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The prospective role of plant products in radiotherapy of cancer: a current overview

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Treatment of cancer often requires exposure to radiation, which has several limitations involving non-specific toxicity toward normal cells, reducing the efficacy of treatment. Efforts are going on to find chemical compounds which would effectively offer protection to the normal tissues after radiation exposure during radiotherapy of cancer. In this regard, plant-derived compounds might serve as "leads" to design ideal radioprotectors/radiosensitizers. This article reviews some of the recent findings on prospective medicinal plants, phytochemicals, and their analogs, based on both *in vitro* and *in vivo* tumor models especially focused with relevance to cancer radiotherapy. Also, pertinent discussion has been presented on the molecular mechanism of apoptotic death in relation to the oxidative stress in cancer cells induced by some of these plant samples and their active constituents.

Keywords: medicinal plants, phytochemicals, radioprotectors, radiosensitizers, cancer radiotherapy, ionizing radiation

INTRODUCTION

Cancer is now the third leading cause of death worldwide, with an estimated 12 million new cases and 7.6 million cancer deaths reported in American Cancer Society (2007). It is projected that by 2030 there would be about 26 million new cases, while a majority of deaths due to cancer will occur in developing countries (Bray and Moller, 2006; World Cancer Report, 2008). In the meantime, the global distribution of cancer along with the predominating types of the disease continues to change. Thus, cancers of the lung, breast, colon/rectum, and prostate are no longer confined to the Western industrialized countries but are among the most common cancers occurring all over the world. As for the therapy and management of cancer, newer strategies comprising multi-faceted and integrative approach involving surgery, followed by chemotherapy along with radiation is currently gaining consensus (Oehler et al., 2007). At the same time, advancement in the understanding of the disease processes at molecular level has offered novel targets for prevention, detection, control, and elimination of cancer.

Application of ionizing radiation, over and above surgery, and chemotherapy, has been the treatment of choice in case of solid malignancies (Kinsella, 2011). However, a substantial fraction of such tumors would fail to respond well to the radiation treatment, and require a very high dose to get killed, posing a severe limitation to the radiotherapy. Additionally, undesirable complications would occur owing to radiation injury to the surrounding normal tissues and to the skin, brain, heart, lung, kidney, liver, or gastrointestinal system of the cancer patient. Also, symptoms like tissue fibrosis, hair loss, xerostomia, xerophthalmia, etc., considerably restrict the application of a high dose of radiation aimed at the tumor-bearing organs (Dest, 2006).

Moreover, co-administration of radiation (delivered in the range of 40–80 Gy) along with the chemotherapeutic regimen might aggravate these complications (Curry and Curran, 2003). Patients undergoing treatment with taxol or vincristine often suffer from peripheral neuropathy as a side effect, while anthracycline drugs like doxorubicin (adriamycin), epirubicin, and mitoxantrone, etc., might lead to cardiac dysfunction (Choy, 2001). Abnormal kidney function and hearing loss were some of the common adverse effects occurring upon radiotherapy given to patients under treatment with platinum compounds (Amorino et al., 2000). Combination with some of the alkylating agents, like cyclophosphamide, ifosfamide, and leukeran (chlorambucil), might cause infertility (Verma et al., 2007). Again, a long term problem might emerge due to the post-radiotherapy incidence of a second tumor appearing either at the site of irradiation or away from it (Ng et al., 2002). Hence, it is a major challenge to radiation oncologists and researchers to develop alternative approaches to minimize the dosage through selective sensitization of tumor cells to respond to the radiation treatment, and thereby evade the detrimental consequences of radiotherapy (Rosenberg and Knox, 2006).

The exposure to radiation would primarily generate intracellular reactive oxygen species (ROS, viz., superoxide and hydroxyl radicals), which in turn would lead to DNA strands breaks and conformational alterations of biomolecules (Halliwell and Gutteridge, 1989). This will inevitably cause damage to surrounding normal cells. Hence, certain compounds/formulations could be envisaged to effectively scavenge the free radicals and thereby protect the surrounding normal cells from radiation induced injury. Historically, the seminal findings on the radioprotective ability of naturally occurring amino-metabolites like cysteine and cysteamine triggered the search for other thiolamines which would protect us from the acute effects of radiation (Patt et al., 1949). Thus, amifostine ([*S*-2-[3-aminopropylamino] ethylphosphorothioic acid)

was developed as a potential radioprotector molecule (Weiss and Landauer, 2000; Grdina et al., 2002; Bensadoun et al., 2006). Nevertheless, its wider applicability has been restricted due to the major limitations associated with nausea, diarrhea, hypotension, hypocalcaemia, sleeplessness, dizziness, nephro- and neuro-toxic effects. Other non-protein thiols possessing antioxidative properties, viz. captopril ([*S*]-1-[3-mercapto-2-methyl-1-oxo-propyl]-L-proline), mesna (sodium-2-mercapto-ethanesulfonate), and *N*-acetyl-L-cysteine (NAC), were also relevant in this regard (Murley et al., 2004). However, these exogenous antioxidants proved to be ineffective if administered at the post-irradiation stage. These scavengers, acting only for a limited period of time (15 min to 1 h under *in vivo* conditions), must be administered shortly before the radiation exposure as the generation of highly reactive free radicals following radiation is a very rapid process, spanning less than 10^{-3} s (Grdina et al., 2002). Hence, there is an urgent need to look for more suitable molecules to be used in combination with chemo- and radio-therapy of cancer in order to minimize the adverse effects, and to enhance the overall curative outcome in the patients.

