Nutrition and Cancer

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t775653687

Curcumin, the Golden Spice From Indian Saffron, Is a Chemosensitizer and Radiosensitizer for Tumors and Chemoprotector and Radioprotector for Normal Organs

Ajay Goel[a]; Bharat B. Aggarwal[b]
[a] Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, Texas, USA [b] Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Online publication date: 04 October 2010

To cite this Article Goel, Ajay and Aggarwal, Bharat B.(2010) 'Curcumin, the Golden Spice From Indian Saffron, Is a Chemosensitizer and Radiosensitizer for Tumors and Chemoprotector and Radioprotector for Normal Organs', Nutrition and Cancer, 62: 7, 919 — 930
To link to this Article: DOI: 10.1080/01635581.2010.509835
URL: http://dx.doi.org/10.1080/01635581.2010.509835

Nutrition and Cancer, 62(7), 919–930

ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635581.2010.509835

Routledge
Taylor & Francis Group

Curcumin, the Golden Spice From Indian Saffron, Is a Chemosensitizer and Radiosensitizer for Tumors and Chemoprotector and Radioprotector for Normal Organs

Ajay Goel
Gastrointestinal Cancer Research Laboratory, Department of Internal Medicine, Charles A. Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, Texas, USA

Bharat B. Aggarwal
Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

Curcumin (diferuloylmethane), the yellow pigment in Indian saffron (*Curcuma longa;* also called turmeric, haldi, or haridara in the East and curry powder in the West), has been consumed by people for centuries as a dietary component and for a variety of proinflammatory ailments. Extensive research within the last decade in cell culture and in rodents has revealed that curcumin can sensitize tumors to different chemotherapeutic agents including doxorubicin, 5-FU, paclitaxel, vincristine, melphalan, butyrate, cisplatin, celecoxib, vinorelbine, gemcitabine, oxaliplatin, etoposide, sulfinosine, thalidomide, and bortezomib. Chemosensitization has been observed in cancers of the breast, colon, pancreas, gastric, liver, blood, lung, prostate, bladder, cervix, ovary, head and neck, and brain and in multiple myeloma, leukemia, and lymphoma. Similar studies have also revealed that this agent can sensitize a variety of tumors to gamma radiation including glioma, neuroblastoma, cervical carcinoma, epidermal carcinoma, prostate cancer, and colon cancer. How curcumin acts as a chemosensitizer and radiosensitizer has also been studied extensively. For example, it downregulates various growth regulatory pathways and specific genetic targets including genes for NF-κB, STAT3, COX2, Akt, antiapoptotic proteins, growth factor receptors, and multidrug-resistance proteins. Although it acts as a chemosensitizer and radiosensitizer for tumors in some cases, curcumin has also been shown to protect normal organs such as liver, kidney, oral mucosa, and heart from chemotherapy and radiotherapy-induced toxicity. The protective effects of curcumin appear to be mediated through its ability to induce the activation of NRF2 and induce the expression of antioxidant enzymes (e.g., hemeoxygenase-1, glutathione peroxidase, modulatory subunit of gamma-glutamyl-cysteine ligase, and NAD(P)H:quinone oxidoreductase 1, increase glutathione (a product of the modulatory subunit of gamma-glutamyl-cysteine ligase), directly quench free radicals, and inhibit p300 HAT activity. These preclinical studies are expected to lead to clinical trials to prove the potential of this age-old golden spice for treating cancer patients.

Submitted 27 February 2010; accepted in final form 16 July 2010.
Address correspondence to Bharat B. Aggarwal, Cytokine Research Laboratory, Department of Experimental Therapeutics, and Department of Radiation Oncology, The University of Texas, M. D. Anderson Cancer Center, Houston, TX 77030. Phone: 713-792-3503. Fax: 713-794-1613. E-mail: aggarwal@mdanderson.org

INTRODUCTION

Curcumin (1,7-bis(4-hydroxy 3-methoxy phenyl)-1,6-heptadiene-3,5-dione), a polyphenol, is a natural compound that is derived from turmeric, the powdered rhizome of the medicinal plant *Curcuma longa Linn* (also known as turmeric). The yellow-pigmented fraction of turmeric primarily consists of various curcuminoids including curcumin I (or curcumin, ≈77%), curcumin II (demethoxycurcumin, ≈17%) and curcumin III (bisdemethoxycurcumin, ≈3%). The curcuminoid complex, collectively, is frequently referred to as Indian saffron, yellow ginger, yellow root, and *haldi*. Curcumin has been used for centuries throughout Asia as a food additive, cosmetic, and as a traditional herbal medicine. As a spice, it provides curry with its distinctive color and flavor. Furthermore, traditional Indian medicine has considered curcumin a drug effective for various respiratory conditions (asthma, bronchial hyperactivity, and allergy) as well as for other disorders including anorexia, coryza, cough, hepatic diseases, and sinusitis (1,2). Over the past decade, several studies have substantiated the potential prophylactic or therapeutic value of curcumin and have unequivocally supported reports of its anti-inflammatory (3,4), antioxidant (5), anticarcinogenic (6–8), hepatoprotective (9), thrombosuppressive (10), cardioprotective (11), antiarthritic (12), and anti-infectious (13) properties. One of the most compelling reasons for continued interest in exploring the cancer chemopreventive and therapeutic uses of curcumin has been curcumin's ability to influence a diverse range of molecular targets within cells. To date, no studies have reported any toxicity associated with the use of curcumin in either animals or humans.

Undisputed scientific evidence suggests that curcumin suppresses all 3 stages of carcinogenesis: initiation, promotion, and progression. Several genetic targets may mediate cancer-related efficacy of curcumin, but inhibition of nuclear factor kappa B (NF-κB) and subsequent downregulation of various NF-κB-related proinflammatory pathways are very likely the primary features accounting for its efficacy (14). Curcumin has been studied for its chemopreventive potential in a wide variety of cancers, in both preclinical studies and in clinical trials (reviewed in Goel et al. (15)). However, recent data indicate that in addition to its chemopreventive role, curcumin has tremendous potential as a chemosensitizer and radiosensitizer as well as chemoprotector and radioprotector. This is of great interest given the plethora of diverse molecular targets curcumin can regulate. The fact that curcumin can achieve all of these effects without any toxicity makes developing curcumin as an adjunct to standard chemotherapy and radiotherapy an important goal. It may offer a therapeutic advantage in the clinical management of various refractory tumors over other, standard modalities.

Constant challenges in cancer chemotherapy and radiotherapy are the adverse toxicity and resistance associated with these treatment regimens. Among these are hair loss, diarrhea, fatigue, mouth sores, and low blood counts. Many patients experience chemotherapy-induced toxicity because these drugs are heavily protein bound and can damage normal cells and tissues in many ways. As much as we understand now that tumor initiation and development is a multistep process involving a series of genetic and epigenetic events, why most therapeutic approaches become increasingly ineffective over the course of treatment remains poorly understood. Regardless, cancer cells become resistant to chemotherapeutic drugs through mechanisms that may involve mutation or overexpression of the drug's specific target, drug inactivation, or efflux of the drug out of the cell (16).

Historically, chemotherapeutic strategies have used a variety of single drugs or drug combinations that interfere with cellular machinery in order to achieve the desired effect. Knowledge gained from these studies and improved understanding of the molecular alterations that are present within tumor cells have paved the way for the development of targeted therapies. Interestingly, resistance appears to occur not only with traditional chemotherapy but also to targeted chemotherapies such as herceptin, which targets human epidermal growth factor receptor 2 (HER-2) in breast cancer (17); tamoxifen, which targets estrogen receptor (ER) in breast cancer (18); remicade or infliximab, which targets tumor necrosis factor (TNFα) in multiple inflammatory diseases (19,20); gleevac, targeted against the kinase activity of BCR-ABL gene in chronic myelogenous leukemia (21); and erbitux or gefitinib, which inhibits epidermal growth factor receptor (EGFR) kinase (22). In some instances, it becomes even more complex when tumors in some patients recur after therapy and show resistance to multiple drugs, a phenomenon often referred to as multidrug resistance (MDR) (23). MDR tumors are not only resistant to many combinations of cancer chemotherapy, but they also tend to metastasize and are a frequent cause of cancer-related deaths in these patients. Therefore, understanding the molecular basis of MDR and developing drugs and treatment regimens to prevent tumor resistance is an important priority.

