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Review Article

Some novel approaches for radioprotection and the beneficial effect of natural products

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Due to the increased use of ionizing radiation in various aspects of human life especially in areas pertaining to radiotherapy of cancer, food preservation, agriculture, industry and power generation, there is a need to develop an effective and non-toxic radioprotector. The currently available ones have many drawbacks including high cost, side effects and toxicity. Several novel approaches are on to locate a potent radioprotector. These include mimics of antioxidant enzymes, nitroxides, melatonin, growth factors, gene therapy, hyperthermia apart from natural products. The latter has several advantages since they are non-toxic with proven therapeutic benefits. These can be classified as natural compounds and plant extracts; polyherbal formulations; besides natural and semi-natural compounds of plant origin. A review of the above agents, their efficacy in radioprotection and possible mechanisms responsible has been carried out. 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.

Keywords: Antioxidants, Ionizing radiation, Medicinal plants, Natural compounds, Novel approaches, Radioprotection, Radiotherapy

In recent years there is an increased awareness and immense interest in the spectacular advances made in various areas of human health. Radiation has been considered an enigma to the general public and the use of radiation for therapeutic and other uses has always been associated with some skepticism. Currently ionizing radiation is being used in a large number of therapeutic, industrial and other applications apart from for generation of nuclear power and developing new varieties of high-yielding crops and enhancing storage-period of food materials. Cancer is one of the leading causes of morbidity and mortality in several populations of the world and radiotherapy is a dominant and effective mode of cancer treatment. In this aspect there is a need to protect normal cells from radiation during radiotherapy. In many instances where radiation is used for power generation, industrial/medical purposes or agricultural uses and food preservation personnel manning the radiation sources may be subjected to low-level exposures. High exposures to radiation may occur due to accidents or during 'nuclear war'. Besides, radiation poses a major, currently un-resolvable risk for astronauts, especially for long-duration space flights. Hence there is a need to understand the mechanisms of radiation damage to humans and its possible prevention by drugs such as 'radioprotectors'. This review deals with some novel approaches to radioprotection and their underlying mechanisms.

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Historical background

The research on development of radioprotectors commenced with the Manhattan project in the US and Walter Reed Army Research Institute synthesized and screened about 4500 compounds for this purpose. Among these, except one compound, 'Amifostine', which finds applications in radiotherapy of cancer to protect normal tissues during radiation exposure, none was found suitable for human applications due to acute toxicities. This is the present scenario in spite of more than six decades of research on the development of radioprotectors or anti-radiation drugs and the spectacular advances made over the last few decades in the areas of cell and molecular biology, synthetic chemistry and biochemistry. The development of a safe and effective non-toxic radioprotector for human use has remained elusive till today. Several compounds, which have been found very effective in

the laboratory studies, have failed in human applications due to toxicity problems or lack of significant protective effects[1-3]. The protection of healthy tissue during radiotherapy for cancer has been one of the strong motivations for continuing research on exogenous radioprotectors. Understanding of radiobiological effects in humans requires studies involving model chemical systems, microorganisms, tissue culture, and animals. Experimentation with animals ultimately provides assurance that conclusions from experimental results obtained in simpler systems have a biomedical reality and clinical application[4].

Importance of research on radioprotection

Many natural and synthetic chemicals have been investigated in the recent past for their efficacy to protect against radiation-induced damage in biological systems[5]. However, the inherent toxicity of some of the synthetic agents at the effective radio-protective concentration warranted further search for safer and more effective radio-protectors. In fact, no radio-protective agent is now available, either alone or in combination to meet all the requisites of an ideal radio-protector[6]. Amifostine is the only one that is currently in use having good radioprotection to normal tissues during radiotherapy, even though there are reports about contra-indications in some cases[7].

Though a large number of compounds have been shown to be promising as radio-protectors in laboratory studies, few could pass the transition from bench to bed-side. Most of them failed even before reaching the preclinical stage due to toxicity and side-effects. For clinical application of any compound as a radio-protector, it would require absolute certainty about its relative protection factors for tumour and normal tissues accompanied by minimum toxicity to avoid unacceptable clinical risk.

Classification of radioprotective agents

Radioprotective agents can be classified as: (i) chemical radioprotectors, (ii) adaptogens, and (iii) absorbents. The first group constitutes mainly sulfhydryl compounds and other antioxidants[8]. Adaptogens act as stimulators of radioresistance. These are natural protectors that offer chemical protection under low levels of ionizing radiations. They are generally extracted from the cells of plants and animals and have least toxicity. They can influence the regulatory system of exposed organisms, mobilize the endogenous background of radio-resistance, immunity, and intensify the overall non-specific resistance of an organism. Absorbents protect organisms from internal radiation and chemicals. These include drugs which prevent the incorporation of radioiodine by the thyroid gland and the absorption of radionuclides like ^{137}Cs, ^{90}Sr and ^{239}Pu.

Post-irradiation radioprotectors are important when an accidental exposure occurs during operation of equipments with radiation source or intentional exposures during war and such unnatural calamities. This area of radiation biology is a very slowly developing area since it is rather difficult to get such effective protectors.

The present review is an attempt to give an overview about novel approaches in radioprotection and radio-protectors of plant origin that are commonly used as dietary ingredients or as drugs in our daily life. Many of these plant products or their active ingredients and related compounds may be used as safe and effective radio-protectors for possible human applications in accidents or intentional exposures to ionizing radiation[9] because of their known use and lack of toxicity. This review also covers plant extracts and some of their ingredients and concentrates more on novel approaches of radioprotection, efficacy of various natural products and their mechanistic aspects.

Mechanisms underlying radioprotection

The radioprotectors can elicit their action by various mechanisms such as: (1) suppressing the formation of free radicals, (2) detoxifying the radiation induced reactive species, (3) inducing the cellular radioprotectors such as superoxide dismutase (SOD), glutathione, prostaglandins and interleukin-1, (4) enhancing the DNA repair by triggering one or more cellular DNA repair pathways, and (5) delaying cell division and inducting hypoxia in the tissues[5].

Importance of free radicals and related species in radiation damage and protection—Most of the cellular alterations induced by ionizing radiation is indirect and is mediated by the generation of free radicals and related reactive species, mainly derived from oxygen. Free radicals can be defined as atoms or a group of atoms having an unpaired electron. Because of the presence of unpaired electron, free radicals are highly reactive and are capable of altering all biological molecules including lipids, DNA and protein. In biological systems radiolysis of water gives rise to a large number of free radicals and

related reactive species collectively known as 'reactive oxygen species' (ROS). These include hydrated electron (e_{aq}^-), hydrogen radical ($^{\cdot}H$), hydroxyl radical ($^{\cdot}OH$), hydrated electron ($e_{aq}^{\cdot-}$), H_2O_2, peroxyl radical ($ROO^{\cdot}$), $O_2^{\cdot-}$, singlet oxygen ($^1O_2$) etc. The most oxidizing species formed in biological systems during exposure to radiation are $^1O_2$ and $^{\cdot}OH$. These two ROS along with other reactive species are capable of inducing severe and undesirable alterations in many biological molecules.

DNA forms the primary cellular target of radiation damage and membrane the alternative target. Mainly two types of changes are observed in DNA at the molecular level namely altered bases and strand breaks. Both types of changes, if not repaired affect the cell structure and function. Among the DNA bases, $^{\cdot}OH$ is non-selective in its reaction while $^1O_2$ reacts mainly with guanosines[10]. Membrane protein and lipids can be damaged by radiation. In proteins it can lead to formation of protein carbonyls and loss of protein thiols besides loss of activity of membrane bound enzymes[11,12]. Membrane lipids are highly susceptible for radiation damage mainly due to the presence of polyunsaturated fatty acids. The resulting damage results in lipid peroxidation. Unchecked peroxidative decomposition of membrane lipids has severe consequences for the cell and the organism. Since many cellular reactions are membrane based they are affected by lipid peroxidation. The products formed during this phenomenon also have effects at other targets away from the site of generation[13].

Antioxidants are substances that can neutralize free radicals or their reactions. Hence many compounds with antioxidant activities proved to be effective radioprotectors. Conversely in several novel approaches, the antioxidant effect has been utilized to demonstrate radioprotective properties.

Radiation exposure syndromes in man

Exposure to ionizing radiation results in various type of sickness and symptoms in man depending upon the radiation dose. Table 1 represents different type of syndromes, their symptoms and consequences.

Criteria for evaluating and screening radio-protectors

Antioxidant compound—As mentioned earlier, ionizing radiation generates free radicals that in turn lead to DNA damage. Due to the induction of DNA double strand breaks, the ionizing radiation is extremely effective in producing chromosomal aberrations leading to genomic instability. Most of the radiation induced biological damage arises from the interaction of the radiation-induced free radicals with the biomolecules. The chemicals that can scavenge free radicals may also reduce the occurrence of the DNA strand breaks. Thus agents that can prevent the formation of free radicals or destroy free radicals by reacting with them, thereby inhibiting their reaction with biomolecules, can function as radio-protectors. Since free radicals are short-lived, it is necessary for such radio-protective molecules to be present in the cellular milieu in sufficient concentration at the time of radiation exposure[14,15].

Anti-emetic and anti-inflammatory compounds—Radiation exposure leads to nausea, vomiting and inflammation during radiation disaster. Plants and their active ingredients that are having anti-emetic and/anti-inflammatory activity could give good radioprotection under such circumstances. For example *Mentha piperata* and *Zingiber officinale* have good anti-emetic activity[9,16] whereas *Tinospora cordifolia*, curcumin, *Glycyrrhizia glabra*, *Allium sativum*, *Aloe vera* and *Ocimum sanctum* have significant anti-inflammatory activity[9,17]. The extracts of these plants have good radio-protecting activity.

Table 1—Different types of radiation syndromes and their consequences in man

Dose (Gy)	Name of the radiation syndrome	Symptoms and consequences
1-2	Nausea, vomiting, diarrhoea (NVD) syndrome	Nausea, vomiting, diarrhoea, anorexia, giddiness, and loss of appetite
2-6	Haematopoietic syndrome	Bone marrow, spleen and thymus get affected. Approximate time of death varies between 10-30 days.
8-15	Gastrointestinal (GI) syndrome	Damage to intestinal crypt takes place resulting in loss of absorption of nutrient, dehydration, loss of weight, severe electrolyte imbalance and low blood pressure. Death occurs usually within 3-5 days.
> 25	Central Nervous System (CNS) syndrome	Irritability, hyper excitability response, epileptic type fits and coma. Symptoms are irreversible. Death usually occurs within 48 hr.

Haemopoietic and Immuno-stimulant compounds—Exposure of animals to ionizing radiation leads to the injury of the lymphoid and haemopoietic system by development of a complex dose-dependent cascade (Haematopoetic syndrome), which can result in septicaemia and death[14]. Hence agents that can modulate the regeneration of haemopoietic cells and simulate immune system by mechanisms such as increasing spleen colony forming unit may have good ability to protect the cells and tissues against radiation exposure. For example *T. cordifolia, Podophyllum hexandrum* and *Hippophae rhamnoides* provide good protection by stimulating haemopoiesis and increasing spleen colony forming units[9,18].

Models for study of radioprotection—Various models corresponding to different levels of organization have been used to examine the radioprotective abilities. These include plasmid DNA, subcellular organelles, cell-cultures and whole animal models. Besides this, mechanistic studies and clinical trials, representing the opposite ends of the spectrum, are also being carried out and at different stages these models provide useful information.

Some novel approaches to radioprotection

In recent years many novel approaches have been made to develop effective radioprotectors[19-38]. Among them are the following:

Mimics of antioxidant enzymes—Exposure of cells to ionizing radiation leads to formation of ROS and therefore, compounds that scavenge ROS may confer radioprotective effects. Superoxide dismutase (SOD) removes superoxide formed during radiation exposure and also inhibits formation of more reactive prooxidants. Manganese superoxide dismutase (MnSOD) exists exclusively in the mitochondria, which is the dominant site for ROS generation. MnSOD protects cells from the damage induced by these ROS. It has been proposed that MnSOD may play a central role in protecting cell against ROS injury during radiation exposure[19]. To extend the potential usefulness of the SOD as a protective antioxidant, SOD mimetics have been designed as possible pharmaceutical tools[20].

One such SOD mimetic, manganese (III) tetrakis-(*N*-methyl-2-pyridyl)porphyrin (MnTMPyP) is cell-permeable. It protects U937 cells and mice against ionizing radiation. Its administration for 14 days at a daily dose of 5 mg/kg body weight provided substantial protection against killing and oxidative damage in mice exposed to whole-body irradiation. This study indicates that MnTMPyP may have great application potential as a new class of *in vivo*, non-sulfur containing radioprotectors[21].

Nitroxides—Nitroxides are a class of stable free radical compounds that have been used as biophysical probes in electron paramagnetic resonance spectroscopy. More recently, the nitroxides were found to have *in vitro* antioxidant activity, protecting mammalian cells against cytotoxicity induced by prooxidants. These studies led to the investigation of the nitroxides as radioprotectors. The water-soluble nitroxide, Tempol, was shown to protect mammalian cells against aerobic radiation cytotoxicity. Tempol is an *in vivo* radioprotector. When administered 5-10 min prior to whole-body radiation, Tempol provided radioprotection. In tumor bearing animals, Tempol did not provide protection to tumour cells but protected normal cells. The differences in radioprotection may result from enhanced intratumor bioreduction of Tempol to its non-radioprotective hydroxylamine analogue[22].