Screening and testing of compounds from natural as well as synthetic sources have been carried out over the last few decades in order to find effective radioprotectors capable of inhibiting radiation damage not only during radiotherapy of cancer patients, but also to healthy individuals undergoing occupational and accidental exposures to radiation (Stone et al., 2003). In this context, several authors have reviewed the prospective application of traditional medicinal plants which are known to contain anti-inflammatory, antioxidant, and immunomodulatory compounds (Arora et al., 2005; Venkatachalam and Chattopadhyay, 2005; Jagetia, 2007). Again, plant-derived polyphenolic compounds with radiosensitizing property have been extensively reviewed elsewhere (Garg et al., 2005). Incidentally, some of these antioxidants and plant products were also shown to be effective in prevention of cancer incidence (Suresh and Vasudevan, 1994; Zhao et al., 1997; Lee et al., 2002; Girdhani et al., 2005). The present article would be following up these developments during the last 5 years, and aim to highlight the current endeavor (since 2006) to identify phytochemicals and secondary metabolites of medicinal plants with relevance to cancer radiotherapy, and at the same time, attempt to elucidate the mechanistic premise in the light of available reports.

POTENTIAL PLANT PRODUCTS FOR APPLICATION IN CANCER RADIOTHERAPY

The global search for naturally occurring phytochemicals as potential radiotherapeutic agents has unearthed a host of plant products broadly categorized as (i) "radioprotectors"- to ameliorate the undesired damages caused to the normal cells, hence, minimize the side effects of radiation therapy; and (ii) "radiosensitizers"- to enhance the radiation-induced cell death inflicted to the tumor, and thereby minimize the dose of radiation treatment. In the present article, some of the major findings on traditional medicinal plants and active phytochemicals with promising radioprotective or radiosensitizing efficacy have been briefly summarized in a tabular form (**Tables 1** and **2**; post-2006).

In **Table 1**, we have enlisted the reports on the crude extracts/semi-purified fractions of plant samples which demonstrated substantial prospect to enhance the clinical success of radiotherapy through a combination treatment. It is to be noted that 14 out of the twenty six plants in this list, viz. *Aloe arborescens*, *Angelica sinensis*, *Azadirachta indica*, *Biophytum sensitivum*, *Boerhaavia diffusa*, *Citrus sinensis*, *Genista sessilifolia*, *Grewia asiatica*, *Isatis indigotica*, *Moringa oleifera*, *Olea europaea*, *Rosmarinus officinalis*, *Rubus* spp., and *Xylopia aethiopica* have not been investigated prior to 2006. Most of the reports were obtained from the *in vivo* study on mouse models, where the radio-protecting activity was found to be associated with significant scavenging of free radicals, and depletion in lipid peroxidation with elevation in the glutathione, catalase, and lactate dehydrogenase enzyme levels. Also, several of these studies were conducted on propagatory cell lines and primary cultures to unravel the underlying mode of action at the molecular level (**Table 1**; Kimura and Sumiyoshi, 2009; Lee et al., 2010; Park et al., 2011).

In **Table 2**, we have presented the pure plant constituents and/or their analogs which could be considered as emerging candidates to be developed for the aforesaid application in future. Here, it is to be noted that the radiotherapeutic prospect of several plant-derived compounds, viz. allicin, betulinic acid, crocetin, diospyrin, honokiol, maytansine, oleuropein, α-santalol, tangeritin, withaferin A, and zingerone have been reported for the first time during the last 5 years.

Here, in **Table 2**, it has to be mentioned that we have not included the established plant-derived anticancer drugs, viz. etoposide, pactitaxel, and *Vinca* alkaloids, which have not only been recognized as potential radiosensitizers, but already under clinical application in association with cancer radiotherapy (Burris and Hurtig, 2010). Nevertheless, these drugs and their analogs are also under continuous appraisal for further development in this regard (Hiro et al., 2010; Orditura et al., 2010; Lillo et al., 2011; Schwarzenberger et al., 2011).

Again, prospective radiotherapeutic application of herbal formulations composed of traditional medicinal plants, and marketed as Triphala, Abana, Mentat, Septilin, Chyavanaprasha, Oligonol, HemoHIM, Fuzheng zengxiao formula, etc., have been reported by Sandhya et al. (2006), Jagetia (2007), Kundu et al. (2008), Park et al. (2010), Huang et al. (2011). In fact, the potent radioprotective property of Triphala, a mixture of three plants, might actually be attributed to the presence of *Emblica officinalis* (vide **Table 1**), which is also a major constituent of some of the other Oriental rejuvenators (Chyavanaprasha, Septilin, etc.) found to offer protection against radiation damage. Likewise, some herbal products, like HemoHIM from Far-East countries, contain rhizhomes of *Angelica* spp., a prospective source of radioprotectants (vide **Table 1**), while Oligonol is composed of modified plant phenolics. Therefore, these commercial formulations comprising poly-herbal mixtures have been kept outside the purview of the present article in order to focus on the search for new plants and phytochemicals with prospective radiotherapeutic property, and not included in our Tables.

MOLECULAR MECHANISM OF NATURAL RADIOPROTECTORS/RADIOSENSITIZERS

Over the years, multi-modal therapy involving more than one anticancer agent applied in combination has been found to be

Table 1 | Traditional medicinal plants and/or their bioactive constituents with prospective radioprotective/radiosensitizing efficacy (2006–2011).