Drug resistance and toxicity can also be dictated by several factors including metabolism and excretion of the drug, inadequate or poor access of the drug to the tumor, and the role of various drug metabolizing enzymes such as cytochrome P450s, which are often overexpressed (24). In recent years, a new concept has been proposed that suggests that another important reason why cancer therapies might fail and tumors develop relapse is because these strategies do not target rare tumor cells or so-called cancer stem cells. According to this hypothesis, which is still in its nascent stages, a small fraction of tumor cells has the unlimited capacity to self-renew, have extensive unlimited slow proliferation potential, and can give rise to phenotypically diverse progeny of cancer cells with variable proliferative capacity (25,26). It is believed that these cancer stem cells are often resistant to chemotherapy and radiation, and treatments that substantially reduce tumor mass by removing proliferating tumor cells often fail to target these stem cells and cure patients completely with certain cancers. According to this viewpoint, these cancer stem cells are immune to any therapies, maintain their "stemness," and continue to repopulate tumor mass with a continuous supply of new cancer cells (27). This new understanding has promoted researchers and pharmaceutical companies to shift their efforts to develop targeted or more effective anticancer therapies that could either induce differentiation of cancer stem cells to lose their stemness or completely eliminate this population.

In this context, curcumin seems to offer an ideal agent because over the last two decades, significant evidence has indicated anticancer potential of curcumin. In fact, it is very encouraging to notice that unlike many "targeted" chemotherapeutic drugs that suffer from toxicity and resistance concerns, curcumin by itself can target several of these molecular targets/pathways without any associated toxicity or resistance. In fact, newer data suggest that in addition to its chemopreventive ability, curcumin can sensitize many human cancers to chemotherapy and radiation, as well as afford protection against the toxicity of these treatment regimens. This review summarizes the potential role of curcumin as both a chemosensitizer and radiosensitizer as well as its ability to function as a chemoprotector and radioprotector in different forms of tumors.

CURCUMIN AS A CHEMOSENSITIZER

Curcumin not only acts as a cancer preventive, but data suggest that curcumin treatment may be able to eliminate chemoresistant cancers by sensitizing these tumors to chemotherapy and radiation by increasing the rate of apoptosis. In this section, we summarize the current state of the biomedical literature on curcumin as a chemosensitizer. Data from both in vitro and in vivo studies have supported the potential chemosensitizing

TABLE 1
Curcumin potentiates the effect of chemotherapy[a]

Chemo Type	Year (Reference)
Chemosensitization in vitro	
Potentiates cytotoxic effects of doxorubicin, 5-FU, and paclitaxel against prostate cancer cells	2002 (41)
Sensitizes multiple myeloma cells to vincristine and melphalan	2003 (55)
Enhances cytotoxicity of cisplatin against ovarian cancer cells in culture	2003 (46)
Potentiates antitumor effects of sodium butyrate against erythroleukemic cells	2003 (57)
Potentiates growth inhibition effects of 5-FU against human gastric carcinoma cells in culture	2004 (35)
Exhibits both additive and sub-additive antitumor and apoptotic effects of doxorubicin against liver cancer cells	2005 (39)
Potentiates the antitumor and apoptotic effects of cisplatin against hepatocellular carcinoma cells	2005 (39)
Enhances antitumor effects of taxol against cervical cancer cells in culture	2005 (49)
Potentiates the cytotoxicity of paclitaxel toward breast cancer cells in culture	2005 (43)
Potentiates apoptotic effects of celecoxib against human pancreatic cancer cells	2005 (36)
Synergistic effects with celecoxib in growth inhibition in colon cancer cells	2005 (33)
Enhances apoptotic effects of cisplatin against cervical cancer SiHa cells, but not HeLa cells	2005 (48)
Enhances apoptotic effects of vinorelbine against human squamous cell lung carcinoma cell line	2005 (50)
Augments apoptotic effects of cisplatin against ovarian cancer and breast cancer cell lines	2006 (44)
Has no effect on cytotoxic effects of paclitaxel against human ovarian cancer and breast cancer cell lines	2006 (44)
Enhances antitumor effects of 5-FU and 5-FU plus oxaliplatin (FOLFOX) against colon cancer cells	2006 (32)
Potentiates apoptosis induced by gemcitabine and paclitaxel in bladder cancer cells in culture	2007 (53)
Potentiates antitumor activity of docetaxel against ovarian cancer cell lines	2007 (47)
Increases antitumor effects of oxaliplatin against colorectal cancer cells in culture	2007 (29)
Augments cytotoxic effects of gemcitabine on pancreatic adenocarcinoma cell line	2007 (37,38)
Enhances the antitumor effects of gemcitabine against prostate cancer cells in culture	2007 (42)
Potentiates cytotoxicity of cisplatin, etoposide, camptothecin, and doxorubicin against human and rat glioma cells	2007 (54)
Enhances antitumor effects of oxaliplatin against colorectal cancer cell lines	2007 (30)
Enhanced the antitumor effects of vincristine and PDE4 inhibitors in B-CLL from patients	2007 (58)
Enhances antitumor effects of 5-FU and FOLFOX against colon cancer cells	2008 (31)
Augments effects of sulfinosine on multi drug resistant human non-small cell lung carcinoma cells	2008 (51)
Potentiate effects of gemcitabine in pancreatic cancer cells	2008 (40)
Sensitizes lung cancer cells to cisplatin-induced apoptosis in lung cancer cells	2009 (52)
Potentiates the effect of thalidomide and bortezomib in multiple myeloma cells	2009 (56)
Chemosensitization in vivo	
Augments growth inhibitory effects of celecoxib against colorectal cancer in rats	2006 (34)
Enhances antitumor effects of oxaliplatin against colorectal cancer in mice	2007 (30)
Potentiates antitumor activity of gemcitabine against pancreatic cancer in mice	2007 (38)
Potentiates antitumor activity of docetaxel against ovarian cancer in mice	2007 (47)
Enhances the antitumor effects of gemcitabine against prostate cancer in mice	2007 (42)
Potentiates the effect of thalidomide and bortezomib against multiple myeloma in nude mice	2009 (56)
Chemoresistance in vitro	
Antagonizes apoptotic effects of camptothecin, mechlorethamine, and doxorubicin in human breast cancer cells	2002 (45)
Reduces nephrotoxicity of cisplatin in rats	2007 (59)
Chemoresistance in vivo	
Antagonizes apoptotic effects of cyclophosphamide in mice	2002 (45)

[a]Abbreviations are as follows: 5-FU, 5-fluorouracil; HeLa, a cervical carcinoma cell line derived from Henrietta Lacks; SiHa, a cervical carcinoma cell line.

ability of curcumin in multiple cancers and have provided evidence for curcumin's use singly or as an adjunct to current chemotherapeutic drugs. Table 1 summarizes these data in order of appearance of these reports in the published literature.

Colon Cancer

Cancers of the gastrointestinal tract, especially colon cancer, remain leading causes of cancer-related deaths in the developed nations, including the United States (28). Although current chemotherapeutic regimens targeting colon cancer have continuously evolved and have significantly improved survival rates by limiting the spread of metastatic disease over the last decade, a large majority of patients develop chemoresistance to these platinum-based and/or 5-fluorouracil (5-FU)-based drug regimens over the course of chemotherapy. Use of curcumin singly or in combination with chemotherapeutic drugs may help overcome some of the resistance issue and improve the efficacy of current chemotherapeutic drugs. In one study, Howells and colleagues (29) investigated the antiproliferative potential of both curcumin and oxaliplatin singly and in combination in normal colonic (HCEC) and colon cancer cell lines (HT29, p53 mutant and HCT116, p53 wild type). Both curcumin and oxaliplatin displayed significant antiproliferative potential in both HT29 and HCT116 cells; and the order of sensitivity to oxaliplatin was HCT116>HT29>HCEC, whereas order of sensitivity to curcumin was HT29>HCT116>HCEC. Apoptosis was enhanced by both compounds, and up to 16-fold increase in expression of p53 protein was observed when the two agents were used in combination. This study suggested that when used in combination with oxaliplatin, curcumin may enhance efficacy of this drug in both p53 mutant and wild type colorectal tumors. Since curcumin in its free form may be poorly absorbed in the gastrointestinal tract, a liposomal encapsulated preparation of curcumin was evaluated individually and in combination with oxaliplatin in LoVo and Colo205 human colorectal cancer cell lines (30). Liposomal curcumin treatment showed a synergistic effect with oxaliplatin at a ratio of 4:1 in LoVo cells in vitro and a significant tumor growth inhibition in Colo205 and LoVo xenografts in mice, substantiating the chemosensitizing ability of this phytochemical (30).

