Natural Resources for Human Health

visagaa publishing house

Review

View Article Online

Check for updates

Received 24 September 2021
Revised 13 December 2021
Accepted 14 December 2021
Available online 07 January 2022

Edited by Si Mi

KEYWORDS:
Ionizing radiation
Reactive oxygen species
Radioprotector
Herbal
Flavonoids

Natr Resour Human Health 2022; 2 (2): 274-286
https://doi.org/10.53365/nrfhh/144880
eISSN: 2583-1194

Herbal Radioprotectors: A mini-review of the Current Status

Teena Haritwal [1,*], Mrinalini Tiwari [2], Paban K Agrawala [1]

[1]Department of Radiation Genetics and Epigenetics, Institute of Nuclear Medicine and Allied Sciences, Brig SK Mazumdar Marg, Timarpur, New Delhi 110054, India

[2]Department of Parasite Host Biology, National Institute of Malaria Research, Indian Council of Medical Research, Dwarka, New Delhi 110077, India

ABSTRACT: Because of our increased dependency on the use of radiation in areas such as the food industry, agriculture, space exploration, diagnostics and treatment of various diseases including cancer, the possibilities of unnecessary exposure to ionizing radiation have considerably increased. Hence, there is a need to develop an effective radioprotective agent that can protect against the deleterious effects of ionizing radiation. So far, many synthetic and natural substances studied for use as radioprotectors have failed to reach clinics. Natural compounds are becoming more popular in radiation research due to their low toxicity, higher efficacy and cost-effectiveness. Plants and herbs contain a plethora of bioactive compounds having antioxidants, anti-inflammatory and immunostimulant properties which can act either in isolation or in combination to protect against the harmful effects of ionizing radiation This review mainly focuses on the radioprotective potential of various herbs and plants. The results obtained from various herbal extracts have shown protection against radiation-induced injuries in preclinical studies. This evaluation may help develop a potent radioprotector of desired efficacy.

1. HISTORY OF RADIOPROTECTOR DEVELOPMENT

The harmful effects of ionizing radiation was discovered ever since the discovery of X-rays by Becquerel in 1896 but the extent of damage was not very clear (Radvanyi & Villain, 2017). The damaging effects of ionizing radiation were more pronounced after the atomic bomb attack in Hiroshima and Nagasaki, Japan in 1945. Since then, the incidence of nuclear terrorism has increased a lot. All these incidences created a global awareness and need to develop a suitable radioprotector. First attempt in the development of radioprotector was made by Patt and his co-workers. They found that the pre-treatment with naturally occurring amino acid cysteine increased the percentage of survival in mice and rats lethally irradiated with X-rays (Patt et al., 1949). However, it was not very successful in clinical trial for human application. Thereafter, several other compounds have been screened and evaluated for their efficacy in rendering radioprotection. However, none of them met the criteria for an ideal radioprotector as of yet. Only Amifostine, a compound created by the Walter Reed Army Research Institute, has been approved by the US Food and Drug Administration (USFDA) for human use (Kuruba & Gollapalli, 2018). However, owing of its high toxicity and inability to provide post-irradiation protection, the use of amifostine is restricted and provided under close medical supervision. Hence the application of amifostine is restricted to radiotherapy only to confer protection to normal cells. Recently, Neupogen and Neulasta have also been approved by United States Food and Drug Administration (USFDA) to treat hematopoietic acute radiation syndromes (H-ARS) (Cheema et al., 2018).

2. BACKGROUND

Radiation protection is the major area of concern in modern world. Ionizing radiations have wide range of applications in agriculture, industries and medical fields. In industries, radiations are frequently used in modification of polymers, polishing of gemstones, waste treatment, tyre industries, and in food industries to improve the shelf life and reduce contamination in foodstuffs (Chmielewski & Mohammad, 2005). In agriculture, it is used to reduce pathogenic microbes, increase juice yield, delay sprouting, improve re-hydration etc. (Kuan et al., 2013). Ionizing radiations are being used in a variety of medical applications, including radiotherapy to kill cancerous cells, in vivo imaging (CT scans, MRIs, ultrasounds, and X-rays) to diagnose disorders, and sterilisation of medical devices (Baskar et al., 2012; T. Gupta, 2013). Apart from that, it is frequently used in military, radiobiology, nuclear technology and space exploration (Moulder, 2002). Despite its significance, exposure to ionizing radiation has

* Corresponding author.
E-mail address: haritwalteena@gmail.com (Teena Haritwal)

always been deleterious to human health. In present scenario, there are many chances for both planned and unplanned ionizing radiation exposure. Planned exposure includes medical imaging, radiotherapy and first responders etc. whereas unplanned exposures may happen during nuclear warfare, terrorist attack and many more scenarios. All of these events have raised the awareness for the development of a suitable radioprotector that can significantly prevent the damage induced by ionizing radiations. Hence the development of proper and safe radioprotector is an area of intense research in the scientific community. Amifostin is the only drug available to be administered as a radioprotector but still under medical supervision because of its side effects (V.K. Singh & Seed, 2017). Recently, Neupogen and Neulasta have also been approved by United States Food and Drug Administration (USFDA) to treat hematopoietic acute radiation syndromes (H-ARS) (Cheema et al., 2018). Extensive efforts have been done since ages, however till date no ideal and safe radioprotector is available. Herbal compounds having anti-inflammatory, anti-oxidant, anti-microbial, immuno-modulatory, free radical scavenging and anti-stress properties may be selected as a possible radioprotector based on the existing knowledge of radiation induced damages caused to living system. Various plants have been explored for development of promising herbal radioprotectors with certain degree of success, at least in preclinical set ups. An ideal radioprotector should be less toxic, cost effective, orally administered, rapidly absorbed, posses a good dose reduction factor (DRF). Determination of DRF is the most reliable parameter to evaluate any radioprotector including herbal preparations or plant extracts. DRF determined at $LD_{50/30}$ of mice is considered most important

DRF=LD $_{50/30}$ radiation dose with drug/ LD $_{50/30}$ radiation dose without drug.

Hematopoietic syndrome can result in death due to sufficient loss of hematopoietic stem cells, hemorrhage, anemia and infection. Signs and symptoms of Gastrointestinal (GI) syndrome are nausea, vomiting, loss of appetite and abdominal pain, diarrhea (Jagetia, 2007b). Loss of crypts, shortening of villi, decreased citrulline level, bacterial translocation from intestinal tract, intestinal epithelial cell denudation, dehydration and weight loss ultimately lead to death due to GI syndrome. Cardiovascular collapses, sepsis, severe hemorrhage, fluctuation in electrolyte concentration likely contribute to multi-organ failure and death (Elliott et al., 2014) at still higher doses of radiation exposure. This review mainly focuses on radioprotective potential of herbal and plant extracts. The results obtained from in vitro and in vivo studies of several herbs such as *Tinospora cordifolia* (Guduchi), *Phyllanthus niruri* (Bhumiamla), *Allium sativum* (Garlic), *Podophyllum hexandrum*, *Hippophae rhamnoides*, *Ocimum sanctum*, *Tinospora cordifolia*, *Rhodiola imbricate*, *Emblica officinalis*, *Centella asiatica*, *Curcuma longa*, *Piper longum*, *Mentha piperita*, *Aegle marmelos* and *Zingiber officinalis* have shown protection against radiation induced deaths in preclinical models (Dowlath et al., 2021).

3. RADIATION INDUCED DAMAGE

Exposure to ionizing radiation induces several types of damage and sickness depending upon the dose and dose rate received. Majority of damages induced by ionizing radiation are indirect and are mediated through the generation of free radical and reactive oxygen species (ROS). Exposure of ionizing radiation induces radiolysis of water which generates reactive oxygen species like hydroxyl ion (OH^-), superoxides ($O_2{}^-$), Hydrogen peroxides (H_2O_2), hydrogen radical (.H) which reacts with cellular components like nucleic acids, lipids, proteins and induces cellular damage and death. DNA is the primary and most important target of radiation. ROS generated by radiation can induce alteration in nucleotide bases, strand breakage (both single and double), cross linkage which ultimately results in chromosomal abnormalities, mutations and cancer. Degradation of proteins by radiation, results in the loss of the activity of several enzymes and also the formation of protein carbonyls (Lakshmi et al., 2005; Reisz et al., 2014). Membrane lipids are also very susceptible to damage which results in lipid peroxidation ultimately affecting major cellular activities. Depending on the radiation dose, all of these changes result in cellular damage, cell death, altered cell division and depletion of stem cell pool, major organ system failure like hematopoietic system, gastrointestinal system, reproductive system, central nervous system and ultimately death (Hosseinimehr et al., 2006). Hematopoietic system is readily affected by radiation exposure which results in haemorrhage, depletion of bone marrow progenitor cells, increased chances of opportunistic infections and anaemia (Kumar et al., 2007) (Zhou & Mi, 2005). The salivary gland and small intestine are extremely radiosensitive in the gastrointestinal tract. Radiation can cause damage to the intestinal villi and crypt cells in the intestine (N. Gupta et al., 2020). Changes in puberty, gonadotropin deficit, hyperprolactinemia, and infertility are all symptoms of it in the reproductive system. Ionizing radiation has a significant impact on the central nervous system. It causes brain tissue destruction, neuroinflammation, changes in motor function, behaviour and eventually numerous neurological diseases. Long-term consequences include lung fibrosis, cancer, and other life-threatening disorders. (Figure 1).

