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*REVIEW ARTICLE*

# Radioprotection by Plant Products: Present Status and Future Prospects

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**The development of radioprotective agents has been the subject of intense research in view of their potential for use within a radiation environment, such as space exploration, radiotherapy and even nuclear war. However, no ideal, safe synthetic radioprotectors are available to date, so the search for alternative sources, including plants, has been on going for several decades. In Ayurveda, the traditional Indian system of medicine, several 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 systematic screening approach can provide leads to identifying potential new candidate drugs from plant sources, for mitigation of radiation injury. This article reviews 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. Plants and their constituents with pharmacological activities that may be relevant to amelioration of radiation-mediated damage, including antiemetic, antiinflammatory, antioxidant, cell proliferative, wound healing and haemopoietic stimulatories are also discussed. Copyright © 2005 John Wiley & Sons, Ltd.**

*Keywords:* herbal radioprotection; ionizing radiation; plants; traditional medicine; radioprotectors; bioactive principles.

## INTRODUCTION

The development of effective radioprotectors and radiorecovery drugs is of great importance in view of their potential application during both planned radiation exposure (e.g. radiotherapy) and unplanned radiation exposure (e.g. in the nuclear industry, natural background radiation emanating from the earth or other sources) (Arora and Goel, 2000; Bump and Malaker, 1998; Coleman *et al.*, 2003; Moulder, 2002; Nair *et al.*, 2001). These drugs are also likely to be useful in nuclear warfare to provide protection to personnel (Giambaressi and Jacobs, 1987). Over the past 50 years, research in the development of radioprotectors worldwide has focused on screening a plethora of chemical and biological compounds (Maisin, 1998; Sweeney, 1979; Weiss *et al.*, 1990; Weiss and Landauer, 2003). Numerous drugs of both synthetic and natural origin, e.g. antioxidants (Hahn *et al.*, 1994, 1999; Kumar *et al.*, 2002; Mitchell *et al.*, 1991, 2000; Vijaylaxmi *et al.*, 1996), cytoprotective agents (Links and Lewis, 1999), angiotensin-converting enzyme (ACE) inhibitors (Molteni *et al.*, 2000; Moulder *et al.*, 1998a,b), or angiotensin-II type-1 (AT1) receptor antagonists (e.g. losartan) (Moulder *et al.*, 1998c), metalloelements (Matsubara *et al.*, 1987; Miko *et al.*, 1998; Satoh *et al.*, 1989), immunomodulators (Furuse *et al.*, 1997; Guenechea *et al.*, 1997; Kalechman *et al.*, 1995a,b; Landauer *et al.*, 1997; Real *et al.*, 1992; Weiss and Simic, 1988), sulphydryl compounds (Capizzi and Oster, 1995; Livesey and Reed, 1987; Ramnath *et al.*, 1997; Spencer and Goa, 1995; Tannehill and Mehta, 1996; Wasserman, 1994; Weiss, 1997), lipopolysaccharides and prostaglandins (Hanson *et al.*, 1988; Joshima *et al.*, 1992; Riehl *et al.*, 2000; Van Buul *et al.*, 1999), vitamin A, C and E (Haranpanhalli *et al.*, 1994) and DNA binding ligands (Denison *et al.*, 1992; Martin *et al.*, 1996; Martin and Anderson, 1999) have been tested in both *in vitro* and *in vivo* models, and in human clinical trials to mitigate injuries caused by ionizing radiation exposure in the sublethal to supralethal range. Combinations of agents have also been tested with little success (Weiss *et al.*, 1990; Kumar and Gupta, 2002). The potential combination of differential radiomodifiers with metabolic modulators has been demonstrated in cell culture and animal models (Dwarakanath *et al.*, 1999; Sharma *et al.*, 2000a,b; Sharma and Jain, 2002).

Among the molecular radioprotectors, WR-2721 [S-2-(3-aminopropyl-amino) ethyl phosphorothioic acid], also known as amifostine, ethiophos (USA) or gammaphos (former USSR), is the most thoroughly investigated radioprotective drug, initially developed at the Walter Reed Army Research Institute, USA under the Antiradiation Drug Development Program of the US Army Medical Research and Development Command (Schuchter and Glick, 1993; Sweeney, 1979). However, the radioprotective effects

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of phosphorothioate compounds, including amifostine, are short term, and associated with severe side effects (e.g. nausea, vomiting, diarrhoea, hypotension, hypocalcaemia, nephro- and neuro-toxicity) at clinically effective doses (Cairnie, 1983; Kligerman *et al.*, 1984; Glover *et al.*, 1983; Landauer *et al.*, 1987). These limitations have greatly restricted their clinical use. Despite its drawbacks, amifostine (Ethyol®) is the only radioprotector that has been approved by the Food and Drug Administration (FDA), USA. Amifostine is being used clinically for ameliorating the incidence of xerostomia (dry mouth) in patients undergoing radiotherapy for the treatment of head and neck cancer (Brizel *et al.*, 2000).

In recent years, an array of haemopoietic growth factors and cytokines such as interleukin-7 (Bolotin *et al.*, 1996), interleukin-11 (Van der Meeren *et al.*, 2002), granulocyte-colony stimulating factor (G-CSF) (Russel *et al.*, 2000), granulocyte, macrophage-colony stimulating factor (GM-CSF) (Mettler and Guskova, 2001; Vose and Armitage, 1995), stem cell factor (SCF) (Zsebo *et al.*, 1992), antiapoptotic cytokine combinations (Herodin *et al.*, 2003), and epithelial cell-specific growth factors such as keratinocyte growth factor (Dorr *et al.*, 2001) have been used to mitigate radiation-induced damage and to augment recovery of stem cells and their precursors after radiation exposure. However, the success with these compounds has also been limited.

The fact remains that to date there is not a single radioprotective agent available which meets all the prerequisites of an ideal radioprotector, i.e. produces no cumulative or irreversible toxicity, offers effective long-term protection, possesses a shelf life of 2–5 years, and can be easily administered (Maisin, 1998; Coleman *et al.*, 2003). In view of this, the search for newer, less toxic and more effective radioprotector drugs continues.

Plants have been utilized since time immemorial for curing diseases. Even today, nearly 70% of the world's population is dependent on plants for handling their health related problems (Fabricant and Farnsworth, 2001).

A number of plants have been utilized successfully for the treatment of free radical-mediated diseases in humans such as rheumatoid arthritis, atherosclerosis, cancer, Alzheimer's disease, Parkinson's disease, aging and several other conditions including inflammatory diseases (Singh *et al.*, 2000; Das, 2002). It is, therefore, reasonable to expect that plants may contain certain compounds that can protect against radiation-induced reactive oxygen species (ROS)-mediated damage.

A number of medicinal plants evaluated for their radioprotective efficacy have shown protective effects against the damaging effects of ionizing radiation (Arora and Goel, 2000; Arora *et al.*, 2003a,b, 2004; Ben-Hur and Fulder, 1981; Gupta *et al.*, 2003a; Jagetia *et al.*, 2002; Jagetia and Baliga, 2002a,b; Kamat *et al.*, 1999; Maharwal *et al.*, 2003; Shen *et al.*, 1989; Shimoi *et al.*, 1994, 1996; Uma Devi *et al.*, 1999). Plant extracts eliciting radioprotective efficacy contain a plethora of compounds including antioxidants, immunostimulants, cell proliferation stimulators, antiinflammatory and antimicrobial agents, some of which may act in isolation as well as in combination with other constituents from the same plant. They may also augment the efficacy of compounds present in other plant species, to provide protection against radiation-induced damage (Fig. 1). In traditional Ayurveda, Chinese, Japanese, Korean, Siddha, European, Tibetan and Unani systems of medicine it is a common practice to use a multi-plant formulation for treating diseases. Synergistic effects may be present, and some of the toxic effects generated by active constituents of one plant may be countered by other constituents present. Most studies using natural plant products have focused on evaluation of radioprotective efficacy of whole extracts or polyherbal formulations, and in some cases fractionated extracts and isolated constituents (Abraham *et al.*, 1993; Agarwal and Nagaratnum, 1981; Arora and Goel, 2000; Arora *et al.*, 2003a,b, 2004; Hsu *et al.*, 1993; Gupta *et al.*, 2003a; Hsu *et al.*, 1997; Kim *et al.*, 2003; Kumar *et al.*, 1996; Kure, 1992; Narimanov 1993; Ohara *et al.*, 2001; Pande *et al.*, 1998b; Wang *et al.*, 1992; Wang, 1996; William *et al.*, 1996; Yang *et al.*, 1997) (Table 1; Fig. 1).

