REVIEW

Plant Extracts and Plant-Derived Compounds: Promising Players in Countermeasure Strategy Against Radiological Exposure: A Review

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Abstract

Radiation exposure leads to several pathophysiological conditions, including oxidative damage, inflammation and fibrosis, thereby affecting the survival of organisms. This review explores the radiation countermeasure properties of fourteen (14) plant extracts or plant-derived compounds against these cellular manifestations. It was aimed at evaluating the possible role of plants or its constituents in radiation countermeasure strategy. All the 14 plant extracts or compounds derived from it and considered in this review have shown some radioprotection in different *in vivo*, *ex-vivo* and or *in vitro* models of radiological injury. However, few have demonstrated advantages over the others. *C. majus* possessing antioxidant, anti-inflammatory and immunomodulatory effects appears to be promising in radioprotection. Its crude extracts as well as various alkaloids and flavonoids derived from it, have shown to enhance survival rate in irradiated mice. Similarly, curcumin with its antioxidant and the ability to ameliorate late effect of radiation exposure, combined with improvement in survival in experimental animal following irradiation, makes it another probable candidate against radiological injury. Furthermore, the extracts of *P. hexandrum and P. kurroa* in combine treatment regime, *M. piperita, E. officinalis, A. sinensis*, nutmeg, genistein and ginsan warrants further studies on their radioprotective potentials. However, one that has received a lot of attention is the dietary flaxseed. The scavenging ability against radiation-induced free radicals, prevention of radiation-induced lipid peroxidation, reduction in radiation cachexia, level of inflammatory cytokines and fibrosis, are some of the remarkable characteristics of flaxseed in animal models of radiation injury. While countering the harmful effects of radiation exposure, it has shown its ability to enhance survival rate in experimental animals. Further, flaxseed has been tested and found to be equally effective when administered before or after irradiation, and against low doses (≤5 Gy) to the whole body or high doses (12-13.5 Gy) to the whole thorax. This is particularly relevant since apart from the possibility of using it in pre-conditioning regime in radiotherapy, it could also be used during nuclear plant leakage/accidents and radiological terrorism, which are not pre-determined scenarios. However, considering the infancy of the field of plant-based radioprotectors, all the above-mentioned plant extracts/plant-derived compounds deserves further stringent study in different models of radiation injury.

Keywords: Radiation - plant extracts - antioxidant - inflammation - fibrosis - radioprotection

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Introduction

Human beings have been and, will be exposed to different doses of radiation naturally, accidentally or while undergoing therapy. The concern of radiation hazards increases with the use of more and more radiation clinically, particularly, as a treatment regime for different types of cancers. At the same time, radiation exposure, because of nuclear plant leakage/accidents, and the threat of radiological terrorism has compounded our fear of radiation hazards.

Radiation, particularly the ionizing radiation (IR), has been known to cause different types of effects in biological systems ranging from oxidative damages caused by ionization products, free radicals, and reactive oxygen species (ROS) to damages to DNA and its interaction with macromolecules such as proteins (Chen et al., 2007; Swarts et al., 2007; Sharma et al., 2008; 2009; Shuryak and Brenner, 2010; Cramers et al., 2011; Ramachandran and Nair, 2011; Sharan et al., 2011; Mukherjee et al., 2012; Barg et al., 2013; Francois et al., 2013). The interactions of these agents with cells has been shown to cause alterations in the gene expression pattern, mutations, weakening of repair mechanisms (Little, 2000; Sharma et al., 2009;

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Cramers et al., 2011; Mukherjee et al., 2012; Francois et al., 2013; Mikhailenko et al., 2013). Agents that can be radioprotective must counter some or all the damaging effects of radiological exposure in the cell including those mentioned above. Radiation-induced inflammation, an important side effect that contributes to normal tissue injury, has been reported in many species (Linard et al., 2004; Fliedner et al., 2005; Kong et al., 2005; Fleckenstein et al., 2007; Haston et al., 2007; Rodemann and Blaese, 2007; Hill et al., 2011; Multhoff and Radons, 2012; Rastogi et al., 2012; Cho et al., 2013; Fu et al., 2013; Jiang et al., 2013; McCurdy et al., 2013; Moore et al., 2013; Mukherjee et al., 2014). The initial phase of radiation-induced injury is marked by the increase in the synthesis of pro-inflammatory cytokines such as transforming growth factor-beta1 (TGF-β1), tumor necrosis factor-alpha (TNF-α) and several other members of interleukin (IL) family (Linard et al., 2004; Fliedner et al., 2005; Kong et al., 2005; Mehta, 2005; Fleckenstein et al., 2007; Haston et al., 2007; Rodemann and Blaese 2007; Jindal et al., 2009; Hei et al., 2011; Janko et al., 2012; Monceau et al., 2013). The hallmark late effect of radiation exposure in several experimental animals is fibrosis, which is often permanent (Han et al., 2006; Lee et al., 2009; Flechsig et al., 2010; Qiu et al., 2011; Gorshkova et al., 2012; Cho et al., 2013; Ding et al., 2013; Horton et al., 2013). A number of chemical agents showed mitigation to radiation-induced injuries in animal models (Gandhi and Nair, 2004; Parihar et al., 2007; Thotala et al., 2009; Brown et al., 2010; Gao et al., 2012; Kma et al., 2012; Peebles et al., 2012; Alok et al., 2013; Copp et al., 2013).

Among chemical radioprotectors (thiols, aminothiols, thiadiazoles, benzothiazoles, etc) that has been tested clinically, the efficacy is limited by high toxicity and unwanted side effects associated with them (Chen and Okunieff, 2004; Reboul, 2004; Prouillac et al., 2009; Peebles et al., 2012; Copp et al., 2013). Therefore, the focus has been shifted to the evaluation of the radioprotective potential of plants and herbs (Citrin et al., 2010; Pal et al., 2013), and compounds derived from them. This review attempts to evaluate the roles of fourteen (14) plant extracts or plant-derived compounds in mitigation of radiological effects. Although, radioprotection by these plants has been evaluated by looking at the modulation of different cellular/molecular events, the emphasis has been laid on their antioxidant, anti-inflammation and anti-fibrotic potential, and on survival in animal models. This review evaluates the radioprotective effects based on studies on these cellular aspects carried out to test the radioprotective potential of plant extracts or plant-derived compounds in several *in vivo*, *ex vivo* and *in vitro* experimental systems in the last 10-12 years.

Plant Extracts

Chelidonium majus

Chelidonium majus L. (Family: Papaveraceae), is an important plant which has been used for the treatment of many diseases in different part of Western Europe, and in Chinese herbal medicines for centuries. It has multiple applications in folk medicine because of its antitumoral, cytotoxic, anti-inflammatory and antimicrobial activities (Saglam and Arar, 2003; Lanvers-Kaminsky et al., 2006; Biswas et al., 2008; Kulp and Bragina, 2013) and has recently been reported to contain different pathogenesis-related and low molecular inducible antimicrobial peptides (Nawrot et al., 2014). Reports showed that the crude extracts and its main components-isoquinoline, other alkaloids (such as sanguinarine, chelidonine, chelerythrine, berberine, protopine and coptisine), flavonoids and phenolic acids contain anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, antitumoral and many other therapeutic properties (Jiang and Dusting, 2003; Palombo, 2006; Talhouk et al., 2007; Nadova et al., 2008; Zuo et al., 2008; Cahlíkova et al., 2010; Gilca et al., 2010, Kulp et al., 2011, Li et al., 2011; Yao et al., 2011; Zhang et al., 2011; Koriem et al., 2013; Kuenzel et al., 2013). Reports also showed that the methanolic extract of *C. majus* (CME) administered orally to collagen-induced arthritis (CIA) mice (at a dose of 400 mg/kg body weight (b.w.), once a day for 4 weeks) resulted in significant decrease ($p<0.001$) in the absolute number of CD19+B cells, and an increase ($p<0.05$) in the absolute number of CD4+CD25+ regulatory T cells in spleen in comparison to the CIA control mice (CT) (Lee et al., 2007). In the same study, it was also shown that TNF-α ($p<0.05$), IL-6 ($p<0.01$), interferon-gamma (IFN-γ) ($p<0.05$), immunoglobulin (IgG, $p<0.05$; IgM, $p<0.01$) productions in spleen and serum were reduced by CME in compared to CT mice. Since these molecules play key roles in the maintenance of chronic inflammation and tissue damage during the progression of rheumatoid arthritis, it was concluded in this study that CME reduced the inflammatory response resulting into tissue damages in CIA mice by suppressing the generation of pro-inflammatory cytokines including IL-6, TNF-α and IFN-γ. The histological analysis of knee joint from CIA model mice supports this by showing severe cartilage erosion and synovial cell infiltration that can lead to articular destruction. However, mice administered with CME exhibited significantly reduced histological evidence of destruction and inflammation. These findings on the role of CME's ability to reduce inflammation and tissue damage are significant since the cause of these cellular events is the induction of radiation (Kong et al., 2005; Mehta, 2005; McFarland et al., 2012). This was further supported by an earlier report that CME significantly ($p<0.05$) increase the number of bone marrow cells, spleen cells and platelets, and to favour survival (80%) at lethal doses in irradiated mice when administered intraperitoneally, 24 h before irradiation, compared to untreated irradiated control (Song et al., 2003).