4. CRITERIA OF AN IDEAL RADIOPROTECTOR

Thousands of chemical compounds and drugs have been evaluated for their radioprotective potential but most of them are still under preclinical trial. Most important prerequisite in the development of an ideal radioprotector is their minimal toxicity at the dose at which they are delivered. Besides this, it should have free radical scavenging ability, immunomodulation capability, anti-inflammatory, promote the DNA repair enzymes, upregulate antioxidant enzymes and enhance the recovery of hematopoietic and immune system (Figure 2). To meet these requirements a variety of immuno-modulatory agents, hematopoiesis stimulating factors, various chelating agents and growth factors have

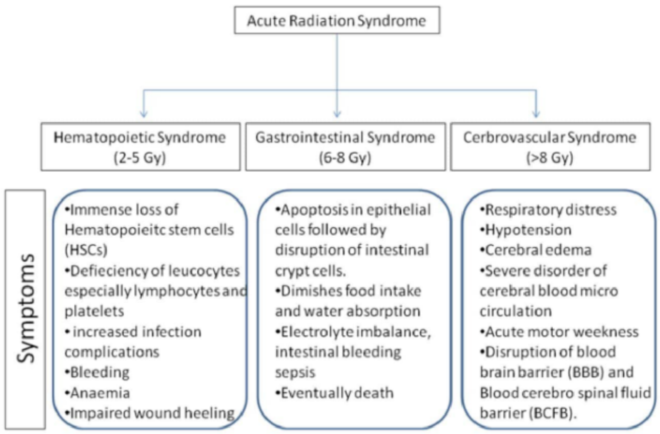

Figure 1. Classification of acute radiation syndrome based on radiation doses. Effects and symptoms of radiation syndromes on patients.

been screened. However, most of these agents showed a varied extent of protection and none of them are still applicable for human trial. Most importantly none of them have the ability to provide radiomitigation (post irradiation protection). We have categorized radioprotection into two types: Chemical or synthetic radioprotections and natural or herbal radioprotection.

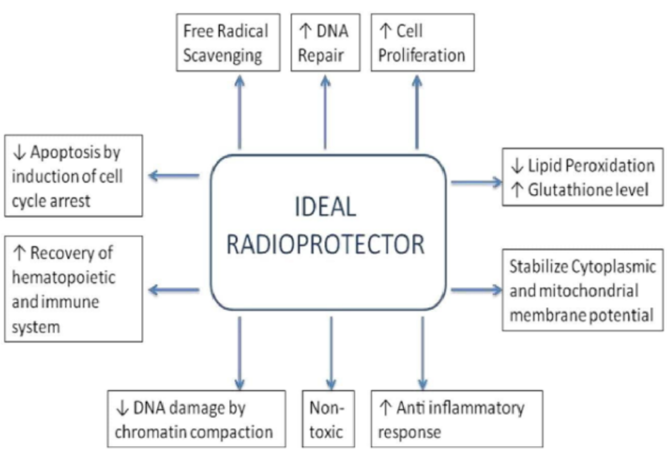

Figure 2. Criteria to become ideal radioprotectors.

5. SYNTHETIC RADIOPROTECTORS

Since last six decades, extensive efforts have been done in the area of radiation biology to develop synthetic radioprotector with minimal toxicity. Various compounds including cyto-protective agents, immuno-modulators, cytokines, vitamins and many DNA binding compounds have been evaluated for their radioprotective potential both in animal models and in vitro conditions (Haritwal et al., 2017). Synthetic sulfhydryl compounds like cysteine, mercaptoethylamine, cystine gained significant attention but their high toxicity and other side effects like nausea, vomiting, hypotension limited their use necessitating the search for other compounds with minimal toxicity and more acceptability (Maisin, 1989). Among all the sulfhydryl compounds, WR2721 (Amifostine) was found to be most effective and is currently used as adjuvant in radiotherapy (V.K. Singh & Seed, 2019). Certain immuno-modulator drugs and organometallic compounds were also screened. Immuno-modulators are non-cytokine compounds which facilitate the proliferation and differentiation of hematopoietic system susceptible to radiation induced damage. They have also been reported to suppress tumour growth in animal model. Application of gamma interferon (IFN-γ) enhances immune stimulation by activating T-cells and enhancing the expression of class-II major histocompatibility complex (MHC) (Castro et al., 2018). Few bacterial extracts, heat killed lactobacillus cells and protein associated polysaccharides have immunomodulatory effects (Taverniti & Guglielmetti, 2011). An immunomodulator, Ammonium trichloro-(dioxyethylene-O, O') telluride (AS101) is under clinical trial for its application in treatment of cancer patients (Nair et al., 2001). 5-substituted-1,3,4-thiadiazole-2-thiols and 5-substituted-2-(3,4,5 trihydroxyphenyl)-1,3,4-oxadiazoles have shown wide range of potent antioxidant activities which can be investigated and evaluated for its radioprotection activity (Rabie et al., 2018). Few cytokines such as IL-1, IL-6, TNF-α (Tumor necrosis factor-α) also show effective protection against lethal dose of radiation in animal model. Antioxidant enzymes mimicking compounds such as those of superoxide dismutase (SOD) with metals like Mn, Cu, and Fe at their active centres have also been developed (Borek et al., 1986; Nair et al., 2001; Vasilyeva et al., 2015). Certain nitroxides are also showing promising results in conferring radioprotection in animal model. Tempol is a nitroxide which is SOD mimetic and acts as free radical scavenger (Rosa et al., 2021). Vitamin A, C, E, K being antioxidants can effectively scavenge free radical induced by ionizing radiation. Selenium along with vitamin E was found to be an effective free radical scavenger and enhancer of peroxide breakdown. Under the category of DNA binding ligands, Hoechst 33342 is the most studied radioprotector. It binds to the minor groove of DNA and induces protection by electron transfer (Lubimova et al., 2001).

Most of the synthetic compounds studied so far exert their protective role by one of the following mechanism- i) Suppressing the generation of ROS.

ii) Enhancing DNA repair process.

iii) Upregulating free radical scavenging, or

iv) Reducing lipid peroxidation.

Although many of the screened synthetic compounds showed effective radioprotection in vitro and in vivo system but majority of them failed to show promising results in clinical trial for human application. Most significant drawback in using these synthetic compounds is their severe toxicity. Other limitations are high cost, inability to differentiate between normal cells and tumor cells (Demiral et al., 2002). They are also unable to provide post irradiation protection which is very essential in case of unplanned exposure like nuclear accidents, terrorist attack using nuclear warfare. Few possibilities to overcome these limitations are either chemical modification of these toxic compounds to relatively less toxic derivatives with same efficacy or to explore for other non- toxic alternative.

