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Radioprotective Potential of Plants and Herbs against the Effects of Ionizing Radiation

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Summary **Ionizing radiations produce deleterious effects in the living organisms and the rapid technological advancement has increased human exposure to ionizing radiations enormously. There is a need to protect humans against such effects of ionizing radiation. Attempts to protect against the deleterious effects of ionizing radiations by pharmacological intervention were made as early as 1949 and efforts are continued to search radioprotectors, which may be of great help for human application. This review mainly dwells on the radioprotective potential of plant and herbal extracts. The results obtained from *in vitro* and *in vivo* studies indicate that several botanicals such as *Gingko biloba*, *Centella asiatica*, *Hippophae rhamnoides*, *Ocimum sanctum*, *Panax ginseng*, *Podophyllum hexandrum*, *Amaranthus paniculatus*, *Emblica officinalis*, *Phyllanthus amarus*, *Piper longum*, *Tinospora cordifoila*, *Mentha arvensis*, *Mentha piperita*, *Syzygium cumini*, *Zingiber officinale*, *Ageratum conyzoides*, *Aegle marmelos* and *Aphanamixis polystachya* protect against radiation-induced lethality, lipid peroxidation and DNA damage. The fractionation-guided evaluation may help to develop new radioprotectors of desired activities.**

Key Words**: radioprotection, antioxidant, survival, micronuclei**

Introduction

Need for chemical radioprotection

The discovery of X-rays by Roentgen in the year 1895 and radioactivity by Becquerel in the year 1896 can be considered as the turning point in human health care as the X-rays allowed to peep inside the human body [*1*, *2*]. Although harmful effects of ionizing radiations were reported within a few months of discovery of X-rays, the real magnitude was not known. Study of occupational workers like physicians and scientists handling radioactivity gave a clear picture of the harmful effects of ionizing radiations, which was further strengthened after the study of Japanese atomic bomb survivors of 1945. It is now fairly well established that radiation produces deleterious effects on the organisms and widespread use of radiation in diagnosis therapy, industry, energy sector and inadvertent exposure during air and space travel, nuclear accidents and nuclear terror attacks requires safeguard against human exposures. Lead shielding and other physical measures are cumbersome to use in such situations, therefore pharmacological intervention could be the most prudent strategy to protect humans against the harmful effect of ionizing radiations.

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Chemical radioprotection

The use of chemicals to protect against the harmful effects of radiation was attempted after World War II with the realization of the need to safeguard humans against the military use of atomic weapons. Patt and his co-workers (1949) were the first to investigate the effect of amino-acid cysteine in rats exposed to lethal doses of X-rays [*3*]. They found that pretreatment of rats protected them against the radiation-induced lethality. Thereafter, several chemical compounds and their analogues have been screened for their radioprotective ability however, their high toxicity at optimum protective doses precluded their clinical use [*4*, *5*]. The other major drawback of these compounds was that they were unable to provide post-irradiation protection. With the recognition that normal tissue protection during radiotherapy is as important as the destruction of cancer cells, the focus of protection research became more therapy oriented. Recent terror attacks throughout the world has strengthened the idea that it its necessary to devise appropriate measures against the nuclear terror attacks by using pharmacological agents that can protect against the ill effects of radiation.

The high toxicity of thiol compounds necessitated search for alternative agents, which could be less toxic and highly effective at non-toxic dose levels. It was also thought that products/compounds isolated from natural sources could be of substantial use as non-toxic radioprotectors. Therefore, investigators diverted their attention towards the plant and natural products during the last two decades. Plants have been reported to play an important role in the discovery of new drugs for the treatment of human diseases, which indicated that natural products play a highly significant role in the drug discovery and development process [*6*]. This was particularly evident in the areas of cancer and infectious diseases, where over 60% and 75% of these drugs, respectively, were shown to be of natural origin. A good chemical protector should be able to protect against the deleterious effect of ionizing radiation during therapeutic procedures as well as during nuclear accidents, space flight and background irradiation etc. An ideal radioprotector should be cheap, does not have toxic implications in a wide dose range, orally administered, rapidly absorbed, possesses a reasonably good dose reduction factor and can act through multiple mechanisms. The plant and natural products have all these qualities. They are usually non-toxic, relatively cheap, can be orally administered and could act through multiple mechanisms due to the presence of many chemicals. Therefore, screening of plants and natural products is a useful paradigm for radioprotection. The advantage of plants and natural products is that they are used in several traditional systems of medicines. They are usually considered non-toxic and widely accepted by humans. Their use as radioprotectors needs scientific evaluation and validation. Once this is done their use, as radioprotectors could be more successful than synthetic chemicals.