Plants (family)	Radioprotective/radiosensitizing efficacy of extracts/fractions
Aegle marmelos (L.) Corr. (Rutaceae)	Extracts protected mice against radiation-induced decline in hemoglobin, total leukocyte, and lymphocytes counts, and the clonogenicity of hemopoietic progenitor cells; decreased lipid peroxidation accompanied by a significant elevation in the GSH concentration in the mouse intestine; elevated the peripheral cell count as well as villus height and crypt number accompanied by a decline in goblet and dead cells; hydroalcoholic leaf extract significantly reduced micro nucleated polychromatic, normo chromatic erythrocytes, and polychromatic/normochromatic erythrocyte ratio in γ-irradiated mice bone marrow cells (Baliga et al., 2010)
Aloe arborescens Mill. (Liliaceae)	Leaf extract showed radioprotective efficacy (Bakuridze et al., 2009)
Alstonia scholaris L. (Apocynaceae)	Hydro-alcoholic extract of bark exhibited radioprotective efficacy in γ-irradiated mice (7.5 Gy) through lowering of lipid peroxidation with significant increase in glutathione levels in serum as well as in liver (Gupta et al., 2008); combination treatment of bark extract with γ-radiation (2.5 Gy) exhibited decrease in lipid peroxidation and increase in GSH level; protected against radiation-induced chromosomal damage and micronuclei induction in mice bone marrow (Jahan and Goyal, 2010)
Angelica sinensis (Oliv.) Diels (Apiaceae)	Root extract down-regulated hydroxyproline and Tgfb1 and provides protection in mice with radiation-induced pulmonary fibrosis (Han et al., 2006); suppressed TNF-α and TGF-β1 expression in irradiated lung tissue in mice (Xie et al., 2006)
Aphanamixis polystachya (Wall.) (Meliaceae)	Ethyl acetate fraction of the stem bark reduced radiation-induced chromosome damage in mice through free radical scavenging and reduction of lipid peroxidation activity (Jagetia and Venkatesha, 2006)
Azadirachta indica (L.) Adelb. (Meliaceae)	Leaf extracts exhibited radiosensitizing effect by activating pro-apoptotic signals in neuroblastoma xenografts exposed to single (10 Gy) or fractionated (2 Gy/day × 5 day) doses of radiation (Veeraraghavan et al., 2011)
Biophytum sensitivum (L.) DC. (Oxalidaceae)	Methanol extract protected γ-radiation-induced hemopoietic damage through immunomodulation as well as sequential induction of IL-1β, GM-CSF, and IFN-γ (Guruvayoorappan and Kuttan, 2008)
Boerhaavia diffusa L. (Nyctaginaceae)	Whole-plant extract prevented γ-radiation-induced DNA damage in mice bone marrow(Manu et al., 2007)
Citrus sinensis (L.) Osbeck (Rutaceae)	Potentially counteracted UV-B-induced damage in human keratinocytes (HaCaT), through NF-κB and AP-1 translocation and procaspase-3 cleavage (Cimino et al., 2007)
Emblica officinalis L. (Phyllanthaceae)	Extract demonstrated significant depletion in lipid peroxidation and elevation in glutathione and catalase levels before γ-irradiation (5 Gy) to mice (Jindal et al., 2009); fruit extract inhibited UV-induced ROS and collagen damage in human dermal fibroblast (Adil et al., 2010; Majeed et al., 2011)
Genista sessilifolia DC. and *Genista tinctoria* L. (Leguminosae)	Methanol extract of the aerial part inhibited UV light and nitric oxide-induced DNA damage on plasmid vector pBR322 and human melanoma (M14) cell growth (Rigano et al., 2009)
Grewia asiatica L. (Malvaceae)	Post-treatment of fruit pulp extract inhibited γ-radiation-induced glutathione depletion and ameliorating lipid peroxidation levels in mice (Sisodia et al., 2008; Sharma and Sisodia, 2009)
Isatis indigotica Fort. (Brassicaceae)	Root exhibited anti-inflammatory ability to reduce the mucosal damage caused by radiation (You et al., 2009a); reduced serum TNF-α, IL-1β, and IL-6 level along with restoration of leukocytopenia following whole body irradiation in mice (You et al., 2009b)
Mentha piperita and *Mentha arvensis* (Lamiaceae)	Protected against γ-radiation-induced hematopoietic damage in bone marrow of mice by significantly decreasing micronucleus formation and increasing erythropoietin level (Samarth, 2007); aqueous extract showed radio-protecting efficacy in testis, gastrointestinal and hemopoetic systems in mice through free radical scavenging, antioxidant, metal chelating, anti-inflammatory, antimutagenic, and enhancement of the DNA repair processes (Baliga and Rao, 2010)
Moringa oleifera Lam. (Moringaceae)	Aqueous ethanolic leaf extract protected against γ-radiation-induced liver damage in mice through inhibition of of NF-κB translocation and lipid peroxidation, with increases in SOD, CAT, GSH, and FRAP (Sinha et al., 2011)
Olea europaea L. (Oleaceae)	Prevented UV-B-induced skin damage in hairless mice by inhibiting the expression of matrix metalloproteinase MMP-2, MMP-9, and MMP-13, vascular endothelial growth factor (VEGF), and cyclooxygenase-2 (COX-2) in the skin; histological evaluation showed suppression of Ki-67 and CD31-positive cells expression induced by irradiation (Kimura and Sumiyoshi, 2009)
Panax ginseng L. (Araliaceae)	Red ginseng showed photoprotective effect of against ultraviolet radiation-induced chronic skin damage in the hairless mouse (Lee et al., 2009); radioprotective potential on human lymphocytes when applied at 90 min post-irradiation, through scavenging free radicals and enhancement of intracellular total antioxidant capacity; inhibited radiation-induced (7 Gy) apoptosis in gastrointestinal tract of small intestine by decreasing pro-apoptotic p53 and Bax

(Continued)