Ukrain, an alkaloid thiophosphoric acid derivative of *C. majus*, used as an antitumor drug (Uglyanitsa et al., 2000; Zemskov et al., 2002; Grinevich et al., 2005; Kapoor, 2013), have been reported to minimize the consequences of irradiation in the endocrine system in rats when administered intraperitoneally before irradiation at the dose of 0.4 mg/kg b.w. (Luksa-Lichtenthaeler et al., 2000). Its radiomodulatory effects was also studied in human tumour cell lines such as MDA-MB-231 (breast), PA-TU-8902 (pancreas), CCL-221 (colorectal),

U-138MG (glioblastoma), and normal human skin and lung fibroblastic cells using colony assay, flow cytometry (cell-cycle, annexin-V staining for apoptosis) and Western blotting (Cordes et al., 2002). This experiment involves the use of ukrain in concentrations of one μg/ml for 24 h plus exposure to IR (2-8 Gy). The combination of ukrain+IR exhibited enhanced toxicity in CCL-221 and U-138MG cells, but not in MDA-MB-231 and PA-TU-8902 cells. Radioprotective effect also resulted in normal human skin and lung fibroblasts. Flow-cytometry analyses corroborated the differential cytotoxicity of ukrain. Studies show that CCL-221 and U-138MG cells accumulated in G2 phase of cell cycle after 24 h ukrain treatment, whereas normal fibroblasts remained unaltered. Western blotting of tumor suppressor protein p53 (Tp53) demonstrated non-functional overexpression in all tumour cell lines without affecting p21 (a regulator of cell cycle progression at G1 phase). Annexin-V staining showed no induction of apoptosis after ukrain treatment in comparison with untreated controls in this investigation. This study proposes that ukrain might have potential properties for use in clinical radio chemotherapy. Interestingly, mass spectrometric analysis of ukrain revealed that the known *C. majus* alkaloids-chelidonine, sanguinarine, chelerythrine, protopine and allocryptopine were the major components of ukrain (Habermehl et al., 2006). Also provided the detailed mechanism of action of ukrain in their study on its role in apoptosis induction. In this investigation, apoptosis induction was analysed in a Jurkat T-lymphoma cell model. Fluorescence microscopy analysis revealed that the ukrain treatment (10 μg/ml for 24 h) triggered morphological alterations that are the hallmark of apoptotic cell death including chromatin condensation, nuclear shrinkage and fragmentation. Flow cytometry analysis revealed that it induced a concentration (5, 10 and 50 μg/ml ukrain for 24 h), and time (3, 6, 12 and 24 h treated with 10 μg/ml ukrain)-dependent increase of apoptotic rates in Jurkat vector cells compared to the respective untreated controls. Ukrain (10 μg/ml) also induced depolarisation of the mitochondrial membrane potential and activation of caspase-8 and -3 within 6 h after treatment. Results also show that the expression of caspase-8 and Fas-associated protein with death domain (FADD) was not essential for ukrain-induced apoptosis. Expression of cFLIP-L (FLICE inhibitory protein; a caspase-8 inhibitor) or resistance to death receptor ligands also did not interfere with ukrain-induced apoptosis. Moreover, over-expression of anti-apoptotic proteins Bcl-2 (B-cell lymphoma 2) or Bcl-xl (B-cell lymphoma-extra large) and expression of dominant negative caspase-9 partially reduced ukrain-induced apoptosis pointing to Bcl-2 controlled mitochondrial signalling events. Reports indicated that ukrain-mediated apoptosis might operate via a death receptor independent mitochondrial pathway, initiated by the release of caspase activators such as cytochrome c and SMAC (small mitochondria-derived activator of caspases) from the mitochondria. These activators might then activate the initiator caspases other than caspase-8, which in turn activate the effector caspases such as caspase-3 to accomplish apoptosis. The study showed that constituents of ukrain such as sanguinarine, chelerythrine and chelidonine were also potent inducer of apoptosis triggering cell death at concentrations of 0.001mM, while protopine and allocryptopine were less effective. It was also confirmed that similar to ukrain, apoptosis signalling of chelidonine involved Bcl-2 controlled mitochondrial alterations and caspase activation, indicating that the effect of ukrain on apoptosis is largely due to its constituents, particularly chelidonine.

It is evident from the above observations and other studies (Korolenko et al., 2000; Gagliano et al., 2007) that *C. majus* contain constituents that are capable of radioprotection *in vitro* as well as in experimental animals, while being very effective to kill the cancer cell mainly via apoptotic induction. Since radiation is also known to induce apoptosis (Claro et al., 2007; Han et al., 2009; Panganiban et al., 2013), therefore, it is expected that the extract of *C. majus* or its constituent and IR will exhibit synergistic effect in killing of cancer cells, while it exhibited radioprotection in normal cells as mentioned previously.

Hippophae rhamnoides

Hippophae rhamnoides L. (Family: Elaeagnaceae; commonly known as sea-buckthorn) has been reported to possess beneficial properties (Suleyman et al., 2002; Cheng et al., 2003; Zeb, 2004) including antioxidant activity (Goel et al., 2002; Agrawala and Adhikari, 2009). Alcoholic extract of its whole berries (RH-3) was used in the antioxidant study on human malignant glioma (U87 HG) cells (Agrawala and Adhikari, 2009). The reduction in radiation-induced cell toxicity by the extract was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. It was shown that the extract, at a concentration of 7.5 or 10 μg/ml, added to the U87 cell culture, 15 min prior to IR (2 Gy) exposure, resulted in significant ($p<0.01$) reduction in radiation-induced cell toxicity. It was reported that the extract could mitigate cellular and mitochondrial free radicals generated by IR. Prevention of the depletion in mitochondrial membrane potential (studied up to 12h) by the extract further supported the free radical scavenging property of the extract. In the same study, it was also shown that the extract prevented radiation-induced increase in mitochondrial mass at 48 and 72 h post-treatment close to that of control cells. The extract also modulated the apoptotic event. Pre-treatment with the extract resulted in normalizing the radiation-induced lowering in the level of anti-apoptotic protein Bcl-2 at 24 and 48h. Furthermore, the Annexin-V-FITC assay at 12 and 24 h, which was equivalent in pre-treated and irradiated U 87 cells and the un-irradiated control cells, indicated the anti-apoptotic role of the extract upon IR exposure. These observation corroborated the earlier reports of induction of apoptosis by RH-3 in murine thymocytes at the concentration of 100 μg/ml (Goel et al., 2004) and alteration in apoptosis-related genes expression profile in human breast carcinoma cell line Bcap-37 induced by flavonoids from seed residues of *H rhamnoides* using the cDNA microarray technique (Zhang et al., 2005). It has also been reported that RH-3 possess the ability to interact with chromatin and DNA, and prevent radiation-induced lethality, lipid peroxidation

and DNA damages (Kumar et al., 2002; Jagetia, 2007; Sureshbabu et al., 2008). Other extracts of this plant were also reported to prevent mitochondrial and and genomic DNA damages (Shukla et al., 2006).

RH-3 also provided radioprotective activity in terms of survival of mice against whole body lethal irradiation (10 Gy) (Goel et al., 2003; Prakash et al., 2005). Even the the aqueous extract from *H rhamnoides* exhibited the radioprotective efficacy in mice (Agrawala and Goel, 2002). In this case, pre-irradiation administration of 30 mg/kg b.w. of the extract rendered more than 80% survival in mice against ionizing radiation induced mortality, protected against cytogenetic damage, and enhanced bone marrow cell proliferation as compared to irradiated control mice.

Although the radioprotection exhibited by the extract of *H rhamnoides* in mice looks encouraging, there is a need for more studies to assess its potential as an effective radioprotective agent. Particular interest will probably be on a comparative assessament of its effectiveness in killing the cancer cells, and protecting the normal cells from radiation.

Caesalpinia digyna

Caesalpinia digyna Rottl. (Family: Fabaceae; Subfamily: Caesalpinioideae), a large, scandent, prickly shrub growing wild in the shrub forests of the eastern Himalayas, Nilgiris, Ceylon, Malaya islands etc. have been studied for its free radical scavenging property, and protection from oxidative damages (Srinivasan et al., 2007; Singh et al., 2009). Singh et al. (2009) showed that the methanolic root extract (E1; for polar constituents) and acetone root extract (E2; for non-polar constituents), standardized with bergenin (the active constituent of the plant) content is a potent inhibitor of superoxide ($O_2^{\bullet-}$; xanthine/xanthine oxidase method), hydroxyl ($^{\cdot}OH$) and 2, 2'-diphenyl picrylhydrazyl hydrate (DPPH) radicals (nanosecond pulse radiolysis technique, which were generated upon by 13-15 Gy IR exposure (Dose rate of 40 Gy/min). Bergenin was also isolated in the pure form from E1 and characterized by infrared, nuclear magnetic resonance and liquid chromatography-mass spectrometry analysis. It was found to show that E1 was more effective than E2 in scavenging the $O_2^{\bullet-}$ and DPPH radicals, and its activity was even higher than that of pure bergenin at similar concentration. IC_{50} values (μg/ml; the effective concentration of sample required to scavenge radicals by 50%) for scavenging DPPH free radicals were 2.66±0.13 (E1) *vs* 4.97±0.24 (E2) and 377.5±18.8 (Bergenin). Similarly, the IC_{50} values for inhibition of $O_2^{\bullet-}$ were 6.6±0.3 (E1) *vs* 8.9±0.4 (E2) and 23.2±1.2 (Bergenin). However, reports indicated the similarity between $^{\cdot}OH$ reaction with the extracts and bergenin. Evaluation of the *in vitro* radio protecting ability of was in terms of inhibition of IR-induced protein carbonylation in BSA (bovine serum albumin), DNA damage in plasmid pBR322 and lipid peroxidation in liposomes. A similar pattern was displayed by IC_{50} values for DNA damage (50 Gy), protein carbonylation (50 Gy) and lipid peroxidation (240 Gy), which was lowest in case of E1 in comparison to E2 or bergenin. The observed antioxidant properties of *C digyna* were attributed to homoisoflavonoids, flavonoids and bergenin isolated from methanolic and ethanolic extracts of the roots (Roy et al., 2012).

In vitro radioprotective studies have thus shown that the polar constituents of the root extract of *C digyna* were more effective than the non-polar ones. However, further investigations in experimental animals using the methanolic root extract containing the polar constituents would be necessary to realize its true radioprotective potential.

Curcuma longa

The rhizome of Indian spice plant *Curcuma longa* L. (Family: Zingiberaceae) yields turmeric that contains curcumin (diferuloylmethane) as a naturally occurring biphenolic compound, which has been found to possess antioxidant, anti-inflammatory and anti-tumor activity in a variety of animal models of human diseases (Anand et al., 2008; Hatcher et al., 2008) and radioprotective property in different experimental systems (Nemavarkar et al., 2004; Pal and Pal, 2005; Jagetia, 2007). It was demonstrated in systemic LPS-induced sepsis that curcumin inhibit transmigration and infiltration of neutrophils from blood vessels to the underlying liver tissue, suppressing damage to the tissue (Madan and Ghosh, 2003). Another study revealed the antioxidant potential of curcumin against radiation-induced oxidative stress (Lee et al., 2010). In this study, pulmonary microvascular endothelial cells (PMVEC) isolated from mouse lungs were pre-treated with curcumin (5, 10, 25, 50, 100 μg) 4 h prior to γ-irradiation (2 Gy; dose rate of 1.7 Gy/min). ROS, which was assayed from fluorescent images of cells using dichlorodihydrofluorescein diacetate (H_2DCFDA), was found to get significantly reduced in curcumin-treated irradiated cells, in a dose-dependent manner, compared to untreated irradiated controls ($p<0.0001$). The fluorescence did not increase with either radiation or addition of curcumin in control experiments using 5-(and-6)-carboxy-2', 7'-dichlorofluorescein diacetate (carboxy-DCFDA), a non-oxidizable analog of H_2DCFDA. These observation corroborated earlier report that radiation-induced DNA damages and lipid peroxidation was mitigated by curcumin treatment in cultured human lymphocytes (Srinivasan et al., 2006) and was further supported by the observation that radiation-induced lipid peroxidation was mitigated by its treatment in murine skin (Jelveh et al., 2013).