6. HERBAL RADIOPROTECTORS: SAFE ALTERNATIVE

Plants and herbal medicines are being used since ancient times for the treatment of many deadly diseases. Ayurvedic, Unani, Chinese, Japanese and Korean medicines rely on herbal preparations for the treatment of almost all diseases. Plants have inherent ability to tolerate environmental stress and sustain in varying environmental conditions. They are equipped with several enzymes and primary and secondary metabolites which favours their survival during environmental fluctuations. Some of these compounds have anti- inflammatory, immunostimulating, cytoprotective, antimicrobial, antioxidant ability which makes them important target for the development of radioprotector (Jagetia & Baliga, 2002; Maharwal et al., 2003; Parham et al., 2020). Some of the important factors favouring the development of herbal radioprotector are their less toxicity, easy availability, cost effectiveness. Many herbal formulations exhibits highly promising effects when delivered in case of deadly diseases like Parkison's disease, Alzheimer's diseases, Rheumatoid Arthritis, cancer and many other inflammatory diseases (Jena et al., 2010). This shows that plants and their formulations can relieve oxidative stress and thus can also be evaluated for their efficacy in providing protection against the damaging effects of ionizing radiation. Plants are very rich source of flavonoids such as orientin, catechin, vicenin, epigallocatechin. These flavonoids have potent antioxidant activity. Also many plant extracts contain carotene, ubiquinone, hydroubiquinone, polyphenols, fatty acids and certain amino acids which are having immunostimulating functions. Certain polyphenols, thiols, fatty acids, vitamins confer protection from carcinogenesis. Polyphenols, garlic extracts were also found effective in case of reducing radiation induced damage to hematopoietic system and central nervous system (Faramarzi et al., 2021). These herbal preparations have been tested for their radioprotective efficacy as whole extracts, isolated constituents, fractionated formulations, polyherbal formulations (Paul et al., 2011)

Extracts of various herbs/ plants have been tested for their radioprotective activity viz: *Podophyllum hexandrum*, *Hippophae rhamnoides*, *Ocimum sanctum*, *Tinospora cordifolia*, *Rhodiola imbricate*, *Emblica officinalis*, *Centella asiatica*, *Curcuma longa*, *Allium sativum*, *Piper longum*, *Mentha piperita*, *Aegle marmelos* and *Zingiber officinalis* on different animal models. They have shown a promising radioprotection against variety of radiation induced damages.

The protection mediated by these natural plant extracts, their derivatives and some semi-natural compounds are through one or many of the following ways-

6.1. Free radical scavenging

Scavenging of free radicals is the most important mechanism of radiation protection induced by herbal radioprotectors. Free radical scavenging is mediated by several antioxidant enzymes present in cells which ultimately reduce the oxidative stress. Herbal extracts are known to contain a complex mixture of several polyphenols which could up-regulate mRNAs of antioxidant enzymes such as catalase, glutathione transferase, glutathione peroxidase, superoxide dismutase and thus may counteract the oxidative stress induced by ionizing radiations. For example, studies on *Phyllanthus amarus* shows that it enhances the activities of antioxidant enzymes including SOD, GSHPx, GR, GST in blood and tissues (K.H. Kumar & Kuttan, 2004). Tulsi, another important medicinal herb of Indian ethnic system, is widely studied for its radioprotective property. It contains two important flavonoids, orientin and vicenin which have been demonstrated for its radical scavenging activity (Devi et al., 2000) . Some other herbal plants having rich polyphenolic content are *Prunus Avium* (Sweet Cherry) which is very rich in anthocyanin (Sisodia et al., 2011). *Mentha Piperita* (Pudina), (Samarth & Samarth, 2009), leaves of palak (*Spinacia Oleracea*) are rich in carotenoid content (beta-carotene, lutein, Zeaxanthine), ascorbic acid, flavonoids and p-Coumaric acid (Bhatia & Jain, 2004). The polyphenolic compounds present in different herbal preparations helps to counteract the oxidative stress induced by ionizing radiation.

6.2. Decrease in lipid peroxidation

Free radicals generated by ionizing radiations oxidise cellular and membrane lipids resulting in lipid peroxidation (LPO). One of the most important criteria of an ideal radioprotector is the ability to inhibit lipid peroxidation and scavenge free radical. Majority of plant extracts and their formulations have been studied for their ability to inhibit lipid peroxidation. Extract of *Tinospora cordifolia* inhibited ferrous sulphate mediated lipid peroxidation (I.P. Kumar et al., 2002). A wide variety of plants exert their radioprotective effect by decreasing LPO like *Adhatoda vasica* (Adulsa) (A. Kumar et al., 2005), *Amarantus paniculatus* (Maharwal et al., 2003), *P. hexandrum* (Mittal et al., 2001) etc.

6.3. Anti-inflammation

A wide variety of plants and their extracts exert radioprotection through their anti- inflammatory activity. The flavonoids present in plants exhibit anti-inflammation activity either by stimulating the production of anti- inflammatory cytokines or by modulating radiation induced signal transduction pathway. They also inhibit the production of pro inflammatory cytokines such as IL-1, TNF-α, and IL-8. A number of plants, e.g. *Tinospora cordifolia* (H.C. Goel et al., 2004) , *Ginkgo biloba*, *Centella asiatica*, *Hippophae rhamnoides*, *Ocimum sanctum*, *Panax ginseng*, *Mentha arvensis*, *Syzygium cumini*, *Zingiber officinale* (Jagetia, 2007b) and some of their bioactive constituents such as quercetin, curcumin, c-phycocyanin, allicin, gingerol, caffeine exhibit anti-inflammatory properties.

6.4. Activation of antioxidant enzymes

The phytochemicals present in herbal plants up-regulate mRNA of antioxidant enzymes such as catalase, GSH transferase, GSHPx, superoxide dismutase (SOD) which is responsible for scavenging ROS ultimately reducing oxidative stress in cells induced by ionizing radiation. The polyphenols present in plants have antioxidant property which stimulates transcription of antioxidant genes (M.T. Lee et al., 2017).

6.5. Protection and stimulation of hematopoietic system

A wide variety of plant products and their polyherbal formulations are found to be capable of recovering hematopoietic system following radiation damage. They enhance the regeneration of lymphoid and hematopoietic cells and thus minimize the chances of opportunistic infection after radiation injury. *Ginkgo biloba*, *Podophyllum hexandrum*, *Spirulina sp.*, *Tinospora cordifolia* are some of the examples which show increased survival by enhancing hematopoietic recovery (Chen et al., 2004; H.C. Goel et al., 2007, 2004). Few polyherbal formulations like Triphala, Abana (Jagetia et al., 2003) etc. are also evaluated for their ability to protect hematopoietic system. Similarly, *Rhodiola sp.* has many health promoting effects as well as it is being used to treat hernia, hysteria gastrointestinal ailments, infection, nervous disorder, head ache, post traumatic and vascular lesion of brain etc. It is also reported that *Rhodiola* has the potential to develop as radioprotective agent because of its enhanced hematopoiesis which leads to increase in whole body survival against lethal dose of radiation (H.C. Goel et al., 2006). These herbal formulations have potency to alter the hematopoietic damage by maintaining the higher number of hematopoietic stem cells, RBC count, haemoglobin, erythropoietin level. They also increases spleen Colony Forming Unit (CFUs) count and restore haematological parameters.

6.6. Protection to the GI system

A high radiation dose damages GI system by damaging the gastrointestinal barrier leading to the loss of water and electrolytes from the body (Hosseinimehr et al., 2006). Many of the plant extracts have successfully been found to confer protection against radiation induced GI damage. For example, extract of *Podophyllum hexandrum* has been reported to protect against radiation induced GI damage by increasing villi cellularity and survival of crypt cells by reducing apoptosis in crypt cells (Salin et al., 2001). Studies done on ginseng extract also shows reduced apoptosis in jejunal crypt cells and decrease in apoptotic cell death (S.H. Kim et al., 2001).

6.7. Protection of reproductive system

Reproductive system contains highly dividing cells. Exposure to ionizing radiation leads to the death of actively dividing cells. The impact of radiation exposure to testis and ovary leads increasing risk of passing on genetic diseases. Majority of the herbal plants and their extracts have the ability to reduce the radiation induced reproductive system damage. The efficacy of *Podophyllum hexandrum* extract to protect the male testicular system has been tested. Administration of *Podophyllum hexandrum* exhibited significant increases in testis weight, repopulation of the seminiferous tubules, increase in sperm count and mainly maintained stem-cell survival index. Reduction in the abnormalities of sperm morphology was also observed. The extract has also exhibited its ability to modulate antioxidant enzymes in the male reproductive system (H.C. Goel, Prasad, et al., 2002). Aqueous extract from leaves of *Achillea millefolium* L restores the reproductive organ weight, sperm count and sperm morphology as well (Dalsenter et al., 2004). Extract of *Xylopia aethiopica* (Annonaceae) increases spermatozoa motility, sperm count, decrease in radiation induced sperm abnormality and restores the damage induced in seminiferous tubules (Adaramoye et al., 2010).