When curcumin treatment was evaluated in conjunction with either 5-FU alone or 5-FU + oxaliplatin (FOLFOX), it resulted in significantly greater growth inhibition and increased apoptosis in HCT116 and HT29 colon cancer cells than that caused by curcumin, 5-FU, curcumin + 5-FU, or FOLFOX alone (31). Such effects were associated with decreased expression and activation of EGFR, HER-2, HER-3, and insulin-like growth factor 1 receptor (IGF-1R), together with their downstream signaling targets such as Akt and cyclooxygenase-2 (Cox-2) (31). It was concluded that the potentiation of curcumin's effect with FOLFOX were due to attenuation of EGFR and IGF-1R signaling pathways (31). Similarly, Du and coworkers (32) recently demonstrated synergistic inhibition of cell growth and sixfold reduction in Cox-2 expression after combination treatment with curcumin and 5-FU in HT-29 cells. The importance of the Cox-2 pathway in mediating efficacy of curcumin was further highlighted in another report in which curcumin potentiated the growth inhibitory effect of celecoxib in multiple colon cancer cell lines (33). In a follow-up study, these investigators determined the chemopreventive effects of celecoxib and curcumin alone and in combination using the 1,2-dimethylhydrazine (DMH) rat model (34). In this in vivo study, curcumin augmented the growth inhibitory effect of celecoxib as indicted by significantly fewer aberrant crypt foci in the combined curcumin and celecoxib group compared to when these agents were fed individually (34). Such effects of curcumin are not limited to colon cancer, but others have shown similar results in gastric (35), pancreatic (36–38), and liver cancers (39) as well.

Gastric Cancer

Using physiologically relevant and very small doses of curcumin together with 5-FU, much stronger G2/M cell cycle block was achieved in AGS gastric cancer cells compared to the block in control groups in which cells were treated with single agents (35).

Pancreatic Cancer

Pancreatic adenocarcinoma is a fatal disease with very poor prognosis. Data indicate that specific Cox-2 inhibitors (such as celecoxib) may have some promise in this disease. However, sustained and robust Cox-2 inhibition for the long term is a practical challenge in managing these individuals. In this regard, Lev-Ari et al (36) questioned whether curcumin may potentiate growth inhibitory effects of a celecoxib in a panel of Cox-2-expressing (P-34) and low/nonexpressing (MIA PaCa and Panc-1) human pancreatic cell lines. Curcumin synergistically augmented growth inhibition of celecoxib in Cox-2-expressing cell lines, suggesting that celecoxib may be used at much lower and safer concentrations. The same group of investigators later reported similar effects of curcumin when used in combination with the first-line chemotherapeutic agent gemcitabine in pancreatic cancer cells (36). These data were further substantiated by other studies in which it has been demonstrated that curcumin potentiated the antitumor effects of gemcitabine in cultured pancreatic adenocarcinoma cells by suppressing cellular proliferation and activating NF-κB and other genetic targets of the NF-κB signaling pathway (37,38,40) In vivo studies with tumors from nude mice injected with pancreatic cancer cells and treated with both curcumin and gemcitabine showed significant reduction in tumor volume, Ki-67 proliferation index, NF-κB activation, expression of NF-κB gene products [cyclin D1, c-myc, B-cell non-Hodgkin lymphoma-2 (Blc-2), Bcl extra large (Bcl-xl), CIAP-1, Cox-2, matrix metalloproteinase (MMP), and vascular epithelial growth factor (VEGF)], and suppression of angiogenesis compared to tumors from control animals (38).

Liver Cancer

While investigating antitumor effects of curcumin, singly or together with cisplatin or doxorubicin, it was noticed that the combination of curcumin with cisplatin resulted in synergistic activity against liver cancer; whereas with doxorubicin, the effects were at best additive (39). Such effects were in part mediated by downregulation of expression of different genes including c-myc, Bcl-xl, c-IAP-2, NAIP, and XIAP (39).

Prostate Cancer

The literature on similar potential for curcumin in other solid organ malignancies has grown continuously over the last decade. In this context, while studying the modulatory effects of curcumin on the cytotoxic effects of chemotherapeutic agents (5-FU, doxorubicin, and paclitaxel) in androgen-independent prostate cancer cell lines (PC-3 and DU-145), a significant degree of G1-cell cycle arrest was observed in the combination treatment group (41). It was proposed that such cell cycle changes may be associated with an increase in p21 and C/EBP β and inhibition of constitutive and TNFα-induced NF-κB activation (41). Curcumin treatment in combination with gemcitabine in PC-3 cells inhibited growth and increased apoptosis but via downregulation of MDM2, an ubiquitin E3 ligase of p53 gene (42). In further support of these data, when experiments were performed in tumor-bearing nude mice, curcumin inhibited growth of PC3 xenografts and enhanced the antitumor efficacy of gemcitabine and radiation (42).

Breast Cancer

Presently, other than radiation and chemotherapy, there is no effective therapy for metastatic breast cancer. Curcumin is a potent NF-κB suppressor, while most conventional chemotherapeutic agents activate NF-κB. Keeping this in mind, Aggarwal and colleagues (43) hypothesized that curcumin potentiates the effects of chemotherapy in advanced breast cancer and inhibits lung metastasis. Using paclitaxel (Taxol)-resistant breast cancer cells and a human breast cancer xenograft model, they showed that curcumin inhibited paclitaxel-induced NF-κB activation, and these effects were mediated through inhibition of IκBα kinase activation and IκBα phosphorylation and degradation (43). In addition, curcumin also suppressed the paclitaxel-induced expression of several antiapoptotic (XIAP, IAP-1, IAP-2, Bcl-2, and Bcl-xl), proliferative (Cox-2, c-myc, and cyclin D1), and metastatic (VEGF, MMP-9, and ICAM-1) proteins (43). Curcumin also inhibited the mono-ubiquitination of the FANCD2 protein and sensitized ovarian and breast tumor cells lines to cisplatin through enhanced apoptotic death (44).

Generation of reactive oxygen species (ROS) and activation of the c-Jun N-terminal protein kinase (JNK) pathway is a frequent manifestation of proapoptotic ability offered by many chemotherapeutic drugs. Somasundaram et al. (45) asked whether curcumin may antagonize the antitumor effects of various chemotherapeutic drugs in both cultured cells and an animal model of breast cancer. Curcumin inhibited camptothecin-, mechlorethamine-, and doxorubicin-induced apoptosis of MCF-7, MDA-MB-231, and BT-447 human breast cancer cells (45). In animal experiments, curcumin significantly inhibited cyclophosphamide-induced tumor regression, suggesting that dietary curcumin can inhibit chemotherapy-induced apoptosis via inhibition of ROS generation and blocking JNK signaling.

Ovarian Cancer

High levels of certain serum proinflammatory cytokines, including IL-6, have been associated with poor prognosis and cisplatin resistance in multiple human cancers. Since curcumin inhibits production of many cytokines, its effects were studied in CAOV3 ovarian cancer cells, singly, and in combination with cisplatin (46). As anticipated, curcumin inhibited IL-6 production in cisplatin-treated cells, suggesting that one mechanism for curcumin action is by reduction of autologous production of IL-6, which has potential for enhancing drug sensitivity in multiple human cancers. In another study, curcumin when given together with docetaxel to HeyA8 and HeyA8-MDR athymic mice, significantly reduced tumor growth, cellular proliferation, and microvessel density compared to controls, emphasizing the potential of curcumin-based therapies in patients with ovarian cancer (47).

