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Phenylpropanoids in radioregulation: double edged sword

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Abbreviations: CAPE, caffeic acid phenethyl ester; CAT, catalase; DC, dicentric aberration; EGCg, epigallocatechin-3-gallate; GPx, glutathione peroxidase; IR, ionizing radiation; MN, micronuclei; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances

Abstract

Radiotherapy, frequently used for treatment of solid tumors, carries two main obstacles including acquired radioresistance in cancer cells during radiotherapy and normal tissue injury. Phenylpropanoids, which are naturally occurring phytochemicals found in plants, have been identified as potential radiotherapeutic agents due to their anti-cancer activity and relatively safe levels of cytotoxicity. Various studies have proposed that these compounds could not only sensitize cancer cells to radiation resulting in inhibition of growth and cell death but also protect normal cells against radiation-induced damage. This review is intended to provide an overview of recent investigations on the usage of phenylpropanoids in combination with radiotherapy in cancer treatment.

Keywords: phenylpropanoids; radioprotection; radiosensitization; radiotherapy

Introduction

Radiotherapy is one of the cancer treatments that employ ionizing radiation (IR) for destruction of cancer cells and shrinkage of tumors. It also induces normal tissue injury as a side effect through alteration of their intracellular materials, resulting in cell death. Although IR causes damage to both cancer cells and normal cells, the purpose of radiotherapy is to maximize killing of cancer cells and to minimize injury to nearby healthy tissue (Grdina *et al.*, 2002).

The effects of IR are caused mainly by formation of reactive oxygen species (ROS) such as superoxide anion, hydrogen peroxide, and singlet oxygen (Riley, 1994). These ROS, generated by radiolysis of water, can interact with biological macromolecules producing various toxic secondary free radicals and reactive nitrogen species (RNS), which could result in further alteration of DNA, proteins, and lipids, leading to cellular damage (Jagetia and Reddy, 2005). Lipid peroxidation by IR-induced ROS can have harmful effects on biological membranes (Prasad *et al.*, 2005). In addition, because endogenous protective and enzymatic antioxidant defense systems are insufficient for scavenging of IR-induced free radicals, ROS can also cause the unbalance of intracellular redox status (Prasad *et al.*, 2005). The presence of antioxidants is capable to delay or inhibit oxidation processes and thus to provide protection against radiation through reduction of free radicals (Torres *et al.*, 2002). Furthermore, scavenging of free radicals and reduction of ROS by antioxidants can be linked to decrease of tumorigenesis (Halliwell, 1996).

Various trials to increase the efficiency of radiotherapy have focused on use of several chemotherapeutic agents (Candelaria *et al.*, 2006). Many radiosensitizing agents have been investigated to inhibit IR-induced activation of specific intracellular molecules, which play a role in anti-apoptotic, pro-survival, and proliferative signaling, such as ErbB family of receptor tyrosine kinases, Ras, Akt, and MAPKs, then leading to cancer cell death (Gana-Weisz *et al.*, 2002; Nyati *et al.*, 2004; Fujiwara *et al.*, 2007; Marampon *et al.*, 2011). The radioprotective agents, including the sulfhydryl compounds and WR-2721 (amifostine), have been also suggested to protect from IR-induced damage by scavenging of free radicals (Patt *et al.*, 1949; Yuhas *et al.*, 1980). These attempts have led to an effective therapeutic outcome in several cases. Nevertheless, there are a number of factors to explain the reduced efficiency, such as normal tissue damage and unexpected side effects (Seiwert *et al.*, 2007).

