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ScienceDirect
Cancer Letters 267 (2008) 133–164
CANCER Letters
www.elsevier.com/locate/canlet

Curcumin and cancer: An "old-age" disease with an "age-old" solution

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Received 11 March 2008; received in revised form 11 March 2008; accepted 12 March 2008

Abstract

Cancer is primarily a disease of old age, and that life style plays a major role in the development of most cancers is now well recognized. While plant-based formulations have been used to treat cancer for centuries, current treatments usually involve poisonous mustard gas, chemotherapy, radiation, and targeted therapies. While traditional plant-derived medicines are safe, what are the active principles in them and how do they mediate their effects against cancer is perhaps best illustrated by curcumin, a derivative of turmeric used for centuries to treat a wide variety of inflammatory conditions. Curcumin is a diferuloylmethane derived from the Indian spice, turmeric (popularly called "curry powder") that has been shown to interfere with multiple cell signaling pathways, including cell cycle (cyclin D1 and cyclin E), apoptosis (activation of caspases and down-regulation of antiapoptotic gene products), proliferation (HER-2, EGFR, and AP-1), survival (PI3K/AKT pathway), invasion (MMP-9 and adhesion molecules), angiogenesis (VEGF), metastasis (CXCR-4) and inflammation (NF-κB, TNF, IL-6, IL-1, COX-2, and 5-LOX). The activity of curcumin reported against leukemia and lymphoma, gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers, and sarcoma reflects its ability to affect multiple targets. Thus an "old-age" disease such as cancer requires an "age-old" treatment.

Keywords: Curcumin; Cancer; Inflammation; Anticancer activity; Chemoprevention; Chemosensitization; Radiosensitization

1. Introduction

Studies have estimated that genetic factors cause only 5–10% of all human cancers, while the remaining percentage is caused by lifestyle. In spite of an extensive search for safe and efficacious treatments for cancer, it has involved the use of harmful substances, such as poisonous mustargen introduced in 1941; chemotherapy, introduced in 1971; and then now targeted therapies, introduced in 1991. The progress in cancer research is determined by the number of approvals from the U.S. Food and Drug Administration (FDA), as indicated by very few in 1970; seven in 1987; 16 in 1996; 21 in 1998, and 28 in 2006 [1]. More than 70% of the FDA approved anticancer drugs can be traced back to

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doi:10.1016/j.canlet.2008.03.025

their origin in plant-derived natural products, which were traditionally used as ancient remedies for various ailments. Vinblastine from *Vinca rosea* is one of the earliest example that originated from an Ayurvedic medicine described for cancer and paclitaxel is perhaps one of the most recent example that originated from Chinese pacific yew plant.

Cancer is well recognized as a disease of old age (Fig. 1). It is estimated that the process of tumorigenesis starts at around the age of 20 and detection of cancer is normally around the age of 50 or later (Table 1); thus with an estimated incubation time of around 20–30 years. Recent studies indicate that in any given type of cancer 300–500 normal genes have been modified somehow to result in the cancerous phenotype. Although cancers are characterized by the dysregulation of cell signaling pathways at multiple steps, most current anticancer therapies involve the modulation of a single target. The ineffectiveness, lack of safety, and high cost of monotargeted therapies have led to a lack of faith in these approaches. As a result, many pharmaceutical companies are increasingly interested in developing multitargeted therapies. Many plant-based products, however, accomplish multitargeting naturally and, in addition, are inexpensive and safe compared to synthetic agents. However, because pharmaceutical companies are not usually able to secure intellectual property rights to plant-based products, the development of plant-based anticancer therapies has not been prioritized. Nonetheless, curcumin, a plant-based product, has shown significant promise against cancer and other inflammatory diseases.

Curcumin is a hydrophobic polyphenol derived from turmeric: the rhizome of the herb *Curcuma longa*. Chemically, it is a bis-α,β-unsaturated β-diketone (commonly called diferuloylmethane) that exhibits keto-enol tautomerism, having a predominant keto form in acidic and neutral solutions and a stable enol form in alkaline media. Commercial curcumin is a mixture of curcuminoids, containing approximately 77% diferuloylmethane, 18% demethoxycurcumin, and 5% bisdemethoxycurcumin. Traditionally, turmeric and other curcuminoids have been used in therapeutic preparations for various ailments in different parts of the world. Numerous therapeutic effects of curcumin/turmeric have been confirmed by modern scientific research. Herein, we present a systematic review of the clinical and experimental data on the use of curcumin in the treatment of cancer.

2. Molecular targets of curcumin

Extensive research conducted within the past two decades has revealed that cancer is a result of the dysregulation of multiple cell signaling pathways. Curcumin is a highly pleiotropic molecule that modulates numerous targets (Fig. 2), including the activation of transcription factors (e.g., NF-κB, STAT3, AP-1, NRF-2, PPAR-γ, and HIF-1), receptors (e.g., HER-2, IL-8, and CXCR-4), kinases (e.g., EGFR, ERK, JAK, and AAPK), cytokines (e.g., TNF, IL, MIP, and MCP), enzymes (e.g., MMP, iNOS, GST,

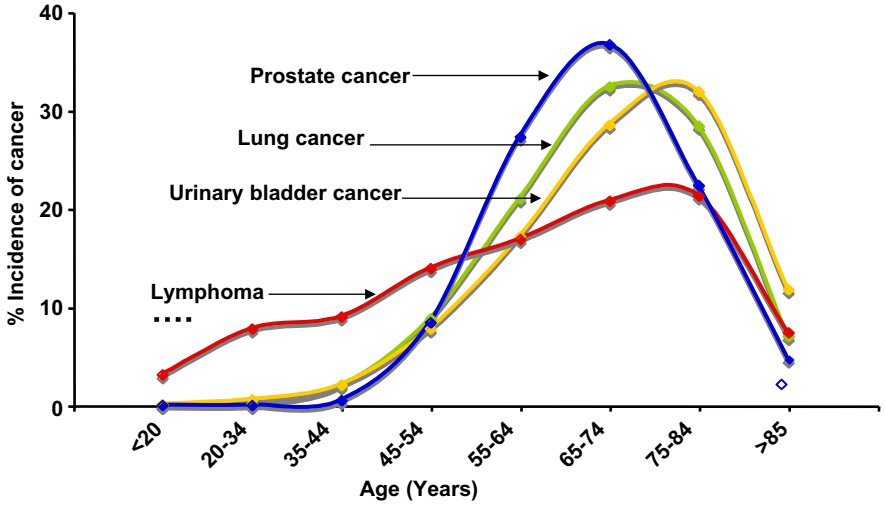

Fig. 1. Age dependency of cancer incidence. Data presented in the figure is based on the cancer statistics published in 2007 [3].

Table 1
Median age at which most cancers are diagnosed in American population

Cancer site	Median age at diagnosis (years)
Breast cancer	61
Gastrointestinal cancers	
Esophagus cancer	69
Stomach cancer	71
Intestine cancer	67
Liver cancer	65
Pancreatic cancer	72
Colorectal cancer	71
Genitourinary cancers	
Bladder cancer	73
Kidney cancer	65
Prostate cancer	68
Gynecologic cancers	
Cervical cancer	48
Ovarian cancer	63
Uterine cancer	67
Thoracic/Head and neck cancer	
Lung cancer	70
Oral cancer	62
Thymus cancer	50
Hematologic cancers	
Leukemia	67
Lymphoma	64
Multiple Myeloma	70
Melanoma	59
Bone cancer	39
Brain tumor	56

Data presented in the table is based on the cancer statistics published in 2007 [3].

and ATPase), and growth factors (e.g., EGF, NGF, HGF, and PDGF). Because of its ability to interact with a diverse range of molecular targets, curcumin can affect numerous molecular and biochemical cascades. One of our recently published reviews presents a more detailed description of the molecular targets of curcumin [2]. Extensive research conducted during the past century has established the complexity and involvement of multiple signaling pathways in the cancer growth and progression, which in turn suggests that a drug, which can interact with multiple target molecules, will be more efficacious than the current monotargeted anticancer drugs. Curcumin's multitargeting ability may be the key to its therapeutic potential against cancer. In the next section of this review, we analyze the current status of curcumin's potential against various cancers.

3. Anticancer potential

Curcumin has been shown to exhibit therapeutic potential against variety of different cancers including leukemia and lymphoma; gastrointestinal cancers, genitourinary cancers, breast cancer, ovarian cancer, head and neck squamous cell carcinoma, lung cancer, melanoma, neurological cancers and sarcoma (Fig. 3). The current status of curcumin's anticancer potential against various cancers is systematically analyzed and presented below under different headings.

3.1. Breast cancer

Breast cancer is the most common and frequently diagnosed cancer at a median age of 61 years in women [3]. In the United States, breast cancer accounts for about 26% of all newly diagnosed neoplasms [4]. Even though substantial advances in therapy and diagnosis have enhanced the survival rate of patients with breast cancer, late recurrences of the disease account for more than 60% of deaths from breast cancer [5]; the survival rate among patients with metastatic disease does not seem to be significantly affected by the current treatment modalities [6]. Indeed, further studies are needed to optimize therapeutic interventions in patients with metastatic breast cancer.

Several reports have described the anticarcinogenic activity of curcumin in a variety of breast cancer cell lines. One of our early studies established that the antiproliferative effect of curcumin in human breast cancer cell lines, including hormone-dependent, hormone-independent, and multidrug-resistant cells, was time- and dose-dependent and correlated with curcumin's inhibition of ornithine decarboxylase activity [7]. Several mechanisms have been proposed to account for the action of curcumin in breast cancer cells. For example, curcumin was found to inhibit the aryl hydrocarbon receptor and cytochrome P450 1A1 [7]; the tyrosine kinase activity of p185neu; the expression of Ki-67, PCNA, p53 mRNAs; COX-I and COX-II enzymes. Curcumin also induced p53-dependent Bax expression, inhibited vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF) [8,9], disrupted mitotic spindle structure and induced micronucleation [10]. It has been shown to inhibit telomerase activity through human telomerase reverse transcriptase [11], downregulate the expression of