Table 1 | Continued

Plants (family)	Radioprotective/radiosensitizing efficacy of extracts/fractions
	as well as augmenting anti-apoptotic Bcl-2 following 24 h after irradiation; increase γ-ray-induced apoptotic cell death in human lung cancer cells (NCI-H460, both in culture and in nude mice xenograft model) through intracellular ROS generation, nuclear fragmentation, mitochondrial membrane potential loss, and activation of caspase-3; inhibited micronuclei formation in human peripheral blood lymphocytes following 1–2 Gy radiation exposure (Lee et al., 2008b, 2010; Park et al., 2011)
Phyllanthus amarus Schum. and Thonn. (Phyllanthaceae)	Found to protect the clastogenic effects of radiation as seen from decreased number of micronuclei and chromosomal aberrations percentage (Harikumar and Kuttan, 2007)
Pothomorphe umbellate C. DC. (Piperaceae)	Inhibited UV-B-induced hyperplasic response and increased p53-positive cells in hairless mouse epidermis (da Silva et al., 2009)
Punica granatum Linn. (Lythraceae)	Showed protective effects in UV-A and UV-B irradiated human skin fibroblasts (Pacheco-Palencia et al., 2008); fruit extract inhibited UV-B radiation-induced carcinogenesis in SKH-1 hairless mouse epidermis through suppressing nuclear translocation of NF-κB, activation of IKKα, phosphorylation, and degradation of IκBα; pomegranate-derived products, viz., POMx juice, POMx extract, and pomegranate oil (POMo) inhibited UV-B-induced (i) collagenase (MMP-1), (ii) gelatinase (MMP-2, MMP-9), (iii) stromelysin (MMP-3), (iv) matrilysin (MMP-7), (v) elastase (MMP-12), and (vi) tropoelastin c-Fos and phosphorylation of c-Jun protein expression in reconstituted human skin (EpiDerm(TM) FT-200; Afaq et al., 2009, 2010)
Rosmarinus officinalis L. (Lamiaceae)	Extract inhibited γ-radiation (3 Gy) induced lipid peroxidation and elevated glutathione levels in irradiated mice (Jindal et al., 2010)
Rubus spp.(Rosaceae)	Inhibited UV-induced activation of NF-κB and AP-1 in cultured mouse epidermal cells (Huang et al., 2007); sensitized human breast cancer cell line (MCF-7) to radiation by inhibiting radiation-induced activation of NF-κB, and NF-κB regulated IAP1, IAP2, XIAP, and surviving activity, suppressed IR-induced TNFα, IL-1α, and MnSOD levels (Madhusoodhanan et al., 2010)
Syzygium cumini L. Skeels (Myrtaceae)	Extract inhibited γ-radiation-induced DNA damage through scavenging of free radicals in cultured splenocytes of mice (Jagetia et al., 2011)
Tinospora cordifolia (Thunb.) Miers. (Ranunculaceae)	Combination treatment of dichloromethane extract with γ-radiation (1–4 Gy) declined viability of HeLa cells by increasing lactate dehydrogenase and decreasing glutathione S-transferase activity (Rao and Rao, 2010b); prevented radiation-induced testicular injury (Sharma et al., 2011)
Viscum album L. (Santalaceae)	Reduced side effects of conventional radiotherapy in cancer (Kienle and Kiene, 2010)
Xylopia aethiopica (Dunal) A. Rich (Anonaceae)	Combination treatment with Vit.C protected against γ-radiation-induced testicular damage in rats through antioxidant activity (Adaramoye et al., 2010a); dried fruit extract attenuated serum alanine and aspartate aminotransferases level in whole body irradiated rats (Adaramoye et al., 2011); methanol extract of fruit reduced γ-radiation-induced oxidative stress in brain of adult male Wistar rats (Adaramoye et al., 2010b)

favorable in the management of cancer. The precise efficacy and degree of tumor control exhibited by combination regimen, however, remains variable. Although the reasons for variability remain unclear, discovery of additional novel drugs that synergize with an existing radiation therapy would allow multiple combinations to choose from, thereby increasing the likelihood of clinical success. Recently, Edwards et al. (2011) has developed an interesting *Drosophila* larvae model which could be used to screen and identify molecules that would act in conjunction with radiation therapy (Edwards et al., 2011). On the whole, a number of phytochemicals with anti-/pro-oxidant, or immunomodulatory activity hold greater promise in pre-clinical/clinical trials. Emerging data also demonstrated that many phytochemicals, especially camptothecin, epigallocatechin gallate (EGCG), paclitaxel, etoposide, curcumin, etc., have potent growth inhibitory and apoptosis inducing effects on human as well as animal cancer cells by targeting multiple cellular signaling pathways *in vitro*. Therefore, these compounds could be useful in combination with conventional chemotherapeutic agents/radiation for the treatment of cancer, and expected to have lower toxicity but higher effectiveness. Also, recent *in vivo* pre-clinical studies and clinical trials have provided increasing evidence in support of multi-targeted therapies in combination with natural products. A comprehensive view on the molecular mechanisms to rationalize the prospective role of such phytochemicals acting on relevant signaling pathways has been given in **Table 2**.

SCAVENGING OF REACTIVE OXYGEN SPECIES

Natural products in conjunction with irradiation are likely to exert the protective action through several mechanisms. Scavenging of free radicals generated during radiolysis would be a credible mode of action. Hence, naturally occurring polyphenolic compounds and antioxidant vitamins, primarily retinoids, would be the plausible candidates to offer radio-protection. It is a fact that the chances of developing cancer could be minimized through optimum nutritional supplementation by consuming a variety of fruits and vegetables, some of which have displayed chemopreventive activity by inhibiting tumorigenesis induced by chemical carcinogens and other genotoxic agents (Loo, 2003).

However, clinical reports on application of plant extracts with antioxidant property as adjuvants in cancer radiotherapy are still

Table 2 | Phytochemicals with prospective radioprotective/radiosensitizing efficacy: reports from last 5 years study.

