REVIEW ARTICLE

A review of radioprotective plants

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Radioprotective compounds have been used to diminish morbidity or mortality produced by ionizing irradiation. Initial developments of such agents concentrated on thiol synthetic compounds, like amifostine. This agent decreased mortality; however, there were difficulties in administering aminothiols that led to adverse effects. Unfortunately, no ideal, safe synthetic radioprotectors are available to date; hence, the exploration for other sources, including plants, has been ongoing for several decades. A methodical screening strategy can offer leads to isolating prospective novel candidate drugs from plant sources, for alleviation of radiation injury. This article reviews some of the most promising plants, and their bioactive principles, that are extensively used in traditional systems of medicine, and which have rendered noteworthy radioprotection in both *in vitro* and *in vivo* model systems.

Key words: Plants, radiation-toxicity, radioprotection

INTRODUCTION

The global burden of cancer continues to increase largely because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviours, particularly smoking, in economically developing countries. Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008. Of these, 56% of the cases and 64% of the deaths occurred in the economically developing world.[1] There would be about 26 million new cases by 2030 and the majority of deaths due to cancer will occur in developing countries.[2] There continues to be a change in the global distribution pattern of cancer and the predominating type of cancers. Thus, cancers of the lung, breast, colon/rectum, and prostate are among the most common cancers occurring all over the world and not just restricted to the western industrialized countries. Multi-faceted and integrative approach involving surgery, followed by chemotherapy along with radiation is currently gaining consensus for its treatment.[3] Simultaneously, progress in the understanding of the disease processes at a molecular level has led to the development of innovative strategies for prevention, detection, control, and elimination of cancer.

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DRAWBACKS OF RADIATION THERAPY

Application of ionizing radiation, over and above surgery, and chemotherapy has been the treatment of choice in case of solid malignancies.[4] There remains a substantial toxicity of radiotherapy to normal tissues and organs despite progress in the development of clinical radiotherapy treatment planning and treatment delivery technologies. Better local control of cancer by radiotherapy dose escalation is accompanied by significant acute toxicity and normal tissue damage. Unfortunately, higher radiation doses that would be more effective cannot be used due to acute toxicities occurring during the clinical course of radiotherapy. These acute toxicities, which can extend beyond the treated area are accompanied by tissue inflammatory response and are not always limited to the normal tissue in the irradiation beam. Being transitory in nature, acute toxicities resolve weeks after completion of treatment. However, these toxicities could reduce the patient's ability to comfortably finish the treatment protocol. Moreover, occurrence of late-manifesting toxicities (defined as those appearing months to years after completion of a successful treatment course) in patients treated with radiotherapy is a growing concern. The late toxicity is generally restricted to tissues treated and does not typically affect survival. Hence, to reduce these toxicities and improve the therapeutic ratio (that is ratio of cancer cell killing to normal tissue toxicity caused by a given dose), radioprotective drugs are receiving significant interest.[5]

However, currently there is no effective clinical treatment to protect normal tissues against radiation injury. Certain pharmacological agents are available to ameliorate the

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radiation injury as per limited evidence. There appears to be a tissue-specific response to different pharmacological agents; hence care must be taken while administering some of these substances for the management of different aspects of radiation damage. Moreover, beneficial results obtained from animal models may not be correlated clinically; hence, this factor should be borne in mind. In addition, differing results may arise from differences in the pathophysiologic processes involved in the development of radiation lesions in different tissues, and in the markers used to assess the efficacy of treatment agents.[6]

MECHANISMS INVOLVED IN RADIATION INJURY

The molecular biological mechanisms of ionizing irradiation induced cell killing at the level of single cells, tissues and organs will help in understanding and developing agents for radiation protection. Ionizing radiations induce reactive oxygen species in the form of OH, H, singlet oxygen and peroxyl radicals that follow a cascade of events leading to deoxyribonucleic acid (DNA) damage such as single- or double-strand breaks (DSB), base damage, and DNA-DNA or DNA-protein cross-links, and these lesions cluster as complex local multiply damaged sites. The DNA-DSBs are considered the most lethal events following ionizing radiation and has been found to be the main target of cell killing by radiation. Moreover, ionizing irradiation, which produces radical oxygen species such as superoxide and hydroxyl radical deplete cellular antioxidant stores, most prominently glutathione (GSH). Replacement of cellular antioxidant capacity by increasing levels of the enzymes is an example of one radioprotector strategy at the cellular level. Inflammatory cytokines released by both dying and surviving cells within an irradiated tissue cell can act as cytotoxins at both the local tissue level. In addition, they can affect distant sites through action on specific cellular surface receptors. Another strategy for radiation protection could include agents, which limit cytokine binding or action at the cellular receptor level e.g., Toll-like receptor-5 receptor agonist. Hence, identification of potential radioprotective pathway targets is dependent on understanding the causal molecular biology of irradiation cellular killing.[5]

NEED FOR CHEMICAL RADIOPROTECTION

The turning point in human health-care was the discovery of X-rays by Roentgen in the year 1895 and radioactivity by Becquerel in the year 1896, which allowed peeping inside the human body. Within a few months of discovery of X-rays harmful effects of ionizing radiations were reported; however, the real magnitude was not known. A clear picture of the harmful effects of ionizing radiations was possible following the study of occupational workers such as physicians and scientists handling radioactivity. This was additionally confirmed subsequent to the study of Japanese atomic bomb survivors of 1945. That radiation produces deleterious effects on the organisms is now fairly well- established. Hence, extensive usage of radiation in diagnosis therapy, industry, energy sector besides unintended exposure during air and space travel, nuclear accidents and nuclear terror attacks necessitates protection against human exposures. Lead shielding and other physical measures are cumbersome to use in such situations. Hence, pharmacological intervention could be the most sensible approach to safeguard humans against the detrimental consequences of ionizing radiations.[7]

