been investigated as an *in-vivo* method of micronucleus tests simultaneously. De Moraes Ramos et al. have claimed that vitamin E could protect the salivary glands of rats against radiation, which confirms the radioprotective effects of these vitamins against gamma radiation (26). Furthermore, in the study by Karabulut-Bulan et al. entitled the "Protective Effects of Vitamin E and Selenium on the Small Intestine in Abdominal Radiotherapy", the findings indicated that antioxidant intake before radiotherapy could protect the small intestine cells against radiation-induced damage (27).

According to Rostami et al., injection of selenium and vitamin E before radiation could reduce the genetic effects of radiation on humans (28). On the other hand, Tabeie et al. reported that vitamin E alone had no effect on the survival of irradiated animals, whereas the combination of vitamin E and β-D-Glucan could increase the survival of the animals irradiated with gamma rays (29). Nair et al. claimed that the peritoneal injection of water soluble vitamin E (TMG) could reduce the lethal effects of radiation and rate of embryonic mortality in mice (30).

Evidence suggests that the daily consumption of antioxidants decreases the damage caused by oxidative stress. Therefore, regular consumption of fruits and vegetables, vitamin C, and phenolic compounds (e.g., flavonoids) plays a key role in the reduction of oxidative stress (31).

Vitamin C

Vitamin C is a water-soluble vitamin that plays a pivotal role in the immune system and antioxidant chain against oxidative damage (32). In a study in this regard, Mozdarani et al. compared the frequency of micronuclei in rat embryos after gamma radiation in the presence and absence of vitamin C, reporting that vitamin C reduced the frequency of the chromosomal aberrations produced by gamma radiation in mice, which was attributed to the free-radical scavenging properties of vitamin C (33).

Melatonin is a hormone released by the pituitary gland, which eliminates hydroxyl

and peroxyl radicals. Melatonin administration to animals and humans could diminish radiation-induced genetic damage, while it could be lethal as well (34). According to Reiter et al., melatonin is able to scavenge hydroxyl and peroxyl free radicals (35). Furthermore, Minaei Zangi et al. have claimed that melatonin could neutralize the free radicals produced by oxygen (36).

In another research, Fernández et al. reported that the oral consumption of melatonin could protect the small intestine against gamma radiation (37). Rostami et al. also denoted that the injection of melatonin and vitamin C before radiation decreased radiation genotoxicity in humans (38). In addition, Naeeji et al. stated that the ingestion of famotidine, vitamin C, and cimetidine two hours before gamma radiation was associated with radioprotective effects on mice. However, no significant differences were observed in the single doses of the mentioned compounds (39). Despite the effectiveness of the drug, its effects on sleep patterns should also be examined (40).

Herbs and plants have long been used in medicine. Recently, numerous medicinal plants have been investigated in terms of radioprotective properties, and the majority of these studies have been conducted in Asian countries due to the geographical climate and importance of medicinal plants in their traditional medicine. Some researchers have evaluated the pure chemical compounds found in medicinal plants. Antioxidant compounds could be used for radiation protection since these plants have the ability to entrap free radicals, inhibit lipid peroxidation, and reduce glutathione in tissues, demonstrating significant protective effects against radiation.

Mentha Piperita (Citrus Peels)

According to a study, the level of IC_{50} (required concentration to reduce free radicals by 50%) was lower in *Mentha piperita* compared to other plants, while DRF was reported to be higher. Therefore, a direct correlation was observed between the antioxidant activity and radiation protection of *Mentha piperita* (41). In another study conducted by the author, citrus peel extract showed antioxidant effects, and the fruit extract could eliminate the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical and H_2O_2 in *in-vitro* tests (42). Furthermore, intraperitoneal administration of the herbal extract to rats one hour before gamma radiation (1.5 Gy) decreased the micronucleus in the bone marrow cells.

Flavonoid hesperidin and naringin are the most important compounds in citrus fruits. In a research performed by Jagetia et al. in India, administration of naringin to mice before radiation exposure was reported to decrease micronuclei (43). In another study conducted by the author, hesperidin administration (80 mg/kg) to mice before gamma ray irradiation (2 Gy) reduced micronuclei by 65% (44).