Cervical Cancer

NF-κB activation plays a pivotal role in drug-mediated apoptosis and possible resistance in various human cancers. Using a cervical cancer model of HeLa and SiHa cells that differ in their response to cisplatin treatment, it was demonstrated that SiHa cells, which are more resistant to cisplatin, showed much lesser cell viability when NF-κB binding was blocked by curcumin (48). Such effect was not evident in cisplatin-responsive HeLa cells. These data suggest that NF-κB may contribute to cisplatin-induced chemoresistance in cervical cells and highlights the potential applicability of combination therapy with NF-κB inhibitors such as curcumin in this scenario. Curcumin was also shown to downregulate taxol-induced activation of NF-κB and phosphorylation of serine/threonine kinase Akt in 293 cervical cells and 293 embryonic kidney cells (49).

Lung Cancer

Due to toxicity concerns and older age, some lung cancer patients are not suited for classical cancer chemotherapy. Combination approaches using phytochemicals such as curcumin are being advocated as a possible alternative to get around some of the practical constraints posed by conventional chemotherapeutic drugs. Pretreatment of squamous cell lung carcinoma H520 cells with curcumin, followed by chemotherapy using vinorelbine, enhanced the apoptotic capacity of this drug (50), suggesting that curcumin can act as an adjuvant chemotherapeutic agent and enhance the chemotherapeutic drugs in a subset of lung cancer patients.

MDR is a frequent limiting factor for a successful chemotherapeutic regimen. However, data indicate that curcumin can

overcome MDR induced by sulfinosine in NCI-H460/R non-small-cell lung carcinoma cells (51). Combination of curcumin and sulfinosine produced more pronounced S and G2/M cell cycle arrest compared to treatment with these agents individually. When cisplatin was used as a chemotherapeutic drug, curcumin sensitized cisplatin-induced apoptosis in non-small-cell lung cancer H460 cells via downregulation and degradation of Bcl-2 (52).

Brain and Bladder Cancers

Since NF-κB serves as nexus in human cancers, in another interesting study by Kamat and coworkers (53), it was shown that curcumin blocked both gemcitabine- and TNFα-induced activation of NF-κB in KU-7 bladder cancer cells. Curcumin's ability to overcome glioma cell resistance and chemoresistance was investigated in a panel of human (T98G, U87MG, and T67) and rat (C6) glioma cell lines (54). It was demonstrated that curcumin sensitized glioma cells to several chemotherapeutic agents (cisplatin, etoposide, camptothecin, and doxorubicin) and radiation by reducing the expression of Bcl-2 and IAP family member proteins as well as DNA repair enzymes (MGMT, DNA-PK, Ku70, Ku80, and ERCC-1) (54).

Hematological Cancers

As is the case with solid organ malignancies, NF-κB also plays a central role in cell survival and proliferation in hematological cancers. As curcumin is a potent NF-κB inhibitor, Bharti et al. (55) explored the effects of curcumin in multiple myeloma (MM) cell lines, which express NF-κB in a constitutively active manner. Curcumin induced significant apoptosis, suppressed the constitutive IκBα phosphorylation, and downregulated several NF-κB gene products. Similarly, in a recent study, when chemosensitizing effects of curcumin were evaluated in cell culture and xenograft model of MM, curcumin overcame chemoresistance and sensitized MM cells to thalidomide and bortezomib by downregulating NF-κB and its gene products (56). These data provided a molecular basis for treatment of MM patients with curcumin, that is, its ability to downregulate NF-κB. Curcumin also potentiated antitumor effects of sodium butyrate by reducing overall cell growth in human erythroleukemic cells (57). In a more recent study, curcumin treatment reduced basal NF-κB levels and augmented both vincristine and PDE4 inhibitor rolipram-induced apoptosis in cultured primary chronic lymphocytic leukemia cells (58). Taken together, all of these studies have indicated a potent chemosensitizing potential of curcumin in overcoming resistance afforded by standard chemotherapeutic drugs. In a more recent study, curcumin treatment reduced basal NF-κB levels and augmented both vincristine and PDE4 inhibitor rolipram-induced apoptosis in cultured primary chronic lymphocytic leukemia (B-CLL) cells (59).

CURCUMIN AS A RADIOSENSITIZER

In addition to its role as a potent chemosensitizer, increasing evidence suggests that curcumin can also function as a very promising radiosensitizing agent in a wide variety of human cancers as summarized in Table 2.

Colon Cancer

Radiation therapy, alone or in conjunction with chemotherapy, is one of the preferred modalities in patients with colon cancer who develop resistance to individual chemotherapies. Mechanisms for developing such resistance are unclear, but it has been suggested that some of this resistance may be mediated by NF-κB and its gene products. Because curcumin has been shown to suppress activation of NF-κB, it was hypothesized that curcumin may sensitize colon cancer to gamma-irradiation in a xenograft nude mice model (60). Curcumin significantly enhanced the effectiveness of radiation therapy by prolonging tumor regrowth, by reducing Ki-67 proliferation index, and by suppressing NF-κB activity and its gene products (60). Combined curcumin and radiation treatment also suppressed angiogenesis.

Prostate Cancer

Curcumin has also been shown to have radiosensitizing effects in prostate carcinoma. In this regard, curcumin significantly improved radiation-induced clonogenic inhibition and apoptosis in cultured prostate cancer PC3 cells (61). Curcumin, in combination with radiation treatment, inhibited TNFα-mediated NF-κB activity, downregulated Bcl-2 protein, but had no effect of Bax protein in PC3 cells. Collectively, these data suggest that curcumin is a potent radiosensitizing agent, and it acts by negating the effects of radiation-induced prosurvival genes in prostate cancer. In another study, curcumin showed anticancer and radiosensitization effects by downregulating MDM2 levels in cultured PC3 prostate cancer cells, as well as growth of xenografts in nude mice, by enhancing the antitumor effects of irradiation (42).

Cervical Cancer

Cervical cancer is the second leading cancer among women, and these cancers are typically very radioresistant. Consequently, for locally advanced disease, radiation therapy is often used in conjunction with chemotherapy, which is severely toxic. Curcumin may be an ideal adjunct for radiation therapy if it has radiosensitizing properties. In support of this, it was recently demonstrated that pretreatment of 2 cervical cancer cell lines HeLa and SiHa with curcumin prior to ionizing radiation resulted in radiosensitization of cancer cells but had no effect on normal human diploid fibroblasts (62). Such effects of curcumin were due to its ability to sensitize cancer cells for increased production of ROS, which in turn led to activation of ERK1 and ERK2. These data provide a novel mechanism of curcumin-mediated radiosensitization and suggest that curcumin may be an effective radiosensitizer in cervical cancer.

TABLE 2
Curcumin potentiates the effect of radiotherapy[a]

Radiosensitization	Year (Reference)
In vitro	
Inhibits UV-radiation induced oxidative stress and apoptotic changes in epidermal carcinoma cells	2003 (65)
Inhibits apoptotic effects of photodynamic therapy against human epidermal carcinoma cells	2004 (64)
Enhances the antitumor effects of irradiation against prostate cancer cells in culture	2004 (61)
Radiosensitizes squamous cell carcinoma cells in culture	2005 (69)
Enhances the antitumor effects of irradiation against prostate cancer cells in culture	2007 (42)
Potentiates cytotoxicity of radiation (5 Gy) against human and rat glioma cell lines	2007 (54)
Increases anti-proliferative effects of radiation (UVA and visible light) against human keratinocyte cell line	2007 (66)
Increases apoptotic effects of radiation (UVB) against human keratinocyte cell line	2007 (68)
Enhances antitumor effects of radiation (2 Gy) against human neuroblastoma cells in culture	2008 (63)
Enhances antitumor effects of ionizing radiation against cervical carcinoma cells in culture	2008 (62)
In vivo	
Enhances the antitumor effects of irradiation against prostate cancer cells in mice	2007 (42)
Enhances antitumor effects of fractionated radiation therapy (4 Gy) against colorectal cancer in mice	2008 (60)
In combination with visible light inhibits tumor growth in xenograft tumor model	2009 (67)

[a]Abbreviations are as follows: UV, ultraviolet; Gy, gray units; UVA, UV A light; UVB, UV B light.

