# 23 Curcumin Derived from Turmeric (*Curcuma longa*): a Spice for All Seasons

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## CONTENTS



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## 23.1 INTRODUCTION

*Curcuma longa* or turmeric is a tropical plant native to southern and southeastern tropical Asia. A perennial herb belonging to the ginger family, turmeric measures up to 1 m high with a short stem and tufted leaves (Figure 23.1A). The parts used are the rhizomes. Perhaps the most active component in turmeric is curcumin, which may make up 2 to 5% of the total spice in turmeric (Figure 23.1B). Curcumin is a diferuloylmethane present in extracts of the plant. Curcuminoids are responsible for the yellow color of turmeric and curry powder. They are derived from turmeric by ethanol extraction. The pure orange-yellow, crystalline powder is insoluble in water. The structure of curcumin ($C_{21}H_{20}O_6$) was first described in 1815 by Vogel and Pellatier and in 1910 was shown to be diferuloylmethane by Lampe et al. [1]. Chemical synthesis in 1913 confirmed its identity [2].

Turmeric is widely consumed in the countries of its origin for a variety of uses, including as a dietary spice, a dietary pigment, and an Indian folk medicine for the treatment of various illnesses. It is used in the textile and pharmaceutical industries [3] and in Hindu religious ceremonies in one form or another. Current traditional Indian medicine uses it for biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis [4]. The old Hindu texts have described it as an aromatic stimulant and carminative [5]. Powder of turmeric mixed with slaked lime is a household remedy for the treatment of sprains and swelling caused by injury, applied locally over the affected area. In some parts of India, the powder is taken orally for the treatment of sore throat. This nonnutritive phytochemical is pharmacologically safe, considering that it has been consumed as a dietary spice, at doses up to 100 mg/day, for centuries [6]. Recent phase I

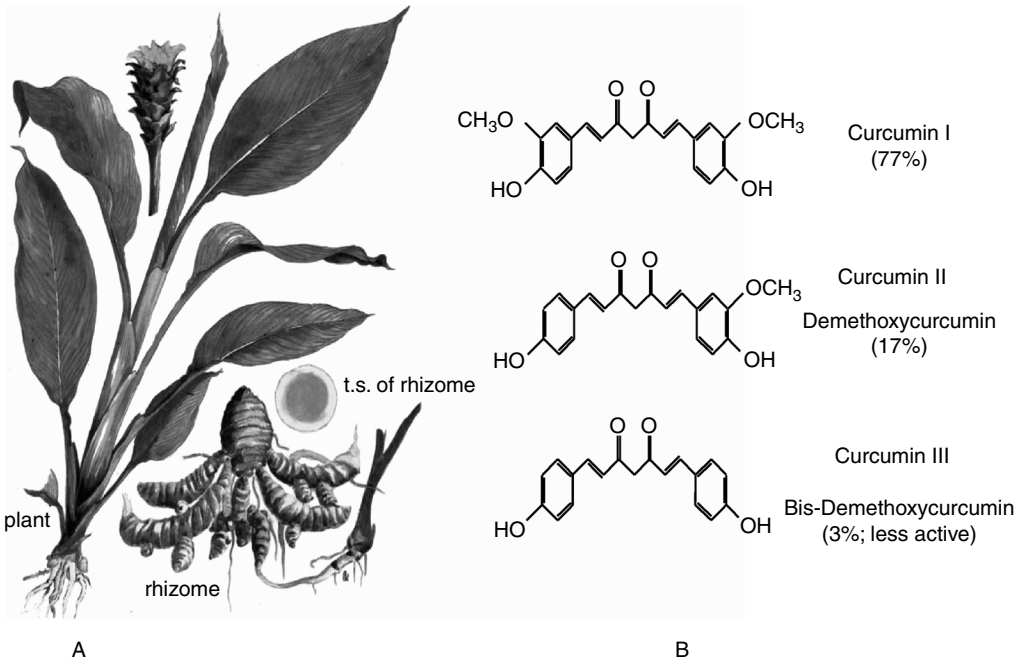


**FIGURE 23.1** The plant *Curcuma longa* (panel A), from which curcumin is derived, and its structure (panel B).

clinical trials indicate that people can tolerate a dose as high as 8 g/day [7]. In the U.S., curcumin is used as a coloring agent in cheese, spices, mustard, cereals, pickles, potato flakes, soups, ice-creams, and yogurts (www.kalsec.com).

Curcumin is not water-soluble, but it is soluble in ethanol or in dimethylsulfoxide. The degradation kinetics of curcumin under various pH conditions and the stability of curcumin in physiological matrices have been established [8]. When curcumin was incubated in 0.1*M* phosphate buffer and serum-free medium (pH 7.2 at 37°C), about 90% decomposed within 30 min. A series of pH conditions ranging from 3 to 10 were tested, and the results showed that decomposition was pH-dependent and occurred faster at neutral-basic conditions. It is more stable in cell culture medium containing 10% fetal calf serum and in human blood. Less than 20% of curcumin decomposed within 1 h, and after incubation for 8 h, about 50% of curcumin still remained. Trans-6-(4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexenal was predicted to be the major degradation product, and vanillin, ferulic acid, and feruloyl methane were identified as minor degradation products. The amount of vanillin increased with incubation time.

Numerous studies have indicated that curcumin has antioxidant and anti-inflammatory properties. A Medline search revealed over 1000 publications describing various activities of this polyphenol. The following sections describe some of its major biological and clinical effects.

