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Phytochemicals as radioprotective agents—A Review

Piya Paul[1], M K Unnikrishnan[2] and A N Nagappa[3]*

[1]Department of Pharmacology, [2]Department of Pharmacy Practice, [3]Department of Pharmaceutical Management, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal-576 104, Karnataka, India

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The development of radioprotective agents has been a subject of intense research in view of their potential for use within a radiation environment, such as space exploration, radiotherapy and even nuclear war. Since no ideal, safe synthetic radioprotectors are available to date, the search for alternative sources, including plants, has been on-going for several decades. In the Traditional Indian system of medicine, several plants have been used to treat radiation-mediated ailments. A systematic screening approach can only provide leads to identify potential new molecular entities from plant sources, for mitigation of radiation injury. This article reviews the milestones in development of radioprotectors with emphasis on perspectives of variety of plants, their bioactive principles and several alternative approaches tested in *in vitro* and *in vivo* model systems for radioprotection. With an overview of our own work carried out in this area, this review highlights the unique inherent properties in plants and the phytochemicals that aid in preventing free radical-induced oxidative stress during radiation therapy. The structural characteristics of these phytochemicals, rendering them suitable for radioprotection, have also been discussed, with the scope of their applications in the fields involving imbalanced redox status and oxidative stress.

Keywords: Antioxidant, Cancer, Dose reduction factor, Herbals, Oxidative stress, Radiation, Radioprotectors.

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Introduction

Radiotherapy is the most common modality for treating human cancers. Eighty percent of cancer patients need radiotherapy at some time or other, either for curative or palliative purpose[1]. The use of radiation therapy to treat cancer inevitably involves exposure of normal tissues. Radiation therapy injures/destroys cells in the exposed area by damaging their genetic material[2]. As a result, patients may experience symptoms during the course of therapy for a few weeks after therapy or months or years later.

Radiation protection is an area of great significance due to its wide applications in planned radiotherapy as well as unplanned radiation exposure[2,3]. Research in the development of radioprotectors worldwide has focused on screening a variety of chemical and biological compounds. Treatments that reduce the risk or severity of damage to normal tissue or those that facilitate the healing of radiation injury are being developed. Various natural and synthetic compounds such as antioxidants, cytoprotective agents, immunomodulators, vitamins and DNA binding molecules, have been evaluated extensively for their radioprotective potentials in both *in vitro* and *in vivo* models[2,4-7]. However, the strategy becomes jeopardized when it comes to using synthetic molecules during radiotherapy to reduce the unwanted radiation side effects. Conflicting preclinical and clinical reports make it difficult to either ignore or accept the use of synthetic molecules during cancer radiotherapy in an unequivocal manner[8]. Randomized clinical trials on antioxidant vitamins to prevent acute adverse effects of radiation suggest that use of high doses of antioxidants as adjuvant therapy might compromise radiation treatment efficacy[8]. The fact therefore, indicates that there is no ideal synthetic radioprotector available which meets all the prerequisites i.e., produces no cumulative or irreversible toxicity, provides effective long-term protection, remains stable for a number of years without losing shelf-life and can be easily administered[9].

Considering, the drawbacks associated with the currently available radioprotectors, several novel approaches exploring and experimenting with the

*Correspondent author: E-mail: anantha1232000@gmail.com; Phone: 0820-2922482 Extn. 162; Fax: 0820-2571998