Brain Cancer

Malignant gliomas are a debilitating class of neoplasms that are often resistant to standard radiation and chemotherapeutic regimens. High levels of NF-κB and AP-1 expression in gliomas is in part responsible for increased chemoresistance and radioresistance. Due to its strong NF-κB inhibitory properties, Dhandapani and colleagues (54) determined whether curcumin can sensitize human and rat glioma cells by shortening their survival in cultured cells. Interestingly, combined curcumin and radiation treatment of T98G, U87MG, and T67 cells reduced cell survival and inhibited AP-1 and NF-κB signaling pathways, suggesting a role for curcumin as an adjunct to traditional radiation therapy in brain cancers (54). Similar effects were independently validated in another study in which curcumin inhibited NF-κB-mediated radioprotection and modulated expression of apoptosis-related genes in human neuroblastoma cells (63).

Epidermal Cancer

Ultraviolet (UV) light is known to be a trigger for apoptotic signaling, which results in induction of caspase-dependent biochemical changes in cells. UV irradiation can not only activate caspase-3 but also cleave and activate p21-activated kinase 2 (PAK2) in human epidermoid carcinoma (A431) cells. Given the anti-inflammatory and antioxidant potential of curcumin, curcumin was studied for its ability to prevent UV irradiation-induced apoptotic changes, JNK activation, caspase-3-activation, and cleavage/activation of PAK2 in the A431 cell line (64). Curcumin significantly inhibited UV irradiation-induced generation of ROS and blocked JNK activation, caspase activation, and subsequent apoptotic changes (64). In a follow-up study, these investigators demonstrated that curcumin had similar radiosensitization effect in inhibiting photodynamic treatment (PDT)-induced caspase activation in A431 cells (65).

Skin Cancer

One of the unfortunate but relatively frequent manifestations of excessive exposure to UV or visible light is the possibility of skin cancers. Because curcumin has traditionally been used for different cosmetic applications and has been proposed to possess skin-healing properties, multiple studies have hypothesized that some of its effect may be attributable to its radiosensitizing ability. Experimental evidence in this regard was provided in a recent study in which cultured human skin keratinocytes treated with curcumin in combination with UV or visible light increased apoptosis and fragmented cell nuclei, activated caspase-9 and caspase-8, and inhibited NF-κB activity (66). Subsequently, these investigators performed similar studies in an animal model system and reported that curcumin in combination with visible light inhibited tumor growth in a xenograft tumor model (67). Curcumin-induced radiosensitization resulted in increased apoptosis, and this correlated with reduced Ki-67 expression, as well as lower levels of extracellular regulated kinases (ERK1 and 2), and epidermal growth factor receptor (EGFR). Park and Lee (68) showed similar results when curcumin was combined with photodynamic therapy in which synergism was observed between curcumin and UVB-irradiation in HaCaT cells. Taken together, these results indicate that a combination of curcumin and light is a possible therapeutic approach to enhance the overall efficacy of treatment regimens in skin cancers.

Squamous Cell Cancer

Radiosensitization of cancer cells is in part dictated by the distribution of cells in various phases of the cell cycle, with much better responses in cells that are in G2/M phase. It seems prudent that if cancer cells are pretreated with curcumin, this may result in enhanced radiosensitization as one of its secondary effects. Khafif et al (69) studied whether curcumin can sensitize squamous cell carcinoma cells exposed to 1 to 5 Gy of ionizing irradiation. Curcumin treatment of cells exposed to such doses of ionizing radiation decreased cell growth and reduced ability to form colonies, an effect that may have been partly due to curcumin's ability to block cells in G2/M cell cycle phase (69).

CURCUMIN AS A CHEMOPROTECTOR

NF-κB activation is a common feature of most cancers, and inhibiting its activation and suppressing its downstream gene targets is one of the goals for most cancer preventive and therapeutic approaches. Although many of the current chemotherapeutic drugs may inhibit NF-κB in tumor cells, their toxic effects on surrounding peritumoral mucosa and other normal cells is one of the limiting factors and concerns. However, pretreatment of cancer patients with the potent NF-κB inhibitor curcumin may preferentially affect tumor cells and at the same time afford sufficient protection for normal cells (Table 3).

One of the limitations of cisplatin-based chemotherapy is development of nephrotoxicity. Data suggest that increased inflammatory and oxidative stress may in part be responsible for cisplatin-induced acute renal failure. Because curcumin is a promising anti-inflammatory and antioxidant, Kuhad et al. (59) investigated the effect of curcumin in an animal model of renal injury induced by cisplatin. Curcumin treatment reverted all cisplatin-induced alterations including significant lowering of serum TNFα levels, restoring renal function, reducing lipid peroxidation, and enhancing the levels of glutathione and activities of superoxide dismutase and catalase (59).

Van't Land and colleagues (70) hypothesized that in gastrointestinal cancers, mucosal barrier injury is initiated and propagated by multiple proinflammatory cytokines and chemokines as well as NF-κB-regulated mediators. To address this, these researchers undertook a study of curcumin's ability to inhibit NF-κB in the onset of arabinoside cytosine- and methotrexate-induced mucosal barrier injury in human intestinal epithelial (IEC-6) cells. Both drugs resulted in NF-κB activation as well as induction of TNFα and other downstream targets (70). Interestingly, NF-κB inhibition increased the susceptibility of IEC-6 cells to the drug-induced cell death upon addition of caffeic acid phenethyl ester (CAPE) but not that induced by curcumin. In addition, in an animal model of methotrexate-induced mucosal barrier injury, treatment with curcumin resulted in NF-κB inhibition and partial amelioration of villous atrophy. These results provided evidence that inhibition of NF-κB does not necessarily increase intestinal side effects of the anticancer drugs and suggested a safe use of curcumin and CAPE in combination with anticancer therapy.

Curcumin has also been used to attenuate acute Adriamycin-induced myocardial (11) and nephrotoxicity (71) in rats. In these studies, curcumin pretreatment reversed the increase in lipid peroxidation and catalase, with simultaneous decrease in glutathione content and glutathione peroxidase activity caused by Adriamycin in cardiac tissues of rats (11). Curcumin pretreatment also restored renal function in Adriamycin-treated rats by inhibiting Adriamycin-induced increase in urinary excretion of N-acetyl-beta-D-glucosaminidase, fibronectin, glycosaminoglycan, and plasma cholesterol (71). These data indicate that curcumin may serve as an adjunct to Adriamycin therapy by reducing myocardial toxicity and nephrosis.

In another model of nephrotoxicity, when cisplatin was used as a chemotherapeutic drug, pretreatment of rats with various does of curcumin protected against cisplatin-induced nephrotoxicity by preventing alterations in various biochemical and inflammatory markers (59). Oral treatment with curcumin 10 days before, or daily after a single intratracheal installation of bleomycin, protected against bleomycin-induced pulmonary fibrosis, as evidenced by protection against changes in total lung hydroxyproline, alveolar macrophage production of TNFα superoxide, and nitric oxide (72). Collectively, these reports clearly highlight the chemoprotective role of curcumin and support its potential use as an adjunct to chemotherapy for multiple human cancers.