## 23.2 ANTICANCER PROPERTIES OF CURCUMIN

### 23.2.1 Curcumin Inhibits Tumorigenesis

Numerous reports suggest that curcumin has chemopreventive and chemotherapeutic effects (Figure 23.2). Its anticancer potential in various systems was recently reviewed by our laboratory [9]. Curcumin blocks tumor initiation induced by benzo[a]pyrene and 7,12dimethylbenz[a]anthracene

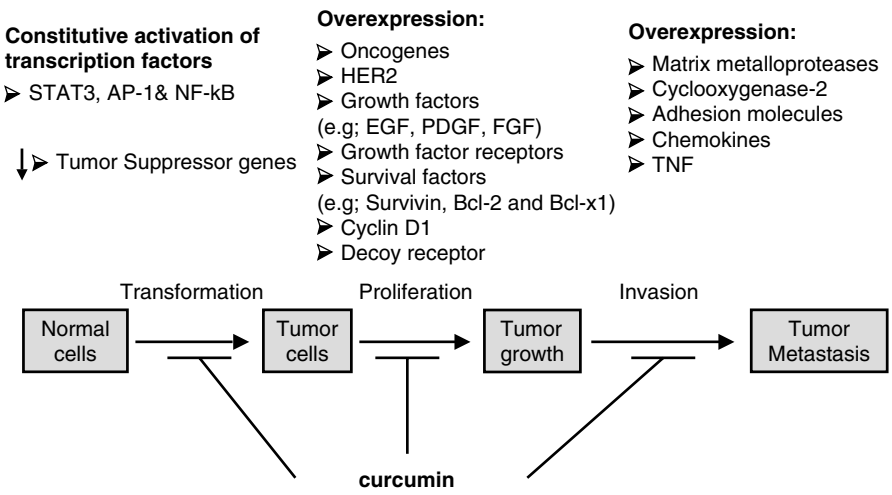


**FIGURE 23.2** Various steps involved in tumorigenesis and metastasis and their suppression by curcumin.

[10], and it suppresses phorbol ester-induced tumor promotion [11, 12]. *In vivo,* curcumin was found to suppress carcinogenesis of the skin [12–15], the forestomach [16, 17], the colon [18–20], and the liver [21] in mice. Curcumin also suppresses mammary carcinogenesis [22–24].

### 23.2.2 Curcumin Exhibits Antiproliferative Effects against Cancer Cells

Compounds that block or suppress the proliferation of tumor cells have potential as anticancer agents. Curcumin has been shown to inhibit the proliferation of a wide variety of tumor cells, including B-cell and T-cell leukemia [25–28], colon carcinoma [29], and epidermoid carcinoma cells [30]. It has also been shown to suppress the proliferation of various breast carcinoma cell lines in culture [31–33]. We showed that the growth of the breast tumor cell lines BT20, SKBR3, MCF-7, T47D, and ZR75-1 is completely inhibited by curcumin, as indicated by MTT dye uptake, [$^3$H] thymidine incorporation, and clonogenic assay [31]. We also showed that curcumin can overcome Adriamycin resistance in MCF-7 cells [31]. Recently, we have shown that curcumin can activate caspase-8, which leads to cleavage of Bid, thus resulting in sequential release of mitochondrial cytochrome C and activation of caspase-9 and caspase-3 [34]. More recently, we have demonstrated that curcumin can suppress the proliferation of multiple myeloma cells [35]. Woo et al. [36] have demonstrated that curcumin can cause cell damage by inactivating the Akt-related cell survival pathway and release of cytochrome c, providing a new mechanism for curcumin-induced cytotoxicity.

Zheng et al. [37] explored the apoptosis-inducing effects of curcumin in human ovarian tumor A2780 cells. They found that curcumin could significantly inhibit the growth of ovarian cancer cells by inducing apoptosis through up-regulation of caspase-3 and down-regulation of expression of NF-κB. Studies have also been performed to examine the synergy of curcumin with other antiproliferative agents. Deeb et al. [38] investigated whether curcumin and TNF-related apoptosis-inducing ligand (TRAIL) cooperatively interact to promote death of LNCaP cells. At concentrations at which neither of the two agents alone produced significant cytotoxicity in LNCaP cells, cell death was markedly enhanced (two- to three-fold) if tumor cells were treated with curcumin and TRAIL together. The combined curcumin and TRAIL treatment increased the number of hypodiploid cells and induced DNA fragmentation in LNCaP cells. The combined treatment induced cleavage of procaspase-3, procaspase-8, and procaspase-9, truncation of BID, and release

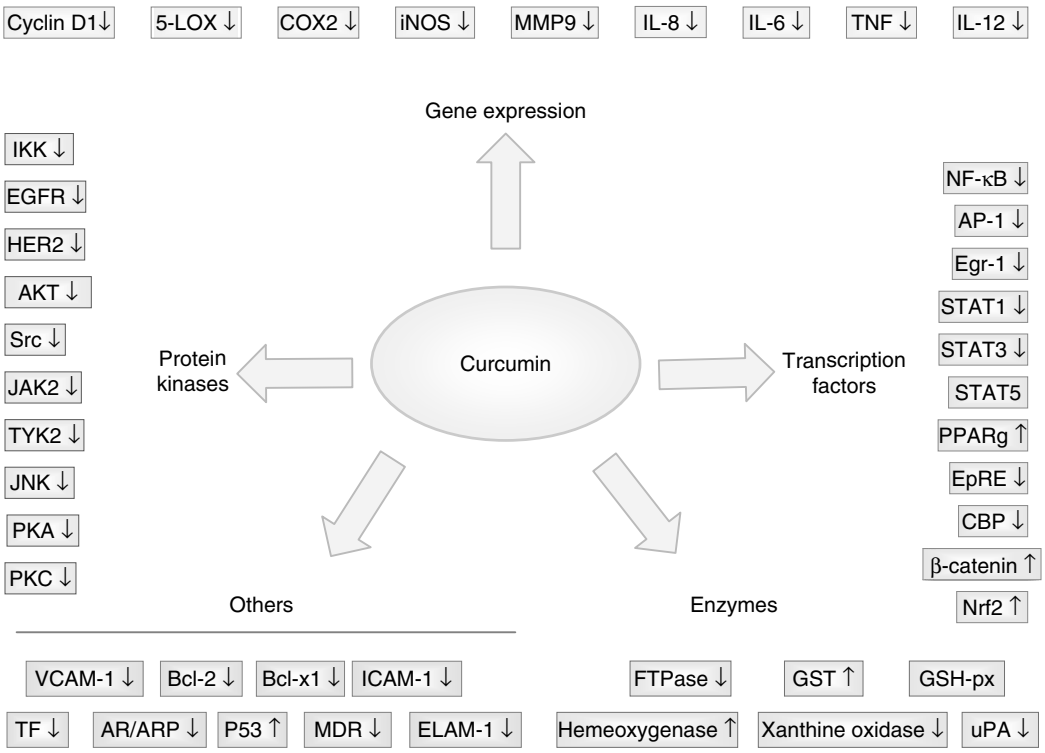


**FIGURE 23.3** Molecular targets shown to be regulated by curcumin.

of cytochrome c from the mitochondria, indicating that both the extrinsic (receptor mediated) and intrinsic (chemical induced) pathways of apoptosis are triggered in prostate cancer cells treated with a combination of curcumin and TRAIL. These results define a potential use of curcumin to sensitize prostate cancer cells for TRAIL-mediated immunotherapy.