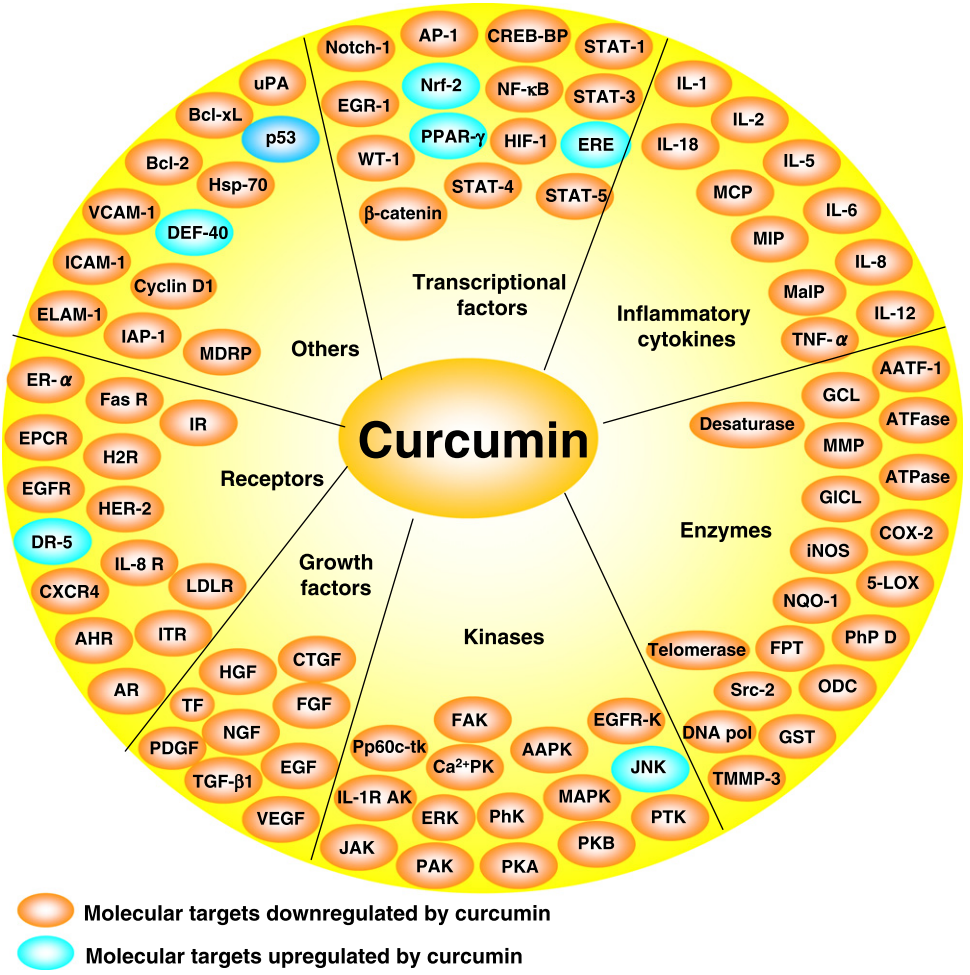

Fig. 2. Molecular targets of curcumin. These include, NF-κB, nuclear factor-kappa B; AP-1, activating protein1; STAT, signal transducers and activators of transcription; Nrf-2, nuclear factor 2-related factor; Egr-1, early growth response gene-1; PPAR-γ, peroxisome proliferator-activated receptor-gamma; CBP, CREB-binding protein; EpRE; CTGF, connective tissue growth factor; EGF, epidermal growth factor; EGFRK, epidermal growth factor receptor-kinase; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; NGF, nerve growth factor; PDGF, platelet-derived growth factor; TGF-β1, transforming growth factor-β1; VEGF, vascular endothelial growth factor; AR, androgen receptor; Arh-R, aryl hydrocarbon receptor; DR-5, death receptor-5; EGF-R, epidermal growth factor-receptor; EPC-R, endothelial protein C-receptor; ER-α, estrogen receptor-alpha; Fas-R, Fas receptor; H2-R, histamine (2)-receptor; InsP3-R, inositol 1,4,5-triphosphate receptor; IR, integrin receptor; IL-8-R, interleukin 8-receptor; LDL-R, low density lipoprotein–receptor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase-3; iNOS, inducible nitric oxide oxidase; COX-2, cyclooxygenase-2; LOX, lipoxygenase; Gcl, glutamate-cysteine ligase; NAT, arylamine *N*-acetyltransferases; IAP, inhibitory apoptosis protein; HSP-70, heat-shock protein 70; TNF-α, tumor necrosis factor alpha; IL, interleukin; MCP, monocyte chemoattractant protein; MIF, migration inhibition protein; MIP, macrophage inflammatory protein; ERK, extracellular receptor kinase; IARK, IL-1 receptor-associated kinase; cAK, autophosphorylation-activated protein kinase; CDPK, Ca^{2+}-dependent protein kinase; cPK, protamine kinase; JAK, janus kinase; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; TK, protein tyrosine kinase; FAK, focal adhesion kinase; PhK, phosphorylase kinase; pp60c-src, pp60c-src tyrosine kinase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; FPTase, farnesyl protein transferase; GST, glutathione *S*-transferase; HO, hemeoxygenase; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; ELAM-1, endothelial leukocyte adhesion molecule-1; SHP-2, Src homology 2 domain-containing tyrosine phosphatase 2, uPA, urokinase-type plasminogen activator.

matrix metalloproteinase-2 (MMP-2), upregulate tissue inhibitor of metalloproteinase-1 (TIMP-1) [12], and block NF-κB and AP-1 activation [13–16]. Studies have also shown curcumin to inhibit LOX pathways [17], induce the degradation of cyclin E expression through a ubiquitin-dependent pathway, upregulate cyclin-dependent kinase inhibitors p21 and p27 [18] and downregulate

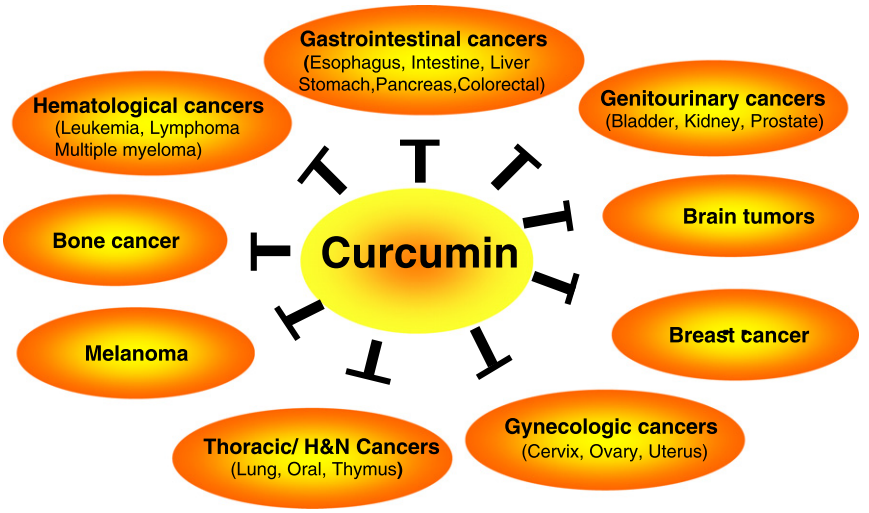

Fig. 3. Various cancers against which curcumin has potential for prevention and treatment.

the insulin-like growth factor-1 (IGF-1) [19] in breast cancer cell lines.

In a study by Zhang et al. [20], exposure of mouse breast tumor cells to curcumin caused a dose-dependent increase in ubiquitinated exosomal proteins compared to those in untreated cells. The exosomes isolated from tumor cells pretreated with curcumin have a much attenuated inhibition of IL-2-stimulated-NK cell activation. The tumor exosomes isolated from curcumin-pretreated tumor cells had lower potency for inhibition of IL-2-stimulated NK cell cytotoxicity compared to those from non-treated cells, suggesting that the partial reversal of tumor exosome-mediated inhibition of NK cell tumor cytotoxicity may account for the anticancer properties of curcumin. The antitumor activities of curcumin and its isoxazole analog were not affected by multiple gene expression changes in a multidrug-resistant (MDR) model of the MCF-7 breast cancer cell line [21]. Treatment of breast cancer cells, having up-regulated expression of nicotinamide *N*-methyltransferase (NNMT), with curcumin resulted in reduction of the Nicotinamide *N*-methyltransferase (NNMT) level [22]. In addition to curcumin, several derivatives [7,23–25] and analogs [7,21,26] of curcumin were also found to have anticarcinogenic property against various breast cancer cell lines.

Several in vivo studies have established the chemopreventive effect of curcumin against breast cancer. In 1998 a group studied curcumin's capacity to inhibit 7,12-dimethylbenzanthracene (DMBA) induced mammary tumor and the in vivo formation of mammary DMBA–DNA adducts in the female rat. Administration (i.p.) of curcumin at 100 and 200 mg/kg doses prevented the development of the number of palpable mammary tumors and mammary adenocarcinomas significantly. The in vivo formation of mammary DMBA–DNA adducts also was depressed in animals administered with curcumin and there was no significant enhancement of liver GST activity following curcumin administration. However, it was also showed that animals fed with diets containing 1.0% curcumin had no effect on DMBA-induced mammary tumor. In 1996, Pereira et al. showed that curcumin (8 and 16 g/kg in diet) was weakly effective in DMBA induced mammary carcinogenesis. Another study evaluated the modulating effects of turmeric (T), ethanolic turmeric extract (ETE) and curcumin-free aqueous turmeric extract (CFATE) on the initiation or post-initiation phases of DMBA-induced mammary tumorigenesis in female Sprague–Dawley rats. Dietary administration of 1% turmeric/0.05% ethanolic turmeric extract 2 weeks before, on the day of DMBA treatment (day 55) and 2 weeks after the single dose (15 mg/animal) of DMBA (during the initiation period) resulted in significant suppression of DMBA-induced mammary tumorigenesis as seen by a reduction in tumor multiplicity, tumor burden and tumor incidence. In another study it was showed that feeding 1% dibenzoylmethane (DBM), a derivative of curcumin in AIN 76A diet, inhibited both the multiplicity and incidence of DMBA-induced mammary tumor by 97%. In 2001, it was also showed that feeding 1% DBM diet

inhibited formation of DMBA–DNA adducts in mammary glands and the development of mammary tumors in Sencar mice. The chemopreventive effect of curcumin on diethylstilbestrol (DES)-induced tumor promotion of rat mammary glands initiated with radiation was evaluated in a study. The administration of dietary curcumin significantly reduced the incidence (28.0%) of mammary tumors. Multiplicity and Iball's index of mammary tumors were also decreased by curcumin. Rats fed with the curcumin diet showed a reduced incidence of the development of both mammary adenocarcinoma and ER(+)PgR(+) tumors in comparison with the control group. Whole mounts of the mammary glands showed that curcumin yielded morphologically indistinguishable proliferation and differentiation from the glands of the control rats. The effect of curcumin on gamma-radiation induced mammary tumors was also demonstrated in rats [2].

In addition to the chemopreventive effects, antimetastatic effect of curcumin was also established by the in vivo model studies. In a xenograft model study (nude mice) conducted in our own laboratory, the primary tumor was surgically removed after 58–60 days of tumor cell inoculation and dietary curcumin (2%) was given to the animals starting from fifth day to 5 week of primary tumor removal. We observed that administration of curcumin significantly decreased the incidence of breast cancer metastasis to the lung and suppressed the expression of NF-κB, COX-2, and MMP-9. Another group also evaluated the effect of curcumin on lung metastasis of breast cancer. In this study, intercardiac inoculation of breast cancer cells was done in the nude mice and the animals were fed with diet containing 1% curcumin. Thirty-five days after tumor implantation the animals were sacrificed and enumerated the lung metastases. It was observed that all the animals in the untreated group had lung metastasis whereas 21% animals in the treated group were metastases free. In the control group only 17% animals were having few metastatic nodules (metastatic score <3) whereas in curcumin-treated group 68% animals had few metastatic nodules [2]. In contrast to the above in vivo studies, Somasundaram et al., [27] reported a significant inhibition of tumor regression in a xenograft mouse model of human breast cancer. These contradictory findings could have been caused by the difference in administered doses as well as the time of treatment. For example, the authors studied the effect of curcumin in a breast xenograft model for 3 days, which is not normally suitable for the xenograft model studies. Even though it is the only study reporting the inhibition of tumor regression, further studies are needed to resolve the contradictions about the effectiveness of curcumin against breast cancer in vivo.

An early clinical trial, evaluated the effectiveness of topical application of a curcumin ointment in seven patients with breast cancer. In this study, 71% of the patients showed a positive response measured as reduction in lesion size, pain, itching and exudates [7].