6.8. Decrease in DNA damage

Many of the medicinal plants have been evaluated for their ability to protect against radiation induced chromosomal aberrations and micronuclei formation which reflects DNA damages. For example, extract of pudina (*Mentha Piperita*) have shown significant decrease in micronuclei frequency in bone marrow of irradiated swiss albino mice (S.K. Rao & Rao, 2010). Similarly, treatment with leaf extract of *Syzygium cumini* (Jamun) also reduced micronuclei formation in human peripheral blood lymphocytes (Jagetia & Baliga, 2002). Pretreatment of tulsi (*Ocimum sanctum*), well known indian medicinal plant prevent clastogenesis in 2 Gy irradiated mice. Moreover, some clinical studies on small number of patients have also shown radioprotective activity of Tulsi. (Baliga et al., 2016). Few other examples are *Tinospora cordifolia* (Guduc), *Phyllanthus niruri* (Bhumiamla), *Allium sativum* (Garlic) etc. All these plant extracts have inherent ability to protect against DNA damage and mortality caused due to exposure to ionizing radiation. The complex chemical constituents of these plants inhibit the action of several genes such as Protein Kinase C (PKC), Mitogen Activated Protein Kinase (MAPK) and many others leading to cell cycle arrest and facilitates repair of damage induced by ionizing radiations.

6.9. Activation of DNA repair process

Free radical production by radiation exposure leads to damage of genetic material which is the most severe damage induced by ionizing radiation. Herbal radioprotectors induce DNA repair by upregulating DNA repair genes and thus activating DNA repair enzymes (Kamran et al., 2016). A wide variety of medicinal plants have been shown to activate DNA repair enzymes in irradiated mice such as mentha (S.K. Rao & Rao, 2010).

Plant extracts or their various formulations meet practically all of the parameters necessary for the development of an ideal radioprotector because herbal plant extracts exhibit their beneficial effects through multiple mechanisms (Table 1). Most importantly, these can be administered at the dose which is non-toxic and highly effective.

Table 1
Table represents various plant extracts and their biological activities which make them promising radioprotective agents.

S. No.	Name of plants	Test System	Maximum Tolerance Dose (MTD)	Uses and radioprotective efficacy	Reference
1.	*Hippophae rhamnoides*	Rats, mice	Berries extract (40mg/kg body weight) Leaf extract (10-120 mg/kg Body weight)	Berries extract (RH1,2 and 3) ↑ whole body survival by acceleration of stem cell proliferation and immunostimulation. Whereas leaf extract (SBL-1) reduce GI damage by enhancing the proliferation of intestinal crypt cells and reducing chromosomal damage	(Bala et al., 2015, 2009; H.C. Goel, Prasad, et al., 2002; I.P. Kumar et al., 2002; Sureshbabu et al., 2008)
2.	*Podophyllum hexandrum*	Mice	200mg/kg body weight	Enhance survival by modulation of protein associated with cell death, enhance iron chelation in hematopoietic, GI and reproductive systems	(H.C. Goel et al., 1998) (A. Kumar et al., 2005; I.P. Kumar & Goel, 2000; R. Kumar et al., 2009; Mittal et al., 2001; Sagar et al., 2006; Salin et al., 2001; Samanta et al., 2004)
3.	*Ocimum sanctum*	Mice	6 g/kg	Antioxidant and anticarcinogenic activity, enhance survival by reducing oxidative stress by ↑ glutathione level	(Devi, 2001; Reshma et al., 2005; Subramanian et al., 2005; Tiwari et al., 2016)
4.	*Rhodiola imbricata*	Swiss albino mouse	1100-1300 mg/kg	Enhanced survival by enhanced proliferation of hematopoietic stem cells	(H.C. Goel et al., 2006)
5.	*Allium sativum*	Mice, Rats	500 mg/kg (Oral)	Strengthening of anti - oxidant system	(Batcioglu et al., 2012; Katoch et al., 2012; Tsubura et al., 2011)
6.	*Ginkgo biloba*	Rats, Human	0.11g/kg B.W. (E) 500μg/kg. (Human)	Attenuate radiation induced oxidative organ injury, Anticlastogenic, Antiapoptotic	(Emerit et al., 1995; Hannequin et al., 1983; Khedr et al., 2018; Shin et al., 2009)
7.	*Tinospora cordifolia*	HeLa cells, Mice	10mg/kg (7 days prior to radiation) 75 mg/kg B.W. (testes) 200 mg/kg. B.W.	Metal chelation, enhance survival of mice against sublethal dose of radiation, radioprotective potential in testes, Reduce hematopoietic depression by increasing the level of growth factors	(H.C. Goel, Kumar, & Rana, 2002; I.P. Kumar et al., 2002; Pahadiya & Sharma, 2003; S.K. Rao & Rao, 2010; P. Sharma et al., 2011; L. Singh et al., 2007; Subramanian et al., 2003)

Continued on next page

Table 1 continued

8.	*Aegle marmelos*	HPBLs and Mice	Bael fruit 2250 mg/kg (MTD) Leaf extract 6 g/kg B.W. (Oral route), 2.5 g/kg (i.p.)	Increase survival by reducing radiation induced sickness and organ damage, Reduce radiation induced DNA damage and genomic instability, Anticancer	(Baliga et al., 2010; Dhankhar et al., 2011; Jagetia et al., 2003, 2004a, 2004b)
9.	*Piper longum*	Mice	100 mg/kg (5 consecutive days)	Increase Glutathione level and reduce Alkaline phosphatase and lipid peroxidation in liver and serum	(Sunila & Kuttan, 2005)
10.	*Emblica officinalis*	Rats and Mice	3 g/kg (MTD)	Enhance Survival by recovery crypt cells and glutathione and lipid peroxidation in blood and GI , Antiulcerogenic activity	(Bhattacharya et al., 2006; Jindal et al., 2009; Kb et al., 2004; I. Singh et al., 2005)
11.	*Centella asiatica*	Rat and Mice	500 mg/kg B.W.	Enhance survival by maintaining antioxidant enzyme level and prevent radiation induced behavioural changes	(Joy & Nair, 2009; J. Sharma & Sharma, 2002; Shobi & Goel, 2001)
12.	*Curcuma longa*	Mice, Rats and Humans	2000-8000 mg/day (MTD)	Inhibit acute and chronic effects of radiation, Reduce oxidative stress and provide protection to organs against radiation	(Aravindan et al., 2008; A. Goel & Aggarwal, 2010; Inano & Onoda, 2002; Jagetia, 2007a; Nada et al., 2012)
13.	*Allium cepa*		40 mg/ml B.W. (E.D.)	Reduce radiation induced chromosomal damage, Modulate radiation induced changes in lipid peroxidation, glutathione, superoxide dismutation, Protect neuronal cells from oxidative stress	(Ammar, 2016; B.K. Lee & Jung, 2016)
14.	*Amaranthus paniculatus*	Mice	800 mg/kg (E. D.)	Enhanced survival by modifying glutathione and lipid peroxidation in liver and blood.	(A. Kumar et al., 2005)
15.	*Glycyrrhiza glabra*	Mice, Rats and Humans	100 µg/ml (E.D.)	Protect cellular DNA from radiation induced damage, microsomal membrane by reducing lipid peroxidation	(Gandhi et al., 2004; Shetty et al., 2002)
16.	*Mentha* arvensis	Mice	1000 mg/kg B.W.	Protection against radiation induced sickness and mortality	Jagetia and Baliga (2002)
17.	*Moringa oleiferia* (Leaf Extract)	Mice,	300 mg/kg B.W. (E D)	Ameliorate liver damage by decreasing radiation induced oxidative stress and chromosomal breaks in Bone marrow cells, Antitumor	(Bin-Meferij & El-Kott, 2015; A.V. Rao et al., 2001; A. Singh et al., 2015; Sinha et al., 2011)

Continued on next page

Table 1 continued

18.	*Zinziber officinalis*	Mice	300 mg/kg	Enhanced survival by reducing antioxidants and modulating the level of lipid peroxidation and glutathione	(Haksar et al., 2006; Jagetia et al., 2003)
19.	*Phyllanthus amarus*	Mice	750 mg/kg. (E.D.)	Protect Bone marrow and GI damage by reducing chromosomal damage and modulating the level of lipid peroxidation and glutathione	(Harikumar & Kuttan, 2007; K.H. Kumar & Kuttan, 2004; Londhe et al., 2009)
20.	*Panax ginseng*	Mice	1200 mg/kg (Root extract)	Enhanced survival by improving radiation induced body weight loss, DNA damage and reducing crypt cells damage in GI, also reduced radiation induced infertility	(H.J. Kim et al., 2007; S.H. Kim et al., 1993, 2001; M. Kumar et al., 2003; H.J. Lee et al., 2006; T.K. Lee et al., 2005; Pande et al., 1998)

All these features make them an attractive target for the development of safe and effective drug in comparison to the synthetic formulations. However for actual practical applicability of the herbal radioprotectors it is essential to have exact composition of the drug, mode of action of each component, knowledge of the side effects of any drug if present, pharmacokinetics of the drug inside the body, possibility of interaction between different components, interaction of different components of drug with different cellular components.