CHEMICAL RADIOPROTECTION

The usage of compounds to safeguard against the deleterious effects of radiation was endeavoured following World War II with the awareness of the requirement to protect humans from the military use of atomic weapons. The pre-treatment of amino-acid cysteine protected rats from the detrimental effects of X-rays was first demonstrated by Patt *et al*., (1949).[8] Radioprotective agents, although widely studied in the past four decades and including several thousand agents, have not reached the level of providing the field of medicine with an agent that conforms to all criteria of an optimal radioprotectant, including effectiveness, availability, specificity and tolerance. In addition, their high toxicity at ideal protective doses prohibited their clinical use.[9,10] In addition, these compounds were inept in providing post-irradiation protection. The attention of protection research became more therapy oriented following the appreciation that normal tissue protection during radiotherapy is as imperative as the destruction of cancer cells. The significant toxicity associated with thiol compounds demanded exploration for alternative agents. It was presumed that products/compounds isolated from natural sources could be of significant use as non-toxic radioprotectors. Consequently, attention was focused towards the plant and natural products. Plants have been described to play an extremely important role in the drug discovery and development process.[11]

Therefore, investigation of plants and natural products is a beneficial example for radioprotection. The benefit of plants and natural products is that they are used in numerous traditional systems of medicines. They are generally considered non-toxic and extensively acknowledged by humans. Their use as radioprotectors needs systematic assessment and validation. Subsequent to the completion of these requirements their use as radioprotectors could be more successful than synthetic chemicals.

ASSESSMENT OF RADIOPROTECTIVE POTENTIAL

The most practical methodology to choose the promising candidate for assessing its radioprotective effect is to look into the available properties of the substance. A substance

with anti-inflammatory, antioxidant, antimicrobial, immunomodulatory, free radical scavenging or anti-stress properties may act as a potential radioprotector.

The following short-term *in vitro* tests can provide a basis for detailed evaluation of radioprotective activity:

- Evaluation of lipid peroxidation (LPO) *in vitro* (simplest test)
- Assay of free radicals and antioxidant status of a pharmacological agent (product should inhibit LPO and scavenge free radicals)
- *In vitro* cell survival and micronuclei assays (product should elevate cell survival and reduce radiation-induced micronuclei formation).

Other short-term tests:

- DNA strand breaks,
- Apoptosis,
- Estimation of GSH,
- Estimation of enzymes such as catalase, glutathione peroxidase (GSHPx).

The most dependable techniques comprise determination of a dose reduction factor (DRF). In animal studies, DRFs are usually evaluated by irradiating mice with or without administering radioprotective agent at a range of radiation doses and subsequently comparing the endpoint of interest. For example, the DRF for 30-day survival Lethal Dose ($LD_{50/30}$ drug-treated divided by $LD_{50/30}$ vehicle-treated) quantifies protection of the haematopoietic system.[12,13] With sufficient loss of haematopoietic stem cells, death follows due to infection, haemorrhage, and anaemia. The gastrointestinal (GI) syndrome in mice can be assessed by determining survival up to 10 days (measure of GI death) after exposure to comparatively high doses of whole-body radiation, whereas haematopoietic syndrome can be assessed by monitoring the survival of irradiated animals up to 30 days post-irradiation.[12-16] The intestinal crypt cell assay or functional changes also serve as indicators of GI damage.[17] The most informative and useful preclinical studies relate protective effects to the drug's toxicity in the same animal model.

$$DRF = \frac{\text{Dose of radiation in presence of drug}}{\text{Dose of radiation in absence of drug}} \text{ to produce given level of lethality}$$

Nonetheless, the gold standard for radioprotective activity is the evaluation of 30-day survival in rodents, since the animal studies with death as the end point are the most confirmatory, because the 30-day survival after lethal whole body irradiation clearly indicates the capacity of the pharmacological agent in test to modulate the recovery and regeneration of the gastrointestinal epithelium and the haematopoietic progenitor cells in the bone marrow, the two most radiosensitive organs that are essential for sustenance of the life.[7,14]

The efficacy of radioprotectors in clinical practice necessitates different end points. Among other endpoints amenable to the determination of beneficial effects of radioprotectors, the most readily evaluable is protection against mucositis and xerostomia resulting from head and neck radiotherapy and various side effects when the GI tract is in the radiation field.[18]

RADIOPROTECTIVE PATHWAYS

The systematic/biological basis for improvement of a radioprotective approach demands an understanding of the fundamental molecular biology behind the mechanism of the cellular, tissue and organ specific radiation damage response. Examples of the pathways for focus include: Nuclear DNA strand breaks, communication of nuclear stress responses through the cell cytoplasm to mitochondria, mitochondrial response to nuclear signalling and mitochondrial initiation of apoptosis.[19-21] Finally other cells respond to the inflammatory cytokine cascade that follows cell killing in a second wave of cell death.[5] This second wave may slowly persist or may occur in a delayed, but severe fashion leading to the rapid onset of what is called chronic effects described above.