Assessment of radioprotective potential of plants and herbs

The most pragmatic approach to select the possible candidate to evaluate radioprotective effect is to look into the available properties of the substance. Whether a substance has anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, free radical scavenging or anti-stress properties, if so, it may act as a potential radioprotector and could be the right candidate for evaluation of its radioprotective activity.

Short-term *in vitro* tests can provide a basis for detailed evaluation of radioprotective activity. The simplest tests could be the evaluation of lipid peroxidation *in vitro*. Assay of free radicals and antioxidant status of a pharmacological agent can also provide some leads regarding the radioprotective potential of such agents. If a plant or a natural product is found to inhibit lipid peroxidation and scavenge free radicals, it may act as a possible radioprotector. The next step is to evaluate its radioprotective potential *in vitro* using cell survival and micronuclei assays. If it is found to elevate cell survival and reduce radiation-induced micronuclei formation, it certainly has a potential as a radioprotector.

There are other short-term tests like DNA strand breaks, apoptosis and estimation of glutathione (GSH) and enzymes like catalase, glutathione peroxidase etc. that can also provide an inkling of the radioprotective activity of any pharmacological agent. However, the gold standard for radioprotective activity is the evaluation of 30-day survival in rodents, since the animal studies with death as the end point are the most confirmatory, because the 30-day survival after lethal whole body irradiation clearly indicates the capacity of the pharmacological agent in test to modulate the recovery and regeneration of the gastrointestinal epithelium and the hemopoietic progenitor cells in the bone marrow, the two most radiosensitive organs that are essential for sustenance of the life [*7*]. The most reliable procedures involve determination of a dose reduction factor (DRF). In animal studies, DRFs are typically determined by irradiating mice with or without administering radioprotective agent at a range of radiation doses and then comparing the endpoint of interest. For example, the DRF for 30-day survival ($LD_{50/30}$ drug-treated divided by $LD_{50/30}$ vehicle-treated) quantifies protection of the hemopoietic system [*8*, *9*]. With sufficient loss of hemopoietic stem cells, death follows due to infection, hemorrhage, and anemia. The GI syndrome in mice can be assessed by determining survival up to ten days (measure of GI death) after exposure to comparatively high doses of whole-body radiation, whereas hemopoeitic syndrome can be assessed by monitoring the survival of irradiated animals up to 30 days post-irradiation [*7–11*]. The intestinal crypt cell assay or functional changes also serve as indicators of GI damage [*12*]. The most informative and useful preclinical studies relate protective effects to the drug's toxicity in the same animal model.

The efficacy of radioprotectors in clinical practice requires

different end points. Among other endpoints amenable to the determination of beneficial effects of radioprotectors, the most readily evaluable is protection against mucositis and xerostomia resulting from head and neck radiotherapy and various side effects when the GI tract is in the radiation field [*13*].

Plants and herbs as radioprotectors

Several botanicals have been screened for their radioprotective activity (Table 1). An intravenous infusion of an ethanol extract of *Gingko biloba* leaves, at a dose of 100 mg/person was found to be effective in patients with vasogenic edema observed after irradiation of the brain [*14*]. It has been reported to protect against the clastogenic factors from plasma of human subjects exposed to irradiation [*15*]. Treatment of recovery workers from the Chernobyl accident site was found to be effective when an oral dose of 40 mg/day of *G. biloba* was given 3 times daily for 2 months [*16*].

Aqueous extract of *Centella asiatica* reduced the adverse effect of low dose irradiation in Sprague Dawley rats by inhibiting radiation-induced body weight loss and conditioned taste aversion [*17*]. Similarly, it has been found to protect against the radiation-induced weight loss in mice exposed to 8 Gy γ-radiation [*18*].