7. CONCLUSION

Development of radioprotector is very important requirement in present scenario. Although many synthetic drugs show effective radioprotection but practical applicability of these drugs is restricted owing to their high toxicity. The need to develop more effective and non-toxic alternative favours the development of herbal radioprotector. The complex chemical constituents of plants enable them to withstand and survive under harmful environmental radiations. This characteristic makes them important targets for the development as radioprotector. The efficacy of herbal extract largely depends upon its active constituents, the concentration of which is regulated by several factors. Some major factors include mode of extract preparation, climatic fluctuations, geographical location and the season of sample collection. All these factors result in variations in overall efficacy of herbal preparation. However, proper characterisation and scientific evaluation of herbal preparation may result in the development of an ideal radioprotector with minimal toxicity and highest efficacy.

CONFLICTS OF INTEREST

All authors declare that there is no conflict of interest.

ACKNOWLEDGMENTS

The work was supported by Defence Research and Development Organisation (DRDO), Government of India. The authors are thankful to the Director for his constant support and encouragements.

ORCID

Teena Haritwal	0000-0001-6332-5740
Mrinalini Tiwari	0000-0002-5555-4647
Paban K Agrawala	0000-0002-7460-0231

FUNDING

TH and MT were supported by Indian Council of Medical Research (ICMR) for their research fellowship.

AUTHOR CONTRIBUTIONS

TH and MT did the literature survey and compilation. PKA prepared the final draft and all authors approved.

REFERENCES

Adaramoye, O.A., Adedara, I.A., Popoola, B., Farombi, E.O., 2010. Extract of Xylopia aethiopica (Annonaceae) protects against gamma-radiation-induced testicular damage in wistar rats. Journal of Basic and Clinical Physiology and Pharmacology. 21(4), 295–314. https://doi.org/10.1515/JBCPP.2010.21.4.295

Ammar, A.A., 2016. Use of onion and curcumin as radioprotectors against ionizing radiation induced hepato-testicular alterations in rats. The Egyptian Journal of Hospital Medicine. 65(1), 468–473. https://doi.org/10.12816/0033754

Aravindan, N., Madhusoodhanan, R., Ahmad, S., Johnson, D., Herman, T.S., 2008. Curcumin inhibits NFκB mediated radioprotection and modulate apoptosis related genes in human neuroblastoma cells. Cancer Biology & Therapy. 7(4), 569–576. https://doi.org/10.4161/cbt.7.4.5534

Bala, M., Gupta, M., Saini, M., Abdin, M.Z., Prasad, J., 2015. Sea buckthorn leaf extract protects jejunum and bone marrow of 60cobalt-gamma-irradiated mice by regulating apoptosis and tissue regeneration. Evidence-Based Complementary and Alternative Medicine. 2015, 765705. https://doi.org/10.1155/2015/765705

Bala, M., Prasad, J., Singh, S., Tiwari, S., Sawhney, R.C., 2009. Whole-body radioprotective effects of SBL-1: a preparation from leaves of Hippophae rhamnoides. Journal of Herbs, Spices & Medicinal Plants. 15(2), 203–215. https://doi.org/10.1080/10496470903139496

Baliga, M.S., Bhat, H.P., Pereira, M.M., Mathias, N., Venkatesh, P., 2010. Radioprotective effects of Aegle marmelos (L.) Correa (Bael): a concise review. The Journal of Alternative and Complementary Medicine. 16(10), 1109–1116. https://doi.org/10.1089/acm.2009.0604

Baliga, M.S., Rao, S., Rai, M.P., Souza, P., 2016. Radio protective effects of the Ayurvedic medicinal plant Ocimum sanctum Linn.(Holy Basil): a memoir. Journal of Cancer Research and Therapeutics. 12(1), 20–20. https://doi.org/10.4103/0973-1482.151422

Baskar, R., Lee, K.A., Yeo, R., Yeoh, K.W., 2012. Cancer and radiation therapy: current advances and future directions. International journal of medical sciences. 9(3), 193–193. https://doi.org/10.7150/ijms.3635

Batcioglu, K., Yilmaz, Z., Satilmis, B., Uyumlu, A.B., Erkal, H.S., Yucel, N., 2012. Investigation of in vivo radioprotective and in vitro antioxidant and antimicrobial activity of garlic (Allium sativum). European Review for Medical and Pharmacological Sciences. 16, 47–57.

Bhatia, A.L., Jain, M., 2004. Spinacia oleracea L. protects against gamma radiations: a study on glutathione and lipid peroxidation in mouse liver. Phytomedicine. 11(7-8), 607–615. https://doi.org/10.1016/j.phymed.2003.07.004

Bhattacharya, S., Subramanian, M., Kamat, J.P., Bandyopadhyay, S.K., Chattopadhyay, S., 2006. Radioprotective Property of Emblica officinalis Fruit Ethanol Extract. Pharmaceutical biology. 44(9), 682–690. https://doi.org/10.1080/13880200601009131

Bin-Meferij, M.M., El-Kott, A.F., 2015. The radioprotective effects of Moringa oleifera against mobile phone electromagnetic radiation-induced infertility in rats. International Journal of Clinical and Experimental Medicine. 8(8), 12487–12487.

Borek, C., Ong, A., Mason, H., Donahue, L., Biaglow, J.E., 1986. Selenium and vitamin E inhibit radiogenic and chemically induced transformation in vitro via different mechanisms. Proceedings of the National Academy of Sciences. 83(5), 1490–1494. https://doi.org/10.1073/pnas.83.5.1490

Castro, F., Cardoso, A.P., Gonçalves, R.M., Serre, K., Oliveira, M.J., 2018. Interferon-gamma at the crossroads of tumor immune surveillance or evasion. Frontiers in immunology. 9, 847–847. https://doi.org/