PLANTS AND HERBS AS RADIOPROTECTORS

A comprehensive pursuit for naturally occurring phytochemicals as prospective radiotherapeutic agents has unearthed a multitude of plant products largely categorized as (i) 'Radioprotectors' - to ameliorate the detrimental effects caused to the normal cells; therefore, diminish the side-effects of radiation therapy; and (ii) 'Radiosensitisers' - to augment the radiation-induced cell death caused to the tumour, and thus curtail the dose of radiation treatment. In the present article, some of the foremost findings on traditional medicinal plants and active phytochemicals with encouraging radioprotective efficacy have been briefly mentioned.

Mechanism of Action

Since plants contain different phytochemicals their radioprotective activity may be mediated through several mechanisms. Scavenging of radiation-induced free radicals and elevation of cellular antioxidants might be foremost mechanism for radioprotection due to the presence of polyphenols. These polyphenols could up-regulate messenger RNA of antioxidant enzymes such as catalase, GSH transferase, GSHPx, superoxide dismutase (SOD) and hence counteract the oxidative stress-induced by ionizing radiations. Protection against radiation-induced damage is

also conferred by the up-regulation of DNA repair genes, which bring about an error free repair of DNA damage. Certain extent of radioprotective activity is provided by the reduction in LPO and elevation in non-protein sulfhydryl groups. The plants and herb may also inhibit activation of protein kinase C, mitogen activated protein kinase, cytochrome P-450, nitric oxide and several other genes that may be responsible for inducing damage after irradiation.[7]

RADIOPROTECTIVE EFFECT OF VARIOUS HERBS AND PLANTS

Withania somnifera (*Ashwagandha*)

Ayurvedic system of medicine has been using WS Dunal, commonly known as *ashwagandha*, since centuries increase longevity and vitality. Western research supports its polypharmaceutical use, confirming antioxidant, anti-inflammatory, immune-modulating, and anti-stress properties in the whole plant extract and several separate constituents. Besides reducing tumour cell proliferation, WS has demonstrated to increase overall animal survival time. Furthermore, by possibly alleviating undesirable side-effects it has been shown to augment the efficacy of radiation therapy. Without interfering with the tumour-reducing actions of the drugs, WS also decreases the side effects of chemotherapeutic agents cyclophosphamide and paclitaxel. These effects have been demonstrated *in vitro* on human cancer cell lines, and *in vivo* on animal subjects, however, there have been no human trials to date.[22] WS resulted in a major increase in heme oxygenase activity as well as a noteworthy reduction in reduced GSH content. Furthermore, the activities of antioxidant enzymes, including SOD and GSHPx in hepatic tissues were also reduced. Given its broad spectrum of cytotoxic and tumour-sensitizing actions, WS presents itself as a novel complementary therapy for integrative oncology care.[23] Administration of a 75% methanolic extract of the plant was found to significantly increase the total white blood cell (WBC) count in normal Balb/c mice and reduce the leucopoenia induced by sublethal dose of gamma radiation (γ-GR). Major activity of WS seemed to be in the stimulation of stem cell proliferation.[24]

Eugenia Jambolana (*Jamun*)

E. jambolana Lam., commonly known as black plum or '*jamun*' is an important medicinal plant in various traditional systems of medicine. It is effective in the treatment of diabetes mellitus, inflammation, ulcers and diarrhoea and preclinical studies have also shown it to possess antineoplastic, chemopreventive and radioprotective properties.[25]

Curcuma Longa (*Haldi*)

Curcumin (diferuloylmethane), the yellow pigment in Indian saffron (*C. longa*; also called turmeric, *haldi*, or *haridara* in the East and curry powder in the West), has been consumed by people for centuries as a dietary component and for a variety of proinflammatory ailments. Widespread research within the last decade in cell culture and in rodents has shown that curcumin can sensitize tumours to different chemotherapeutic agents. Likewise evidence too demonstrates that this agent can sensitize a variety of tumours to γ-GR including glioma, neuroblastoma, cervical carcinoma, epidermal carcinoma, prostate cancer, and colon cancer. The mechanism behind its chemosensitiser and radiosensitiser activity too has also been researched comprehensively. Studies demonstrates that it down regulates several growth regulatory pathways and precise genetic targets including genes for nuclear factor kappa-light-chain-enhancer of activated B cells, Signal transducer and activator of transcription 3, Cyclooxygenase-2, Akt (also known as Protein Kinase B), antiapoptotic proteins, growth factor receptors, and multidrug-resistance proteins. While it acts as a chemosensitiser and radiosensitiser for tumours in some cases, curcumin has also been revealed to safeguard normal organs from chemotherapy and radiotherapy-induced toxicity. The protective effects of curcumin seem to be facilitated by its ability to induce the activation of (nuclear factor (erythroid-derived 2)-like 2) and expression of antioxidant enzymes, directly quench free radicals, and inhibit p300 histone acetyl transferase (HAT) activity (E1A binding protein p300 histone acetyltransferase). These preclinical studies are expected to lead to clinical trials to prove the potential of this age-old golden spice for treating cancer patients.[26,27] Nada *et al*., conducted a study to evaluate the modulatory effect of aqueous (PnAq) extract of *C. longa* against γ-GR, which induces biochemical disorders in male rats. Overall, *C. longa* exerted a beneficial radioprotective effect against radiation-induced oxidative stress in male rats by alleviating pathological disorders and modulating antioxidant enzymes.[28]

Tinospora Cordifolia (*Guduchi*)