Chan et al. [39] demonstrated that curcumin increased the sensitivity of ovarian cancer cells (CAOV3 and SKOV3) to cisplatin. The effect was obtained both when the compound was added simultaneously with cisplatin and when it was added 24 h before. Curcumin inhibited the production of interleukin 6 (IL-6) in these cell lines (Figure 23.3), suggesting that one of the mechanisms for synergy between cisplatin and curcumin involved reducing the autologous production of IL-6. However, the synergy was also observed in the low IL-6 producer, SKOV3, indicating that additional targets were responsible. The down-regulation of IL-6 by curcumin was also noted in multiple myeloma cells [35].

### 23.2.3 Curcumin Down-Regulates the Activity of Epidermal Growth Factor Receptor (EGFR) and Expression of HER2/neu

HER2/neu and epithelial growth factor receptor (EGFR) activity represent one possible mechanism by which curcumin suppresses the growth of breast cancer cells. Almost 30% of the breast cancer cases have been shown to overexpress the HER2/neu protooncogene [40], and both HER2 and EGF receptors stimulate proliferation of breast cancer cells. Overexpression of these two proteins correlates with progression of human breast cancer and poor patient prognosis [40]. Curcumin has been shown to down-regulate the activity of EGFR and HER2/neu [30, 41] and to deplete the cells of HER2/neu protein [42]. Additionally, we have recently found that curcumin can down-regulate bcl-2 expression, which may contribute to its antiproliferative activity [43].

Like geldanamycin, curcumin has been shown to provoke the intracellular degradation of HER2 [44]. HER2 mutations, however, limit the capacity of geldanamycin to disrupt the tyrosine kinase activity of HER2. Thus these HER2 mutants are resistant to geldanamycin-induced degradation, but they maintain their sensitivity to curcumin through ErbB-2 degradation.

### 23.2.4 Curcumin Down-Regulates the Activation of Nuclear Factor-κB (Nf-κB)

Curcumin may also operate through suppression of NF-κB activation (Figure 23.3). NF-κB is a nuclear transcription factor required for the expression of genes involved in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy [45]. This factor is activated in response to inflammatory stimuli, carcinogens, tumor promoters, and hypoxia, which is frequently encountered in tumor tissues [46]. Several groups, including ours, have shown that activated NF-κB suppresses apoptosis in a wide variety of tumor cells [47–49], and it has been implicated in chemoresistance [47]. We have shown that cells that overexpress NF-κB are resistant to paclitaxel-induced apoptosis [50]. Furthermore, the constitutively active form of NF-κB has been reported in human breast cancer cell lines in culture [51], carcinogen-induced mouse mammary tumors [52], and biopsies from patients with breast cancer [53]. Our laboratory has shown that various tumor promoters, including phorbol ester, TNF, and $H_2O_2$, activate NF-κB and that curcumin down-regulates the activation [54]. Subsequently, others showed that curcumin-induced down-regulation of NF-κB is mediated through suppression of IκBα kinase activation [55, 56]. Recently, Shishodia et al. [57] have shown that curcumin down-regulated cigarette smoke-induced NF-κB activation through inhibition of IκBα kinase in human lung epithelial cells. This led to the down-regulation of cyclin D1, cyclooxygenase 1 (COX-2), and matrix metalloproteinase 9 (MMP9) by curcumin. Philip et al. [58] have recently reported that curcumin down-regulates osteopontin (OPN)-induced NF-κB-mediated promatrix metalloproteinase-2 activation through IκBα/IKK signaling.

### 23.2.5 Curcumin Down-Regulates the Activation of STAT3 Pathway

Numerous reports suggest that IL-6 promotes survival and proliferation of various tumors, including multiple myeloma (MM) cells, through the phosphorylation of a cell signaling protein, signal transducers, and activators of transcription (STAT3). Thus agents that suppress STAT3 phosphorylation have potential for the treatment of MM. Bharti et al. [59] demonstrated that curcumin inhibited IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. Curcumin had no effect on STAT5 phosphorylation but inhibited the interferon α-induced STAT1 phosphorylation. The constitutive phosphorylation of STAT3 found in certain MM cells was also abrogated by treatment with curcumin. Curcumin-induced inhibition of STAT3 phosphorylation was reversible. Compared with AG490, a well-characterized JAK2 inhibitor, curcumin was a more rapid (30 min vs. 8 h) and more potent (10 μ*M* vs. 100 μ*M*) inhibitor of STAT3 phosphorylation. Similarly, at the dose of curcumin that completely suppressed proliferation of MM cells, AG490 had no effect. In contrast, the STAT3 inhibitor peptide that can inhibit the STAT3 phosphorylation mediated by Src blocked the constitutive phosphorylation of STAT3 and also suppressed the growth of myeloma cells. TNF-α and lymphotoxin (LT) also induced the proliferation of MM cells, but through a mechanism independent of STAT3 phosphorylation. In addition, dexamethasone-resistant MM cells were found to be sensitive to curcumin. Overall, these results demonstrated that curcumin was a potent inhibitor of STAT3 phosphorylation, and this plays a role in curcumin's suppression of proliferation of MM.

Li et al. [60] showed that curcumin suppressed oncostatin-M-stimulated STAT1 phosphorylation, DNA-binding activity of STAT1, and c-Jun N-terminal kinase activation without affecting Janus kinase 1 (JAK1), JAK2, JAK3, ERK1/2, and p38 phosphorylation. Curcumin also inhibited OSM-induced MMP1, MMP3, MMP13, and TIMP3 gene expression.