Clonogenic survival assay after treatment of murine Lewis lung carcinoma (LLC) cells or PMVEC with 10 or 25 μM curcumin or dimethyl sulfoxide (DMSO; vehicle control) 4 h prior to IR exposure (2, 4 and 6 Gy) revealed that curcumin was able to radiosensitize these cells but not normal endothelial cells (Lee et al., 2010). Curcumin treatment resulted in significant increase ($p<0.05$) in radiation killing of the LLC cells in a dose-dependent manner (particularly at 6 Gy) but did not increase the killing of PMVEC cells. This study also shows that dietary curcumin supplementation did not ameliorate markers of acute radiation pneumonitis in mice. At 3 weeks after a single fraction of radiation (13.5 Gy) to the whole thorax, mice develop radiation pneumonitis.

Analysis of bronchoalveolar lavage fluid (BALF) to measure lung inflammation and injury have shown that in comparison to mice fed with the control diet, mice fed with 5% curcumin for 2 weeks prior to irradiation did not exhibit any significant differences in BALF measures of inflammatory cell accumulation (macrophages or neutrophils) or alveolar damage (BAL proteins). However, curcumin exhibited antifibrotic activity in mice in the same treatment regime. It was reported that irradiated lungs from mice fed with 5% curcumin had a 45% increase in hydroxyproline (OH-proline) content after irradiation, while irradiated lungs from mice fed with the control diet had a 112% increase from non-irradiated controls ($p=0.05$). In the same study, Kaplan-Meier survival analysis showed a statistically significant improvement ($p<0.0001$) in survival rates in 5% curcumin-fed compared to control-diet fed mice, which was 45% compared to 23%, respectively.

Significant reports are also available indicating the ability of curcumin to confer radioprotection in normal cells (Kunwar et al., 2007) and to inhibit radioprotection and modulation of apoptosis related genes in human cancer cells as revealed by the microarray analysis (Aravindan et al., 2008). Evidently, curcumin has displayed its ability to scavenge radiation-induced ROS *ex vivo*, and caused reduction in radiation-induced fibrosis, thereby increasing survival in irradiated mice. It further triggered radiosensitization of cancer cells and radioprotection in normal cells. All these, combined with other beneficial effects of curcumin reported elsewhere as mentioned earlier, probably makes it a good candidate against radiological damages.

Linum usitatissimum

Linum usitatissimum L. (Family: Linaceae) produces flaxseed (FS), rich in omega-3 fatty acids and lignans, and has been reported to exhibit antitumor (Wang et al., 2005; Saarinen et al., 2006; Bergman et al., 2007; Zhang et al., 2008; Chen et al., 2009; Lindahl et al., 2011), free radical-scavenging ability and prevention against oxidative tissue damages when administered prior to radiation exposure (Kinniry et al., 2006; Dupasquier et al., 2007; Lee et al., 2008; Razi et al., 2011). Antioxidant action of FS was evaluated in PMVEC, isolated from murine lungs (Lee et al., 2009). It was grown to confluence on culture dishes and treated with increasing concentrations (0.1, 0.2, 0.5, 10 and 25 μM) of secoisolariciresinol diglucoside (SDG), isolated from FS. Cultures were then exposed to 2 Gy of IR (Dose rate of 1.14 Gy/min). As mentioned earlier (Lee et al., 2010), ROS produced by the pulmonary endothelium was detected by H_2DCF-DA fluorescence. It was found that a significant increase in ROS generation occurred shortly after radiation (assess by fluorescent imaging), which was diminished in a dose-dependent manner by SDG ($p<0.001$). In the same study (Lee et al., 2009), it was demonstrated that mice fed with 10% FS as dietary supplementation, 3 weeks before irradiation (a single fraction of 13.5 Gy of X-radiation to the whole thorax) could mitigate oxidative lung injury. In this case, it was further revealed by BALF analysis that white blood cell (WBC) influx and lipid peroxidation was significantly ($p=0.001$) reduced in irradiated FS-fed mice as compared to irradiated mice fed with control diet. Reverse transcriptase-polymerase chain reaction (RT-PCR) analysis of markers of lung injury such as Bax, p21 and TGF-β1 expression levels at 24 h post-thoracic irradiation have shown that 10% FS-fed irradiated mice had significantly ($p<0.001$) reduced expression of Bax, p21 and TGF-β1 compared to control diet fed irradiated mice. These observations were very significant since these biomarkers show strong correlation with the severity of radiation-induced lung injury in different experimental models (Bouvard et al., 2000; Machtay et al., 2006; Wang et al., 2012). Analysis of hematoxylin and eosin (H and E) stained lung sections from all animals that survived the 4-month long-term experiments demonstrated that IR induced influx of alveolar neutrophils (PMN) and macrophages (MF) were significantly ($p<0.0001$) reduced by 10% FS compared to mice fed with control diet. Moreover, at 4-month post-irradiation, the trichrome staining of lung tissue showed reduction in the degree of radiation fibrosis and structural damage in 10% FS treated group in comparison to control diet-fed irradiated mice. The histopathological changes were scored as radiation fibrotic index (FI) and it indicated significant decrease in lung fibrosis in irradiated lungs from 10% FS *vs* 0% FS fed irradiated mice ($p=0.005$). The fibrotic changes were supported by the hydroxyproline (OH-proline) assay result, which showed significantly decreased lung OH-proline content four months after IR exposure as compared to irradiated mice fed control diet ($p=0.002$).

Using a different strategy, Christofidou-Solomidou et al. (2011) evaluated the role of 10% FS administered to mice at 3 weeks prior to a single dose of 13.5 Gy (Dose rate of 1.7 Gy/min) thoracic irradiation, and at 0, 2, 4 and 6 weeks following the irradiation. The mice were sacrificed at 4-months post-irradiation. Analysis of radiation-induced oxidative damage in lungs was carried out by determining the amount of malondialdehyde (MDA/g of wet lung tissue), a product of lipid peroxidation. It was revealed that mice fed with a 10% FS diet (prior to or post-irradiation) maintained a significantly ($p\leq 0.0002$) lower MDA level at 4 months post-IR exposure in all the treatment groups as compared to irradiated mice fed with 0% FS diet. Reports indicated that among the irradiated FS-fed groups and the non-irradiated FS group, there was no statistically significant variation. Analysis of the BALF revealed a reduction in radiation cachexia in all FS-fed groups compared to irradiated controls. In these groups, particularly in IR+FS (0 week) and IR+FS (2 weeks), the inflammatory cell (such as WBC) influx to lungs decreased significantly ($p\leq 0.05$) in comparison to irrradiated group with 0% FS. Estimation of total proteins in BALF and histopathlogical analysis revealed that FS diet significantly decreased lung injury and edema in all the IR+FS treated group of mice by decreasing the IR-induced alveolar protein levels ($p<0.01$) when administered before or after irradiation. Since there is an indication that radiation pneumonopathy associates with compromised pulmonary function resulting in poor oxygenation levels, the arterial blood oxygenation levels was compared in the treatment groups. Using the pulse oximetry, a non-invasive way

of determining arterial blood oxygenation levels, it was shown that mice fed with 10% FS diet had an significant ($p \leq 0.05$) increase percentage of arterial O_2 levels, particularly in IR+FS (0 week) and IR+FS (2 weeks) compared to mice fed 0% diet following IR exposure. Additionally, cytokine analysis of BALF in mice sacrificed 4 months post-irradiation indicated a significant ($p \leq 0.0005$ to ≤ 0.05) reduction in the levels of IL-1β, IL-2, IL-4, macrophage inflammatory protein-1α (MIP-1α), IL-6, IL-12, IL-17 and vascular endothelial growth factor (VEGF), in all of the irradiated FS diet fed groups as compared to irradiated mice on control diet (Christofidou-Solomidou et al., 2011). Reports indicate a similar reduction even after delaying FS diet by as long as 6 weeks post-radiation exposure. FS exhibited radioprotective effects against experimental radiation fibrosis as indicated by OH-proline content and collagen staining in the lungs of mice at 4 months post-irradiation. All irradiated FS-fed mice had significantly ($p \leq 0.005$) decreased fibrosis compared to those fed with 0% FS. Lung OH-proline content ranged from 96.5±7.1 to 110.2±7.7 μg/lung in all irradiated FS-fed mouse groups, as compared to 138±10.8μg/lung for mice on 0% FS. This finding corroborated earlier report of Lee et al. (2009) on mitigation of radiation-induced fibrosis by FS. The OH-proline data was supported by the fibrotic index and histology of lung tissue which showed significant ($p \leq 0.005$) reduction in fibrosis in lungs from irradiated 10% FS-treated mice in comparison to irradiated mice treated with 0% FS diet. In was also reported that 10% FS conferred protection against radiation-induced fibrosis in both pre- and post-treatment regime. Moreover, mice exposed to radiation and fed with 10% FS had 70-80% survival in comparison to 40% in irradiated mice without FS, monitored over a period of 4 months. It was also seen in this experiment that 10% FS diet, when started preventively, i.e., 3 weeks prior to irradiation, survival was enhanced significantly (70%; $p<0.05$) in comparison to irradiated groups. The enhanced survival mice on FS diet could be attributed to its effect on the overall health of the mice since it was shown that IR exposure decreased the body weight of animals on the 0% control diet significantly ($p \leq 0.01$) as compared with their non-irradiated counterparts. It was also shown that the 10% FS supplementation, whether given 3 weeks prior to irradiation or several weeks thereafter, significantly ($p \leq 0.01$) prevented IR-induced weight loss. These results were further supported by similar observations following a single-dose (13.5 Gy) thoracic x-ray treatment in mice fed with 10% FS and evaluated 4 months post-irradiation (Christofidou-Solomidou et al., 2012; Pietrofesa et al., 2013). Even in these cases, radioprotection was conferred by decreasing inflammation, lung injury (Pietrofesa et al., 2013) and eventual fibrosis (Pietrofesa et al., 2013) while improving survival in mice (Christofidou-Solomidou et al., 2012; Pietrofesa et al., 2013). It was also reported that 10% FS treatment up-regulated gene expression as well as protein levels of protective antioxidant enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1). Importantly, the dietary FS also induced radiosensitizing effects in the murine model of metastatic lung cancer. In the same study, it was shown that FS conferred protection against radiation pneumonopathy *in vivo* without hindering the tumoricidal effects of radiotherapy (Christofidou-Solomidou et al., 2012).