Following this study, a number of water soluble nitroxides were screened for *in vivo* radioprotection in C3H mice at a single radiation dose[23]. Selected nitroxides were administered by the intraperitoneal route 10 min prior to a whole body radiation dose of 9 Gy. All of the nitroxides studied demonstrated radioprotection compared to saline-treated controls. The 6-membered piperidine ring nitroxides including Tempol were reduced to the inactive hydroxylamine rapidly over 10-20 min. The 5-membered ring nitroxides were reduced more slowly over time. *In vivo* radioprotection for most of the compounds may be at least partly explained by the induction of hypotension and bone marrow hypoxia. Other mechanisms for radioprotection, including scavenging of free radicals are also likely.

As mentioned earlier, Tempol, a cell-permeable hydrophilic nitroxide has been shown to be an *in vitro* and *in vivo* radioprotector. The limitations of Tempol as a systemic radioprotector are that it causes substantial reductions in arterial blood pressure when administered intravenously and is associated with seizure activity. Furthermore, Tempol is rapidly reduced to its hydroxylamine form, Tempol-H, which limits the period of time the active form of the nitroxide is available for radioprotection. To circumvent these difficulties, Tempol-H was evaluated as a radioprotector[24]. Tempol-H provided protection against the lethality of whole-body

irradiation in C3H mice at 30 days with a dose modification factor of 1.3 which is similar to the results obtained with Tempol. Hemodynamic measurements in C3H mice after intravenous injection showed that Tempol-H produced little effect on blood pressure or pulse compared with Tempol. Hence Tempol-H is a systemic *in vivo* radioprotector of mice and is associated with less hemodynamic toxicity than Tempol.

Melatonin—Melatonin, a secretory product of the pineal gland in human brain, has been reported to participate in the regulation of a number of physiological and pathological processes. It is a hormone with multiple functions in humans and is stimulated by β-adrenergic receptors. It has been shown to act as an antioxidant and scavenge hydroxyl and peroxyl radicals besides peroxynitrite. Human peripheral blood lymphocytes that were pretreated with melatonin showed radioprotection *in vitro* as assessed by the formation of chromosomal aberrations and micronuclei. In another study peripheral blood samples were collected from human volunteers after a single oral dose of 300 mg melatonin and then subjected to irradiation. Irradiated lymphocytes from such volunteers showed less primary DNA damage and reduced frequencies of chromosomal aberrations and micronuclei[25,26]. The following mechanisms were proposed: the melatonin in the nucleus will bestow a direct protection by reducing the extent of primary DNA damage by scavenging the radiation-induced free radicals. The melatonin acting at the membrane and in the cytosol will generate 'signal(s)' that trigger the activation of one or more of the existing DNA repair enzymes, and/or activation of a set of gene(s) that lead to *de novo* protein synthesis associated with DNA repair[26].

In mice high doses of melatonin (e.g. 250 mg/kg body weight) are non-toxic and are effective in protecting mice from lethal effects of acute whole-body irradiation[27]. The study by Badr *et al*.[28] has shown that melatonin administration confers protection to mice against damage inflicted by radiation when given prior to exposure to irradiation and not after, and support the contention that melatonin radioprotection is achieved by its ability as a scavenger for free radicals generated by ionizing radiation. In cultured skin fibroblasts, by pre-incubation with melatonin, a significant preventive effect was noted on the increase in the absolute number of surviving cells and the levels of malonaldehyde were markedly decreased[29]. This study suggests that melatonin pretreatment inhibits radiation-induced apoptosis, and melatonin exerts its radioprotective effect by inhibition of lipid peroxidation and without involvement of the p53/p21 pathway.

Results from many *in vitro* and *in vivo* investigations have confirmed that melatonin protects mammalian cells from the toxic effects of ionizing radiation. Furthermore, several clinical reports indicate that melatonin administration, either alone or in combination with traditional radiotherapy, results in a favourable efficacy:toxicity ratio during treatment of human cancers[30].

Growth factors—Normal toxicity remains a dose limitation for cancer radiotherapy and chemoradiotherapy. Growth factors offer a novel means of mitigating normal tissue radiotoxicity. In particular, keratinocyte growth factor (rHuKGF), whose proliferative activity is restricted to epithelial cells, holds promise on the basis of the findings of preclinical models of epithelial cytoprotection and the clinical developments to date. Experimental evidences in mice show that an increase in tissue cellularity, caused by rHuKGF treatment before irradiation, protected the lung from damage due to pneumonitis[31].

Hyperthermia—Whole body hyperthermia (WBH) is another novel approach to radioprotection. For instance, exposure of Swiss mice to WBH at 40°C for 1 hr, 20 hr prior to total body irradiation (TBI), at 9 Gy affords significant protection of mice against radiation as assessed by their survival. The studies on mechanisms responsible suggest that WBH induced radioprotection of mice could be due to immunomodulation manifested through induction of cytokines responsible for protection and proliferative response, leading to accelerated recovery from hemopoietic damage, a major cause of radiation induced death[32]. Further studies also showed that mild hyperthermia results in reduction in TBI–induced apoptosis. The results from this study imply that WBH-induced impairment of apoptosis may have some role in WBH-induced radioprotection in Swiss mice[33]. However, this may not be true with other strains.

Superoxide dismutase gene therapy—Organ and tissue damage caused by ionizing radiation is directly related to volume irradiated, total dose and dose rate. Radiation pneumonitis remains a critical dose-limiting toxicity of total body irradiation for use in bone marrow transplantation. In the lung, as in other organs, recovery from the acute effects of radiation

does not always correlate with prevention of the critical late effects, which contribute to organ failure. SOD gene therapy can prevent the late effects of irradiation lung damage. Overexpression of a transgene for human manganese SOD delivered by plasmid-liposome, or adenovirus to the lungs of C57BL/6J or Nu/J mice, respectively, before irradiation, decreased the late effects of whole lung irradiation[34]. Effective prevention of irradiation-induced lung damage and improved survival in mice was achieved by MnSOD plasmid/liposome gene therapy. There is a two-phase mechanism in the molecular pathology of irradiation lung injury, in which IL-1 cytokine mRNA levels correlated with the acute pneumonitis phase and delayed elevation of TNF-α, TGF-β1 and TGF-β2 were associated with the fibrosis phase. Insight into the cell-specific and tissue-specific molecular mechanisms of ionizing irradiation induction of mRNA for pulmonary cytokines may provide new strategies for treatment of radiation pneumonitis in TBI patients[35].

After radiation therapy, oxidative stress is present at 15-20 weeks after initial exposure, which correlates with the delayed clinical onset of radiation-induced lung damage. Overexpression of extracellular SOD (EC-SOD) in transgenic mice appears to confer protection against this radiation-induced lung injury, with a corresponding decrease in oxidative stress. EC-SOD may be a potential therapeutic agent for radio-protection in the treatment of thoracic malignancies[36].

Radiation esophagitis remains a major complication of combined modality protocols for the radiation therapy of lung cancer. Stickle *et al*.[37] have shown that overexpression of the human MnSOD transgene in the esophagus can prevent irradiation-induced esophagitis in the mouse model. In a further development, Epperly *et al*.[38] have shown that intraesophageal administration of manganese super-oxide dismutase-plasmid/liposome (MnSOD-PL) prior to single fraction radiation can protect mice from lethal esophagitis. This treatment significantly improved tolerance to fractionated radiation and modulated radiation effects on levels of GSH and lipid peroxidation. These studies provide further support for translation of MnSOD-PL treatment into human esophageal radiation protection.

Though the above-mentioned studies show some of the novel approaches to radioprotection, use of natural products including plant extracts as possible radio-protectors is gaining momentum in recent years due to less toxicity, reduced cost and other advantages. Hence in the remaining part of our review we give more details on the use of natural products and related compounds as radioprotectors and the mechanisms behind their protective effects.

Natural compounds and plant extracts in radio-protection

Many natural antioxidants, whether consumed before or after radiation exposure, are able to confer some level of radioprotection. In addition to achieving beneficial effects from established antioxidants such as vitamins E and C and folic acid, some protection is conferred by several novel molecules, such as flavonoids, epigallocatechin, and other polyphenols. Immune system was protected against radiation by the following natural compounds: polyphenols, vitamin C, glutamine and arginine, Palm carotene, fatty acids, ubiquinone and hydroquinone. Similarly central nervous system was protected by the following components: aged garlic extract and polyphenols. Eye was protected against radiation by vitamin C, fruits and vegetables as well as by aged garlic extract. Radiation induced carcinogenesis can be reduced by the following components: zinc, vitamins C and E, selenite, polyphenols, thiols, fatty acids, yellow-green vegetables/fruits, curcumin, niacin and nicotinamide adenine dinucleotide[2-4].

A. Plant extract based radio-protectors

Plant extracts, in certain cases, proved to be very effective radioprotectors. These extracts originate from diverse group of plants (Table 2). Some individual plants that show a variety of significant protective effects are dealt with in detail, as given below.

Citrus plants—Fruits and leaves of citrus plants (Citrus sp.) are rich sources of radioprotective compounds. The main flavonoids found in most cultivated citrus species are flavonone glycosides, such as hesperdin, and naringin. These compounds can account for up to 5% of the dry weight of the leaf and fruit tissues. Citrus flavonoids were reported to decrease capillary fragility and to improve blood flow, and were labeled "Vitamin P". Other therapeutic uses are anticancer[39], and antiulcer effects[40]. Its flavonoid, hesperdin, exhibits strong antioxidant activity[41]. It reduces the frequencies of micro-nucleated polychromatic erythrocytes and normo-chromatic erythrocytes and protects mouse bone marrow by a factor of 2.2 against the side-effects of γ-irradiation[42].

Table 2—Radioprotective effect of medicinal plants

Plants	Medicinal / beneficial properties	Radioprotective effects	Ref.
1	2	3	4
Acanthopanax senticosus (Shigoka)	-	Protect against radiation-induced suppression of haemopoiesis.	62
Acorus calamus	-	Protect prenatal irradiation induced development and neurophysiological effect.	63
Aegle marmelos	Anticancer effects	Reduces the symptoms of radiation-induced sickness and increase survival of mice. The possible mechanism is free radical scavenging and elevation of GSH and other antioxidant enzymes (64) Reduced the frequency of micronuclei in human peripheral blood lymphocytes (65)	64, 65
Allium sativum (Garlic, Lahsuna)	Antimicrobial, cardioprotective, antiarthritic, hypoglycemic, antithrombatic	Protects against γ-radiation induced micronuclei (chromosomal damage) *in vivo*.	66, 67
Aloe vera (Gritkumari)	Anticancer effects	Protects skin of Swiss mice (68) Protects against radiation induced injury in intestinal mucosa of Swiss mice (69)	68, 69
Aspalanthus linearis (Rooibos tea)	-	Reduced the frequency of MNRETs upon γ-radiation exposure.	70
Asparagus racemosus (Shatavari)	Reduce effect of stressors	Protects mitochondria against radiation-induced lipid peroxidation, protein oxidation, and depletion of protein thiol and levels of SOD.	71
Centella asiatica	Good wound healing properties	Protects radiation induced conditioned taste aversion in rats (72) Reduce prenatal irradiation-induced changes in brain function (73) Enhanced the survival of mice exposed to lethal dose and also reduces the weight loss (74)	72-74
Citrus aurantium var. *amara*	Rich in vitamin C and carotenoids	Reduces the frequencies of micronucleated polychromatic erythrocytes and normochromatic erythrocytes. Protects mouse bone marrow by a factor of 2.2 against the side effects of γ-irradiation.	42
Dang-Gui-Shao-Yao-San (DGSYS)	-	Prevents hematopoietic injury caused by sublethal dose of radiation	75
Emblica officinalis (Amalaki)	Antibacterial, Anti-inflammatory, Reduce stress	Pre-treatment inhibits mortality and provides protection against radiation induced deleterious alteration in intestinal mucosa of mice (76) Modulates TNF-α and IL-1β and prevents radiation induced gastric damage (77)	76, 77
Lycium chinense	-	Protects against radiation induced bone marrow death.	78
Mentha piperata	Mint for flavouring	Enhances the survival of mice (46) Oil affords protection in terms of survival percentage and haematological parameters in mice (47) Oral administration before exposure to γ-radiation protects against chromosomal damage in bone marrow of mice with a DRF value 1.78 (45)	45-47
Myristica fragrans	-	Protects testes of mice by inhibiting γ-radiation induced TBARS and increased the level of GSH.	79

(*Contd*)