Aqueous extract of TCE inhibited Fenton ($FeSO_4$) reaction and radiation mediated 2-deoxyribose degradation in a dose dependent fashion. Similarly, it showed a moderate but dose dependent inhibition of chemically generated superoxide. The extract inhibited ferrous sulphate mediated LPO in a dose-dependent manner. The results reveal that the direct and indirect antioxidant actions of TCE probably act in corroboration to manifest the overall radioprotective effects.[29] The radiosensitising activity of dichloromethane extract of TCE in the mice transplanted with ehrlich ascites carcinoma (EAC) was investigated. The EAC mice receiving TCE showed a dose-dependent elevation in tumour-free survival and increased life span. This was evident by more number of long-term survivors as well as survivors beyond 120 days. The radiosensitisation of TCE may be due to depletion of GSH and GSH-S-transferase (GST),

accompanied by elevated levels of LPO and DNA damage of tumour cells. Thus, TCE may offer an alternative treatment strategy for cancer in combination with γ-GR.[30] A preparation of TCE administered to mice 1 h before the whole body γ-GR was evaluated for its radioprotective efficacy in terms of the whole body survival, spleen colony forming units (CFU), haematological parameters, cell cycle progression, and micronuclei induction. Pre-irradiation treatment with TCE rendered 76.3% survival (30 days and prevented radiation induced weight loss. Pre-irradiation administration of TCE increased CFU counts and could restore total lymphocyte counts by the 15th day to normal. It also increased the S-phase cell population that was reduced following two Gy irradiation in a time dependent manner. Two Gy irradiation-induced micronuclei were also decreased by a pre-irradiation administration of TCE.[31]

Ocimum Sanctum (*Tulsi*)

Several *Ocimum* species are regularly used for the treatment of inflammation, stress, diarrhoea, and as an antioxidant drug in the Indian ethnic system of medicine. Monga, *et al*., evaluated the antimelanoma and radioprotective activity of *Ocimum* in C (57) BL and Swiss albino mice. The PnAq extract of *Ocimum* caused a substantial decline in tumour volume, increase in average body weight, and survival rate of mice. The extracts exhibited modulatory effect against radiation-induced chromosomal damage, induced an increase in reduced GSH level and GST activity. These findings demonstrate that *Ocimum* species have antimelanoma and radioprotective activity against B (16) F (10) metastatic melanoma cell line-induced metastasis and could be exploited as one of the potential sources for plant-based pharmaceutical products.[32] Joseph, *et al*., determined the radioprotective effect of *O. sanctum* on the salivary gland of rats administered radioiodine (131) I and compared its efficacy with a known radioprotectant, amifostine. Parotid gland histology displayed atrophy with lipomatosis in only (131) I exposed rats. *O. sanctum* and amifostine pre-supplemented and subsequently exposed to (131) I rats demonstrated similar histopathology with controls. Thus results suggests potential radioprotective effect of *O. sanctum* and amifostine against high-dose (131) I exposure.[33] Two flavonoids, orientin and vicenin, isolated from the leaves of the Indian plant *O. sanctum* were investigated their radioprotective role in mice. Both compounds resulted in protection against death from gastrointestinal syndrome as well as bone marrow syndrome when injected intraperitoneally (i.p.) before whole-body exposure to 11 Gy γ-GR. Radical scavenging activity has been demonstrated for both orientin and vicenin, and this appears to be one of the mechanisms of protection by these flavonoids.[34]

Adhatoda Vasica (*Adulsa*)

Oral administration of *A. vasica* leaf extract (800 mg/kg body weight) prior to the whole body irradiation showed a significant protection in terms of survival percentage and haematological parameters. *A. vasica* leaf extract pre-treated irradiated animals displayed a noteworthy increase in GSH content and decrease in LPO level.[35] Death of *A. vasica*-pre-treated irradiated mice was reduced to 70% at 30 days. The radiation DRF was 1.43. There was significantly diminution in level of damage to testis tissue architecture and several cell populations including spermatogonia, spermatids and Leydig cells. Similarly, a substantial decline in the LPO and an enhancement in the GSH concentrations were witnessed in testis and liver of *A. vasica*-pre-treated irradiated mice. Likewise, a major drop in level of acid phosphatase and increase in level of alkaline phosphatase were observed. *A. vasica* pre-treatment significantly prevented radiation-induced chromosomal damage in bone marrow cells. The study indicates that *A. vasica* plant extract has significant radioprotective effects on testis that merits additional systematic studies designed at ascertaining the role of key constituents in the extract.[36]

Rajgira (*Amarantus Paniculatus*)

Radiomodulatory effect of *Amarantus Paniculatus (Rajgira)* leaf extract against 6, 8 and 10 Gy γ-GR has been assessed by 30 day survival of Swiss Albino mice. Animals of control groups (untreated irradiated) exhibited diarrhoea, ruffled hairs, epilation, facial oedema and consistent decrease in body weight. In experimental groups (*Rajgira* treated irradiated) these signs were less severe/absent. In addition, recovery in body weight was also early and faster. 100, 60 and 25% survivability was observed in experimental groups at 6, 8 and 10 Gy respectively. The DRF was computed as 1.36. *Rajgira* pre-treated irradiated animals the level of GSH was recorded significantly higher but LPO level decreased significantly. Thus, results suggest that *Rajgira* pre-treatment provide protection against γ-GRin mice.[37,38]

Allium Sativum (*Garlic*)

The result of the bone marrow micronucleus test revealed that pre-treatment with garlic extract was effective in reducing γ-GR-induced chromosomal damage. In the garlic extract, pre-treated irradiated animals, a significant reduction was observed in the sulphydryl content and GST activity.[39]

Prunus Avium (*Sweet Cherry*)