plant kingdom have been tried. Natural and herbal sources are non-toxic with proven therapeutic benefits and have been utilized since ancient times for curing various diseases and disorders. Even today, more than 70% of the world's population depends on plant-based remedies to meet their health care needs[10]. Various plants have been reported to be beneficial for free radical-mediated conditions in humans such as arthritis, atherosclerosis, aging, cancer, Alzheimer's disease, Parkinson's disease and inflammatory disorders. Plants are rich sources of polyphenols which include anthocyanins, flavonoids, stilbenes, tannins, lignins, etc[3]. Among these, several flavonoids (quercetin, orientin, myricetin-flavonol, luteolin-flavone and (−)-epigallocatechin gallate-flavanol, rutin, naringin, etc.), have been reported as potent antioxidants with radioprotective abilities[10]. Flavonoids scavenge free radicals, thereby sparing endogenous antioxidant enzyme system (superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase). This confers protection against radiation-induced reactive oxygen species (ROS) and reactive nitrogen species (RNS) mediated damage[9]. Plant preparations have been classified variedly such as natural compounds, plant extracts, polyherbal formulations, etc. A review of such agents, with their efficacy in radioprotection and possible mechanisms responsible has been carried out in this paper. The enormous heritage of vast natural dietary and time tested medicinal resources in this planet is the motivation behind exploring the possibility of developing efficient, economically viable and clinically acceptable radioprotectors for human application from these resources.

Injuries by radiation – a result of imbalance in endogenous mechanisms of radioprotection

Ionizing radiations damage living tissues through a series of molecular events, triggered by the very first step of free radicals generation, also known as reactive oxygen species (ROS). These ROS such as OH, H, e^{aq-}, HO_2, H_3O^+, etc. deplete cellular antioxidant stores and react with cellular macromolecules, such as DNA, RNA, proteins, membrane lipids, etc. and cause cell dysfunction and mortality[11-13]. A broad spectrum of DNA lesions, including damage to nucleotide bases, cross-linkage, and DNA single- and double-strand breaks are induced. This is followed by altered cell division, cell death, depletion of stem cell pools, organ system dysfunction and, if the radiation dose is sufficiently high, even death. It is now accepted, however, that inappropriately repaired DNA breaks are the principal lesions in the induction of chromosomal abnormalities, mutations and cancer[14]. Radiation-induced lipid peroxidation alters cell membrane fluidity leading to degradation and impaired biological defense[15].

Cells and tissues are equipped with endogenous enzymes e.g. superoxide dismutase (SOD), glutathione peroxidise (GPx), catalase, reduced glutathione (GSH), glutathione S transferase (GST) capable of neutralising free-radical induced cellular damage[16]. GSH performs multifunctional activities to attenuate radiotoxicity by scavenging of free radicals, maintaining thiol-disulphide balance, synthesis of DNA precursors, synthesis of porphyrin and maintaining the cellular ATP levels[17]. However, once the level of reactive oxygen species increases above tolerable limits, the endogenous system fails to protect the cells from the hazardous effects of free radicals. Exposure to high amounts of ionizing radiation results in damage to the haematopoietic, gastrointestinal and central nervous systems depending on radiation dose[18]. The haematopoietic system is among the most radiosensitive in the body as it has a highest cell turnover[17,19]. The primary cause of mortality during the early phases of radiation-induced haematopoietic syndrome is sepsis, resulting from opportunistic infection, due to reduced neutrophils and increased entry of bacteria across the denuded gastrointestinal mucosa. The situation is further complicated by thrombocytopenia and defects in the adaptive immune system[20]. Gastrointestinal syndrome is induced by a higher irradiation dose compared to haematopoietic syndrome. In this syndrome, the gastrointestinal barrier is damaged and high amounts of water and electrolytes are lost from the body, resulting in dehydration and bacteraemia[21].

Milestones and current trends in the development of radioprotectors

The initial development of radioprotective agents led to the discovery of effective, synthetic thiol compounds (Fig. 1)[22-35], however, the side effect profile of these agents necessitated the search for second-generation drugs that are more effective, less toxic and with more acceptable properties with respect to route and frequency of administration[21].