Clearly, FS with its potent effect against radiological challenge in *ex vivo* as well as animal models, could be an ideal candidate for countermeasure strategy against radiation. Apart from the beneficial counter-radiation effects, that include antioxidant, anti-inflammation, anti-fibrosis and enhancement of survival in experimental animals, it was effective when administered before or after irradiation.

Podophyllum hexandrum and Picrorhiza kurroa

Plants with radioprotective properties also include *Podophyllum hexandrum Royale* (Family: Berberidaceae) and *Picrorhiza kurroa* (Family: Scrophulariaceae). These plants are abundant in the Himalayas at an altitude of about 3000-5000 meters. The roots and rhizomes of these plants have been known to possess several medicinal properties (Arora et al., 2005; Tiwari et al., 2012; Hussain et al., 2013; Lachumy et al., 2013; Upadhyay et al., 2013).

A novel fractionated nonpolar extract (REC-2003) of *P. hexandrum* have shown radioprotective efficacy, *in vitro* as well as *in vivo* system (Arora et al., 2010). The free radical scavenging activity of REC-2003 was found to be >75% (20 μg/ml). The maximum superoxide scavenging activity (57.56±1.38%) was recorded at 1 mg/ml concentration. While more than 30% inhibition of nitric oxide radicals was observed at concentrations >0.5 mg/ml, hydroxyl radical scavenging was exhibited at the concentration of 100-600 μg/ml. Ninety percent protection to human erythrocytes against radiation-induced lipid peroxidation was reported at 75 μg/ml. It also rendered protection to DNA at this dose. In the same experiment it was demonstrated that REC-2003 (8 mg/kg BW; intraperitoneal (i.p.),-30 min) rendered >80% total body protection in mice against lethal radiation (10 Gy) in a 30-day survival assay. Phytochemical characterization also revealed the presence of flavonoids along with podophyllotoxin and epi-podophyllotoxin in this extract. The corroborated earlier report on radioprotective ability of *P. hexandrum* extracts *in vitro* (Chawla et al., 2005; 2006), and in mice against radiation exposure (Samanta et al., 2004; Arora et al., 2005; Chawla et al., 2005; Goel et al., 2007; Gupta et al., 2007; Jagetia, 2007; Rajesh et al., 2007; Lata et al., 2009; Dutta et al., 2012). A bioactive molecule, 3-O-beta-D-galactoside of quercetin, present in an aqueous-ethanolic extract of *P. hexandrum* was isolated and characterized by acid hydrolysis, LC-MS, LC-APCI-MS/MS and 13C NMR spectra (Chawla et al., 2005). It was demonastrated that this molecule also possesses the radioprotective property. It has also been reported that *P. hexandrum* extract provides protection from radiation (10 Gy) by countering the radiation-induced reduction in antioxidant enzymes such as glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) activity (Samanta et al., 2004), by modulating the mitochondrial system (Gupta et al., 2004), and by modulation of expression of the proteins associated with apoptosis in mice (Kumar et al., 2005).

The combined radioprotective effects of *P. hexandrum*

and *P. kurroa* as a pre- and post-treatment regimen have been reported (Gupta et al., 2008). This study involved the exposure of mice to a lethal dose of 10 Gy γ-radiations (Dose rate of 0.51-0.45 cGy/sec) to the whole body. Administration of the rhizome extract of *P. hexandrum* (25 mg/kg b.w.; called REC-2001) 1 h prior and *P. kurroa* (8 mg/kg b.w.; called pkre) 1h post-irradiation was oral. The antioxidant potential of these extract was evaluated in terms of ferric reducing activity of plasma (FRAP). Findings suggested that the synergistic effect of the extracts resulted in statistically significant ($p<0.001$) increase in the ferric reduction potential of plasma at 4h as compared to the irradiated control. The early inflammatory response estimated in term of total leucocytes count (TLC) and haemoglobin (Hb) concentration in peripheral blood drawn from the heart of mice, revealed that at 10 day post-irradiation, there was significant increase in TLC ($p<0.05$) and Hb ($p<0.01$) in REC-2001+10 Gy +pkre group compared to 10 Gy alone or REC 2001+10 Gy groups. In the REC-2001+10 Gy+pkre group, the recovery in leucocyte counts and Hb concentration was much faster and the values became comparable to that of untreated control animals by 30th day post-irradiation ($p<0.05$). Even the endogenous colony counts on spleen have shown that REC-2001+10 Gy+pkre group had 15±0.18 colony counts/spleen *vs* none in untreated control or radiation (10 Gy) groups. Observations made in the same study suggested that animals in radiation alone group died within 12 days of exposure. However, the combined effects of extract of *P. hexandrum* and *P. kurroa* have shown to increase survival by 55% against the lethal dose of radiation exposure to the whole body at 30 days post-irradiation period. As reported earlier with other plant extracts, here also the beneficial effects of the plant extracts on the overall health of the mice largely attributes their enhanced survival.

Reports revealed that mice in REC-2001+radiation+pkre group exhibited only up to 20% loss of the original body weight compared to loss of 45-60% of original body weight of animals in radiation control groups.

The evaluation of the radioprotection conferred by the synergistic effect of two plant extracts combined together in a pre-treatment and post-treatment regime was quite interesting and significant. The very fact that the two plant extracts synergistically countered the lethal dose of 10 Gy of IR in mice and increased survival by 55% on the 30th day when none of the untreated irradiated mice could survive beyond 12th day, was indeed remarkable. Probably, the combination of the extract of *P. hexandrum* and *P. kurroa* in the regime already mentioned can be a good choice for radioprotection against higher doses of radiation exposure and deserves further investigation in different models of radiation injury.

Myristica fragrans

Nutmeg, the dried seed kernel of aromatic tree, *Myristica fragrans* Houtt. (Family: Myristicaceae) have been reported to possess various beneficial properties including anti-inflammatory, hepatoprotective and anticancer activities (Morita et al., 2003; Eklund et al., 2005; Tajuddin et al., 2005; Chirathaworn et al., 2007; Piaru et al., 2012; Zhang et al., 2012; Thuong et al., 2013). In the antioxidant study (Sharma and Kumar, 2007), 10 mg/kg b.w. of the alcoholic seed extract was administered to mice orally once a day for three days. On the 3rd day, 30 min after the administration of the extract, mice were exposed to 8 Gy of γ-radiation (Dose rate of 0.93 Gy/min). Here, it was shown that the extract of *M fragrans* (MF) was able to reduce the lipid peroxidation (assayed in testis) significantly ($p<0.01$ and <0.001) compared to untreated irradiated group at day 1, 3, 7, 15 and 30 following irradiation. Similar effect of MF ($p<0.05$, $p<0.01$ and <0.001) was seen in case of acid phosphatase (ACP) activity (mg Pi/gm/h) in testis of mice at the same period following irradiation in comparison to radiation alone group. However, alkaline phosphatase (ALP) activity (mg Pi/gm/h) in the testis at these period following irradiation showed statistically significant ($p<0.05$, $p<0.01$ and <0.001) increase in activity compared to irradiated untreated groups. A significant ($p<0.01$ and <0.001) increase in reduced glutathione (GSH, the vital biological defence molecule against oxidative damage) in liver was reported in this study, in comparison to radiation alone group at day 1, 3, 7, 15 and 30 following irradiation. Some of the recent works (Akinboro et al., 2011; Piaru et al., 2012) further supported the antioxidant property of nutmeg.

For survival study, following similar treatment regimen was essential. On the 3rd day, 30 min after the administration of the extract, mice were exposed to 6, 8 and 10 Gy of γ-radiation. At 6 Gy, 30% of untreated irradiated mice died by 14 days after irradiation whereas all the mice survived in MF treated groups at the corresponding time period. Similarly, at 8 Gy MF treated group, there was >80% survival compared to >40% death in irradiated group without MF at 14 days after radiation exposure. However, there was no survival in 10 Gy radiation alone group compared to >20% survival in MF treated group at 14 days post-irradiation. Overall, the survival at 30 days assessament period after exposure to 6, 8 and 10 Gy post-irradiation exhibited significant improvement (20-40%) in mice treated with MF compared to untreated control. Similar to the combined treatment regime of the extracts of *P. hexandrum* and *P. kurroa* mentioned earlier, the alcoholic seed extract of *M fragrans* too was able to protect the mice from high dose of 8-10 Gy of IR.

Comparison of the 30th day survival of mice indicate that nutmeg seed extract resulted in 20-40% survival, whereas the combined treatment of of the extract of *P. hexandrum* and *P. kurroa* led to 55%, compared to untreated irradiated mice. However, with the ease of using just one extract, and comparable improvement in survival, it could be advantage nutmeg *vs* combined treatment of *P. hexandrum* and *P. kurroa* for high dose radiation exposure. The radioprotective properties of nutmeg was also supported by the analyses of lignans present in the aqueous extract of fresh nutmeg mace in mammalian splenocytes (Checker et al., 2007). Radioprotection was conferred in splenocytes, characterized by reduction in radiation-induced intracellular ROS production and DNA damages. Therefore, further stringent evaluation of the radioprotective property of *M fragrans* is warranted in different models of radiological exposure.

