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Forum Review

Chemosensitization and Radiosensitization of Tumors by Plant Polyphenols

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ABSTRACT

The treatment of cancer with chemotherapeutic agents and radiation has two major problems: time-dependent development of tumor resistance to therapy (chemoresistance and radioresistance) and nonspecific toxicity toward normal cells. Many plant-derived polyphenols have been studied intently for their potential chemopreventive properties and are pharmacologically safe. These compounds include genistein, curcumin, resveratrol, silymarin, caffeic acid phenethyl ester, flavopiridol, emodin, green tea polyphenols, piperine, oleandrin, ursolic acid, and betulinic acid. Recent research has suggested that these plant polyphenols might be used to sensitize tumor cells to chemotherapeutic agents and radiation therapy by inhibiting pathways that lead to treatment resistance. These agents have also been found to be protective from therapy-associated toxicities. How these polyphenols protect normal cells and sensitize tumor cells to treatment is discussed in this review. *Antioxid. Redox Signal.* 7, 1630–1647.

INTRODUCTION

A WIDE VARIETY OF DIETARY phytochemicals have been suggested to block the initiation of cancer or to suppress its development (182). These agents exert their effects by interacting with numerous cellular proteins that, in turn, affect multiple steps in the pathways leading to tumorigenesis. Many of these molecular alterations involve the kinase networks, such as mitogen-activated protein kinases, phosphatidylinositol 3-kinase (PI-3K), and protein kinase, that maintain homeostasis in cells. These kinase pathways converge to activate downstream transcription factors such as nuclear factor-κB (NF-κB) and activator protein 1. In fact, curcumin (turmeric), resveratrol (grapes), genistein (soy), (−)-epigallocatechin gallate (EGCG) (green tea), and other plant phenols are thought to exert their antitumorigenic effects through the inhibition of various mechanisms described in this review (Fig. 1). Furthermore, these plant polyphenols may enhance the tumoricidal effects of chemotherapy and radiotherapy, protect normal cells from therapy-induced damage, and increase systemic bioavailability of chemotherapeutic agents (Table 1). However, some of the evidence has come from studies that used superphysiologic doses of these plant polyphenols, and so these effects must be confirmed in clinical trials before the agents can be recommended as safe adjunct treatments.

MULTIPLE SIGNALING PATHWAYS LEAD TO CHEMORESISTANCE AND RADIORESISTANCE

Reactive oxygen intermediates (ROI) expression

Potent inducers of both pro-apoptotic and prosurvival pathways, such as members of the tumor necrosis factor (TNF) superfamily, contribute to both the tumor cell death response to anticancer treatments and to the development of resistance to these treatments. These effects are mediated through the production of ROI, which are also known as reactive oxygen species (55). For example, TNF alters the membrane permeability of mitochondria, leading to cytochrome *c*

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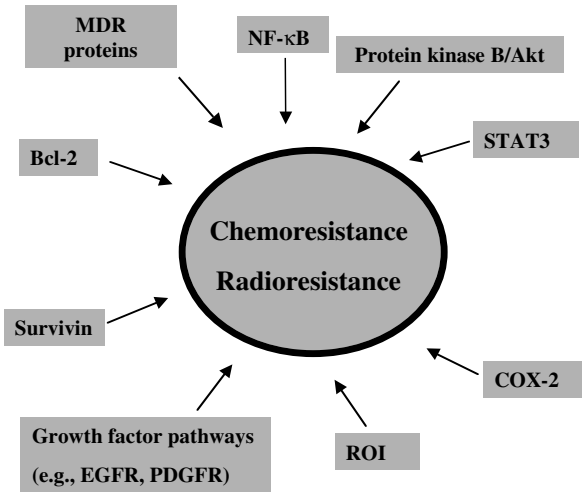

FIG. 1. Cellular molecules implicated in resistance to chemotherapy and radiation therapy. PDGFR, platelet-derived growth factor receptor.

release and subsequent caspase activation, which, in turn, leads to apoptosis. Furthermore, TNF-associated factor signaling has been shown to be directly linked to the electron transport mechanism in mitochondria and subsequent to ROI production (37). A review placed ROI as a common upstream component in TNF-induced apoptosis as well as in caspase, c-Jun N-terminal kinase, mitogen-activated protein kinase, NF-κB, and activator protein 1 activation (55). Through NF-κB activation, ROI has been shown to mediate prosurvival signaling as well. Therefore, ROI mediates both pro-apoptotic and anti-apoptotic signaling, but the precise mechanisms that lead to these polar outcomes are not yet clear.

Chemotherapy and radiotherapy strongly induce TNF signaling and in doing so use the production of ROI to induce both apoptosis and resistance (Fig. 2). Thought to exert their effects in large part through their antioxidant properties, plant polyphenols may also use ROI in signaling (147).

NF-κB activation

The ubiquitously expressed transcription factor NF-κB is involved in a wide spectrum of cellular responses, including cell cycle control, apoptosis, and stress adaptation. Among the many diseases linked to aberrant NF-κB activation, can-

TABLE 1. POLYPHENOLS THAT MAY MODULATE CHEMOTHERAPY AND RADIOTHERAPY

Polyphenol	*Reference*
Genistein	
Chemosensitization	
Enhanced apoptosis induced by docetaxel and cisplatin in pancreatic cancer cells	103
Enhanced apoptosis induced by doxorubicin, etoposide, or cisplatin in lung cancer cells	95
Was synergistic with cyclophosphamide in a lung cancer mouse model	205
Enhanced cisplatin-induced apoptosis in five human melanoma cell lines	188
Potentiated β-lapachone-induced apoptosis of PC3 and LNCaP prostate cancer cells	92
Potentiated the effect of dexamethasone on cell cycle progression in liver and colon cancer cells	139
Enhanced the effects of cisplatin and, to a lesser extent, of vincristine in meduloblastoma cells	84
Enhanced the effects of tiazofurin in human leukemia cells	100
Enhanced the effects of tiazofurin in human ovarian carcinoma cells	99
Was synergistic with quercetin in ovarian carcinoma cells	169
Radiosensitization	
Potentiated the effect of radiation on prostate carcinoma cells	65
Improved the efficacy of chemoradiotherapy in a murine lung tumor model	111
Enhanced radiosensitivity in human esophageal cancer cell lines	4
Enhanced γ-irradiation-induced apoptosis and cell cycle arrest in K562 leukemia cells	138
Resveratrol	
Chemosensitization	
Enhanced paclitaxel-induced apoptosis of lung cancer cells	91
Reduced paclitaxel-induced apoptosis in human neuroblastoma SH-SY5Y cells	130
Reduced TNF-induced apoptosis in human leukemia cells	109
Reduced H_2O_2-induced apoptosis in human neuronal PC12 cells	73
Inhibited H_2O_2, vincristine-, daunorubicin-, and C2-induced apoptosis in human leukemia cells	2
Sensitized multiple myeloma cells and non-Hodgkin's lymphoma cells to paclitaxel-induced apoptosis	25
Reduced H_2O_2-induced apoptosis in leukemia cells by inhibiting leukotriene B4 and prostaglandin E2	108
Radiosensitization	
Enhanced γ-radiation-induced apoptosis and cell cycle arrest of Hela and SiHa cells	216
Curcumin	
Chemosensitization	
Sensitized multiple myeloma cells to vincristine and melphalan	25
Potentiated the cytotoxic effects of doxorubicin, 5-FU, and paclitaxel in prostate cancer cells	67