Crataegus spp.

Crataegus spp. is a plant frequently used in traditional medicine with significant effects on the reduction of blood pressure. In addition, this medicinal herb has antioxidant properties. In a recent study conducted by the author, *Crataegus spp.* extract was administered to mice, leading to the reduction of radiation-induced genetic damage in the bone marrow. Chemical analysis has also indicated that *Crataegus spp.* contains chlorogenic acids and epinephrine.

Considering the efficacy of *Crataegus spp.*, 250 milligrams of the herbal extract was administered to the blood lymphocytes of the human volunteers irradiated with gamma rays *in-vitro*. According to the findings, consumption of this medicinal herb reduced the genetic damage induced by gamma irradiation in human blood lymphocytes before exposure (45).

Flavonoids

Flavonoids are polyphenolic compounds found in plants. These compounds have several properties, including anti-inflammatory, anticancer, anti-diabetic, antimicrobial, and antioxidant effects (46). Moreover, they have proven effective in the treatment and prevention of cardiovascular diseases and cancer. Some flavonoids are potent antioxidants, such as rutin and quercetin. Catechol and hydroxyl groups are found in the chemical structure of these compounds, which are involved in the oxidation and elimination of free radicals (47). Moreover, flavonoids are involved in DNA protection with their special chemical structure (48). In a study in this regard, Haddadi et al. reported that the injection of hesperidin (100 mg/kg) could increase the angiogenic factor through VEGF gene expression in mice (49).

Propolis

Several studies have evaluated the effectiveness of flavonoids as radioprotective agents at low radiation doses using the genetic tests of bone marrow cells (e.g., micronucleus assay) in mice. Propolis is a brown resinous

substance, which is an abundant source of flavonoids and polyphenols similar to seals. Propolis has numerous biological properties, such as antimicrobial, antioxidant, and anti-inflammatory effects. In a study conducted by Yalcin et al., the methanol extract of propolis was injected into animal cells, resulting in the protection of fibroblasts against gamma radiation (3 Gy) (50).

Other Plants and Herbal Compounds

In a study, the effects of five plants were evaluated, including *Spirulina fusiformis, Amaranthus paniculatus, Brassica campestris, Mentha piperita*, and *Adhatoda vasica*. According to the findings, *S. fusiformis* and *A. paniculatus* could scavenge free radicals moderately, while *Brassica campestris*, *Mentha piperita*, and *Adhatoda vasica* demonstrated similar capabilities due to the presence of antioxidants. All the mentioned plants could scavenge the free radicals in the ABTS+ and DPPH assays (51).

In another research, Pavithra et al. examined the leaf extract of *K. foetidissima* and observed that the methanol extract of the plant could be used as a protective agent against gamma radiation as it is an abundant source of antioxidants (52). Moreover, Wang et al. used the injection of the phenolic extracts from the fruits of *Malus baccata* (Linn.). Borkh has also been reported to suppress cell apoptosis and exhibit radioprotective and immunomodulatory functions against whole body irradiation (53).

According to Tiwari et al., administration of Epigallocatechin gallate could protect the hematopoietic system of mice against irradiation (54). On the same note, Szejk et al. reported that the injection of the extracts of *Erigeron canadensis L.* (Ec) and *Sanguisorba officinalis L.* (So) (25 and 5 μg/mL, respectively) could protect lymphocytes against gamma radiation (10 Gy) ($P<0.001$) (55).

In another study, Lee et al. claimed that the oral administration of elm bark extract (50 mg/kg of body weight) increased T-cell and B-cell proliferation in the small intestine of mice and nullifies the intestinal inflammation caused by gamma radiation (15 Gy) (56). According to the results obtained by Saberi et al., administration of ginger extract (50 mg/kg of body weight) could reduce the oxidative damage caused by the radiation dose of 8 Gy as a result of free radical scavenging and antioxidant properties (57).