3.2. Gastrointestinal cancers

3.2.1. Oesophageal cancer

Oesophageal cancer is the seventh leading cause of death from cancer in men, with a mean 5-year survival rate in the United States of 15.6%. In the United States, there were an estimated 15,560 new cases of and 13,940 deaths from oesophageal cancer in 2007 [4]. The standard treatment for surgically resectable tumors is esophagectomy; radiochemotherapy is used for locally advanced, unresectable tumors. Even with these therapies, however, both local regional tumor control and the overall survival of patients with oesophageal cancer remain poor, and treatments are associated with significant adverse effects, including treatment-related pneumonitis, postoperative pulmonary complications, oesophagitis, and pericarditis [28]. Innovative treatment strategies are needed to improve the outcome of patients with oesophageal cancer.

Curcumin could be a potential candidate for use in the treatment of esophageal cancer, few studies have examined it in this disease and no in vitro evaluations of its anticancer effects in oesophageal cancer cells have been reported. However, curcumin was found to inhibit the cytokine-induced activation of iNOS, JNK, VCAM, and NF-κB in human oesophageal microvascular endothelial cells isolated from normal human oesophageal tissues [29]. Since inflammatory molecules-like NF-κB are overexpressed in several tumor tissues, these results may be indirect evidence that curcumin may be effective against oesophageal cancer. Two in vivo studies have been reported with curcumin in oesophageal cancer. In one, dietary curcumin (500 ppm) fed during initiation and post-initiation stages inhibited the incidence of oesophageal carcinogenesis by 27% and 33%, respectively, in rats [2]. In the other study, the efficacy of curcumin as a chemopreventive agent was assessed by measuring the modulation in the

incidence of neoplastic change in rat oesophagus [30].

3.2.2. Gastric cancer

In the United States, in 2007, there were an estimated 21,260 new cases of and 11,210 deaths from gastric cancer [4]. Current major modalities for the treatment of gastric cancer include surgery and chemotherapy, but local recurrence and distant metastases, which lead to poor survival rates, are still unresolved issues in this disease [31], indicating that modified treatment strategies are needed. The cytotoxic effect of curcumin on gastric carcinoma cell lines has been established. In a study curcumin and 5-fluorouracil (5-FU) synergistically inhibited the growth of gastric carcinoma cells. In another study, curcumin reversed the MDR of a human gastric carcinoma cell line in correlation with a decrease in P-gp function and a promotion of caspase-3 activation [7].

Several in vivo chemoprevention studies have been reported with curcumin in gastric cancers. In some of the chemoprevention studies, curcumin fed as dietary turmeric (2% or 5%) to mice and Syrian golden hamsters significantly inhibited the benzopyrene-induced forestomach tumors. Furthermore, the incidence and multiplicity of forestomach tumors induced by benzopyrene in female Swiss mice were significantly inhibited by pure curcumin given 2 weeks before, during and after the carcinogen treatment. Other studies also revealed the chemopreventive effect of curcumin on benzopyrene-induced forestomach cancer. A significant reduction in benzopyrene-induced forestomach papillomas in mice due to treatment with dietary turmeric extract containing curcumin was also reported. It was also showed that curcumin inhibited MNNG-induced duodenal tumor in mice and gastric cancer in rats [7].

3.2.3. Intestinal cancer

According to the estimates of American Cancer Society, 5640 new intestinal cancers will have been diagnosed and 1090 patients will have died from intestinal cancer in 2007 [4]. Recent advances in neoadjuvant therapies have contributed to improved survival for patients with intestinal cancer [32] and various adjuvant treatment modalities are now being explored.

So far, the efficacy of curcumin in intestinal cancer has been shown in a few animal studies. In vivo studies using mouse models have proved that curcumin modifies apoptosis resistance, leading to the inhibition of tumor formation and the prevention of adenoma development in the intestinal tract. The chemopreventive effect of curcumin for intestinal tumors in Min/+ mice was investigated. A dietary level of 0.15% curcumin decreased tumor formation in Min−/− mice by 63%. Examination of intestinal tissue from the treated animals showed the tumor prevention by curcumin was associated with increased enterocyte apoptosis and proliferation. Curcumin also decreased expression of the oncoprotein β-catenin in the erythrocytes of the Min/+ mouse, an observation previously associated with an antitumor effect. Curcumin enhanced PhIP-induced apoptosis and inhibited PhIP-induced tumorigenesis in the proximal small intestine of Apc (min) mice. Evaluation of the preventive effect of curcumin on the development of adenomas in the intestinal tract using a Min/+mouse model showed promising chemopreventive effect. Mice received dietary curcumin for 15 weeks and curcumin at 0.1% in the diet was without effect whereas at 0.2% and 0.5% it reduced adenoma multiplicity by 39% and 40%, respectively. How curcumin is metabolized in intact rat intestinal sacs in situ was evaluated and showed that curcumin undergoes extensive metabolic conjugation and reduction in the gastrointestinal tract and that the process of metabolism is more complex in human than in rat intestinal tissue [7]. Experiments performed on intestinal tumors in C57BL/6J-Min/+ (Min/+) mice demonstrated that curcumin has a regulatory role in lymphocyte-mediated immune function [33]. Further, levels of COX-2 protein expression have been found to reflect the retardation of adenoma development in mouse intestines after treatment with curcumin [34].

In a phase I clinical trial six patients with intestinal metaplasia of the stomach was treated with 0.5–12 g/day of curcumin for 3 months. In this study one out of the six patients showed histologic improvement in precancerous lesions after the treatment [2].

3.2.4. Hepatic cancer

Hepatocellular carcinoma (HCC) is an aggressive cancer, and its incidence is increasing in the United States and worldwide. In 2007, an estimated 19,160 new cases of HCC will have been diagnosed and 16,780 patients will have died from HCC in the United States [4]. Novel neoadjuvant treatments are

being investigated for the improvement of the current treatment strategies [35].

Several studies have examined the anticarcinogenic activity of curcumin in hepatic cancer cells in vitro. In one of these studies, conducted in curcumin-treated human hepatoblastoma cells, several hallmarks of apoptosis, including DNA laddering, chromatin condensation, fragmentation, and apoptosis-specific cleavage of 28S and 18S ribosomal RNA were observed. Curcumin has also exhibited significant antiinvasion activity in human HCC SK-Hep-1 cells, an effect that is associated with curcumin's-inhibitory action on MMP-9 secretion. Curcumin undergoes metabolic conjugation and reduction in subcellular fractions of human and rat hepatic tissues [7]. It has also been established that the elevation of GSH levels mediates the effect of curcumin in hepatocytes [36].

Curcumin has also been found to interrupt the cell cycle, to have cytotoxic effects, and to have a role in antiproliferation and the induction of apoptosis in a hepatocarcinoma cell line. Curcumin is a potent inhibitor of phenol sulfotransferase (SULT1A1) in human liver and extrahepatic tissues [37]. Curcumin inhibited the IL-6 production, histone acetyltransferase (HAT) activity, and AP-1 activation [38] and prevented cell death and apoptotic biochemical changes, such as the mitochondrial release of cytochrome *c*, the activation of caspase-3, and the cleavage of PARP in human hepatoma cells [7,39]. Another proposed mechanism for curcumin's inhibition of tumor growth in HCC is through the inhibition of hypoxia-inducible factor-1 by degrading the aryl hydrocarbon receptor nuclear translocator [40,41]. Further, it has been shown that mitochondrial hyperpolarization is a prerequisite for curcumin-induced apoptosis and that mtDNA damage is the initial event in a chain leading to apoptosis in HepG2 cells [42]. In an in vitro study using hepatic cancer cells, a combination of curcumin and cisplatin had synergistic antitumor effects, and that with doxorubicin additivity or sub-additivity [7].

A considerable number of reports have also described curcumin in HCC in vivo. In one of these studies, curcumin significantly reduced the number of gammaglutamyl transpeptidase-positive foci, a characteristic considered to be the precursor of hepatocellular neoplasm, in rats. Curcumin also had anticarcinogenic effects mediated through the induction of glutathione-linked detoxification enzymes in rat livers. In a murine hepatocarcinogenesis model, 5-week-old C3H/HeN mice were injected intraperitoneally with DENA. One group of the mice were fed with 0.2% curcumin-containing diet, starting 4 days before DENA injection and until termination of the experiment. At the age of 42 weeks, the curcumin group had 81% less multiplicity and 62% fewer hepatocarcinomas than the non-treated group. It also suppressed liver inflammation in rats. Liver was identified as the major site for the metabolism of curcumin, and the major metabolites in suspensions of human or rat hepatocytes were identified as hexahydrocurcumin and hexahydrocurcuminol. In rats, in vivo, curcumin glucuronide and curcumin sulfate were identified as the major products of curcumin biotransformation, whereas hexahydrocurcumin, hexahydrocurcuminol, and hexahydrocurcumin glucuronide were present only in small amounts. Another in vivo study showed that curcumin mixed into a diet could achieve levels of the drug in the liver sufficient to explain its pharmacological effects. Dietary curcumin increased the activity of hepatic UGT enzymes, which can detoxify carcinogens, in male Wistar rats. In an orthotopic implantation model, curcumin suppressed both intrahepatic metastases and the development of altered hepatic foci (AHF) in rat livers. Inhibition of tumor growth by systemic administration of 20 μg/kg curcumin for 6 consecutive days to rats bearing the highly cachectic Yoshida AH-130 ascites hepatoma was also reported. In one of the studies, hepatocellular carcinoma cells were injected subcutaneously in mice and 3 weeks after cell injection, a tumor fragment from the injection site was implanted to liver. Curcumin (100–200 mg/kg) was administered after the implantation for 20 days and then the effect of curcumin treatment was evaluated. Although the growth of tumors at the implanted site was not affected by the curcumin treatment there was a significant and dose dependant decrease in number of intrahepatic metastases [43].

Curcumin also prevented the induction of hepatic hyper plastic nodules, body weight loss, and hypoproteinemia in carcinogen induced as well as xenograft hepatic cancer models. Both curcumin and curcumin complexed with manganese prevented the increase of hepatic lipid peroxidation expressed as MDA level in mice. The antiangiogenic activity of curcumin in hepatocarcinoma cells implanted in nude mice was found to be mediated through the reduction of biomarkers COX-2 and VEGF [43]. In a pilot trial with 12 patients with hepatic metas-

tases from colorectal cancer the concentrations of the curcumin in normal and malignant human liver tissue after patients received 450–3600 mg of curcumin daily for 1 week prior to surgery were not sufficient to elicit pharmacologic activity, perhaps because of the extensive degree to which curcumin was metabolized in the intestine [7].

3.2.5. Pancreatic cancer

Pancreatic cancer is one of the most common cancers, and the fourth leading cause of cancer-related mortality, accounting for about 6% of all cancer-related deaths, in both men and women. The median age of diagnosis is 72 years [3]. Despite advances in molecular pathogenesis, patients with pancreatic cancer have a mean relative 5-year survival rate of 5%, and the disease remains a major unsolved health problem [4]. In an attempt to improve survival rates, recent therapeutic approaches have mostly focused on evaluating chemotherapy regimens in which gemcitabine is combined with a second cytotoxic agent.