Oral administration of a *Hippophae rhamnoides* fruit juice concentrate to rats before or after irradiation increased life span, restored the 11-oxycorticosteroid level in the blood and weight of isolated adrenals, and also normalized their basal activity and response to (ACTH) (corticotropin) under *in vitro* conditions [*19*]. Hydroalcoholic extract of berries of *H. rhamnoides* also protected mice against γ-radiation-induced mortality, decline in endogenous colony forming unit (CFU), micronuclei formation and various other hematological parameters [*20–22*].

The radioprotective property of *Osimum sanctum* was first reported by Jagetia *et al*. [*23*] against the radiation-induced mortality, thereafter studies by Uma Devi and her coworkers established its radioprotective efficacy by evaluating mouse survival, spleen colony assay, and chromosome aberrations in mouse bone marrow cells. Apart from these osmium has

Table 1. Radioprotective effect of various herbs and plants

S. No.	Name	Test system	Observation	Ref. No.
1	*Gingko biloba*	Human	Brain edema, clastogenic factors	*14–16*
2	*Centella asiatica*	Rat, mice	Weight loss, taste aversion	*17, 18*
3	*Hippophae rhamnoides*	Rat,	Survival, ACTH	*19*
		Mice	Survival, CFU, micronuclei	*20*
4	*Osimum sanctum*	Mice	Survival, CFU, chromosome damage, lipid peroxidation, glutathione	*23–25*
5	*Panax ginseng*	Mice	Survival, CFU, apoptosis, testicular enzymes	*26–32*
6	*Podophyllum hexandrum*	Mice	Survival, GI damage, nervous system of developing mice, GST, SOD	*20, 33–36*
7	*Tinospora cordifolia*	Mice	Survival, CFU, Blood cells	*37, 38*
8	*Emblica officinalis*		Survival, weight loss	*39*
9	*Phyllanthus amarus*	Mice	WBC, SOD, catalase, GST, GSHpx, glutathione reductase	*40*
10	*Amaranthus paniculatus*	Mice	Survival, CFU, spleen weight, Lipid peroxidation, GSH	*41*
11	*Piper longum*	Mice	WBC, α-Esterase, glutathione pyruvate transaminase, alkaline phosphatase, lipid peroxidation	*42*
12	*Syzigium cumini*	HPBLS,	Micronuclei	*7*
		Mice	Radiation-sickness, GI & BM deaths	*44–45*
13	*Mentha arvensis*	Mice	Radiation-sickness, GI & BM deaths	*47*
14	*Mentha piperita*	Mice	Hematological constituents, serum phosphatase, CFU, spleen weight, goblet cells/villus section and chromosomal damage	*48–50*
15	*Zingiber officinale,*	Mice	Radiation-sickness, GI & BM deaths, free radicals, GSH lipid peroxidation	*52–53*
16	*Ageratum conyzoides*	Mice	Radiation-sickness, GI & BM deaths, DPPH radical	*54*
17	*Aegle marmelos*	HPBLs	Micronuclei, free radicals	*56*
		Mice	Radiation-sickness, GI & BM deaths, Lipid peroxidation, GSH, CFU, villus height, crypt cells, goblet cells	*57–59*
18	*Aphanamixis polystachya*	Mice	aberrant cells, chromatid breaks, chromosome breaks, dicentrics, acentric fragments and total aberrations	*60*

GSH: glutathione, GST: glutathione-s-transferase; GSHpx: glutathione peroxidase; SOD: superoxide dismutase; GI: gasterointestinal; BM: bone marrow; CFU: colony forming units; HPBLs: Human peripheral blood lymphocytes; DPPH: diphenylpicryl hydrazyl radical

been reported to protect against radiation-induced lipid peroxidation and reduction in glutathione concentration [*24*, *25*].