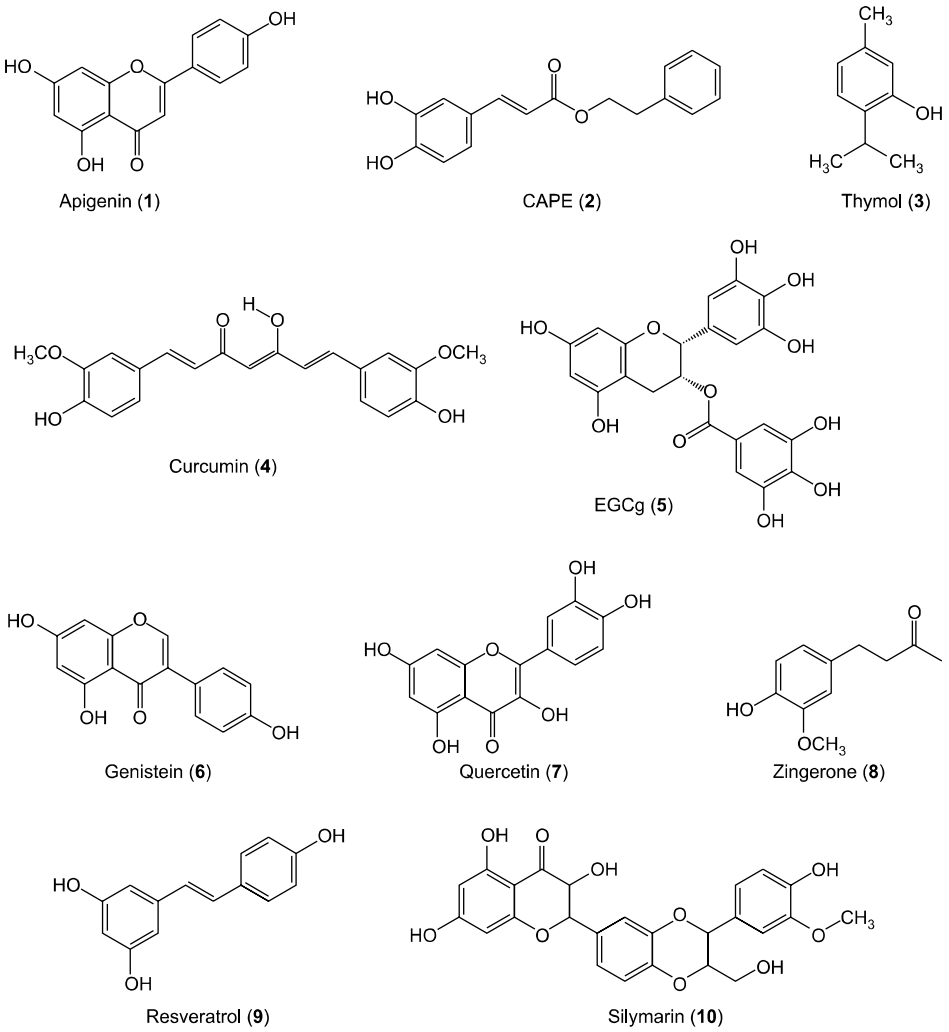

Figure 1. Selected examples of phenylpropanoids showing the radioregulation properties.

Further promising adjuvants for radiotherapy rely on enhancement of the radiosensitivity of cancer cells and decrease of the radiation effects on normal cells. Recently, many investigations have reported on identification of plant-derived phenylpropanoids (Figure 1) as potent radiotherapeutic agents due to their relatively safe level of cytotoxicity (Javvadi *et al.*, 2008). These compounds have been reported to render antioxidative activities involved in the oxidation process. They can play a role as reducing agents, proton donors, and metal chelating agents due to their high redox potential, thus providing antioxidant properties (Tsao and Deng, 2004).

Multiple studies have proposed that phenylpropanoids can inhibit initiation of tumorigenesis or its development through interaction with a number of cellular proteins, followed by regulation of signal transduction pathways, leading to transformation of normal cells to malignant cells (Surh, 2003). Indeed, caffeic acid phenethyl ester (CAPE) (**2**), curcumin (**4**), resveratrol (**9**), genistein (**6**), and other phenylpropanoids are thought to convey their anti-cancer activity by interruption of various molecular mechanisms. Therefore, this review summarized information from studies of radiation and these phenolic compounds, which may enhance the effects of cancer cell death in response to radiotherapy in one point and protect normal tissues against radiation-induced damage in the other point.

Radioprotective effects of phenylpropanoids

Apigenin

Apigenin (**1**) (4',5,7-trihydroxyflavone), one of the

most common flavonoids, has been found to have potent antioxidative and free radical scavenging activities, which could protect cells from oxidative DNA damage (Silvan *et al.*, 2010). One study demonstrated a significant overall increase in the frequency of micronuclei (MN) in irradiated (2 Gy of ^{137}Cs) human lymphocytes, while the frequency was decreased as the concentration of apigenin (**1**) increased (2.5 to 10 μg/ml (v/v)), suggesting the possibility that apigenin (**1**) may be a potent radioprotective agent in normal cells during radiotherapy (Rithidech *et al.*, 2005).