Natarajan et al. [61] showed that treatment of activated T cells with curcumin inhibited IL-12-induced tyrosine phosphorylation of Janus kinase 2, tyrosine kinase 2, and STAT3 and STAT4 transcription factors. The inhibition of the Janus kinase-STAT pathway by curcumin resulted in a decrease in IL-12-induced T-cell proliferation and Th1 differentiation.

### 23.2.6 Curcumin Activates Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ)

Activation of PPAR-γ inhibits the proliferation of nonadipocytes. The level of PPAR-γ is dramatically diminished along with activation of hepatic stellate cells (HSC). Xu et al. [62] demonstrated that curcumin dramatically induced the gene expression of PPAR-γ and activated PPAR-γ in activated HSC (Figure 23.3). Blocking its trans-activating activity by a PPAR-γ antagonist markedly decreased the effects of curcumin on inhibition of cell proliferation.

### 23.2.7 Curcumin Down-Regulates the Activation of Activator Protein-1 (AP-1) and C-Jun N-Terminal Kinase (JNK)

AP-1 is another transcription factor that has been closely linked with proliferation and transformation of tumor cells [63]. The activation of AP-1 requires the phosphorylation of c-jun through activation of stress-activated kinase JNK [64]. The activation of JNK is also involved in cellular transformation [65]. Curcumin has been shown to inhibit the activation of AP-1 induced by tumor promoters [66] and JNK activation induced by carcinogens [67].

Dickinson et al. [68] have demonstrated that the beneficial effects elicited by curcumin appear to be due to changes in the pool of transcription factors that compose EpRE and AP-1 complexes, affecting gene expression of glutamate-cysteine ligase and other phase II enzymes. Squires et al. [69] have demonstrated that curcumin suppresses the proliferation of tumor cells through inhibition of Akt/PKB activation.

### 23.2.8 Curcumin Suppresses the Induction of Adhesion Molecules

The expression of various cell surface adhesion molecules such as intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial leukocyte adhesion molecule-1 on endothelial cells is absolutely critical for tumor metastasis [70]. The expression of these molecules is in part regulated by nuclear factor NF-κB [71]. We have shown that treatment of endothelial cells with curcumin blocks the cell surface expression of adhesion molecules, and this accompanies the suppression of tumor-cell adhesion to endothelial cells [72]. We also have demonstrated that down-regulation of these adhesion molecules is mediated through the down-regulation of NF-κB activation [72]. Jaiswal et al. [73] showed that curcumin treatment causes p53- and p21-independent G(2)/M phase arrest and apoptosis in colon cancer cell lines. Their results suggest that curcumin treatment impairs both Wnt signaling and cell-cell adhesion pathways, resulting in G(2)/M-phase arrest and apoptosis in HCT-116 cells.

### 23.2.9 Curcumin Down-Regulates Cyclooxygenase-2 (COX-2) Expression

Overexpression of COX-2 has been shown to be associated with a wide variety of cancers, including colon [74], lung [75], and breast [76] cancers. The role of COX-2 in suppression of apoptosis and tumor cell proliferation has been demonstrated [77]. Furthermore, Celebrex, a specific inhibitor of COX-2, has been shown to suppress mammary carcinogenesis in animals [78]. Several groups have shown that curcumin down-regulates the expression of COX-2 protein in different tumor cells [29, 56], most likely through the down-regulation of NF-κB activation [56], which is needed for COX-2 expression.

### 23.2.10 Curcumin Inhibits Angiogenesis

For most solid tumors, including breast cancer, angiogenesis (blood vessel formation) is essential for tumor growth and metastasis [79]. The precise mechanism that leads to angiogenesis is not fully understood, but growth factors that cause proliferation of endothelial cells have been shown to play a critical role in this process. Curcumin has been shown to suppress the proliferation of human vascular endothelial cells *in vitro* [80] and abrogate the fibroblast growth-factor-2-induced angiogenic response *in vivo* [81], thus suggesting that curcumin is also an antiangiogenic factor. Indeed curcumin has been shown to suppress angiogenesis *in vivo* [82].

To elucidate possible mechanisms of antiangiogenic activity by curcumin, Park et al. [83] performed cDNA microarray analysis and found that curcumin modulated cell-cycle-related gene expression. Specifically, curcumin induced G0/G1- and G2/M-phase cell-cycle arrest; up-regulated CDKIs, p21WAF1/CIP1, p27KIP1, and p53; and slightly down-regulated cyclin B1 and cdc2 in ECV304 cells. The up-regulation of CDKIs by curcumin played a critical role in the regulation of cell-cycle distribution in these cells, which may underlie the antiangiogenic activity of curcumin.

### 23.2.11 Curcumin Suppresses the Expression of MMP9 and Inducible Nitric Oxide Synthase (INOS)

The MMPs make up a family of proteases that play a critical role in tumor metastasis [84]. One of them, MMP9, has been shown to be regulated by NF-κB activation, and curcumin has been shown to suppress its expression [85]. Curcumin has also been demonstrated to down-regulate iNOS expression, also regulated by NF-κB and involved in tumor metastasis [86]. These observations suggest that curcumin must have antimetastatic activity. Indeed, there is a report suggesting that curcumin inhibits tumor metastasis [87].

### 23.2.12 Curcumin Down-Regulates Cyclin D1 Expression

Cyclin D1, a component subunit of cyclin-dependent kinase Cdk4 and Cdk6, is a rate-limiting factor in progression of cells through the first gap (G1) phase of the cell cycle [88]. Cyclin D1 has been shown to be overexpressed in many cancers including breast, esophagus, head and neck, and prostate [89–94]. It is possible that the antiproliferative effects of curcumin are due to inhibition of cyclin D1 expression. We found that curcumin can indeed down-regulate cyclin D1 expression [35, 43, 95], and this down-regulation occurred at the transcriptional and posttranscriptional level.