(Continued)

TABLE 1. CONTINUED

Polyphenol	*Reference*
Radiosensitization	
Sensitized PC3 prostate cancer cells to radiation through suppression of TNF production	41
Protective effects	
Reduced lung toxicity in rats treated with whole-body radiation	191
Reduced radiation-induced genotoxicity in mice treated with whole-body radiation	192
Decreased acute toxicity from whole-body radiation in rats	71
Protected rats from doxorubicin-induced nephrotoxicity	200
Protected rats from doxorubicin-induced cardiotoxicity	199
Reduceed mucosal injury from trinitrobenzene sulfonic acid-induced colitis in mice	196
Inhibited camptothecin-, mechlorethamine-, and doxorubicin-induced apoptosis of breast cancer cells	176
Green tea polyphenols	
Chemosensitization	
Enhanced antitumor activities of other anthracyclines, cisplatin, and irinotecan in ovarian sarcoma-bearing mice	180
Enhanced antitumor effect of doxorubicin in mice with ascites carcinoma	158
Enhanced inhibitory effects of doxorubicin against Ehrlich ascites carcinoma in mice (green tea)	159
Was synergistic with doxorubicin in mice with M5076 ovarian sarcoma	179
Was synergistic with doxorubicin in inhibition of hepatic metastasis of M5076 ovarian sarcoma in mice	158, 178, 179
Reversed MDR and increased doxorubicin concentration in mice with P388 leukemia	160
Increased pirarubicin concentration in M5076 ovarian sarcoma cells	181
Increased antitumor activity of idarubicin and reduced its toxicity in mice with P388 leukemia	161
Emodin	
Chemosensitization	
Enhanced arsenic trioxide-induced apoptosis in HeLa cells	208
Potentiated effects of *cis*-platinol, doxorubicin, and 5-FU in Merkel cell carcinoma cells (aloe-emodin)	52
Enhanced effects of paclitaxel on Her-2/neu-overexpressing breast cancer cells	213
Enhanced cytotoxic effects of cisplatin, doxorubicin, and etoposide on Her-2/neu-overexpressing non-small cell lung cancer cells	210
CAPE	
Protective effects	
Protected rats from doxorubicin-induced cardiotoxicity	51
Protected rats from cisplatin-induced nephrotoxicity	135
Protected rats from bleomycin-induced lung fibrosis	136
Protected rats from ischemia-reperfusion kidney injury	61
Protected rats from radiation-induced inflammatory changes	106
Flavopiridol	
Chemosensitization	
Potentiated effects of mitomycin c in breast and gastric cancer cells	165
Was synergistic with paclitaxel, cytarabine, topotecan, doxorubicin, etoposide, and cisplatin in non-small cell lung cancer cells	29
Enhanced doxorubicin-induced apoptosis in retinoblastoma protein-deficient sarcoma cells	101
Augmented CPT-11-induced apoptosis in Hct116 colon cancer cells	123
Increased sensitization to gemcitabine in gastrointestinal cancer cells	77
Radiosensitization	
Potentiated γ-radiation-induced apoptosis in colon and gastric cancer cells	78
Enhanced radiosensitivity of ovarian carcinoma cells	150
Silymarin	
Chemosensitization	
Potentiated doxorubicin cytotoxicity in P-glycoprotein-positive breast cancer cells (silymarin)	214
Enhanced doxorubicin-induced growth inhibition in human prostate cancer cells (silymarin)	195
Was synergistic with cisplatin and doxorubicin in breast cancer and ovarian carcinoma cells (silybin)	164
Protective effects	
Protected rat cardiomyocytes from anthracycline-induced toxicity	42
May have protected rat heart membrane from doxorubicin-induced damage	148
Ginger	
Protective effects	
Protected rats and dogs from cisplatin-induced nausea	167, 168
Piperine	
Effects on bioavailability	
Increased bioavailability of propranolol and theophylline in humans	15
Enhanced bioavailability of aflatoxin B1 in rat tissues	6
Enhanced bioavailability of curcumin in rats and humans	173

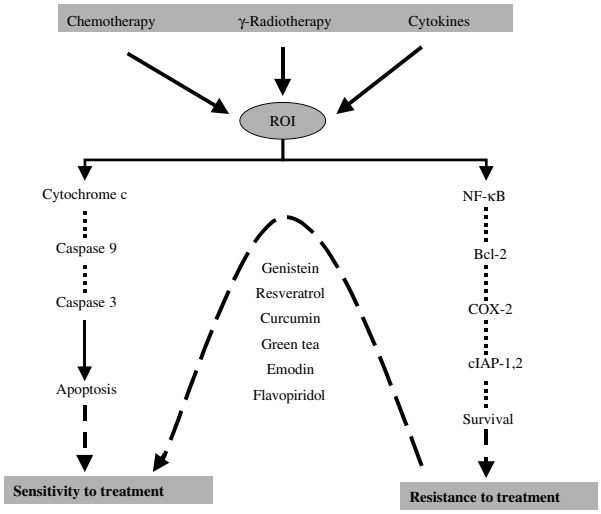

FIG. 2. Chemotherapy and radiotherapy induce both pro-apoptotic signaling, leading to cell death and treatment sensitivity, and anti-apoptotic signaling, leading to increased cell survival and treatment resistance. Plant polyphenols may help increase sensitivity and inhibit the pathways leading to resistance.