P. avium (*Aaluvaalu, Gilaas, Krusabala*) has been used ethnomedicinally for the treatment of many diseases, but its radioprotective efficacy has hardly been explored. Researchers have reported the presence of high anthocyanin content and phenolic compound with good antioxidative capacity. Its radioprotective effect against 5, 7, 10, and 12 Gy γ-GR was evaluated by 30 day survival assay. The DRF was computed as 1.62. The irradiation of animals resulted in a significant elevation of LPO, depletion in GSH and protein levels in blood serum and spleen. This was significantly

controlled by administration of *Prunus Avium Extract* (PAE). Radiation-induced deficit in blood sugar, cholesterol and haematological constituents could also be normalized by supplementation of PAE before and after irradiation. The probable prophylactic and therapeutic action noted by *P. avium* against radiation induced metabolic disorders could be due to synergistic action of various antioxidants, minerals, vitamins, etc., present in the fruit. Additional systematic studies directed at recognizing the role of key components in the extract are desired.[40]

Emblica Officinalis (*Amla*)

The fruit pulp of EO is an important drug used as a tonic and many diseases in Indian systems of medicine. Hence, the plant extract (PnAq) was tested for its radioprotective properties against sublethal γ-GREO (9 Gy) in Swiss Albino mice. The extract increased the survival time and reduced the mortality rate of mice significantly. Moreover, body weight loss in EO administered irradiated animals was significantly less in comparison with animals who were given radiation only.[41]

Myristica Fragrans (*Jaiphal, Javitri*)

Nutmeg, the dried seed kernel of MF besides possessing antifungal, and hepatoprotective activity also exhibits antioxidant properties. Hence, its radioprotective effect against 6, 8 and 10 Gy γ-GR was determined by 30 day survival assay. The DRF was computed as 1.3. Administration of MF significantly enhanced hepatic GSH and decreased testicular LPO level. The present study has implications for the potential use of MF as a radioprotector.[42]

Aegle Marmelos (*Bael*)

Numerous diseases resulting from oxidative stress have been frequently treated by AME, commonly known as *bael*, since ancient times. It has been witnessed that AME prevented radiation-induced ill-effects in studies spanning nearly a decade. Results of these studies suggest that it has the prospects to be an effective, non-toxic radioprotective agent.[43] The radioprotective effect of an extract of AME was investigated in mice exposed to different doses of γ-GR. Treatment of mice with AME before irradiation reduced the symptoms of radiation sickness and delayed death compared with the irradiated controls given sterile physiological saline. AME provided protection against both gastrointestinal and hematopoietic toxicities. The oral administration of AME resulted in an increase in radiation tolerance by 1.6 Gy, and the DRF was found to be 1.2. Pre-radiation treatment of mice with AME caused a significant depletion in LPO followed by a significant elevation in GSH concentration in the liver of mice 31 days after irradiation.[44]

Aloe Vera (*Gheekumari*)

The skin, being a cell-renewal system, is one of the first organs to be affected in total-body irradiation during radiotherapy. An attempt has been made to explore radiation-induced biochemical alterations caused by whole-body γ-GR and their modulation in Swiss Albino mice by *Aloe vera* leaf extract (AVE). In contrast, in experimental animals, DNA, catalase, and SOD in the skin and GSH in the liver and blood increased significantly. However, LPO in the liver and blood decreased in comparison to irradiated control animals. Thus, AVE is found to have damage-resistant properties against radiation-induced biochemical alterations in Swiss Albino mice.[45] The remarkable radioprotective effect of the drug was also revealed by Bakuridze, *et al*.[46]

Mentha Piperita (*Pudina*)

Two species of the commonly used aromatic herb mint, *M. piperita* and *Mentha arvensis* protected mice against the γ-radiation-induced sickness and mortality. Detail investigations have also shown that the PnAq extract of *M. piperita* protected the vital radiosensitive organs: The testis, gastrointestinal and haematopoietic systems in mice. The radioprotective effects are possibly due to free radical scavenging, antioxidant, metal chelating, anti-inflammatory, antimutagenic, and enhancement of the DNA repair processes.[47] Radiation treatment showed a reduction in the testis weight during all days of observation; however, in the *M. piperita* leaf extract-pre-treated irradiated group there was a significant increase in testis weight. Animals pre-treated with *M. piperita* leaf extract and exposed to radiation showed normal testicular morphology with regular arrangement of germ cells and slight degeneration of seminiferous epithelium. Significant decreases in the LPO and acid phosphatase level and increase in level of alkaline phosphatase were observed in testis. The results of the study suggest that phenolic compounds, the content of flavonoids and flavonols of *M. piperita* leaf extract may be held responsible for radioprotective effect due to their antioxidant and radical scavenging activity.[48] Pre-treatment with leaf extract of *M. piperita* followed by radiation exposure resulted in significant increases in the numbers of leucoblasts, myelocytes, metamyelocytes, band/stab forms, polymorphs, pronormoblasts and normoblasts, lymphocytes and megakaryocytes in bone marrow as compared to the control group. It also resulted in significant decreases in micronucleus frequencies in bone marrow of Swiss Albino mice. A significant increase in erythropoietin level was observed at all the studied intervals in leaf extract of *M. piperita* pre-treated irradiated animals. The results of the present investigation suggest the protective effects of leaf extract of *M. piperita* against radiation induced haematopoietic damage in bone marrow may be attributed to the maintenance of Erythropoietin (EPO) level in Swiss Albino mice.[49]

Spinacia Oleracea (*Palak*)