In recent years, an array of immunomodulatory agents, haemopoietic growth and stimulating factors, synthetic chelating agents and natural antioxidants have

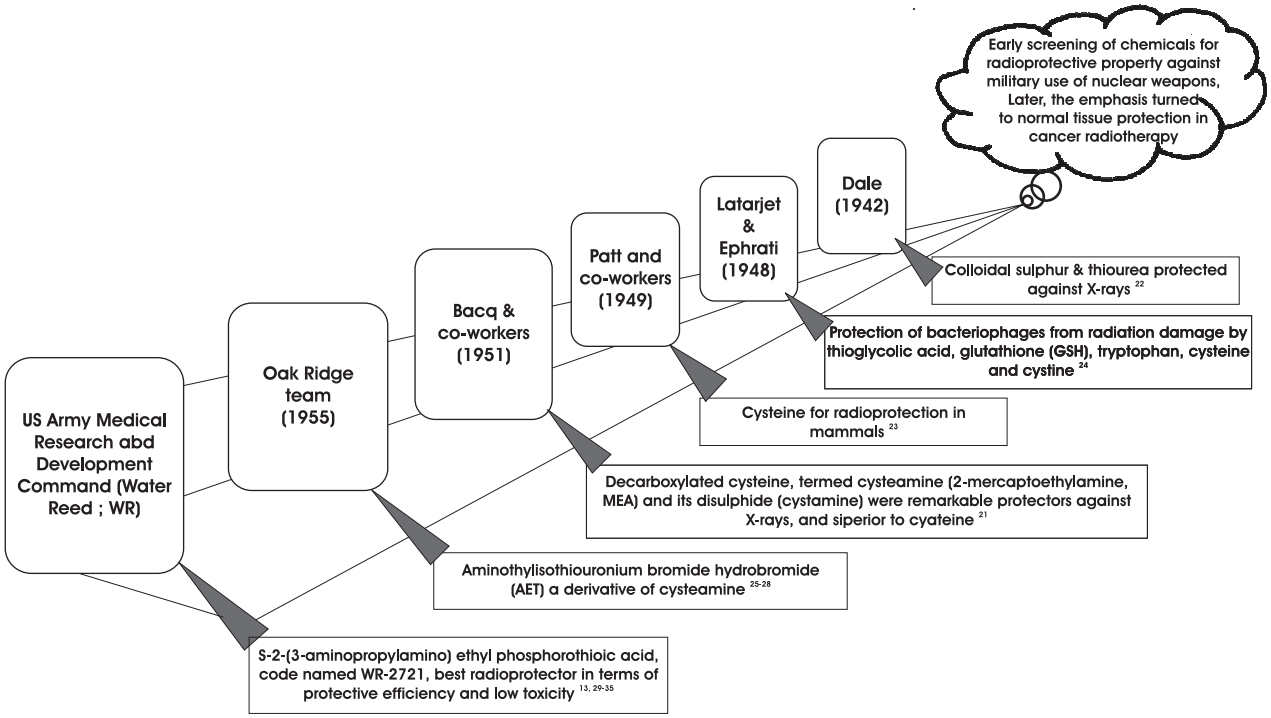

Fig. 1 — Milestones in the development of radioprotectors

been examined for their ability to ameliorate radiation-induced damage[21]. Emphasis has been focused on natural and synthetic compounds based research, including organometallic compounds and biological response modifiers (Table 1)[36-77]. Immunomodulators are non-cytokine drugs, proposed as an alternative to stimulate haematopoietic stem cells. These stimulate growth, differentiation and proliferation of haematopoietic progenitor and stem cells, thus protecting and repairing radiation-induced abnormalities[48]. Natural compounds in the diet provide functional antioxidants, such as vitamins, minerals and enzymes. Reduction of oxidation damage by such natural antioxidants provides a degree of protection against ionizing radiation injury. A group of synthetic super oxide dismutase (SOD) mimetic compounds, with a metal ion (Cu, Fe, Mn and Zn) at their active centres, have also been developed[21]. All such agents have shown varying extent of protection when administered to cancer patients undergoing radiotherapy, and have shown encouraging results. WR-2721 is the best radioprotector studied so far. However, it has failed to find acceptability in routine radiotherapy due to its undesirable side effects and exorbitant cost[78,79]. Therefore, the trend in the radioprotector developmental process has been delineated around the basic property of free radical scavenging, keeping in mind the most acceptable route of administration of these agents to humans.