10.3389/fimmu.2018.00847
Cheema, A.K., Mehta, K.Y., Fatanmi, O.O., Wise, S.Y., Hinzman, C.P., Wolff, J., Singh, V.K., 2018. A Metabolomic and lipidomic serum signature from nonhuman primates administered with a promising radiation countermeasure, gamma-tocotrienol. International journal of molecular sciences. 19(1), 79–79. https://doi.org/10.3390/ijms19010079
Chen, J., Wang, X., Zhu, J., Shang, Y., Guo, X., Sun, J., 2004. Effects of Ginkgo biloba extract on number and activity of endothelial progenitor cells from peripheral blood. Journal of Cardiovascular Pharmacology. 43(3), 347–352. https://doi.org/10.1097/00005344-200403000-00004
Chmielewski, A.G., Mohammad, H.S., 2005. Radiation technology for new materials development, human health and environment protection. Radiation Inactivation of Bioterrorism Agents. 365, 1–1.
Dalsenter, P.R., Cavalcanti, A.M., Andrade, A.J., Araújo, S.L., Marques, M.C., 2004. Reproductive evaluation of aqueous crude extract of Achillea millefolium L.(Asteraceae) in Wistar rats. Reproductive Toxicology. 18(6), 819–823. https://doi.org/10.1016/j.reprotox.2004.04.011
Demiral, A.N., Yerebakan, Ö., Simsir, V., Alpsoy, E., 2002. Amifostine-induced toxic epidermal necrolysis during radiotherapy: a case report. Japanese journal of clinical oncology. 32(11), 477–479. https://doi.org/10.1093/jjco/hyf095
Devi, P.U., 2001. Indian Journal of Experimental Biology (. Radioprotective, anticarcinogenic and antioxidant properties of the Indian holy basil, Ocimum sanctum (Tulasi). 39(3), 185–190.
Devi, P.U., Ganasoundari, A., Vrinda, B., Srinivasan, K.K., Unnikrishnan, M.K., 2000. Radiation protection by the ocimum flavonoids orientin and vicenin: mechanisms of action. Radiation Research. 154(4), 455–460. https://doi.org/10.1667/0033-7587(2000)154[0455:RPBTOF]2.0.CO;2
Dhankhar, S., Ruhil, S., Balhara, M., Dhankhar, S., Chhillar, A.K., 2011. Aegle marmelos (Linn.) Correa: A potential source of Phytomedicine. Journal of Medicinal Plants Research. 5(9), 1497–1507.
Dowlath, M.J., Karuppannan, S.K., Sinha, P., Dowlath, N.S., Arunachalam, K.D., Ravindran, B., Nguyen, D.D., 2021. Effects of radiation and role of plants in radioprotection: A critical review. Science of The Total Environment. https://doi.org/10.1016/j.scitotenv.2021.146431
Elliott, T.B., Deutz, N.E., Gulani, J., Koch, A., Olsen, C.H., Christensen, C., Moroni, .., M., 2014. Gastrointestinal acute radiation syndrome in Göttingen minipigs (Sus scrofa domestica). Comparative medicine. 64(6), 456–463.
Emerit, I., Arutyunyan, R., Oganesian, N., Levy, A., Cernjavsky, L., Sarkisian, T., Asrian, .., K., 1995. Radiation-induced clastogenic factors: anticlastogenic effect of Ginkgo biloba extract. Free Radical Biology and Medicine. 18(6), 985–991. https://doi.org/10.1016/0891-5849(94)00220-E
Faramarzi, S., Piccolella, S., Manti, L., Pacifico, S., 2021. Could Polyphenols Really Be a Good Radioprotective Strategy? Molecules. 26(16), 4969–4969. https://doi.org/10.3390/molecules26164969
Gandhi, N.M., Maurya, D.K., Salvi, V., Kapoor, S., Mukherjee, T., Nair, C.K.K., 2004. Radioprotection of DNA by glycyrrhizic acid through scavenging free radicals. Journal of Radiation Research. 45(3), 461–468. https://doi.org/10.1269/jrr.45.461
Goel, A., Aggarwal, B.B., 2010. Curcumin, the golden spice from Indian saffron, is a chemosensitizer and radiosensitizer for tumors and chemoprotector and radioprotector for normal organs. Nutrition and Cancer. 62(7), 919–930. https://doi.org/10.1080/01635581.2010.509835
Goel, H.C., Bala, M., Prasad, J., Singh, S., Agrawala, P.K., Swahney, R.C., 2006. Radioprotection by Rhodiola imbricata in mice against whole-body lethal irradiation. Journal of Medicinal Food. 9(2), 154–160. https://doi.org/10.1089/jmf.2006.9.154
Goel, H.C., Kumar, I.P., Rana, S.V.S., 2002. Free radical scavenging and metal chelation by Tinospora cordifolia, a possible role in radioprotection. Indian Journal of Experimental Biology. 40(6), 727–734.
Goel, H.C., Prakash, H., Ali, A., Bala, M., 2007. Podophyllum hexandrum modulates gamma radiation-induced immunosuppression in Balb/c mice: implications in radioprotection. Molecular and cellular biochemistry. 295(1), 93–103. https://doi.org/10.1007/s11010-006-9277-5
Goel, H.C., Prasad, J., Sharma, A., Singh, B., 1998. Antitumour and radioprotective action of Podophyllum hexandrum. Indian Journal of Experimental Biology. 36(6), 583–587.
Goel, H.C., Prasad, J., Singh, S., Sagar, R.K., Agrawala, P.K., Bala, M., Dogra, .., R., 2004. Radioprotective potential of an herbal extract of Tinospora cordifolia. Journal of Radiation Research. 45(1), 61–68. https://doi.org/10.1269/jrr.45.61
Goel, H.C., Prasad, J., Singh, S., Sagar, R.K., Kumar, I.P., Sinha, A.K., 2002. Radioprotection by a herbal preparation of Hippophae rhamnoides, RH-3, against whole body lethal irradiation in mice. Phytomedicine. 9(1), 15–25. https://doi.org/10.1078/0944-7113-00077
Gupta, N., Kainthola, A., Tiwari, M., Agrawala, P.K., 2020. Gut microbiota response to ionizing radiation and its modulation by HDAC inhibitor TSA. International Journal of Radiation Biology. 96(12), 1560–1570. https://doi.org/10.1080/09553002.2020.1830317
Gupta, T., 2013. Radiation, ionization, and detection in nuclear medicine,. Springer, Heidelberg, pp. 451–494. https://doi.org/10.1007/978-3-642-34076-5
Haksar, A., Sharma, A., Chawla, R., Kumar, R., Arora, R., Singh, S., Sharma, .., K, R., 2006. Zingiber officinale exhibits behavioral radioprotection against radiation-induced CTA in a gender-specific manner. Pharmacology Biochemistry and Behavior. 84(2), 179–188. https://doi.org/10.1016/j.pbb.2006.04.008
Hannequin, D., Thibert, A., Vaschalde, Y., 1983. Development of a model to study the anti-edema properties of Ginkgo biloba extract. Presse Medicale. 15(31), 1575–1576.
Harikumar, K., Kuttan, R., 2007. An extract of Phyllanthus amarus protects mouse chromosomes and intestine from radiation induced damages. Journal of Radiation Research. 48(6), 469–476. https://doi.org/10.1269/jrr.07039
Haritwal, T., Gupta, N., Tiwari, M., Surve, S., Agrawala, P.K., 2017. Radiation countermeasures: current Status. Defence Life Science Journal. 2, 278–286. https://doi.org/10.14429/dlsj.2.11675
Hosseinimehr, S.J., Zakaryaee, V., Froughizadeh, M., 2006. Oral oxymetholone reduces mortality induced by gamma irradiation in mice through stimulation of hematopoietic cells. Molecular and Cellular Biochemistry. 287(1), 193–199. https://doi.org/10.1007/s11010-005-9111-5
Inano, H., Onoda, M., 2002. Radioprotective action of curcumin extracted from Curcuma longa LINN: inhibitory effect on formation of urinary 8-hydroxy-2′-deoxyguanosine, tumorigenesis, but not mortality, induced by γ-ray irradiation. International Journal of Radiation Oncology* Biology* Physics. 53(3), 735–743. https://doi.org/10.1016/S0360-3016(02)02794-3
Jagetia, G.C., 2007a. Radioprotection and radiosensitization by curcumin. Advances in Experimental Medicine and Biology. 509, 301–320. https://doi.org/10.1007/978-0-387-46401-5_13
Jagetia, G.C., 2007b. Radioprotective potential of plants and herbs against the effects of ionizing radiation. Journal of clinical biochemistry and