cer has been the major focus because of NF-κB's role as a central regulator of the inflammatory response, its regulation of genes involved in cellular survival (Bcl-2, Bcl-xL, c and x forms of inhibitor of apoptosis protein [IAP], and superoxide dismutase) and tumor progression (intercellular adhesion molecule 1, vascular cell adhesion molecule 1, endothelial leukocyte adhesion molecule 1, cyclooxygenase-2 [COX-2], inducible nitric oxide synthase [iNOS], and matrix metalloproteinase [MMP-9]). Furthermore, its constitutive activity has been frequently elevated in many types of tumors, including leukemia, lymphoma, prostate cancer, breast cancer, colon cancer, melanoma, and head and neck cancers (54, 152). Ursolic acid and betulinic acid have been shown to exert their effects through mechanisms that involve the inhibition of NF-κB (172, 186). Also, NF-κB is activated by chemotherapeutic agents and ionizing radiation, and can lead to treatment-induced tumor cell resistance (45, 56, 79). Furthermore, the suppression of NF-κB by different methods can sensitize tumor cells to both chemotherapy and radiotherapy.

In vitro and *in vivo* studies have shown that constitutive activation of NF-κB inhibits chemotherapy-induced apoptosis in a number of tumor types (23, 24, 202). For example, upregulation of NF-κB-inducible genes protected MDA-MB-231 breast cancer cells from paclitaxel-induced and radiation-induced apoptosis (129, 202), and chemotherapy-induced NF-κB activation led resistance to conventional cancer treatment resistance (18, 20, 137, 202). In a recent study of four tumor cell lines, each treated with different chemotherapy regimens (doxorubicin, 5-fluorouracil [5-FU], cisplatin, and paclitaxel), cell survival correlated with the level of NF-κB activity induced by the drugs (43). In another study, NF-κB-binding activity decreased in breast cancer cells treated with anti-Her-2/neu antibody (Trastuzumale; Herceptin), suggesting a role for NF-κB in the therapeutic efficacy of this antibody combined with chemotherapy for patients with Her-2/neu-positive breast cancer (144). Others studies have shown tumor regression due to tumor sensitization to CPT-11 (irinotecan), a topoisomerase I inhibitor, in mouse xenograft models that overexpress inhibitory subunit of NF-κB (IκBα) (45, 203). Additional reports using adenovirus-mediated gene transfection of IκBα demonstrated the potentiation of chemotherapeutic efficacy in both *in vitro* and *in vivo* models of gastrointestinal malignancies (46, 203), human glioma cells (204), and pancreatic cancer cells (11). Compared with cells without the super-repressor, fibrosarcoma cells expressing the IκBα super-repressor were more sensitive to radiation-induced apoptosis (17), and glioblastoma cell lines (A172, M054) expressing the super-repressor were more susceptible to radiotherapy (206). Protease inhibitors are less specific but are a more clinically useful way to examine the effects of NF-κB inhibition. In a preclinical study, the use of protease inhibitors increased radiation-induced apoptosis of lymphoma cells (93).

COX-2 expression

COX-2, an enzyme expressed largely in response to inflammatory disorders and cancer, mediates prostaglandin production and is currently under clinical investigation as a target for anticancer therapy (120, 125). Its presence has been associated with more aggressive tumor phenotypes and worse outcome for patients with breast cancer, colon cancer, head and neck cancers, lung cancer, and pancreatic cancer. Accumulating evidence suggest that COX-2 is involved in multiple aspects of carcinogenesis, including maintenance of tumor growth, facilitation of metastatic spread, and resistance to various therapies (89, 116). As a result, selective inhibitors of COX-2, such as SC-236 and celecoxib, have been used *in vitro* and *in vivo* to test whether its inhibition may sensitize tumor cells to chemotherapy and radiotherapy. For example, SC-236 increased tumor radioresponse in murine tumor models and in a human glioma xenograft in nude mice (87, 118, 142), and celecoxib enhanced the response of A431 human tumor xenografts in nude mice to radiation and docetaxel chemotherapy, radiotherapy, or both (188). The mechanisms that account for these findings and others are not yet clear but may involve the elimination of prostaglandins as protective molecules in response to chemotherapy and radiotherapy (117).

Bcl-2 expression

Bcl-2 is a member of the Bcl-2 family of proteins that regulates both pro-apoptotic and anti-apoptotic signaling in cells. Bcl-2 itself is an anti-apoptotic protein that is inappropriately overexpressed in a number of solid and hematopoietic tumors, and exerts its influence by enhancing cellular survival (81), which contributes to resistance to conventional treatments, including chemotherapy and radiotherapy (36). Furthermore, several investigations have shown that inhibiting Bcl-2 sensitizes tumor cells to chemotherapy and radiotherapy. For example, transfection with the gene *PTEN*, which down-regulates Bcl-2, potentiated the effects of radiotherapy in several types of prostate cancer cells (156). An-

other study, using Bcl-2 antisense oligonucleotide, demonstrated increased apoptosis and enhanced chemotherapeutic efficacy in undifferentiated thyroid carcinomas (86). These results and others (21, 62) have highlighted Bcl-2 as a potential target for chemosensitization and radiosensitization.

Survivin expression

Survivin is a member of the mammalian IAP family and functions primarily to inhibit the apoptosis pathway by blocking caspase 9 activation (162, 170). Both *in vitro* and *in vivo* experiments have demonstrated its cancer-inducing properties (16) and its overexpression in several malignant tissues and its absence in most normal tissues (7, 8). Survivin has been shown to be involved in angiogenesis and to be necessary for the anti-apoptotic effect of vascular endothelial growth factor (114, 132, 193, 215). Furthermore, high levels of survivin have been associated with a high rate of tumor recurrence, low overall patient survival, and high tumor resistance to chemotherapy and radiotherapy (7). Cell sensitization to therapies has been demonstrated in several studies: Inhibition of survivin with a ribozyme or dominant-negative molecule sensitized melanoma and pancreatic cancer cells to radiation (12, 141); survivin inhibition sensitized breast cancer cells to paclitaxel and doxorubicin (133, 201); and survivin inhibition plus radiotherapy resulted in significantly decreased survival of lung cancer cells (107).