Targhi et al. reported that the administration of black mulberry extract (200 mg/kg of body weight) at 72 hours

before and after irradiation exhibited an enhanced radioprotective effect in the liver and bone marrow cells against the gamma ray irradiation doses of 3 and 6 Gy (58). On the other hand, Adjimani et al. stated that iron chelator could scavenge the free radicals of hydrogen peroxide (H_2O_2) and hydroxyl radical (•OH), while caffeic acid had the highest activity in scavenging free radicals (59).

Considering that high doses of gamma rays may give rise to lethal complications, protection against the lethal doses of gamma rays is crucial. In addition, it is essential to evaluate the effectiveness of flavonoids in irradiated mice based on survival tests. Since flavonoids have proven effective in animal, they could be used in other studies involving the irradiation of blood samples via oral administration in human *in-vitro* in order to realize their *in-vivo* effects. To ensure the safety of drug administration in humans, doses and routes of administration should be reviewed comprehensively before using these compounds since in some cases, they are safe for oral administration in mice, while their intravenous or subcutaneous administration might cause severe damage.

Mechanism of Immune System Protection against Natural Radiation

Bone marrow is the most sensitive tissue to radiation. Whole body irradiation leads to the damage and death of blood progenitor cells in the bone marrow. The degree of damage to the hematopoietic stem cell system depends on the amount of the received radiation. Death of these cells causes non-proliferation and lack of differentiation of peripheral blood cells (e.g., white blood cells and platelets), thereby giving rise to infections and hemorrhage, which are among the most significant factors that lead to the death of mammals exposed to radiation doses of higher than 2 Gy.

Protection of the bone marrow cells against radiation is the main factor in determining the survival of mammals. Radioprotective compounds with antioxidant properties have been shown to prevent the damage through the entrapment and scavenging of free radicals. In general, these compounds enter cells before radiation (2, 60), while the other classes of these agents are injected to patients before or after radiation exposure. Additionally, these substances stimulate cell proliferation and differentiation of the hematopoietic system and increase the number of hematopoietic cells, which in turn compensates for white blood cell and platelet counts in peripheral blood (3, 4). Therefore, radioprotective compounds

could be used as healing agents against radiation.

Function of Cytokines

Cytokines such as G-CSF, GM-CSF, interleukins, and CSF participate in the proliferation and differentiation of cells in the blood. For instance, administration of IL-1 before radiation exposure has been shown to reduce the mortality rate in animals (61). However, these compounds are associated with severe complications (e.g., inflammation and pain at the injection site), which limit their application (62).

Immunotherapy Materials

Recently, immunotherapy materials have been used frequently; such example is androstenediol (AED), which has been widely studied as a radioprotective agent since 2000. Subcutaneous injection of AED could increase the survival rate in irradiated animals, while its oral administration has been shown to be more effective compared to injection (63). AED is one of the drugs that has been evaluated in large animals, such as monkeys.

AED and Oxymetholone

In a study, intramuscular injection of AED (15 mg/kg) for five days increased the survival rate by 32% in irradiated animals compared to the control group (12%) (64). AED has few side-effects and is an effective compound for application before and after radiation exposure. AED is the drug of choice to protect individuals against nuclear terrorist attacks.

Oral administration of oxymetholone in animals at 24 hours before exposure to lethal doses of gamma radiation has been shown to increase the survival rate of animals by 75% compared to the control group (15%). Furthermore, oral administration of oxymetholone could increase the red blood cell and platelet counts although it has an insignificant impact on the increased white blood cell count in peripheral blood (5).

Glucan Polysaccharide

Glucan polysaccharide is produced by the membrane of fungal cells and is soluble in water. This compound could stimulate the immune system, and its administration to animals has been reported to enhance the activity of the hematopoietic system (65, 66).

Ginsan, Genistein, Janas, and Ginseng

Some studies have evaluated the effectiveness of other immunomodulatory substances, such as ginsan and genistein. Panax ginseng is a plant that is able to stimulate the immune system, which is mainly used and investigated in South Korea. Panax ginseng contains water-soluble compounds, including polysaccharides, proteins, and saponins.

Pure polysaccharide compounds are extracted from a plant known as janas to increase the number of hematopoietic cells and cytokines (e.g., IL-12) in the bone marrow (67).