Research over the past decade has indicated that curcumin has an anticarcinogenic effect in various pancreatic cell lines, with numerous mechanisms having been proposed to account for this effect. In human pancreatic cancer MIA PaCa-2 cells, curcumin was found to inhibit the farnesyl protein transferase [7]. Also, NF-κB was found to be overexpressed in human pancreatic tumor tissues and cell lines; investigators suggested that this overexpression could be inhibited by curcumin because it has the ability to suppress the NF-κB expression [44–46]. Likewise, curcumin reduces numerous IL-8 bioactivities that contribute to tumor growth and the cell viability of pancreatic carcinoma cells [7,47]. Other mechanisms have been proposed to account for the growth-inhibitory effect of curcumin alone [48] or in combination with celecoxib [49] including the down-regulation of COX-2, EGFR, ERK1/2 [50], and Notch-1 [51]. When coupled with gemcitabine, curcumin has been observed to have synergistic antiproliferative effects in pancreatic cancer cell lines [52,53]. Liposomal curcumin down-regulated NF-κB machinery, suppressed growth and induced apoptosis of human pancreatic cells in vitro [2]. A polymeric nanocurcumin formulation also demonstrated a therapeutic efficacy comparable to that of free curcumin in a panel of human pancreatic cancer cell lines in vitro, and the mechanisms of action of nanocurcumin in pancreatic cancer cells mirrored those of free curcumin[54].

Two in vivo studies were reported showing the antitumor activity as well as chemosensitization effect of curcumin against pancreatic cancer. In a xenograft model study, pancreatic cancer cells were injected subcutaneously on the side of the abdomen of female nude mice. Once tumor masses became established, animals were randomized to receive intravenous liposomal curcumin (40 mg/kg, 3 time per week) for 20 days. Treatment with liposomal curcumin resulted in reduced tumor size and visible blanching of tumors showing decreased expression of CD31 as well as VEGF and IL-8. These results indicate that curcumin suppressed pancreatic carcinoma growth in murine xenograft models and inhibited tumor angiogenesis [55]. A recent study conducted in our group investigated the chemosensitization effect of curcumin using an orthotopic pancreatic cancer model. After 1 week of implantation, mice were randomized into the following treatment groups: untreated control (olive oil, 100 μL daily), curcumin alone (1 g/kg/day), gemcitabine alone (25 mg/kg twice weekly by i.p. injection) and combination of curcumin and gemcitabine. The animals were sacrificed 6 weeks after tumor cell injection and 5 weeks from the date of treatment. The tumor volume in the combination of curcumin and gemcitabine group was significantly lower than the gemcitabine alone or control group indicating the chemosensitizing effect of curcumin. Our results showed that curcumin in combination with gemcitabine significantly down-regulated the expression of cell proliferation marker Ki-67 in tumor tissues compared with the control group. Further, curcumin alone significantly suppressed the expression of microvessel density marker CD31 and the presence of gemcitabine further enhanced the down-regulation of CD31 [2].

In a clinical trial, researchers evaluated the effect of oral curcumin with piperine on the pain, and the markers of oxidative stress in patients with tropical pancreatitis (TP). 20 patients with tropical pancreatitis were randomized to receive 500 mg of curcumin with 5 mg of piperine, or placebo for 6 weeks, and the effects on the pattern of pain, and on red blood cell levels of malonyldialdehyde (MDA) and glutathione (GSH) were assessed. There was a significant reduction in the erythrocyte MDA levels following curcumin therapy compared with placebo; with a significant increase in GSH levels. There was no corresponding improvement in pain [2].

The studies from our group [56] showed that curcumin inhibited pancreatic cancer in patients. 25

patients were enrolled in this study. Patients received 8 grams of curcumin by orally every day until disease progression, with restaging every 2 months. Serum cytokine levels for interleukin IL-6, IL-8, IL-10, and IL-1 receptor antagonists and peripheral blood mononuclear cells (PBMC) expression of NF-κB and COX-2 were monitored. Out of 25 patients, 21 were evaluable for response. Circulating curcumin was detectable in glucuronide and sulfate conjugates forms, albeit at low steady-state levels, suggesting poor oral bioavailability. Two patients demonstrated clinical biologic activity. One had ongoing stable disease for more than 18 months and, interestingly, one additional patient had a brief, but marked, tumor regression (73%), accompanied by significant increases (4- to 35-fold) in serum cytokine levels (IL-6, IL-8, IL-10, and IL-1 receptor antagonists). No toxicities were observed. Curcumin down-regulated expression of NF-κB, COX-2 and phosphorylated STAT3 in PBMC from patients (most of whom had baseline levels considerably higher than those found in healthy volunteers).

3.2.6. Colorectal cancer

Colorectal cancer is the third leading cause of cancer-related death in American adults, accounting for 10% of all cancer deaths in the country. Patients have a mean 5-year survival rate of 61% [4]. Because approximately 90% of all deaths from this cancer are a result of metastases from primary tumors and investigators are working to modify treatment strategies specifically to control the metastatic activity.

Studies using various colorectal cell lines have proven curcumin's use as a therapeutic agent and its ability to act through numerous target molecules. For example, curcumin has been shown to disrupt Lovo cells in the S, G2/M phase and interrupt Wnt signaling and adhesion pathways causing G2/M phase arrest and apoptosis in HCT-116 cells, regardless of prostaglandin synthesis. Curcumin-induced apoptosis is a result of PARP cleavage, caspase 3, reduction in Bcl-xL level, and increased activity of caspase-8, which encourages Fas signaling of apoptosis. Curcumin reduces NAT1 mRNA expression and AF-DNA adducts formation in human colon tumor cells. Curcumin was found to inhibit the proliferation of and induce apoptosis in colorectal cell lines; [7,57]. Heat shock aids colon cancer cells by inhibiting the discharge of apoptosis-inducing factors, an event that is enhanced by curcumin [58]. Curcumin causes cell shrinkage, chromatin condensation, and DNA fragmentation, by enhancing DNA damage in HT-29 cells and HCT-116 colonocytes; it also increases GADD153 mRNA and protein expression [7,59]. Curcumin upregulates TRAIL-induced apoptosis via ROS-mediated DR5 activation in human renal cancer cells [7]. Likewise, curcumin enhanced the silencing of hsp70 expression and may therefore prove to be a valuable therapeutic agent for cancers whose resistance is due to hsp70 expression [60]. EF24, a synthetic curcumin analog, induces apoptosis in HT-29 cells through a redox-dependent mechanism [7]. Similarly, the curcumin derivative HBC disrupts cell cycle progression in HCT15 cells by antagonizing Ca^{2+}/CaM function [61].

The fact that curcumin-induced apoptosis is regulated by Bax suggests that the targeting of Bcl-xL or Smac can be used to treat Bax-deficient, chemotherapy-resistant cancers [62,63]. Together, curcumin and either 5-FU or celecoxib downmodulate COX-2 expression via the inhibition of prostaglandin formation by curcumin and curcuminoids [7,64]. Curcumin can also induce apoptosis via a parallel ceramide-associated pathway and ROS-associated mechanism that converges at JNK activation [65]. In vitro, curcumin activates JNK, p38 MAPK, and AP-1 transcriptional activity. Similarly, it inhibits neurotensin-mediated activator protein-1, NF-κB activation, Ca^{2+} mobilization, PGE-2, and EGFR and downregulates COX-1 and -2, MMP-2 and -9, IL-8 gene induction, and colon cancer cell migration [65–70]. Curcumin has also proven effective at the mRNA level [71]. Curcumin downregulates sulfoconjugation and weakly inhibits the glucuronosyl conjugation of 1-naphthol in Caco-2 cells [72]. Curcumin coupled with ERRP significantly regulates downstream effectors, including NF-κB, Akt, BAD activation, and procaspase-3, in HCT-116 and HT-29 cells [73]. Curcumin in conjugation with FOLFOX inhibits colon cancer cells by inhibiting the EGFR and IGF-1R signaling pathways [74]. Treatment with curcumin and epigallocatechin gallate reduced the amount of viable Apc mutant cells by 220–430%, more than each agent alone did [75].

Curcuminoids obstruct cell proliferation and programmed cell death in primary colon cancer cells [76]. Liposomal curcumin attenuates colorectal cancer by reducing CD31, VEGF, and IL-8 expression. This inhibition may be enhanced by the addition of oxaliplatin for the treatment of p53wt and p53

mutant colorectal tumors, as shown in HCEC, HT-29, and HCT-116 cell lines [77,78]. Some curcumin derivatives were also found to be effective against colon cancer cells. Dimethoxycurcumin, for example, is more potent than curcumin in inhibiting proliferation and inducing apoptosis in HCT116 cells [79].

Several in vivo studies were reported to show the chemopreventive as well as anticancer activity of curcumin against colorectal cancer. Wargovich et al. [80] also showed the chemopreventive activity of curcumin against carcinogen-induced ACF in rats. Sulindac, curcumin, and PEMC administered during promotion and progression have been found to upregulate apoptosis in rat colonic tumors [7]. Dietary curcumin (0.2%) inhibited the formation of carcinogen-induced colorectal tumors in rats [81]. In rodent models, curcumin hinders tumor suppressor p53 function, but in AOM-induced rat models, apoptosis is induced via a mitochondrial pathway [2,82]. The modulatory role of dietary curcumin on azoxymethane (AOM) induced aberrant crypt foci (ACF) formation in the colon of F344 rats was evaluated and showed that AOM-induced colonic ACF were significantly inhibited in the animals fed with the curcumin (2000 ppm/day) diet. The chemopreventive activity of curcumin was also observed when it was administered before, during, and after carcinogen treatment as well as when it was given only during the promotion/progression phase of colon carcinogenesis in rats. The effect of tetrahydrocurcumin (THC) on 1,2 dimethylhydrazine (DMH) induced colon carcinogenesis was evaluated and the results showed that THC significantly decreased both upper and lower half compartments of colonic crypts. Several studies evaluated the effect of curcumin on azoxymethane (AOM) induced colon cancer and showed a significant inhibition of colon carcinogenesis after the treatment with curcumin. Curcumin inhibited TNBS-, DNB-, and DNCB-induced colitis in rodents [2].

Dimethylhydrazine (DMH)-induced rat colon carcinogenesis model was used for evaluation of the synergistic-inhibitory effect between curcumin and catechin in light of ACF formation and tumor incidence. The results of this study indicated that curcumin, catechin and their co-treatment caused significant inhibition of DMH-induced ACF and colon carcinogenesis as compared with untreated DMH-induced rat models [83]. Similarly, in another study it was showed that curcumin and celecoxib additively inhibits the growth of DMH-induced colorectal cancer in rats [2]. An in vivo study by Kwon and Magnuson [84] suggested that during initiation, AOM inhibits colonic COX-1 expression without affecting COX-2 and dietary curcumin may increase COX-2 expression to compensate AOM-induced reduction of COX-1 expression in rats. In male rats, curcumin and curcumin analog increased celecoxib-mediated growth inhibition [7]. Similarly, intragastric administration of a bisdemethoxy curcumin analog (BDMCA) or curcumin to DMH-treated rats significantly decreased colon tumor incidence [85,86].

The preclinical anticancer activity of a liposomal curcumin formulation in colorectal cancer was also recently evaluated. This study also compared the efficacy of liposomal curcumin (40 mg/kg administered i.v.) with that of oxaliplatin, a standard chemotherapeutic agent for colorectal cancer. Significant tumor growth inhibition was observed in Colo205 and LoVo xenograft models in mice. Tumors from animals treated with liposomal curcumin showed an antiangiogenic effect measured as attenuation of CD31, vascular endothelial growth factor, and interleukin-8 expression. Thus, this study established the comparable or greater growth-inhibitory and apoptotic effects of liposomal curcumin with oxaliplatin in vivo in colorectal cancer [77].