Multidrug resistance (MDR) protein expression

MDR proteins and MDR-associated proteins are two subfamilies of the ATP-binding cassette family proteins that regulate the P-glycoproteins that remove drugs from cells at the cost of ATP hydrolysis (49, 166). The relationship between MDR protein expression and chemoresistance is fairly well established (96, 185). For example, *in vitro* and *in vivo* investigations have suggested the involvement of MDR proteins in multiple mechanisms that lead to chemoresistance in prostate cancer (197). This result was consistent with that from a study that used an NF-κB inhibitor to down-regulate the expression of MDR proteins, thereby leading to increased apoptosis in prostate cancer cells (53). The association between MDR protein expression and radioresistance is less clear. For example, cancer cells that expressed the *MDR* gene were no more resistant to radiotherapy than their non-MDR counterparts (57).

AKT expression

The protein kinase B/Akt pathway is a downstream effector of PI-3K and has been described as a mediator of anti-apoptotic signaling in cancer cells. Akt has been shown to affect cell cycle progression and foster tumorigenesis when overexpressed (209). This overexpression may contribute to chemoresistance and radioresistance. The ectopic expression of constitutively active Akt1 resulted in enhanced resistance of non-small cell lung cancer cells to a panel of chemotherapeutic agents (68). In breast cancer cells, inhibition of the PI-3K/Akt pathway led to enhanced paclitaxel, doxorubicin, and 5-FU cytotoxicity (75), and dominant-negative expression vectors sensitized the cells to the induction of apoptosis by paclitaxel, doxorubicin, 5-FU, etoposide, and camptothecin (88). However, in pancreatic cancer cells, the PI-3K/Akt pathway did not seem to be involved in gemcitabine resistance (11). Accumulating evidence has suggested that the PI-3K/Akt pathway may also be a major contributor to radioresistance (209). One report indicated that activated Akt in bile duct cancer cells was associated with radioresistance, as evidenced by the enhanced radiosensitization via Akt inhibition (189). This report and another (112) indicated the PI-3K/Akt pathway as a target for tumor sensitization to radiotherapy.

Signal transducer and activator transcription (STAT)3 expression

STAT3 is a ubiquitously expressed member of the STAT family of transcription factors that is activated by tyrosine phosphorylation via upstream receptors that bind to growth factors such as epidermal growth factor (EGF) and platelet-derived growth factor and cytokines such as interleukin-6 (IL-6) (5, 97, 98). STAT3 has diverse biologic functions, including cell growth regulation, apoptosis regulation, and cell differentiation. STAT3 has also been shown to be consitutively active in a number of human cancers and to be necessary for tumor cell growth (32). Moreover, STAT3 may mediate chemoresistance, and its inhibition may sensitize cells to apoptosis. For example, STAT3 inhibition contributed to the decreased survival of multiple myeloma cells (26), and it may have sensitized pancreatic cancer cells to apoptosis (59). Blockade of STAT3 using various techniques sensitized estrogen receptor-negative breast cancer cells to chemotherapy-induced apoptosis (153). Finally, STAT3 inhibition with a STAT3 antisense oligonucleotide enhanced radiation-induced apoptosis in prostate cancer cells (36).

EGF receptor (EGFR) expression

EGFR is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. On binding with EGF or transforming growth factor-beta, EGFR regulates a signaling cascade that, in turn, regulates cell growth and proliferation. EGFR overexpression has been linked to aggressive tumor phenotypes, poor patient prognosis, and poor tumor response to therapies (113). For example, the magnitude of EGFR expression correlated with increased tumor chemoresistance and radioresistance in a variety of *in vivo* tumors, including murine carcinoma, squamous cell carcinoma, ovarian adenocarcinoma, hepatocarcinoma, and adenosquamous carcinoma (3, 119, 126). Use of the anti-EGFR antibody C225 greatly enhanced the response of A431 human tumor xenografts in nude mice to docetaxel, radiation, or both (119, 126). Other investigators also reported the increased sensitization of tumor cells to radiotherapy through EGFR inhibition (28, 69, 70). Mechanisms that account for this effect by EGFR inhibitors are becoming clearer with time, and likely involve sensitization to treatment-induced apoptosis, inhibition of treatment-induced repair mechanisms, and inhibition of tumor angiogenesis (120).

BACKGROUND ON SELECTED POLYPHENOLS

Genistein is a soy-derived isoflavone that acts as a tyrosine kinase inhibitor and has a structure with an affinity for the estrogen receptor and androgen-mediated pathways (33). Therefore, it is not surprising that it has received considerable attention as a chemopreventive agent in breast, prostate, and other cancers (163). In fact, epidemiologic studies have linked the lower incidences of breast and prostate cancers in Asian populations than in non-Asian populations to significant differences in diet, including a higher concentration of soy isoflavones such as genistein. Genistein is thought to inhibit the growth of cancer cells by modulating genes related to cell cycle control and apoptosis and is a potent inhibitor of angiogenesis and metastasis. *In vitro* and *in vivo* investigations have shown that this mechanism may be mediated through NF-κB inhibition (128). Furthermore, genistein combined with chemotherapy and radiotherapy may enhance the efficacy of these therapies.

Resveratrol (*trans*-3,5,4′-trihydroxystilbene) was first isolated in 1940 as a constituent of the roots of white hellebore (*Veratrum grandiflorum* O. Loes) but has since been found in various plants, including grapes, berries, and peanuts. Research in recent years has focused on the anticancer properties of resveratrol, as suggested by its ability to suppress the proliferation of lymphoid and myeloid cancers, multiple myeloma, breast cancer, prostate cancer, colon cancer, pancreatic cancer, melanoma, head and neck squamous cell carcinoma, ovarian carcinoma, and cervical carcinoma (14, 35, 50).

Curcumin, a diferuloylmethane derived from turmeric (*Curcuma longa*), has been the subject of intense study as a chemopreventive agent and as a complement to chemotherapy and radiotherapy. Notable findings in recent years have included its ability to suppress proliferation in a variety of tumor cell types; down-regulate NF-κB target genes such as *COX-2*, *iNOS*, *MMP-9*, *urokinase-type plasminogen activator*, and *cyclin D1*; inhibit the expression of growth factor receptors, including EGFR and human EGFR 2; and inhibit several protein kinases involved in the signaling pathways leading to tumorigenesis (1). Moreover, curcumin inhibits NF-κB activation induced by various inflammatory stimuli (54, 124, 151), the IκB kinase (IKK) activation needed for NF-κB activation (17, 31, 122), and NF-κB-induced osteoclastogenesis (27). An epidemiologic study suggested that low incidences of gastrointestinal malignancies in India may be attributable to the presence of natural additives, including curcumin, in the Indian diet (121).