There is a need to critically review the radioprotective properties of these plant products. The present review attempts to provide an overview of plants and their constituents with pharmacological activities relevant to radioprotection, radiorecovery, and treatment of radiation injuries, including antioxidant, antiinflammatory,

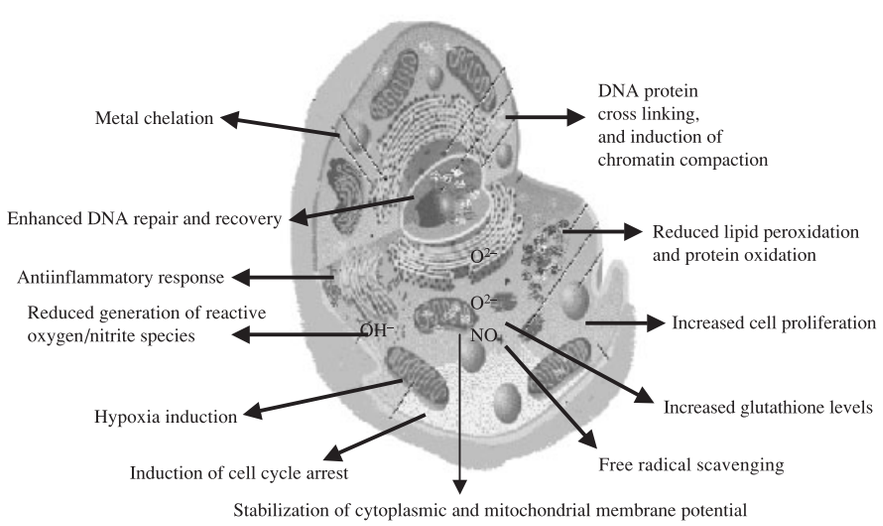


**Figure 1.** Some mechanisms by which natural plant products render radioprotection.

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**Table 1. Traditional herbal plants showing therapeutic activities relevant to radioprotection**

| Plant | Family | Traditional uses and radioprotective efficacy | Reference |
|---|---|---|---|
| *Aegle marmelos* Corr. Ex Roxb | Rutaceae | To promote digestion, treat colic, diarrhoea and dysentery, intermittent fever, melancholia and heart palpitation | Jagetia *et al.*, 2003e |
| | | *A. marmelos* provided protection against radiation-induced sickness and mortality in mice. Optimum protective dose was 15 mg/kg b.w. [1/82 of the $LD_{50}$ dose (2250 mg/kg b.w.)] | |
| *Acanthopanax senticosus* Harms *(Shigoka)* | Araliaceae | To restore normal functioning of spleen and kidneys. Also used as a remedy for bronchitis, heart ailments and rheumatism | Yonezawa *et al.*, 1989 |
| | | Pre-irradiation administration of Shigoka extract (5 mg/kg b.w.; –24 h; i.p.) rendered maximum survival (80%), while post-irradiation administration (+12 h; 9.5 Gy) exhibited 30% survival. The extract also increased leukocyte counts and diminished cerebral haemorrhage | Miyanomae and Frindel, 1988. |
| *Ageratum conyzoides* L. | Asteraceae | In India *A. conyzoides* leaves are applied to cuts and sores, while the juice is considered as antilithic. | Jagetia *et al.*, 2003d; Satyavati *et al.*, 1987 |
| | | An alcoholic extract of *A. conyzoides* (75 mg/kg b.w.; –1 h) effectively protected mice against 10 Gy-induced gastrointestinal and bone marrow related death (DMF: 1.3) | |
| *Allium cepa* L. | Alliaceae | Dried bulb has been used orally for treating diabetes, dropsy, colic, diabetes, dysentery, fever, chronic bronchitis, body heat and as an emmenagogue | Bakina *et al.*, 1967 |
| | | Administration of the dried bulb of *Allium cepa* at a concentration of 20 mg/kg was active against x-irradiation | |
| *Allium sativum* L. *Gaertn* | Alliaceae | The plant has been reported to possess antixidant, antimicrobial, antitumour, antimutagenic, antiinflammatory, antiviral and antiulcer properties. Radioprotective efficacy of aged garlic extract (produced by storing sliced raw garlic in 15–20% ethanol for 20 months and containing compounds such as S-allylcysteine, S-allylmercaptocysteine, allixin and selenium which are stable, highly bioavailable and possess significant antioxidant and anticarcinogenic properties) has been reported | Reeve *et al.*, 1993; Singh *et al.*, 1995a; Gupta, 1996 |
| *Aloe arborescens* | Liliaceae | Acts as a cell proliferant, healer, demucent and allergy reducer. Topically it is used for skin ulcers, burns, irritations and bites | Sato *et al.*, 1990 |
| | | An extract of *Aloe arborescens* (AA S6-3-b) provided protection to mouse skin against soft x-irradiation by scavenging hydroxyl radicals and reducing alterations in enzyme activity (SOD and glutathione peroxidase activity) | |
| *Archangelica officinalis* Hoffm. | Umbelliferae | Used in traditional Chinese medicine (TCM) to promote fertility, relieve fatigue, migraine and dysmenorrhoea, and ease anxiety and nervous tension | Narimanov *et al.*, 1991; Narimanov, 1993. |
| | | Administration of a combination of *Archangelica officinalis* and *Ledum palustre* extracts to mice 5–15 min before irradiation [7.5 Gy ($LD_{90/30}$)] rendered 70% survival (DMF: 1.48) | |
| *Angelica sinensis* (Oliver) Diels | Apiaceae | Used in TCM to replenish blood, improve the rhythmicity and tonicity of uterine muscles, as an emollient and laxative for chronic constipation in aged and debilitated humans. *Angelica sinensis* is used externally for burns | Liu and Xiao, 1993; Mei *et al.*, 1988, 1991 |
| | | *Angelica sinensis* root extract, administered to mice via i.v. route (post-irradiation), restored 80% of pregnancy rate vs none in controls. The polysaccharide fraction, containing a ferulic acid, increased survival in irradiated mice (>30 days) by promoting haemopoietic stem cell proliferation | |
| *Amaranthus paniculatus* Linn. | Amaranthaceae | It is used for purifying blood and treating scrofulous sores | Verma *et al.*, 2003 |
| | | *A. paniculatus* leaf extract (600 mg/kg b.w./ day for 2 wks) protected mice against 5 Gy by reducing lipid peroxidation, glycogen and cholesterol levels in brain | |

**Table 1. (*continued*)**

| Plant | Family | Traditional uses and radioprotective efficacy | Reference |
|---|---|---|---|
| *Curcuma longa* Linn. | Zingiberaceae | *Curcuma longa* rhizome is widely used in Indian cuisine as well as in traditional medicine. Pharmacological activities include antiinflammatory, anti-HIV, antibacteria, antitumour, antioxidant and nematocidal effects. Curcumin (diferuloylmethane) has been reported to render radioprotective effect | Ammon, 1993; Ammon and Wahl, 1991; Chaudhary *et al.*, 1999 |
| *Glycyrrhiza glabra* L. | Fabaceae | *Glycyrrhiza glabra* finds use in both Indian and TCM due to its antibacterial, antiinflammatory, antiviral, antimutagenic, antioxidant free radical scavenging and immunomodulating activities<br>*G. glabra* (70% methanol extract; 100 μg/mL) protected rat microsomal membranes from γ-radiation (up to 500 Gy) induced lipid peroxidation, while 20 μg/mL could provide almost complete (99%) protection to plasmid (pBR322) DNA from radiation-induced strand breaks | Agarwal and Singh, 1999; Belinky *et al.*, 1998; Kovalenko *et al.*, 2003; Shetty *et al.*, 2002 |
| *Hypericum perforatum* Linn. | Hypericaceae | Traditionally used in several European countries and USA for healing of wounds, depression, nervous disorders, insomnia, Herpes infections, inflammations and menstrual complaints. In India, it is used as an antihelmintic and emmenagogue<br>In murine model, *Hypericum perforatum* aqueous extract protected bone marrow and intestinal mucosa against x-ray in a concentration and time-dependent manner | Smyshlieva and Kudriashov, 1992 |
| *Lycium chinense* | Solanaceae | Used in TCM as a tonic for general debility, replenishment of blood, eyesight improvement, vertigo, lumbago and impotence<br>Administration of root extract (500 mg/kg body wt) prior to x-irradiation significantly improved the recovery of leukocyte, erythrocyte and thrombocyte counts and haematocrit in ICR strain mice | Hsu *et al.*, 1999 |
| *Mentha arvensis* Linn. | Lamiaceae | It has carminative, antiseptic, refrigerant, stimulant, emmenagogue and diuretic properties<br>Pre-irradiation treatment with chloroform extract protected mice against gastrointestinal and bone marrow death (DMF: 1.2) | Jagetia and Baliga, 2002a |
| *Moringa oleifera* Lam. | Moringaceae | *M. oleifera* is used in Ayurveda to treat asthma, gout, rheumatism, inflammation, epilepsy, cardiac and circulatory disorders, nervous debility and healing of wounds. Pre-treatment (i.p.) with a leaf extract (150 mg/kg; single dose) significantly reduced the percent aberrant cells in metaphase chromosomes to normal range by day 7 post-irradiation in mice | Rao *et al.*, 2001 |
| *Syzygium cumini* L. Skeels | Myrtaceae | In Ayurveda, *S. cumini* is used to treat bronchitis, asthma, dyspepsia, diabetes, ulcers and blood impurities. Treatment of human peripheral blood lymphocytes with *S. cumini leaf* extract (0–100 μg/mL) before γ-radiation (3 Gy) significantly reduced micronuclei-induction | Jagetia *et al.*, 2002 |
| *Tephrosia purpurea* (L.) Pers. | Fabaceae | *T. purpurea* roots are used to treat snake bite; diarrhoea, liver and spleen disorders, inflammation, boils and pimples. *Tephrosia* extract (200 mg/kg b.wt) protected Swiss albino mice against radiation (5 Gy)-induced haemopoietic injury | Taraphdar *et al.*, 2002 |

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immunostimulatory, wound healing and antimicrobial effects, are discussed.

## BIOLOGICAL ACTIVITIES RELEVANT TO RADIATION PROTECTION

### Antiemetic activity

Exposure to ionizing radiation induces nausea and vomiting, particularly in scenarios relevant to radiation disaster. Plants with antiemetic activity, e.g. *Centella asiatica, Mentha piperita, Zingiber officinale* have been evaluated for their ability to provide radiation protection (Srivastava *et al.*, 1997; Meyer *et al.*, 1995; Phillips *et al.*, 1993). *C. asiatica* rendered protection against radiation-induced conditioned taste aversion in rats (Shobi and Goel, 2001). An ethanol extract of *Ginkgo biloba*, along with ginger extract, has been shown to have antiemetic activity as observed by conditioned taste aversion (CTA) studies (Frisch *et al.*, 1995), and these workers opined that it might be useful in achieving radioprotection too. In human clinical trials, *Zingiber officinale* (ginger) has been reported to ameliorate chemotherapy-induced nausea and vomiting and to protect against gastrointestinal haemorrhage (Meyer *et al.*, 1995). Recently, Jagetia *et al.* (2003b) have also shown the radioprotective property of *Zingiber officinale*. The antiemetic principles present in *Zingiber officinale* include shogaols (6-, 8-, 10-shogaol) and gingerols (6-, 8-, 10-gingerol) (Akita *et al.*, 1998; Yang *et al.*, 2002). However, the role of *Zingiber officinale* and its bioactive compounds in mitigation of radiation-induced emesis has not been worked out so far, and the same remains true for several other plants.