It is found that radiation-induced augmentation in malondialdehyde contents and depletion in GSH changes in

the liver can be altered by *S. oleracea*. The protection may be attributed to the combined effects of its constituents rather than to any single factor as the leaves are rich in carotenoid content (beta-carotene, lutein, Zeaxanthine), ascorbic acid, flavonoids and p-coumaric acid. Thus *S. oleracea*, showing protection in the liver, may prove promising as a rich source of antioxidants because its use is cost-effective, especially for peoples in adverse and hazardous circumstances who are living in poverty.[50]

Boerhaavia Diffusa (*Punarnava*)

The radioprotective effect of the hydro-alcoholic extract of *B. diffusa* (also called Vishkhapara/Santha/Gahadpurna) was studied using the *in vivo* mice model. The total white blood cell count was lowered only to 4000 ± 400 cells/mm (3) on the 3rd day, and it reached an almost normal level (6250 ± 470 cells/mm^3) by the 9th day in animals treated with *B. diffusa*. *B. diffusa* decreased the elevated level of serum and liver alkaline phosphatase after radiation exposure. It also diminished the raised levels of serum and liver glutamate pyruvate transferase besides a significant reduction in LPO levels. The agarose gel electrophoresis of DNA isolated from bone marrow of mice exposed to γ-GR showed heavy damage that was reduced by treatment with *B. diffusa*. These results are indicative of the radioprotective effect of the whole-plant extract of *B. diffusa*.[51]

Zingiber Officinale (*Ginger*)

The rhizome of *Z. officinale* commonly known as ginger (*Sunthi/Ardraka*) has widely been used as a spice and condiment in different societies since antiquity. That ginger possesses chemopreventive and antineoplastic properties has been documented by numerous preclinical studies. Side-effects of γ-GR, doxorubicin and cisplatin have been effectively reduced by *Z. officinale*. In addition, it is also reported to inhibit the efflux of anticancer drugs by P-glycoprotein and to possess chemosensitising effects in certain neoplastic cells *in vitro* and *in vivo*.[52] Preclinical studies carried out in the last decade has shown that ginger and its phytochemicals dehydrozingerone, zingerone possess radioprotective effects in laboratory animals and in cultured cells *in vitro*. Mechanistic studies have indicated that the free radical scavenging, antioxidant affects anti-inflammatory and anti-clastogenic effects may contribute towards the observed protection. Additionally, studies with tumour bearing mice have also shown that zingerone selectively protects the normal tissues against the tumoricidal effects of radiation.[53]

Azadirachta Indica (*Neem*)

Radiosensitization by neem oil was studied using Balbc/3T3 cells and Severe combined immunodeficiency cells. Neem oil enhanced the radiosensitivity of the cells when applied both during and after x-irradiation under aerobic conditions. Neem oil completely inhibited the repair of sublethal damage and potentially lethal damage repair in Balbc/3T3 cells. The cytofluorimeter data show that neem oil treatment before and after x-irradiation reduced the G (2) + M phase, thus inhibiting the expression of the radiation induced arrest of cells in the G (2) phase of the cell cycle. These results suggest that neem oil enhanced the radiosensitivity of cells by interacting with residual damage after x-irradiation, thereby converting the sublethal damage or potentially lethal damage into lethal damage, inhibiting the DSB repair or reducing the G (2) phase of the cell cycle.[54]

Piper Betle (*Betel Leaf/Pan*)

Oral administration of PBL extract 1 h before irradiation in mice significantly enhanced radiation abated antioxidant potential of plasma and GSH level in all the observed organs. The treatment with extract effectively lowered the radiation induced LPO at 24 h in all the selected organs with maximum inhibition in. After 48 h, LPO was maximally inhibited in the group treated with the extract. Frequency of radiation induced micronucleated cells declined significantly at 24 h post-irradiation interval by PBL extract administration. The results suggest that PBL extract has high antioxidant potential and relatively non-toxic and thus could be assertively used to mitigate radiotherapy inflicted normal tissues damage and also injuries caused by moderate doses of radiation during unplanned exposures.[55]

Moringa Oleifera (*Drumstick Tree/Sahjan*)

Protective effect of *Moringa oleifera* leaf extract (MoLE) against radiation-induced LPO has been investigated. It was observed that, MoLE treatment restored GSH in the liver and prevented radiation induced augmentation in hepatic LPO. Phytochemical analysis showed that MoLE possess various phytochemicals such as ascorbic acid, phenolics (catechin, epicatechin, ferulic acid, ellagic acid, myricetin) etc., which may play the key role in prevention of hepatic LPO by scavenging radiation induced free radicals.[56] The hepatoprotective effect of MoLE against radiation-induced oxidative stress was assessed in terms of inflammation and LPO. Mice treated with MoLE prior to irradiation demonstrated an increase in SOD, Catalase (CAT), GSH and fluorescence recovery after photobleaching. Therefore pre-treatment with MoLE protected against γ-GR-induced liver damage. The protection may be attributed to the free radical scavenging activity of MoLE, through which it can ameliorate radiation-induced oxidative stress.[57]

Biophytum Sensitivum (*Lajjalu*)

B. sensitivum (*Lajjalu*) diminishes the elevated concentrations of Alkaline phosphatase, serum glutamic pyruvic transaminase and LPO levels in irradiated animals. Likewise, *B. sensitivum* substantially increased GSH content in the liver and intestinal mucosa of irradiated animals. There was an improvement in the total WBC count, cellularity of bone marrow, alpha-esterase positive cells, and relative organ weight of spleen as well as

thymus following *B. sensitivum* treatment. The amount of haematopoietic colonies on the surface of the spleen was exhibited to be increased subsequent to *B. sensitivum* administration. *B. sensitivum* treatment led to an induction in the production of cytokines like Interleukin (IL)-1beta, Interferon (IFN)-gamma and Granulocyte macrophage colony-stimulating factor (GM-CSF) in animals exposed to the whole body γ-GR. The present investigation suggests that the protective effect of *B. sensitivum* on Radiation-Induced haemopoietic damage is mediated through immunomodulation as well as sequential induction of IL-1beta, GM-CSF and IFN-gamma.[58]