Used as a medicinal agent in Asia for more than 4,000 years, green tea is derived from the leaves of *Camellia sinensis* and is an efficacious chemopreventive agent and modulator of chemotherapy (140, 182). Several investigations, including a phase I clinical trial (146), have demonstrated a decreased relative risk of many cancers, including lung, colorectal, pancreatic, and stomach cancers with the consumption of green tea. Growing evidence from animal studies has also suggested the chemopreventive potential of green tea (140). Two components of green tea, EGCG and γ-glutamylethylamide (theanine), have been the particular focus of ongoing research. Several other plant polyphenols (*e.g.,* emodin, caffeic acid phenethyl ester [CAPE], flavopiridol, silymarin, ginger, and piperine) are currently under investigation and are discussed below.

SENSITIZATION OF TUMOR CELLS BY POLYPHENOLS TO CHEMOTHERAPEUTIC AGENTS

Green tea polyphenols

Mounting evidence has suggested that the amino acid theanine, a major component of green tea, plus chemotherapy has a synergistic effect for a varity of cancers. An investigation of the combined effects of theanine and glutamate transporter inhibitors on the antitumor activity of doxorubicin in M5076 ovarian sarcoma-bearing mice revealed that, compared to the doxorubicin-alone group, theanine significantly enhanced the inhibitory effect of doxorubicin on tumor growth and increased the drug's concentration in the tumors (188). Oral administration of theanine or green tea similarly enhanced the antitumor activity of doxorubicin. Theanine plus doxorubicin also suppressed the hepatic metastasis of ovarian sarcoma. An increase in doxorubicin concentration was not observed in normal tissues such as the liver and heart. The investigators described novel mechanisms of enhancement of antitumor efficacy of doxorubicin via the inhibition of glutamate transporters by theanine. Moreover, theanine enhanced the antitumor activities of other anthracyclines, cisplatin, and irinotecan (188).

Another study showed that, compared with doxorubicin alone, theanine plus doxorubicin enhanced the antitumor effect over twofold in mice with Ehrlich ascites carcinoma (158). Furthermore, theanine caused an almost threefold increase in the concentration of doxorubicin within the tumor, which correlated with the increased efficacy of the drug combination and decreased tumor weight (188). Consistent with these results, theanine and doxorubicin acted synergistically in mice with M5076 ovarian sarcoma, enhancing tumor concentration of chemotherapy, inhibiting tumor growth, and decreasing hepatic metastasis (159, 178, 179). Theanine was also effective in reversing MDR in mice with P388 leukemia by increasing the doxorubicin concentration within the tumor and decreasing tumor weight (160). In both the ovarian sarcoma and leukemia cells, theanine attacked the same transport process for doxorubicin, elevated the doxorubicin concentration, and increased the doxorubicin-induced antitumor activity. Other studies have also demonstrated the inhibition of MDR-associated proteins by green tea components (44, 66).

Like theanine, the green tea components—caffeine, EGCG, and flavonoids—inhibit doxorubicin efflux from Ehrlich ascites carcinoma cells. Thus, EGCG and flavonoids may enhance doxorubicin-induced antitumor activity and increase doxorubicin concentration in tumors by inhibiting the efflux. These components in green tea probably exhibit low toxicity, and green tea plus chemotherapy probably has few adverse effects. Similar synergistic effects have been noted

for theanine plus pirarubicin (181, 194), idarubicin (161), cisplatin (155, 217), and CPT-11 (175). However, one report found no association between intake of green tea and risk of breast cancer in Japanese women (183).

Studies have demonstrated the potent chemopreventive effect of EGCG in several types of cancer cells. In the prostate cancer cell lines LNCaP and DU-145, EGCG inhibited NF-κB activation, thereby leading to increased apoptosis and decreased expression of the prometastatic genes encoding for MMP-2 and MMP-9 (60, 63, 198). In human epidermoid carcinoma A431 cells, EGCG activated caspases, which led to increased apoptosis and inhibition of NF-κB (60). In YCU-H891 head and neck cancer cells and MDA-MB-231 breast carcinoma cell lines, EGCG inhibited both constitutive NF-κB activation and EGFR activation and strongly inhibited vascular endothelial growth factor production (110). Also in breast cancer cells, EGCG inhibited basal Her-2/neu receptor tyrosine phosphorylation, leading to subsequent inhibition of PI-3K, Akt, and NF-κB activation (145). In the lung cancer cell line PC-9, EGCG inhibited NF-κB-inducing kinase, an upstream kinase leading to IκB kinase and NF-κB activation (134). Finally, in EGF- and 12-*O*-tetradecanoylphorbol 13-acetate-stimulated mouse JB6 epidermal cells, EGCG inhibited ultraviolet B-induced NF-κB-mediated transcription (131). Taken together, these results suggested that the chemopreventive properties of EGCG may derive from the modulation and inhibition of a variety of signaling pathways that lead to NF-κB activation and tumorigenesis.

Genistein

Several reports have highlighted the enhanced efficacy of chemotherapy when it is combined with several plant polyphenols. Genistein has been shown to potentiate the effects of chemotherapy for numerous tumor types. In the pancreatic cancer cell line, treatment with genistein before docetaxel or cisplatin administration enhanced tumor cell death compared with treatment with either chemotherapeutic drug alone. This effect may have been mediated by the inhibition of NF-κB by genistein, causing increased apoptosis (188). In EGFR-expressing lung cancer cells, genistein combined with cisplatin, doxorubicin, or etoposide enhanced the antiproliferative effects of these drugs and induced programmed cell death (95). This result was consistent with that from another report using a lung cancer mouse model to show the synergistic effect of genistein and cyclophosphamide (205). In another study using five human melanoma cell lines, genistein plus cisplatin enhanced apoptosis in all cell lines versus either treatment alone; furthermore, genistein significantly reduced levels of the anti-apoptotic proteins Bcl-2 and Bcl-xL and increased levels of the pro-apoptotic protein Apaf-1 (188). In prostate cancer cell lines PC3 and LNCaP, genistein plus β-lapachone resulted in more potent cell killing than either treatment alone did (92). In liver and colon cancer cell lines, genistein plus dexamethasone resulted in enhanced expression of $p21^{WAF1/CIP1}$, an inhibitor of cyclin-dependent kinase 2, thereby halting cell cycle progression (139). In medulloblastoma cells, genistein potentiated the effects of cisplatin and, to a lesser extent, those of vincristine (84). In human leukemia cells (188) and ovarian carcinoma cells (188), genistein plus tiazofurin resulted in greater cells growth inhibition and increased cell differentiation compared to either treatment alone. Finally, genistein and quercetin acted synergistically in ovarian carcinoma cells (169).