With the growing need for behavioural radioprotectors, in view of their potential applications during space exploration and rescue operations, there is a need to search for more effective antiemetic drugs from plants.

### Antiinflammatory activity

A number of plants and their bioactive constituents, including flavonoids, exhibit antiinflammatory properties (Handa *et al.*, 1992; Middleton *et al.*, 2000) and the radioprotective response in several cases is mediated by this effect. Novel antiinflammatory drugs could, therefore, be useful in ameliorating radiation damage with less severe side effects than the synthetic drugs currently available. *Glycyrrhiza glabra*, liquorice, a plant with antiinflammatory and chemopreventive properties (Jo *et al.*, 2004), is known to possess radioprotective properties. Topical application of glycyrrhizin, an active constituent of the rhizome, has been shown to exhibit antiinflammatory properties (Ozaki and Ono, 2002). A number of plants, e.g. *Allium sativum, Aloe vera, Tinospora cordifolia, Hippophae rhamnoides, Curcuma longa, Centella asiatica, Stephania tetrantra, Spirullina platensis, Syzygium cumini, Ocimum sanctum, Moringa oleifera, Zingiber officinale, Eleutherococcus senticosus* (Ammon and Wahl, 1991; Ben-Hur and Fulder, 1981; Chen *et al.*, 1999; Ezeamuzie *et al.*, 1996; Jaiswal and Bordia, 1996; Park *et al.*, 1998; Penna *et al.*, 2003; Thomson *et al.*, 2002; Udupa *et al.*, 1994; Vazquez *et al.*, 1996) and some of their bioactive constituents such as quercetin, curcumin, c-phycocyanin, allicin, gingerol, caffeine exhibit antiinflammatory properties (Hebbar *et al.*, 2002; Romay *et al.*, 1998; Sidhu *et al.*, 1999; Zhang *et al.*, 1997) and may have potential in the management of radiation injury. Future developments may head towards evaluation of more herbal products that either stimulate the production of antiinflammatory cytokines (e.g. IL-10, IL-13) or selectively inhibit radiation-induced signal transduction pathways.

### Antimicrobial activity

One of the major causes of death following radiation-induced myelosuppression is infection arising primarily from translocated endogenous Gram-negative gastrointestinal bacteria (Gordon *et al.*, 1955). A number of antibiotics e.g. aminoglycosides, such as gentamycin, netilimycin, tobramycin and amikacin, ureido-penicillins and monobactams have been used for therapeutic purposes post-irradiation to suppress infection. Plants such as *Ocimum sanctum, Podophyllum hexandrum, Mentha arvensis, Stephania tetrantra, Hypericum perforatum, Syzygium cumini, Moringa oleifera, Terminalia chebula, Curcuma longa* that exhibit antimicrobial activity have been reported to be radioprotective (Agarwal and Singh, 1999; Eilert *et al.*, 1981; Jagetia and Baliga, 2002a; Singh and Shah, 1994; Sakar and Tamer, 1990; Schapoval *et al.*, 1988). Compounds reported to have antimicrobial activity include benzopyrans, xanthones, flavonoids and tannins (Ishiguro *et al.*, 1986). The coming years are likely to witness the application of plant products which particularly can stimulate radiorecovery via their antimicrobial effect.

### Antioxidant activity

Antioxidants protect the cell against reactive oxygen/nitrogen species (ROS/RNS) by scavenging the free radicals in the cellular milieu. The increased levels of ROS/RNS generated during irradiation have been shown to be effectively scavenged by some antioxidants present in plants (Gupta *et al.*, 2003a; Uma Devi *et al.*, 2000). Antioxidants delay the oxidation of biomolecules by inhibiting the initiation and propagation of oxidizing chain reactions thereby interfering with the initiation of apoptosis (Halliwell and Gutteridge, 1989, 1990). Antioxidants can be phenolic compounds (tocopherols, flavonoids and phenolic acids), nitrogen compounds (alkaloids, amines, amino acids and chlorophyll derivatives) or carotenoids as well as vitamins including ascorbic acid (Beckman and Ames, 1998; Boloor *et al.*, 2000; Burton *et al.*, 1982; Choi *et al.*, 2002; Diplock *et al.*, 1998; Duthie and Crozier, 2000; Duthie *et al.*, 1997; Havsteen, 1984; Jadhav and Bhutani, 2002; Kandaswami and Middleton, 1994; Parshad *et al.*, 1998; Scarterzzini and Speroni, 2000). A relation between the antioxidant property and radiation protection by plant flavonoids and phenols was suggested by Shimoi *et al.* (1994, 1996) and Emerit *et al.* (1997a,b). Antioxidant molecules have been shown to be present in plant species belonging to different levels of organization (from simple to

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complex): algae (Karpov *et al.*, 2000; Qishen *et al.*, 1989; Sarma *et al.*, 1993; Singh *et al.*, 1995b; Upasani and Balaraman, 2003; Zozulia and Iurchenko, 2000), gymnosperms (Alaoui-Youssefi *et al.*, 1999) and angiosperms and are known to provide protection from oxidative damage in biological systems. The radioprotective property of plants including *Asparagus racemosus, Potentilla alba, Ocimum sanctum, Podophyllum hexandrum, Stephania tetrantra, Tinospora cordifolia, Hippophae rhamnoides, Zingiber officinalis, Centella asiatica, Ginkgo biloba, Syzygium cumini, Ligusticum wallichii, Vitis vinifera, Portulaca oleracea, Panax ginseng*, and the ability to extend life span, has been attributed to the presence of antioxidant molecules in these plants (Arora and Goel, 2000; Arora *et al.*, 2003a,b, 2004; Bestwick and Milne, 2001; Cao *et al.*, 1993; Castillo *et al.*, 2000; Ganasoundari *et al.*, 1997a,b, 1998; Goel *et al.*, 2002a,b; Gupta *et al.*, 2003a; Shetty *et al.*, 2002; Gohil *et al.*, 2000; Jagetia *et al.*, 2003b; Jagetia and Baliga, 2003; Jadhav and Bhutani, 2002; Kamat *et al.*, 2000a,b; Landauer *et al.*, 2000; Pincemail *et al.*, 1989; Shimoi *et al.*, 1994; Uma Devi *et al.*, 2000; Yoshioka, 1997; Zhang and Zhang, 1990).

Plants with radioprotective properties have been shown almost invariably to possess antioxidant biomolecules. The radioprotective effect of antioxidant molecules such as eugenol from *Zingiber officinalis*, genistein from *Glycine max*; orientin, vicenin and ursolic acid from *Ocimum sanctum*, curcumin from *Curcuma longa*, bixin from *Bixa orelleana*, quercetin from *Podophyllum hexandrum*, $\beta$-carotene from the heat-tolerant algae *Dunaliella baradwiil*, luteolin from *Aspalanthus linearis*, allicin from *Allium sativum*, glycyrrhizin from *Glycyrrhiza glabra*, caffeine from *Coffea arabica*, flavan-3-ols (procyanidins) from *Vitis vinifera*, flavone glycosides and terpenes from *Ginkgo biloba*, silymarin from *Silybum marianum*, epigallocatechin from 'Thea viridis' (green tea percolate) and melatonin (N-acetyl-5-methoxytryptamine) from *Hypericum perforatum, Silybum marianum, Lycium spp.* has largely been attributed to the antioxidative properties of these compounds (Abraham *et al.*, 1993; Alaoui-Youssefi *et al.*, 1999; Ben Amotz *et al.*, 1996, 1998; Booth *et al.*, 1999; Chaudhary *et al.*, 1999; Devasagayam and Kesavan, 1996; George *et al.*, 1999; Inano and Onado, 2002; Kamat *et al.*, 2000a; Kumar *et al.*, 2001; Kim *et al.*, 2003; Kropacova *et al.*, 1998; Landauer *et al.*, 2000, 2003; Ramadan *et al.*, 2002; Stelzer *et al.*, 1994; Reiter and Tan, 2002; Shimoi *et al.*, 1994; Theresiamma *et al.*, 1996; Yoshioka, 1997). Evidently, the use of plants and their bioactive constituents with antioxidant activity is highly relevant in mitigation of radiation-induced oxidative damage.

## Haemopoietic stimulation

Exposure of mammals to ionizing radiation leads to the development of a complex dose dependent cascade of changes including injury to the lymphoid and haemopoietic system, which can result in septicaemia and death (Prasad, 1999). Agents capable of enhancing survival in the radiation dose inducing the haemopoietic syndrome have typically been associated with accelerated haemopoietic regeneration. An accelerated ability to regenerate new haemopoietic elements, especially those that are important in controlling microbial infections, such as granulocytes, allows the host to resist opportunistic infections better and, hence, enhances survival. *Acanthopanax senticosus, Ginkgo biloba, Hippophae rhamnoides, Panax ginseng, Podophyllum hexandrum, Tinospora cordifolia, Boerhaavia diffusa, Spirullina* provide total-body radiation protection by stimulating haemopoiesis (Goel *et al.*, 2002a,b,c; Kapoor and Mehta, 1998; Miyanomae and Frindel, 1988; Song *et al.*, 2003; Takeda *et al.*, 1982; Thali *et al.*, 1998; Yonezawa *et al.*, 1981). Both isolated compounds (e.g. ginsan, a purified polysaccharide isolated from *Panax ginseng* (Song *et al.*, 2003; Kim *et al.*, 1998b) and glycyrrhizic acid (Lin *et al.*, 1996) and complex herbal preparations used in Ayurveda [e.g. Liv 52 (Ganapathi and Jagetia, 1995; Saini *et al.*, 1985), Triphala (Jagetia *et al.*, 2002), Abana (Jagetia *et al.*, 2003c), Mentat (Jagetia and Baliga, 2003) Chayawanprash (Agarwal *et al.*, 2003)], Chinese medicine [Si-Jun-Zi-Tang (Hsu *et al.*, 1996a), Si-Wu-Tang (Hsu *et al.*, 1996b), Kuei-Pi-Tang (Hsu *et al.*, 1991; Jeng-Sheng-Yang-Yung-Tang (Hsu *et al.*, 1992), Lifukang (Kim *et al.*, 1998a)] and Japanese medicine [Juzen-Taiho-Toh (Ohnishi *et al.*, 1990)] have been evaluated for their radioprotective effects particularly for attenuating damage to the haemopoietic system. In coming years, it can be expected that plant products that stimulate the haemopoietic system will find a use in mitigating radiation induced-injury and enhancing radiorecovery.