Coleus aromaticus

Coleus aromaticus Benth. (Family: Laminaceae), is an important medicinal plant used widely to treated a number of illness (Lans et al., 2007; Pritima and Pandian, 2007) and has been reported to protect liver and other disorders in rats (Choudhary, 2009; Vijayavel et al., 2013). The antioxidant potential of this plant was investigated in various standard *in vitro* free radical generating model systems that included DPPH, 2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), O_2•-, ˙OH and nitric oxide (NO) (Rao et al., 2006). Different concentrations (10-120 μg/ml) of hydroalcoholic extract of *C aromaticus* (CAE) showed concentration-dependent increase in radical scavenging ability against various free radicals. Specifically, CAE scavenged the DPPH radicals with the maximum scavenging activity of 80% at 80 μg/ml. Similarly, it also demonstrated ABTS radical scavenging activity with 74.25% at 80 μg/ml. CAE also was effective in scavenging $O_2^{\bullet-}$, ˙OH and NO˙ in a concentration-dependent manner (10-120 mg/ml) with the maximum reaching at a concentration of 80 μg/ml for NO˙ and 100 μg/ml for $O_2^{\bullet-}$ and ˙OH. CAE was shown to have the ability to prevent lipid peroxidation with a maximum inhibition of 33% at a concentration of 60 μg/ml. In the same study, the radioprotective effect of CAE was evaluated by its ability to prevent radiation-induced cytogenetic damage, assessed by micronuclei (MN) formation in Chinese hamster lung fibroblast (V79) cells. It was observed that two Gy of γ-radiation resulted in 16.47% of micronucleated cells and 17.87% of total micronuclei. Cell cultures exposed to CAE with different concentrations (1, 5, 10, 20, 50, 100, 500 and 1000 μg/ml) which was added 1h prior to 2 Gy of γ-radiation exposure, resulted in a significant (p<0.05) decrease in the percentage of micronucleated cells and total micronuclei when compared with the radiation alone group. The maximum reduction (51%) in the radiation-induced MN formation was observed when 5 μg/ml of CAE was administered before 2 Gy of γ-radiation exposure. It was also reported that the CAE by itself did not produce any genotoxic or clastogenic effect on V79 cells at 5 μg/ml.

The ability of CAE to inhibit free radicals in different *in vitro* model systems and *in vitro* radioprotective property probably requires further tests using *in vivo* system for expanding its radioprotective potentials.

Mentha piperita

Another Plant of Interest for Radioprotection is the Aromatic Plant Peppermint, *Mentha Piperita* L. (Family: Lamiaceae). It has been reported to contain several important properties including antioxidant, antiperoxidation, radical-scavenging (Grigoleit and Grigoleit, 2005; Sharma et al., 2007; Samarth et al., 2008; Samarth and Samarth, 2009; Alves et al., 2012; Samojlik et al., 2012; Tayarani-Najaran et al., 2013) and anticancer properties (Kasem et al., 2014). The aqueous extract of *M. piperita* (ME) has been shown to be radioprotective in mice when administered prior to 8 Gy of γ-radiation exposure to whole body (Samarth and Kumar, 2003). It was observed in this study that animals which received ME at a dose of 1 g/kg b.w./day for three consecutive days before irradiation displayed protection in hematopoietic tissue against radiation-induced injury as indicated by endogenous spleen colony assay and spleen weight. On 10th day after irradiation, spleen weight of irradiated mice was 20.60±1.04 mg compared to 39.00±1.19 mg for irradiated mice pre-treated with ME, which was significantly high (p<0.001). The number of macroscopic colonies was 15.20±0.91 at 10 days post-irradiation in ME treated mice. However, the data in irradiated untreated mice was not obtained since none survived by 10th day. Hematological parameters indicated maximum decrease of the total erythrocytes at 24 h after irradiation, and an increase in the case of ME treated group, which reached close to normal by the 30th day. The value of hematocrit in ME treated mice was also close to normal by 30th day compared to untreated control mice. Even total leucocytes count was close to normal by 20th day in case of ME treated group in comparison to irradiated control group. Samarth et al. (2004) also corroborated these results where they have shown that Mentha oil from *M. piperita* protected the haematopoietic system and enhanced survival of mice against lethal gamma radiation. It was also reported that the level of GSH in ME treated irradiated group was significantly higher in blood (p<0.005) and liver (p<0.001) in comparison to irradiated control mice at 30th day (Samarth and Kumar, 2003). The thiobarbituric acid reactive substances (TBARS) level was significantly lower in blood (p<0.005) and liver (p<0.001) in ME treated mice compared to untreated irradiated mice indicating decrease in lipid peroxidation in liver and blood of treated mice in comparison to untreated controls. The level of ALP in ME treated group was significantly (p<0.001) higher than untreated irradiated control, and was reported to come to normal range by 5th day post-irradiation. At the same time, the level of ACP was significantly (p<0.005) lower than radiation alone group which also came close to normal at 5th day. The survival rate, monitored up to 30 days after total body irradiation was 82% in mice treated with ME as compared to the radiation-alone group, where none could survive by day 30. At the same time, the ME treated group of mice have also shown normal pattern of body weight gain, not observed in untreated controls. The radioprotective property of *M. piperita* was also supported by the observation that its leaf extracts protected radiation-induced damage in testis of Swiss albino mice (Samarth and Samarth, 2009). Moreover, *in vitro* and *in vivo* studies, which showed that ME provided protection against radiation-induced lethality, lipid peroxidation, hematopoietic and DNA damages in mice models further strengthens its radioprotective roles (Jagetia et al., 2007; Samarth et al., 2007). It was reported that its phenolic compounds, flavonoids and flavonols might be responsible for radioprotection (Samarth and Samarth, 2009). Recently, it was shown that Mentha extracts act as a neuron-protective agent against radiation-induced apoptosis in Central Nervous System (Hassan et al., 2013). Gamma irradiated mice pretreated with Mentha extract showed significant improvement in brain apoptosis and stabilization of DNA cycle. It was also reported that the extract could normalized the cell cycle and antioxidant defense system in irradiated mice compared to untreated

irradiated mice. In the same study, it was also shown that Mentha extracts down-regulated p53 expression and up-regulated Bcl-2 domain and therefore, protected the brain structure from extensive damage by radiation. *M. piperita* could thus be another plant with potential use against relatively high dose of IR (8-10 Gy). The ability of its extract to induced cellular antioxidant defence system to confer radiological protection combined with other radioprotective abilities is noteworthy. Moreover, the increase in survival of ME treated irradiated mice (up to 80%), monitored over a period of 30 days where none of the mice survived without ME treatment, speaks for its effectiveness in radioprotection, and therefore warrants further studies to explore its full potential as radioprotective agent.

Aegle marmelos

Aegle marmelos L. (Family: Rutaceae Subfamily: Aurantioideae), commonly known as bael, had been studied for its radioprotective effect using hydroalcoholic extract of its fruit (AME) (Jagetia et al., 2003). In this investigation, MN assay was conducted in cultured human peripheral blood lymphocytes (HPBLs). At a concentration of 5 μg/ml of ME, there was significant ($p<0.01$) reduction in the number of MN formation in HPBLs when added to the culture before exposure to 3 Gy of γ-radiation in comparison with radiation alone control group. Further, it was shown that ME was able to scavenge the $^{\cdot}OH$, $O_2^{\bullet-}$, DPPH and $NO^{\cdot}$ generated *in vitro*. Maximum inhibition in the generation of $^{\cdot}OH$, $O_2^{\bullet-}$ and DPPH radicals was observed at 500 μg/ml of ME. Highest scavenging of $NO^{\cdot}$ was observed at the ME concentration of 400 μg/ml. In addition, ABTS assay measured ME exhibiting total antioxidant activity. Achievement of maximum inhibition of the ABTS+radical was at concentration of 200 μg/ml AME.

The *ex vivo* and *in vitro* radioprotective ability of ME was tested in animal model (Jagetia and Venkatesh, 2005). Mice were administered orally ME 250 mg/kg b.w. orally daily for 5 consecutive days before exposure to 6, 7, 8, 9, 10, or 11 Gy of γ-radiation, monitored over a period of 30 days after irradiation. It was reported that treatment of mice with ME before irradiation reduced the symptoms of radiation sickness and delayed death compared to the irradiated controls. It was also shown that ME protected radiation-induced gastrointestinal and hematopoietic damages. It was also shown that pre-treatment of mice with ME resulted in significant reduction in lipid peroxidation. Significant elevation in glutathione concentration in the liver of mice 31 days post-irradiation was also reported in this study. These results corroborated earlier reports of radioprotection by AME in different tissues of mice against lethal dose of radiation and the resultant increase in survival (Jagetia et al., 2004a; 2004b; 2006) and was further supported by the report that it provided protection against radiation-induced lethality, lipid peroxidation and DNA damage (Arora et al., 2005; Jagetia, 2007; Baliga et al., 2010). However, the extracts of *A marmelos* perhaps requires further investigation in other models of radiation injury to assess its effectiveness in countering radiological damages and also to elucidate its mechanism of action.

Emblica officinalis gaertn or *Phyllanthus emblic**a***

Emblica officinalis gaertn or *Phyllanthus emblica L*. (Family: Euphorbiaceae), extensively used in Indian system of medicine (Krishnaveni and Mirunalini, 2010), has been reported to possess anticancer (Baliga and Dsouza, 2011) and radioprotective properties (Hari Kumar et al., 2004; Arora et al., 2005). In one of these studies involving this plant against radiation-induced damages in mice, its hydroalcoholic fruit extract (EO; 2.5g/kg b.w.) was administered orally once daily, 10 days before a single dose of total body irradiation (7 Gy; dose rate of 1.33 Gy/min) (Hari Kumar et al., 2004). The treatment was stopped at the 10th day before irradiation (Group I), or continued for next 15 day after irradiation (Group II). There was significant improvement in the hematopoietic system which was indicated by TLC at day 9 ($p<0.001$), or BMC viability at day 10 ($p<0.005$) and day 15 ($p<0.001$) in group II *vs* irradiated control or group I mice. Even the Hb content at day 6 exhibited similar pattern. The antioxidant enzyme superoxide dismutase (SOD) in blood showed significant elevation at day 10 and 15 ($p<0.001$), and catalase (CAT) at day 5 ($p<0.005$), 10 and 15 ($p<0.001$) in group II compared to irradiated control or group I. Glutathione peroxidase (GPx), GSH and glutathione S-transferase (GST) in blood also showed similar significant elevation, the maximum being at day 15 post-irradiation ($p<0.001$) in comparison to mice in radiation alone or group I. On day 15 post-irradiation, the level of lipid peroxidation in liver tissue was also reduced ($p<0.001$) in group II compared to irradiated control. A latter study supported this effect of EO on lipid peroxidation and antioxidant enzymes (Jindal et al., 2009). In this investigation, the fruit extract of *Emblica* was administered orally to mice at a concentration of 100 mg/kg b.w., once daily for seven consecutive days before γ-irradiation (5 Gy). A higher number of crypt cell population and mitotic figures in small intestine (jejunum) was observed in EO-treated mice compared to irradiated control at different autopsy intervals of 1 to 30 days post-irradiation. There was depletion in lipid peroxidation and elevation in GSH and CAT levels ($p<0.005$) in the intestine at 1h post-irradiation in EO-treated group *vs* irradiated control. It has also been shown that EO (100 mg/kg b.w.), administered before exposure to 9 Gy γ-radiation increased the survival time and reduced the mortality of mice significantly (Singh et al., 2005). It was also reported that body weight loss in EO was significantly lower than the untreated irradiated controls.