The radioprotective efficacy of ginseng (*Panax ginseng*) has been reported by several workers [*26–30*]. Ginseng treatment caused recovery of thrombocyte and erythrocyte counts in blood after irradiation [*31*]. The whole extract of ginseng and the relative protective effects of various fractions (carbohydrate, protein and saponins) have been evaluated. The results showed that the water-soluble whole extract of ginseng provided best protection against radiation induced damage in C3H mice, whereas isolated protein and carbohydrate fractions were less effective, the saponin fraction was ineffective [*32*]. Similar results were obtained by Kim and coworkers, who found that whole ginseng extract and its fractions increased endogenous spleen colony formation in irradiated mice and also reduced apoptosis in jejunal crypt cells [*27*]. The radioprotective effect of ginseng root extract on testicular enzymes (acid and alkaline phosphatases and lipid peroxidation) has also been reported [*28*].

Podophyllum. hexandrum has been reported to protect against radiation-induced mortality, gastrointestinal damage and embryonic nervous system of developing mice [*20*, *33–35*]. It has also been reported to protect against radiation-induced decline in glutathione-S-transferase, superoxide dismutase in the liver and intestine of irradiated mice [*36*].

Oral administration of an aqueous extract of guduchi, *Tinospora cordifolia* has been reported to increase the survival of mice exposed to radiation [*37*]. Treatment of mice with hydroalcoholic extract of *Tinospora cordifolia* has been found to protect against the radiation-induced micronuclei formation and oxidative stress and decline in the mouse survival, spleen CFU and hematological parameters [*38*].

The fruit pulp of Amala, *Emblica officinalis* (EO) has been reported to increase the survival and inhibit radiation-induced weight loss in mice [*39*]. *Phyllanthus amarus* has been reported to protect against the radiation-induced decline in white blood cells (WBC), superoxide dismutase, catalase, glutathione-S-transferase, glutathione peroxidase, and glutathione reductase [*40*].

Daily oral administration of 800 mg/kg body weight (b. wt.) of *Rajgira* (*Amaranthus paniculatus*) leaf extract for 15 consecutive days before whole body exposure to γ-radiation protected mice against the radiation-induced lethality with a dose reduction factor of 1.36. It increased endogenous spleen colony forming units and spleen weight without any side effects or toxicity. Rajgara extract also arrested radiation-induced lipid peroxidation and the decline in reduced glutathione in the liver and blood of mice [*41*].

The ethanolic extract of *Piper longum* (pippali) fruits was found to protect mice against the radiation-induced decline in WBC, bone marrow cells α-esterase positive cells and GSH. Pippali extract also reduced the elevated levels of glutathione pyruvate transaminase (GPT), alkaline phosphatase (ALP), lipid peroxidation (LPO) in liver and serum of irradiated animals [*42*].

Several plant and herbal products form the supplements of daily human diet. The potential of dietary ingredients for radioprotection has remained unexplored area until now. The dietary supplements, if found radioprotective may be of crucial importance, as they are in daily human use, nontoxic and have wide acceptability. Jamun, *Syzigium cumini* Linn. Skeels also known as *Eugenia cumini* (family Myrtaceae), and has been reported to posses several medicinal properties in the folklore system of medicine [*43*]. The micronucleus study of radioprotective effect of dichloromethane and methanol (1:1) extract of jamun (SCE) in human peripheral blood lymphocytes (HPBLs) ascertained its radioprotective potential, where 12.5 μg/ml SCE was found to reduce the micronuclei up to a maximum extent. *In vivo* evaluation further established its radioprotective activity where it was found to reduce radiation-induced sickness, gastrointestinal and bone marrow deaths [*7*, *44*]. Not only leaf but the hydroalcoholic extract of jamun seeds (JSE) also exhibited a greatest protective effect at 80 mg/kg JSE. The JSE was more effective when administered through the intraperitoneal route at equimolar doses than the oral. The JSE treatment protected mice against the gastrointestinal as well as bone marrow deaths with a DRF of 1.24 [*45*].