### 23.2.13 Curcumin Is Chemopreventive

Several studies suggest that curcumin has chemopreventive potential. Huang et al. [96] found that topical application of curcumin inhibits tumor initiation by benzo[a]pyrine (BaP) and tumor promotion by TPA in mouse skin. Dietary curcumin (commercial grade) inhibits BaP-induced forestomach carcinogenesis, N-ethyl-N′-nitro-N-nitrosoguanidine (ENNG)-induced duodenal carcinogenesis, and azoxymethane (AOM)-induced colon carcinogenesis. Dietary curcumin had little or no effect on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis and 7,12-dimethylbenz[a]anthracene (DMBA)-induced breast carcinogenesis in mice. Poor circulating bioavailability of curcumin may account for the lack of lung and breast carcinogenesis inhibition.

Perkins et al. [97] showed that curcumin prevents the development of adenomas in the intestinal tract of the C57Bl/6J Min/+ mouse, a model of human familial adenomatous polyposis coli (APC). To aid in the rational development of curcumin as a colorectal cancer-preventive agent, the group explored the link between its chemopreventive potency in the Min/+ mouse and levels of drug and

metabolites in target tissue and plasma. Mice received dietary curcumin for 15 weeks, after which adenomas were enumerated. Levels of curcumin and metabolites were determined by high-performance liquid chromatography (HPLC) in plasma, tissues, and feces of mice after either long-term ingestion of dietary curcumin or a single dose of [$^{14}$C] curcumin (100 mg/kg) via the intraperitoneal (i.p.) route. Whereas curcumin at 0.1% in the diet was without effect, at 0.2 and 0.5%, it reduced adenoma multiplicity by 39 and 40%, respectively, compared with untreated mice. Hematocrit values in untreated Min/+ mice were drastically reduced compared with those in wild-type C57Bl/6J mice. Dietary curcumin partially restored the suppressed hematocrit. Traces of curcumin were detected in the plasma. Its concentration in the mucosa of the small intestine, between 39 and 240 nmol/g of tissue, reflected differences in dietary concentration. [$^{14}$C] curcumin disappeared rapidly from tissues and plasma within 2 to 8 h after dosing. Curcumin may be useful in the chemoprevention of human intestinal malignancies related to Apc mutations. The comparison of dose, resulting curcumin levels in the intestinal tract, and chemopreventive potency suggested tentatively that a daily dose of 1.6 g of curcumin is required for efficacy in humans. A clear advantage of curcumin over nonsteroidal anti-inflammatory drugs is its ability to decrease intestinal bleeding linked to adenoma maturation.

*Helicobacter pylori* is a Group 1 carcinogen and is associated with the development of gastric and colon cancer. Mahady et al. [98] have demonstrated that curcumin inhibits the growth of *H. pylori* cagA+ mouse strains *in vitro*, and this may be one of the mechanisms by which curcumin exerts its chemopreventive effects.

In another study, Perkins and coworkers [97] found that the nonsteroidal anti-inflammatory drug aspirin and curcumin retard adenoma formation when administered long-term to Apc(Min/+) mice, a model of human familial APC. Aspirin administered to Apc (Min/+) mice postweaning was not effective, though curcumin given postweaning was active. Here the hypothesis was tested that dietary aspirin (0.05%) or curcumin (0.2%) prevents or delays adenoma formation in offspring when administered to Apc (Min/+) mothers and up to the end of weaning. Whereas curcumin was without effect when administered afterward, aspirin reduced the numbers of intestinal adenomas by 21%. When aspirin given up to the end of weaning was combined with curcumin administered from the end of weaning for the rest of the animals' lifetime, intestinal adenoma numbers were reduced by 38%. The combination was not superior to intervention postweaning with curcumin alone. These results show that aspirin exerts chemopreventive activity in the Apc(Min/+) mouse during tumor initiation/early promotion, while curcumin is efficacious when given at a later stage of carcinogenic progression. Thus, the results suggest that in this mouse model, aspirin and curcumin act during different "windows" of neoplastic development.

Recently, Van der Logt et al. [99] demonstrated that curcumin exerted its anticarcinogenic effects in gastrointestinal cancers through the induction of UDP-glucuronosyltransferase enzymes.

### 23.2.14 Curcumin Inhibits Tumor Growth and Metastasis in Animals

Kuttan et al. [100] examined the anticancer potential of curcumin *in vitro* using tissue culture methods and *in vivo* in mice using Dalton's lymphoma cells grown as ascites. Initial experiments indicated that curcumin reduced the development of animal tumors. They encapsulated curcumin (5 mg/ml) into neutral and unilamellar liposomes prepared by sonication of phosphatidylcholine and cholesterol. An aliquot of liposomes (50 mg/kg) was given i.p. to mice the day after giving the Dalton's lymphoma cells and continued for 10 days. After 30 days and 60 days, surviving animals were counted. When curcumin was used in liposomal formulations at concentration of 1 mg/animal, all animals survived 30 days, and only two of the animals developed tumors and died before 60 days.

Busquets [101] showed that systemic administration of curcumin (20 μg/kg body weight) for 6 consecutive days to rats bearing the highly cachectic Yoshida AH-130 ascites hepatoma resulted in an important inhibition of tumor growth (31% of total cell number). Interestingly, curcumin was

also able to reduce by 24% *in vitro* tumor cell content at concentrations as low as 0.5 μ*M* without promoting any apoptotic events. Although systemic administration of curcumin has previously been shown to facilitate muscle regeneration, administration of the compound to tumor-bearing rats did not result in any changes in muscle wasting, when compared with the untreated tumor-bearing animals. Indeed, both the weight and protein content of the gastrocnemius muscle significantly decreased as a result of tumor growth, and curcumin was unable to reverse this tendency. It was concluded that curcumin, in spite of having clear antitumoral effects, has little potential as an anticachectic drug in the tumor model used in the study.

Menon et al. [102] reported curcumin-induced inhibition of B16F-10 melanoma lung metastasis in mice. Oral administration of curcumin at concentrations of 200 nmol/kg body weight reduced the number of lung tumor nodules by 80%. The life span of the animals treated with curcumin was increased by 143.85% [102]. Moreover, lung collagen hydroxyproline and serum sialic acid levels were significantly lower in treated animals than in the untreated controls. Curcumin treatment (10 μg/ml) significantly inhibited the invasion of B16F-10 melanoma cells across the collagen matrix of a Boyden chamber. Gelatin zymographic analysis of the trypsin-activated B16F-10 melanoma cells' sonicate revealed no metalloproteinase activity. Curcumin treatment did not inhibit the motility of B16F-10 melanoma cells across a polycarbonate filter *in vitro*. These findings suggest that curcumin inhibits the invasion of B16F-10 melanoma cells by inhibition of MMPs, thereby inhibiting lung metastasis.