The pharmacodynamic and pharmacokinetic effect of oral *Curcuma* extract in patients with colorectal cancer was evaluated. Fifteen patients with advanced colorectal cancer refractory to standard chemotherapies received *Curcuma* extract daily for up to 4 months. The results showed that oral *Curcuma* extract was well tolerated, and dose-limiting toxicity was not observed. Neither curcumin nor its metabolites were detected in blood or urine, but curcumin was recovered from feces. Curcumin sulfate was identified in the feces of one patient. A dose-escalation pilot study of a standardized formulation of *Curcuma* extract in 15 patients with advanced colorectal cancer revealed a dose dependant inhibition of COX-2 activity, measured as basal and LPS-mediated PGE(2) production, in blood revealing the efficacy of curcumin in colorectal cancer. Ingestion of 440 mg of *Curcuma* extract for 29 days was accompanied by a 59% decrease in lymphocytic glutathione *S*-transferase activity. At higher dose levels, this effect was not observed. Leukocytic M(1)G levels were constant within each patient and unaffected by treatment. Radiologically stable disease was demonstrated in five patients for

2–4 months of treatment. Another study showed that a daily dose of 3.6 g curcumin engendered 62% and 57% decreases in inducible PGE(2) production in blood samples taken 1 h after dose on days 1 and 29, respectively, in advanced colorectal cancer patients. Yet another pilot trial, involving 12 patients with hepatic metastases from colorectal cancer who received 450–3600 mg of curcumin daily, for 1 week prior to surgery, oral administration of curcumin results in concentrations of the agent in normal and malignant human liver tissue, which are sufficient to elicit pharmacological activity. The results of this study suggested that hepatic curcumin levels sufficient to exert pharmacological activity are not achieved in humans with the above-mentioned dose of curcumin and that this may be due to extensive intestinal metabolism of curcumin leading to lower bioavailability. Curcumin coupled with quercetin significantly decreased the size and number of ileal and rectal adenomas in patients with FAP [2,7].

3.3. Genitourinary cancers

3.3.1. Bladder cancer

More than 67,000 people in the United States are diagnosed each year with bladder cancer [3]. Bladder cancer causes 14,000 deaths each year [4], many of which involve advanced, unresectable, chemotherapy-resistant tumors [87]. Consequently, new chemotherapeutic regimens are needed.

Numerous reports indicate that curcumin has activity against bladder cancer. For example, curcumin has been shown to suppress the proliferation of bladder cancer cells in culture either through the suppression of NF-κB [88,89] or through the down-regulation of cyclin A and up-regulation of p21 [90]. Certain synthetic analogs of curcumin have been shown to exhibit activity against bladder cancer cell lines [91,92]. It was demonstrated that curcumin effectively inhibits tumor implantation and growth in a murine bladder tumor model [7]. A phase I clinical trial in patients with resected bladder cancer has indicated that up to 12 g per day of curcumin for 3 months is pharmacologically safe, and the investigators also noted an indication of histologic improvement of precancerous lesions in one out of two patients [2].

3.3.2. Kidney cancer

The most common type of kidney cancer develops within the small tubes of the kidneys and is referred to as renal cell adenocarcinoma (RCC). In 2007, 51,190 new cases of RCC will have been diagnosed and 12,890 patients will have died of RCC in the United States [4]. Despite definitive surgical treatment, one third of the patients diagnosed with RCC develop postoperative metastases. The 5-year overall survival for patients with metastatic RCC is 0–10%, with a median survival time of 10 months [4]. Unresectable and metastatic RCC are associated with poor prognosis chemoresistance, and radioresistance, which leads to lower survival rates. Efforts are ongoing to overcome the chemo- and radioresistance of RCC using new treatment regimens.

Curcumin has been shown to have apoptotic and antiproliferative effects against RCC in vitro and in vivo. In human kidney cancer cells, curcumin upregulates apoptotic events such as cell shrinkage, chromatin condensation, and DNA fragmentation [93] and inhibits FPTase [94]. Curcumin serves as a COX-I and COX-2 inhibitor [95]; inhibits microsomal lipid peroxidation and DNA damage [96]; deactivates the Akt pathway; downregulates Bcl-2, Bcl-xL, and IAP proteins [97]; and increases TRAIL-induced apoptosis by augmenting DR5 expression at the mRNA and protein levels by producing reactive oxygen species (ROS) [98]. In HKC cells, curcumin reduces tumor growth and the side effects when activated via the hydrolysis of prodrugs [91]. An in vivo study demonstrated that dietary curcumin treatment reduced risk for kidney cancer metastasis in rats [99].

3.3.3. Prostate cancer

Prostate cancer remains the second most lethal cancer after lung cancer [4]. Curcumin has shown activity against various prostate cancer cells, such as LNCaP, DU145, C4-2B, and PC3. Curcumin can induce programmed cell death in androgen-dependent and androgen-independent prostate cancer cells. It can inhibit capillary tube formation and cell migration and exert significant effects on actin cytoskeletons in prostate cancer cells [7,100–102]. Several mechanisms have been proposed to explain curcumin's anticancer effects in prostate cancer cells. For example, curcumin upregulates the expression of the maspin gene and downmodulates the expression of androgen receptor (AR), AP-1, cyclin D1, NF-κB, and camp response element binding (CREB)-binding protein and EGFR tyrosine kinase activity [7,103]. By inducing p21 and C/EBPbeta expression and suppressing NF-κB activation, curcumin augments the cytotoxicity of chemotherapeu-

tic agents in prostate cancer cells and induces the degradation of cyclin E expression [7].

In prostate cancer cells curcumin was found to act as an inhibitor of arachidonate 5-lipoxygenase [104]. Likewise, curcumin and TRAIL together cause apoptosis via both receptor-mediated and chemical-induced pathways, owing to an enhanced sensitivity of tumor cells to NF-κB [105–107]. Curcumin interferes with osteoblastic and osteoclastic cell components, inhibiting growth factor collaboration between prostate cancer cells [108]. Due to its organic structure as a Michael acceptor, curcumin serves as a HAT inhibitor [109]. Curcumin downregulates the expression of NKX3.1 via AR expression and DNA-binding activity [110]. Curcumin upregulates MKP5, thus decreasing cytokine-induced p38-dependent proinflammatory changes in normal epithelial cells [111]. Curcumin inhibits VIP-induced COX-2 expression and VIP-stimulated VEGF mRNA expression via the inhibition of AP-1 binding [112–114]. In PC3 cells, curcumin downregulates MDM2 proteins and mRNA. enhances the expression of the tumor suppressor p21, and inhibits IκBα [101,115]. Curcumin can also inhibit prostate cancer via the Akt pathway or the induction of apoptosis by Bcl-2 family members and mitochondrial p53 [102,116,117].

A curcumin derivative, HMBME, also targets the Akt and NF-κB pathway [118]. Likewise, other curcumin derivatives, diacetyldemethoxycurcumin, triacetyldemethylcurcumin, and 4-ethoxycarbonylethyl curcumin may exhibit greater activity against prostate cancer cells than curcumin itself and serve as potential agents against prostate cancer [24,119,120]. Another curcumin analog, EF24, shows anticancer effects that are regulated by the redox-mediated induction of apoptosis, while other analogs act as AR antagonists [121,122]. Still some curcuminoids may reduce the sprout formation of endothelial cells via the inhibition of P-12-LOX [123]. Curcumin and its derivatives possess therapeutic abilities as potent radiosensitizers by overcoming the effects of radiation-induced prosurvival gene expression in prostate cancer [7]. PEITC and curcumin inhibit cell proliferation and cause apoptosis by targeting EGFR, Akt, and NF-κB signaling pathways [124].

In order to investigate the anticancer potential of curcumin against prostate cancer, androgen-dependent LNCaP prostate cancer cells were injected subcutaneously to mice. The experimental group received a synthetic diet containing 2% curcumin for up to 6 weeks. At the endpoint, mice were killed, and sections taken from the excised tumors were evaluated for pathology, cell proliferation, apoptosis, and vascularity. Curcumin induced a marked decrease in the extent of cell proliferation as measured by the BrdU incorporation assay and a significant increase in the extent of apoptosis as measured by an in situ cell death assay. Moreover, microvessel density as measured by CD31 antigen staining decreased significantly [18]. In vivo, PEITC and curcumin alone or in combination possess significant cancer-preventive characteristics in PC-3 prostate tumor xenografts in mice [125]. In another study [126] researchers subcutaneously injected highly metastatic androgen-independent prostate cancer cell lines into the footpads of SCID mice. The mice were grouped in to control and experimental groups. The control group was given a placebo via oral gavage. And the experimental group received an equal volume of placebo, mixed with curcumin, at a dosage of 5 mg/kg. All mice continued to receive placebo or curcumin (three times per week) for 10 weeks. The mean tumor volumes at 4 weeks after tumor inoculation in the control and experimental animals were determined to be $168.6 \pm 40.7\ mm^3$ and $99.5 \pm 27.2\ mm^3$, respectively. Curcumin was shown to induce a marked reduction of MMP-2, and MMP-9 activity in the tumor-bearing site. The metastatic nodules in vivo were significantly fewer in the curcumin-treated group than untreated group. Li et al. [115] evaluated the antitumor, chemosensitizing and radiosensitizing effect of curcumin using a xenograft prostate cancer model. The xenograft model was established by injecting prostate cancer cells into the left inguinal area of nude mice. Mice bearing tumors of 100 mg were randomly divided into multiple treatment and control groups. Curcumin, dissolved in cottonseed oil, was given by gavage (5 mg/day, 5 days per week) for 4 weeks. Gemcitabine (160 mg/kg) was given by i.p. injection on days 7, 14, and 21, and radiation (3 Gy) was administered on days 4, 6, and 10. Analysis of tumors collected at the end of the experiment showed that curcumin reduced the expression of MDM2 oncogene in xenografts treated with curcumin alone, and in xenografts treated with combinations of curcumin plus gemcitabine or irradiation. These results indicate a novel mechanism of action that may be essential for curcumin's chemotherapeutic effects.

The effect of zyflamend, a herbal preparation containing curcumin against high-grade prostatic

intraepithelial neoplasia (HGPIN) was evaluated in patients. A patient with HGPIN was treated with zyflamend, three times a day for 18 months. After 6 months the biopsy revealed benign prostatic hyperplasia alone and after 18 months biopsy was negative for cancer and PIN indicating that the patient was cancer and HGPIN free [2].

3.4. Gynecologic cancers

3.4.1. Cervical cancer

Cervical cancer is important not only because it is the most prevalent cancer in women in several developing countries, but also because it is often diagnosed in young patients – the age at diagnosis 48 years – giving the treatment of this disease a degree of societal importance [3]. The understanding that infection with human papillomaviruses (HPVs) leads to the development of cervical cancer, predominantly through the action of viral oncogenes, may lead to effective treatment strategies. If applied wisely, HPV-related technology should minimize the incidence of cervical cancer, along with the morbidity and mortality associated with the disease. The in vitro antitumor activity of curcumin in HPV-associated cells has been established [127]. Curcumin modulates the in vitro expression and function of P-gp in multidrug-resistant human KB-V1 cells [7,128] and sensitizes cisplatin-resistant SiHa cells to cisplatin-induced apoptosis [129], indicating its ability to reverse MDR in cervical cancer cells. The effect of curcumin in HPV-associated cells was found to involve the down-regulation of viral oncogenes, NF-κB and AP-1 [7,130]. Similarly, a major metabolite of curcumin called THC increased the sensitivity of vinblastine, mitoxantrone, and etoposide in a drug-resistant human cervical carcinoma cell line [131]. In a phase I clinical trial, a daily 0.5–12 g dose of curcumin taken orally for 3 months resulted in the histologic improvement of precancerous lesions in one out of four patients with uterine cervical intraepithelial neoplasms [2].