nutrition. 40(2), 74–81. https://doi.org/10.3164/jcbn.40.74
Jagetia, G.C., Baliga, M.S., 2002. Influence of the leaf extract of Mentha arvensis Linn.(mint) on the survival of mice exposed to different doses of gamma radiation. Strahlentherapie und Onkologie. 178(2), 91–98. https://doi.org/10.1007/s00066-002-0841-y
Jagetia, G.C., Venkatesh, P., Baliga, M.S., 2003. Evaluation of the radioprotective effect of Aegle marmelos (L.) Correa in cultured human peripheral blood lymphocytes exposed to different doses of γ-radiation: a micronucleus study. Mutagenesis. 18(4), 387–393. https://doi.org/10.1093/mutage/geg011
Jagetia, G.C., Venkatesh, P., Baliga, M.S., 2004a. Evaluation of the radioprotective effect of bael leaf (Aegle marmelos) extract in mice. International Journal of Radiation Biology. 80(4), 281–290. https://doi.org/10.1080/09553000410001679776
Jagetia, G.C., Venkatesh, P., Baliga, M.S., 2004b. Fruit extract of Aegle marmelos protects mice against radiation-induced lethality. Integrative Cancer Therapies. 3(4), 323–332. https://doi.org/10.1177/1534735404270641
Jena, G., Vikram, A., Tripathi, D.N., Ramarao, P., 2010. Use of chemoprotectants in chemotherapy and radiation therapy: the challenges of selecting an appropriate agent. Integrative Cancer Therapies. 9(3), 253–258. https://doi.org/10.1177/1534735410376633
Jindal, A., Soyal, D., Sharma, A., Goyal, P.K., 2009. Protective effect of an extract of Emblica officinalis against radiation-induced damage in mice. Integrative cancer therapies. 8(1), 98–105. https://doi.org/10.1177/1534735409331455
Joy, J., Nair, C.K.K., 2009. Protection of DNA and membranes from gamma-radiation induced damages by Centella asiatica. Journal of Pharmacy and Pharmacology(7), 941–947. https://doi.org/10.1211/jpp/61.07.0014
Kamran, M.Z., Ranjan, A., Kaur, N., Sur, S., Tandon, V., 2016. Radioprotective agents: strategies and translational advances. Medicinal Research Reviews. 36(3), 461–493. https://doi.org/10.1002/med.21386
Katoch, O., Khan, G.A., Dwarakanath, B.S., Agrawala, P.K., 2012. Mitigation of hematopoietic radiation injury by diallyl sulphide. Journal of Environmental Pathology, Toxicology and Oncology. 31(4), 357–365. https://doi.org/10.1615/JEnvironPatholToxicolOncol.2013005833
Kb, H.K., Sabu, M.C., Lima, P.S., Kuttan, R., 2004. Modulation of haematopoetic system and antioxidant enzymes by Emblica officinalis Gaertn and its protective role against γ-radiation induced damages in mice. Journal of Radiation Research. 45(4), 549–555. https://doi.org/10.1269/jrr.45.549
Khedr, M.H., Shafaa, M.W., Abdel-Ghaffar, A., Saleh, A., 2018. Radioprotective efficacy of Ginkgo biloba and Angelica archangelica extract against technetium-99m-sestamibi induced oxidative stress and lens injury in rats. International journal of radiation biology. 94(1), 37–44. https://doi.org/10.1080/09553002.2018.1407463
Kim, H.J., Kim, M.H., Byon, Y.Y., Park, J.W., Jee, Y., Joo, H.G., 2007. Radioprotective effects of an acidic polysaccharide of Panax ginseng on bone marrow cells. Journal of Veterinary Science. 8(1), 39–44. https://doi.org/10.4142/jvs.2007.8.1.39
Kim, S.H., Cho, C.K., Yoo, S.Y., Koh, K.H., Yun, H.G., Kim, T.H., 1993. In vivo radioprotective activity of Panax ginseng and diethyldithiocarbamate. In vivo. 7, 467–470.
Kim, S.H., Son, C.H., Nah, S.Y., Jo, S.K., Jang, J.S., Shin, D.H., 2001. Modification of radiation response in mice by Panax ginseng and diethyldithiocarbamate. In Vivo. 15(5), 407–411.
Kuan, Y.H., Bhat, R., Patras, A., Karim, A.A., 2013. Radiation processing of food proteins-A review on the recent developments. Trends in Food Science & Technology. 30(2), 105–120. https://doi.org/10.1016/j.tifs.2012.12.002
Kumar, A., Ram, J., Samarth, R.M., Kumar, M., 2005. Modulatory influence of Adhatoda vasica Nees leaf extract against gamma irradiation in Swiss albino mice. Phytomedicine. 12(4), 285–293. https://doi.org/10.1016/j.phymed.2003.12.006
Kumar, I.P., Goel, H.C., 2000. Iron chelation and related properties of Podophyllum hexandrum, a possible role in radioprotection. Indian Journal of Experimental Biology. 38(10), 1003–1006.
Kumar, I.P., Namita, S., Goel, H.C., 2002. Modulation of chromatin organization by RH-3, a preparation of Hippophae rhamnoides, a possible role in radioprotection. Molecular and Cellular Biochemistry. 238(1), 1–9. https://doi.org/10.1023/A:1019905211392
Kumar, K.H., Kuttan, R., 2004. Protective effect of an extract of Phyllanthus amarus against radiation-induced damage in mice. Journal of Radiation Research. 45(1), 133–139. https://doi.org/10.1269/jrr.45.133
Kumar, M., Sharma, M.K., Saxena, P.S., Kumar, A., 2003. Radioprotective effect of Panax ginseng on the phosphatases and lipid peroxidation level in testes of Swiss albino mice. Biological and Pharmaceutical Bulletin. 26(3), 308–312. https://doi.org/10.1248/bpb.26.308
Kumar, R., Singh, P.K., Arora, R., Chawla, R., Sharma, R.K., 2009. Radioprotective activities of Podophyllum hexandrum: current knowledge of the molecular mechanisms. Trees for Life Journal. 4, 1–9.
Kuruba, V., Gollapalli, P., 2018. Natural radioprotectors and their impact on cancer drug discovery. Radiation oncology journal. 36(4), 265–265. https://doi.org/10.3857/roj.2018.00381
Lakshmi, B., Tilak, J.C., Adhikari, S., Devasagayam, T.P.A., Janardhanan, K.K., 2005. Inhibition of lipid peroxidation induced by γ-radiation and AAPH in rat liver and brain mitochondria by mushrooms. Current Science, 484–488.
Lee, B.K., Jung, Y.S., 2016. Allium cepa extract and quercetin protect neuronal cells from oxidative stress via PKC-ε inactivation/ERK1/2 activation. Oxidative Medicine and Cellular Longevity. 2016, 2495624. https://doi.org/10.1155/2016/2495624
Lee, H.J., Kim, S.R., Kim, J.C., Kang, C.M., Lee, Y.S., Jo, S.K., Kim, .., H, S., 2006. In vivo radioprotective effect of Panax ginseng CA Meyer and identification of active ginsenosides. Phytotherapy Research. 20(5), 392–395. https://doi.org/10.1002/ptr.1867
Lee, M.T., Lin, W.C., Yu, B., Lee, T.T., 2017. Antioxidant capacity of phytochemicals and their potential effects on oxidative status in animals-A review. Asian-Australasian Journal of Animal Sciences. 30(3), 299–299. https://doi.org/10.5713/ajas.16.0438
Lee, T.K., Johnke, R.M., Allison, R.R., O'brien, K.F., Dobbs, L.J., 2005. Radioprotective potential of ginseng. Mutagenesis. 20(4), 237–243. https://doi.org/10.1093/mutage/gei041
Londhe, J.S., Devasagayam, T.P., Foo, L.Y., Ghaskadbi, S.S., 2009. Radioprotective properties of polyphenols from Phyllanthus amarus Linn. Journal of Radiation Research. 50(4), 303–309. https://doi.org/10.1269/jrr.08096
Maharwal, J., Samarth, R.M., Saini, M.R., 2003. Radiomodulatory influence of Rajgira (Amaranthus paniculatus) leaf extract in Swiss albino mice. Phytotherapy Research. 17(10), 1150–1154. https://doi.org/10.1002/ptr.1340
Maisin, J.R., 1989. Chemical protection against ionizing radiation. Advances in Space Research. 9(10), 205–212. https://doi.org/10.1016/0273-1177(89)90439-0
Mittal, A., Pathania, V., Agrawala, P.K., Prasad, J., Singh, S., Goel, H.C., 2001. Influence of Podophyllum hexandrum on endogenous antioxidant defence system in mice: possible role in radioprotection. Journal of Ethnopharmacology. 76(3), 253–262. https://doi.org/10.1016/S0378-8741(01)00243-4

Moulder, J.E., 2002. Report on an Interagency Workshop on the Radiobiology of Nuclear Terrorism: Molecular and Cellular Biology of Moderate Dose (1-10 Sv) Radiation and Potential Mechanisms of Radiation Protection. Radiation research. 158(1), 118–124. https://doi.org/10.1667/0033-7587(2002)158[0118:ROAIWO]2.0.CO;2

Nada, A.S., Hawas, A.M., Amin, N.E.D., Elnashar, M.M., Elmageed, Z.Y., 2012. Radioprotective effect of Curcuma longa extract on γ-irradiation-induced oxidative stress in rats. Canadian Journal of Physiology and Pharmacology. 90(4), 415–423. https://doi.org/10.1139/y2012-005

Nair, C.K., Parida, D.K., Nomura, T., 2001. Radioprotectors in radiotherapy. Journal of Radiation Research. 42(1), 21–37. https://doi.org/10.1269/jrr.42.21

Pahadiya, S., Sharma, J., 2003. Alteration of lethal effects of gamma rays in Swiss albino mice by Tinospora cordifolia. Phytotherapy Research. 17(5), 552–554. https://doi.org/10.1002/ptr.1156

Pande, S., Kumar, M., Kumar, A., 1998. Evaluation of radiomodifying effects of root extract of Panax ginseng. Phytotherapy Research. 12(1), 13–17. https://doi.org/10.1002/(SICI)1099-1573(19980201)12:1<13::AID-PTR179>3.0.CO;2-T

Parham, S., Kharazi, A.Z., Bakhsheshi-Rad, H.R., Nur, H., Ismail, A.F., Sharif, S., Berto, .., F., 2020. Antioxidant, antimicrobial and antiviral properties of herbal materials. Antioxidants. 9(12), 1309–1309. https://doi.org/10.3390/antiox9121309

Patt, H.M., Tyree, E.B., Straube, R.L., Smith, D.E., 1949. Cysteine protection against X irradiation. Science. 110, 213–214. https://doi.org/10.1126/science.110.2852.213

Paul, P., Unnikrishnan, M.K., Nagappa, A.N., 2011. Phytochemicals as radioprotective agents-A review. Indian Journal of Natural Products and Resources. 2(2), 137–150.

Rabie, A.M., Tantawy, A.S., Badr, S.M., 2018. Design, synthesis, and biological evaluation of new 5-substituted-1, 3, 4-thiadiazole-2-thiols as potent antioxidants. Researcher. 10, 21–43.