## Immunostimulant activity

Numerous plants have been reported to exert radioprotective effect via immunostimulatory activity in *in vitro* and *in vivo* models (Agarwal and Singh, 1999; Song *et al.*, 2003). Plants possessing immunostimulatory activity, e.g. *Podophyllum hexandrum*, *Hippophae rhamnoides*, *Viscum album*, *Ocimum sanctum, Tinospora cordifolia*, have been reported to provide protection by increasing spleen colony forming units (Ganasoundari *et al.*, 1997b, 1998; Goel *et al.*, 2002b; Narimanov *et al.*, 1992). Several triterpenoids such as glycyrrhizic acids, ursolic acid and oleanolic acid possess immunopotentiating activity (Raphael and Kuttan, 2003). The radioprotective effects of glycyrrhizin and glycyrrhizic acid on cellular immunocompetence has been reported by Lin *et al.* (1996). *Panax ginseng*, a known radioprotective plant, is known to augment natural killer (NK) cell activity (Kim *et al.*, 1990), production of interleukin-1 (IL-1) (Kim *et al.*, 1998b), interleukin-2 (IL-2) (Ma *et al.*, 1995), tumor necrosis factor-alpha (TNF-$\alpha$) (Gao *et al.*, 1996), granulocyte macrophage-colony stimulating factor (GM-CSF; Kim *et al.*, 1998b), increase in population of CD3, CD4, CD8 cells (Mizuno *et al.*, 1994). An acidic polysaccharide (ginsan) isolated from *Panax ginseng* has been reported to activate multiple effector pathways of the immune system thereby rendering radioprotection (Kim *et al.*, 1998b).

Thatte *et al.* (1988) suggested that *Tinospora cordifolia* activates macrophages to release GM-CSF activity, while Kapil and Sharma (1997) have reported enhanced humoral and cell mediated immunity by syringin (TC-4) and cordiol (TC-7), the active constituents of *Tinospora cordifolia.* Other plants with

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immunostimulant properties such as *Allium sativum, Ocimum sanctum* (which augments NK cells, stimulates T cells and IL-2 production), *Aloe vera* (which stimulates IL-1 and TNF-$\alpha$ (Agarwal and Singh, 1999) and *Eleutherococcus senticosus*, have been shown to provide radioprotection (Ben-Hur and Fulder, 1981).

### Metal chelation activity

Iron is considered to be an important contributor in the generation of reactive oxygen species (Stevens *et al.*, 2000). Agents that chelate free iron can reduce ROS-mediated damage including radiation-induced damage (Morel *et al.*, 1993; Ramadan *et al.*, 2002). Polyphenolic compounds, including flavonoids, present in a number of medicinal plants have been reported to possess metal chelating properties (Bars *et al.*, 1994; Sgaragli *et al.*, 1993). Flavonoids (orientin and vicenin) from *Ocimum sanctum*, catechin present in *Camellia sinensis*, and quercetin present in *Podophyllum hexandrum* extract are known to play a pivotal role in metal (iron) chelation (Ganasoundari *et al.*, 1997a; Prem Kumar and Goel, 2000; Sestili *et al.*, 1998; Uma Devi *et al.*, 2000). Other phytoconstituents such as quercetin, catechin, silymarin and luteolin are also known to chelate metal ions, thereby rendering radioprotection (Duthie *et al.*, 2000; Gebhardt, 2002; Korina and Afanas'ev, 1997; Morel *et al.*, 1993; Ramadan *et al.*, 2002). Afanas'ev and coworkers (1989) have reported that rutin and quercetin can inhibit iron ion-dependent lipid peroxidation by chelating iron ions. Rutin has been shown to protect against tert-butyl hydroperoxide-induced oxidative damage to DNA by acting as a metal ion chelator (Aherne and O'Brien, 2000). Another compound, mimosine, can chelate iron and reversibly block cell cycle progression in mammalian cells (Kulp and Vulliet, 1996) via inhibition of cyclin-dependent kinase (cdk) activity (Kulp *et al.*, 1996). One of the mechanisms whereby *Podophyllum* provides radioprotection, apart from iron chelation (Prem Kumar and Goel, 2000), could include its ability to arrest the cell cycle in G1 phase.

### Wound healing activity

In the aftermath of a nuclear accident, a number of patients will present combined injury wounds (i.e. wounds from burns and/or trauma with local or systemic radiation exposure before, during or after the injuries). The wound healing response in these patients is likely to be delayed due to their compromised immunological state and the synergistic characteristic of combined injury. The mortality of radiation injury is greatly increased by concomitant trauma and thermal injuries. Topical application of steroidal or non-steroidal antiinflammatory agents is the most common treatment for radiation injury of the skin, however, the results are usually not satisfactory and local toxicity has been observed (Chen *et al.*, 1999). Therefore, plant products with wound healing activity could be useful for treating combined injury wounds.

A number of plants containing triterpenes, alkaloids and other constituents are known to promote wound healing (Fleischner, 1985; Sarma *et al.*, 1990). These bioactive constituents influence different phases of the healing process namely, inflammation that leads to haemostasis and clot formation, fibroplasias and neovascularization, formation of a granulation tissue, reepithelialization and finally the formation of new extracellular matrix and tissue remodelling (Chitra *et al.*, 1998).

Several plants, e.g. *Aloe vera, Angelica sinensis, Centella asiatica, Terminalia chebula, Hippophae rhamnoides, Ocimum sanctum* and *Curcuma longa*, with radioprotective properties, possess antibacterial, antifungal, antioxidant, antiinflammatory and cell proliferative activity (Ahmad *et al.*, 1998; Dutta *et al.*, 1998; Klein and Penneys, 1988; Sakar and Tamer, 1990; Udupa *et al.*, 1994) and are useful for the treatment of burns and wounds (Davis *et al.*, 1987; Ianev *et al.*, 1995; Suguna *et al.*, 2002; Shetty *et al.*, 1999; Rodriques-Bigas *et al.*, 1988). Ascorbic acid has been reported to alter glutathione, superoxide dismutase and lipid peroxidation in mouse skin exposed to fractionated $\gamma$-radiation, thereby protecting the skin (Jagetia *et al.*, 2003a). *Aloe arborescens* and *Aloe vera* have been shown to be effective for treating radiation-induced burns (Chitra *et al.*, 1998; Sato, 1990, 1991) and acute radiation dermatitis (Chen *et al.*, 1999). Chamomile cream and almond ointment has also been reported to mitigate acute radiation skin reactions (Maiche, 1991). *Centella asiatica, Curcuma longa, Hypericum perforatum* and *Hippophae rhamnoides* extracts have been traditionally used to accelerate wound healing (Ianev *et al.*, 1995), and in recent years particularly in cases of chronic post-surgical and post-traumatic wounds (Jadhav and Bhutani, 2002). *Curcuma longa* has been used for healing of corneal wounds (Mehra *et al.*, 1984), while *C. asiatica* extracts have been used as a therapy in the treatment of second- and third-degree burns (WHO Monographs, 1999). *Centella asiatica* extracts (marketed under the trade name Madecassol®) and tetrandrine (a bisbenzylisoquinoline alkaloid isolated from *Stephania tetrantra* S. Moore) have been shown to reduce acute radiation reactions via their antiinflammatory activity (Chen *et al.*, 1999). Shukla and coworkers (1999) have shown that asiaticoside obtained from *Centella asiatica* helps in wound healing. The search for promising plant extracts that can stimulate wound healing, while decreasing pain, is therefore warranted.

## PLANTS WITH RADIOPROTECTIVE EFFICACY: THEIR PHARMACOLOGICAL BASIS

### *Centella asiatica* Linn

*Centella asiatica* (Apiaceae), is prescribed in the Indian system of medicine for the treatment of various diseases (Diwan *et al.*, 1991; Zafar and Naaz, 2002). It has traditionally been used to improve mental ability (Sarma *et al.*, 1995; Sanjay, 2000), healing of ulcers, wounds and skin lesions (Srivastava *et al.*, 1997; Tan *et al.*, 1997), and in an attempt to restore youth, memory and longevity (Kapoor, 1990). *Centella* has also been reported to have CNS depressant effects and improve maze learning capability in rats (Rao *et al.*, 1999). *Centella asiatica* contains several antioxidant molecules such as carotenoids, ascorbic acid, terpenoids and other biologically

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active components such as asiaticoside, asiatic acid, brahmoside, brahminoside, brahmic acid, centoic acid, centellic acid, isobrahmic acid and thankunic acid (Srivastava *et al.*, 1997; Brinkhaus *et al.*, 2000).