Caffeic acid phenethyl ester (CAPE)

In various studies, CAPE (**2**), an active component of propolis extract, has been found to have anticancer, anti-inflammatory and immuno-regulatory activities (Grunberger *et al.*, 1988; Natarajan *et al.*, 1996). A protective role for CAPE (**2**) in oxidative status through its free radical scavenging and antioxidant activities has been proposed (Calikoglu *et al.*, 2003; Gurel *et al.*, 2004). An investigation using lung tissues of Wistar albino rats revealed that the activities of antioxidant enzymes including catalase (CAT) and superoxide dismutase (SOD) were decreased in the radiation only group compared with the saline (control) and radiation with CAPE (**2**) groups, indicating that CAPE (**2**) treatment with radiation therapy attenuated radiation-induced pulmonary injury *in vivo*, possibly by its antioxidant effect (Yildiz *et al.*, 2008). CAPE (**2**) induced blockade of IR-induced NF-κB activation leading to suppression of several pro-inflammatory cytokines, including IL-1β, IL-6, and IL-8, and an increase of anti-inflammatory cytokines, including IL-10, thereby resulting in reduced inflammatory response to radiation (Linard *et al.*, 2004).

Curcumin

Curcumin (**4**), a dietary antioxidant derived from turmeric, has been known to have therapeutic activities including scavenging of oxygen free radicals, inhibition of lipid peroxidation, and protection against radiation-induced damage (Araujo *et al.*, 1999; Inano and Onoda, 2002; Kalpana and Menon, 2004; Polasa *et al.*, 2004; Cho *et al.*, 2005). Several studies have identified curcumin (**4**) as a potent radioprotective agent. One study reported on the radioprotective effect of curcumin (**4**), which was evaluated by cellular changes in response to γ-radiation in cultured human lymphocytes. γ-radiation at different doses (1, 2 and 4 Gy) was found to induce a significant increase in levels of MN, dicentric aberration (DC) frequencies and thiobarbituric acid reactive substances (TBARS), whereas the levels of GSH and antioxidant enzymes including SOD, CAT, and glutathione peroxidase (GPx) were significantly decreased. Curcumin (**4**) pretreatment (1, 5 and 10 μg/ml) resulted in a significant decrease of the frequency of MN and DC and the level of TBARS and a significant increase in the activities of SOD, CAT and GPx along with GSH levels. Thus, pretreatment with curcumin (**4**) provides protection to lymphocytes against γ-radiation induced cellular damage (Srinivasan *et al.*, 2006). Another report showed that treatment with curcumin (**4**) before or after radiation resulted in mitigation of radiation-induced skin damage in mice. In addition, curcumin (**4**) induced a marked reduction of the mRNA levels of several cytokines mediating early inflammatory response, including IL-1, IL-6, IL-18, TNF-α, and lymphotoxin-μ, and fibrogenic cytokines, such as TGF-β, in cutaneous tissues. Taken together, curcumin (**4**) provides protection against radiation-induced cutaneous damage in mice by down-regulation of both inflammatory and fibrogenic cytokines, specifically in the early phase of post-radiation (Okunieff *et al.*, 2006).

Epigallocatechin-3-gallate (EGCg)

EGCg (**5**), a green tea-derived molecule, is a potent antioxidant that regulates the harmful effects induced by oxidative stress. Several studies have been reported to protective effects of EGCg (**5**) in response to UV radiation, which then result in inhibition of cutaneous photoaging (Vayalil *et al.*, 2004; Jeon *et al.*, 2009). In addition, a study using mice presented that EGCg (**5**) showed radioprotective effects against γ-radiation-induced responses, including the spleen index, haematological parameters, SOD activity, and malondialdehyde level (Guo *et al.*, 2010).

Genistein

Genistein (**6**) (4',5,7-trihydroxyflavone), a naturally occurring isoflavone found in soybeans, has been reported to have protective effects against cellular damage such as UVB-induced oxidative stress and IR-induced damage (Shimoi *et al.*, 1994; Wei *et al.*, 2002). One study demonstrated that administration of genistein (**6**) resulted in alleviation of the lethal effects of radiation exposure in mice without changes in behavior, body weight or histopathology. In that investigation, genistein (**6**) was shown to be radioprotective when administered 24 h prior to γ-irradiation (9.5 Gy), but was not effective when administered 1 hr prior to irradiation, possibly due

to the antioxidant properties and immuno-stimulatory activity of genistein (**6**) (Landauer *et al.*, 2003). Genistein (**6**) treatment resulted in reduced expression of inflammatory cytokines including TNF-α, IL-1β, and TGF-β and resulted in a reduction of oxidative stress and protection against DNA damage in lungs of rats after irradiation (Calveley *et al.*, 2010).