Ginseng stimulates the secretion of cytokines (e.g., GM-CSF and CFU-S), as well as the proliferation of blood progenitor cells in the bone marrow. Furthermore, use of ginseng has been shown to increase platelet, lymphocyte, and neutrophil counts and stimulate the immune system with its potent antioxidant properties (68).

Genistein is an isoflavone found in various plants, such as soybean. The chemical structure of this substance is similar to 17–estradiol, and it has poor estrogenic activity. Genistein could increase the number of blood progenitor cells in the hematopoietic tissues. Subcutaneous injection of 200 milligrams of this compound at 24 hours before radiation results in the DRF of 1/16 in irradiated animals (16, 69).

The number of the medicinal herbs as immunomodulators in the form of natural extracts for radiation protection is more limited compared to the plants with antioxidant mechanism. Some of these natural compounds stimulate the immune system and have inherent antioxidant properties. Natural products with long-term effects on the stimulation of the immune system could be employed before radiation exposure. One of the predominant advantages of these compounds is their application as radioprotective agents rather than antioxidants.

4. Conclusion and Recommendations

Considering the damage caused by high doses of ionizing radiation in living beings, as well as the subsequent cell and tissue death, it is essential to protect humans against radiation. Radioprotective agents are life-saving drugs that protect patients against the adverse effects of radiation in radiotherapy and possible nuclear and radiological accidents. Although synthetic compounds, especially thiol-containing drugs (e.g., amifostine), are considered optimal in this regard, their side-effects often restricts their application in patients.

Several medicinal plants with various antioxidant properties and ability to stimulate the immune system have been evaluated as alternative radioprotective agents. High effectiveness of some of these herbs and natural compounds has been confirmed in previous studies. Moreover, recent findings have indicated the positive effects of herbal compounds on the survival of irradiated cells *in-vitro*

and *in-vivo* (Table 1). It is notable that most of the studies focusing on the function of medicinal plants have been performed on animal models, while their effectiveness has rarely been assessed in the patients undergoing radiation therapy. Therefore, it is recommended that further investigation be conducted on the use of medicinal plants with proper efficacy and few side-effects at appropriate doses in the patients undergoing radiotherapy.

Conflicts of interest: None declared.

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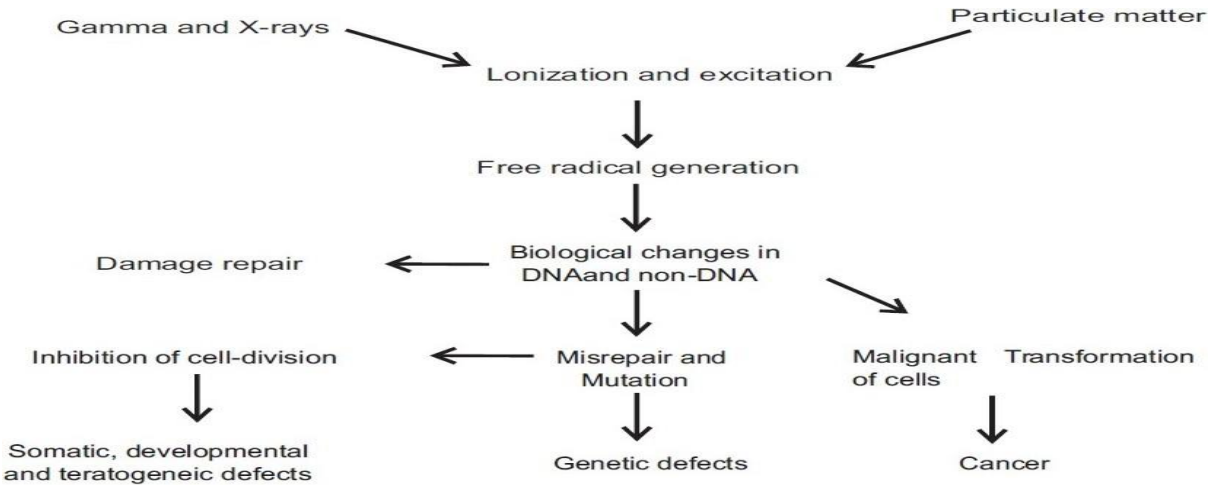