Compounds/plants (family)	Radioprotective/radiosensitizing efficacy (reference)
Allicin/*Allium sativum* L. Gaertn. (Alliaceae)	Down-regulated γ-ray-induced ICAM-1 expression via inhibition of both AP-1 activation and JNK pathway in human umbilical vein endothelial cells (HUVECs; Son et al., 2006)
Betulinic acid/*Ziziphus mauritiana* Lam. (Rhamnaceae)	Enhanced cellular toxicity with decreased clonogenic survival in combination with radiation (4 Gy) on redioresistant head and neck squamous carcinoma cell line (Eder-Czembirek et al., 2010); induced cytotoxicity and radiosensitivity in glioma cells under hypoxic conditions (Bache et al., 2011)
Camptothecin (Irinotecan)/*Camptotheca acuminata* Decne (Nyssaceae)	Concurrent chemoradiation with capecitabine and weekly irinotecan showed promising efficacy in preoperative treatment for rectal cancer (Phase I and II study; (Klautke et al., 2006); preoperative radiotherapy and weekly irinotecan in combination with protracted venous infusion of 5-FU found effective in advanced rectal cancer (Phase II study; Navarro et al., 2006); irinotecan plus cisplatin with concurrent radiotherapy showed effectiveness for patients with limited-disease small cell lung cancer (Phase II study; Jeong et al., 2006); preoperative chemotherapy with S-1 and irinotecan sensitized radiation therapy in patients with locally advanced rectal cancer (Phase I/II study; Sato et al., 2007; Shin et al., 2010); weekly irinotecan and cisplatin induced effectiveness of radical thoracic radiation in locally advanced non-small cell lung carcinoma (Phase I study; Langer et al., 2007); combination of cetuximab, bevacizumab, and irinotecan sensitized radiation therapy in patients with primary glioblastoma and prevented progression after treatment (Phase II trial; Hasselbalch et al., 2010); topoisomerase I as possible target for radiosensitizing effect of irinotecan in rectal cancer (Illum, 2011)
Crocetin (Trans sodium crocetinate)/*Crocus sativus* Linn. (Iridaceae)	Combination regimen with radiation enhanced the efficiency of radiotherapy by increased oxygen diffusion in the brain and elevated the partial brain oxygen level in rat C6 glioma model (Sheehan et al., 2008); induced apoptosis through inhibiting nucleic acid synthesis, and hindering growth factor signaling pathways (Gutheil et al., 2011)
Curcumin/*Curcuma longa* Linn. (Zingiberaceae)	Protected γ-radiation-induced DNA damage and lipid peroxidation in cultured human lymphocytes (Srinivasan et al., 2006); demonstrated protective effect on radiation-induced (50 Gy) cutaneous damage in mice characterized by down-regulation of IL-1 IL-6, IL-18, TNF-α, lymphotoxin-β, and TGF-β in irradiated skin and muscle (Okunieff et al., 2006); prevented radiation-induced incidence of thymic lymphoma in mice (Dange et al., 2007) and ileal mucosal damage in rat (Akpolat et al., 2009) through antioxidant property; combination with visible light inhibits human epithelial carcinoma A431 tumor growth in a xenograft model in mice through ERK1/2 and EGF-R inhibition leading to apoptosis (Dujic et al., 2009); accelerated wound repair in excision wound of mice exposed to fractionated γ-radiation (Jagetia and Rajanikant, 2011); significantly inhibited IR-induced NF-κB, telomerase and telomerase reverse transcriptase promoter mRNA (TERT) activation in human neuroblastoma cells (Aravindan et al., 2011)
Diospyrin (Diospyrin dimethylether)/*Diospyros montana* Roxb. (Ebenaceae)	Enhanced radiation-induced cytotoxicity and apoptosis in human breast cancer cell line (MCF-7) through down-regulation of Bcl-2 and COX-2 gene, and up-regulation of p53 and p21 (Kumar et al., 2007); showed enhancement in cytotoxicity and apoptotic induction and decrease in clonogenic survival of human and mouse fibrosarcoma cells by inhibiting radiation-induced NF-κB activation, generation of intracellular reactive oxygen species, caused significant suppression of tumor growth *in vivo*, and restoration of liver enzyme activity to the "normal" level (Kumar et al., 2008)
β-Elemene/*Curcuma wenyujin* Linn. (Zingiberaceae)	Combination treatment with 4 Gy X-ray irradiation enhanced single and double strand DNA break and inhibited DNA repair system in human lung adenocarcinoma cell line (A549), induced apoptosis through up-regulation of p53 and downregulation of Bcl-2 protein (Li et al., 2011)
Ellagic acid/*Punica granatum* Linn. (Lythraceae)	Suppressed inflammation and photoageing associated with chronic UV-B exposure by diminishing IL-1β and IL-6 production, and blocked infiltration of macrophages in the integuments of SKH-1 hairless mice (Bae et al., 2010); enhanced radiosensitivity by increased superoxide generation, upregulated p53 protein expression, decreased antioxidant enzyme level, enhanced capase-3 activity, increased intracellular calcium levels, phospholipase C, and a drop in mitochondrial potential in HeLa cells (Bhosle et al., 2010)
Epigallocatechin-gallates/*Camellia sinensis* L. (Kuntze) (Theaceae)	Protected against UV-B-induced apoptosis via oxidative stress and JNK1/c-Jun pathway in retinal pigment epithelium cells (Cao et al., 2012); protected liver tissue against the mobile phone-like radiofrequency-induced oxidative damage by enhancing antioxidant enzyme activities (Ozgur et al., 2010); protected dendritic cells following UV-B irradiation by modulating IL-10 and IL-12 level (Jin et al., 2009); exhibited radio-protection in mice following γ-radiation (Lee et al., 2008a); combined treatment with low dose ionizing radiation, induced cells death in human brain endothelial cells (McLaughlin et al., 2006)
Ferulic acid/Ubiquitous in dietary plants and fruit seeds	Suppressive effect on UV-B radiation-induced matrix metalloproteinases MMP-2 and -9 expression in mouse skin, mediated via the proteasome pathway (Staniforth et al., 2011)
Flavopiridol/*Dysoxylum binectariferum* (Roxb.) Hook (Meliaceae)/*Amoora rohituka* (Meliaceae)	Increased radiation sensitivity of GL261 murine glioma model (Newcomb et al., 2006); improved radiation responses of esophageal adenocarcinoma cell and xenografts by targeting cyclin-dependent kinases (Raju et al., 2006); combination treatment with radiation exhibited potential to conquer the radioresistance of human glioma cell line by inducing genetic alteration of p53 or bcl-2 (Hara et al., 2008)

(Continued)