Pudina or Mint (*Mentha arvensis* Linn., Family Lamiaceae), a plant, native of Japan, is used as a food seasoner, household remedy, and for industrial purposes [*46*]. Treatment of mice with 10 mg/kg b. wt. of chloroform extract of mint (*Mentha arvensis* Linn) protected against the radiation-induced sickness, gastrointestinal and bone marrow deaths with a DRF of 1.2. Further it was non-toxic up to a dose of 1000 mg/kg b. wt., the highest drug dose that could be tested for acute toxicity [*47*]. Pre-treatment of mice with leaf extract of another species of pudina, i.e. *Mentha piperita* has been reported to protect mice against the radiation-induced decline in hematological constituents, serum phosphatase, endogenous spleen colonies formation, spleen weight, goblet cells/villus section and chromosomal damage [*48–50*].

The rhizome of *Zingiber officinale*, commonly known as ginger, is consumed daily worldwide as a spice and flavoring agent. The rhizome of ginger has been reported to possess diverse medicinal properties in the traditional Indian system of medicine, the Ayurveda, and it is widely used in several medicinal preparations [*51*]. Administration of 10 mg/kg (i.p) or 250 mg/kg (orally) hydroalcoholic extract once daily, consecutively for 5 days was found to protect mice against the radiation-sickness, gastrointestinal as well as bone marrow deaths with a DRF of 1.15. Ginger has been reported to increase glutathione, reduce lipid peroxidation *in vivo* and scavenging of various free radicals *in vitro* [*52*, *53*].

Ageratum conyzoides, (family: Asteraceae) is commonly known as Billy Goat Weed. It has been used in various parts of Africa, Asia and South America for curing various diseases. The study of various doses of alcoholic extract of *Ageratum conyzoides*, Linn. revealed that the best protective dose was 75 mg/kg and it reduced radiation-induced, sickness gastrointestinal as well as bone marrow deaths. A DRF was found to be 1.3. The radioprotective effect was due to scavenging of DPPH (1,1-diphenyl-2-picrylhydrazyl), free radical [*54*].

Aegle marmelos Correa, commonly known as bael, is a spinous tree belonging to family Rutaceae. It is grown throughout the sub-continents as well as Bangladesh, Burma and Srilanka [*55*]. The hydroalcoholic extract of *Aegle marmelos* (AME) protected cultured HPBLs against the radiation-induced micronuclei at a concentration of 5 µg/ml. It was also reported to scavenge $^{\cdot}OH$, $O_2^{\cdot-}$, DPPH, $ABTS^{\cdot+}$ and NO (nitric oxide) radicals *in vitro* in a concentration dependent manner [*56*]. The radioprotective efficacy of 15 or 250 mg/kg AME was further confirmed in animal studies where its intraperitoneal as well as oral administration has been found to protect mice against the radiation-induced sickness, gastrointestinal and bone marrow deaths and mortality giving a DRF of 1.2. It also protected mice against the radiation-induced lipid peroxidation and elevated GSH concentration in the liver, kidney, stomach and intestine at 31 days post-irradiation. Oral administration also protected mice against the gamma radiation-induced decline in erythrocytes, leukocytes, lymphocytes and clonogenicity of hemopoietic progenitor cells assessed by exogenous spleen colony forming assay. Pretreatment of mice with AME elevated the villus height and the crypt number accompanied by a decline in goblet and dead cell number [*57*, *58*]. Not only leaf but also the hydroalcoholic extract of *Aegle marmelos* fruit administered intraperitoneally at a dose of 20 mg/kg once daily, consecutively for five days found to protect mice against the radiation-induced sickness, gastrointestinal as well as bone marrow deaths with a DRF of 1.1 [*59*].

Rohituka, *Aphanamixis polystachya* Wall. Parker [*Amoora rohituka*, *Amoora aphanamixis* (Roxb.) Wight & Arn.] is a member of the family Meliaceae. The ethyl acetate fraction of *Aphanamixis polystachya* at a dose of 7.5 mg/kg b. wt. before exposure to 1–5 Gy of whole body gamma-radiation significantly reduced the frequencies of aberrant cells and chromosomal aberrations like acentric fragments, chromatid and chromosome breaks, centric rings, dicentrics, exchanges and total aberrations at all post-irradiation scoring times. It also showed a concentration dependent scavenging of hydroxyl, superoxide, 2,2'-diphenyl-1-picryl hydrazyl (DPPH) radicals and the 2,2-azino-bis-3-ethyl benzothiazoline-6-sulphonic acid (ABTS) cation radicals *in vitro*. EAP treatment also reduced lipid peroxidation in bone marrow cells in a concentration dependent manner [*60*].