The efficacy of any radioprotector is expressed in terms of dose modifying factor (DMF) or dose reduction factor (DRF). DRF is evaluated by plotting the percentage survival at the end of 30 days against the different doses of radiation[11].

$$\frac{\text{DMF}}{\text{DRF}} = \frac{\text{Radiation LD}_{50} \text{ in the presence of the protector}}{\text{Radiation LD}_{50} \text{ in the absence of protector}}$$

Where, LD_{50} is the lethal dose of radiation causing 50% death in animals.

Herbal radioprotectors – An alternative and safe approach towards developing radioprotectors

Recently, many of the investigators have focused the radioprotective research towards the phytochemicals and plant extracts. A review by Arora *et al*, on the present status of herbal radioprotectors and future prospectives emphasize the potential in the area of natural product based radioprotector drug discovery[2]. A summary of the progress of research in this area is presented in the following section.

Plants have been utilized since time immemorial for curing diseases. Even today, nearly 70% of the world's healthcare is dependent on plants[80]. A number

Table 1 — List of biological modifiers used in radioprotection

Biological response modifiers	DRF/DMF	Reference (s)
Cytokines		
IL-1	1.2-1.25	36
TNF-α	1.15	37
PGEs	1.5	38-43
Leucotrienes	1.65-2.07	44
Polysaccharides		
Bacterial lipopolysaccharide	1.22	45
Glucan	1.08	45
Bacillus Calmette-Guerin	*	46
Carboxymethylglucans	1.21-1.4	45, 47-52
Mannane mannozyne	2.16	53
Immunomodulatory agents		
Ammonium trichloroethylene-o-o'-tellurate	*	54-58
Ribomunyl	*	59
Metals and metal complexes		
Zinc aspartate	*	60, 61
Selenium with thiols-cysteamine	*	62
Selenomethionine	80% at 9 Gy	63
Selenomethionine + WR-2721	2.6	64
Simple salts of Cu and Zn	*	65, 66
Copper complexes such as copper glycinate, copper(II) 2(3,5-diisopropylsaicylate) and copper(II)(chloride)	67 %	67, 68
Nitroxide tempol	1.25-2.5	69
Diltiazem	100%	70
Cimetidine	> 1.5	71
Captopril I and II	1.1-1.3	73
Naturally occurring substances		
Vitamins E, A and C, superoxide dismutase	*	
Algal mutant *Chlorella vulgaris*	1.11-1.15	72
Melatonin	*	74, 75
Methylxanthines	(1.2-2.0)(1.3-2.3)	76
Caffeine	1.1-1.2	77

*Data not available on dose reduction/modifying factors
DMF= Dose modifying factor, DRF= Dose reduction factor

of plants have been utilized successfully for the treatment of free radical-mediated diseases such as rheumatoid arthritis, atherosclerosis, cancer, Alzheimer's disease, Parkinson's disease, aging and several other conditions including inflammatory diseases[8,9]. It is, therefore, reasonable to expect that plants may contain certain compounds that can protect against ROS-mediated damage.

A number of medicinal plants evaluated for their radioprotective efficacy have shown protective effects against the damaging effects of ionizing radiation[81-92]. Plant extracts eliciting radioprotective efficacy contain a plethora of compounds including antioxidants, immunostimulants, cell proliferation stimulators, anti-inflammatory and antimicrobial agents, some of which may act in isolation as well as in combination with other constituents from the same plant. Most studies using plant products have focused on evaluation of radioprotective efficacy of whole extracts or polyherbal formulations, and in some cases, fractionated extracts and isolated constituents[83-85,93-108]. Many Ayurvedic preparations, Chinese herbal medicines, Japanese, Korean, Siddha, European, Tibetan, Unani systems of medicine and different extracts/constituents from plant sources have been reported to be radioprotective in various model systems. These include cruciferous vegetables (e.g. cabbage and broccoli), green tea (polyphenols), *Spirulina platensis*, *Mentha arvensis* Linn. (mint), *Podophyllum hexandrum* Linn. (Himalayan May