Using human dermal fibroblast cells HS68 (Adil et al., 2010), it has been shown that treatment (24 h before and after irradiation) with EO (10, 20 and 40 μg/ml) resulted in a dose dependent protective (21-30%, $p<0.001$) effect against ultraviolet B (UVB) radiation-induced (10 mJ/cm^2) loss of cell viability. UVB irradiation was shown to significantly increase the apoptotic cells (13.4%) compared to normal untreated cells (2.1%). Treatment with EO at 20 and 40 μg/ml, resulted in decrease in apoptotic cells to 9.8 and 7.1%, respectively. In the same study, it was also reported that treatment of skin fibroblast with EO at 10, 20 and 40 μg/ml significantly ($p<0.001$) reduce the radiation-enhance level of pro-matrix metalloproteinase 1

by about 94%. It was further shown that exposure of skin fibroblast to UVB radiation resulted in 8.7-fold decrease in pro-collagen I levels. However, the reduction in pro-collagen I content was restored by EO treatment at 10, 20 and 40 μg/ml in a range of 47-72% ($p<0.001$). These observations indicated a possible therapeutic use of the EO to prevent radiation-induced fibrosis.

The radioprotective property of EO in mice against sub-lethal doses (5-7 Gy) of IR is quite significant in that it has displayed its ability to induce cellular antioxidant defence system and reduce lipid peroxidation in different organs in response to radiological exposure. Moreover, prevention of collagen damage against non-ionizing radiation such as UVB indicated its antifibrotic effect and needed to be tested against IR as well. Further evaluation of this and other radioprotective effects perhaps will make it a suitable radioprotector against sub-lethal doses.

Plant-derived Compounds

Genistein

Genistein, isolated from *Genista tinctoria* L. (Family: Fabaceae) have been shown to exhibit anticancer property (Regenbrecht et al., 2008; Gullett et al., 2010; Si et al., 2010; Tokalov et al., 2010; Zhang et al., 2010) and confer protection against a range of radiological damages/injuries (Weiss and Landauer, 2003; Brand and Jendrzejewski, 2008; Day et al., 2008; Kitagawa et al., 2010; Wang et al., 2010; Ha et al., 2013). It was shown by Day et al. (2008) that genistein (GN; 200 mg/kg) was able to ameliorate both the acute and late effects of IR. Here, GN was administered to mice subcutaneously 24 h before total body irradiation (7.75 Gy 60Co; dose rate of 0.6 Gy/min). At 24 h following irradiation, lung fibroblasts were cultured to evaluate radiation-induced DNA damage using cytochalasin-blocked micronucleus (CBMN) assays. It was shown that the percentage of MN/binuclear cell was significantly ($p<0.05$) lower in GN treated group compared to radiation alone group. GN also displayed anti-fibrotic effect in radiation-induced mice. Masson's trichrome stained lung tissue from the lungs of untreated irradiated mice at 90 days post-irradiation revealed small collagen-rich foci, populated with fibroblasts. The foci were localized just beneath the surface or pleura of the lung. However, examination of lung tissue from irradiated animals pre-treated with GN at 90 days post-irradiation showed no such foci. Supporting data on the radioprotection role of GN in lung tissue of other experimental models has also been reported (Para et al., 2009; Calveley et al., 2010).

It has also been reported that mice pre-treated with GN had survival rate of 92% ($p<0.001$), compared to 23% for untreated irradiated mice 30 days post-irradiation (Day et al., 2008). Concurrent with the survival, the general health of mice was improved by GN administration in irradiated group. The body weights of individual mice were recorded through day 36 and expressed a change in weight from baseline (2 days before irradiation) for all surviving mice. Genistein showed mitigation of radiation-induced weight loss between days 13-27 post-irradiation. It was shown that on the day of maximal weight loss, day 20 post-irradiation, average weight loss for irradiated mice was 4.1 g, while mice pre-treated with GN lost on average only 1.6 g ($p<0.05$). Works of Davis et al. (2007; 2008) using similar irradiation and treatment regimen, supported the radioprotective ability of GN. It was shown that GN provided significant radioprotection to the hematopoietic progenitor cells and the resultant increased survival of mice (upto 97%) compared to untreated mice, which had 0% survival (Davis et al., 2007). This study corroborated earlier report that GN enhanced post-irradiation repair or enhanced proliferation of the hematopoietic stem cells and increased survival of mice (Zhou and Mi, 2005). Further, quantitative real-time polymerase chain reaction (qRT-PCR) microarrays examination of cell cycle specific genes in bone marrow cells have shown that GN-treated mice expressed fewer DNA damage responsive and cell cycle checkpoint genes than untreated controls, thereby providing protection from acute myelotoxicity (Davis et al., 2008). The radioprotective ability of GN was further supported by some of the recent works showing prevention of irradiation-induced damage to hematopoietic system and intestinal damages (Day et al., 2013; Son et al., 2013), and rendering delay in tumour growth (Son et al., 2013).

Apparently, GN exhibited radioprotective potential and probably require further study. The call for further investigation is justified by the fact that GN pre-treatment resulted in 97% survival in lethally irradiated mice compared to significantly low survival in untreated control at 30 days after irradiation.

Ginsan

Ginsan, an acidic polysaccharide of *Panax ginseng L.* (Family: Araliaceae; Subfamily: Aralioideae) (APG) have been studies for its modulating action on radiation-induced alterations of some antioxidant systems in mice (Han et al., 2005). Ginsan was shown to have the ability to scavenge the stable DPPH radical in a dose-dependent manner, and the highest scavenging activity (34% inhibition) was detected at 2.0 mg ml^{-1} of ginsan ($p<0.005$ *vs* normal control values). For *in vivo* radioprotective study, 100 mg/kg of ginsan was administered to mice intraperitoneally 24 h before exposure to 4.5 Gy γ-radiation (Dose rate of 0.5 Gy/min). It was found that pre-treatment with ginsan induced expression of manganese-superoxide dismutase (Mn-SOD) by 1.7-fold compared to normal control values ($p<0.001$) in spleen of mice on the 5th day after irradiation as revealed by RT-PCR-amplified mRNA transcripts. Importantly, ginsan by itself did not have any effect on the expression of Mn-SOD. It was also reported that ginsan was able to increase the CAT expression in spleen on the 5th day after irradiation compared to untreated irradiated mice. However, this increase was not statistically significant. Similar to Mn-SOD, ginsan treatment resulted in significant increase ($p<0.001$ *vs* irradiated control) in GPx mRNA expression in spleen on the 5th day after irradiation. Even the protein level of Mn-SOD, CAT and GPx in irradiated mice treated with ginsan was significantly higher ($p<0.001$ to $p<0.01$) than irradiated mice without ginsan treatment. Analysis of the effect of antioxidant enzyme activities of SOD, CAT and GPx on lysates of spleen on the 5th day after

irradiation exhibited similar pattern. It was observed that the activity of SOD, which scavenges $O_2^{\bullet -}$, was reduced in the irradiated group as compared with the non-irradiated group (p<0.05). However, the activity of SOD was significantly increased in the ginsan treated group with or without radiation (p<0.001). Corroborating the result of mRNA expression, no significant change in CAT activity was observed in ginsan treated irradiated group compared to untreated control mice. GPx activity was also increased (p<0.001) by administration of ginsan before irradiation, compared with irradiated controls, again corroborating the results of mRNA and protein expression. Since certain types of SOD are known to be modulated by components of immune system (Qiu et al., 2008; Gottfredsen et al., 2014; Pragya et al., 2014; Yu et al., 2014), it is possible that activation of the antioxidant enzymes by ginsan as seen above, could have been alteration in cytokines, TGF-β, etc., thereby conferring radiological protection. This proposition appears to be supported by work of Kim et al. (2007). They have shown that ginsan provide radioprotection in bone marrow cells (BMCs) of mice by significantly increasing the amount of IL-12, a major cytokine for immune responses. In the same study, increase in expression of MHC class II molecules and allergenic CD4(+)T lymphocyte proliferation in BMCs was also reported from mice treated with ginsan compared to control. Moreover, irradiated treated mice had a larger number of BMCs than the control ones.

It has also been shown that mRNA level of heme oxygenase-1 (HO-1), the major 32 kDa stress protein inducible by oxidative stress, was markedly down regulated by combined treatment of both ginsan and radiation in spleen of mice on 5th day after 4.5 Gy irradiation compared to untreated control (Han et al., 2005). Even the HO enzyme activity was significantly decreased in ginsan treated irradiated group compared to untreated control (p<0.01). It was proposed that the modulating effect of ginsan on HO activity could be partially through downregulation of TGF-β since its mRNA expression level was decreased in irradiated groups pre-treated with ginsan in comparison to untreated control. However, the possible mechanism of radioprotective action of ginsan could be derived from the work of Bing et al. (2013). They showed that APG pre-treatment strongly decreased the radiation-induced apoptosis in the jejunum of mice. There was significant increased in the expression levels of anti-apoptotic proteins (Bcl-2 and Bcl-XS/L) and significant reduction in the expression levels of pro-apoptotic proteins (p53, Bax, cytochrome c and caspase-3). It was suggested in this study that APG protected the mouse small intestine from irradiation-induced apoptosis through inhibition of the p53-dependent pathway and the mitochondria/caspase pathway. This study corroborated earlier report that the inhibition of radiation-induced apoptosis by APG was brought about by the reduction in the amount of pro-apoptotic p53 and Bax and enhancement in anti-apoptotic Bcl-2 (Park et al., 2011).

In conclusion, ginsan ability to enhance the gene expression of key players of cellular antioxidant defence system such as SOD, CAT or GPx, and the corresponding proteins in animal model is quite remarkable. Its ability to prevent radiation-induced apoptosis in mice, modulate the immune response against radiation exposure and down-regulate radiation-induced stress protein like HO-1 makes it well suited for mitigation of acute radiation effects. Further evaluation of its radioprotective potential against different types of radiation effects would probably identify its right place in radiation countermeasure strategy.