The chemopreventive outcomes of genistein in several tumor types may be achieved by targeting an NF-κB-dependent pathway. For example, in studies using MDA-MB-231 breast cancer cells and PC3 prostate cancer cells, genistein inhibited cell growth and induced apoptosis via the down-regulation of Akt and NF-κB pathways (58, 102). In T-cell lymphoma cell lines, genistein increased pro-apoptotic caspase 3 activity and reduced activity of the NF-κB-mediated anti-apoptotic factors A1 and cIAP-1 (19). These observations were consistent with those from an *in vivo* investigation of pancreatic cancer, in which genistein significantly improved patient survival, almost completely inhibited metastasis, and increased apoptosis by activating caspase 3 (34). Other studies have shown that genistein inhibited NF-κB-binding activity in human hepatocarcinoma cells (184), prostate cancer cells LNCaP and PC3 (47), and human alveolar epithelial carcinoma cells (38).

Resveratrol

Resveratrol has been shown to potentiate the apoptotic effects of cytokines, chemotherapeutic agents, and γ-radiation. One study assessed the *in vitro* biologic activity of resveratrol in lung cancer cell lines by examining its effect on apoptosis induced by paclitaxel (91). Simultaneous exposure to resveratrol and paclitaxel did not result in significant synergy, but pretreatment with resveratrol (10 μ*M* for 3 days) significantly enhanced the subsequent antiproliferative effect of paclitaxel. The study also examined the effects of resveratrol and paclitaxel on $p21^{waf1}$, $p27^{kip1}$, E-cadherin, EGFR, and Bcl-2 levels in non-small cell lung cancer EBC-1 cells. Resveratrol (10 μ*M* for 3 days) administered before paclitaxel increased $p21^{waf1}$ expression approximately fourfold. These results suggested that lung cancer cells exposed to resveratrol have a lowered threshold for killing by paclitaxel and, thus, that resveratrol may be a compromising alternative therapy for lung cancer (91).

Another study found that resveratrol modified the expression of apoptotic regulatory proteins and sensitized non-Hodgkin's lymphoma and multiple myeloma cell lines to paclitaxel-induced apoptosis (74). Resveratrol down-regulated the expression of anti-apoptotic proteins Bcl-xL and myeloid cell differentiation factor 1 and up-regulated the pro-apoptotic proteins Bax and Apaf-1. Furthermore, inhibition of *Bcl-xL* (an NF-κB target gene) by resveratrol was critical for chemosensitization because functional impairment of Bcl-xL mimicked resveratrol-mediated sensitization to paclitaxel-induced apoptosis (91). In contrast, another study found that *trans*-resveratrol reduced cellular death in SH-SY5Y neuroblastoma cells exposed to paclitaxel by inhibiting paclitaxel-induced activation of caspase 7 and the degradation of poly(ADP-ribose) polymerase (91).

The contrasting effects of resveratrol may be dose-dependent, whereby it potentiates the effects of cytokines and chemotherapeutic agents at higher concentrations and inhibits their effects at lower concentrations. At relatively low con-

centrations, resveratrol abrogated TNF-induced cytotoxicity and caspase activation (109) and attenuated H_2O_2-induced cytotoxicity, DNA fragmentation, and intracellular accumulation of ROI (73). Furthermore, a recent report showed that low concentrations of resveratrol (4–8 μ*M*) inhibited caspase activation, DNA fragmentation, and translocation of cytochrome *c* induced by H_2O_2, vincristine, daunorubicin, etc. (2). The effects of resveratrol at these levels were attributed to increased intracellular superoxide concentration and reduced drug-induced acidification. These results suggested that the protective or inhibitory effects of resveratrol at low concentrations are secondary to its antioxidant mechanism.

Curcumin

Several studies have shown that curcumin sensitizes cells to chemotherapy. One report showed that curcumin down-regulated NF-κB and sensitized multiple myeloma cells to vincristine and melphalan. Furthermore, the NF-κB target genes *Bcl-2*, *Bcl-xL*, *cyclin D1*, and *IL-6* were down-regulated by curcumin, leading to the suppression of proliferation and arrest of cells at the G_1/S phase of the cell cycle (25). In another study, curcumin potentiated the cytotoxic effects of doxorubicin, 5-FU, and paclitaxel in prostate cancer cells, and suppressed both the constitutive and TNF-induced activation of NF-κB (67). Likewise, doxorubicin-induced NF-κB activation was attenuated by curcumin (43). Curcumin has also been shown to modulate the activity of the MDR genes, thereby suppressing drug efflux by P-glycoprotein and leading to chemosensitization (10, 105). These results, when taken together, support the further investigation of curcumin plus chemotherapeutic drugs as a synergistic therapy.

Emodin

Emodin may sensitize cancer cells to chemotherapy. For example, it sensitized HeLa cells to arsenic trioxide via generation of ROI and ROI-mediated inhibition of two major prosurvival transcription factors, NF-κB and activator protein 1 (208), and it effected apoptosis in human promyeloleukemic HL-60 cells by inducing caspase 3, but independently of ROI (40). In a study using several chemotherapeutic agents including *cis*-platinol (abiplastin), doxorubicin (adriablastin), 5-FU, and tyrosine kinase inhibitor STI 571, aloe-emodin potentiated their inhibitory effects on Merkel cell carcinoma cells (52). In cholangiocarcinoma cells and epithelial stem-like cells, emodin and celecoxib synergistically suppressed cell growth and increased activation of caspases 9 and 3; this mechanism was suggested to work through Akt inhibition (94). In Her-2/neu-overexpressing breast cancer cells, emodin inhibited Her2/neu tyrosine kinase activity, suppressed cell growth, induced cell differentiation, and sensitized cells to paclitaxel chemotherapy (211, 212, 213). In Her-2/neu-overexpressing non-small cell lung cancer cells, emodin suppressed cell proliferation, reduced Her-2/neu tyrosine kinase activity, and enhanced the inhibitory effects of cisplatin, doxorubicin, and etoposide on cell proliferation (210). However, one study showed no chemosensitizing effect of emodin in ovarian cancer cells (64).