Quercetin

Quercetin (**7**) is one of the major dietary flavonoids found widely in fruits, red wine, tea, and propolis of honeybee hives (Havsteen, 1983). Multiple studies of quercetin (**7**) have demonstrated its protective properties against oxidative stress-induced DNA damage, lipid peroxidation and cell death (Laughton *et al.*, 1991; Noroozi *et al.*, 1998; Pietta, 2000; Inal *et al.*, 2002). Quercetin (**7**) could also scavenge free radical species generated by ultraviolet radiation (Fahlman and Krol, 2009a, 2009b). A study using human peripheral blood lymphocytes found that quercetin (**7**) induced a decrease in MN frequencies and TBARS when applied 30 min before 4 Gy γ-radiation, demonstrating the radioprotective potential of quercetin (**7**) (Devipriya *et al.*, 2008).

Resveratrol

Resveratrol (**9**) (trans-3,5,4'-trihydroxy-stilbene), which is found in many plant species, including grapes, blueberries, cranberries, and peanuts, has gained increasing attention for its antioxidant effects and its low toxicity (Baur and Sinclair, 2006). These properties are mediated by its capability to scavenge free radicals and to enhance the activities of antioxidant enzymes including SOD and CAT (Losa, 2003; Li *et al.*, 2006). In normal bone marrow cells of mice, pretreatment with 100 mg/kg resveratrol (**9**) before 3 Gy whole-body γ-radiation resulted in significant reduction of the mean total chromosome aberration frequency per metaphase, compared with the radiation-only group, which supported the radioprotective effects of resveratrol (**9**) *in vivo*. Decrease in chromosome aberration frequency in normal cells is considered to be the result of resveratrol's (**9**) cellular properties, including its antioxidant activities (Carsten *et al.*, 2008).

Silymarin

Silymarin (**10**) is a flavonoid complex consisting of silybin, silydianin and silychristin (Valenzuela *et al.*, 1986). A critical role for silymarin (**10**) in free radical scavenging, inhibition of lipid peroxidation and stabilization of plasma membrane has been suggested (Muriel *et al.*, 1992; Haková *et al.*, 1996). Silymarin (**10**) is frequently used in treatment of liver diseases for protection of liver cells against lipid peroxidation and prevention of liver glutathione depletion (Valenzuela *et al.*, 1989; Mira *et al.*, 1994). Several investigations have reported that silymarin (**10**) alleviated irradiation-induced damage, including changes in nucleic acids and histone proteins, and inhibited radiation-induced free radical generation and lipid peroxidation (Gakova *et al.*, 1992; Adhikari *et al.*, 2010). Silymarin (**10**) treatment resulted in significant protection against radiation-induced hepatotoxicity in liver of rats by antioxidant and free radical scavenging properties of silymarin (**10**) (Ramadan *et al.*, 2002).

Thymol

Thymol (**3**), a monocylic phenolic compound, is used in medicine for its anti-microbial, anti-septic, and wound-healing activities through its antioxidant properties (Aeschbach *et al.*, 1994; Shapiro and Guggenheim, 1995). One report demonstrated that thymol (**3**) pretreatment resulted in a significant increase in cell viability after irradiation due to its potential for free radical scavenging, which suggested that thymol (**3**) can optimally antagonize radiation-induced cytotoxicity through normalization of the intracellular antioxidant levels (Archana *et al.*, 2009).