apple), *Syzygium cuminii* (Linn.) Skeels (Jamun, Black plum), *Panax ginseng* Linn., *Aspalathus linearis* (N.L. Burm.) R. Dahlgr (Rooibos tea), soy products, venoruton (rutoside), bixin (carotenoid), *Gingko biloba* Linn. extract (flavone glycosides and terpene lactones), milk thistle (silymarin), grape seed extract, triphala extracts, *Eleutherococcus senticosus* Rupr. & Maxim. or Shigoka extract, dithiolthiones, curcumin, chlorogenic acid, quercetin, garlic (allicin), lycopene, methylxanthines, melatonin, ellagic acid, etc.

Most studies using phytochemicals have focused on evaluation of radioprotective efficacy of whole extracts or polyherbal formulations and in some cases fractionated extracts and isolated constituents, for their ability to protect against radiation-induced chromosomal aberrations and micronuclei formation[21]. A few plants (Plate 1), their extracts and fractions are enlisted in Table 2.

It is apparent, that many plants exhibit, or have the potential to show, a diverse array of biological activities that may be relevant to the mitigation of ionizing radiation-induced damage in mammalian systems. However, so far, only a fraction of these plants have been investigated systematically. Isolation of the bioactive constituents responsible for radioprotection needs attention in many plants showing promise[109].

In our laboratory, the free radical scavenging, antioxidant and radioprotective potential of plants such as *Coronopus didymus* (Linn.) Sm., *Pilea microphylla* (Linn.) Liebm., *Ocimum sanctum* Linn. and *Ficus racemosa* Roxb. (to name a few important ones) have been carried out. A part of the collaborative project on the flavonoids (orientin and vicenin) derived from *O. sanctum* was carried out earlier. It was observed that orientin and vicenin showed a significantly greater *in vitro* free radical-inhibiting activity and provided almost equal protection against radiation-induced lipid peroxidation in mouse liver[92].

A systematic chemical investigation of *C. didymus* has been performed and a new flavone glycoside, viz. chrysoeriol (6´´-OAc)-4´-βD-glucoside, along with free chrysoeriol and stigmastanol, have been isolated and characterized on the basis of chemical and spectral studies. Chrysoeriol and its glucoside are reported antioxidants and free radical scavengers[144]. Results from radioprotection studies show that the most active free radical scavenging fraction (CDF1) confers maximum *in vivo* radioprotection of 70% at a dose of 400 mg/kg b. wt. (mice) prior to 10 Gy radiation dose. A DRF at the same dose for 30 day survival was found to be 1.07. The levels of endogenous antioxidant enzymes and lipid peroxidation

Aloe arborescens

Biophytum sensitivum

Coronopus didymus

Emblica officinalis

Ginkgo biloba

Mentha arvensis

Plate 1 — Some radioprotective plants

Table 2 — Traditional herbal plants showing therapeutic activities relevant to radioprotection