AngelicA. sinensis

Chemical and pharmacological studies of extracts of AngelicA. sinensis Oliv. (Family: Apiaceae) (AS) or compounds purified from AS root have found to exhibit antioxidant (Yang et al., 2007; Zhang et al., 2010), immunomodulatory (Yang et al., 2006; 2012; Chen et al., 2010) and antitumor activities (Cao et al., 2010a; 2010b). AS has also been used in treating cancer patients with radiation-induced pneumonitis as an empirical practice based on the theory of Chinese medicine, and has shown clinical efficacy with low/no toxicity (Cai and Luo, 2003). In another study, its root extract has been reported to mitigate radiation-induced pulmonary injury (Xie et al., 2006). Here, mice were administered with *A. sinensis* extract (25%, pharmaceutical reagent for human use), intraperitoneally (0.2ml/10g/day, in a single injection). The injection was initiated one week before thoracic irradiation (a single fraction of 12 Gy X-ray; dose rate of 2.0 Gy/min) and continued up to two weeks after irradiation. Immunohistochemistry (IHC) analysis of TNF-α protein expression (expressed as positive cell count) in the lung tissue of mice undergoing thoracic irradiation revealed that AS+radiation treatment group had significant decrease (p<0.01) in TNF-α protein expression from 1 week until 24 weeks after irradiation when compared with the radiation alone group. Similarly, AS+radiation treatment group showed a significant decrease (p<0.01) in TGF-β1 protein expression for almost every time-point (except 72 h) post-irradiation when compared with the radiation alone group. Quantitative RT-PCR analysis of TNF-α mRNA expression in the lung tissue of mice undergoing thoracic irradiation corroborated the IHC result. It was observed that AS+radiation treatment group had significant decrease (p<0.01) in TNF-α mRNA expression for time-points at 1h and 8, 16 and 24 weeks post-irradiation when compared with the radiation alone group. Similar result was obtained in case of TGF-β1 mRNA expression in the lung tissue of mice undergoing thoracic irradiation. Even here, AS+radiation treatment group resulted in a significant decrease (p<0.01) in TGF-β1 mRNA expression for different time-points of 4, 8 and 16 weeks post-irradiation when compared with the radiation alone group. Similar study was carried out in mouse model, which corroborated the role of TGF-β1 in the progression of pulmonary injury (Han et al., 2006). In this case, *A. sinensis* extract down regulated the production of OH-proline and TGF-β1, reducing radiation-induced pulmonary fibrosis. The radioprotective roles of AS appeared to be conferred by its constituent polysaccharides such as APS-1a and APS-3a, which was isolated from the roots and shown to protect bone marrow hematopoiesis from radiological damages (Sun et al., 2005; Liu et al., 2010; Lee et al., 2012; Zhao

Table 1. Summary Chart of The Fourteen (14) Different Plant Extracts/Plant-Derived Compounds That Exhibited Radioprotective Property in Different Models of Radiation Injury

Family	Plants	Extract/plant-derived compounds (information in parentheses indicate the amount used for extraction)	Experimental systems	Route of administration	Administered before (BI) or after irradiation (AI)	Effects of plant extracts/plant-derived compounds
Papaveraceae	*Chelidonium majus* L.	Methanolic extract (20g of powdered dried aerial part); ukrain, chelidonine, etc	Human and murine leukemia cell lines; normal human fibroblasts; mice; rat	Intraperitoneal; oral	BI	Exhibits antioxidant and anti-inflammatory activities; enhances radiation-induced cytotoxicity in cancer cells, andradioprotection in normal fibroblasts; reduces radiation-induced cytokine production, etc; exhibits radioprotection of endocrine system ; increases survival in irradiated mice
Elaeagnaceae	*Hippophae rhamnoides* L.	Alcoholic extract of berries	Human malignant glioma cells; mice	Oral	BI	Reduces radiation-induced free radicals, cell toxicity and apoptosis in cancer cells; prevent DNA damages, thereby enhances radioprotection and survival in mice
Fabaceae (Subfamily: Caesalpinioideae	*Caesalpinia digyna* Rottl.	Methanolic extract (100g of root powder); bergenin	*In vitro* radioprotection studies		BI	Inhibits radiation-induced $O_2^{\bullet -}$, $^{\cdot}OH$ and DPPH* radicals; mitigation of radiation-induced lipid peroxidation, protein carbonylation and DNA damage *in vitro*
Zingiberaceae	*Curcuma longa* L.	Curcumin	PMVEC[b] isolated from mouse lungs; murine LLC[c] cells; mice	Oral	BI	Reduces radiation-induced ROS[a] in PMVEC; increases radiation-induced killing of LLC cells, but not in PMVEC; prevents radiation-induced DNA damages in cultured lymphocytes; modulates apoptosis related genes; reduces pulmonary fibrosis, and improves survival of irradiated mice
Linaceae	*Linum usitatissimum* L.	Flaxseed; SDG##	PMVEC, isolated from murine lungs; Mice	Oral	BI & AI	Reduces radiation-induced ROS in PMVEC; decreases radiation-induced WBC[c] influx and lipid peroxidation in lung of mice; improves radiation-induced lung inflammation and impaired blood oxygenation; reduces radiation cachexia, level of inflammatory cytokines, MIP-1α[d],VEGF[e] and lung fibrosis; increases survival in irradiated mice
Berberidaceae (*P hexandrum*) and Scrophulariaceae (*P kurroa*)	*Podophyllum hexandrum* Royale and *Picrorhiza kurroa*	Alcoholic extract	Mice	Oral	BI	Free radical scavenging activity; protection against radiation-induced lipid peroxidation and DNA damages; prevents radiatio-induced reduction in GPx[g], GR[h], GST[i]; improves survival in irradiated mice. Increases antioxidant activity in plasma in response to radiation; reduces radiation-induced inflammatory response, and increases survival in irradiated mice
Myristicaceae	*Myristica fragrans* Houtt.	Alcoholic extract of nutmeg seeds	Mice	Oral	BI	Exhibit anti-inflammatory and hepatoprotective properties against radiation; increases in liver GSH[f], reduces lipid peroxidation in testis and improves survival in reponse to radiation
Laminaceae	*Coleus aromaticus* Benth.	Hydroalcoholic extract (100g of leaf powder)	Chinese hamster lung fibroblast cells		BI	Inhibits free radicals, prevents lipid peroxidation, and radiation-induced DNA damage *in vitro*
Lamiaceae	*Mentha piperita* L.	Aqueous extract (100g of leaf powder)	Mice	Oral	BI	Increases GSH level, and decreases in lipid peroxidation in liver and blood in response to radiation; protects from radiation-induced hematopoietic and DNA damages and improves survival in irradiated mice
Rutaceae (Subfamily: Aurantioideae)	*Aegle marmelos*, L.	Hydroalcoholic extract (100g of leaf powder)	Human peripheral blood lymphocytes; mice	Oral	BI	Exhibits free radical scavenging ability *in vitro*; improves radioprotection, marked by significant reduction in the number of micronucleus formation; protects mice from radiation sickness, gastrointestinal, hematopoietic and DNA damages and improves survival
Euphorbiaceae	*Emblica officinalis Gaertn*. or *Phyllanthus emblica* L.	Hydroalcoholic extract (1kg of fruit)	Mice; human dermal fibroblast cells	Oral	BI	Depletes radiation-induced lipid peroxidation in liver and intestine; elevates GSH, GPx, GST and CAT[g] levels; improves survival; inhibits collagen damage in dermal fibroblasts
Fabaceae	*Genista tinctoria* L.	Genistein	Mice	Subcutaneous	BI	Prevents radiation-induced DNA damage in lung fibroblasts; protection from radiation-induced damage to hematopoietic system, intestines and DNA in mice; reduces radiation-induced fibrosis in lungs of mice; increases survival of mice against radiation
Araliaceae (Subfamily: Aralioideae)	*Panax ginseng* L.		Mice	Intraperitoneal	BI	Scavenges free radicals; enhances expression of Mn-SOD[k], CAT, GPx transcripts and corresponding proteins, and down-regulates stress protein HO-1[l] in response to radiation; modulates immune response against radiation in mice
Apiaceae	*Angelica sinensis* Oliv.	*A sinensis* extract; 25%, pharmaceutical reagent for human use	Mice	Intraperitoneal	BI	Reduces inflammation and pulmonary fibrosis, characterized by reduction in expression of TNF-α[m], TGF-β1[n] and hydroxyproline connent; protect bone marow hematopoiesis from radiological damages

*2, 2'-diphenyl picrylhydrazyl hydrate; **Pulmonary microvascular endothelial cells; ***Lewis lung carcinoma; [a]Reactive oxygen species; [b]Secoisolariciresinol diglucoside; [c]White blood cells; [d]Macrophage inflammatory protein-1α; [e]Vascular endothelial growth factor; [f]Reduced glutathione; [g]Glutathione peroxidase; [h]glutathione reductase; [i]Glutathione-S-transferase; [j]Catalase; [k]Manganese-superoxide dismutase; [l]Heme oxygenase-1; [m]Tumor necrosis factor-α; [n]Transforming growth factor beta1

et al., 2012).

The experimental evidences mentioned previously suggest that AS conferred radioprotection by reducing the mediators of inflammation and fibrosis such as TNF-α and TGF-β1. This information generated using the thoracic irradiation model in mice, requires evaluation in other models of radiation injury. Presuming that AS will display similar radiation protection in other models and since reports indicated that it conferred protection against radiological damages in human patients, it can thus, play a vital role in radiation countermeasure strategy.