Mechanism of action

Ionizing radiations induce reactive oxygen species in the form of $^{\cdot}OH$, $^{\cdot}H$, singlet oxygen and peroxyl radicals that follows a cascade of events leading to DNA damage such as single- or double-strand breaks (DSB), base damage, and DNA-DNA or DNA-protein cross-links, and these lesions cluster as complex local multiply damaged sites. The DNA-DSBs are considered the most lethal events following ionizing radiation and has been found to be the main target of cell killing by radiation. The putative mechanisms of radio-protection by plant and herbal radioprotectors are shown in Fig. 1. The radioprotective activity of plant and herbs may be mediated through several mechanisms, since they are complex mixtures of many chemicals. The majority of plants and herbs contain polyphenols, scavenging of radiation-induced free radicals and elevation of cellular antioxidants by plants and herbs in irradiated systems could be leading mechanisms for radioprotection. The polyphenols present in the plants and herbs may upregulate mRNAs of antioxidant enzymes such as catalase, glutathione transferase, glutathione peroxidase, superoxide dismutase and thus may counteract the oxidative stress-induced by ionizing radiations. Upregulation of DNA repair genes may also protect against radiation-induced damage by bringing error free repair of DNA damage. Reduction in lipid peroxidation and elevation in non-protein sulphydryl groups may also contribute to some extent to their radioprotective activity. The plants and herb may also inhibit activation of protein kinase C (PKC), mitogen activated protein kinase (MAPK), cytochrome P-450, nitric oxide and several other genes that may be

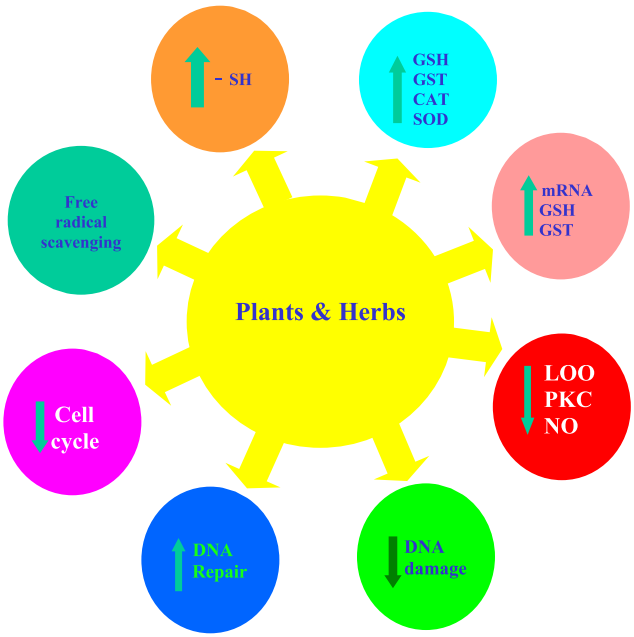

Fig. 1. The putative mechanisms of radioprotection by various plants and herbs.

responsible for inducing damage after irradiation.

Conclusions

Humans are exposed to ionizing radiations during diagnostic, therapeutic and industrial purposes. Apart from these humans also get exposed to ionizing radiations during air and space travel, background radiation nuclear accidents, and use of electronic devices. Nuclear terror attacks are not distant possibility, therefore it is essential to protect humans from ionizing radiations by pharmacological intervention. Recently, focus of radiation protection has shifted to test the radioprotective potential of plants and herbs in the hope that one day it will be possible to find a suitable pharmacological agent/s that could protect humans against the deleterious effects of ionizing radiation in clinical and other conditions as well as during nuclear terror attack. Majority of plant and herbs described in this review have medicinal properties and are being used in traditional Ayurvedic or Chinese systems of medicine to treat various ailments in humans. Most of these plants and herbs certainly have potential as radioprotectors of future. They protect against the radiation-induced damage by scavenging of free radicals and increasing antioxidant status. Fractionation guided evaluation may result in the development of ideal radioprotector/s in the near future.

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