CURCUMIN AS A RADIOPROTECTOR

Accumulating evidence suggests that curcumin may not only have a chemoprotective role, but several studies have indicated its potential as a radioprotective agent as well (Table 3). Parshad and colleagues (73) were among the first to suggest a radioprotective role for curcumin when they studied radiation-induced chromosomal defects in human skin fibroblasts and blood lymphocytes. It was demonstrated that pretreatment with curcumin and other plant polyphenols to cultured skin fibroblasts or PHA-stimulated lymphocytes reduced the frequency of radiation-induced chromatid breaks. It was surmised that such effects of curcumin were due to its strong antioxidant capacity, which scavenged toxic free radicals induced by radiation exposure of these cells (73). Similar effects of curcumin on blood cells were investigated in a later report in which it was shown that pretreatment of cultured peripheral blood lymphocytes with very low doses of curcumin (1–10 μg/ml) protected against even up to 2 Gy dose of gamma radiation (74). In this study, curcumin pretreatment protected against increases in micronuclei and dicentric nuclei formation, increases in lipid peroxidation, and decreases in superoxide dismutase, catalase, and glutathione peroxidase activities induced by radiation treatment (74). Findings from the study by Kunwar et al (75) reiterated the radioprotective role of curcumin when these investigators reported delayed activation of PKCδ and NF-κB in splenic

TABLE 3
Curcumin protects from the toxic effects of chemotherapy and radiotherapy

Radioprotection/Chemoprotection	Reference
In vitro	
Protects against radiation-induced DNA damage in cultured human cells	1998 (73)
Reduces apoptotic effects of arabinoside cytosine (Ara-C) against human intestinal epithelial cells	2004 (70)
Enhances radioprotection in cultured human lymphocytes	2006 (74)
Enhances radioprotection in mice splenic lymphocytes	2007 (75)
In vivo	
Protects against gamma radiation induced chromosomal damage in mice	1993 (76)
Reduces lung toxicity of whole-body irradiation in rats	1996 (78)
Reduces genotoxicity of whole-body irradiation in mice	1998 (77)
Reduces cardiotoxicity of doxorubicin in rats	1998 (11)
Prevents doxorubicin nephrotoxicity in rats	2000 (71)
Inhibits bleomycin-induced pulmonary fibrosis in rats	2000 (72)
Decreases acute toxicity of whole-body irradiation in rats	2002 (79)
Reduces radiation-induced oral mucositis in rats	2004 (80)
Reduces mucosal barrier injury from methotrexate in rats	2004 (70)
Enhances repair of wounds in mice exposed to whole-body γ-irradiation	2004 (81,82)
Enhances repair of wounds in mice exposed to hemibody γ-irradiation	2005 (83)
Protects against radiation-induced cutaneous cytotoxicity in mice	2006 (84)
Reduces nephrotoxicity of cisplatin in rats	2007 (59)

lymphocytes by curcumin and a curcumin:copper complex (1:1 ratio) in radiation-exposed lymphocytes.

In addition to in vitro evidence, data from several animal studies have now confirmed that curcumin has a strong radioprotective function. Abraham and colleagues (76) used the mouse bone marrow micronucleus test to interrogate the protective role of 3 dietary agents including curcumin in mice exposed to gamma radiation. The data from this study indicated that oral administration of curcumin 2 h before or immediately after exposing the animals to whole-body, high-energy gamma irradiation significantly reduced the frequency of micronucleated polychromatic erythrocytes (76). Similar protective effects were noticed in mice pretreated with curcumin before exposure to gamma irradiation in which curcumin helped reduce the number of bone marrow cells with chromosomal aberrations and other chromosomal fragments (77).

Such radioprotective effects of curcumin were still noticeable when much higher radiation doses (up to 10 Gy) were used in rats in which curcumin pretreatment significantly reduced the number of micronucleated cells and inhibited superoxide dismutase activity with a concomitant increase in catalase activity in liver tissues (78). Curcumin treatment for 3 days before and/or 2 days after irradiation in female rats also inhibited levels of urinary 8-hydroxy-2′-deoxyguanosine and significantly decreased the incidence of mammary and pituitary tumors (79). In another study, curcumin treatment of animals exposed to localized irradiation of their tongues resulted in an overall improvement against radiation-induced oral mucositis (80).

Wound healing following radiation therapy is a frequent concern, as radiation treatment often disrupts normal response to injury and results in delayed recovery periods. Radioprotective effects of curcumin have been investigated on wound healing in mice exposed to 2 to 8 Gy doses of whole-body gamma radiation (81,82). Pretreatment with curcumin significantly enhanced the rate of wound contraction; shortened wound healing duration; and increased collagen synthesis and hexosamine, DNA, and nitric oxide formation (81). In a related study, the same group of researchers used hemibody radiation exposure combined with curcumin pretreatment to make similar observations on wound healing (83). In an effort to better understand these radioprotective effects on a molecular level, it was shown that curcumin pretreatment protected against radiation-induced acute and chronic cutaneous toxicity in mice by decreasing gene expression of inflammatory (IL-1, IL-6, IL-18, TNFα, and lymphotoxin-β) and fibrogenic cytokine (TGFβ) at 21 days postradiation (84). Taken together, these studies have indicated a potential use of curcumin as a radioprotective agent in patients with radiation-inflicted skin injuries.

CLINICAL IMPLICATIONS AND CONCLUSIONS

Given the shortcomings of current chemotherapy and radiation treatments for cancer management, it is obvious that such treatments in the future must be combined with more effective and safer drugs/compounds. In this regard, given all the encouraging evidence summarized in the previous sections, curcumin

seems to be an ideal, safe, and highly effective compound that can be used as an adjunct in such therapeutic strategies. Use of a curcumin-based, anticancer therapeutic strategy would also allow use of lower doses of chemotherapeutic drugs and radiation but still achieve much higher antitumor efficacy and yet lower toxicity and resistance in the management of variety of human cancers. In this context, it may also be important to gain more meticulous insights into identifying cancer stem cells in various solid organ tumors and determine how these differ from normal stem cells and other neoplastic cells within the same tissue. We believe that given the undisputed and encouraging data for curcumin as a safe and effective cancer preventive and newer data as a potential therapeutic agent, combining curcumin with current chemotherapy and/or radiation may also reduce the need for palliative surgery in some instances, as cancers may be stopped before they become invasive and widely metastatic. These effects combined with its ability to prevent depression, fatigue, neuropathic pain, lack of sleep, and lack of appetite, all symptoms that induced by cancer and cancer treatment, makes curcumin an ideal agent for cancer patients.