Table 2—Radioprotective effect of medicinal plants—*Contd*

1	2	3	4
Ocimum sanctum (Tulsi)	Anticancer, antimicrobial, stimulant	Water extract enhances the survival of mice with a DMF of 1.28 (53) Enhances the bone marrow protection (54)	53, 54
Panax ginseng	Cardioprotective	Enhances the jejunal crypt survival and endogenous spleen colony formation and reduces the frequency of radiation induced apoptosis.	80
Phyllanthus amarus	Antidiabetic	Significantly increased the total W.B.C count, bone marrow cellularity, and alpha-esterase activity. It also increases the antioxidant defense enzymes such as CAT, SOD, GST, GPx and GR both in blood and tissue, which were reduced by radiation treatment (81). Protect mouse chromosome against radiation-induced damage (82)	81, 82
Podophyllum hexandrum	Anti-tumor effect	Enhanced liver GST and SOD, intestinal SOD and survival of mice (58) Protects plasmid pBR 322 DNA against radiation induced damage (57) Prevents radiation-induced neuronal damage in postnatal rats exposed *in utero* (59)	57-59
Amaranthus paniculatus (Ragira)	-	The oral administration of aqueous *Rajgira* extract at 800 mg / kg body weight / day for 15 consecutive days before whole body exposure to radiation was found to be effective with a dose reduction factor of 1.36.	83
Rubia cordifolia	Platelet activating property	Protects plasmid pBR322 DNA against strand breaks and microsomal and mitochondrial membranes against lipid peroxidation induced by γ-radiation.	84
si-jun-zi-tang	Energy tonic	Protects jejunal crypt and increased the endogenous spleen colony formation and reduces the frequency of radiation induced apoptosis (85) Protects mouse bone marrow cells (86)	85, 86
si-wu-tang	Blood building decoction	Protects jejunal crypt and increased the endogenous spleen colony formation and reduces the frequency of radiation induced apoptosis.	85
Syzygium cumini (Jamun)	Anti-diabetic	Leaf extract reduces radiation induced micronuclei formation in human peripheral blood lymphocytes (87) Delayed the onset of mortality and reduced the symptoms of radiation sickness (88)	87, 88
Terminalia chebula	Anti-bacterial, Reduce effect of stressors	Protects plasmid pBR322 DNA and human peripheral blood leukocytes (89) Inhibits γ-radiation-induced lipid peroxidation in rat liver microsomes and damage to superoxide dismutase enzyme in rat liver mitochondria besides γ-radiation-induced strand breaks in plasmid pBR322 DNA (90)	89, 90
Tinospora cordifolia (Guduchi)	Antibacterial, Antihyperglycemic, Reduce toxic effect of cyclophosphamide, Improve surgical outcome	Enhanced the survival of mice and modulate macrophage response to radiation (18) Reduces radiation induced damage in the liver cells Protects Swiss albino mice against radiation injury and regain the weight loss Pre-irradiation treatment with RTc rendered 76.3% survival (30 days), compared to 100% mortality in irradiated control and prevented radiation induced weight loss. It restores total lymphocyte counts and increases the S-phase population which was reduced after 2 Gy exposure (61)	18, 61
Zingiber officinale	Anti-inflammatory, Anti-cancer, Anti-stressor, Anti-proliferative	Reduces the severity of radiation sickness and mortality. Protects mice from GI and bone marrow syndromes.	91

Hippophae rhamnoides (Linn.)—*Hippophae rhamnoides* (Sea Buckthorn) is being used in the Indian and Tibetan system of medicine for centuries. The plant has antioxidant, anti-inflammatory, antimicrobial and immunostimulatory properties. Its aqueous extract enhances the survival of strain 'A' mice when administered 30 min prior to whole body γ-irradiation[43]. It provides protection to the gastro-intestinal system against lethal whole-body γ-irradiation. Administration of a hydroethanol (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[44].

Mentha piperita (Linn.)—This is an aromatic plant (peppermint) with several reported therapeutic properties pertaining to treatment for nausea and vomiting. The oral administration of Mentha extract (ME) (1g/kg body weight/day) before exposure to γ-radiation was found to be effective in increasing the frequency of radiation-induced endogenous spleen colonies. A significant increase in the weight of the spleen was observed in animals of the Mentha treated and radiation exposed group in comparison to the irradiated group on day 10 of post-irradiation. Oral administration of 1g/kg body weight/day before exposure to γ-radiation protects against radiation induced chromosomal damage in bone marrow of mice with a dose modifying factor (DRF) value 1.78[45]. Mentha extract and its oil enhanced the survival of mice[46,47] besides improving hematological parameters[47].

Ocimum sanctum (Linn.)—*Ocimum sanctum* (Tulsi or Indian holy basil) is a medicinal herb widely used in the Ayurveda system of medicine in India. It is used for treating infections, skin diseases, common cold and cough, malarial fever besides hepatic disorders. It is also having antibacterial[48], anti-inflammatory[49], anti-viral[50], anti-carcinogenic[51], antioxidant and immunostimulaory activities[52]. Uma Devi and Ganasoundari reported its radioprotective property for the first time[53]. Aqueous and alcoholic extracts of leaves have radio-protective properties, but its aqueous extract (optimum dose was 50 mg/kg body weight, acute LD_{50} was 6 g/kg body weight) was more effective in increasing survival[53]. Its extract was compared to WR-2721, a standard radioprotector. An intraperitoneal injection of an optimum dose (10 mg/kg daily for 5 days) of leaf extract to mice before delivering sub-lethal (2 Gy) total body γ-radiation produced a significantly higher bone marrow stem cell survival than such a pre-treatment with 300 mg/kg of WR-2721[54]. Two active components of *O. sanctum,* orientin and vicenin, did not exhibit any systemic toxicity in mice even at a dose of 100 mg/kg b.wt and both significantly increased the survival of mice when administered 30 min prior to lethal whole body γ-irradiation. Vicenin has DMF value of 1.37 whereas orientin has 1.30 in the murine system[55]. These compounds also significantly inhibited the Fenton reaction-induced OH radical under *in vitro* conditions[56] and protected human lymphocyte chromosomes against radiation[51].

Podophyllum hexandrum (Royle)—*Podophyllum hexandrum* (Himalayan Mayapple) has been shown to mitigate radiation injuries and especially the haemopoietic syndrome in adult mice. It protects plasmid pBR322 DNA against radiation-induced damage *in vitro*[57]. It enhanced survival of mice and increased levels of liver GST and SOD besides intestinal SOD[58]. It also prevents radiation-induced neuronal damage in postnatal rats exposed *in utero*[59]. Podophyllotoxin is one of the major constituents of the extract of Podophyllum and it has radioprotective action in *Saccharomyces cerevisiae*[60].

Tinospora cordifolia (Miers)—*Tinospora cordifolia* (Guduchi) is widely used in Ayurvedic medicines. It is known for its immunomodulatory, anti-hepatotoxic, anti-stress and antioxidant properties. It has been used in combination with other plant products to prepare a number of Ayurvedic formulations. A preparation of *T. cordifolia* (RTc) administered ip (200 mg/kg body weight) to male mice 1 hr before whole body γ-irradiation was evaluated for its radioprotective efficacy, in terms of whole body survival, spleen colony forming units (CFU), hematological parameters, cell cycle progression and micronuclei induction. Pre-irradiation treatment with RTc rendered 76.3% survival (30 days), compared to 100% mortality in irradiated control and prevented radiation induced weight loss. It restores total lymphocyte counts and increases the S-phase population that was reduced after 2 Gy exposures[61]. Its aqueous extract enhances the survival of mice against a sublethal dose of gamma radiation[18]. It protects Swiss albino mice against radiation injury and helps to regain the weight lost. It also reduces radiation induced damage in the liver cells[18,61].

B Polyherbal formulations

There are some polyherbal formulations that show radioprotective effects. A compilation of such effects is given in Table 3.

Abana—Abana's active ingredients are from *Terminala arjuna* (arjuna), *Centella asiatica* (Gotu-Kola) and *Withania somnifera* (ashwagandha). It reduces hypertension[92,93] and other cardiovascular diseases in man[94]. It inhibits platelet aggregation[95]. Abana protects mouse bone marrow against radiation-induced micronuclei formation[96]. The alcoholic extract of abana (20 mg/kg body weight) provided protection against gastrointestinal (GI) death and enhanced the survival of mice after exposure to γ-radiation. Acute toxic studies revealed that Abana was non-toxic up to a dose of 1.6 g/kg body weight, where no drug induced mortality was observed. The LD_{50} dose of abana was found to be 1.8 g/kg body weight. This study demonstrated the ability of abana as a good radioprotective agent and the optimum protective dose of abana was 1/90 of its LD_{50} dose[97,98].

Cystone—Some of Cystone's active ingredients are *Rubia cordifolia* (Indian madder), *Didymocarpus pedicellata* (Shilapushpa), *Saxifrago ligulata* (Pasanavheda), *Cyperus scariosus* (Umbrella's edge), *Achyranthes aspera* (Rough Chaff tree) and *Tinospora cordifolia* (Guduchi). It is very effective in supporting the urinary tract function. It reduces susceptibility to urinary problems by maintaining mucosal integrity. Cystone keeps the kidneys and urinary tract flushed and working at optimum efficiency. Cystone inhibits calculogenesis by reducing stone-forming substances like oxalic acid, calcium hydroxyproline etc., and causes their expulsion by micropulverization. Treatment of mice with different doses of cystone, consecutively for five days before irradiation, delayed the onset of mortality and reduced the symptoms of radiation sickness[99].

Table 3—Radioprotective effect of polyherbal formulations

Plants	Medicinal/beneficial properties	Radioprotective effects	Ref.
Abana (a polyherbal formulation)	Reduces hypertension and other cardiovascular diseases	Treatment of mice with different doses of abana delayed the onset of mortality and reduced the symptoms of radiation sickness as compared to the irradiated controls (97) Pre-treatment of mice with abana before irradiation delayed the onset of mortality and reduced the symptoms of radiation sickness. Provided protection against both the gastrointestinal and haemopoietic death (98).	97, 98
Bu-zhong-yi-qi-tang (a Chinese formulation)	-	Protects intestine and hematopoietic organs against radiation damage.	106
Cystone (an ayurvedic herbal medicine)	Keeps the kidneys and urinary function at optimum efficiency	Treatment of mice with different doses of cystone, consecutively for five days before irradiation, delayed the onset of mortality and reduced the symptoms of radiation sickness.	99
Geriforte (Polyherbal formulation)	Anti-aging effects, and improves hormonal effectiveness	Delayed the onset of mortality and reduces radiation sickness. Protects against GI and bone marrow death with a DRF of 1.14.	100
Mentat (a polyherbal formulation)	Improves memory and minimize deficits associated with aging.	Mentat, consecutively for five days administration before irradiation delayed the onset of mortality and reduced the symptoms of radiation sickness. It also protects against GI syndrome.	101
Triphala (an Ayurvedic formulation)	Anti-bacterial Anti-malarial, Anti-fungal, Anti-allergic, and anti-viral	Delayed the radiation induced mortality and reduced the symptoms of radiation sickness. Provide protection against gastrointestinal and hematopoietic deaths (104) Differentially protect normal cells more than tumor cells in culture (105)	104, 105
Y Rad A (a herbal formulation)	-	Protects hematological parameters and reduces micronuclei. Inhibits lipid peroxidation and reduced glutathione content in RBC.	107

Geriforte—Geriforte is a completely natural product. Some of its active ingredients are Chyavanprash, *Withania somnifera* (ashwagandha), *Emblica officinalis* (Indian gooseberry), *Mucuna urens* (Cow-itch plant) etc. It has strong antioxidant properties, the key to its reported anti-aging benefits. It improves hormonal effectiveness, the key to its menopausal benefit. It is also found to be effective in stress related conditions like premature aging, fatigue, insomnia or emotional imbalance. Treatment of mice with different doses of geriforte, consecutively, for five days before irradiation delayed the onset of mortality and reduces radiation sickness. A dose of 10 mg/kg body weight ($1/_{475}^{th}$ of the LD_{50}) protects against GI and bone marrow death with a DRF of 1.14 upon γ-radiation exposure[100].

Mentat—Mentat is an herbal formulation of several medicinal plants that have been categorized in Ayurveda as "Medharasayanas". It is used to regulate behavior, improve memory and minimize deficits associated with aging. This formulation includes *Bacopa monniera* (Brahmi), *Centella asiatica* (Gotu-Kola), *Adoxa moschatellina* (Musk root), *Terminalia arjuna* (Arjuna) as some of the active ingredients. Mentat supports the brain function in normal situations as well as when facing various mental and emotional pressures. Administration of Mentat consecutively for five days before irradiation delayed the onset of mortality and reduced the symptoms of radiation sickness. It also protects against GI syndrome[101].

Triphala—Triphala, is one of the important formulations commonly used in the Ayurvedic system of medicine. It is a formulation of three herbs namely, *Terminalia chebula, Phyllanthus emblica* (or *Emblica officinalis)* and *Terminalia bellerica.* It has been described in the Ayurveda as a 'tridoshic rasayan'. This is an antioxidant rich formulation[102,103]. Triphala and/or its individual plant constituents have antibacterial anti-malarial, anti-fungal, anti-allergic and anti-viral activities. It has good radioprotecting effect at a dose of 1/28 of its LD_{50} dose. It enhances the survival of mice and reduces the symptoms of radiation sickness upon exposure to γ-radiation and provides protection to gastrointestinal and hematopoietic deaths[104]. Under culture condition it differentially protects normal cell MOE than tumor cell[105].