There are several reports regarding the neuromodulatory effect of *Centella asiatica*, but only a few studies document the protective effects against radiation-induced behavioural changes and performance deficits (Goel *et al.*, 2000d; Shobi and Goel, 2001). Studies related to behavioural radioprotection assume importance since radiation is known to cause severe behavioural perturbations such as conditioned taste aversion (CTA), performance decrement and learning. Total-body exposure to even very low doses (0.1 cGy) of electron beam can induce retrograde amnesia (Wheeler and Hardy, 1985), while higher dose of radiation (10–100 Gy) induce emesis, nausea, taste aversion and diarrhoea, besides behavioural degradation in terms of coordination, performance, learning and memory (Brogo, 1984; Burghardt and Hunt, 1985; Franz, 1985). An aqueous extract of *Centella asiatica* (100 mg/kg body weight; i.p.; single dose; –1 h) when used to protect Sprague Dawley rats against the adverse effects of low-dose ionizing radiation (2 Gy) rendered significant protection against radiation-induced body weight loss and conditioned taste aversion (since there is no emesis in rodents, taste aversion is an equivalent manifestation), suggesting that *Centella asiatica* could be useful in preventing radiation-induced behavioural changes during clinical radiotherapy (Shobi and Goel, 2001).

*Centella asiatica* extract (100 mg/kg body wt.) administered orally has recently been shown to provide total-body protection in mice against sublethal (8 Gy) $^{60}$Co gamma radiation (Sharma and Sharma, 2002). These workers have reported significantly less radiation-induced body weight loss in drug treated animals. Though the precise reason for radioprotection has not been elucidated, some of the reasons put forth include reduction of lipid peroxidation and membrane peroxidation, increase in haemoglobin percentage, and increased secretion of serotonin (a known radioprotective agent). The detoxification effect of *Centella asiatica* against combined toxicity of $\gamma$-radiation and cadmium chloride has been reported by Agarwal and coworkers (2001), while the effect on cognition and markers of oxidative stress in rats has been reported by Kumar and Gupta (2002).

### *Ginkgo biloba* Linn.

*Ginkgo biloba* (Cycadaceae), a plant indigenous to China, Japan and Korea, has been reported to stimulate endogenous antioxidants such as glutathione and attenuate oxidative stress (Rong *et al.*, 1996a,b). It has also been used in the modern system of medicine for the treatment of circulatory (Heinjen and Knipschild, 1992) and equilibrium disorders (Haguenauer *et al.*, 1986), asthma and senility. A *Ginkgo biloba* extract (Egb761), which is a mixture of flavonoids, heterosides and terpenes with antioxidant properties (De Feudis, 1991; Huguet *et al.*, 1994), has been shown to prevent mitochondrial aging by reducing oxidative damage (Sastre *et al.*, 1998). *Ginkgo biloba* extract is also useful in the treatment of cerebral disorders due to aging and hypoxia (Duche *et al.*, 1988).

*G. biloba* contains nearly 300 compounds including ascorbic acid, $\alpha$-carotene, $\beta$-carotene, flavonoids (kaempferol, quercetin, myricetin, ginkgetin, isoginkgetin etc.), coumarins, catechins, ginkgolides, bilobalide, rhamnetin, $\gamma$-tocopherol to name a few (De Feudis, 1991), many of which individually in isolated form render radioprotective effects.

An ethanol (30%) extract of the dried leaf at a concentration of 100 µg/mL was effective when tested on a culture exposed to clastogenic factors from plasma of human subjects exposed to irradiation (Emerit *et al.*, 1995a). Treatment of recovery workers from the Chernobyl accident site was found to be effective when an oral dose of 40 mg/day was given 3 times daily for 2 months (Emerit *et al.*, 1995b).

An intravenous infusion of an ethanol extract of *G. biloba* leaves, at a dose of 100 mg/person was found to be effective on patients with vasogenic oedema observed after irradiation of the brain (Hannequin *et al.*, 1986).

*G. biloba* extract provided protection to brain neurons against oxidative stresss (Oyama *et al.*, 1996; Smith *et al.*, 1996). *G. biloba* leaf extract (30%) at a concentration of 100 µg/mL assayed in rat cerebellar neuronal cell culture, was active on neurons against hydroxyl radical-induced apoptosis (Ni *et al.*, 1996). Agents that inhibit free radical-mediated apoptosis are known to provide radioprotection, which could help to explain the radioprotective effect of *G. biloba*.

### *Hippophae rhamnoides* Linn.

*Hippophae rhamnoides* (Sea Buckthorn; Family: Elaegnaceae) has been used in traditional Tibetan and Indian systems of medicine for centuries. In Tibet, the plant was used as early as 900 AD. The plant has been extensively exploited for treatment of sluggish digestion, stomach malfunctioning (Nikitin *et al.*, 1989; Xiao *et al.*, 1992), burn and wound healing (Ianev *et al.*, 1995; Nikulin *et al.*, 1992), circulatory disorders, ischaemic heart disease (Liu *et al.*, 1998; Zhang, 1987), hepatic injury (Cheng *et al.*, 1994) and neoplasia (Nikitin *et al.*, 1989). Sea Buckthorn oil is used as a treatment of oral mucositis, vaginal mucositis, cervical erosion, burns, scalds, duodenal ulcers, gastric cancers and skin ulcers (Li, 1999). The plant has been well documented to have antioxidative, antiinflammatory, antimicrobial, pain-relieving, immunostimulative and regenerative properties.

The berries of *H. rhamnoides* contain polyphenolic compounds (namely, isorhamnetin, rhamnetin, quercetin, kaempferol), carotenes ($\alpha$, $\beta$, $\gamma$), vitamins (A, E, C, K), riboflavin, folic acid, tannins, glycerides of palmitic, stearic and oleic acids, and some essential amino acids (Chan *et al.*, 1990), which play a major role in contributing towards bioactivities such as free radical scavenging, chromatin compaction and hypoxia induction (Goel *et al.*, 2000c, 2001c, 2003b; Prem Kumar *et al.*, 2002), all of which have been demonstrated to play a vital role in radioprotection.

Gileva and Lukin (1984) reported the radioprotective efficacy of compounds from *Hippophae*, while Mizina and Sitnikova (1999) showed that oral administration of a *H. rhamnoides* fruit juice concentrate to rats before or after irradiation (x-ray; 1 Gy) was accompanied by an increase in life span, restoration of the

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11-oxycorticosteroid level in the blood and weight of isolated adrenals, and also normalization of their basal activity and response to ACTH (corticotropin) under *in vitro* conditions.

An aqueous-alcohol (50% ethanol) extract of berries of *H. rhamnoides* (30 mg/kg body weight) when administered to Strain 'A' mice 30 min before whole-body $^{60}$Co $\gamma$-irradiation (10 Gy) increased life span and rendered 82% survival (at 30 days) compared with 100% mortality (within 15 days) in irradiated controls (Goel *et al.*, 2002a; Sharma *et al.*, 2004). The endogenous colony forming unit (CFU) counts in mouse spleen on post-irradiation day 10, and various other haematological parameters, clearly demonstrated the radioprotective effects of the extract. In addition, the herbal extract of *H. rhamnoides* also inhibited the Fenton reaction and radiation-induced generation of hydroxyl radicals *in vitro*, superoxide anion-mediated nitroblue tetrazolium reduction and ferrous sulphate-mediated lipid peroxidation in mouse liver.

The hydroalcohol extract of *H. rhamnoides* has also been shown to protect mice against gamma radiation-induced genotoxicity (Agarwal and Goel, 2002). Pre-irradiation administration of the herbal extract to mice reduced the radiation-induced micronuclei frequency in a dose-dependent manner, suggesting its radioprotective efficacy. Treatment with *H. rhamnoides* extract enhanced DNA synthesis (S-phase) in unirradiated controls and also countered the radiation-mediated depression of S-phase to facilitate replenishment of cells lost as a result of radiation injury.

Irradiation causes damage to mitochondria, leading to a bio-energetic catastrophe in the cell (Kroemer and Reed, 2000). Since energy is essentially required for repair and restoration of normal cellular (metabolic) functions, protecting mitochondria against the deleterious effects of ionizing radiation can help to provide radiation protection and radiorecovery.

A hydro-alcohol extract of fruits (berries) of *H. rhamnoides* has been shown to protect the functional integrity of mouse liver mitochondria against lethal $\gamma$-radiation (10 Gy) under *in vivo* conditions (Gupta *et al.*, 2003c). It was found that pre-irradiation treatment of mice with the extract (30 mg/kg body weight; i.p.; single dose; –30 min) significantly inhibited the radiation-induced increase of superoxide anions, oxidized glutathione (GSSG), thiobarbituric acid reactive substances (TBARS), mitochondrial complex I and complex I/III activity and protein oxidation. The mitochondrial complex II/III activity and mitochondrial membrane potential (MMP; which was reduced during irradiation) was significantly enhanced.

*H. rhamnoides* has been shown to provide protection to the gastrointestinal system against lethal whole-body $\gamma$-radiation (Goel *et al.*, 2003a). Administration of a hydoroethanol (50:50 v/v) extract 30 min before irradiation increased the number of surviving crypts in the jejunum by a factor of 2.02 and villi cellularity by 2.5 fold in comparison with the irradiated control. The extract also reduced the incidence of apoptotic bodies in the crypts in a time-dependent manner and increased cellularity in the crypts and villi (84 h post-irradiation) compared with the control. Caspase-3 activity was also found to be significantly lower in the mice administered *Hippophae* extract before irradiation compared with irradiated control, thereby implying that by reducing the caspase activity, *Hippophae* extract might play a pivotal role in the protection of crypts from apoptosis. The study showed that reduction in the radiation-induced loss of cellularity of crypts and villi, and also the decrease in frequency of apoptosis by *H. rhamnoides* extract could have contributed to the overall radioprotective effect.