Plant	Family	Use in radioprotection	Optimum radioprotective dose	References (s)
Aegle marmelos Corr. ex Roxb.	Rutaceae	Provided protection against radiation-induced sickness and mortality in mice	15 mg/kg b.wt.	122, 123
Acanthopanax senticosus (Rupr. and Maxim.) Maxim.	Araliaceae	Pre-irradiation administration of Shigoka extract. The extract also increased leukocyte counts and diminished cerebral haemorrhage	24 mg/kg b.wt. ; 24 h i.p. pre irradiation	129, 130
Aphanamixis polystachya (Wall.) R.N. Parker	Meliaceae	The ethyl acetate fraction of *Aphanamixis polystachya* 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	7.5 mg/kg b. wt. before exposure to 1-5 Gy of whole body gamma-radiation	120
Ageratum conyzoides Linn.	Asteraceae	An alcoholic extract effectively protected mice against 10 Gy-induced gastro intestinal and bone marrow related death	75 mg/kg b.wt. ; 1 h pre irradiation	119
Allium cepa Linn.	Alliaceae	Administration of the dried bulb effective against X-irradiation	20 mg/kg b.wt.	2
Allium sativum L. Gaertn.	Alliaceae	Radioprotective efficacy of aged garlic extract (S-allylcysteine, S-allylmercaptocysteine, allixin and selenium)possess significant antioxidant and anticarcinogenic properties	*	131, 132
Aloe arborescens Mill.	Liliaceae	Extract provided protection to mouse skin against soft x-irradiation by scavenging hydroxyl radicals and reducing alterations in enzyme activity	*	133
Archangelica officinalis Hoffm.	Apiaceae	Administration of a combination of extracts *Archangelica officinalis* and *Ledum palustre* to mice rendered 70% survival (DMF: 1.48)	5-15 min before 7.5 Gy irradiation	134
Angelica sinensis (Oliver) Diels	Apiaceae	The polysaccharide fraction, containing a ferulic acid, increased survival in irradiated mice (> 30 days) by promoting haemopoietic stem cell proliferation	i.v. route (post-irradiation)	135
Amaranthus paniculatus Linn.	Amaranthaceae	Leaf extract protected mice against 5 Gy by reducing lipid peroxidation, glycogen and cholesterol levels in brain	600 mg/kg b.wt. for 2 weeks	118
Biophytum sensitivum (Linn.) DC.	Oxalidaceae	Administration of B. sensitivum could reduce the enhanced serum level of ALP, GPT, LPO and liver GSH in irradiated animals. The protective effect of Biophytum sensitivum on radiation-induced hemopoietic damage is mediated through immunomodulation as well as sequential induction of IL-1ß, GM-CSF and IFN-γ	50mg/kg b.wt.	125
Centella asiatica (Linn.) Urban	Apiaceae	Aqueous extract protects Sprague Dawley rats against the adverse effects of low-dose ionizing radiation (2 Gy). Administered orally, provides total body protection in mice against sublethal (8 Gy) 60Co gamma radiation	100 mg/kg b.wt; i.p.; single dose; -1 h	108

(Contd.)

Table 2 — Traditional herbal plants showing therapeutic activities relevant to radioprotection— *Contd*

Plant	Family	Use in radioprotection	Optimum radioprotective dose	References (s)
Coronopus didymus Linn.	Brassicaceae	Optimum radioprotection was observed upon i.p. administration, 30 min prior to 10 Gy irradiation and DRF was found to be 1.07.	400 mg/kg b.wt.	126-128
Curcuma longa Linn.	Zingiberaceae	Curcumin (diferuloylmethane) has been reported to render radioprotective effect	*	136
Emblica officinalis Linn.	Euphorbiaceae	EOE is effective in preventing gamma radiation- induced lipid peroxidation and protected mitochondrial SOD. It also prevents radiation-induced DNA strand breaks in a concentration-dependent manner.	*	117
Ginkgo biloba Linn.	Cycadaceae	An ethanol (30%) extract of the dried leaf is reported effective when tested on a culture exposed to clastogenic factors from plasma of human subjects exposed to irradiation and on rat cerebellar neuronal cell culture against hydroxyl radical-induced apoptosis.	100 µg/ml	110-112
Glycyrrhiza glabra Linn.	Fabaceae	70% methanolic extract protected rat microsomal membranes from gamma radiation-induced lipid peroxidation.	100 µg/ml	138
Hypericum perforatum Linn.	Hypericaceae	In murine model aqueous extract protected bone marrow and intestinal mucosa against X-ray in a concentration and time dependent manner.	*	139
Hippophae rhamnoides Linn.	Elaegnaceae	An aqueous-alcohol (50% ethanol) extract of berries of *H. rhamnoides* when administered to Strain 'A' mice 30 min before whole-body Co60 γ-irradiation (10 Gy) increased life span and rendered 82% survival (at 30 days) compared with 100% mortality (within 15 days) in irradiated controls.	30 mg/kg b. wt.	113
Lycium chinense Mill.	Solanaceae	Administration of root extract prior to x-irradiation significantly improved the recovery of leucocyte, etythrocyte and thrombocyte counts and hematocrit in ICR strain mice.	*	140
Mentha arvensis Linn.	Lamiaceae	Pre-irradiation treatment with chloroform extract protected mice against gastrointestinal and bone marrow death (DMF: 1.2).	*	81
Moringa oleifera Lam.	Moringaceae	Leaf extract significantly reduced the percent aberrant cells in metaphase chromosomes to normal range by day 7 post-irradiation in mice.	150 mg/kg single dose, pretreatment i.p.	141
Ocimum sanctum Linn.	Lamiaceae	Compounds orientin and vicenin significantly increased mouse survival when administered 30 min prior to lethal whole-body γ-irradiation Vicenin provided a slightly higher protection (DMF: 1.37), compared to orientin (DMF: 1.30) in murine model system. Reduced the chromosomal aberrations in the bone marrow of mice exposed to 2 Gy γ-irradiation.	50 µg/kg/i.p.	114, 145