Table 2 | Continued

Compounds/plants (family)	Radioprotective/radiosensitizing efficacy (reference)
Genistein; Daidzein/ – Soy isoflavones and metabolites from *Glycine max* Linn. (Merr.) (Fabaceae)	Showed radiosensitization via inhibition of NF-κB, altered cyclin B and/or p21WAF1/Cip1 expression, and G2/M arrest in prostate cancer cells; combination with radiation showed enhanced control on primary tumor growth in orthotopic metastatic mouse model; increased cytotoxicity correlated with inhibition of Bcl-xL and survivin, and upregulation of Bax and PARP cleavage in prostate cancer cell line; (Raffoul et al., 2006, 2007); sensitized apoptotic effect of γ-irradiation in CaSki cervical cancer cells via increased expression of p53, p21, and Cdc2-tyr-15-p, supporting the occurrence of G2/M arrest (Shin et al., 2008); showed radiosensitizing effect through cell growth inhibition by modulating APE1/Ref-1, NF-κB, and HIF-1α level in prostate cancer cell lines (Singh-Gupta et al., 2010); protected UV-B-induced senescence-like characteristics in human dermal fibroblasts via maintenance of antioxidant enzyme activities and modulation of mitochondrial oxidative stress through down-regulation of p66Shc-dependent signaling pathway (Wang et al., 2010); prevented formation of excess radiation-induced centrosomes via p21 up-regulation in human U2OS and mouse NIH3T3 cells (Shimada et al., 2011); mitigated radiation-induced lung injury in combination with EUK-207 in rat model (Mahmood et al., 2011). 7,3′,4′-trihydroxyisoflavone, a major metabolite of daidzein, suppressed the incidence and multiplicity of UV-B-induced tumors in hairless mouse skin, and inhibited UV-B-induced COX-2 expression through the inhibition of NF-κB transcription activity in mouse skin epidermal JB6 P+cells (Lee et al., 2011)
Honokiol/*Magnolia* spp. (Magnoliaceae)	Liposomal encapsulation of the honokiol showed radiosensitizing activity (5 Gy) in Lewis lung carcinoma cells (LL/2) through induction of apoptosis and angiogenesis suppression (Hu et al., 2008); reduced UV-B-induced skin cancer through caspase-3, caspase-8, caspase-9, poly (ADP-ribose) polymerase (PARP), and p53 activation leading to the induction of DNA fragmentation and apoptosis (Chilampalli et al., 2010)
β-Lapachone/*Tabebuia rosea* Bertol. (Bignoniaceae)	Synergistic interaction with radiation induce toxicity in DU-145 human prostate cancer cells *in vitro* through elevating NAD(P)H:quinone oxidoreductase 1 (NQO1) activity and by inhibiting sub-lethal radiation damage repair (Suzuki et al., 2006); intravenous injection of Au-nanoparticle containing β-lapachone exhibited enhanced efficacy in mice bearing xenograft human tumors (Jeong et al., 2009); suppressed radiation-induced (4 Gy) activation of NF-κB, bcl-2, gadd45β, and cyclinD1 in A549 human lung cancer cell lines (Dong et al., 2010a); combination with IR in NQO1(+) prostate cancer cells significantly elevated SSB level and γ-H2AX foci formation, caused poly(ADP-Ribose) polymerase-1 hyperactivation, and induction of μ-calpain-induced programmed cell death (Dong et al., 2010b)
Maytansine (Maytansinol isobutyrate)/*Maytenus* spp. (Celastraceae)	Enhanced the effect of radiation in *Drosophila* and in human cancer cells by microtubule depolymerization and p53 dependent pathway (Edwards et al., 2011)
Oleuropein/*Olea europaea* Linn. (Oleaceae)	Prevented UV-B-induced skin damage in hairless mice by inhibiting the expression of matrix metalloproteinase (MMP)-2, MMP-9, and MMP-13, vascular endothelial growth factor (VEGF), and cyclooxygenase-2 (COX-2) in the skin; histological evaluation showed suppression of Ki-67 and CD31-positive cells expression induced by irradiation (Kimura and Sumiyoshi, 2009)
Plumbagin/*Plumbago zeylanica* Linn. (Plumbaginaceae)	Showed radiosensitization effect through apoptosis in human cervical cancer cells (Nair et al., 2008)
Resveratrol/*Vitis* spp. (Vitaceae); *Vaccinium* spp. (Ericaceae)	Showed protective effect on UV-A and UV-B-induced damage in HaCaT cells by enhancing SOD, GSH-Px activity, reducing intracellular ROS generation and expression of caspase-3 and 8 proteins (Chen et al., 2006; Park and Lee, 2008); sensitized DU-145 to ionizing radiation by potentiating radiation-induced ceramide accumulation, through promoting its *de novo* biosynthesis (Scarlatti et al., 2007); reduced radiation-induced chromosome aberration in mouse bone marrow cells (Carsten et al., 2008); combination with γ-radiation inhibited NF-κB-dependent transcription, suppressed cFLIP and Bcl-xL expression, activated MAPK- and ATM-Chk2-p53 pathways, upregulated TRAIL promoter activity, and TRAIL surface expression in melanoma cell lines (Johnson et al., 2008); increased radiosensitivity and induced apoptosis in CD133-positive cells derived from atypical teratoid/rhabdoid tumor (Kao et al., 2009); sensitized A431 human epidermoid carcinoma cells to UV-B-induced cell death through disrupting NF-κB pathway by blocking phosphorylation of serine 536 and degradation of IκBα; decreased the phosphorylation of tyrosine 701, inhibited translocation of phospho-STAT1 to nucleus and suppressed metastatic LIMK1 protein (Roy et al., 2009); Suppressed tumorigenicity and enhances radiosensitivity in primary glioblastoma tumor initiating cells by inhibiting the STAT3 pathway (Yang et al., 2011); protected human keratinocytes HaCaT cells from UV-A-induced oxidative stress damage by down-regulating Keap1 expression (Liu et al., 2011)
α-Santalol/*Santalum album* Linn. (Santalaceae)	Prevented UV-B-induced skin cancer development by increasing in apoptosis proteins, caspase-3 and -8 levels and tumor suppressor protein, p53 in CD-1, SENCAR, and SKH-1 mice (Arasada et al., 2008)
Silymarin/*Silybum marianum* (L.) Gaertn. (Asteraceae)	Caused decrease in E2F2 and E2F3 accompanied by reduced levels of p53, cyclin-dependent kinases, cyclins, CDC25C, mitogen activated protein kinases, Akt signaling, and subsequent inhibition of cell proliferation on skin, 15 and 25 weeks