Radvanyi, P., Villain, J., 2017. The discovery of radioactivity. Comptes Rendus Physique. 18(9), 544–550. https://doi.org/10.1016/j.crhy.2017.10.008

Rao, A.V., Devi, P.U., Kamath, R., 2001. In vivo radioprotective effect of Moringa oleifera leaves. Indian Journal of Experimental Biology. 39(9), 858–863.

Rao, S.K., Rao, P.S., 2010. Alteration in the radiosensitivity of HeLa cells by dichloromethane extract of guduchi (Tinospora cordifolia). Integrative cancer therapies. 9(4), 378–384. https://doi.org/10.1177/1534735410387598

Reisz, J.A., Bansal, N., Qian, J., Zhao, W., Furdui, C.M., 2014. Effects of ionizing radiation on biological molecules-mechanisms of damage and emerging methods of detection. Antioxidants & Redox signaling. 21(2), 260–292. https://doi.org/10.1089/ars.2013.5489

Reshma, K., Ashalatha, V.R., Dinesh, M., Vasudevan, D.M., 2005. Effect of ocimum flavonoids as a radioprotector on the erythrocyte antioxidants in oral cancer. Indian Journal of Clinical Biochemistry. 20(1), 160–164. https://doi.org/10.1007/BF02893064

Rosa, A.C., Corsi, D., Cavi, N., Bruni, N., Dosio, F., 2021. Superoxide Dismutase Administration: A Review of Proposed Human Uses. Molecules. 26(7), 1844–1844. https://doi.org/10.3390/molecules26071844

Sagar, R.K., Chawla, R., Arora, R., Singh, S., Krishna, B., Sharma, R.K., Qazi, .., N, G., 2006. Protection of the hemopoietic system by Podophyllum hexandrum against gamma radiation-induced damage. Planta Medica. 72(02), 114–120. https://doi.org/10.1055/s-2005-873148

Salin, C.A., Samanta, N., Goel, H.C., 2001. Protection of mouse jejunum against lethal irradiation by Podophyllum hexandrum. Phytomedicine. 8(6), 413–422. https://doi.org/10.1078/S0944-7113(04)70059-8

Samanta, N., Kannan, K., Bala, M., Goel, H.C., 2004. Radioprotective mechanism of Podophyllum hexandrum during spermatogenesis. Molecular and Cellular Biochemistry. 267(1), 167–176. https://doi.org/10.1023/B:MCBI.0000049375.34583.65

Samarth, R.M., Samarth, M., 2009. Protection against radiation-induced testicular damage in Swiss albino mice by Mentha piperita (Linn.). Basic & Clinical Pharmacology & Toxicology. 104(4), 329–334. https://doi.org/10.1111/j.1742-7843.2009.00384.x

Sharma, J., Sharma, R., 2002. Radioprotection of Swiss albino mouse by Centella asiatica extract. Phytotherapy Research. 16(8), 785–786. https://doi.org/10.1002/ptr.1069

Sharma, P., Parmar, J., Verma, P., Goyal, P.K., 2011. Radiation-induced testicular injury and its amelioration by tinospora cordifolia (an Indian medicinal plant) extract. Evidence-Based Complementary and Alternative Medicine. 2011, 643847. https://doi.org/10.1155/2011/643847

Shetty, T.K., Satav, J.G., Nair, C.K.K., 2002. Protection of DNA and microsomal membranes in vitro by Glycyrrhiza glabra L. against gamma irradiation. Phytotherapy Research. 16(6), 576–578. https://doi.org/10.1002/ptr.927

Shin, J.H., Go, Y.J., Jeong, K.S., Park, S.J., Kwak, D.M., Kwon, O.D., Kim, .., H, T., 2009. Protective effect of Gingko biloba against radiation-induced cellular damage in human peripheral lymphocytes and murine spleen cells. International Journal of Low Radiation. 6(3), 209–218. https://doi.org/10.1504/IJLR.2009.028889

Shobi, V., Goel, H.C., 2001. Protection against radiation-induced conditioned taste aversion by Centella asiatica. Physiology & behavior. 73(1-2), 19–23. https://doi.org/10.1016/S0031-9384(01)00434-6

Singh, A., Dayal, R., Cjha, R.P., Mishra, K.P., 2015. Promising role of Moringa oleifera [Lam] in improving radiotherapy: an overview. Journal of Innovations in Pharmaceutical and Biological Sciences. 2, 182–192.

Singh, I., Sharma, A., Nunia, V., Goyal, P.K., 2005. Radioprotection of Swiss albino mice by Emblica officinalis. Phytotherapy Research. 19(5), 444–446. https://doi.org/10.1002/ptr.1600

Singh, L., Tyagi, S., Rizvi, M.A., Goel, H.C., 2007. Effect of Tinospora cordifolia on gamma ray-induced perturbations in macrophages and splenocytes. Journal of Radiation Research. 48(4), 305–315. https://doi.org/10.1269/jrr.07001

Singh, V.K., Seed, T.M., 2017. A review of radiation countermeasures focusing on injury-specific medicinals and regulatory approval status: part I. Radiation sub-syndromes, animal models and FDA-approved countermeasures. International journal of radiation biology. 93(9), 851–869. https://doi.org/10.1080/09553002.2017.1332438

Singh, V.K., Seed, T.M., 2019. The efficacy and safety of amifostine for the acute radiation syndrome. Expert opinion on drug safety. 18(11), 1077–1090. https://doi.org/10.1080/14740338.2019.1666104

Sinha, M., Das, D.K., Bhattacharjee, S., Majumdar, S., Dey, S., 2011. Leaf extract of Moringa oleifera prevents ionizing radiation-induced oxidative stress in mice. Journal of Medicinal Food. 14(10), 1167–1172. https://doi.org/10.1089/jmf.2010.1506

Sisodia, R., Singh, S., Meghnani, E., Srivastava, P., 2011. Radioprotection of Swiss albino mice by Prunus avium with special reference to hematopoietic system. Journal of Environmental Pathology. 30(1). https://doi.org/10.1615/JEnvironPatholToxicolOncol.v30.i1.60

Subramanian, M., Chintalwar, G.J., Chattopadhyay, S., 2003. Radioprotective property of polysaccharide in Tinospora cordifolia. Indian Journal of Biochemistry and Biophysics. 40(1), 22–26.

Subramanian, M., Chintalwar, G.J., Chattopadhyay, S., 2005. Antioxidant and radioprotective properties of an Ocimum sanctum polysac-

charide. Redox Report. 10(5), 257–264. https://doi.org/10.1179/135100005X70206
Sunila, E.S., Kuttan, G., 2005. Protective effect of Piper longum fruit ethanolic extract on radiation induced damages in mice: a preliminary study. Fitoterapia. 76(7-8), 649–655. https://doi.org/10.1016/j.fitote.2005.08.008
Sureshbabu, A.V., Barik, T.K., Namita, I., Kumar, I.P., 2008. Radioprotective properties of Hippophae rhamnoides (sea buckthorn) extract in vitro. International Journal of Health Sciences. 2(2), 45–45.
Taverniti, V., Guglielmetti, S., 2011. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept). Genes & nutrition. 6(3), 261–274. https://doi.org/10.1007/s12263-011-0218-x
Tiwari, M., Murugan, R., Tulsawani, R., Gota, V., Sarin, R.K., Devi, P.U., Agrawala, .., K, P., 2016. Factors affecting radioprotective efficacy of Ocimum sanctum (Tulsi) extract in mice. Journal of Advances in Medical and Pharmaceutical Sciences, 1–12. https://doi.org/10.9734/JAMPS/2016/28152
Tsubura, A., Lai, Y.C., Kuwata, M., Uehara, N., Yoshizawa, K., 2011. Anticancer effects of garlic and garlic-derived compounds for breast cancer control. Anti-Cancer Agents in Medicinal Chemistry. 11(3), 249–253. https://doi.org/10.2174/187152011795347441
Vasilyeva, I., Bespalov, V., Baranova, A., 2015. Radioprotective combination of α-tocopherol and ascorbic acid promotes apoptosis that is evident by release of low-molecular weight DNA fragments into circulation. International Journal of Radiation Biology. 91(11), 872–877. https://doi.org/10.3109/09553002.2015.1087066
Zhou, Y., Mi, M.T., 2005. Genistein stimulates hematopoiesis and increases survival in irradiated mice. Journal of Radiation Research. 46(4), 425–433. https://doi.org/10.1269/jrr.46.425