Zingerone

Zingerone (**8**), a phenolic alkanone, has various biological functions including inhibition of ultraviolet-induced mutation in *E. coli* and scavenging of ROS and RNS (Motohashi *et al.*, 1997; Shin *et al.*, 2005). Zingerone (**8**) has been shown to exert radioprotective potentials against γ-radiation-induced damage in Swiss albino mice (Rao *et al.*, 2009). Zingerone (**8**) pretreatment caused an increase of cell viability, reduction of radiation-induced DNA fragmentation, and delay of IR-induced collapse of mitochondrial membrane potential. In addition, gluthione-S-transferase, GSH, SOD, and CAT levels were significantly increased by zingerone (**8**) treatment before radiation. Zingerone (**8**) effectively suppressed IR-induced apoptosis by inducing a decrease in caspase-3 activity, up-regulation of anti-apoptotic protein Bcl-2, and down-regulation of pro-apoptotic molecule Bax. Finding from this investigation demonstrated that zingerone (**8**) exhibited an antagonistic effect against IR-induced toxicity and provided significant anti-genotoxic, anti-

apoptotic, and anti-lipid peroxidative potentials due to its antioxidant and free radical scavenging properties (Rao and Rao, 2010).

Radiosensitizing effects of phenylpropanoids

Caffeic acid phenethyl ester (CAPE)

Synergy between CAPE (**2**) and radiation has been suggested. One study for investigation of the cytotoxicity and radiosensitization effects of CAPE (**2**) in a human lung adenocarcinoma A549 cell line and a normal lung fibroblast WI-38 cell line found that CAPE (**2**) caused differential cytotoxicity and apoptosis, GSH and H_2O_2 depletion, and S/G2 cell cycle arrest in A549 cells, compared with WI-38 cells. In addition, CAPE (**2**) showed a radiosensitization effect on A549 lung cancer cells, which suggested the possibility that treatment with CAPE (**2**) can result in enhancement of local control of lung cancer by radiotherapy without normal lung damage *in vivo* (Chen *et al.*, 2004). Other studies have demonstrated that CAPE (**2**) not only showed itself as a strong activator of ROS generation possibly due to GSH depletion and reduction of mitochondrial membrane potential, but also had a radiosensitizing capability for IR co-treatment through inhibition of IR-induced NF-κB activation, resulting in sensitivity to IR and enhanced IR-induced apoptosis in several cancer cells (Chen *et al.*, 2005; Lee *et al.*, 2008; Kudugunti *et al.*, 2010).

Curcumin

Although curcumin (**4**) has chemopreventive properties due to its antioxidant activities, it is well documented that curcumin (**4**) can act as a pro-oxidant and anti-proliferative agent via causing mitochondrial dysfunction under certain conditions (Bhaumik *et al.*, 1999; Galati *et al.*, 2002; Wang *et al.*, 2011). Using a clonogenic survival assay and MTT assay, pretreatment with curcumin (**4**) caused sensitivity to IR in cervical cancer cell lines, SiHa and HeLa, in contrast with radioprotective effects in normal diploid fibroblast (MRC-5) cells after treatment with curcumin (**4**) and IR. In addition, radiosensitization by curcumin (**4**) is associated with prolonged ERK activation and increased ROS generation in both types of cancer cells, resulting in cell death (Javvadi *et al.*, 2008). Curcumin (**4**) rendered a radiosensitization potential to cancer cells through inhibition of telomerase activity, which is generally activated in malignant cells. Indeed, curcumin (**4**) induced significant inhibition of IR-induced NF-κB activation in neuroblastoma cells, SK-N-MC and SH-SY5Y, resulting in suppression of NF-κB-mediated transcription, such as *hTERT* mRNA, which is essential for activation of telomerase (Aravindan *et al.*, 2011). In addition, curcumin (**4**) also induced suppression of many NF-κB-regulated gene products including cyclin D1, c-myc, Bcl-2, Bcl-xL, cellular inhibitor of apoptosis protein-1, cyclooxygenase-2, matrix metalloproteinase-9, and vascular endothelial growth factor, which could be induced by radiation therapy and mediate radioresistance (Kunnumakkara *et al.*, 2008). Alto-