C Natural and semi-natural compounds of plant origin as radio-protectors

There are many natural and related compounds that show radioprotective effects. A compilation of such compounds and their effects are given in Table 4. Among these a detailed analysis is done for the following compounds:

Ascorbic acid—Vitamin C protects Allium[108] and barley seeds[109] against ionizing radiation. The radioprotective effects of ascorbate seem to be due to its interactions with radiation-induced free radicals[110]. Earlier studies had shown a protection factor of 2 for dietary vitamin C following irradiation from ^{131}I [111]. Ascorbic acid pretreatment inhibited the radiation-induced elevation in lipid peroxidation and significantly elevates the antioxidant enzymes[112]. It protected mice against radiation-induced sickness, mortality and improves the healing of wounds after exposure to whole-body γ-radiation[113]. It also leads to early recovery from radiation injury. The significant inhibition of the biochemical alterations in liver suggests the prophylactic role of vitamin C against γ-irradiation[114].

Caffeine—Caffeine scavenges hydroxyl radicals[115,116] and competes with oxygen for radiation-induced electrons[10,117,118]. Caffeine offers radioprotection against oxygen-dependent radiation-induced damage in barley seeds[119], in Chinese hamster ovary cells[120], rat liver mitochondria[121,122] and plasmid DNA[123]. Caffeine is radioprotective in bone marrow chromosomes of mice whether given before or after whole-body γ-irradiation[124]. Post-treatment with caffeine did not influence radiation-induced damage in mouse L cells[125], or Chinese hamster cells[126]. Caffeine restores the normal cell cycle following X-ray-induced arrest in G_2 phase in one and two-cell mouse embryos[127]. The effect of caffeine was blocked by cycloheximide, suggesting that caffeine action depends on protein synthesis[128]. Caffeine reduced the concentration of an X-ray-induced protein in melanoma cells[129]. Caffeine protects against radiation-induced lethality in mice[130].

Chlorophyllin—Chlorophyllin acts both as an antimutagen[131] and as a radioprotector[132-138]. The mutagenicity of 26 krad X-rays given to yeast (*S. cerevisiae*), was inhibited by chlorophyllin[139]. Chlorophyllin protects mitochondrial membranes against γ-radiation., *in vitro*[133,134], strand breaks and plasmid DNA[140] sister chromosomal exchange (SCE) in murine bone marrow cells, *in vivo*[137]. It signi-

Table 4—Radioprotective effect of natural and semi-natural compounds

Natural compounds	Radioprotective effects	Ref.
1	2	3
Ascorbic acid Vitamin C	Protects *Allium* and barley seeds against ionizing radiation (109) Inhibited radiation-induced elevation in lipid peroxidation and significantly elevated the anti-oxidant enzymes (112) Protected mice against radiation induced sickness, mortality and improve the healing of wounds after exposure to whole-body γ-radiation (113)	109, 112, 113
Caffeine	Differentially protects against oxic component of damage but not anoxic component in rat liver mitochondria (122) Inhibits chromosomal aberrations in bone marrow cells of mice (120) Offers radioprotection against oxygen-dependent radiation-induced damage in barley seeds (119)	119, 120, 122
β-carotene	Inhibits radiation induced micronuclei as well as PCEs/NCEs and mitotic index of bone marrow cells (199-201) Inhibits MN frequency in mouse splenocytes, reticulocytes and spermatids but not in bone marrow cells (202)	199-202
Chlorophyllin	Protects mitochondrial membranes against γ-radiation (133) *In vivo* protection against γ-ray-induced sister chromatid exchange (SCE) in murine bone marrow cells (138) Radioprotective effect on somatic cell of Drosophila (135) Reduce the incidence of micronucleated polychromatic erythrocytes in bone marrow cell upon γ-ray exposure (136)	133, 135, 136, 138
Curcumin	Curcumin pretreatment has a conducive effect on the irradiated wound. Protects rat liver microsomes against lipid peroxidation induced by radiation.	203
Cystamine	Inhibits radiation induced changes in composition of fatty acid (204). Ameliorates radiation induced haemopoiesis (205).	204, 205
Eugenol	Effectively prevents membrane and cellular damage in irradiated thymocytes	206
Ferulic acid	Protects against the γ-radiation induced damage to plasmid pBR322 DNA *in vitro*, mouse blood leukocytes and bone marrow cells *in vivo*, also enhances the DNA repair process *in vivo* in mouse blood leukocytes.	146
Genistein	At non-toxic doses provides protection against acute radiation injury.	207
Glutathione (GSH)	GSH is a radioprotector of cells in culture (150) and animals *in vivo* (151).	150, 151
Glycyrrhizic acid	Protects against γ-radiation induced DNA damage to plasmid pBR322 *in vitro*, human peripheral blood leukocytes *ex vivo* and mouse blood leukocytes and bone marrow cells *in vivo.*	158
L-Lysine	Protects against radiation induced hemolysis of human RBCs and enhances the survival of Swiss mice.	208
Mangiferin	Reduces the radiation induced damage and enhances the repair of DNA double strand breaks in human peripheral blood lymphocytes.	209
Naringin	Protects against the radiation-induced genomic instability in terms of micronuclei and chromosomal aberrations in the mouse bone marrow (210, 211).	210, 211
Orientin	It also inhibits radiation peroxidation of lipid upon gamma-radiation exposure. (56) Protects the human lymphocytes against the clastogenic effect of radiation. (212) Orientin (50 μg/ kg body weight) is having DMF value 1.6 for stem cell survival, exogenous spleen colony (CFU-S) (213) It protects against foetal irradiation-induced genomic damage and instability. (214)	56, 212, 213, 214
Sesamol	Significantly reduced γ-radiation-induced micronuclei and dicentrics in human lymphocytes.	215

(*Contd*)

Table 4—Radioprotective effect of natural and semi-natural compounds—*Contd*

1	2	3
Tocopherol Monoglucoside (TMG)	TMG has been shown to have a radioprotective effect in mammalian systems and yeast (195). Reduces radiation clastogenecity in mouse bone marrow when administered after irradiation (197) In a multi organ study using mice exposed to gamma radiation, it has been reported that administration of TMG resulted in preferential protection of cellular DNA in normal tissue such as liver, spleen, blood and bone marrow but not in tumour (198)	195, 197, 198
α-tocopheryl succinate (α -TS)	It enhances the levels of γ-irradiation-induced chromosomal damage in cancer cells, whereas it protects normal cells against such damage	190
Trigonelline	Protects plasmid pBR322 DNA and *Saccharomyces cerivisiae* cells against γ-radiation.	216
Troxerutin	During radiotherapy of head and neck cancer, administration of a mixture of troxerutin and coumarin offered protection to salivary glands and mucosa. (168) Inhibited lipid peroxidation in membranes of sub-cellular organelles as well as normal tissues of tumour-bearing mice exposed to γ-radiation. And differential protection of DNA in blood leukocytes and bone-marrow cells and not in cells of tumour in whole body irradiated tumour-bearing mice (169) Enhanced the DNA repair process in mouse blood leukocytes *in vivo* (170)	168-170
Vanillin	It suppresses the chromosomal aberrations induced by X-rays in V79 cells *in vitro* (176) and in mice *in vivo* (177)	176, 177
Vicenin	It also inhibits radiation peroxidation of lipid upon gamma-radiation exposure. (56) Protects the human lymphocytes against the clastogenic effect of radiation. (212) Vicenin (50 μg/ kg body weight) is having DMF value 1.6 for stem cell survival, exogenous spleen colony (CFU-S) (213) It protects against foetal irradiation-induced genomic damage and instability. (214)	56, 212, 213, 214
Vinblastine sulfate	Offers protection to the normal tissues against γ-radiation-induced DNA strand breaks.	217
Vitamin E (α-Tocopherol)	Protects intestinal crypt of rat (180) Reduces the frequency of micronuclei and chromosomal aberrations in bone marrow cells. Significantly radio-protects the hematological parameters- RBC count, serum-SH level, blood GSH etc. (181).	180, 181

ficantly reduces the incidence of micronucleated polychromatic erythrocytes in bone marrow cells upon γ-ray exposure[136]. Chlorophyllin exhibited radioprotective activity in *Drosophila melanogaster*[132]. A dose of 100 μg of chlorophyllin /g body weight protected against the induction of sister chromatid exchange in murine bone marrow cells by 1 Gy of γ-rays[137,138].

Ferulic acid—Ferulic acid is a monophenolic phenylpropanoid occurring in plant products such as rice, green tea and coffee beans. It has ability to act as an antioxidant against peroxyl radical induced oxidation in neuronal culture and synaptosomal membranes[141]. It scavenges the reactive oxygen species such as hydroxyl radical ($^{\cdot}OH$), hypochlorous acid (HOCl) and peroxyl radical ($RO_2^{\cdot}$)[142] besides the stable free radical 1, 1-diphenyl-2-picrylhydrazyl (DPPH)[143]. No *in vivo* data is available, but *in vitro* studies on cytotoxicity indicate that in rat hepatocyte the LD_{50} is 25 mM[144]. Short-term feeding study showed that ferulic acid-sulfoglucuronide is the main metabolite in the plasma of rat administered with ferulic acid or its sugar esters[145]. Administration of ferulic acid 1 hour prior to irradiation significantly reduced the DNA damages in mouse blood leukocyte and bone marrow cells. Also, ferulic acid given 1 h prior and/or immediately after γ-radiation exposure significantly reduces the micronucleated reticulocytes (MNRETs) in mouse blood. It also enhances the DNA repair in mouse peripheral blood leukocytes[146].

Glutathione (GSH)—Glutathione is a very important cellular antioxidant. Most normal cells have a large excess of glutathione. Cells deprived of glutathione suffer severe oxidative damage associated with degeneration of mitochondria. Intracellular glutathione increases the resistance of tumor cells to alkylating agents and ionizing radiation[147,148], while depletion of glutathione inhibits tumor cell growth[149]. GSH is a radioprotector of cells in culture[150] and animals *in vivo*[151]. Patients with higher GSH levels, treated with radiation for squamous cell carcinoma of the oral cavity, had less severe mucositis[152].

Glycyrrhizic acid (GZA)—Root extracts of the plant *Glycyrrhiza glabra* L, known as Yashtimadhu in Ayurveda have been used for curing various diseases due to their anti-inflammatory, antibacterial, antiviral and immune-modulating activities[153]. The extract, generally called liquorice, is widely used as sweetner in food products and chewing tobacco. The active compounds of the extract have been reported to have immunomodulating[154] and anti-oxidant effects[155]. The radioprotective effect of the extract on γ-radiation induced DNA and membrane damages have been reported[156]. One of the major components of the extract is glycyrrhizic acid. In biological systems most of the damage induced by gamma rays is indirect and mediated through free radicals that interact with important macromolecules including DNA and membranes[157]. Membrane damage occurs mainly due to peroxidation of membrane lipids. In the earlier study we have investigated the mechanism of radiation protection of DNA by glycyrrhizic acid (GZA) *in vitro, ex-vivo,* and *in vivo*. GZA offered protection to plasmid pBR322 DNA from radiation-induced strand breaks with a dose-reduction factor of 2.04 at 2.5 mM concentration. Under *ex vivo* condition GZA protected the cellular DNA of human peripheral blood leukocytes exposed to gamma radiation in a concentration-dependent manner. Intraperitoneal administration of the GZA (4 mg/ kg body weight) to mice one hour prior to radiation exposure protected cellular DNA of peripheral blood leucocytes and bone marrow cells. Pulse radiolysis studies indicated that GZA offered radioprotection by scavenging free radicals[158].

Troxerutin—Troxerutin, a derivative of the natural flavonoid rutin extracted from *Sophora japonica* (Japanese pogoda tree) has been commonly used in the treatment of Chronic Venous Insufficiency (CVI) disease[159-162]. It improves capillary function, reduces capillary fragility[163] and abnormal leakage and has anti-erythrocytic, anti-thrombotic, fibrinolytic and rheological activity[159]. Its effectiveness and safety has been evaluated in both elderly patients[164] and pregnant women[165], with excellent results. It scavenges oxygen-derived free radicals[166,167]. It has been reported that during radiotherapy of head and neck cancer, administration of a mixture of troxerutin and coumarin offered protection to salivary glands and mucosa[168]. It has been shown that troxerutin inhibited lipid peroxidation in membrane of sub-cellular organelles as well as normal tissues of tumor-bearing mice exposed to γ-radiation. Further, it was found that administration of troxerutin resulted in differential protection of DNA in blood leukocytes and bone-marrow cells and not in cells of tumor in whole body irradiated tumor-bearing mice[169]. Maurya *et al.*[170] have recently shown that it enhances the process of DNA repair and having concentration dependent radioprotection to mouse blood and bone marrow cells. It significantly inhibited the micronuclei in human peripheral blood lymphocytes and mouse blood reticulocytes.