Centella Asiatica (*Brahmi*)

C. asiatica rendered radioprotection to DNA and membranes against radiation exposure, both *in vitro* and *in vivo*. Administration of the extract prevents a radiation-induced decline in antioxidant enzyme levels. This suggests that radioprotection by *C. asiatica* extract could be mediated by mechanisms that act in a synergistic manner, especially involving antioxidant activity.[59]

Aphanamixis Polystachya (*Amoora Rohituka/Rohitak/Pithraj*)

Jagetia and Venkatesha investigated the effect of ethyl acetate fraction of EAP, commonly called as Rohituka, on the radiation-induced chromosome damage in the bone marrow cells of Swiss Albino mice exposed to various doses of γ-GR. Irradiation of mice to different doses of γ-GR caused a dose dependent elevation in the frequency of aberrant cells and chromosome aberrations such as chromatid breaks, chromosome breaks, dicentrics, acentric fragments and total aberrations at all the post-irradiation times studied. EAP treatment also reduced LPO in bone marrow cells in a concentration dependent manner. Thus EAP protects mouse bone marrow cells against radiation-induced chromosomal aberrations and this reduction in radiation-induced chromosome damage may be due to free radical scavenging and reduction in LPO.[60]

Phyllanthus Niruri (*Bhuiamla*)

The effects of PnAq and alcoholic (PnA1) extract of *P. niruri* on *in vivo* γ-GR induced chromosome aberration and *in vitro* antioxidant were studied. PnA1 showed highly significant *in vitro* free radical scavenging ability when compared to Dimethyl sulfoxide. It also showed highly significant decrease in chromosomal aberrations compared to radiation treated group. Radioprotective potential of PnA1 extract was found to be more effective than the PnAq extract. Higher radioprotective effect of the PnA1 extract may be attributed to rich presence of antioxidant polyphenolic compounds.[61]

Miscellaneous

There has been a great deal of interest in current years globally in the area of radioprotection for first responders going to work in the hot zones at the incident site. Evidence has been documented for the radioprotective potential of *Rhodiola imbricate* (*Roseroot*), a Himalayan high-altitude plant.[62-64] *Podophyllum hexandrum* (*Podophyllum emodi/Himalayan May Apple/Ladakhi/Papra)* is a promising radioprotective fraction that can be effectively used against lethal doses of γ-GRafter further investigations in higher animal models.[65] *Grewia asiatica* (*Phalsa*) fruit pulp extract was found to have strong radical scavenging activity and also showed *in vitro* radioprotective activity in protein carbonyl assay in a dose-dependent manner.[66,67] Possibly by down-regulating the expression of the proinflammatory cytokine Tgfb1, *Angelica sinensis* (*Dong qua)* may be useful in preventing and/or treating radiation-induced pulmonary fibrosis in the clinic.[68] Radix of *Isatis indigotica* (indigowood root, IR) has been used in traditional medicine for its potential anti-inflammatory effect. Evidences show that IR has potential to be a radioprotector, especially in recovery of hematopoietic system, reduction of inflammatory cytokines and intestinal toxicity. Indirubin may play a crucial role, but the underlying mechanism is not very clear and warrants further studies.[69] It is postulated that indirubin may play a pharmaceutical role in improvement of radiation mucositis, anorexia and difficulty in swallowing in the clinical trial. However, the exact mechanisms and pathways still need further analysis.[70] *Olea europaea* L. (*Olive tree/Jaitun*) leaves showed a significant anticlastogenic activity both before and after X-ray irradiation treatments.[71] *Rosemarinus officinalis* (Rosemary) extract (ROE) pre-treatment exhibited a significant increase in the number of crypt cells, mitotic figures and villus length. ROE treatment before irradiation caused a significant depletion in LPO and elevation in GSH levels.[72-75] The dried fruit extract from *Xylopia aethiopica* (XA) increased the antioxidant defence systems in the liver, kidney, brain and testis of irradiated animals, and may protect from adverse effects of the whole body radiation.[76-78] *Hippophae rhamnoides* (*Sea Buckthorn*), has been reported to exhibit significant radioprotection against whole body lethal irradiation by preventing radiation induced DNA damage.[79] The PnA1 extract of the plant *Ageratum conyzoides* Linn (*Sahadevi*) (ACE) was found to scavenge (2,2-diphenyl-1-picrylhydrazyl) DPPH radicals in a concentration-dependent manner, indicating that the radioprotection afforded by ACE may be in part due to the scavenging of reactive oxygen species induced by ionizing radiation.[80] Betulinic acid, a pentacyclic triterpene, is a new cytotoxic compound active on melanoma, neuroblastoma, glioblastoma and head and neck squamous cell carcinoma cells. It has been shown to have an additive effect on growth inhibition in melanoma cells when combined with irradiation. Betulinic acid could be a promising treatment agent in radioresistant head and neck cancer. A combination of betulinic acid with radiotherapy seems to be beneficial.[81] For patients harbouring glioblastomas multiforme (GBM) adjuvant treatment with radiation (radiation therapy or