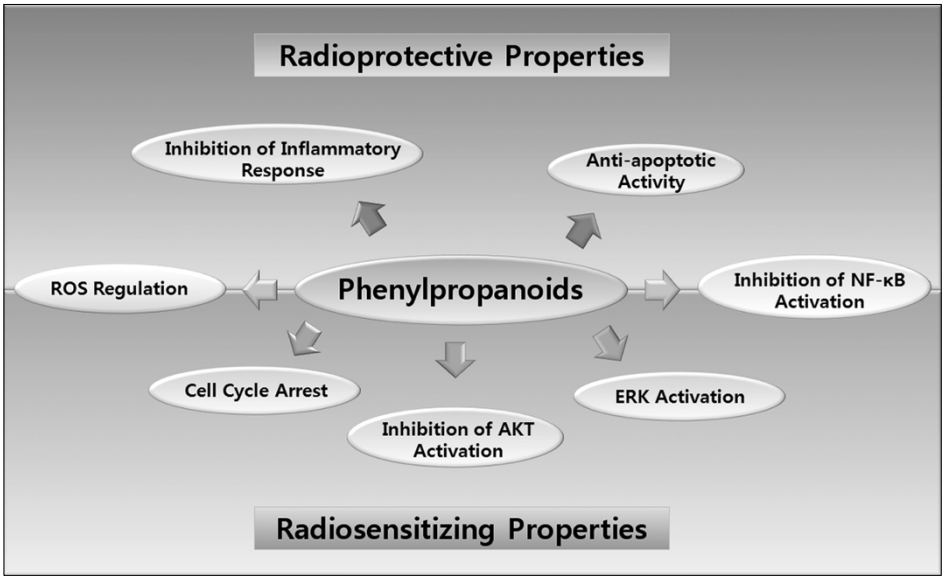

Figure 2. The mechanisms of phenylpropanoids in radioregulation.

gether, curcumin (**4**) can potentiate the anti-cancer activity of radiation therapy.

Epigallocatechin-3-gallate (EGCg)

EGCg (**5**) has been identified as having many biological functions, including inhibition of cancer cell growth (Baatout *et al.*, 2004b), cell cycle arrest (Gupta *et al.*, 2003; Kim and Moon, 2005), pro-apoptotic activities (Yokoyama *et al.*, 2001; Baatout *et al.*, 2004b; Fassina *et al.*, 2004), inhibition of invasion and metastasis (Pilorget *et al.*, 2003; Annabi *et al.*, 2005), and anti-angiogenic properties (Kojima-Yuasa *et al.*, 2003; Fassina *et al.*, 2004). Several reports have proposed that EGCg (**5**) can sensitize cancer cells to radiotherapy. EGCg (**5**) pretreatment resulted in growth inhibition of U87 glioma cells by antagonizing IR-induced expression of survivin and RhoA. EGCg (**5**) might potentiate the inhibitory effect of IR on malignant cell proliferation by targeting pro-survival and the RhoA-mediated signaling pathway resulting in cancer cells in a radiosensitive state (McLaughlin *et al.*, 2006). Pretreatment of human umbilical vein endothelial cells with EGCg (**5**) resulted in prevention of IR-induced cell migration and tubulogenesis by inhibition of several angiogenic cell surface proteins, including caveolin-1, MT1-MMP, and integrin β3, which then were sensitive to IR- induced apoptosis (Annabi *et al.*, 2003).

Table 1. The radioregulation properties of phenylpropanoids

Phenylpropanoids	Radioregulation properties					
	Radioprotection	Doses/ Concentrations	References	Radioprotection	Doses/ Concentrations	References
Apigenin (**1**)	Antioxidant activity	0-25 μg/ml	Rithidech *et al.*, 2005	-		-
CAPE (**2**)	Antioxidant activity, Inhibition of NF-κB-mediated inflammatory response	30 mg/kg i.p.; 50 μM/kg i.p.	Linard *et al.*, 2004; Yildiz *et al.*, 2008	Cell cycle arrest, ROS generation, inhibition of NF-κB activation	0-8 μg/ml;	Chen *et al.*, 2004; Chen *et al.*, 2005; Lee *et al.*, 2008
Curcumin (**4**)	Antioxidant activity, Down-regulation of inflammatory and fibrogenic cytokines	1-10 μg/ml; 50-200 mg/kg i.g. or i.p.;	Okunieff *et al.*, 2006; Srinivasan, *et al.*, 2006	ERK activation, ROS generation, inhibition of NF-κB-mediated survival pathway	0-10 μM; 1 g/kg p.o.;	Javvadi *et al.*, 2008; Kunnumakkara *et al.*, 2008; Aravindan *et al.*, 2011
EGCg (**5**)	Antioxidant activity	0-50 mg/kg p.o.	Guo *et al.*, 2010	Inhibition of RhoA-mediated pathway, inhibition of angiogenic proteins	0-30 μM	Annabi *et al.*, 2003; McLaughlin *et al.*, 2006
Genistein (**6**)	Antioxidant activity, Down-regulation of inflammatory cytokines	0-400 mg/kg s.c.; 20-50 mg/kg p.o. or i.p.	Landauer, *et al.*, 2003; Calveley *et al.*, 2010	Cell cycle arrest, Inhibition of AKT activation	0-100 μM; 5 mg/day p.o.;	Hillman *et al.*, 2001; Hillman *et al.*, 2004; Yashar *et al.*, 2005; Raffoul *et al.*, 2006; Zhang *et al.*, 2006; Hillman *et al.*, 2007
Quercetin (**7**)	Antioxidant activity	0-48 μM	Devipriya *et al.*, 2008	-		-
Resveratrol (**9**)	Antioxidant activity	100 mg/kg by gavage	Carsten *et al.*, 2008	The production of *de novo* ceramide	0-32 μM	Scarlatti *et al.*, 2007
Silymarin (**10**)	Antioxidant activity	50-70 mg/kg p.o. or i.v.	Ramadan *et al.*, 2002	-		-
Thymol (**3**)	Antioxidant activity	25 μg/ml	Archana *et al.*, 2009	-		-
Zingerone (**8**)	Antioxidant and anti-apoptotic activity	25 μg/ml	Rao *et al.*, 2010	-		-