Vanillin—Vanillin (4-hydroxy-3-methoxybenz-aldehyde) is the major component of natural vanilla, which is one of the most widely used and important flavouring materials worldwide. The source of vanilla is the bean, or pod, of the tropical Vanilla orchid (principally *Vanilla planifolia* Andrews, syn. *V. fragrans* (Salisb. Ames)). Vanillin is an antioxidant in lipid assay systems[171]. Vanillin and its analogs were strongly antimutagenic or antigenotoxic in most but not all studies[172,173]. Vanillin itself was not mutagenic but in a few studies it enhanced mutagenesis of chemical mutagens[174]. Oral treatment of mice with 500 mg/kg body weight vanillin at 7.5 hr after injection of mitomycin C caused 50% decrease in the frequency of micronucleated polychromatic erythrocytes[175]. The antimutagenic effects of vanillin may be the result of a mutation-dependent, error-free pathway for post-replication DNA repair[172]. It suppresses the chromosomal aberrations induced by X-rays in V79 cells *in vitro*[176] and in mice *in vivo*[177]. It inhibits lipid peroxidation in rat liver mitochondria and reduces DNA damage in plasmid pBR322[178,179].

Vitamin E and its derivatives—Several studies on the radioprotective effects of vitamin E on normal cells in animals have been published[180-183]. Vitamin E, a singlet oxygen scavenger, does not scavenge hydroxyl radicals or hydrogen peroxide[184]. Vitamin E prevents radiation-induced lipid peroxidation. The whole body $LD_{50/30}$ radiation dose in mice fed a vitamin E deficient diet decreased, while excess vitamin E increased the dose. Vitamin E suppressed X-ray-induced transformation of C3H10T1/2 and other cells when present during and after radiation exposure[185,186]. Transformants appeared when vitamin E was removed and cells were allowed to proliferate, indicating that initiated cells were still present[185]. This indicates that vitamin E does not inhibit oxidizing radicals produced by radiation, thought to be responsible for initiating DNA damage. However,

vitamin E (300 mg/kg body weight) did not significantly prevent chromosomal damage in bone marrow cells against a whole body dose of 0.4 Gy X-rays[187].

Alpha-tocopheryl succinate (α -TS): One of the most effective form of vitamin E, α-TS[188,189], enhances the growth-inhibitory effect of X-irradiation on neuroblastoma cells in culture[190]. Recently, it has been shown that α-TS increases the levels of radiation-induced decrease in mitotic accumulation in human cervical carcinoma cells and ovarian carcinoma cells in culture, but it does not modify this effect of irradiation in normal fibroblasts in culture[191]. It has been reported that α-TS by itself induces chromosomal damage in cancer cells, but not in normal cells in culture. In addition, it enhances the levels of γ-irradiation-induced chromosomal damage in cancer cells, whereas it protects normal cells against such damage[192].

Alpha-tocopherol monoglucoside (TMG): TMG is a highly water-soluble derivative of α-tocopherol where the isoprenoid side chain of α-tocopherol is replaced by a glucose moiety through an o-glycosidic bond. This compound has been found to scavenge free radicals and effectively protect DNA and membranes against ionizing radiation[193,194]. TMG has been shown to have a radioprotective effect in mammalian systems and yeast[195-197]. Administration of TMG to mice, five minutes prior to whole-body X-irradiation by an oral route or immediately after by an ip route, protected them from the lethal effects of radiation. Administration of TMG by ip to mice following irradiation prevented gamma-radiation–induced chromosomal aberrations in bone-marrow cells[197]. In a multi organ study using mice exposed to gamma radiation, it has been reported that administration of TMG resulted in preferential protection of cellular DNA in normal tissue such as liver, spleen, blood and bone marrow but not in tumor[198].

Conclusions and future prospects

From the fore-going review it can be surmised that there are several novel approaches to radioprotection. Many have potential applications. The benefits of using natural products for radioprotection are many. Some of the natural compounds and herbal extracts/ preparations could be effective in mitigating radiation injuries and several radiation related syndromes. Major advantage of using these would be their relative non-toxicity and time tested effectiveness in curing symptoms akin to the pathological situations arising from radiation exposures. Exposure to ionizing radiation in early life for diagnostic/therapeutic purposes has been reported to increase the cancers in later life[218]. Pre-natal radiation exposure increases the incidence of tumors in the experimental animals and humans. Protection against radiation induced genetic instability by non-toxic dietary ingredients or herbal preparations form an attractive proposition to prevent radiation-induced carcinogenesis[214,219]. Plants, their products and polyherbal preparations have been used to treat various human ailments from ancient time in Eastern countries as well as in the West. As some of the radiation syndromes exhibit pathological manifestation similar to these human ailments, the herbal medicines useful for treating the ailments could also be effective in case of radiation syndromes. As we 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.

References

1 Bump E A & Malaker K, Radioprotectors: chemical, biological and clinical perspective (CRC Press, Boca Raton, FL) 1998.

2 Turner N D, Braby L A, Ford J & Lupton J R, Opportunities for Nutritional amelioration of radiation-induced cellular damage, *Nutrition,* 18 (2002) 904.

3 Weiss J F & Landauer M R, Protection against ionizing radiation by antioxidant nutrients and phytochemicals, *Toxicology,* 189 (2003) 1.

4 Singh A, Singh H & Henderson J S, Radioprotection by ascorbic acid, desferal, and mercaptoethylamine, *Meth Enzymol,* 186 (1990) 686.

5 Nair C K K, Parida D K & Nomura T, Radioprotectors in radiotherapy, *J Radiat Res*, 42 (2001) 21.

6 Maisin J R, Chemical radioprotection: Past, present and future prospects, *Int J Radiat Biol,* 73 (1998) 443.

7 Tannehill S P & Mehta M P, Amifostine and radiation therapy: Past, present and future, *Semin Oncol,* 23 (1996) 69.

8 Livesey J C & Reed D J, Chemical protection against ionizing radiation. *Adv Radiat Res,* 13 (1987) 285.

9 Arora R, Gupta D, Chawla R, Sagar R, Sharma A, Kumar R, Prasad J, Singh S, Samanta N & Sharma R K, Radioprotection by plant products: Present status and future prospects, *Phytother Res,* 19 (2005) 1.

10 Devasagayam T P A & Kesavan P C, Radioprotective and antioxidant action of caffeine: Mechanistic considerations, *Indian J Expl Biol*, 34 (1996) 291.

11 Devasagayam T P A & Tilak J C. Oxidative damage to mitochondria. in *Oxidative stress, disease and cancer*, edited by K K Singh, Section I. Chapter 3 (Imperial College Press, London) in press.

12 Lakshmi B, Tilak J C, Adhikari A, Devasagayam T P A & Janardhanan KK. Inhibition of lipid peroxidation induced by

γ-radiation and AAPH in rat liver and brain mitochondria by selected mushrooms. *Curr Sci,* 88 (2005) 484.
13 Devasagayam T P A, Boloor K K & Ramasarma T, Methods for estimating lipid peroxidation: Analysis of merits and demerits. *Indian J Biochem Biophys,* 40 (2003) 300.
14 Coogle J E, Biological effects of radiation, (Taylor and Francis Ltd., London) 1983.
15 Von Sonntag C, The chemical basis of radiation biology, (Taylor and Francis, London) 1987.
16 Phillips S, Ruggier R & Hutchinson SE, *Zingiber officinale* (ginger), an antiemitic for day case surgery. *Anaesthesia,* 48 (1993) 715.
17 Udupa S I, Udupa A L & Kulkarni D R, Anti-inflammatory and wound healing properties of *Aloe vera*, *Fitoterapia,* 65 (1994) 141.
18 Pahadiya S & Sharma J, Alteration of lethal effects of gamma rays in Swiss albino mice by *Tinospora cordifolia*, *Phytother Res* 17 (2003) 552.
19 Sun J, Chen Y, Li M & Ge Z, Role of antioxidant enzymes on ionizing radiation resistance, *Free Radical Biol Med,* 24 (1998) 586.
20 Batinic-Haberle I, Liochev S I, Spasojevic I & Fridovic I, A potent superoxide dismutase mimic: Manganese beta-octa-bromo-meso-tetrakis-(N-methylpyridinium-4-yl) porphyrin, *Arch Biochem Biophys,* 343 (1997) 225.
21 Lee J H & Park J W, A manganese porphyrin complex is a novel radiation protector, *Free Radical Biol Med,* 37 (2004) 272.
22 Hahn S M, Sullivan F J, DeLuca A M, Krishna C M, Wersto N, Venzon D, Russso A & Mitchell J B, Evaluation of Tempol radioprotection in a murine tumor model, *Free Radical Biol Med,* 22 (1997) 1211.
23 Hahn S M, DeLuca A M, Coffin D, Krishna C M & Mitchell J B, *In vivo* radioprotection and effects on blood pressure of the stable free radical nitroxides, *Int J Radiation Oncol Biol Phys,* 42 (1998) 839.
24 Hahn S M, Krishna C M, DeLuca A M, Coffin D & Mitchell J B, Evaluation of the hydroxylamine Tempol-H as an *in vivo* radioprotector, *Free Radical Biol Med,* 28 (2000) 953.
25 Vijayalaxmi, Reiter R J, Herman T S & Meltz M L, Melatonin and radioprotection from genetic damage: *In vivo/in vitro* studies with human volunteers, *Mutat Res,* 371 (1996) 221.
26 Vijayalaxmi, Reiter R J, Meltz M L & Herman T S, Melatonin: Possible mechanisms involved in its 'radioprotective' effect, *Mutat Res,* 404 (1998) 187.
27 Vijayalaxmi, Meltz M L, Reiter R J, Herman T S & Sree Kumar K, Melatonin and protection from whole-body irradiation: Survival studies in mice, *Mutat Res,* 425 *(*1999) 21.
28 Badr F M, El Habit O H M & Harraz M M, Radioprotective effect of melatonin assessed be measuring chromosomal damage in mitotic and meiotic cells, *Mutat Res,* 444 (1999) 367.
29 Kim B C, Shon B S, Ryoo Y W, Kim S P & Lee K S, Melatonin reduces X-ray irradiation-induced oxidative damages in cultured human skin fibroblasts, *J Dermatol Sci,* 26 (2001) 194.
30 Vijayalaxmi, Reiter R J, Tan D-X, Herman T S & Thomas Jr. C R, Melatonin as a radioprotective agent: A review, *Int J Radiat Oncol Biol Phys,* 59 (2004) 639.
31 Terry N H A, Brinkley J, Doig A J, Ma J, Patel N, White R A, Mahajan N & Kang Y, Cellular kinetics of muring lung: Model system to determine basis for radioprotection with keratinocyte growth factor, *Int J Radiat Oncol Biol Phys,* 58 (2004) 435.
32 Zaidi A K, Patil M S, Bagewadikar R S, Subramanian M & Kaklij G S, Radioprotection by whole body hyperthermia: Possible mechanism(s), *J Thermal Biol,* 27 (2002) 29.
33 Zaidi A K, Bagewadikar R S, Subramanian M, Kaklij G S & Patil M S, Effect of whole body hyperthermia (39°C, 1h) on radiation-induced apoptosis in Swiss mice, *J Thermal Biol,* 29 (2004) 3.
34 Epperly M, Bray J, Kraeger S, Zwacka R, Engelhardt J, Travis E & Greenberger J, Prevention of late effects of irradiation lung damage by manganese superoxide dismutase gene therapy, *Gene Therapy,* 5 (1998) 196.
35 Epperly M W, Travis E L, Sikora C & Greenberger J S, Magnesium superoxide dismutase (MnSOD) Plasmid/liposome pulmonary radioprotective gene therapy: Modulation of irradiation- induced mRNA for IL-1, TNF-α, and TGF-β correlates with delay of organizing alveolitis/fibrosis, *Biol Blood Marrow Transplant,* 5 (1999) 204.
36 Kang S K, Rabbani Z N, Folz R J, Golson M L, Huang H, Yu D, Samulski T S, Dewhirst M W, Ansher M S & Vujaskovic Z, Overexpression of extracellular superoxide dismutase protects mice from radiation-induced lung injury, *Int J Radiation Oncol Biol Phys,* 57 (2003) 1056.
37 Stickle R L, Epperly M W, Klein E, Bray J A & Greenberger J S, Prevention of irradiation-induced esophagitis by intraesophageal Plasmid/liposome delivery of the human manganese superoxide dismutase (MnSOD), *Radiat Oncol Invest,* 7 (1999) 204.
38 Epperly M W, Kagan V E, Sikora C A, Gretton J E, Defilippi S J, Bar-Sagi D & Greenberger J S, Manganese superoxide dismutase-plasmid/liposome (MnSOD-PL) administration protects mice from esophagitis associated with fractionated radiation, *Int J Cancer (Radiat Oncol Invest),* 96 (2001) 221.
39 Menon L G, Kuttan R & Kuttan, G, Inhibition of lung metastasis in mice induced B16F10 melanoma cells by polyphenolic compounds, *Cancer Lett,* 95 (1995) 221.
40 Martin M J, Marhuenda E, Perez-Guerreo G & Fraco J M, Antiulcer effect of naringin on gastric lesion induced ethanol in rats, *Pharmacology,* 49 (1994) 144.
41 Miyake Y, Yamamato K, Tsujihara N & Osawa T, Protective effect of lemon flavonoids on oxidative stress in diabetic rats, *Lipids,* 33 (1975) 689.
42 Hosseinimehr S J, Tavakoli H, Pourheidari G, Sobhani A & Shafiee A, Radioprotective effects of citrus extract against gamma-irradiation in mouse bone marrow cells, *J Radiat Res* (Tokyo) 44 (2003) 237.
43 Goel H C, Prasad J, Singh S, Sagar R K, Prem Kumar I & Sinha A K, Radioprotection by a herbal preparation of *Hippophae rhamnoides,* RH-3, against whole body lethal irradiation in mice, *Phytomedicine, 9* (2002) 15.
44 Goel H C, Salin C A & Prakash H, Protection of jejunal crypts by RH-3 (a preparation of *Hippophae rhamnoides*) against lethal whole body gamma irradiation, *Phytother Res,* 17 (2003) 222.
45 Samarth R M & Kumar A, *Mentha piperita* (Linn.) leaf extract provides protection against radiation induced

chromosomal damage in bone marrow of mice, *Indian J Exp Biol,* 41 (2003) 229.