(Contd.)

Table 2 — Traditional herbal plants showing therapeutic activities relevant to radioprotection— *Contd.*

Plant	Family	Use in radioprotection	Optimum radioprotective dose	References (s)
Panax ginseng Linn.	Araliaceae	The water-soluble whole plant extract of ginseng provided the best protection against Co60 gamma radiation in C3H mice.	*	137
Podophyllum hexandrum Royle	Berberidaceae	*P. hexandrum* has been shown to act in a multifaceted manner and provide protection to haematopoietic, gastrointestinal, reproductive and central nervous system (CNS).	*	116
Piper longum Linn.	Piperaceae	The ethanolic extract of fruits was found to protect mice against the radiation-induced decline in WBC, bone marrow cells a-esterase positive cells and GSH.	*	121
Pilea microphylla (Linn.) Liebm.	Urticaceae	Ethanolic extract of *Pilea microphylla* conferred 80% protection in Swiss albino mice and a DRF of about 1.12.	900 mg/kg b.wt.	124
Syzygium cuminii (Linn.) Skeels	Myrtaceae	*In vivo* evaluation established its radioprotective activity where it was found to reduce radiation-induced sickness, gastrointestinal and bone marrow deaths	80 mg/kg b.wt.	3
		Treatment of human peripheral blood lymphocytes with leaf extract before gamma radiation (3 Gy) significantly reduced micronuclei induction.	100 µg/ml	86
Tephrosia purpurea (Linn.) Pers.	Fabaceae	Extract protected Swiss albino mice against 5 Gy induced hemopoetic injury.	*	142
Tinospora cordifolia (Thunb.) Miers.	Menispermaceae	A pure arabinogalactan polysaccharide, Genistein provides some protection against radiation-induced intestinal damage in mice. DMF: 1.16.	*	143

* Data not available on radioprotective doses

in the CDF1 treated surviving mice were found to reverse back to their normal levels[128]. Radioprotection of the isolated active principles on normal cell lines has been carried out currently in our laboratory. Pharmacokinetics and pharmacodynamic studies are planned as future studies on these isolated constituents.

Active fraction of *P. microphylla* (PM1), when screened for *in vivo* radioprotection in Swiss albino mice showed 80% protection at a dose of 900 mg/kg, with a DRF of about 1.12. The fraction was also found to protect livers of irradiated mice from depletion of endogenous antioxidant enzymes like glutathione, GST, SOD, catalase and thiols. The fraction conferred protection to the gastrointestinal and hematopoietic system contributing to the overall radioprotective ability[124]. Presently, our team is working on isolating active constiuents from this plant, responsible for these activities.

Ethanolic extract of another plant *F. racemosa* (FRE) exhibited significantly higher steady state antioxidant activity, in a concentration dependent DPPH, ABTS, hydroxyl radical and superoxide radical scavenging and inhibition of lipid peroxidation with IC_{50} comparable with tested standard compounds. *In vitro* radioprotective potential of FRE studied using micronucleus assay in irradiated Chinese hamster lung fibroblast cells (V79), revealed maximum radioprotection at 20 µg/ml of FRE, with administration 1 h prior to 0.5, 1, 2, 3 and 4 Gy gamma-irradiation. Based on all these results, *F. racemosa* can be considered a potent antioxidant and a probable radioprotector[110].