Flavopiridol

Flavopiridol potentiates the effects of chemotherapy in several types of cancer. For example, flavopiridol potentiated the cytotoxic effects of mitomycin c by promoting drug-induced apoptosis in breast and gastric cancer cells; this effect was dependent on the order of treatment (165). An investigation using non-small cell lung cancer cells revealed that the sequence of administration was important to the sensitization effects of flavopiridol: Flavopiridol enhanced the cytotoxic effects of paclitaxel, cytarabine, topotecan, doxorubicin, and etoposide only when administered after treatment; only flavopiridol plus cisplatin showed sequence-independent synergy (29). Flavopiridol sensitized retinoblastoma protein-deficient sarcoma cells to doxorubicin-induced cell killing (101) and colon cancer xenografts cells to CPT-11 through activation of caspase 3 and cleavage of anti-apoptotic factors (123). Furthermore, flavopiridol enhanced the induction of apoptosis by gemcitabine in human pancreatic, gastric, and colon cancer cell lines (77). The mechanism accounting for the sensitization effects of flavopiridol may involve its inhibition of NF-κB. Indeed, in one study, flavopiridol inhibited NF-κB, which in turn down-regulated cyclin D1, COX-2, and MMP-9 (187). Similarly, flavopiridol inhibited NF-κB-dependent gene transcription and enhanced TNF- and TNF-related apoptosis-inducing ligand-induced cytotoxicity (85). Yet another study showed that flavopiridol enhanced tumor cell apoptosis by inhibiting survivin phosphorylation (201).

Silymarin

Silymarin may potentiate the effects of chemotherapy on cancer. In MDR breast cancer cells, it potentiated doxorubicin cytotoxicity by inhibiting P-glycoprotein ATPase activity, which is responsible for cellular efflux of cytotoxic substances (214). This observation was consistent with a recent report demonstrating that silymarin and resveratrol significantly increased breast cancer-resistant protein substrates in breast cancer-resistant protein-overexpressing cells (44). Another study demonstrated the synergistic effects of silybin plus cisplatin or doxorubicin in breast cancer and ovarian cancer cells (164). Likewise, silibinin strongly synergized the growth-inhibitory effect of doxorubicin in prostate cancer cells and was associated with cell cycle arrest (195).

SENSITIZATION OF TUMOR CELLS BY POLYPHENOLS TO RADIATION

Genistein

Genistein and radiation have been suggested to be synergistic. In prostate cancer cells, genistein significantly inhibited DNA synthesis, cell growth, and colony formation and potentiated the effect of low doses of photon (200–300 cGy) or neutron (100–150 cGy) radiation, the latter effect being more pronounced with the combined treatment than with genistein or radiation alone (65). In an *in vivo* murine lung cancer model, chemoradiotherapy plus genistein resulted in significantly lower tumor volume, microvessel density, and vascular endothelial growth factor level than did

chemoradiotherapy alone (111). In human esophageal cancer cell lines, genistein greatly enhanced radiosensitivity by suppressing radiation-induced activation of the survival signals Akt and p42/p44 extracellular signal-regulated protein kinase (4). Finally, in a Bcr/abl-positive leukemic cell line, genistein increased radiation-induced apoptosis and promoted arrest of the G_2 phase cell cycle (138).

Resveratrol

Resveratrol may induce radiosensitization. Reports have suggested that increased activation of NF-κB and up-regulation of NF-κB-mediated expression of COX-2 and of 5-lipooxygenase (5-LOX) contribute significantly to radioresistance (39, 190) and that inhibition of NF-κB, COX-2, and 5-LOX induces radiosensitization (30, 149, 157). Resveratrol has been shown to down-regulate NF-κB (109), COX-2 (177), and 5-LOX (108). Using clonogenic cell survival assays, one study showed that pretreatment with resveratrol enhanced HeLa and SiHa cell killing and induced an early S phase cell-cycle checkpoint arrest after the cells were exposed to ionizing radiation (216).

Curcumin

Resistance to radiation was suggested in one study to be caused by increased expression of NF-κB-induced prosurvival genes, such as *Bcl-2* and *Bcl-xL,* in response to radiation (124). In that investigation, curcumin plus radiation inhibited NF-κB activation in DU-145 and LNCaP prostate cancer cells and resulted in down-regulation of Bcl-2, and curcumin alone enhanced caspase activation and cytochrome *c* release in both cell types, leading to increased apoptosis. Curcumin has also been shown to sensitize PC3 prostate cancer cells to radiation (41).

Green tea

A few studies have suggested that EGCG could modulate radiotherapy. A study using human embryonic endothelial cells found that ionizing radiation induced expression of pro-angiogenesis genes *membrane type 1-MMP* and *caveolin-1* and that this expression was abrogated by pretreatment with EGCG (9). These results demonstrated that radiotherapy, which is better known for its ability to promote cancer cell death, may increase the expression of NF-κB-mediated target genes that may be inhibited by EGCG (48, 143). Another investigation showed that EGCG suppressed oncogenic transformation of mouse embryonic fibroblast C3H10T1/2 cells (90).

Flavopiridol

Growing evidence suggests that flavopiridol may sensitize tumor cells to radiation. In one study, flavopiridol significantly enhanced the induction of apoptosis by radiation in colon and gastric cancer cells; this effect was optimal when flavopiridol followed the radiation treatment (78). Other investigations showed that flavopiridol strongly enhanced the response of ovarian carcinoma cells to radiation and suggested that the underlying mechanisms included inhibition of sublethal DNA damage repair and cell cycle redistribution; in addition, transcriptional regulation by flavopiridol may have been involved (78).

POLYPHENOLS PROTECTS NORMAL CELLS/ORGANS FROM CHEMO/RADIOTHERAPY

Curcumin

Several reports have also identified curcumin as a potent protector against radiation. Oral administration of curcumin (200 μmol/kg) significantly reduced lung toxicity in rats treated with whole-body radiation (10 Gy in five fractions) (191), and curcumin reduced liver and serum lipid peroxidation in rats treated with radiation. In adition, reduced radiation-induced genotoxicity (chromosomal damage) was observed in mice treated with oral curcumin (400 mmol/kg) plus whole-body radiation (1.5–3.0 Gy) (192). In another study, dietary curcumin significantly decreased acute toxicity from whole-body radiation in rats and decreased the incidence of mammary and pituitary tumors at 1-year follow-up (71). These findings, when taken together, demonstrated that curcumin is a promising radioprotective agent and warrants further investigation.