46 Samarth R M & Kumar A, Radioprotection of Swiss albino mice by plant extracts *Mentha piperita* (Linn.). *J Radiat Res,* (Tokyo) 44 (2003) 101.

47 Samarth R M, Goyal P K & Kumar A, Protection of Swiss albino mice against whole-body gamma irradiation by *Mentha piperita* (Linn.), *Phytother Res,* 18 (2004) 546.

48 Phadke S A & Kulkarni S D, Screening of *in vitro* antibacterial activity of *Terminalia chebula*, *Eclipta alba* and *Ocimum sanctum*, *Indian J Med Sci*, 43(1989) 113.

49 Singh S & Agrawal S, Anti-asthamatic and anti-inflammatory activity of *Ocimum sanctum*, *Int J Pharm Pharmacol,* 52 (1991) 306.

50 Kumar R, Singh D P, Chaturvedi V K & Pathak R C, A note on antiviral property of neem (*Melia azadirachta*) and tulsi (*Ocimum sanctum*) against Newcastle disease virus, *Indian J Comp Microbiol Immunol Infect Dis,* 18 (1997) 192.

51 Uma Devi P, Radioprotective, anticarcinogenic and antioxidant properties of the Indian holy basil, *Ocimum sactum*, *Indian J Exp Biol,* 39 (2001) 185.

52 Godhwani S, Godhwani J L & Vyas D S, *Ocimum sanctum*-a preliminary study evaluating its immunoregulatory profile in albino rats, *J Ethnopharmacol,* 24 (1988) 193.

53 Uma Devi P & Ganasoundari A, Radioprotective effect of leaf extract of Indian medicinal plant *Ocimum sanctum*, *Indian J Exp Biol,* 33 (1995) 205.

54 Ganasoundari A, Uma Devi P &, Rao B S S, Enhancement of bone marrow radioprotection and reduction of WR-2721 toxicity by *Ocimum sanctum, Mutat Res*, 397 (1998) 303.

55 Uma Devi P & Ganasoundari A, Rao B S S & Srinivasan K K, *In vivo* radioprotection by *Ocimum sanctum* flavonoids: Survival of mice, *Radiat Res,* 151(1999)74.

56 Uma Devi P & Ganasoundari A, Vrinda B, Srinivasan K K & Unnikrishnan M K, Radiation protection by *Ocimum sanctum* flavonoids orientin and vicenin-mechanism of action, *Radiat Res*, 154 (2000) 455.

57 Chaudhary P, Puri S C, Shukla S K, Arora R, Sagar R K & Sharma R K, Prevention of radiation- induced damage to pBR322 plasmid DNA by fractions of *Podophyllum hexandrum*, *Ind J Radiat Res* 1 (2004) 41.

58 Mittal A, Pathania V, Agrawala P K, Prasad J, Singh S & Goel H C, Influence of *Podophyllum hexandrum* on endogenous antioxidant defence system in mice: Possible role in radioprotection, *J Ethnopharmacol,* 76 (2001) 253.

59 Sajikumar S & Goel H C, *Podophyllum hexandrum* prevents radiation-induced neuronal damage in postnatal rats exposed *in utero*, *Phytother Res,* 17 (2003) 761.

60 Bala M & Goel H C, Radioprotective effect of podophyllotoxin in *Saccharomyces cerevisiae*. *J Environ Pathol Toxicol Oncol,* 23 (2004) 139.

61 Goel H C, Prasad J, Singh S, Sagar R K, Agrawala P K, Bala M, Sinha A K & Dogra R, Radioprotective potential of an herbal extract of *Tinospora cordifolia, J Radiat Res* (Tokyo) 45 (2004) 61.

62 Miyanomae T & Friendel E, Radioprotection of hemopoiesis conferred by *Acanthopanax senticous* (Shigoka) administered before and after irradiation, *Exp Hematol,* 16 (1988) 801.

63 Chetana M, Sulochana B & Uma Devi P, Protection by *Acorus calamus* against prenatal irradiation induced developmental and neurophysiological deficits, *Indian J Radiat Res*, 1 (2004) 35.

64 Jagetia G C, Venkatesh P & Baliga M S, Evaluation of the radioprotective effect of bael leaf (*Aegle marmelos*) extract in mice, *Int J Radiat Biol*, 80 (2004) 281.

65 Jagetia G C, Venkatesh P & Baliga M S, Evaluation of the radioprotective effect of *Aegle marmelos* (L.) Correa in cultured human peripheral blood lymphocytes exposed to different doses of gamma-radiation: A micronucleus, *Mutagenesis,* 18 (2003) 387.

66 Singh S P, Abraham S K & Kesavan, P C, Radioprotection of mice following Garlic pretreatment, *Br J Cancer*, Supp 27 (1996) S 102.

67 Singh S P, Abraham S K & Kesavan P C, *In vivo* radioprotection with Garlic extract, *Mut Res*, 345 (1995) 147.

68 Gehlot P & Saini M R, Radioprotective effects of *Aloe vera* leaf extract on skin of Swiss albino mice after gamma irradiation, *Indian J Radiat Res,* 1 (2004) 52.

69 Gehlot P & Saini M R, Effectiveness of *Aloe vera* leaf extract against low level exposure to gamma radiation induced injury in intestinal mucosa of Swiss albino mice, *Indian J Radiat Res,* 1 (2004) 36.

70 Shimoi K, Masuda S, Shen B, Furugori M & Kinae N, Radioprotective effect of antioxidative plant flavonoids in mice, *Mutat Res,* 350 (1996) 153.

71 Kamat J P, Boloor K K, Devasagayam T P A & Venkatachalayam S R, Antioxiant properties of *Asparagus racemosus* against damage induced by γ-radiation in rat liver mitochondria, *J Ethnopharmacol*, 71 (2000) 425.

72 Shobi,V & Goel H C, Protection against radiation-induced conditioned taste aversion by *Centella asiatica*, *Physiol Behav,* 73 (2001)19.

73 Sulochana Rao B, Chetana, M & Uma Devi P, Effect of *Centella asiatica* on prenatal irradiation induced behavioral deficit. *Indian J Radiat Res*, 1 (2004) 37.

74 Sharma J & Sharma R, Radioprotection of Swiss albino mouse by *Centella asiatica* extract, *Phytother Res*, 16 (2002) 785.

75 Hsu H Y & Lin C C, A preliminary study on the radioprotection of mouse hematopoiesis by Dang-Gui-Shao-Yao-San, *J Ethnopharmacol,* 55 (1996) 43.

76 Jindal A, Sharma A, Singh I & Goyal P K, Radiomodulatory potential of *Emblica officinalis* against enteric lesions in mice, *Indian J Radiat Res,* 1 (2004) 32.

77 Bhattacharya S, Chatterjee S, Bauri A K, Kamat J P, Poduval T B, Chattopadhyay S & Bandyopadhyay S K, *Emblica officinalis*: A Possible preventor of Radiation and NSAID induced gastric damage, *Indian J Radiat Res,* 1 (2004) 33.

78 Hsu H Y, Yang J J, Ho Y H & Lin C C, Difference in the effect of radioprotection between aerial and root parts of *Lycium chinense*, *J Ethnopharmacol*, 64 (1999) 101.

79 Sharma M, Sharma S & Kumar M, Radiomodulatory influence of nutmeg (*Myristica fragrans*) extract in Swiss albino mice after whole body exposure to gamma radiation. Paper presented to the International Conference on Antioxidants & Free Radicals in Health-Nutrition & Radio-Protectors and IV Annual Conference of Society for Free Radical Research-India St. John's National Academy of Health Sciences, Bangalore, India, 10-12 January, 2005.

80 Kim S H, Son C H, Nah S Y, Jo S K, Jang J S & Shin D H, Modification of radiation response in mice by *Panax ginseng* and diethyldithiocarbamate, *In Vivo,* 15 (2001) 407.

81 Kumar K B & Kuttan R, Protective effect of an extract of *Phyllanthus amarus* against radiation-induced damage in mice, *J Radiat Res* (Tokyo) 45 (2004) 133.

82 Uma devi P, Kamath R & Rao B S S, Radioprotective effect of *Phyllanthus niruni* on mouse chromosomes, *Curr Sci,* 78 (2000) 1245.

83 Krishna A & Kumar A, Evaluation of radioprotective effects of *Rajgira* (*Amaranthus paniculatus*) extract in Swiss albino mice, *J Radiat Res,* 46 (2005) 233.

84 Shah V, Kumar S, Maurya D K & Nair C K K, Protection of plasmid pBR322 DNA and membranes of rat liver microsome and mitochondria by *Rubia cardifolia* extract, *Indian J Radiat Res,* 1 (2004) 46.

85 Lee S E, Oh H, Yang J A, Jo S K, Byun M W, Yee S T & Kim S H, Radioprotective effect of two traditional Chinese medicine prescriptions: si-wu-tang and si-jun-zi-tang, *Am J Chin Med,* 27 (1999) 387.

86 Hsu H Y, Ho Y H & Lin C C, Protection of mouse bone marrow by Si-Wu-Tng against whole body irradiation. *J Ethnopharmacol,* 52 (1996) 113.

87 Jagetia G C & Baliga M S, *Syzygium cumini* (Jamun) reduces the radiation-induced DNA damage in the cultured human peripheral blood lymphocytes: A preliminary study, *Toxicol Lett*, 132 (2002) 19.

88 Jagetia G C & Baliga M S, Evaluation of the radioprotective effect of the leaf extract of *Syzygium cumini* (Jamun) in mice exposed to a lethal dose of gamma-irradiation, *Nahrung,* 47 (2003) 181.

89 Gandhi N M & Nair C K K, Radiation protection by *Terminalia chebula:* Some mechanistic aspects*, Mol Cell Biochem*, 277 (2005) 43.

90 Naik G H, Priyadarsini K I, Naik D B, Gangabhagirathi R & Mohan H. Studies on the aqueous extract of *Terminalia chebula* as a potent antioxidant and a probable radio-protector, *Phytomedicine*, 11 (2004) 530.

91 Jagetia G C, Baliga M S, Venkatesh P & Ulloor J N, Influence of ginger rhizome (*Zingiber officinale* Rosc) on survival, glutathione and lipid peroxidation in mice after whole-body exposure to gamma radiation, *Radiat Res,* 160 (2003) 584.

92 Dadkar V N, Tahiliani R R, Jaguste V S, Damle V B & Dhar H L, Double blind comparative trial of abana and methyldopa form onotherapy of hypertension in Indian patients, *Japanese Heart J,* 31 (1990) 193.

93 Tiwari A K & Gode J D, A comparative study of abana and cholesramine on serum lipids and lipoproteins in hyper-cholesterolemic rabbits. *Arogya J Health Sciences,* 16 (1990) 88.

94 Yajnik V H & Acharya H K, Cardiovascular response to mental and physical stress: Modification by abana, *Probe*, 4 (1992) 299.

95 Sankaranarayana A, Mukherjee S, Thusu K, Gyawali K & Luthra N, Effect of abana on exercise induced tachycardia and *in vitro* platelet aggregation, *Probe,* 1 (1985) 25.

96 Jagetia G C & Aruna R, The herbal preparation abana protects against radiation-induced micronuclei in the mouse bone marrow, *Mutat Res*, 393 (1997) 157.

97 Jagetia G C, Baliga M S, Aruna R, Rajanikant G K & Jain V, Effect of abana (a herbal preparation) on the radiation-induced mortality in mice, *J Ethnopharmacol,* 86 (2003) 159.

98 Baliga M S, Jagetia G C, Venkatesh P, Reddy R & Ulloor J N. Radioprotective effect of abana, a polyherbal drug following total body irradiation, *Br J Radiol,* 77 (2004) 1027.

99 Jagetia G C & Baliga M S, Cystone, an ayurvedic herbal drug imparts protection to the mice against the lethal effects of gamma-radiation: A preliminary study, *Nahrung*, 46 (2002) 332.

100 Ravi Kiran P B, Baliga M S & Jagetia G C, Evaluation of the radioprotective action of geriforte (a polyherbal formulation) in mice exposed to different doses of γ-radiation, *Indian J Radiat Res,* 1 (2004) 44.