The mode of action of the alcoholic extract (50%) of whole berries of *H. rhamnoides* at molecular and cellular level has been partially elucidated (Goel *et al.*, 2001c, 2003b; Prem Kumar *et al.*, 2002). Single cell gel electrophoresis (comet assay) revealed that the extract inhibits radiation-induced DNA strand breaks in mouse thymocytes in a dose-dependent manner (Goel *et al.*, 2001c; Prem Kumar *et al.*, 2002). *Hippophae* extract under *ex vivo* conditions induced a strong compaction of chromatin making the nuclei resistant to a radiation dose as high as 1000 Gy (Goel *et al.*, 2000c, 2001c). The compaction of chromatin was not reversed even by relaxation buffer, indicating that the salt concentration, did not have any role to play in the herbal extract-induced chromatin compaction. The alkaline halo assay also corroborated the results of the comet assay. A thermal denaturation assay was used to show that the extract interacts with DNA.

Further investigations on *H. rhamnoides*, done in cultured thymocytes, revealed an ability to bring about a concentration-dependent compaction of both a reversible (<100 μg/mL) and irreversible (>100 μg/mL) nature, which was further correlated to the magnitude of DNA-protein crosslinks formed (Goel *et al.*, 2003b). *H. rhamnoides* extracts can maintain chromatin organization and block the cell cycle at G2-M phase by interfering with topoisomerase I activity (Goel *et al.*, 2003b), thereby contributing towards the radioprotective efficacy of the extract. Thus, *H. rhamnoides* appears to be a promising herb in the prophylactic treatment of radiation-induced damage but further research is necessary to identify appropriate dosing regimes and to characterize the active constituents.

### *Mentha piperita* Linn.

*Mentha piperita* (Lamiaceae) is an aromatic plant with a diverse array of medicinal properties. Its stimulative and carminative properties have been used for allaying nausea, flatulence and vomiting for over a thousand years. The antioxidant and antiperoxidant properties have been attributed to the presence of caffeic acid, eugenol, rosmarinic acid and $\alpha$-tocopherol (Rastogi and Mehrotra, 1991). *Mentha* extract and mint oil have been shown to possess antibacterial and antifungal activities. Antimutagenic properties (ability to enhance error-free repair of DNA damage) of *Mentha* has also been reported (Vokovic-Gacis and Simic, 1993). The chemopreventive effect against shamma (a complex mixture of powdered tobacco used in Saudi Arabia which has been linked to oral cancer) induced carcinogenesis may be largely due to the antimutagenic properties of *Mentha* (Samman *et al.*, 1998).

Leaves of *Mentha piperita* contain 7-O-rutinosides of eriodictyol and luteolin, while *Mentha* oil contains menthol, menthone, neomenthone, cineole, menthyl acetate, isomenthol, limonene and pinene (Rastogi and Mehrotra, 1995).

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Pre-treatment with a *Mentha piperita* extract protected haematological constituents and serum phosphatases activity in Swiss albino mice against γ-radiation (Samarth *et al.*, 2001, 2002b). *M. piperita* administration elevated the counts of endogenous spleen colonies and spleen weight significantly (Samarth *et al.*, 2001). The leaf extract of *M. piperita* was shown to provide protection against radiation-induced alterations (reduction in villus height, mucosal, total cells and mitotic figures/crypt section) in the intestinal mucosa of mice (Samarth *et al.*, 2002a). *M. piperita* pre-treatment also protected against the radiation-induced increase in goblet cells/villus section and dead cells/crypt section in the jejunum of mice.

Oral administration of *M. piperita* (1 g/kg body weight/day) prior to sublethal radiation exposure (8 Gy) was found to be effective against the chromosomal damage in bone marrow of Swiss albino mice (Samarth and Kumar, 2003). Irradiated animals exhibited chromosomal aberrations in the form of chromatid and chromosome breaks, centric rings, dicentrics exchanges and acentric fragments, while animals pre-treated with *M. piperita* extract showed a significantly lesser number of aberrant cells. It also significantly increased GSH levels and decreased the lipid peroxidation level in irradiated mice. The radioprotective effect of *M. piperita* was also demonstrated by determining dose modification factor, which was 1.78 (DMF refers to the ratio of the radiation dose required to elicit the same effect in the presence and in the absence of the radioprotectant) (Samarth and Kumar, 2003).

Jagetia and Baliga (2002a) have reported the protective effect (DMF: 1.27) of a chloroform extract of *Mentha arvensis*, a related species, in mice exposed to 10 Gy radiation.

### *Ocimum sanctum* Linn.

*Ocimum sanctum* (Holy Basil; Tulasi; Family: Lamiaceae) is an Indian medicinal herb widely distributed in the semi-tropical and tropical regions of the country. The medicinal value of the plant has been well documented in various ancient Indian texts, and virtually every part of this plant is used in the traditional, Ayurvedic and Siddha systems of medicine for treating a plethora of human ailments. In particular, *O. sanctum* is used for treating infections, skin diseases, hepatic disorders, common cold and cough, malarial fever and as an antidote for bites by snakes and poisonous insects (Satyavati *et al.*, 1987). During the past few decades, the plant has been investigated extensively and has been shown to possess a range of biological activities, many of which are relevant to radiation protection, e.g. antibacterial (Phadke and Kulkarni, 1989), antifungal (Rai, 1996), hypoglycaemic (Chattopadhyay, 1999), antiinflammatory (Godhwani *et al.*, 1987; Singh and Agarwal, 1991; Singh *et al.*, 1996), antiviral (Kumar *et al.*, 1997), antioxidant (Uma Devi, 2001), antiulcer (Dharmani *et al.*, 2002), anticarcinogenic (Uma Devi, 2001), hepatoprotective (Chattopadhyay *et al.*, 1992), analgesic (Godhwani *et al.*, 1987), immunostimulatory (Godhwani *et al.*, 1988) and wound healing activities (Shetty *et al.*, 1999). The antistress effect of *O. sanctum* has also been reported in a rodent model (Bhargava and Singh, 1981).

The leaves and stem of *O. sanctum* contain a number of constituents including apigenin, carvacrol, cirsilineol, cirsimaritin, eugenol, isothymonin, luteolin, methyl eugenol, orientin, rosmarinic acid, sesquiterpene hydrocarbon caryophyllene, ursolic acid, vicenin, etc. (Nair *et al.*, 1982). The presence of vicenin-2, rosmarinic acid, galuteolin, cirsilineol gallic acid, gallic acid methylester, gallic acid ethylester, protocatechic acid, vanillic acid, vanillin, caffeic acid has been reported in the ethanol extract of *O. sanctum* (Norr and Wagner, 1982).

The radioprotective property of *O. sanctum* was first reported by Uma Devi and Ganasoundari (1995). Thirty-day lethality studies in Swiss albino mice were carried out following treatment with single graded doses of aqueous and ethanol extracts from dried leaves of *O. sanctum* (Krishna Tulasi; the dark-leafed variety of *O. sanctum*) and it was found that the aqueous extract was more effective in increasing survival, compared with the ethanol extract. The optimal dose for protection was reported to be 50 mg/kg b.w (intraperitoneal administration), while the acute $LD_{50}$ was 6 g/kg b.w. Administration of a fractionated dose of the herbal extract via the i.p. route (10 mg/kg/day for 5 consecutive days to mice prior to irradiation) was more effective compared with a single dose (50 mg/kg b.w.). The optimum dose (fractionated dose of 10 mg/kg/day of aqueous extract of *O. sanctum* for 5 consecutive days via the intraperitoneal route) administered to mice prior to irradiation gave a dose modification factor of 1.28. It was also found that the i.p. route of drug administration was more effective than the oral route.

Ganasoundari *et al.* (1997a) studied the effect of *O. sanctum* on the survival of mice after whole-body lethal irradiation and compared it with WR-2721, a standard radioprotector. Their results indicated that *O. sanctum* promotes recovery and regeneration of haemopoietic progenitor cells in mice bone marrow. An intraperitoneal (i.p.) injection of an optimum dose (10 mg/kg daily for 5 days) of leaf extract of *O. sanctum* to mice before delivering sub-lethal (2 Gy) total-body γ-radiation produced a significantly higher bone marrow stem cell survival than a pre-treatment with 300 mg/kg (approx. 40% of its $LD_{50}$) of WR-2721 (amifostine), suggesting that in terms of the protective dose and toxicity, the herbal extract is a better radioprotector than the synthetic drug. Analysis of chromosomal aberrations in mouse bone marrow exposed to γ-radiation showed that the *O. sanctum* extract could significantly reduce the percentage of aberrant metaphases and other chromosomal aberrations, including dicentrics and rings, induced by sublethal whole-body radiation doses (3–5 Gy). The decline in the percent aberrant metaphases by *O. sanctum* pre-treatment was comparable to that provided by 400 mg/kg of WR-2721. *O. sanctum* pre-treatment did not manifest any toxic side effects, while WR-2721 (300–400 mg/kg b.w.) administration prior to irradiation resulted in an increase in the percent aberrant cells at 14 days post-irradiation. Administration of a combination of *O. sanctum* and WR-2721 to mice prior to γ-irradiation considerably enhanced the chromosome protection by nearly two-fold, compared with individual administration, and also eliminated the delayed chromosome toxicity associated with the treatment of WR-2721. In addition, *O. sanctum* extract also protected mouse liver against radiation-induced lipid peroxidation.

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The responses of single or sequential doses of *O. sanctum* were not substantially different. The anti-lipid peroxidative effect was attributed to increased levels of cellular antioxidants such as reduced glutathione (GSH), GSH-transferase, GSH-peroxidase and reductase as well as superoxide dismutase (SOD).

The work of Ganasoundari *et al.* (1997b) showed that the aqueous extract of leaves of *O. sanctum* significantly inhibited the OH radical–induced deoxyribose degeneration. A combination of WR-2721 and *O. sanctum* extract produced a significantly higher inhibition of the OH radical activity compared with either agent individually (Ganasoundari *et al.*, 1998).