REFERENCES

1. Rahman I, Biswas SK, and Kirkham PA: Regulation of inflammation and redox signaling by dietary polyphenols. *Biochem Pharmacol* **72**, 1439–1452, 2006.
2. Tirkey N, Kaur G, Vij G, and Chopra K: Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys. *BMC Pharmacol* **5**, 15, 2005.
3. Brouet I and Ohshima H: Curcumin, an anti-tumour promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages. *Biochem Biophys Res Commun* **206**, 533–540, 1995.
4. Dikshit M, Rastogi L, Shukla R, and Srimal RC: Prevention of ischaemia-induced biochemical changes by curcumin and quinidine in the cat heart. *Indian J Med Res* **101**, 31–35, 1995.
5. Sreejayan xxand Rao MN: Nitric oxide scavenging by curcuminoids. *J Pharm Pharmacol* **49**, 105–107, 1997.
6. Chen J, Bai H, Wang C, and Kang J: Trichostatin A improves the anticancer activity of low concentrations of curcumin in human leukemia cells. *Pharmazie* **61**, 710–716, 2006.
7. Chen J, Tang XQ, Zhi JL, Cui Y, Yu HM, et al.: Curcumin protects PC12 cells against 1-methyl-4-phenylpyridinium ion-induced apoptosis by bcl-2-mitochondria-ROS-iNOS pathway. *Apoptosis* **11**, 943–953, 2006.
8. Divya CS and Pillai MR: Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. *Mol Carcinog* **45**, 320–332, 2006.
9. Kiso Y, Suzuki Y, Watanabe N, Oshima Y, and Hikino H: Antihepatotoxic principles of Curcuma longa rhizomes. *Planta Med* **49**, 185–187, 1983.
10. Srivastava R, Dikshit M, Srimal RC, and Dhawan BN: Anti-thrombotic effect of curcumin. *Thromb Res* **40**, 413–417, 1985.
11. Venkatesan N: Curcumin attenuation of acute adriamycin myocardial toxicity in rats. *Br J Pharmacol* **124**, 425–427, 1998.
12. Deodhar SD, Sethi R, and Srimal RC: Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J Med Res* **71**, 632–634, 1980.
13. Chan MM, Adapala NS, and Fong D: Curcumin overcomes the inhibitory effect of nitric oxide on Leishmania. *Parasitol Res* **96**, 49–56, 2005.
14. Singh S and Khar A: Biological effects of curcumin and its role in cancer chemoprevention and therapy. *Anticancer Agents Med Chem* **6**, 259–270, 2006.
15. Goel A, Kunnumakkara AB, and Aggarwal BB: Curcumin as "curecumin": from kitchen to clinic. *Biochem Pharmacol* **75**, 787–809.
16. Gottesman MM, Ludwig J, Xia D, and Szakacs G: Defeating drug resistance in cancer. *Discov Med* **6**, 18–23, 2006.
17. Theodoulou M, Batist G, Campos S, Winer E, Welles L, et al.: Phase I study of nonpegylated liposomal doxorubicin plus trastuzumab in patients with HER2-positive breast cancer. *Clin Breast Cancer* **9**, 101–107, 2009.
18. Ali S and Coombes RC: Endocrine-responsive breast cancer and strategies for combating resistance. *Nat Rev Cancer* **2**, 101–112, 2002.
19. Davies A, Cifaldi MA, Segurado OG, and Weisman MH: Cost-effectiveness of sequential therapy with tumor necrosis factor antagonists in early rheumatoid arthritis. *J Rheumatol* **36**, 16–26, 2009.
20. Thayu M, Leonard MB, Hyams JS, Crandall WV, Kugathasan S, et al.: Improvement in biomarkers of bone formation during infliximab therapy in pediatric Crohn's disease: results of the REACH study. *Clin Gastroenterol Hepatol* **6**, 1378–1384, 2008.
21. Weisberg E, Manley PW, Cowan-Jacob SW, Hochhaus A, and Griffin JD: Second generation inhibitors of BCR-ABL for the treatment of imatinib-resistant chronic myeloid leukaemia. *Nat Rev Cancer* **7**, 345–356, 2007.
22. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, et al.: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* **316**, 1039–1043, 2007.
23. Gottesman MM, Fojo T, and Bates SE: Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat Rev Cancer* **2**, 48–58, 2002.
24. Raguz S and Yague E: Resistance to chemotherapy: new treatments and novel insights into an old problem. *Br J Cancer* **99**, 387–391, 2008.
25. Al-Hajj M and Clarke MF: Self-renewal and solid tumor stem cells. *Oncogene* **23**, 7274–7282, 2004.
26. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, et al.: Identification of a cancer stem cell in human brain tumors. *Cancer Res* **63**, 5821–5828, 2003.
27. Jiang X, Zhao Y, Smith C, Gasparetto M, Turhan A, et al.: Chronic myeloid leukemia stem cells possess multiple unique features of resistance to BCR-ABL targeted therapies. *Leukemia* **21**, 926–935, 2007.
28. Jemal A, Siegel R, Ward E, Hao Y, Xu J, et al.: Cancer statistics, 2009. *CA Cancer J Clin* 2009.
29. Howells LM, Mitra A, and Manson MM: Comparison of oxaliplatin- and curcumin-mediated antiproliferative effects in colorectal cell lines. *Int J Cancer* 2007.
30. Li L, Ahmed B, Mehta K, and Kurzrock R: Liposomal curcumin with and without oxaliplatin: effects on cell growth, apoptosis, and angiogenesis in colorectal cancer. *Mol Cancer Ther* **6**, 1276–1282, 2007.
31. Patel BB, Sengupta R, Qazi S, Vachhani H, Yu Y, et al.: Curcumin enhances the effects of 5-fluorouracil and oxaliplatin in mediating growth inhibition of colon cancer cells by modulating EGFR and IGF-1R. *Int J Cancer* **122**, 267–273, 2008.
32. Du B, Jiang L, Xia Q, and Zhong L: Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon cancer cell line HT-29. *Chemotherapy* **52**, 23–28, 2006.
33. Lev-Ari S, Strier L, Kazanov D, Madar-Shapiro L, Dvory-Sobol H, et al.: Celecoxib and curcumin synergistically inhibit the growth of colorectal cancer cells. *Clin Cancer Res* **11**, 6738–6744, 2005.
34. Shpitz B, Giladi N, Sagiv E, Lev-Ari S, Liberman E, et al.: Celecoxib and curcumin additively inhibit the growth of colorectal cancer in a rat model. *Digestion* **74**, 140–144, 2006.
35. Koo JY, Kim HJ, Jung KO, and Park KY: Curcumin inhibits the growth of AGS human gastric carcinoma cells in vitro and shows synergism with 5-fluorouracil. *J Med Food* **7**, 117–121, 2004.
36. Lev-Ari S, Zinger H, Kazanov D, Yona D, Ben-Yosef R, et al.: Curcumin synergistically potentiates the growth inhibitory and pro-apoptotic effects of celecoxib in pancreatic adenocarcinoma cells. *Biomed Pharmacother* **59**(2 Suppl), S276–S280, 2005.