Curcumin decreases the proliferative potential and increases apoptotic potential of both androgen-dependent and androgen-independent prostate cancer cells *in vitro*, largely by modulating the apoptosis-suppressor proteins and by interfering with the growth factor receptor signaling pathways as exemplified by the EGF receptor. To extend these observations, Dorai et al. [103] investigated the anticancer potential of curcumin in a nude mouse prostate cancer model. The androgen-dependent LNCaP prostate cancer cells were grown, mixed with Matrigel, and injected subcutaneously. The experimental group received a synthetic diet containing 2% curcumin for up to 6 weeks. At the end point, mice were killed, and sections taken from the excised tumors were evaluated for pathology, cell proliferation, apoptosis, and vascularity. Results showed that curcumin induced a marked decrease in the extent of cell proliferation, as measured by the BrdUrd (bromodeoxyuridine) incorporation assay, and a significant increase in the extent of apoptosis, as measured by an *in situ* cell death assay. Moreover, a significant decrease in the microvessel density, as measured by CD31 antigen staining, was also seen. It was concluded that curcumin was a potentially therapeutic anticancer agent, as it significantly inhibited prostate cancer growth, as exemplified by LNCaP *in vivo*, and it had the potential to prevent the progression of this cancer to its hormone refractory state.

### 23.2.15 Curcumin Inhibits Androgen Receptors and AR-Related Cofactors

Nakamura et al. [104] have evaluated the effects of curcumin in cell growth, activation of signal transduction, and transforming activities of both androgen-dependent and -independent cell lines. The prostate cancer cell lines LNCaP and PC-3 were treated with curcumin, and its effects on signal transduction and expression of androgen receptor (AR) and AR-related cofactors were analyzed. Their results showed that curcumin down-regulates transactivation and expression of AR, AP-1, NF-κB, and CREB (cAMP response element-binding protein)-binding protein (CBP). It also inhibited the transforming activities of both cell lines, as evidenced by reduced colony forming ability in soft agar. These studies suggest that curcumin has a potential therapeutic effect on prostate cancer cells through down-regulation of AR and AR-related cofactors, AP-1, NF-κB, and CBP.

Overall, numerous mechanisms as indicated above could account for the tumor-suppressive effects of curcumin (Figure 23.3). Curcumin also has modulatory effects in diseases besides cancer (Figure 23.4). These effects are described in Section 23.3 and Section 23.4.

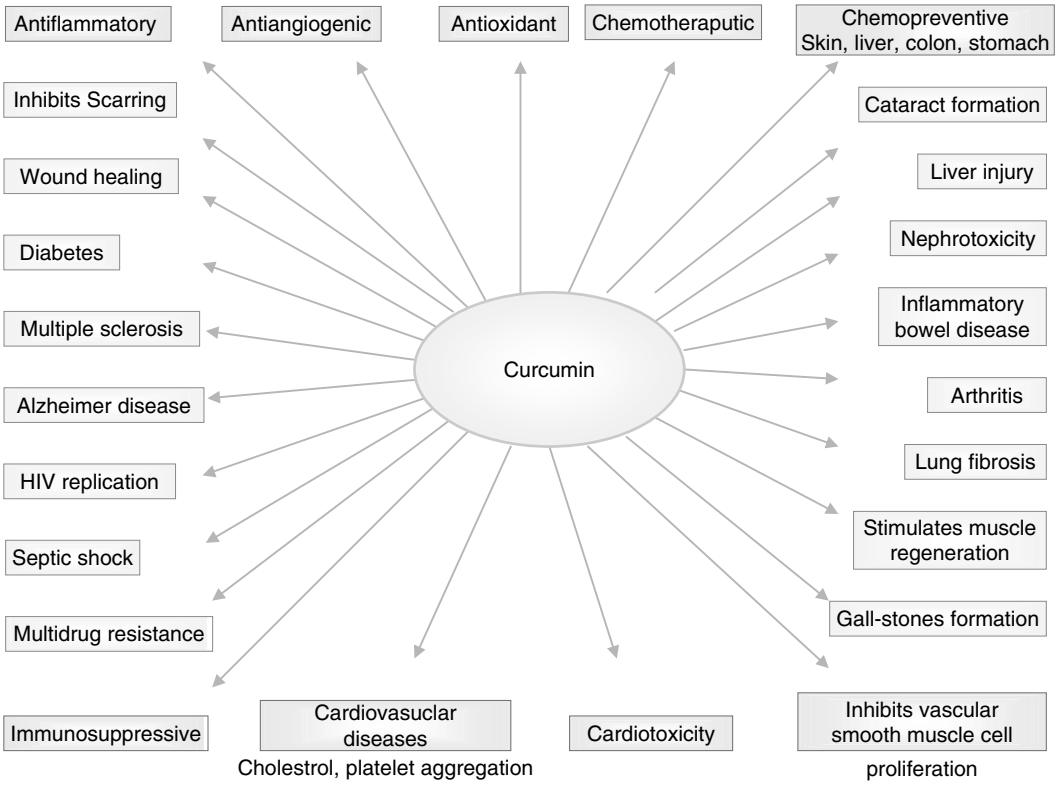


**FIGURE 23.4** Effect of curcumin on various diseases.

## 23.3 EFFECT OF CURCUMIN ON ATHEROSCLEROSIS AND MYOCARDIAL INFARCTION

### 23.3.1 Curcumin Inhibits the Proliferation of Vascular Smooth Muscle Cells

The proliferation of peripheral blood mononuclear cells (PBMC) and vascular smooth muscle cells (VSMC) is a hallmark of atherosclerosis. Huang et al. [10] investigated the effects of curcumin on the proliferation of PBMC and VSMC from the uptake of [$^3$H]thymidine. Curcumin dose dependently inhibited the response to phytohemaglutinin and the mixed lymphocyte reaction in human PBMC at dose ranges of 1 to 30 μ*M* and 3 to 30 μ*M*, respectively. Curcumin (1 to 100 μ*M*) dose-dependently inhibited the proliferation of rabbit VSMC stimulated by fetal calf serum. Curcumin had a greater inhibitory effect on platelet-derived growth factor (PDGF)-stimulated proliferation than on serum-stimulated proliferation. Analogs of curcumin (cinnamic acid, coumaric acid, and ferulic acid) were much less effective than curcumin as inhibitors of serum-induced smooth muscle cell proliferation. This suggested that curcumin may be useful for the prevention of the pathological changes associated with atherosclerosis and restenosis.