Orientin (8-C-$\beta$-D-glucopyranosyl-luteolin) and vicenin-1 (6-C-$\beta$-D-xylopyranosyl-8-C-$\beta$-D-glucopyranosyl apigenin), water-soluble compounds from *O. sanctum* did not exhibit any systemic toxicity in mice even at a dose of 100 mg/kg b.w. Both compounds significantly increased mouse survival when administered 30 min prior to lethal whole-body $\gamma$-irradiation. The optimum dose for protection was found to be 50 µg/kg b.w. via the i.p. route. Other routes of administration, e.g. oral and intravenous route were also found to be effective, but to a lesser extent. Vicenin provided a slightly higher protection (DMF: 1.37), compared with orientin (DMF: 1.30) in murine model system (Uma Devi *et al.*, 1999) and also reduced the chromosomal aberrations better than amifostine in the bone marrow of mice exposed to 2 Gy $\gamma$-irradiation (Uma Devi *et al.*, 1998). Both the flavonoids, orientin and vicenin, were found to be equally effective in rendering protection against $\gamma$-radiation-induced lipid peroxidation in mouse liver. These compounds also significantly inhibited the Fenton reaction-induced OH radical activity under *in vitro* conditions (Uma Devi *et al.*, 2000) and protected human lymphocyte chromosomes (Vrinda and Uma Devi, 2001). Though the role of orientin and vicenin in radiation protection has been established, it is plausible that other constitutents present in *O. sanctum*, may also be involved in the observed radioprotective effects, since radioprotection of the whole organism usually requires multifarious activities, i.e. simultaneous protection of various target tissues and organs.

## *Panax ginseng* CA Meyer

Ginseng is one of the most extensively used medicinal plants, particularly in traditional oriental medicine for the treatment of various diseases. The plant has been thoroughly exploited for its adaptogenic, antistress, antitumor, antioxidant, antiaging, antifungal and rejuvenating properties (Keum *et al.*, 2000; Kim *et al.*, 1993, 1998b, 2002; Lam and Ng, 2002). Ginseng root and its major bioactive constituents have complex and multiple pharmacological actions (Attele *et al.*, 2002).

The stem and leaves of ginseng contain ginsenosides-Rb-1, Rb-2, Rc, Rd, Re, Rf, Rg-1, Rg-2, Rg-3, kaempferol, triofolin, salicylic, p-coumaric, gentisic and caffeic acids, while roots have been reported to contain panaxan A, B, C, D, E, F, G, H, acidic polysaccharides, tripalmatin, panxynol, panaxytriol, linolein, palmitic acid, $\beta$-sitoserol (Dewick, 2002).

The radioprotective efficacy of ginseng has been reported by several workers (Kim *et al.*, 1993, 2001; Kumar *et al.*, 2003; Pande *et al.*, 1998a; Takeda *et al.*, 1982). Yonezawa and coworkers (1985) showed that recovery of thrombocyte and erythrocyte counts in blood after irradiation was the major factor responsible for radiation protection. The whole extract of ginseng and the relative protective effects of various fractions (carbohydrate, protein and saponins) have been evaluated. The results showed that the water-soluble whole extract of ginseng provided the best protection against $^{60}$Co gamma radiation in C3H mice, while isolated protein and carbohydrate fractions were less effective, the saponin fraction was ineffective (Zhang *et al.*, 1987). Similar results were obtained by Kim and coworkers (2001), who found that whole ginseng extract and its fractions increased endogenous spleen colony formation in irradiated mice and also reduced apoptosis in jejunal crypt cells. Ginsan, a purified polysaccharide (molecular weight 2000 kD) isolated from the ethanol-soluble fraction of *P. ginseng* aqueous extract, possesses immunological activities such as induction of several cytokines (IL-1, IL-2, IL-8, interferon-$\gamma$ and GM-CSF) (Sonoda 1998), mitogenic activity, stimulation of natural killer (NK) cells, lymphokine-activated killer (LAK) cells and macrophages (Song *et al.*, 2002; Ma *et al.*, 1995).

Song and coworkers (2003) have studied the protective effect of ginsan on irradiated mice, due to its ability to induce proliferation of murine bone marrow as well as the release of haematopoietic growth factors. Ginsan was found significantly to induce production of bone marrow, spleen and granulocyte-macrophage colony-forming cells (GM-CFU), and also circulating neutrophils, lymphocytes and platelets in irradiated mice. Ginsan also induced a battery of cytokines in spleen cells including Th1-type (IL-2, IL-12, IFN-$\gamma$), Th-2-type (IL-4, IL-5, IL-10), and proinflammatory (IL-1, IL-6, TNF-$\alpha$) cytokines under *in vitro* conditions. The expression patterns of cytokines after ginsan treatment *in vitro* and *in vivo* were different. Ginsan induced the endogenous production of cytokines such as IL-1, IL-6, IFN-$\gamma$ and IL-12, which are required for haematopoietic recovery, and also enhanced TH-1 function while interfering with the TR-2 response in irradiated mice. Pre-treatment of BALB/c mice, 24 h prior to irradiation, with ginsan (100 mg/kg body weight; i.p.; single dose) protected mice from the lethal effects of ionizing radiation (8 Gy) more effectively than when it was administered immediately (within 15 min) or at various times after irradiation (+3 h and +24 h) (Lee *et al.*, 1997).

The radioprotective effect of *P. ginseng* root extract on testicular enzymes (acid and alkaline phosphatases and lipid peroxidation) has been recently reported by Kumar *et al.* (2003). These workers administered 10 mg/kg b.w. of *P. ginseng* extract continuously for 4 days to Swiss albino mice, and on the day 4 they were given 8 Gy $\gamma$-radiation 30 min after extract administration and a protective effect was reported.

## *Podophyllum hexandrum* Royale (Syn. *P. emodi* Wall.)

*Podophyllum hexandrum* (Himalayan Mayapple; Berberidaceae) is a perennial herb, thriving in the Himalayan region at altitudes ranging between 2500 to 4000 m. The root and rhizome of the plant have been extensively used in India, for over 2000 years to treat a

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number of ailments such as cold, constipation, biliary fever, septic wounds, erysipelas, insect bites, mental disorders and rheumatism (Singh and Shah, 1994). *P. hexandrum* has been used to provide symptomatic relief in some allergic and inflammatory conditions of skin. This herb, and its constituents, have also been used in the treatment of cancer (Singh and Shah, 1994), venereal warts (Beutner and Von Krogh, 1990), monocytoid leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma and cancer of the brain, bladder and lung (Blasko and Cordell, 1988; Singh and Shah, 1994). Antiviral and anti-HIV properties of this plant have also been reported (Gowdey *et al.*, 1995).

*P. hexandrum* contains a number of bioactive constituents including lignans (podophyllotoxin, podophyllotoxone, podophyllin, peltatins $\alpha$ and $\beta$) and flavonoids including quercetin, kaempferol, astragalin and kaempferol-3-glucoside (Singh and Shah, 1994; Wong *et al.*, 2000).

The radioprotective effect of *P. hexandrum* has been reported in Swiss albino mice by Goel and co-workers (Goel *et al.*, 2000a,b, 2001a). Pre-irradiation administration of *P. hexandrum* rhizome extract protected mice in a dose-dependent manner (optimal dose being 200 mg/kg body weight rendering 80% survival for 30 days) against whole-body lethal $\gamma$-irradiation (10 Gy). The extract was also found to provide cytogenetic protection, as observed by a decrease in radiation (2 Gy)-induced micronuclei frequency upon pre-irradiation treatment. Radioprotective properties of *P. hexandrum* were found to be comparable and in some cases even better than synthetic radioprotectors such as diltiazem and WR-2721. Subsequent 30-day survival studies by our group revealed over 80% protection against 10 Gy and a DMF of 1.33, was observed (unpublished data).

*P. hexandrum* chelated $Fe^{2+}$ more efficiently than $Fe^{3+}$ (in a dose dependent manner; measured using chelating agents 2-2 bipiridyl and potassium thiocyanate, respectively), and also modulated the $Fe^{2+}/Fe^{3+}$ ratio (Prem Kumar and Goel, 2000).

Radiation doses in the range 7–12 Gy cause a gastrointestinal syndrome (Coleman *et al.*, 2003), which is characterized by denuded, eroded and shrunken villi, stromal cores, elongated and dilated crypts, depopulated crypts, decrease in crypt cell numbers and a decrease in the mitotic index and apoptotic bodies in the crypts. The effect of an aqueous extract of *P. hexandrum* rhizome in ameliorating radiation (10 Gy)-induced gastrointestinal damage, resulting from destruction of clonogenic crypt cells and eventual depopulation and denudation of villi, has been reported (Salin *et al.*, 2001). Using an *in vivo* micro colony survival assay these workers demonstrated that pre-irradiation administration of *P. hexandrum* extract (200 mg/kg b.w. per mouse by i.p. route 2 h prior to gamma irradiation) increased (3-fold) the number of surviving crypts in the jejunum and villi cellularity (2.7-fold). The herbal extract induced cell division arrest and also reduced radiation-induced apoptosis in crypt cells, thereby rendering protection against lethal $\gamma$-radiation.

*P. hexandrum* extract has been shown to render radioprotection to the developing nervous system (Goel *et al.*, 2002c). Since cells of the embryonic nervous system are radiosensitive and actively differentiating and maturing during the fetal and early postnatal periods (Reyners *et al.*, 1992), the effect of sublethal (2 Gy) $\gamma$-radiation was studied in rats *in utero* on day 17 of gestation to monitor radiation-induced retardation of neurophysiological development in new-borns. Treatment of rats with *P. hexandrum* extract (200 mg/kg b.w.; single dose; i.p. route) 120 min before irradiation mitigated radiation-induced physiological alterations (Goel *et al.*, 2002c).