radiosurgery) is a basis of treatment. However, radiation therapy becomes less sensitive in hypoxic areas inside the tumour. Trans sodium crocetinate (TSC) has been shown to increase oxygen diffusion in the brain and elevate the partial brain oxygen level. Sheehan *et al*., demonstrated that the use of TSC improves the extent of GBM tumour regression following radiation therapy and enhances survival. Radiosensitisation of hypoxic tumours through increased oxygen diffusion may have clinical utility in patients with GBM tumours but must be explored in a clinical trial.[82] A major problem in clinical cancer radiotherapy is radio-resistance in tumour cells and associated escape from apoptotic mechanism. Hence, as an approach to augment the apoptosis, a combination of radiation and tumour-selective cytotoxic agents could increase the effectiveness of treatment. Thus, the radiomodifying potential of diospyrin diethylether (D7), a plant-derived antitumor agent, was studied in fibrosarcoma tumour, both *in vitro* and *in vivo*. A combination of D7 and radiation *in vivo* caused significant inhibition of tumour growth *in vivo*, and restoring the liver enzyme activity to the 'normal' level. The combined treatment with quinonoid D7 and radiation caused increased cytotoxicity compared to a single treatment with either agent alone in fibrosarcoma tumour systems, both *in vitro* and *in vivo*.[83]

Many plant-derived polyphenols have been studied intently for their potential chemopreventive properties and are pharmacologically safe. These compounds include genistein, curcumin, resveratrol, silymarin, caffeic acid phenethyl ester, flavopiridol, emodin, green tea polyphenols, piperine, oleandrin, ursolic acid and betulinic acid. Recent research has suggested that these plant polyphenols might be used to sensitize tumour cells to chemotherapeutic agents and radiation therapy by inhibiting pathways that lead to treatment resistance. These agents have also been found to be protective from therapy-associated toxicities.[84]

DISCUSSION AND CONCLUSION

Because of repeated exposure to ionizing radiation in several aspects of human life particularly in areas relating to radiotherapy of cancer, food preservation, agriculture, industry and power generation, there is a necessity to develop an effective and non-toxic radioprotector. Thus, increasing use of nuclear radiation for human welfare necessitates the search for new, safe and cost-effective radioprotectors not only for the personnel charged with the responsibility of testing or working with radiation in laboratories, but also for the general public.

Initial developments of such agents focused on thiol synthetic compounds, such as amifostine. This agent decreased mortality; unfortunately, there were difficulties in administering aminothiols that led to adverse effects. Hence, the development of radioprotective agents with lesser toxicity and a protracted window of protection have gained much attention. Natural compounds have been assessed as radioprotectants and they appear to exert their effect through antioxidant and immunostimulant activities. In Ayurveda, the traditional Indian system of medicine, numerous plants have been used to treat free radical-mediated ailments and, therefore, it is logical to expect that such plants may also render some protection against radiation damage. A methodical screening strategy can offer clues to isolating prospective new candidate drugs from plant sources, for alleviation of radiation injury.

In present practical radiobiology, there exists an incredible effort in basic and translational research to isolate unique treatment modalities combining ionizing radiation with anticancer agents. This is mainly due to the vastly enhanced molecular understanding of intrinsic radioresistance and the profiling of cellular stress responses to irradiation during recent years.

The success in development of radioprotective agents will depend increasingly on an understanding of the molecular biology of radiation damage, cellular, tissue, organ responses to irradiation, the effect of co-morbid factors, and differences between tumour and normal cell biology. Approaches for producing normal tissue radioprotectors have in the past depended on upon recognized variances in tumour specific versus. Normal cell biology in terms of cell cycle, expression of specific growth factor receptors, cell surface adhesion molecules, or other biological or immunological characteristics. Molecular targets of innovative radioprotectors should focus on the mechanisms of action on irradiation-induced damage, after nuclear DNA strand breaks are repaired, concentrating instead on distal steps in the cellular response, including nuclear to mitochondrial transport of signalling molecules, and steps in induction of the cell death pathways including autophagy, apoptosis and necrosis. New strategies to identify metabolic differences between normal tissue and tumour cells will also be critical to the design of new classes of radioprotectors for clinical use.[5,85-87]

Certain conventionally prevalent medicinal plants have lately gained consideration for their capability to modify a number of signalling pathways that could initiate and facilitate the proliferation of cancer. In many cases, the potency of these compounds/formulations to protect the cancer cells from radiotherapy could be corroborated with the inhibition/activation of the relevant molecular markers. However, the literature citations on supporting clinical trials showing similar observations are quite limited. Nonetheless, a number of reports are available on antioxidants being able to protect against radiation-induced injury in experimental systems. In addition, this article has

reviewed some of the most promising plants, and their bioactive principles that are widely used in traditional systems of medicine, and which have rendered significant radioprotection in both *in vitro* and *in vivo* model systems. Based on these informations it has been presumed that intake of health promoting plant products in the diet might reduce the harmful side-effects of standard therapeutic modalities and enhance their selective toxicity towards malignant cells, leading to an overall improvement in the efficacy of anticancer treatment. As India and many Eastern countries have an enormous heritage of vast natural dietary and time tested medicinal resources it is worth exploring the possibility of developing efficient, economically viable and clinically acceptable radioprotectors for human application from these resources. Plants and their constituents with pharmacological activities that may be relevant to amelioration of radiation-mediated damage, including antiemetic, anti-inflammatory, antioxidant, cell proliferative, wound healing and haemopoietic stimulators too need to be explored. Thus, it is hoped that future research would add up positively, and would bring more of the aforesaid phytochemicals from 'bench to bedside' of the suffering humanity seeking relief from the awful maladies of cancer.

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