Chen and Huang [67] examined the possible mechanisms underlying curcumin's antiproliferative and apoptotic effects using the rat VSMC cell line A7r5. Curcumin (1 to 100 μ*M*) inhibited serum-stimulated [$^3$H]thymidine incorporation of both A7r5 cells and rabbit VSMC. Cell viability, as determined by the trypan blue dye exclusion method, was unaffected by curcumin at the concentration range 1 to 10 μ*M* in A7r5 cells. However, the number of viable cells after 100-μ*M* curcumin treatment was less than the basal value. Following curcumin (1 to 100 μ*M*) treatment,

cell cycle analysis revealed a G0/G1 arrest and a reduction in the percentage of cells in S phase. Curcumin at 100 μ*M* also induced cell apoptosis, as demonstrated by hematoxylin-eosin staining, TdT-mediated dUTP nick end labeling, DNA laddering, cell shrinkage, chromatin condensation, and DNA fragmentation. The membranous protein tyrosine kinase activity stimulated by serum in A7r5 cells was significantly reduced by curcumin (10 to 100 μ*M*). On the other hand, phorbol myristate acetate-stimulated cytosolic protein kinase C (PKC) activity was reduced by 100 μ*M* curcumin. The levels of c-myc mRNA and bcl-2 mRNA were significantly reduced by curcumin but had little effect on the p53 mRNA level. These results demonstrate that curcumin inhibited cell proliferation, arrested cell cycle progression, and induced cell apoptosis in VSMC. These results may explain how curcumin prevents the pathological changes of atherosclerosis and postangioplasty restenosis.

### 23.3.2 Curcumin Lowers Serum Cholesterol Levels

Numerous studies suggest that curcumin lowers serum cholesterol levels [105–111]. Soudamini et al. [108] investigated the effect of oral administration of curcumin on serum cholesterol levels and on lipid peroxidation in the liver, lung, kidney, and brain of mice treated with carbon tetrachloride, paraquat, and cyclophosphamide. Oral administration of curcumin significantly lowered the increased peroxidation of lipids in these tissues produced by these chemicals. Administration of curcumin also significantly lowered the serum and tissue cholesterol levels in these animals, indicating that the use of curcumin helps in conditions associated with peroxide-induced injury such as liver damage and arterial diseases. Soni and Kuttan examined the effect of curcumin administration in reducing the serum levels of cholesterol and lipid peroxides in 10 healthy human volunteers receiving 500 mg of curcumin per day for 7 days [112]. A significant decrease in the level of serum lipid peroxides (33%), an increase in high-density lipoproteins (HDL) cholesterol (29%), and a decrease in total serum cholesterol (12%) were noted. Because curcumin reduced serum lipid peroxides and serum cholesterol, the study of curcumin as a chemopreventive substance against arterial diseases was suggested.

*Curcuma xanthorrhiza* Roxb., a medicinal plant used in Indonesia (known as "temu lawak" or "Javanese turmeric"), has been shown to exert diverse physiological effect. However, little attention has been paid to its effect on lipid metabolism. Yasni et al. [113] investigated the effects of *C. xanthorrhiza* on serum and liver lipids, serum HDL cholesterol, apolipoprotein, and liver lipogenic enzymes. In rats given a cholesterol-free diet, *C. xanthorrhiza* decreased the concentrations of serum triglycerides, phospholipids, and liver cholesterol and increased the concentrations of serum HDL cholesterol and apolipoproteins. The activity of liver fatty acid synthase, but not glycerophosphate dehydrogenase, was decreased by the medicinal plant. In rats on a high-cholesterol diet, *C. xanthorrhiza* did not suppress the elevation of serum cholesterol, although it did decrease liver cholesterol. Curcuminoids prepared from *C. xanthorrhiza* had no significant effects on the serum and liver lipids. These studies, therefore, indicate that *C. xanthorrhiza* contains an active principle other than the curcuminoids that can modify the metabolism of lipids and lipoproteins.

In later studies, Yasni et al. [114] identified the major component (approx. 65%) of the essential oil as alpha-curcumene. Addition of essential oils (0.02%), prepared by steam distillation, to a purified diet lowered hepatic triglyceride concentration without influencing serum triglyceride levels, whereas addition of the hexane-soluble fraction (0.5%) lowered the concentration of serum and hepatic triglycerides. Rats fed the essential oil and hexane-soluble fraction had lower hepatic fatty acid synthase activity. The fraction containing α-curcumene, prepared from the hexane-soluble fraction by silica gel column chromatography, suppressed the synthesis of fatty acids from [$^{14}$C] acetate in primary cultured rat hepatocytes.

Skrzypczak-Jankun et al. [115] showed the three-dimensional structural data and explained how curcumin interacts with the fatty-acid-metabolizing enzyme soybean lipoxygenase. Curcumin binds to lipoxygenase in a noncompetitive manner. Trapped in that complex, it undergoes

photodegradation in response to x-rays, but utilizes enzyme catalytic ability to form the peroxy complex Enz-Fe-O-O-R as 4-hydroperoxy-2-methoxy-phenol, which later is transformed into 2-methoxycyclohexa-2,5-diene-1,4-dione. However, when Rukkumani et al. [116] compared the effects of curcumin and photo-irradiated curcumin on alcohol- and polyunsaturated fatty acid-induced hyperlipidemia, they found that photo-irradiated curcumin was more effective than curcumin in treating the above pathological conditions.