3.4.2. Ovarian cancer

Ovarian cancer is the eighth most commonly diagnosed cancer in women in the United States. Of the estimated 22,430 women who will have been diagnosed with ovarian cancer in 2007, the majority will present with advanced-stage disease [4]. Early-stage ovarian cancer has a good prognosis, but the majority of patients with advanced-stage disease have relapses despite optimal primary therapy. This has been attributed largely to limitations in cytotoxic therapy, including intrinsic and acquired drug resistance and the lack of specificity of agents targeting mechanisms of disease progression [132]. The treatment of recurrent disease often prioritizes palliative care and seeks to provide symptom control, trigger tumor regression, and improve quality of life.

Some in vitro studies over the past decade have shown that curcumin [7,133,134] and a curcumin–paclitaxel conjugate [135] had therapeutic effects in ovarian cancer cell lines. Curcumin was found to act through the down-regulation of NF-κB [7,136,137] and allied gene products [138–140]. Furthermore, curcumin was found to increase the sensitivity of chemotherapy-resistant ovarian cancer cell lines to standard chemotherapeutic agents by activating both the cells' extrinsic and intrinsic pathways of apoptosis [7,141]. A recent study of ours also showed that curcumin had therapeutic and chemosensitization effects and reversed multidrug resistance both in vitro and in vivo in athymic mice. In the in vivo study, tumors were grown by orthotopic injection of cells and 1 week after orthotopic implantation animals were treated with curcumin (500 mg/kg/day, gavage) alone or in combination with docetaxel (35–50 μg/animal/week, i.p.) for 4 weeks. Curcumin alone resulted in 49–55% reductions in mean tumor growth compared with controls whereas when combined with docetaxel 77% reductions in mean tumor growth compared with controls was obtained for curcumin in normal ovarian tumor models. In these ovarian tumors, curcumin alone and with docetaxel decreased both proliferation and microvessel density and increased tumor cell apoptosis. In mice with multidrug-resistant ovarian tumors, treatment with curcumin alone and combined with docetaxel resulted in significant 47% and 58% reductions in tumor growth, respectively [142].

3.4.3. Uterine cancer

Among women in the United States, uterine cancer is the third most common cancer diagnosis and the eighth most common cause of death from cancer [4]. Uterine carcinosarcoma is a rare, fast-growing form of uterine cancer that contains a mix of two types of cancer cells, an unusual feature of this disease. Surgery to remove the uterus can cure these mixed uterine tumors if the disease has not spread beyond the uterus. When the disease has spread, however, it usually does not respond well to chemo-

therapy, and the outlook for patients is poor. Several single-agent chemotherapeutic regimens, such as those based on cisplatin, ifosfamide, and paclitaxel, have been reported to have response rates of 10–40% in clinical trials, Consequently, newer combination regimens are being tested to achieve higher response rates. In a phase III clinical trial, although the overall survival of women with disseminated carcinosarcoma of the uterus improved after treatment with a combination of paclitaxel and ifosfamide, the authors of that study proposed that the poor overall survival rates for the disease still requires the development of new active agents [143].

On the basis of the ability of curcumin to affect multiple targets, it is tempting to speculate that curcumin may serve as an effective agent for use in combination chemotherapy for uterine cancer. However, very few studies on the anticancer activity of curcumin against uterine cancer have been reported. In one of the few that have, curcumin displayed in vitro apoptosis-inducing activity against an endometrial cancer cell line [57] by the down-regulation of Ets-1 and Bcl-2 expression [144]. Further. in vitro studies revealing other molecular mechanisms of curcumin activity in uterine cancer cells, animal model studies, and clinical trials have yet to be reported.

3.5. Thoracic/head and neck cancers

3.5.1. Pulmonary cancer

Lung cancer is the most commonly diagnosed and leading cause of death by cancer in men in the United States [4]. The median age of diagnosis is 70 years [3]. Although many patients achieve disease-free survival, some experience a long-term impairment of their quality of life, and disease recurrence is common [145]. Numerous chemotherapeutic combination regimens are continuously being introduced for the treatment of advanced lung cancer to improve patient outcomes.

Curcumin exhibits anticancer effects in various lung cancer cells through a variety of molecular targets. At the cellular level, curcumin derivatives inhibit FPTase in A549 cells. Curcumin inhibits AP-1 transcription and mediastinal lymph node metastasis in Lewis lung carcinoma cells and ornithine decarboxylase activity in rat tracheal epithelial cells [146,147]. Curcumin eradicated the DNA-binding of NF-κB, IκBα kinase activation, IκBα deterioration and phosphorylation, and p65 nuclear translocation, and it down-regulated COX-2 [7,148]. Likewise, treatment with curcumin induces apoptosis and inhibits growth in A549 and H1299 cells [149]. In A549 cells, curcumin interferes with cell growth and downregulates NAT activity and STAT1 activation [150–152]. Curcumin regulates the invasive activity of CL1-5 cells and demonstrates antiproliferative properties in NCI-H460 and -H520 cells, suggesting its suitability as an adjunct chemotherapeutic agent [7,153,154].

Orthotopic implantation of a metastatic cell line of Lewis lung carcinoma (LLC-MLN), which was isolated by an in vivo selection method, resulted in greater metastatic growth in mediastinal lymph nodes as compared with that of the original LLC cells. Oral administration of curcumin significantly inhibited the mediastinal lymph node metastasis of orthotopically implanted LLC cells in a dose-dependent manner, but did not affect the tumor growth at the implantation site. Combined treatment with curcumin and *cis*-diamine-dichloroplatinum (CDDP), resulted in a marked inhibition of tumor growth at the implanted site and of lymphatic metastasis, and a significant prolongation of the survival time [147]. Deshpande and Maru [155] showed that curcumin can inhibit BP-derived DNA adducts by interfering with the metabolic enzymes and its physical presence is essential for this effect. In the year 1999 one group [7] studied the activity of curcumin as chemopreventive agent against lung tumor induction in A/J mice by the tobacco smoke carcinogens benzopyrene (BaP) and 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The treatment of curcumin (2000 ppm) 1 week after carcinogen treatment until termination had no effect on lung tumor multiplicity. In another study, oral administration of curcumin (200 nmol/kg body weight) was, however, found to inhibit the lung metastasis of melanoma maximally as seen by the reduction in the number of lung tumor nodules (80%). Consequent to the inhibition of the lung tumor nodules, the life span of animals treated with curcumin was also found to be increased (143.85%). The results indicate a possible use of these compounds in arresting the metastatic growth of tumor cells. In Wistar rats, however, marker enzymes and plasma lipid levels decreased after treatment with 80 mg/kg of curcumin or a curcumin analog [7].

3.5.2. Oral cancer

Oral cancer accounts for 2–4% of the cancers diagnosed annually in the United States. In 2007, an estimated 34,360 patients will have been diag-

nosed with the disease; approximately 7550 will have died. Only half of the patients diagnosed with oral cancer will be alive 5 years after they receive the diagnosis. Ninety-five percent oral cancers occur among persons older than 40 years, and the mean age at diagnosis is 62 years [3]. Tobacco smoking, particularly when combined with heavy alcohol consumption, has been identified as the primary risk factor for approximately 75% of oral cancers in the United States [156]. The most common treatments for oral cancer are surgery and chemotherapy. After surgical ablation, recurrence and metastasis are frequent events; and this clearly indicates the need for a standardized multimodality therapy for oral cancer.

Curcumin inhibited the growth of oral cancer cell lines in vitro [7,157,158] by blocking the S/G2M phase. It acted synergistically with a G1 phase blocker, epigallocatechin-3-gallate [7]. Curcumin inhibited the growth of and DNA synthesis in SCC-25 oral cancer cells [7,159]. Curcumin increased both the expression and function of cytochrome P450 (CYP) 1A1 and/or CYP1B1 in oral cancer cells, indicating that it has chemopreventive properties mediated by the inhibition of carcinogen bioactivation [160]. Further, curcumin exhibited radiotherapy-sensitizing effects on SCC cells in vitro [161]. Moreover, the ability of curcumin to induce apoptosis in oral cancer cells was associated with the inhibition of COX-2 [162]. A recent study of ours also revealed that curcumin downregulates smokeless tobacco-induced NF-κB activation and COX-2 expression in human oral premalignant and malignant cells [163].

Several in vivo studies have also revealed the potency of curcumin against oral cancer. Curcumin alone or in combination with other has acted as a chemopreventive agent in oral cancer models in rats and hamsters. It was showed that male F344 rats fed with dietary curcumin (0.5 g/kg) during the initiation and post-initiation stages exhibited 91% reduction in the frequency of 4-nitroquinoline-1-oxide-induced tongue carcinoma with a decrease in incidence of oral preneoplasia [7]. Another study showed that curcumin alone or in combination with catechin inhibited methyl-(acetoxymethyl)-nitrosamine (MNA)-induced oral mucosal tumors in Syrian golden hamsters. In Syrian golden hamsters, 10 mmol curcumin (applied topically 3 times/week) decreased the number of visible oral papillomas and papilloma volume by 39.6% and 61.3%, respectively. Further, curcumin treatment also decreased the incidence of oral squamous cell carcinoma (SCC) and reduced the number of oral SCC lesions by 51.3%. In this study, curcumin treatment resulted in inhibition of tumor angiogenesis in the case of papilloma and SCC. Decrease of tumor proliferation index in hyperplasia, displasia and papilloma was also observed due to curcumin treatment [7].

Reports of two clinical trials have also revealed the effectiveness of curcumin in human oral carcinoma. In an early clinical trial topical application of a curcumin ointment showed decrease in pain, exudates, itching, and lesion size. In another phase I clinical trial, it was reported histologic improvements in precancerous lesions (in 29% of the patients) after treatment with curcumin (0.5–12 g/day) for 3 months [2].

3.5.3. Thymic cancer

Cancer of the thymus is associated with a high risk of recurrence and a poor survival rate. Advanced invasive thymomas are not usually manageable using surgical resection and radiotherapy [164]. An appropriate multidisciplinary treatment approach is essential for the long-term survival of patients with recurrent disease. The anticancer effect of curcumin in murine thymoma cells was found to be due to the blocking of interleukin-1 (IL-1) signaling by the inhibition of the recruitment of the IL-1 receptor-associated kinase IRAK [165]. A recent study showed that curcumin could prevent tumor-induced thymic atrophy in thymic T cells, leading to the neutralization of tumor-induced oxidative stress and the restoration of NF-κB activity and the re-education of the TNF-α signaling pathway, resulting in thymic protection [166]. We were unable to locate animal or clinical studies on curcumin in cancer of the thymus.

3.6. Hematologic cancers

3.6.1. Leukemia

Cancer of the blood or bone marrow, or leukemia, is characterized by the atypical proliferation of blood cells. An estimated 44,240 new cases of leukemia will have been diagnosed in the United States in 2007. Chronic leukemias account for 7% more cases than do acute leukemias. Most cases occur in older adults; more than half of all cases occur after age 67 years. It is anticipated that approximately 21,790 deaths in the United States will have been attributed to leukemia in 2007 [4]. Primary therapy usually involves a combination of several

drugs but treatment approaches are undergoing intensive study throughout the world, as investigators attempt to achieve complete disease remission.

In vitro, curcumin has been shown to have synergistic and remedial properties in leukemia. In HL-60 cells, a regimen of 10 μM curcumin for 48 h has been the most effective in decreasing cell proliferation and increasing differentiation. These effects were exacerbated when curcumin was given in conjunction with RA, vitamin D3, and vitamin D3 analogs [127,167–169]. Curcumin alone causes a significant reduction in NF-κB expression, Bcl-2 activity, and TPA-induced DNA binding. It also induces ER stress bax and caspases 3 and 8; and degrades PARP [7,168,170–172]. The proposed mechanism involves the interruption of G0/G1 phases associated with the up-regulation of P27kipl, P21wafl, and pRbp-expression and the down-regulation of cyclin D3 [7,173].