Figure 1. Events after Irradiation of Cells

Table 1. Effectiveness of Herbal/Natural Compounds

Reference	Mechanism	DRF	Radiation dose (Gy)	Time of Administration (hour)	Mode of Administration	Dose (mg/kg)	Radioprotective Agent

23, 70	Antioxidant	1/23	10/5	24	Subcutaneous	400 (IU/Kg)	Vitamin E
71	Antioxidant	1/2	-	1 (5 days)	Intraperitoneal	10	*Mentha arvensis*
72	Antioxidant	-	-	1 (5 days)	Intraperitoneal	10	Ginger Rhizome
15	Antioxidant	1/09	10	0.5	Intraperitoneal	100	Dihydroergotamine
73	Antioxidant	-	10	1 (5 days)	Intraperitoneal	10	Triphala
74	Antioxidant	-	10	0.5	Intraperitoneal	30	*Hippophae rhamnoides*
76	Antioxidant	-	10	1 (5 days)	Intraperitoneal	2	*Mangifera indica*
20	Antioxidant	1/2	-	0.5	Intraperitoneal	900	*Pilea microphylla*
76	Antioxidant	-	10	1 (5 days)	Intraperitoneal	20	Abana
77	Immune System Stimulation	-	8	0.5 (4 days)	Intraperitoneal	10	Panax Ginseng
78	Antioxidant	-	8	1 (7 days)	Oral	10	*Tinospora cordifolia*
79	Antioxidant	1/15	-	1 (5 days)	Intraperitoneal	15	*Aegle marmelos*
69	Antioxidant	1/36	-	24 (15	Oral	800	*Amaranth*

				days)			*us paniculatus*
80	Antioxidant	1/3	-	0.5	Intraperitoneal	75	*Ageratum conyzoides*
81	Antioxidant	1/2	-	1 (7 days)	Oral	500	Liv 52
82	Antioxidant	1/37	-	0.5	Intraperitoneal	50 (µg/kg)	Vicenin
83	Antioxidant	1/3	-	0.5 (4 days)	Oral	10	*Myristica fragrans*
84	Antioxidant	-	9	0.5 (7 days)	Oral	100	*Emblica officinalis*
85	Antioxidant	-	10	1 (5 days)	Intraperitoneal	100	Septilin
63	Immune System Stimulation	1/26	9/5	24	Subcutaneous	160	Androstenediol
5	Immune System Stimulation	1/16	-	24	Subcutaneous	200	Genistein
53	Immune System Stimulation	1/4	-	0.16	Intravenous	20	Glucan
24			2 GY		Intraperitoneal	2.4	Vitamin A
33	Antioxidant	1.7	2 GY	24	Intraperitoneal	50, 100, and 200	Vitamin C
51	Antioxidant	1.6	*	*	*	800	*Adhatoda vasica*
51	Antioxidant	1.36	*	*	*	800	*Amaranthus*

51	Antioxidant	1.59	*	*	*	800	*Brassica campestris*
51	Antioxidant	1.78	*	*	*	1,000	*Mentha piperita*
51	Antioxidant	1.3	*	*	*	800	*Spirulina fusiformis*
29	*	1	6, 7, and 8	One Month	*	1 mg/body-weight	Vitamin E
29	Antioxidant	1/33	6, 7, and 8	One Month	*	*	Beta D-glucan + vitamin E
29	Antioxidant	1/17	6, 7 and 8	One Month	*	*	D-glucan
28	Antioxidant	*	2	One hour before Irradiation	Oral	Selenium (400 IU) + Vitamin E (50 mg)	Selenium + Vitamin E
30	Antioxidant	*	2	*	Intraperitoneal	1.15 g/kg	Water Soluble Vitamin E (TMG)
39	Antioxidant	*	2	Gavaged Three Days before Irradiation Every 12 Hours and 2 Hours	Oral	15, 1.5, and 100, respectively	Famotidine, Vitamin C, and Cimetidine

				before Irradiation			
37	Suppression of Cell Pathways and Intracellular Signaling	*	7.5 Gy/day for 5 days	*	Oral	45 mg/day	Melatonin