*P. hexandrum* has been shown to modulate antioxidant enzyme levels. The effect of an aqueous extract of *P. hexandrum* in modulating the antioxidant defence system in murine liver, jejunum and ileum with special reference to enzymes such as glutathione-S-transferase (GST), which neutralizes electrophiles by conjugation with glutathione thereby making them readily excretable from the body, superoxide dismutase (SOD), which scavenges superoxide anion to form $H_2O_2$ and catalase, which inactivates $H_2O_2$ to form water has been investigated (Mittal *et al.*, 2002). Pre-irradiation treatment with *P. hexandrum* extract significantly enhanced liver GST and SOD at 12 h post-irradiation and intestinal SOD at 84 h post-irradiation intervals, while no significant change was manifested in hepatic catalase activity.

*P. hexandrum* has also been demonstrated to provide protection to the male reproductive system. The suitability of the aqueous extract of rhizome of *P. hexandrum* in rendering radioprotection, was evaluated in male germinal tissue in mice (Samanta and Goel, 2002). Administration of *P. hexandrum* via the i.p. route 2 h prior to irradiation produced a significant increase in the testis weight, repopulating the seminiferous tubules and increasing resting primary spermatocytes, stem cell survival index, sperm counts and reduction in abnormalities of sperm morphology. This suggests that *Podophyllum* extract, if put to clinical application, will not be harmful to the testicular system.

*P. hexandrum* has been shown to protect mammalian mitochondrial systems against radiation damage (Gupta *et al.*, 2002, 2003a,b). Radioprotection by an aqueous extract of *P. hexandrum* has been investigated in HepG2 cells (human hepatoma) by evaluating colony forming efficiency, redox status of mitochondria, reactive oxygen species (ROS), nitric oxide (NO) generation, peroxidation of lipids and intracellular glutathione (Gupta *et al.*, 2003b). Lower concentrations of the extract (0.1 and 1.0 μg/mL) rendered maximum radioprotection when administered 1 or 2 h before irradiation, while higher concentrations (5 and 10 μg/mL) were more effective at greater time intervals (4 or 8 h). The time of drug administration is very important for achieving radioprotection, as shown by several workers (Coleman *et al.*, 2003; Weiss and Landauer, 2003). Pre-treatment with *P. hexandrum* extract significantly inhibited radiation-induced MTT reduction in a concentration and time-dependent manner by decreasing gamma radiation-induced leakage of electrons from the mitochondrial electron transport chain. Pre-irradiation administration of the extract significantly reduced both ROS and NO generation and enhanced glutathione levels, and inhibited lipid peroxidation, thereby rendering radiation protection.

Since mitochondria play a vital role in cell metabolism, they are crucial in post-irradiation repair and recovery processes, being the site of ATP production (Haraguchi *et al.*, 2000). The role of *P. hexandrum* in affording radiation protection at the whole-body level, and the crucial role played by mitochondria therein,

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was investigated at *in vivo* level (Gupta *et al.*, 2004). Exposure of γ-radiation (10 Gy) to mice significantly increased the generation of mitochondrial superoxide anions $O_2^-$, while pre-irradiation treatment of mice with *P. hexandrum* extract significantly reduced the formation of radiation-induced superoxide anions. Increased levels of mitochondrial glutathione were observed upon irradiation, whereas in the case of pre-irradiation treatment, levels were found to be significantly higher at all time periods studied, indicative of stimulation of endogenous antioxidants. The radiation-mediated increase in complex I (NADH: UQ oxidoreductase) activity was significantly ameliorated upon pre-irradiation administration with the herbal extract. The radiation-mediated alteration in the flow and leakage of electrons from complex I/III (NADH: cytochrome c oxidoreductase) and complex II/III (succinate: cytochrome c oxidoreductase) were also properly maintained by pre-irradiation administration of the extract. Pre-irradiation administration of *P. hexandrum* extract to mice inhibited the radiation mediated decrease in mitochondrial membrane potential (MMP). Administration of the extract to mice prior to irradiation also lowered radiation-induced oxidative damage to lipids and proteins, increased antioxidant levels, and simultaneously inhibited radiation-induced alterations in mitochondrial membrane potential (MMP), lipid peroxidation, protein oxidation and electron transport chain (ETC) activity, thereby affording protection to the hepatic mitochondria against lethal γ-radiation. *P. hexandrum* has been shown to act in a multifaceted manner and provide protection to haematopoietic, gastrointestinal, reproductive and central nervous system (CNS) (Goel *et al.*, 2000a,b, 2001a; Samanta and Goel, 2002; Sajikumar and Goel, 2003). It is apparent that *P. hexandrum* is a promising radioprotector and may be useful in providing protection during both planned and unplanned radiation exposures. Fractionation of the herbal extract(s), isolation of the individual active components, and evaluation of their bioactivities has not yet been reported. Identification of the bioconstituents, determination of appropriate dosing regimens, and potential effects of long-term usage also need to be considered before undertaking clinical trials, especially in view of the cytotoxic nature of podophyllotoxin.

### *Tinospora cordifolia* (Willd.) Miers

*Tinospora cordifolia* (Menispermaceae) is considered to be a Rasayana, Medha and anti-aging drug in Ayurveda. It is considered as a tonic, vitalizer, antidiabetic, hepatoprotective, antipyretic, antistress, antiulcer, anticancer, antioxidant and immunomodulatory agent, and has been widely used for the treatment of various ailments including jaundice, skin diseases, anaemia, emaciation and infections (Stanley *et al.*, 1999a,b). The aqueous stem extract of *Tinospora cordifolia* has been reported to prevent abdominal infections and sepsis, to improve Kupffer cell function and poly-morphonuclear cell (PMN)-mediated phagocytosis in rats with chronic liver damage and patients of surgical jaundice (Subramanium *et al.*, 2003). The antioxidant properties of *Tinospora cordifolia* may be substantially responsible for these medicinal effects.

*Tinospora cordifolia* contains syringin and cordiol, which reduce immunohaemolysis and significantly increase IgG antibodies (Kapil and Sharma, 1997). Cordioside, cordiofolioside, cordiofolioside B and clerodane furanoditerpene glucosides have been reported to have immunostimulatory properties (Wazir *et al.*, 1995).

The radioprotective property of *Tinospora* was first reported by Goel and co-workers (2001b). The aqueous stem extract of *Tinospora cordifolia* exhibited free radical scavenging and metal chelation properties and thereby provided protection against ionizing radiation (Goel *et al.*, 2002b). The extract quenched radiation-mediated 2-deoxyribose degradation in a dose-dependent fashion ($IC_{50}$ value: 700 μg/mL), and inhibited the formation of $Fe^{2+}$-bipiridyl complex and formation of the comet tail in irradiated thymocytes by chelating $Fe^{2+}$ ions. It also inhibited ferrous sulphate mediated lipid peroxidation in liver homogenate. The authors opined that the direct antioxidant mechanisms (chelation of metal ions) of action of *Tinospora cordifolia* aqueous extract contributed in a comprehensive and competitive manner to ameliorate the radiation-induced oxidative stress. The antioxidant properties (both direct and indirect mechanisms), along with other properties such as immunomodulation and cell proliferative capacity, could also be responsible for radioprotective manifestation, as was also revealed by survival against radiation (10 Gy)-induced mortality in Strain 'A' mice (Goel *et al.*, 2004).

The radioprotective activity of a pure arabinogalactan polysaccharide, isolated from the aqueous extract of the dried stem of *Tinospora cordifolia*, has been established using *Saccharomyces cerevisiae* X 2180 strain as the *in vivo* test model (Subramanian *et al.*, 2003). The radioprotective activity was attributed entirely to the superior radical scavenging capacity of the preparation, since it did not enhance expression of the protective endogenous antioxidant enzymes, namely, catalase and superoxide dismutase in the yeast cells. The preparation, even at a low concentration of 6.9 mg/mL, provided nearly 39% protection to plasmid (pBR322) DNA against γ-ray induced single strand breaks as was revealed by an increase in the supercoiled form of the plasmid. Exposure of pBR322 to γ-radiation led to the complete conversion of the supercoiled form to the open circular form.

Oral administration of an aqueous extract of *Tinospora cordifolia* (5 mg/kg body weight per day) to Swiss albino mice 1 h prior to sublethal whole-body radiation exposure (8 Gy) provided 33% survival (at 30 days). The same dose, when given for 15 consecutive days, produced 100% survival until day 9 and 50% of the animals survived until day 24. All the animals died within 30 days (Pahadiya and Sharma, 2003) suggesting that *Tinospora cordifolia* is partially effective against sublethal radiation dose.

## CONCLUSIONS

It is apparent that many plants exhibit, or have the potential to show, a diverse array of biological activities that may be relevant to the mitigation of ionizing radiation-induced damage in mammalian systems.

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However, so far, only a fraction of these plants have been investigated. There is an urgent need to develop newer, more efficient and reliable bioassays for large-scale rapid evaluation of radioprotective efficacy of plant extracts.

Further studies are necessary systematically to evaluate efficacy using standardized extracts, and to identify the bioactive compounds responsible for the radioprotective manifestation. Isolation of the bioactive constituents, and subsequent combination in appropriate proportions along with bio-enhancers may further potentiate the effects of herbal radioprotective drugs.

Most radioprotectors are prophylactic in nature rather than therapeutic, restricting their usage. There is usually a 'window' of time (in most cases 30 min to 2 h) prior to irradiation, when the administration of the relevant herbal preparations renders maximum survival. There is, therefore, a need to develop simultaneously therapeutic formulations that can also be of use in a post-irradiation scenario.

Several plants found to render radioprotection, e.g. *Ginkgo biloba* and *Podophyllum hexandrum* already fall in the category of endangered plants, and efforts need to be made to save these plants from overexploitation. Biotechnological interventions for large-scale production of high-value, low-volume radioprotective constituents could also reduce the reliance on field-grown plants, and lead to the production of novel biomolecules with substantially improved radioprotective efficacy.

Clinical trials have not yet been undertaken with most herbal radioprotectors. If these are performed, herbal radioprotective drugs for human use from several of these plants may soon be available.

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