(Continued)

Table 2 | Continued

Compounds/plants (family)	Radioprotective/radiosensitizing efficacy (reference)
	after UV-B exposure (Gu et al., 2006); inhibited UV-B-induced photocarcinogenesis in mice through reduction of IL-10 and enhancement of IL-12 level (Meeran et al., 2006); protected A375-S2 cell against UV-induced apoptosis was partially through SIRT1 pathway and modulation of the cell cycle distribution (Li et al., 2007); attenuated UV-A-induced damage to human keratinocytes (Svobodová et al., 2007); inhibited UV-induced oxidative stress through targeting infiltrating CD11b + cells in mouse skin (Katiyar et al., 2008); prevented X-ray induced formation of DNA single-strand breaks (Fu et al., 2010; Vaid and Katiyar, 2010); inhibited UV-B radiation-induced DNA damage as demonstrated by reducing cyclobutane pyrimidine dimmers formation and induction of nucleotide excision repair leading to reduced apoptosis of normal human epidermal keratinocytes (Katiyar et al., 2011)
Tangeritin/(citrus fruits)	Reduced UV-B-induced cyclooxygenase-2 expression in mouse epidermal cells by blocking mitogen activated protein kinase (MAPK) activation and reactive oxygen species generation (Yoon et al., 2011)
Withaferin A/*Withania somnifera* L. (Dunal) (Solanaceae)	Augmented x-ray induced cell death in chicken B lymphocyte (Uma Devi et al., 2008); combination with fractionated regimen of radiation showed delayed proliferation of melanoma (Kalthur and Pathirissery, 2010); increased the radiation-induced apoptosis in Caki cells through ROS generation, down-regulation of Bcl-2, and Akt dephosphorylation (Yang et al., 2011a); enhanced IR-induced apoptosis associated with PARP cleavage, caspase-3 activation, down-regulation of anti-apoptotic protein Bcl-2 in human lymphoma U-937 cell line (Yang et al., 2011b)
Zingerone/*Zingiber officinale* Roscoe (Zingiberaceae)	Radiomodifying and anticlastogenic effect on Swiss albino mice (Rao et al., 2011); antagonistic effects against radiation-induced cytotoxicity, genotoxicity, apoptosis, and oxidative stress in Chinese hamster lung fibroblast cells (Rao and Rao, 2010a); act as radioprotectant by significantly reducing micronuclei formation, DNA damage, generation of reactive oxygen species and percentage of apoptotic cells induced by 2 Gy γ-radiation in human lymphocyte cells (Rao et al., 2009)

sparse in literature. Apparently, there is an apprehension that the antioxidants would protect not only the normal cells, but also the tumors, from the attack of free radicals generated during the course of treatment with ionizing radiation and anticancer agents. The lack of strong experimental evidences to address this concern resulted in poor enthusiasm from radiation oncologists to recommend their patients to consume such antioxidant products during the course of therapy. However, the pros and cons of this aspect have been critically reviewed, based on *in vitro* and *in vivo* experimentations (Prasad, 2005; Prasad and Cole, 2006).

In this context, hydrogen peroxide (H_2O_2) has been known to play a crucial role in the proliferation of cancer cells. In fact, many human cancers, like melanoma, neuroblastoma, colon carcinoma, and ovarian carcinoma, were found to constitutively generate a high amount of H_2O_2 (Szatrowski and Nathan, 1991). This indicated that the tumor cells would require a certain level of oxidative stress for maintaining a balance to undergo either proliferation or apoptotic death, and a minor fluctuation in the concentration of ROS might be critical to the intracellular signaling mechanism (Droge, 2002). The production of a larger amount of H_2O_2 was demonstrated by transforming NIH3T3 cells with Ras oncogene to cancer cells (Benhar et al., 2001), and a similar observation was noted in our laboratory when thymus cells in mice were transformed to thymic lymphoma after whole body radiation exposure (Pandey et al., unpublished data). The elevated production of ROS in cancer cells might be routed through mitochondrial electron transport chain, peroxisomes or NAD(P)H oxidase pathways, but the involvement of some direct mechanism of H_2O_2 generation may also be suggested. The constitutive production of ROS caused sub-lethal DNA damage in tumors, which was evidenced by a higher level of 8-hydroxy-2′-deoxyguanosine, while the increase of 4-hydroxy-2-non-enal, the lipid peroxidation product, indicated damage in cell membrane of carcinoma tissues (Toyokuni et al., 1995; Kondo et al., 1999). The cancer cells, in spite of having some amount of sub-lethal DNA damage, are generally adapted to survive in such stress conditions, and do not undergo cell cycle arrest or apoptosis (Elledge and Lee, 1995). In fact, at the basal level, the ROS would provide a stimulatory environment conducive to the proliferation of cancer cells, and become somewhat vital to their survival, rather than being merely useless cytotoxic products. Therefore, it may be hypothesized that the phenolic compounds with antioxidant properties could induce cell cycle arrest and apoptosis through scavenging of H_2O_2, presumably by depriving the cancer cells of an essential factor vital to their sustenance. It could also be speculated that a relatively lower level of constitutive ROS in normal cells would make them less vulnerable to the phenolic antioxidants (Simone et al., 2007).