101 Jagetia G C & Baliga M S, Treatment of mice with a herbal preparation (mentat) protects against radiation-induced mortality, *Phytother Res*, 17 (2003) 876.

102 Jose K & Kuttan R, Inhibition of oxygen free radical by *Emblica officinales* extract and Chyavanprash, *Amala Res Bull,* 15 (1995) 46.

103 Naiwu F, Lanping Q, Lei H, Zhank R & Chen Y, Antioxidant action of extracts of *Terminalia chebula* and its preventive effect on DNA strand breaks in human white cells induced by TPA, *Chinese Traditional and Herbal Drug,* 23 (1992) 26.

104 Jagetia G C, Baliga M S, Malagi K J & Kamath M S, The evaluation of the radioprotective effect of Triphala (an Ayurvedic rejuvenating drug) in the mice exposed to γ-radiation, *Phytomedicine,* 9 (2002) 99.

105 Sandhya T & Mishra K P, Radiosensitizing effect of Triphala on cancer cells: *In vitro* and *in vivo* studies, *Indian J Radiat Res,* 1 (2004) 48.

106 Kim S H, Lee S E, Oh H, Kim S R, Yee S T, Yu Y B, Byun M W & To S K, The radioprotective effects of bu-zhong-yi-qi-tang: A prescription of tradition Chinese medicine, *Am J Chin Med,* 30 (2002) 127.

107 Tripathi Y B, Mehta R G, Singh A V & Arjmandi B H, Radioprotective and chemotherapeutic potential of Y Rad A, a patented formulation, *Indian J Radiat Res,* 1 (2004) 13.

108 Selimbekova D D, Radioprotective properties of ascorbic acid, *Pol Akad Nauk Azerb* SSR, 25 (1969) 78.

109 Conger B V, Radioprotective effects of ascorbic acid in barley seeds, *Radiat Biol,* 15 (1975) 39.

110 Duschesne J, Gilles R & Mosora F, Effect of antioxidant substances on the level of free organic radicals naturally present in the rat diaphragm, *C R Acad Sci* (Paris), 281 (1975) 945.

111 Narra V R, Howell R W, Sastry K S R & Rao D V, Vitamin C as a radioprotector against ^{131}I *in vivo*, *J Nucl Med, 34* (1993) 637.

112 Jagetia G C, Ascorbic acid treatment reduces the radiation-induced delay in the skin excision wound of Swiss albino mice, *Indian J Radiat Res,* 1 (2004) 7.

113 Mallikarjuna Rao, K V N & Jagetia G C, Ascorbic acid treatment enhances wound healing in mice exposed to gamma-radiation, *Indian J Radiat Res,* 1 (2004) 25.

114 Gajawat S, Sancheti G & Goyal P K, Role of Vitamin C (Ascorbic Acid) Against Radiation-Induced Biochemical Hepatic Alterations in Mice, *Indian J Radiat Res,* 1 (2004) 24.

115 Shi X, Dalal N S & Jain A C, Antioxidant behaviour of caffeine: Efficient scavenging of hydroxyl radicals, *Food Chem Toxicol,* 29 (1991) 1.

116 Devasagayam T P A, Kamat J P, Mohan H & Kesavan P C, Caffeine as an antioxidant: Inhibition of lipid peroxidation induced by reactive oxygen species in rat liver microsomes. *Biochim Biophys Acta*, 1282 (1996) 63.

117 Singh S P & Kesavan P C, Barley seed radiosensitivity following post-hydration in oxygen-, nitrogen- and nitrous oxide-saturated water. I. Influence of caffeine and t-butyl alcohol, *J Radiat Res,* 31 (1990) 162.

118 Kesavan P C, Oxygen effect in radiation biology: Caffeine and serendipity, C*urr Sci,* 89 (2005) 318.

119 Kesavan P C & Ahmad A, Modification of genetic damage by post-treatment with caffeine applied during oxygenated and oxygen free hydrated in *Hordeum vulgare*, *Mutat Res,* 23 (1974) 337.

120 Kesavan P C & Natarajan A T, Protection and potentiation of radiation clastogenesis by caffeine: Nature of possible initial events, *Mutat Res,* 143 (1985) 61.

121 Kamat J P, Boloor K K, Devasagayam T P A & Kesavan P C, Protection of superoxide dismutase by caffeine in rat liver mitochondria against γ-irradiation, *Curr Sci,* 77 (1999) 286.

122 Kamat J P, Boloor K K, Devasagayam T P A, Jayashree B & Kesavan P C, Differential modification of oxygen-dependent and -independent effects of γ-irradiation in rat liver mitochondria by caffeine, *Int J Radiat Biol,* 76 (2000) 1281.

123 Santosh Kumar S, Devasagayam T P A, Jayashree B & Kesavan P C, Mechanism of protection against radiation-induced DNA damage in plasmid pBR322 by caffeine, *Int J Radiat Biol,* 77 (2001) 617.

124 Farooqi Z & Kesavan P C, Radioprotection by caffeine pre- and post-treatment in the bone marrow chromosomes of mice given whole-body γ-irradiation, *Mutat Res,* 269 (1992) 225.

125 Rauth A M, Evidence for dark-reactivation of ultraviolet light damage in mouse L cells, *Radiat Res,* 31 (1967) 121.

126 Kihlman B A, Sturelid S, Hartley-Asp B & Nilsson K, The enhancement by caffeine of the frequencies of chromosomal aberrations induced in plant and animal cells by chemical and physical agents, *Mutat Res,* 26 (1974) 105.

127 Grinfeld S & Jacquet P, An unusual radiation-induced G_2 arrest in the zygote of BALB/c mouse strain, *Int J Radiat Biol,* 51 (1988) 353.

128 Jung T & Streffer C, Effects of caffeine on protein phosphorylation and cell cycle progression in X-irradiated two-cell mouse embryos, *Int J Radiat Biol,* 62 (1992) 161.

129 Hughes E N & Boothman D A, Effect of caffeine on the expression of a major X ray-induced protein in human tumor cells, *Radiat Res,* 125 (1991) 313.

130 George K C, Hebbar S A, Kale S P & Kesavan P C, Caffeine protects mice against whole-body lethal dose of gamma-irradiation, *J Radiol Protect,* 19 (1999) 171.

131 Ong T M, Whong W Z, Stewart J & Brockman H E, Chlorophyllin: a potent antimutagen against environmental and dietary complex mixtures, *Mutat Res*, 173 (1986) 111.

132 Zimmering S, Olvera O, Hernandez M E, Cruces M P, Areco C & Pimentel E, Evidence for radioprotective effect of chlorophyllin in Drosophila, *Mutat Res,* 245 (1990) 47.

133 Boloor K K, Kamat J P & Devasagayam T P A, Chlorophyllin as a protector of mitochonfrial membranes against γ-radiation and photosensitization, *Toxicology,* 155 (2000) 63.

134 Kamat J P, Boloor K K & Devasagayam T P A, Chlorophyllin as an effective antioxidant against membrane damage *in vitro* and *in vivo*, *Biochim Biophys Acta,* 1487 (2000) 113.

135 Pimentel E, Cruces M P & Zimmering S, On the persistence of the radioprotective effect of chlorophyllin (CHLN) in somatic cells of Drosophilla, *Mutat Res,* 446 (1999) 189.

136 Abraham S K, Sarma L & Kesavan P C, Role of chlorophyllin as an *in vivo* anticlastogen: Protection against gamma-radiation and chemical clastogens, *Mutat Res,* 322 (1994) 209.

137 Morales-Ramirez P T, Vallarino-Kelly T & Rodriquez-Reyes R, *In vivo* persistence of sister chromatid exchange (SCE) induced by γ-rays in mouse bone marrow cells, *Environ Mutagen,* 6 (1984) 529.

138 Morales-Ramirez P & Garcia-Rodriquez M C, *In viv*o effect of chlorophyllin on γ-ray-induced sister chromatid exchange in murine bone marrow cells, *Mutat Res,* 320 (1994) 329.

139 Galli A, Della Croce C & Bronzetti G, Study on the antimutagenic effect of chlorophyllin, XVII EEMS Annual Meeting, Zurich (1987) 54.

140 Santosh Kumar S, Chaubey R C, Devasagayam T P A, Priyadarsini K I & Chauhan P S, Inhibition of radiation-induced DNA damage in plasmid pBR322 by chlorophyllin and the possible mechanisms, *Mutat Res,* 425 (1999) 71.

141 Kanski J, Aksenova M, Stoyanova A & Butterfield D A, Ferulic acid antioxidant protection against hydroxyl and peroxyl radical oxidation in synaptosomal and neuronal cell culture system *in vitro*: Structure activity studies, *J Nutr Biochem,* 13 (2002) 273.

142 Scott B C, Butler J, Halliwell B & Aruoma O I, Evaluation of the antioxidant action of ferulic acid and catechins, *Free Radic Res Commun*, 19 (1993) 241.

143 Kikuzaki H, Hisamoto M, Hirose K, Akiyama K & Taniguchi H, Antioxidant properties of ferulic acid and its related compounds, *J Agric Food Chem,* 50 (2003) 2161.

144 Majid Y M, Hugle S & Peter J O'Brien, Metabolism of caffeic acid by isolated rat hepatocytes and subcellular fractions, *Toxicol Lett,* 133 (2002) 141.

145 Zhao Z, Egashira Y & Sanada H, Ferulic acid sugar esters are recovered in rat plasma and urine mainly as the sulphoglucuronide of ferulic acid, *Nutr,* 133 (2003) 1355.

146 Maurya D K, Salvi V P & Nair C K K, Radiation protection of DNA by ferulic acid under *in vitro* and *in vivo* conditions, *Mol Cell Biochem,* 280 (2005) 209.

147 Meister A, Glutathione, ascorbate, and cellular protection, *Cancer Res,* (Supp) 54 (1994) 1969.

148 Meister A, On the antioxidant effects of ascorbic acid and glutathione, *Biochem Pharmacol,* 44 (1992) 1905.

149 Peinado P, Martinez-Liarte J H, del Marmol V, Salano F & Lozano J A, Glutathione depletion in mouse melanoma cells increases their sensitivity to oxidative lysis, *Cancer J,* 5 (1992) 348.

150 Saunders E L, Meredith M J, Eisert D R & Freeman M L, Depletion of glutathione after γ-irradiation modifies survival, *Radiat Res,* 125 (1991) 267.

151 Grozdov S P, Effect of glutathione on the course of radiation sickness with a marked gastrointestinal syndrome and the effectiveness of parenteral feeding in an experiment, *Radiobiology,* 27 (1987) 657.