37. Lev-Ari S, Vexler A, Starr A, Ashkenazy-Voghera M, Greif J, et al.: Curcumin augments gemcitabine cytotoxic effect on pancreatic adenocarcinoma cell lines. *Cancer Invest* **25**, 411–418, 2007.
38. Kunnumakkara AB, Guha S, Krishnan S, Diagaradjane P, Gelovani J, et al.: Curcumin potentiates antitumor activity of gemcitabine in an orthotopic model of pancreatic cancer through suppression of proliferation, angiogenesis, and inhibition of nuclear factor-kappaB-regulated gene products. *Cancer Res* **67**, 3853–3861, 2007.
39. Notarbartolo M, Poma P, Perri D, Dusonchet L, Cervello M, et al.: Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells: analysis of their possible relationship to changes in NF-kB activation levels and in IAP gene expression. *Cancer Lett* **224**, 53–65, 2005.
40. Holcomb B, Yip-Schneider MT, Matos JM, Dixon J, Kennard J, et al.: Pancreatic cancer cell genetics and signaling response to treatment correlate with efficacy of gemcitabine-based molecular targeting strategies. *J Gastrointest Surg* **12**, 288–296, 2008.
41. Hour TC, Chen J, Huang CY, Guan JY, Lu SH, et al.: Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21(WAF1/CIP1) and C/EBPbeta expressions and suppressing NF-kappaB activation. *Prostate* **51**, 211–218, 2002.
42. Li M, Zhang Z, Hill DL, Wang H, and Zhang R: Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. *Cancer Res* **67**, 1988–1996, 2007.
43. Aggarwal BB, Shishodia S, Takada Y, Banerjee S, Newman RA, et al.: Curcumin suppresses the paclitaxel-induced nuclear factor-kappaB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. *Clin Cancer Res* **11**, 7490–7498, 2005.
44. Chirnomas D, Taniguchi T, de l, V, Vaidya AP, Vasserman M, et al.: Chemosensitization to cisplatin by inhibitors of the Fanconi anemia/BRCA pathway. *Mol Cancer Ther* **5**, 952–961, 2006.
45. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, et al.: Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. *Cancer Res* **62**, 3868–3875, 2002.
46. Chan MM, Fong D, Soprano KJ, Holmes WF, and Heverling H: Inhibition of growth and sensitization to cisplatin-mediated killing of ovarian cancer cells by polyphenolic chemopreventive agents. *J Cell Physiol* **194**, 63–70, 2003.
47. Lin YG, Kunnumakkara AB, Nair A, Merritt WM, Han LY, et al.: Curcumin inhibits tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor-kappaB pathway. *Clin Cancer Res* **13**, 3423–3430, 2007.
48. Venkatraman M, Anto RJ, Nair A, Varghese M, and Karunagaran D: Biological and chemical inhibitors of NF-kappaB sensitize SiHa cells to cisplatin-induced apoptosis. *Mol Carcinog* **44**, 51–59, 2005.
49. Bava SV, Puliappadamba VT, Deepti A, Nair A, Karunagaran D, et al.: Sensitization of taxol-induced apoptosis by curcumin involves down-regulation of nuclear factor-kappaB and the serine/threonine kinase Akt and is independent of tubulin polymerization. *J Biol Chem* **280**, 6301–6308, 2005.
50. Sen S, Sharma H, and Singh N: Curcumin enhances Vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway. *Biochem Biophys Res Commun* **331**, 1245–1252, 2005.
51. Andjelkovic T, Pesic M, Bankovic J, Tanic N, Markovic ID, et al.: Synergistic effects of the purine analog sulfinosine and curcumin on the multidrug resistant human non-small cell lung carcinoma cell line (NCI-H460/R). *Cancer Biol Ther* **7**, 1024–1032, 2008.
52. Chanvorachote P, Pongrakhananon V, Wannachaiyasit S, Luanpitpong S, Rojanasakul Y, et al.: Curcumin sensitizes lung cancer cells to cisplatin-induced apoptosis through superoxide anion-mediated Bcl-2 degradation. *Cancer Invest* **27**, 624–635, 2009.
53. Kamat AM, Sethi G, and Aggarwal BB: Curcumin potentiates the apoptotic effects of chemotherapeutic agents and cytokines through down-regulation of nuclear factor-kappaB and nuclear factor-kappaB-regulated gene products in IFN-alpha-sensitive and IFN-alpha-resistant human bladder cancer cells. *Mol Cancer Ther* **6**, 1022–1030, 2007.
54. Dhandapani KM, Mahesh VB, and Brann DW: Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NFkappaB transcription factors. *J Neurochem* **102**, 522–538, 2007.
55. Bharti AC, Donato N, Singh S, and Aggarwal BB: Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and IkappaBalpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. *Blood* **101**, 1053–1062, 2003.
56. Sung B, Kunnumakkara AB, Sethi G, Anand P, Guha S, et al.: Curcumin circumvents chemoresistance in vitro and potentiates the effect of thalidomide and bortezomib against human multiple myeloma in nude mice model. *Mol Cancer Ther* **8**, 959–970, 2009.
57. Indap MA and Barkume MS: Efficacies of plant phenolic compounds on sodium butyrate induced anti-tumour activity. *Indian J Exp Biol* **41**, 861–864, 2003.
58. Everett PC, Meyers JA, Makkinje A, Rabbi M, and Lerner A: Preclinical assessment of curcumin as a potential therapy for B-CLL. *Am J Hematol* **82**, 23–30, 2007.
59. Kuhad A, Pilkhwal S, Sharma S, Tirkey N, and Chopra K: Effect of curcumin on inflammation and oxidative stress in cisplatin-induced experimental nephrotoxicity. *J Agric Food Chem* **55**, 10150–10155, 2007.
60. Kunnumakkara AB, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, et al.: Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. *Clin Cancer Res* **14**, 2128–2136, 2008.
61. Chendil D, Ranga RS, Meigooni D, Sathishkumar S, and Ahmed MM: Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. *Oncogene* **23**, 1599–1607, 2004.
62. Javvadi P, Segan AT, Tuttle SW, and Koumenis C: The chemopreventive agent curcumin is a potent radiosensitizer of human cervical tumor cells via increased reactive oxygen species production and overactivation of the mitogen-activated protein kinase pathway. *Mol Pharmacol* **73**, 1491–1501, 2008.
63. Aravindan N, Madhusoodhanan R, Ahmad S, Johnson D, and Herman TS: Curcumin inhibits NFkappaB mediated radioprotection and modulate apoptosis related genes in human neuroblastoma cells. *Cancer Biol Ther* **7**, 569–576, 2008.
64. Chan WH, Wu CC, and Yu JS: Curcumin inhibits UV irradiation-induced oxidative stress and apoptotic biochemical changes in human epidermoid carcinoma A431 cells. *J Cell Biochem* **90**, 327–338, 2003.
65. Chan WH and Wu HJ: Anti-apoptotic effects of curcumin on photosensitized human epidermal carcinoma A431 cells. *J Cell Biochem* **92**, 200–212, 2004.
66. Dujic J, Kippenberger S, Hoffmann S, Ramirez-Bosca A, Miquel J, et al.: Low concentrations of curcumin induce growth arrest and apoptosis in skin keratinocytes only in combination with UVA or visible light. *J Invest Dermatol* 2007.
67. Dujic J, Kippenberger S, Ramirez-Bosca A, Diaz-Alperi J, Bereiter-Hahn J, et al.: Curcumin in combination with visible light inhibits tumor growth in a xenograft tumor model. *Int J Cancer* **124**, 1422–1428, 2009.
68. Park K and Lee JH: Photosensitizer effect of curcumin on UVB-irradiated HaCaT cells through activation of caspase pathways. *Oncol Rep* **17**, 537–540, 2007.
69. Khafif A, Hurst R, Kyker K, Fliss DM, Gil Z, et al.: Curcumin: a new radio-sensitizer of squamous cell carcinoma cells. *Otolaryngol Head Neck Surg* **132**, 317–321, 2005.
70. van't LB, Blijlevens NM, Marteijn J, Timal S, Donnelly JP, et al.: Role of curcumin and the inhibition of NF-kappaB in the onset of chemotherapy-induced mucosal barrier injury. *Leukemia* **18**, 276–284, 2004.
71. Venkatesan N, Punithavathi D, and Arumugam V: Curcumin prevents adriamycin nephrotoxicity in rats. *Br J Pharmacol* **129**, 231–234, 2000.
72. Punithavathi D, Venkatesan N, and Babu M: Curcumin inhibition of bleomycin-induced pulmonary fibrosis in rats. *Br J Pharmacol* **131**, 169–172, 2000.

73. Parshad R, Sanford KK, Price FM, Steele VE, Tarone RE, et al.: Protective action of plant polyphenols on radiation-induced chromatid breaks in cultured human cells. *Anticancer Res* **18**, 3263–3266, 1998.
74. Srinivasan M, Rajendra PN, and Menon VP: Protective effect of curcumin on gamma-radiation induced DNA damage and lipid peroxidation in cultured human lymphocytes. *Mutat Res* **611**, 96–103, 2006.
75. Kunwar A, Narang H, Priyadarsini KI, Krishna M, Pandey R, et al.: Delayed activation of PKCdelta and NFkappaB and higher radioprotection in splenic lymphocytes by copper (II)-Curcumin (1:1) complex as compared to curcumin. *J Cell Biochem* 2007.
76. Abraham SK, Sarma L, and Kesavan PC: Protective effects of chlorogenic acid, curcumin and beta-carotene against gamma-radiation-induced in vivo chromosomal damage. *Mutat Res* **303**, 109–112, 1993.
77. Thresiamma KC, George J, and Kuttan R: Protective effect of curcumin, ellagic acid and bixin on radiation induced genotoxicity. *J Exp Clin Cancer Res* **17**, 431–434, 1998.
78. Thresiamma KC, George J, and Kuttan R: Protective effect of curcumin, ellagic acid and bixin on radiation induced toxicity. *Indian J Exp Biol* **34**, 845–847, 1996.
79. Inano H and Onoda M: Radioprotective action of curcumin extracted from Curcuma longa LINN: inhibitory effect on formation of urinary 8-hydroxy-2′-deoxyguanosine, tumorigenesis, but not mortality, induced by gamma-ray irradiation. *Int J Radiat Oncol Biol Phys* **53**, 735–743, 2002.
80. Rezvani M and Ross GA: Modification of radiation-induced acute oral mucositis in the rat. *Int J Radiat Biol* **80**, 177–182, 2004.
81. Jagetia GC and Rajanikant GK: Role of curcumin, a naturally occurring phenolic compound of turmeric in accelerating the repair of excision wound, in mice whole-body exposed to various doses of gamma-radiation. *J Surg Res* **120**, 127–138, 2004.
82. Jagetia GC and Rajanikant GK: Effect of curcumin on radiation-impaired healing of excisional wounds in mice. *J Wound Care* **13**, 107–109, 2004.
83. Jagetia GC and Rajanikant GK: Curcumin treatment enhances the repair and regeneration of wounds in mice exposed to hemibody gamma-irradiation. *Plast Reconstr Surg* **115**, 515–528, 2005.
84. Okunieff P, Xu J, Hu D, Liu W, Zhang L, et al.: Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines. *Int J Radiat Oncol Biol Phys* **65**, 890–898, 2006.