Curcumin has been shown to protect cells from doxorubicin-induced renal injury (200), cardiotoxicity (199), and gastrointestinal injury (196). These protective effects could be secondary to the suppression of oxidative stress and inflammatory damage (80). One study revealed that curcumin inhibited camptothecin-, mechlorethamine-, and doxorubicin-induced apoptosis in tissue cultures of MCF-7, MDA-MB-231, and BT-474 human breast cancer cells by up to 70%; inhibition occurred after relatively brief 3-h exposures to curcumin, or at curcumin concentrations of 1 μ*M* (176). In an *in vivo* model of human breast cancer, dietary supplementation with curcumin significantly inhibited cyclophosphamide-induced tumor regression, and it was concluded that dietary curcumin could inhibit chemotherapy-induced apoptosis by inhibiting reactive oxygen species generation and blocking of c-Jun N-terminal kinase function. However, because NF-κB is a major regulator of the transcriptional response to cellular oxidative stress (54), it is tempting to believe that the suppression of NF-κB-induced gene expression is responsible, at least in part, for these therapeutic effects.

CAPE

Several reports have indicated that CAPE has strong chemoprotective properties. Our investigation demonstrated that pretreatment with CAPE significantly attenuated doxorubicin-induced cardiotoxicity in rats and suggested that these effects may have been due to its antioxidant properties (51). The free-oxygen-radical scavenging properties of CAPE in rats account for its protective effects on renal tissue treated with cisplatin (135) and against lung toxicity after exposure to bleomycin (136). CAPE also protected rat renal cells from ischemia-reperfusion injury (61). CAPE has been shown to

inhibit NF-κB (127), which may account for its chemopreventive effects in intestinal, colon, skin, and liver cancers and reduce inflammation in rats exposed to radiation (106). Furthermore, CAPE suppressed COX-2 expression in human oral epithelial cells and in a rat model of inflammation (115). It may also help to prevent cancer progression by inhibiting angiogenesis, tumor invasion, and metastasis in mice (104) and, when combined with sulindac, by suppressing lung adenocarcinoma motility (171).

Silymarin

Silymarin appears to protect rat cardiomyocytes against anthracycline-induced oxidative stress, perhaps through its effects on cell membrane stabilization (176). These results were consistent with those from another report that suggesed silymarin may prevent doxorubicin-mediated damage to rat heart membrane, possibly through a free-radical scavenging mechanism (148).

Ginger

Ginger may prevent chemotherapy and radiotherapy-induced nausea. In shrews, rats, and dogs, ginger inhibited chemotherapy-induced gastric emptying and showed comparable results to standard antiemetic compounds (167, 168, 207). Furthermore, ginger reduced radiation-related sickness and free-radical production in mice (72).

ENHANCEMENT OF DRUG BIOAVAILABILITY BY POLYPHENOLS

Piperine

Piperine, an ingredient of black pepper, increases the bioavailability of chemotherapeutic drugs. A study using hepatic tissue in rats demonstrated that piperine was a nonspecific inhibitor of drug metabolism and discriminated little between different cytochrome P-450 forms (13), and another study found that it modified the rate of glucuronidation by lowering endogenous UDP-glucuronic acid content and inhibiting transferase activity (174). This observation was consistent with that of another report that suggested piperine was a potent inhibitor of UDP-glucose dehydrogenase in rats and that its effect on glucuronidation was stronger in the intestines than in the liver (154). In a clinical crossover study in which six subjects in each group received a single dose of propranolol or theophylline alone or piperine, piperine enhanced the systemic availability of oral propranolol and theophylline (15). In rat jejunum cells, piperine significantly stimulated γ-glutamyl transpeptidase activity, enhanced the uptake of radiolabeled L-leucine, L-isoleucine, and L-valine, and increased lipid peroxidation, suggesting that piperine may increase intestinal permeability through interaction with the mucosal lipid environment (76). These results were consistent with those from studies that showed that piperine modulates membrane dynamics and permeation characteristics and results in an increase in the small intestine absorptive surface, thereby enabling efficient permeation through the epithelial barrier (82, 83). Piperine was also shown to inhibit both the drug transporter P-glycoprotein and the major drug-metabolizing enzyme CYP3A4, *in vitro*, indicating that dietary piperine could affect plasma concentrations of P-glycoprotein and CYP3A4 substrates in humans (22). Using rat liver, another study showed that piperine markedly inhibited aflatoxin metabolism *in vitro* and *in vivo*, suggesting enhanced aflatoxin bioavailability (6). Piperine was also shown to enhance curcumin bioavailability in both rats and humans (173). These results, when taken together, warrant the further investigation of piperin as a supplement to chemotherapeutic drugs to enhance their bioavailability.

CONCLUSIONS

Cancer is a multifactorial disease that, in many cases, requires multimodal therapy, including chemotherapy and radiotherapy. The mechanisms for modulation of signaling pathways that account for the efficacy of these treatments have become increasingly clear in recent years, leading to the clinical and laboratory study of numerous biologic modifiers that may increase their potency and reduce their adverse effects. Despite extensive use for thousands of years because of their alleged medicinal value, plant polyphenols have only recently received significant attention in the literature for their ability to modulate a number of signaling pathways that lead to the initiation and progression of cancer. The ability of these products to sensitize tumor cells to chemotherapy and radiotherapy often correlates with their ability to inhibit well-studied molecular markers. The data are still limited, but the results appear promising, and the use of plant polyphenols as potential modulators of chemotherapy and radiotherapy deserves further investigation.

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ABBREVIATIONS

CAPE, caffeic acid phenethyl ester; COX-2, cycloxygenase-2; EGCG, (−)-epigallocatechin gallate; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil; IAP, inhibitor of apoptosis protein; IκBα, inhibitory subunit of nuclear factor-κB; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; 5-LOX, 5-lipooxygenase; MDR, multidrug resistance; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; PI-3K, phosphatidylinositol 3-kinase; ROI, reactive oxygen intermediates; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor.

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