Within HL-60 cells, curcumin and its analog, alpha-diisoeugenol, induced ROS levels, and curcumin alone up-regulated Ca^{2+} production and the release of cytochrome *c* and lowered MMP levels [162,174,175]. When coupled with TSA, curcumin increased histone acetylation, increasing cytotoxicity for HL-60 cells [176]. In Raji cells, curcumin selectively blocks tumor cells in the G0/G1 and G2/M phases; dose-dependently upregulates Ac-histone H4 expression; inhibits the proliferation and degradation of IκBα and Notch 1; and inhibits the translocation of the NF-κB/p-65 subunit via the downmodulation of HDAC1 and p300/Notch 1 signal molecules [177–180]. Similarly, in the presence of curcumin, TERT is translocated, causing a loss of telomerase activity, and the expression of STAT3, -5a, and -5b are reduced without altering STAT1 or the phosphorylation states of STAT1, -3, or -5 in the K562 cell line via the release of cytochrome *c* from mitochondria [181,182]. Curcumin also affects GST-modulated lipid peroxidation, AP-1 and NF-κB binding to GSTP1-1 promoters, ADP ribose polymerase cleavage, and pro-caspases 8 and 9 induction in K562 cells [183,184].

Curcumin dose-dependently downregulates JAK and STAT phosphorylation, causing growth inhibition and apoptosis in T cell leukemia, HTLV-I–transformed T cell leukemia, MT-2, HuT-102, and SLB-1 cell lines. It does so by inhibiting cyclin D1, cdk1 Cdc25C, and XIAP and Survin expression [185,186]. Curcumin suppresses the proliferation of WEHI-3B cells and blocks STAT5 mRNA expression and STAT5 activation in CML cells [187,188]. In TK-10, and UACC-62 cell lines, curcumin initiates apoptosis via telomerase II poisoning, resulting in DNA damage [189]. Acute leukemia cells exposed to curcumin for 4 h have increased nitric oxide (NO) levels [190]. This increased NO production by macrophages and the inhibition of Th1 cytokines in NK cells in the presence of curcumin lead to significant tumoricidal results [191]. Likewise, MDR1 mRNA levels were reduced more significantly in leukemia cells from patients with higher MDR1 gene groups [192]. The proliferation of Jurkat cells was reduced with curcumin treatment, resulting in chromatin condensation and caspase-3 induction via the prevention of a decrease in glutathione levels [193,194]. In Bcr-Abl-transfected mouse progenitor 32D cells, curcumin inhibits proliferation by arresting cells in the G(2)-M phase of the cell cycle, resulting in irregular chromatin organization, multipolar chromosome segregation, aberrant cytokinesis, and multinucleated cells with morphologic changes [195]. Like curcumin, curcumin analogs in KBM-5 cells blocked TNF-induced NF-κB activation and proliferation, and curcuminoids inhibited COX-I and COX-II enzymes [7,196].

Studies have also demonstrated curcumin's therapeutic properties in vivo. In 6-week-old mice, the administration of a 2% curcumin diet via oral gavage resulted in a 53% reduction in lymphomas and leukemias. When topically applied prior to the administration of TPA in mice, curcumin down-regulated TPA-induced NF-κB and AP-1. It was also showed that oral administration of curcumin (50–200 mg/kg) inhibits the development of leukemia (HL-60) cells induced xenografts in nude mice [7]. In a group of 10 male smokers, 10 male non-smokers, and 10 non-smoking women between 25 and 45 years of age, curcumin reduced BP-stimulated strand breaks in a sex-dependent manner [197]. In 70 samples of childhood leukemia from patients, curcumin reduced WT1 gene expression in 35 samples [198].

3.6.2. Lymphoma

The American Cancer Society estimated that 71,380 cases of lymphoma will have been diagnosed in the United States in 2007, and 19,730 people will have been expected to die of the disease. Lymphoma is the fifth most common cancer in the United States, with the elderly having the highest risk of developing lymphoma [3,4]. The most common treatment approach today is to use chemotherapy and radiotherapy. Patients with fast-growing,

aggressive lymphomas are frequently treated with chemotherapy that consists of four or more drugs. New approaches to therapy are under study to improve treatment outcomes and reduce side effects.

Curcumin was found to inhibit cellular proliferation and enhance apoptosis in a variety of lymphoma cell lines in vitro [7,199–201]. The proposed mechanism of curcumin's action in the majority of these studies involves the suppression of the expression of NF-κB-regulated gene products. One study suggested a novel function for curcumin as a suppressor of JAK-1 and STAT3 activation in primary effusion lymphoma cells, a function that would lead to the inhibition of proliferation and the induction of caspase-dependent apoptosis [202]. It was showed that oral administration of curcumin (50–200 mg/kg) inhibits the development of lymphoma (SGC7901) cells induced xenografts in nude mice [2]. Curcumin inhibited the growth of both murine and human B lymphoma cells in vitro and murine B lymphoma cells in vivo by the down-regulation of spleen tyrosine kinase (Syk) activity accompanied by the down-regulation of Akt activation [203].

3.6.3. Multiple myeloma

Multiple myeloma (MM) is a B cell malignancy characterized by the latent accumulation of secretory plasma cells in bone marrow that have a low proliferative index and an extended life span. About 19,900 patients in the United States will have been diagnosed with MM in 2007; approximately 10,790 will have died of MM in the same year [4]. The agents used to treat have included combinations of vincristine, BCNU, melphalan, cyclophosphamide, adriamycin, and prednisone or dexamethasone. Aggressive, high-dose chemotherapy, bone marrow transplantation, and intensive supportive care can increase median survival rates. More recently, agents with novel mechanisms of action, such as the proteasome inhibitor bortezomib and immunomodulatory drugs like thalidomide and its derivative, lenalidomide, have shown promise for the treatment of patients with refractory and relapsed disease as well as for patients with previously untreated MM. Recent combinations of thalidomide, bortezomib, and lenalidomide with or without alkylating agents, anthracyclines, and steroids have produced rapid remissions (within 1–3 cycles), resulting in improvements in both overall response rates (75–95%) and complete response rates of 5–25 in patients receiving induction therapy.

Numerous reports suggest that curcumin exhibits antiproliferative effects against MM cells. The mechanisms of the antiproliferative effects of curcumin in MM cells have been studied and described extensively. The role of the NF-κB and STAT3 pathway as a target for curcumin in MM cells has been demonstrated [7,204,205]. Curcumin has shown activity against not only MM cell lines but also against fresh CD138+ MM cells derived from patient bone marrow. Curcumin was also found to synergize with the dexamethasone used routinely in the treatment of MM patients [7]. Curcumin is known to suppress both the production and signaling of IL-6, a critical growth factor for MM cells [39]. Curcumin also interrupts the interaction between MM cells and endothelial cells by reducing TrκB expression in endothelial cells and inhibiting brain-derived neurotrophic factor (BDNF) production in MM cells, eventually resulting in the inhibition of angiogenesis [206].

3.7. Melanoma

In 2007, it is estimated that 59,940 patients in the United States will have been diagnosed with melanoma, and 8110 will have died of the disease [4]. It is the most deadly form of skin cancer, and is very aggressive and resistant to present therapies. Several reports describe the antitumor activity of curcumin and of a formulation of the synthetic curcumin analog, EF24 [26] in various melanoma cell lines. The effects of curcumin were found to be mediated through the inhibition of glutathione *S*-transferase activity [207], the inhibition of COX-1 and COX-2 enzymes, the induction of apoptosis through the Fas receptor/caspase-8 pathway and the down-regulation of the NF-κB pathway [7,208,209]. The modulation of integrin receptors and collagenase activity, the expression of Nm23 and E-cadherin [210], the down-regulation of FAK, and the reduction of MMP-2 activity [211] were found to be responsible for the antimetastatic effect of curcumin in melanoma cells. Curcumin was found to reverse the resistance of melanoma cells to multiple drugs by inhibiting glutathione-*S*-transferases [212,213].

The chemopreventive effects of curcumin on several carcinogen-induced skin cancer models have been investigated. Topical application of curcumin (even lower doses of 20–100 nmol) together with tumor promoter TPA, twice weekly for 20 weeks to female CD-1 mice strongly inhibited TPA-induced papilloma formation. Further, in female

Swiss mice dietary administration of 2% turmeric significantly inhibited DMBA plus TPA-induced skin tumor formation. In this benzopyrene-initiated and TPA-promoted two-stage skin tumorigenesis model, curcumin reduced the number of tumors per mouse and decreased the number of tumor-bearing mice. Another study conducted showed that curcumin inhibited UV-induced dermatitis in mouse skin [2].

The in vivo antimetastatic effect of curcumin was also established. In one study, oral administration of curcumin (200 nmol/kg body weight) was found to inhibit the lung metastasis, induced by B16F10 melanoma cells, measured as the reduction in the number of lung tumor nodules (80%) and there was an increase in the life span of mice by 143.85%. The lung metastasis inhibition of curcumin was correlated with its ability to inhibit the invasion of B16F10 melanoma cells by inhibiting the metalloproteinases. The ability of curcumin to inhibit melanoma growth and tumor-specific angiogenesis in mouse models was also reported. The effectiveness of a prophylactic immune preparation of soluble proteins from B16-R cells, or a treatment with curcumin alone or in combination was evaluated using a mouse melanoma model. The combination treatment resulted in substantial inhibition of melanoma growth compared to each treatment by itself. A significant percentage increase in the median survival time was also observed in the combination group (>82.8%) as opposed to the 48.6% increase in immunization only group and 45.7% increase in the curcumin only group [7,43].

3.8. Bone cancer

Bone cancer and its subtypes affect fewer than 200,000 people in the United States, qualifying it as a rare disease according to the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). According to 2007 cancer statistics, 2370 new cases for bone/joint cancer were expected in the United States, and 1330 deaths were expected from this disease in the same year [4]. Surgery with preoperative and/or postoperative chemotherapy is considered standard treatment. As in most other cancers, new chemotherapeutic regimens are being explored to improve treatment outcomes.

Curcumin and its analogs were found to have antitumor effects in bone cancer cells. Numerous mechanisms have been proposed for the activity of curcumin against fibrosarcoma cells in particular. Curcumin induced apoptosis by inhibiting NF-κB [214] and the expression of IL-6 and IL-11 [215] and by abolishing the inhibitory effect of TGF-β on GR-mediated gene expression [216,217] in fibrosarcoma cells. Curcumin suppressed MMP-13 expression in chondrosarcoma cells. Synthetic curcumin analogs were also found to be potent against bone cancer cells. In fibrosarcoma cells, synthetic curcumin analogs inhibit activator protein-1 transcription and tumor-induced angiogenesis by down-regulating the expression of angiogenesis-associated genes, VEGF and MMP-9. Further, in human osteosarcoma cells curcumin was found to inhibit the ERK expression. Curcumin was found to induce apoptosis in a variety of osteosarcoma cells by down-regulating the Bcl-2 expression [7,218].

In an in vivo study in rats, dietary curcumin with cisplatin modulated tumor marker indices of fibrosarcoma towards normal controls [219]. Treatment with radiotherapy and curcumin resulted in enhanced tumor cell-killing and reduced radioresistance in mice bearing fibrosarcoma, as indicated by the significant inhibition of radiation-induced ERK and NF-κB expression [220].