i.g., intragastrically; i.p., intraperitoneally; i.v., intravenously; p.o., orally; s.c., subcutaneously administered.

Genistein

In addition to radioprotective properties, genistein (**6**) also has many possible mechanisms for its anti-cancer activities. Genistein (**6**) has been reported to prevent growth of cancer cells from multiple malignant tissues, including breast, lung, prostate, and lymphoma (Wei *et al.*, 1995; Davis *et al.*, 1998; Shao *et al.*, 1998; Arai *et al.*, 2000). Combined treatment with genistein (**6**) and IR resulted in significantly reduced expression of survivin mRNA and protein contents of survivin and cyclin B in cervical HeLa cells, leading to the G2/M phase of cell cycle arrest and then apoptosis (Zhang *et al.*, 2006). Genistein (**6**) also potentiated the effect of low doses of photon or neutron radiation in prostate carcinoma PC-3 cells through inhibition of DNA synthesis, resulting in inhibition of cell division and growth (Hillman *et al.*, 2001). Genistein (**6**) combined with radiation caused a synergistic inhibition of primary tumor growth and metastasis in orthotopic models of prostate cancer and renal cell carcinoma (Hillman *et al.*, 2004; Hillman *et al.*, 2007). These radiosensitive properties of genistein (**6**) could result from its inhibitory effect on radiation-induced NF-κB activation, leading to a signaling pathway for cells undergoing an apoptotic process, followed by enhancement of cell death (Raffoul *et al.*, 2006). Genistein (**6**) also caused inhibition of growth and G2/M arrest in cervical cancer cells by inhibition of radiation-induced AKT activation and Mcl-1, demonstrating the radiosensitive properties of genistein (**6**) (Yashar *et al.*, 2005).

Resveratrol

Resveratrol (**9**) is known as a radiosensitizing agent in different cancer cell lines, including HeLa, K-562, IM-9, and EOL-1 cell lines through inhibition of proliferation and the process of IR-induced cell death (Baatout *et al.*, 2004a, 2005). Resveratrol (**9**) induced synergistic enhancement of IR-induced cell death in DU 145 cells, which were shown to be resistant to IR treatment, by promoting production of *de novo* ceramide thereby leading to cell death (Scarlatti *et al.*, 2007).

Conclusions

The present review addresses both properties for radioprotection and radiosensitization of phenylpropanoids (Figure 2). Radiosensitizing effects of these phytochemicals are thought to interact with several intracellular signaling molecules which then mediate signaling cascades including cell cycle arrest and cell death, while the radioprotective effect of those has been highly dependent on their antioxidant activities for protection against radiation-induced damage as summarized in Table 1. Although a number of studies for the effects of phytochemicals in radioregulation have been reported so far, the each exact mechanism of them has not yet been determined. In the clinical aspect, one of the most important applications is the use of phenylpropanoids as radiotherapeutic agents in patients suffering from cancer and other diseases. Systemic analyses will be required for determination of optimal doses of these compounds to function their appropriate properties for use as potential regulators of radiotherapy.

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