Our team has also worked on a few synthetic molecules in this direction and the results obtained till now have been summarised below:

1. Pre-treatment with 5-amino salicylic acid (5ASA) significantly reduced the micronuclei counts to 40-50% compared to radiation control, giving a dose modification factor (DMF) of 2.02 (MPCE) and 2.53 (MNCE)[145].
2. Sulfasalazine (SAZ) treatment at 120 mg/kg b. wt. showed optimum protection without toxicity.

At this dose, SAZ produced >60% reduction in the radiation-induced percent aberrant metaphases and micronucleated erythrocytes. SAZ protected mice against RT-induced chromosomal damage and cell cycle progression delay. SAZ also protected plasmid DNA (pGEM-7Zf) against Fenton's reactant-induced breaks, suggesting free radical scavenging as one of the possible mechanism for radiation protection[146].

3. 3,3'-Diselenodipropionic acid (DSePA), a diselenide and a derivative of selenocystine, was evaluated for *in vivo* radioprotective effects in Swiss albino mice, at an intraperitoneal dose of 2 mg/kg b. wt., for 5 days before whole-body exposure to gamma-radiation. DSePA improved the 30-day survival of irradiated mice by 35.3%. The mRNA expression analysis of genes revealed that DSePA augmented GADD45alpha and inhibited p21 in both spleen and liver tissues. DSePA also inhibited radiation-induced apoptosis in the spleen and reversed radiation-induced alterations in the expression of the proapoptotic BAX and the antiapoptotic Bcl-2 genes[147].

In line with the above studies and results, our team is aiming to work in this direction targeting the molecular and signalling pathways involved.

Prospective aspects of herbal radioprotectors

Plants are naturally gifted with the ability to withstand the harmful radiations from the sun. Therefore, it can be said that they are equipped with several defensive machineries to protect themselves from the radiation stimulated injuries and oxidative stress. The use of phytochemicals in radioprotection has received much attention in the last decade owing to certain discoveries with special properties as antioxidants. Generally, they are popular because the phytochemicals are lower in toxicity in human beings (as many of these are used in alternative medicine in Asian countries for centuries), easy availability, inexpensive and good radioprotection exhibited in preclinical studies. The radioprotective activity of phytochemicals may be mediated through several mechanisms such as free radical scavenging, improvement in the antioxidant status, and anti lipid-peroxidation potential, conferred due to the presence of variety of phenolic hydroxyl gropus attached to the ring structure[148]. Polyphenols especially flavonoid glycosides, isoflavones and their derivatives (quercetin, catechin, myricetin, luteolin, orientin, naringin, apigenin, etc.) have ketone groups conjugated to aromatic rings which are activated by electron donor substituents, thus inhibiting energy transfer, suppressing oxidative stress and stabilizing redox processes in cells[149]. The polyphenols may up-regulate mRNAs of antioxidant enzymes such as catalase, glutathione transferase, glutathione peroxidase and superoxide dismutase, thus counteracting the oxidative stress induced by ionizing radiations[150]. Up-regulation of DNA repair genes and inhibition of genes such as protein kinase C (PKC), mitogen activated protein kinase (MAPK), cytochrome P-450, and nitric oxide may also protect against radiation-induced DNA damage. Herbal extracts efficiently restore the disturbed equilibrium during radiation injury, in a collective and holistic manner owing to their varied phytochemical spectrum[151].

Conclusion

The scope in the field of herbal formulations lies in characterisation of the responsible phytoconstituents followed by structural elucidation. Further, studies may be designed to bring out lead radioprotector molecules in the market with patient acceptable profile. The phytochemicals exhibit applications not only in radioprotection but also in cancer chemotherapy owing mainly to their antioxidant properties.

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