3.9. Brain tumor

Malignant gliomas are a debilitating class of brain tumors that are resistant to radiation and chemotherapeutic drugs. In the United States, the annual incidence of brain cancer generally is 15–20 cases per 100,000 people. Brain cancer is the leading cause of cancer-related death in patients younger than age 35 [4]. The therapeutic efficacy of curcumin in various human malignant glioblastoma cells has been established [221], and curcumin was found to inhibit the NF-κB signaling pathways in these cell lines [222–224].

Numerous other mechanisms, like the induction of heat shock proteins [7], the inhibition of MMP transcriptions [225,226], TRAIL-induced apoptosis [227], the inhibition of G6PT gene expression [228], the activation of both receptor-mediated and mitochondria-mediated proteolytic pathways [229], the induction of histone hypoacetylation leading to apoptosis in a (PARP)- and caspase 3-mediated manner [230], the inhibition of the ING4 signaling pathway [231], and the induction of non-apoptotic autophagic cell death [232,233] have also been established. Further, curcumin was found to sensi-

tize glioma cells to several chemotherapeutic agents and to radiation therapy [224].

In an in vivo study, curcumin significantly decreased the incidence of radiation-induced pituitary tumors in rats [7]. In the subcutaneous xenograft model of glioblastoma cells, curcumin inhibited tumor growth significantly and induced autophagy. In this study, tumor cells were injected and when the tumors reached 50–70 mm^3 in volume, intratumoral injections of curcumin (100 mg/kg in DMSO/PBS) were administered every 24 h for 7 days. Evaluation of the effect was performed on day 16 of the initial curcumin treatment. An approximate three fold decrease in mean tumor volume was observed in the curcumin-treated group compared to the controls [233].

4. Control of cancer symptoms by curcumin

Patients with cancer suffer from various treatment-related symptoms, including neuropathic pain, depression, fatigue, decreased appetite, and sleep disturbance. Many of these symptoms may cause treatment delays and prevent the delivery of full-dose therapy in the scheduled time. In the course of targeting cancer, most chemotherapeutic agents activate NF-κB and induce TNF release. Consequentially, many of the symptoms related to cytokine dysregulation are affected by both the disease and the treatment. For example, chemotherapy commonly causes neuropathic pain, depression, fatigue, decreased appetite, and sleep disturbance, all of which have been linked to proinflammatory pathways that include NF-κB and TNF, as well as other key factors, such as IL-1 and IL-6 [234,235]. Animal models of "sickness behavior" support this thesis [236,237], in that fluctuations in inflammatory cytokines, primarily IL-1, IL-6, and TNF-α, are related to fluctuations in components of sickness in animals (e.g., anorexia, disturbed sleep, hyperalgesia, and disrupted learning). The administration of these cytokines can produce sickness behavior, which, in turn, can be eliminated by antibodies to these cytokines. The fact that curcumin can suppress the activation of NF-κB and NF-κB-regulated TNF, IL-1, and IL-6 expression, indicates that it could have potential effects against these symptoms.

4.1. Neuropathic pain

Although the exact etiologic factors responsible for neuropathic pain are not fully understood, inflammatory cytokines appear to play a major role in it. For example, TNF has been identified as an important mediator of neuropathic pain [238]. Nociceptors (pain receptors) are activated by various inflammation-associated factors, such as TNF-α [239,240], IL-1, and IL-6 [239,241], which are released from damaged tissue and/or tumors [242]. Various chemotherapeutic drugs including vincristine, taxanes, and cisplatin have been associated with neuropathic pain [243,244]. More recently, the administration of bortezomib to patients with MM was also found to result in neuropathic pain [245,246]. Although pain in advanced MM is usually attributed to bone destruction (prominently contributed to by IL-6) inflammation also plays a role in the transmission of pain and in the hyperalgesia associated with some treatments (bortezomib) for MM.

Numerous studies indicate that curcumin may have potential activity against neuropathic pain. In experiments using tail immersion and hot-plate assays in mice, curcumin (15–60 mg/kg) was found to alleviate neuropathic pain, which correlated with the down-regulation of TNF and the release of NO [247]. Besides inflammatory cytokines, curcumin may also mediate its effects through interaction with CD13/aminopeptidase N (APN), a membrane-bound, zinc-dependent metalloproteinase linked with neuropathic pain through the inactivation of opioid peptides, such as enkephalins [248]. Interestingly, curcumin was found to directly bind to APN and irreversibly inhibit its activity [7]. This may be another novel mechanism by which curcumin mediates its effects.

4.2. Depression

Some patients with cancer exhibit IFN-2β-induced depression and an increase in IL-2 levels [249–252] Cancer patients with depression have markedly higher plasma concentrations of IL-6 than do healthy comparison subjects and cancer patients without depression [253]. The plasma IL-2 was associated with mood state, and the plasma TNF-α increased after pharmacotherapy in depressed patients [254]. Endogenous IFN-α may play a role in sleep alteration [255].

Curcuma longa is a major component constituent of the traditional Chinese medicine, Xiaoyao-san, which is used to treat stress and depression-related symptoms in China. Behavioral despair tests in mice (tail suspension test) showed that curcumin had

antidepressant activity [256,257]. Curcumin has also been shown to inhibit the activity of monoamine oxidase, (MAO) which plays a central role in various psychiatric neurological disorders, including clinical depression and anxiety [258]. In the forced swimming test and in bilateral olfactory bulbectomy models of depression in rats, the oral administration of 1.25–10 mg/kg curcumin when administered from 1.25–10 mg/kg orally, was found to be quite effective at counteracting symptoms of depression [19,259]. In subsequent studies, the same investigators showed that curcumin alleviates stress-induced depressive behavior by acting on the hypothalamic–pituitary–adrenal axis by down-regulating the expression of brain-derived neurotrophic factor (BDNF) and inhibiting the phosphorylation of camp response element-binding (CREB) protein in rats [73,260]. Another study showed that chronic mild stress in rats leads to an increased production of serum IL-6 and TNF levels, whereas the administration of curcumin reverses these effects [261]. These reports indicate that curcumin's effects on depression could be mediated through multiple mechanisms.

4.3. Fatigue

Patients with cancer-related fatigue exhibit overexpressed IL-6, IL-1 receptor antagonist (IL-1RA), IL-1, TNF, and albumin [262]. Fatigued breast cancer survivors who reported having the behavioral problems concurrent with fatigue had significantly higher serum levels of several markers, such as IL-1RA, soluble TNF receptor type II (sTNF-RII), and neopterin [263]. Later studies in fatigued patients demonstrated that increase in plasma-soluble IL-6 receptor (sIL-6R) levels resulted from the shedding of the receptor and were accompanied by significant reductions in cell surface expression of IL-6R on CD14+ monocytes. IL-6 was discriminative only when flow cytometry was used to measure the stimulated intracellular production of IL-6 in monocyte populations [264]. Evidence from chronic fatigue syndrome and studies of sickness behavior suggest that immune and neuroendocrine factors may play a causative role in the development of fatigue. Prechemotherapy and chemotherapy-induced changes in inflammation are related to changes in fatigue and quality of life in response to chemotherapy [265].

There is increasing evidence that inflammatory pathways may be involved in fatigue response. Inflammation has been linked to exercise-induced fatigue [266]. The systemic injection of TNF in patients with cancer has been shown to cause increased fatigue [267]. In patients, cancer treatment with chemotherapeutic agents such as docetaxel can also cause fatigue; this correlates with NF-κB-mediated TNF expression [268,269]. Chronic fatigue syndrome (CFS) has been linked with the increased activation of NF-κB [270]. Similarly, IL-6 expression has been shown to increase after repeated bouts of eccentric exercise. Both TNF blockers and NF-κB blockers have been found to reduce chemotherapy-induced fatigue [269,271,272]. Using an eccentrically biased downhill treadmill running model in mice, Davis et al. showed that curcumin decreased the expression of IL-1, IL-6, and TNF and offset the performance [273]. It was showed that the systemic administration of curcumin stimulates muscle regeneration after traumatic injury, which is commonly associated with fatigue through the inhibition of NF-κB [7]. The use of curcumin has been proposed for patients with CFS [270].

4.4. Neurodegeneration

Inflammatory mechanisms within the central nervous system have been proven to contribute to cognitive impairment via interactions between neurons and glial cells that are mediated by cytokines, which are vital to the activation of the hypothalamic–pituitary–adrenal axis relevant to stress and depression. This is consistent with the role of cytokines as the mediators of bidirectional communication between the central nervous system and the peripheral immune system. Peripheral and central cytokine dysregulation can affect cognition in many ways, such as by impairing the regulation of sleep, suppressing appetite such that it results in a deficiency of micronutrients, and stimulating an array of other endocrine interactions [274].

Oxidative damage and inflammation have both been identified as having roles in age-related neurodegenerative diseases such as Alzheimer's disease (AD). In rat models of AD, curcumin has been found to be quite effective [7]. Wu et al. showed that dietary curcumin can counteract the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition [275]. Another study [276] found that curry consumption resulted in better cognitive function in non-demented elderly Asians. Kumar et al. demonstrated that curcumin had a neuroprotective effect in that it attenuated 3-nitro-

propionic acid (NP)-induced neurotoxicity [277]. The intraperitoneal administration of 3-NP resulted in a loss of body weight, reduced motor function, poorer memory retention, and changes in the oxidative stress (lipid peroxidation, reduced glutathione, and nitrite level) parameters in the brain. Chronic treatment with curcumin (10, 20, and 50 mg/kg) given orally once daily for 8 days dose-dependently improved the 3-NP-induced motor and cognitive impairment. Thus, these reports suggest that curcumin has the potential to improve cognitive function.

Pretreatment with 50 mg/kg of intraperitoneal curcumin also suppressed kainic acid-induced excitotoxicity in rat hippocampi [278]. Curcumin also suppressed the ethanol-induced changes in surachiasmatic nuclei in the anterior hypothalamus [279]. Kuhad et al. reported that the oral administration of curcumin (60 mg/kg) could attenuate diabetic encephalopathy in rats [280]. Curcumin, when administered to mice, can bind to amyloid proteins in the brain and disrupt the existing plaque commonly seen in AD [281]. Thus, these studies suggest that curcumin has the potential to act against a wide variety of neurologic diseases.

5. Curcumin can cross the blood–brain barriers

Because of the low serum concentrations normally observed in rodents and humans, there is a major concern that curcumin may not reach particular organs in sufficient concentrations to have an effect. Recent studies, however, suggest a favorable tissue distribution of curcumin. At least two studies suggest that curcumin does reach the brain by crossing the blood–brain barrier. Because curcumin is a fluorescent compound that binds to amyloid deposits, Garcia-Alloza et al. were able to use multiphoton microscopy to demonstrate that curcumin administered systemically in mice crossed the blood–brain barrier, bound to amyloid plaque in the brain, and reversed existing amyloid pathology [281]. Using fluoropropyl-substituted synthetic curcumin, Ryu et al. also showed that curcumin is taken up by the brain [282].

6. Conclusions

As detailed in this review, curcumin can modulate multiple cellular signaling pathways and interact with numerous molecular targets. Thus, it may have the potential to act against a large number of cancers. In vitro, in vivo, and human clinical studies have all established curcumin's promise and revealed its therapeutic value. More extensive randomized clinical trials are now needed. The safety, low cost, and already proven efficacy of this "age-old" natural medicine makes it a promising agent for the treatment of an "old-age" disease like cancer.

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