GENERATION OF REACTIVE OXYGEN SPECIES

Another category of phytochemicals showing antitumor activity are those which would enhance the generation of ROS, instead of scavenging the cellular free radicals. Such ROS-generators would apparently sensitize cancer cells endowed with persistent oxidative stress to undergo apoptotic death. We have already discussed about the critical maintenance of constitutively produced ROS, which is probably just below the threshold level required to induce apoptosis in tumors, the basal level being much lower in case of normal cells (Droge, 2002). Therefore, ROS-generating quinones could presumably create the requisite imbalance to lead the tumors cells, rather than the normal ones, to apoptotic death. Thus, the pro-oxidant quinones like β-lapachone (Suzuki et al., 2006; Dong et al., 2010a,b), plumbagin (Nair et al., 2008), and diospyrin derivatives (Hazra et al., 2007; Kumar et al., 2007, 2008) have

been found to induce apoptosis in tumor cells through DNA damage, lipid peroxidation, mitochondrial membrane depolarization, and related signaling events. Incidentally, a few other anticancer plant products, such as paclitaxel, vinca alkaloids, and maytansinol, have been found to enhance the effect of radiation in human cancer cells through the involvement of microtubule interference to inhibit the proliferation of tumor (Edwards et al., 2011).

INDUCTION OF APOPTOTIC PATHWAY

Further, the phytochemicals could also interact directly with molecular pathways involving kinase networks, like mitogen activated protein kinases (MAPK), phosphatidylinositol-3-kinase (PI-3K), etc., thereby showing the potential to inhibit tumor growth in combination with anticancer drugs and radiation therapy by inducing programmed cell death or apoptosis (Garg et al., 2005).

Again, the higher level of ROS could result in the increase in protein tyrosine kinase (PTK)-mediated phosphorylation of epidermal growth factor receptor (EGF-R; Kamata et al., 2000), sequentially activating the Ras- and MAPK-signaling pathways (Loo, 2003). Further, the over-activated MAPK would trigger expression of transcription factors, like nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), and c-myc (a proto-oncoprotein; Meyer et al., 1994; Muller et al., 1997). It is to be noted that these transcription factors by themselves are redox-sensitive (Meyer et al., 1994; Muller et al., 1997; Loo, 2003), and may be regulated directly by the higher level of ROS.

The molecular mechanism of anticancer property of plant-derived polyphenolic compounds, such as EGCG, resveratrol, quercetin, genistein, etc., has been primarily attributable to their ability to scavenge the constitutively expressed endogenous redox modulators (H_2O_2/$OH^{\cdot}$). Further studies revealed that EGCG inhibited the phosphorylation of MAPK-enzymes, viz. ERK (extracellular signal regulated kinases), JNK (c-Jun N-terminal kinases), and p38-MAPK (p38 mitogen activated protein kinases), activated by UV-B radiation in human epidermal keratinocytes (Katiyar et al., 2001). Similar observation was obtained in UV-C-irradiated HeLa cells, pretreated with resveratrol, a polyphenolic constituent present in grapes and berries (Yu et al., 2001). Resveratrol was also found to check NF-κB activation induced by tumor necrosis factor (TNF) in U-937, Jurkat, HeLa, and H4 glioma cells *in vitro* (Manna et al., 2000). A few other plant phenolics, such as quercetin and genistein, have been reported to initiate apoptosis in pancreatic carcinoma cells, by inducing mitochondrial depolarization, cytochrome c release, and activation of caspases (Mouria et al., 2002).

In our laboratory, we are investigating the radiomodulating potential of a diethtylether derivative (D7) of diospyrin, an anti-tumor quinonoid plant-product, in human breast carcinoma cells (MCF-7). It was observed that D7, in combination with radiation, could increase the apoptosis in tumor cells through down-regulation of the anti-apoptotic Bcl-2 and COX-2 gene expression, and up-regulation of pro-apoptotic genes, like p53 and p21. The higher expression of PUMA (p53 upregulated modulator of apoptosis), a pro-apoptotic protein, was also observed in the combination treatment. Further, the up-regulation of p21 expression in irradiated MCF-7 cells was found to be concomitant with the cell cycle arrest in the G1 phase (Kumar et al., 2007). Further studies in mouse and human fibrosarcoma cells (viz., Wehi164 and HT1080, respectively) showed marked enhancement of cytotoxicity with decreased clonogenic survival following treatment with D7 in combination with radiation. Moreover, increased radiosensitivity of tumor cells by D7 was found to occur through inhibition of radiation-induced NF-κB activation with substantial generation of intracellular ROS, ultimately leading to programmed cell death. Further, a combination regimen of D7 with 5 Gy radiation administered in two fractionated doses (2.5 Gy each) could cause a significant inhibition of tumor growth and increased life span of experimental mice bringing the liver enzyme activity to the normal level (Kumar et al., 2008).

CONCLUSION

Cancer patients need to go through extensive treatment involving chemotherapy, surgical intervention, recurring exposure to gamma-irradiation, or a combination therapy. Some traditionally popular medicinal plants have recently gained attention for their ability to modulate a number of signaling pathways that could initiate and facilitate the proliferation of cancer. In many cases, the potency of these compounds/formulations to sensitize the cancer cells to radiotherapy could be corroborated with the inhibition/activation of the relevant molecular markers. However, the literature citations on supporting clinical trials showing similar observations are quite limited. Nevertheless, a number of reports are available on antioxidants being able to protect against radiation-induced oncogenic transformations in experimental systems. Based on these information it has been presumed that supplementation of vitamins in a good measure, and intake of health promoting plant products in the diet might reduce the harmful side effects of standard therapeutic modalities and enhance their selective toxicity toward malignant cells, leading to an overall improvement in the efficacy of anticancer treatment.

Furthermore, the underlying mechanism of survival and proliferation in some types of cancer would reveal the inherent dependence of these cells on their constitutive oxidative stress. This mechanistic interpretation, in the light of the well-studied role of plant-polyphenolics in scavenging cellular free radical species, might resolve the prevailing dilemma on whether antioxidants would provide the desirable relief, to some extent, to the normal cells in preference to the tumor-bearing ones. Again, this hypothesis would be relevant to the radiosensitizing effect exhibited by a few ROS-generating antitumor agents as well. Thus, it is hoped that future research would add up positively, and would bring more of the aforesaid phytochemicals from "bench to bedside" of the suffering humanity seeking relief from the awful maladies of cancer.

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