152 Bhattathiri T T, Sreelekha P, Sebastian *et al*. Influence of plasma GSH level on acute radiation mucositis of the oral cavity, *Int J Radiat Oncol Biol Phys,* 29 (1994) 383.
153 Devasagayam T P A & Sainis K B, Immune system and antioxidants, especially those derived from Indian medicinal plants. *Indian J Exp Biol,* 40 (2002) 639.
154 Kores B H, Beukelman C J, van-den-Berg, Wolbink G J, van-Dijk M & Labadie R P, Inhibition of human complement by beta-glycyrrhetinic acid, *Immunology,* 90 (1997) 115.
155 Vaya J, Belinky VA & Aviram M, Antioxidant constituents from Licorice roots: Isolation, structure, elucidation and antioxidative capacity towards LDL Oxidation, *Free Radic Biol Med*, 23 (1997) 302.
156 Shetty T K, Satav J G & Nair C K K, Protection of DNA and microsomal membranes *in vitro* by Glycyrrhizia glabra L., against gamma irradiation, *Phytother Res,* 16 (2002) 576.
157 Green A, Prugr A, Stoudt P M & Murray D, Relationship between DNA damage and the survival of radiosensitive mutant Chinese hamster cell lines, exposed to gamma-radiation, Part1: Intrinsic radiosensitivity, *Int J Rad Biol,* 61 (1985) 465.
158 Gandhi N M, Maurya D K, Salvi V, Kapoor S, Mukherjee T & Nair C K K, Radioprotection of DNA by glycyrrhizic acid through scavenging free radicals, *J Radiat Res,* 45 (2004) 461.
159 Boisseau M R, Taccoen A, Garreau C, Vergnes C, Roudaut M F & Garreau-Gomez B, Fibrinolysis and hemorheology in chronic venous insufficiency: A double blind study of troxerutin efficiency, *J Cardiovasc Surg* (Torino), 36 (1995) 369.
160 Vin F, Chabanel A, Taccoen A, Ducros J, Gruffaz J, Hutinel B, Maillet P & Samama M, Double blind trial of the efficacy of troxerutin in chronic venous insufficiency, *Phlebology,* 9 (1994) 71.
161 Incandela V, De Sanctis V, Cesarone M R, Laurora G, Belcaro G, Taccoen A & Gerentes I, Efficacy of troxerutin in patients with chronic venous insufficiency: A double-blind, placebo-controlled study, *Advanc Ther,* 13 (1996) 161.
162 Krupinski K, Giedrojc J & Bielawiec M, Effect of troxerutin on laser-induced thrombus formation in rat mesenteric vessels, coagulation parameter and platelet function, *Pol J Pharmacol,* 48 (1996), 335.
163 Gueguen-Duchesne M, Durand F, Le Goff M C & Genetet B, Effects of troxerutin on the hemorhhological parameters of patients with moderate arterial hypertension, *Prog Clin Biol Res Centre,* 280 (1988) 401.
164 Marhic C, Clinical and rheological efficacy of troxerutin in obstetric gynecology, *Gynecol. Obstet*, 86 (1991) 209.
165 Wijayanegara H, Moses J C, Achmad L, Sobama R & Permadi W, A clinical trial of hydroxyethylrotusides in treatment of hemorrhoids of pregnancy, *J Int Med Res,* 20 (1992) 54.
166 Kessler M, Ubeaud G, Walter T, Sturm F & Jung L, Free radical scavenging and skin penetration on troxerutin and vitamin derivatives, *Dermatolog Treat,* 13 (2002) 133.
167 Wenisch C, Effect of bioflavonoids (trihydroxyethylrutin and disodium flavodate) *in vitro* on neutrophil reactive oxygen production and phagocytotic ability to assess by flow cytometry, *Curr Med Res Opan,* 17(2) (2001) 123.
168 Grotz A A, Henneicke-von Zepelin H H, Khnen R, al-Nawas B, Bockisch A, Kutzner J, Wustenberg P, Naser-Hijazi B, Belz G G & Wagner W, Prospective double-blind study of radioxerostomia with coumarin/troxerutine in patients with head and neck cancer, *Strahlenther Onkol,* 175 (1999) 397.
169 Maurya D K, Salvi V P & Nair C K K, Radioprotection of Normal Tissues in Tumour-bearing Mice by Troxerutin, *J Radiat Res, 4*5 (2004) 221.
170 Maurya D K, Balakrishnan S, Salvi V P & Nair C K K, Protection of cellular DNA from gamma-radiation induced damages and enhancement in DNA repair by troxerutin, *Mol Cell Biochem,* 280 (2005) 57.
171 Aruoma O I, Evans P J, Kaur H, Sutcliffe L & Halliwell B, An evaluation of the antioxidant properties of food additives and of trolox c, vitamin E and probucol, *Free Rad Res Commun,* 10 (1990) 143.
172 Ohta T, Watanabe M, Shirasu Y & Inoue T, Post-replication repair and recombination in uvrA umuC strains in Escherichia coli are enhanced by vanillin and antimutagenic compounds, *Mutat Res,* 201 (1988) 107.
173 Shaughnessy D T, Setzer R W & DeMarini D M, The antimutagenic effect of vanillin and cinnamaldehyde on spontaneous mutation in Salmonella TA104 is due to a reduction in mutations at GC but not AT sites, *Mutat Res,* 480–481 (2001) 55.
174 Ohta T, Modification of genotoxicity by naturally occurring flavorings and their derivatives, *Crit Rev Toxicol,* 23 (1993) 127-146.
175 Inoue T, Sasaki Y F, Imanishi H, Watanabe M, Ohta T & Shirasu Y, Suppression of mitomycin C-induced micronuclei in mouse bone marrow cells by post-treatment with vanillin, *Mutat Res,* 202 (1988) 93.
176 Keshava C, Keshava N & Nath TOJ, Protective effect of vanillin on radiation-induced micronuclei and chromosomal aberrations in V79 cells, *Mutat Res*, 397 (1998) 149.
177 Sasaki Y F, Ohta T, Imanishi H, Watanabe M, Matsumoto K, Kato T & Shirasu Y, Suppressing effects of vanillin, cinnamaldehyde, and anisaldehyde on chromosome aberrations induced by X-rays in mice, *Mutat Res,* 243 (1990) 29.
178 Kamat J P, Ghosh A & Devasagayam T P A. Vanillin as an antioxidant in rat liver mitochondria: Inhibition of protein oxidation and lipid peroxidation induced by photosensitization, *Mol Cell Biochem* 209 (2000) 47.
179 Santosh Kumar S, Ghosh A, Devasagayam T P A & Chauhan P S, Effect of vanillin on methylene blue plus light-induced single-strand breaks in plasmid pBR322 DNA, *Mutat Res,* 469 (2000) 207.
180 Felemoviious I, Bonsack M E, Baptista M L & Delancy J P, Intestinal radioprotection by vitamin E (alpha-tocopherol), *Ann Surg*, 22 (1995) 504: discussion 505.
181 Sarma L & Kesavan P C, Protective effect of vitamins C and E against gamma-ray-induced chromosomal damage in mouse, *Int J Radiat Biol,* 63 (1993) 759.
182 Konopacka M, Widel M & Rzeszowska-Wolny J, Modifying effect of vitamins C, E and beta-carotene against gamma-ray-induced DNA damage in mouse cells, *Mutat Res,* 417 (1998) 85.
183 Mutlu-Turkoglu U, Erbil Y, Oztezcan S, Olgac V, Toker G & Uysal M, The effect of selenium and/or vitamin E treatments on radiation-induced intestinal injury in rats, *Life Sci,* 66 (2000) 1905.
184 Parshad R, Taylor W, Sanford K, Camalier R F, Gant R & Tarone R E, Fluorescent light-induced chromosome damage

in human IMR-90 fibroblasts. Role of hydrogen peroxide and related free radicals, *Mutat Res,* 73 (1980) 115.

185 Kennedy A R, Implications for mechanisms of tumor promotion and its inhibition by various agents from studies of *in vitro* transformation, in *Progress in cancer research and therapy. tumor promoters,* Vol. 34 edited by R Langenbach, E Elmore & J C Barrett (Raven Press, New York), 1988, 201.

186 Radner B S & Kennedy A R, Suppression of X-ray induced transformation by vitamin E in mouse C3H/10T1/2 cells, *Cancer Lett*, 32 (1986) 25.

187 Umegaki K, Itoh T & Ichikawa T, Effect of vitamin E on chromosomal damage in bone marrow cells of mice having received low dose of X-ray irradiation. Intern, *J Vit Nutr Res,* 64 (1994) 249.

188 Prasad K N & Edwards-Prasad J, Effect of tocopherol (vitamin E) acid succinate on morphological alterations and growth inhibition in melanoma cells in culture, *Cancer Res,* 42 (1982) 550.

189 Kline K, Yu W & Zhao B, Vitamin E succinate: Mechanisms of action as tumor cell growth inhibitor, in *Nutrients in cancer prevention* and *treatment*, edited by K Prasad, L Santamaria & R Williams (Humana Press, New Jersey, USA) 1995, 39.

190 Sarria A & Prasad K N, DL-alpha tocopheryl succinate enhances the effect of gamma-irradiation on neuroblastoma cells in culture, *Proc Soc Exp Biol Med,* 175 (1984) 88.

191 Jha M N, Bedford J S, Cole W C, Edwards-Prasad J & Prasad KN: Vitamin E (d-a tocopheryl succinate) decreases mitotic accumulation in γ-irradiated human tumor, but not in normal cells, *Nutr Cancer*, 35 (1999) 189.

192 Bipin Kumar, Mitra N Jha, Cole W C, Bedford J S & Prasad K N, D-Alpha tocopheryl succinate (Vitamin E) enhances radiation-induced chromosomal damage levels in human cancer cells, but reduces it in normal cells, *J Am College of Nutr,* 21 (2002) 339.

193 Kapoor S, Mukherjee T, Kagiya V T & Nair C K K, Redox reactions of tocopherol monoglucoside in aqueous solutions: A pulse radiolysis study, *J Radiat Res,* 43 (2002) 99

194 Rajagopalan R, Wani K, Huilgol N G, Kagiya V T & Nair C K K, Inhibition of gamma-radiation induced DNA damage in plasmid pBR322 DNA by TMG, a derivative of vitamin E, *J Radiat Res,* 42 (2002) 153.

195 Singh R K, Verma N C & Kagiya V T, Effect of water soluble derivative of alpha-tocopherol on radiation response of *Sachharomyces cerivisiae*, *Indian J Biochem Biophys*, 38 (2001) 399.

196 Nair C K K, Uma Devi P, Shimanskaya R, Kunugita N, Murase H, Gu Y H & Kagiya T V, Water soluble vitamin E (TMG) as a radioprotector, *Indian J Exp Biol,* 41(2003) 1365.

197 Satyamitra M, Uma Devi P, Murase H & Kagiya VT, *In vivo* postirradiation protection by a vitamin E analog, alpha-TMG, *Radiat Res,* 160 (2003) 655.

198 Nair C K K, Salvi V, Kagiya T V & Rajagopalan R, Relevance of radioprotectors in radiotherapy: Studies with tocopherol monoglucoside, *J Environ Path Toxicol Oncol,* 23 (2004) 153.

199 El-Habit O H, Saada H N, Azab K S, Abdel-Rahman M & El-Malsh D F, The modifying effect of beta-carotene on gamma radiation induced elevation of oxidative reactions and genotoxicity in male rats, *Mutat Res*, 466 (2000) 179.

200 Slyshenkov V S, Omelyanchik S N, Moiseenok A G, Petushok N E & Wojtczak L, Protection by pantothenol and beta-carotene against liver damage produced by low-dose gamma- radiation, *Acta Biochim Pol,* 46 (1999) 239.

201 Konopcka M, Widel M & Rzeszowska-Wolny J, Modifying effect of vitamins C, E and beta carotene against gamma-ray induced DNA damage in mouse cells, *Mutat Res,* 417 (1998) 85.

202 Salvadori D M, Ribeiro L R, Xiao Y, Boei J J & Natarajan A T, Radioprotection of beta-carotene evaluated on mouse somatic and germ cells, *Mutat Res*, 356 (1996) 163.

203 Jagetia G C & Rajanikant G K, Role of curcumin, a naturally occurring phenolic compound of turmeric in accelerating the repair of excision wound, in mice whole-body exposed to various doses of gamma-radiation, *J Surg Res,* 120 (2004) 127.

204 Ramanathan R & Misra U K, Effect of whole body gamma irradiation on fatty acid composition of liver lipids of female rats and radioprotection by cystamine, *Strahlentherapie*, 151 (1976) 555.

205 Vacck A, Rotkovska D, Bartonickova A & Kautska J, Amelioration of radiation damage to hemopoiesis by Ivastimul, given after irradiation to mice protected by by peroral cystamine, *Folia Biol,* (Praha) 38 (1992) 323.

206 Pandey B N & Mishra K P, Modification of thymocytes membrane radiooxidative damage and apoptosis by Eugenol, *J Environ Pathol Toxicol Oncol,* 23(2004) 117.

207 Landauer M R, Srinivasan V & Seed T M, Genistein treatment protects mice from ionizing radiation injury, *J Appl Toxicol*, 23(2003) 379.

208 Bagewadikar R S, Chatterjee S, Premachandran S & Poduval TB, Radioprotective effect of L-lysine in Swiss mice exposed to total body irradiation, *Indian J Radiat Res,* 1 (2004) 21, abstracts.

209 Venkatesha V A & Jagetia G C, Reduction in the radiation-induced DNA damage and repair enhancement by mangiferin in cultured human peripheral blood lymphocytes, *Indian J Radiat Res,* 1 (2004) 21, abstracts.

210 Jagetia G C & Reddy T K, The grapefruit flavanone naringin protects against the radiation-induced genomic instability in the mice bone marrow: A micronucleus study, *Mutat Res,* 519 (2002) 37.

211 Jagetia G C, Venkatesha V A & Reddy T K, Naringin, a citrus flavonone, protects against radiation-induced chromosome damage in mouse bone marrow, *Mutagenesis,* 18 (2003) 337.

212 Vrindra B & Uma Devi P, Radiation protection of human lymphocyte chromosomes *in vitro* by Orientin and Vicenin, *Mutat Res,* 498 (2001) 39.

213 Nayak V & Uma Devi P, Protection of mouse bone marrow against radiation-induced chromosome damage and stem cell death by the Ocimum flavonoids orientin and vicenin, *Radiat Res,* 163 (2005) 165.

214 Uma Devi P & Satyamitra M, Protection against prenatal irradiation-induced genomic instability and its consequences in adult mice by Ocimum flavonoids, orientin and vicenin, *Int J Radiat Biol,* 80 (2004) 653.

215 Rajendra Prasad N, Menon V P, Vasudev V, Jeevanram K & Pugalendi K V, Radioprotective effect of sesamol on γ-radiation induced DNA damage in cultured human blood lymphocytes. *Ind J Radiat Res,* 1 (2004) 15.

216 Nemavarkar P, Pasupathy K & Mishra K P, Radioprotective action of Trigonelline: Use of *Saccharomyces cerevisiae* as a test system, *Indian J Radiat Res,* 1 (2004) 29.

217 Rajagopalan R, Ranjan S K & Nair C K K, Effect of vinblastine sulfate on gamma-radiation-induced DNA single-strand breaks in murine tissues, *Mutat Res*, 536(2003) 15.

218 Gonzalez de A B & Darby S, Risk of cancer from diagnostic X-rays: Estimates for UK and 14 other countries, *Lancet*, 363 (2004) 345.

219 Uma Devi P, Radiosensitivity of the developing haemo-poietic system in mammals and its adult consequences: Animal studies, *Br J Radiol,* 76 (2003) 366.