Discussion

Our increasing dependence on radiation for energy requirement, therapeutic usages and the perceived thread of radiological terrorism has led to the hunt for a safe and effective radiological protective agent worldwide. Owing to limitation on the use of chemical radioprotectors, attributed to their high toxicity and unwanted side effects, resulting into reduced clinical efficacy, the focus is on natural product based on plants and active constituents derived from it, with limited or no toxicity. Adding to its advantage is also the easy availability of the plants, which are consumed in one form or the other across the globe. As shown in Table 1, 14 different plants or plant-derived compounds that have been reported to be effective in countering the harmful effect of radiation in different experimental models of radiation injuries, were evaluated for their possible role in radiation countermeasure strategy. As mentioned earlier, radiation exposure can cause numerous pathophysiological conditions including oxidative damage, inflammation and fibrosis, processes known to affect the survival of organisms. Most of the plants or plant-derived compounds that has been considered in this article, act in general, by countering the free radicals such as $O_2^{\bullet -}$, $^{\cdot}OH$, $NO^{\cdot}$, DPPH, etc. Most of these

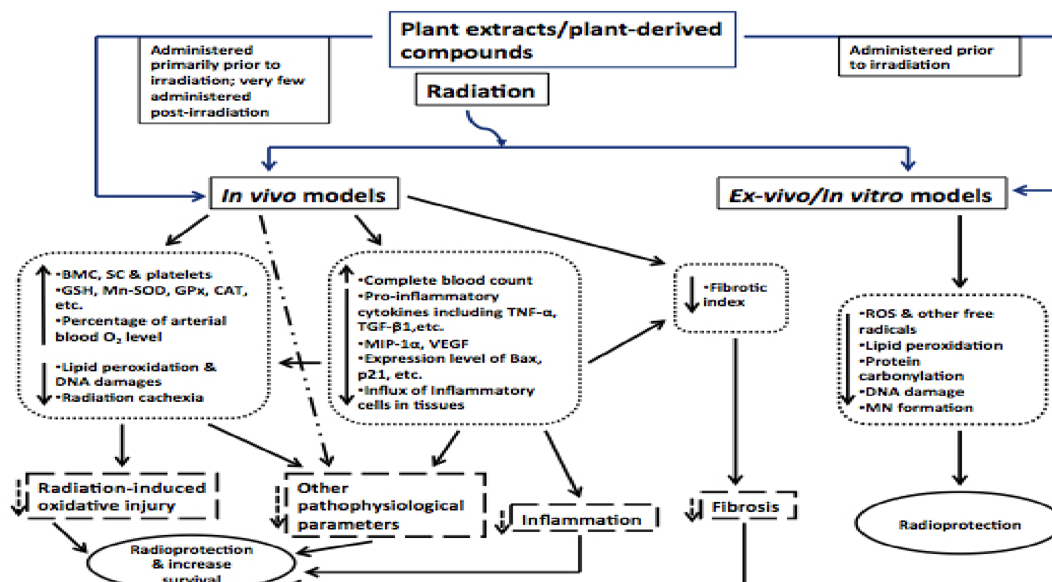

Figure 1. Schematic Representation of The Possible Mechanisms of Radioprotection Provided by Plant Extracts or Plant-Derived Compounds. Items in the 'round dot' boxes indicate cellular molecules/processes affected by irradiation, which might be countered by the plant extracts/plant-derived compounds. 'Up' or 'down' solid arrows inside the boxes indicate 'increase' or 'decrease' respectively, in cellular components/response by the plant extracts/plant-derived compounds against the radiation-induced effects. Items in 'long dash' boxes indicate the manifestation of the harmful effects of radiation, which might be reduced/prevented by the plant extracts/plant-derived compounds ('Down square dot' arrows outside the boxes) that might lead to radioprotection, and improvement in survival of organisms. BMC: Bone marrow cells; SC: Spleen cells; GSH: Reduced glutathione; Mn-SOD: Manganese-superoxide dismutase; GPx: Glutathione peroxidase; CAT: Catalase; TNF-α: Tumor necrosis factor-α; TGF-β1: Transforming growth factor-βeta1; MIP-1α: Macrophage inflammatory protein-1α; VEGF: Vascular endothelial growth factor; ROS: Reactive oxygen species, MN: Micronuclei

radicals are known to be generated *in vivo* because of radiation exposure (Parihar et al., 2007; Swarts et al., 2007; Sharan et al., 2011; Peebles et al., 2012; Francois et al., 2013; Mikhailenko et al., 2013), and hence scavenging them can protect the cells or tissue from oxidative injury. At the same time, some of the plants/plant-derived compounds also induce the biological antioxidant defence system such as SOD, GSH, CAT and GPx to counter the radiological effects in experimental animals in order to prevent cell/tissue injury. The details of the significant effects of the plants/plant-derived compounds against radiation exposure obtained from *in vivo*, *ex vivo* and *in vitro* studies have been summarized in Table 1.

There seems to be a very intricate relationship among antioxidant, anti-inflammatory and antifibrotic action of the plant extracts/plant-derived compounds in response to radiological insult. Table 1 shows that many of them act by scavenging ROS and other free radicals, and by decreasing the radiation-induced increase in the level of TGF-β1, TNF-α, IFN-γ, WBC influx in tissue, IL-1β, IL-2, IL-4, IL-6, IL-12, IL-17, MIP-1α, VEGF, etc, all of them being key players in inflammatory response (Xie et al., 2006; Kim et al., 2007; Lee et al., 2007; Day et al., 2008; Qiu et al., 2008; Christofidou-Solomidou et al., 2011; Hei et al., 2011; Janko et al., 2012; Monceau et al., 2013; Pragya et al., 2014). Others act against radiation exposure by inducing the expression of Mn-SOD, GSH, CAT, and GPx, the important members of antioxidant defence system (Han et al., 2005; Gottfredsen et al., 2014) or modulate the immune response against radiation exposure (Kim et al., 2007; Qiu et al., 2008; Pragya et al., 2014; Yu et al., 2014). Additionally, some of these plant extract/plant-derived compounds have also been found to reduce ROS, suppress cytokines, TNF-α and TGF-β1, thereby reducing the OH-proline level (the fibrotic index) in radiation-induced lung tissue (Han et al., 2006; Xie et al., 2006; Lee et al., 2009; Lee et al., 2010; Flechsig et al., 2010; Qiu et al., 2011; Gorshkova et al., 2012; Cho et al., 2013; Ding et al., 2013; Horton et al., 2013). Therefore, in general, the plant extracts/plant-derived compounds might act, either by suppressing some of these radiation-induced proinflammatory cytokines and other mediators of inflammatory response such as TNF-α, which in turn can induce the antioxidant defence system, or might activate the antioxidant defence system directly, in response to radiation exposure. In either case, the plant extracts/plant-derived compounds could prevent the long-term effect of radiation such as fibrosis, and enhance survival. The probable general mechanism of action is schematically represented in Figure 1.

It is possible that different plant extracts/plant-derived compounds will respond differentially to low and high dose of radiation to the whole body or part of it. Some of plants/plant-derived compounds have been tested against relatively low dose (≤5 Gy), and indicated radioprotection. However, others have been tested at relatively high dose of 8-10 Gy to the whole body, and appeared to be effective radioprotectors. In response to a high dose of 12-13.5 Gy to the whole thorax, some of them mitigated the radiation-induced oxidative damages, inflammation and fibrosis in mice. A comparative study involving high and low dose of radiation might be necessary to evaluate the degree of radioprotection displayed by these plant extracts/plant-derived compounds in order to establish

the suitable candidate for radioprotection against high or low dose of radiation or both. Notwithstanding the fact that the research in plant-based radioprotectors is still at its infancy, our preparedness to deal with high or low dose radiation exposure in the event of a radiological accident or explosion in future using cheap and readily available plant material might save precious lives.

Majority of the plant extracts/plant-derived compounds were administered orally in experimental animals and hence can be considered as safe, effective and convenient route (Table 1). This becomes advantageous when it comes to route of preference for drug administration particularly in case of mass exposures. As mentioned previously, most of these extracts were effective in small amount in animal models, which was obtained using different parts of plants such as leaves, root, fruits, seeds or compounds derived from it (Table 1). It effectively means that this amount can be obtained by oral consumption of plant extracts/compounds derived out of it. However, its effectiveness as radioprotectors in humans will depend on the pharmacokinetics, particularly the bioavailability, of the components of the plant extract/plant-derived compounds. This information will be critical in determining an effective concentration of the potential plant-based radioprotectors for any possible clinical use. With the available information, it will be presumptuous to say that similar concentration known to be effective in experimental animals will hold good even in human subjects. There is a need for further works to be carried out in addressing this critical point.

Apart from determining the effective concentration, the time of treatment with the plant extracts/plant-derived compounds could be a crucial factor in its effectiveness in radioprotection. However, hunt for plant-based radioprotectors appeared to be focussed largely on preventive modality since out of 14 plants/plant-derived compounds considered in this review, 12 of them has been exclusively used before irradiation (Table 1). Only flaxseed has been tested for radioprotection both before and after irradiation, while extract of *P. hexandrum* (prior to irradiation) and *P. kurroa* (post-irradiation) were used as a lone combined treatment strategy. In order to counter scenarios of accidental radiation exposure such as the recent Fukushima Dai-ichi nuclear plant leakage in Okuma, Japan or a deliberate act of radiological terrorism, which are very difficult to predict, testing the radioprotective efficacy of these plant extracts/plant-derived compounds after radiation exposure might be necessary, keeping in mind their potential clinical use in the long run.

In conclusion, all the 14 plant extracts or compounds derived from it and considered in this review have shown some radioprotection in different *in vivo*, *ex vivo* and or *in vitro* models of radiological injury. However, few have demonstrated advantages over the others. *C. majus* possessing antioxidant, anti-inflammatory and immunomodulatory effects appeared to be promising in radioprotection. Its crude extracts as well as various alkaloids and flavonoids derived from it, have shown to enhance survival rate in irradiated mice. Similarly, curcumin with its antioxidant and the ability to ameliorate late effect of radiation exposure, combined with improvement in survival in experimental animal following irradiation, makes it another probable candidate against radiological injury. Furthermore, the extract of *P. hexandrum* and *P. kurroa* in combine treatment regime, nutmeg, ME, EO GN, ginsan and AS warrants further studies on their radioprotective potentials, considering the infancy of the field of plant-based radioprotectors. However, based on current information available on the plant extracts/plant-derived compounds considered in this article, one that has the advantage over all the others, and perhaps received a lot of attention, is the dietary flaxseed. The scavenging ability against radiation-induced free radicals, prevention of radiation-induced lipid peroxidation, reduction in radiation cachexia, level of inflammatory cytokines and fibrosis, are some of the remarkable characteristics of flaxseed in animal models of radiation injury. While countering the harmful effects of radiation exposure, it has shown its ability to enhance survival rate in experimental animals. Further, flaxseed has been tested and found to be equally effective when administered before or after irradiation, and against low doses (≤5 Gy) to the whole body or high doses (12-13.5 Gy) to the whole thorax. This is particularly relevant since apart from the possibility of using it in pre-conditioning regime in radiotherapy, it could also be used during nuclear plant leakage/accidents and radiological terrorism, which are not pre-determined scenarios. However, it has not been tested for radioprotection against high dose of radiation (8-10 Gy) to the whole body.

Therefore, considering the infancy of the field of plant-based radioprotectors, further stringent study involving these plant extracts/plant-derived compounds in different models of radiation injury is required to establish their feasibility as effective radioprotectors for any possible clinical use in the near future. In this quest, flaxseed could probably be accorded preference.

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