### 23.3.3 Curcumin Inhibits LDL Oxidation

The oxidation of low-density lipoproteins (LDL) plays an important role in the development of atherosclerosis. Atherosclerosis is characterized by oxidative damage, which affects lipoproteins, the walls of blood vessels, and subcellular membranes. Several studies suggest that curcumin inhibits oxidation of LDL [117–120]. Naidu and Thippeswamy [120] examined the effect of curcumin on copper-ion-induced lipid peroxidation of human LDL by measuring the formation of thiobarbituric acid reactive substance (TBARS) and relative electrophoretic mobility of LDL on agarose gel. Curcumin inhibited the formation of TBARS effectively throughout the incubation period of 12 h and decreased the relative electrophoretic mobility of LDL. Curcumin at 10 $\mu M$ produced 40 to 85% inhibition of LDL oxidation. The inhibitory effect of curcumin was comparable with that of BHA but more potent than ascorbic acid. Further, curcumin significantly inhibited both initiation and propagation phases of LDL oxidation.

Ramirez-Tortosa et al. [118] evaluated the effect of curcumin on LDL oxidation susceptibility and plasma lipids in atherosclerotic rabbits. A total of 18 rabbits were fed for 7 weeks on a diet containing 95.7% standard chow, 3% lard, and 1.3% cholesterol to induce atherosclerosis. The rabbits were divided into groups, two of which were also orally treated with turmeric extract at doses of 1.66 (group A) and 3.2 (group B) mg/kg body weight. A third group (group C) acted as an untreated control. Plasma and LDL lipid composition, plasma alpha-tocopherol, plasma retinol, LDL TBARS, and LDL lipid hydroperoxides were assayed, and aortic atherosclerotic lesions were evaluated. The low but not the high dosage of turmeric extracts decreased the susceptibility of rabbit LDL to lipid peroxidation. Both doses produced lower levels of total plasma cholesterol than the control group. Moreover, the lower-dosage group had lower levels of cholesterol, phospholipids, and triglycerides than the group treated with the 3.2-mg dosage.

Quiles et al. [117] evaluated the antioxidant capacity of a *C. longa* extract on the lipid peroxidation of liver mitochondria and microsome membranes in atherosclerotic rabbits. Male rabbits fed a 3% (w/w) lard and 1.3% (w/w) cholesterol diet were randomly assigned to three groups. Two groups were treated with different dosages of a turmeric extract (A and B), and the third group (control) was treated with a curcumin-free solution. Basal and *in vitro* 2,2′-azobis(2-amidinopropane)dihydrochloride-induced hydroperoxide and TBARS production in liver mitochondria and microsomes were analyzed. Group A had the lowest concentration of mitochondrial hydroperoxides. In microsomes, the basal hydroperoxide levels were similar in all groups, but after the induction of oxidation, group C registered the highest value; TBARS production followed the same trend in mitochondria. These findings suggest that active compounds in curcuma extract may be protective against lipoperoxidation of subcellular membranes in a dosage-dependent manner.

Asai and Miyazawa [119] examined the effect of curcumin on lipid metabolism in rats fed a control, moderately high-fat diet (15 g soybean oil/100 g diet) and those given supplements of 0.2 g curcuminoids/100 g diet. Liver triacylglycerol and cholesterol concentrations were significantly lower in rats fed curcumin than in control rats. Plasma triacylglycerols in the very-low-density lipoproteins fraction were also lower in curcumin-fed rats than in control ($P < 0.05$). Hepatic acyl-CoA oxidase activity of the curcumin group was significantly higher than that of the control. Furthermore, epididymal adipose tissue weight was significantly reduced with curcuminoid intake in a dose-dependent manner. These results indicated that dietary curcuminoids have lipid-lowering potency *in vivo*, probably due to alterations in fatty acid metabolism.

### 23.3.4 Curcumin Inhibits Platelet Aggregation

Platelet aggregation contributes to the pathway resulting in atherosclerosis. There are reports suggesting that curcumin can inhibit platelet aggregation [121–123]. Srivastava et al. [122] examined the effect of curcumin on platelet aggregation and vascular prostacyclin synthesis. *In vitro* and *ex vivo* effects of curcumin and acetylsalicylic acid (ASA) on the synthesis of prostacyclin ($PGI_2$) and on platelet aggregation has been studied in rats. Both drugs inhibited adenosine diphosphate and epinephrine (adrenaline)- and collagen-induced platelet aggregation in monkey plasma. Pretreatment with ASA (25 to 100 mg/kg), but not curcumin (100 to 300 mg/kg), inhibited $PGI_2$ synthesis in rat aorta. In the *in vitro* system, curcumin also caused a slight increase in the synthesis of $PGI_2$, while ASA inhibited it. Curcumin may, therefore, be preferable in patients prone to vascular thrombosis and requiring antiarthritic therapy.

Srivastava *et al*. showed that curcumin inhibited platelet aggregation induced by arachidonate, adrenaline, and collagen [123]. This compound inhibited thromboxane B2 production from exogenous [$^{14}$C] arachidonate (AA) in washed platelets and concomitantly increased the formation of 12 lipoxygenase products. Moreover, curcumin inhibited the incorporation of [$^{14}$C] AA into platelet phospholipids and inhibited the deacylation of AA-labeled phospholipids (liberation of free AA) on stimulation with calcium ionophore A23187. Curcumin's anti-inflammatory properties may, in part, be explained by the compound's effects on eicosanoid biosynthesis.

### 23.3.5 Curcumin Inhibits Myocardial Infarction

The effect of curcumin on myocardial infarction (MI) in the cat and the rat has been investigated [124–126]. Dikshit et al. [124] examined the prevention of ischemia-induced biochemical changes by curcumin in the cat heart. Myocardial ischemia was induced by the ligation of the left descending coronary artery. Curcumin (100 mg/kg, i.p.) was given 30 min before ligation. Cats were killed and hearts were removed 4 h after coronary artery ligation. Levels of glutathione (GSH), malonaldehyde (MDA), myeloperoxidase (MPO), superoxide dismutase (SOD), catalase, and lactate dehydrogenase (LDH) were estimated in the ischemic and nonischemic zones. Curcumin protected the animals against decrease in the heart rate and blood pressure following ischemia. In the ischemic zone, after 4 h of ligation, an increase in the level of MDA and activities of MPO and SOD (cytosolic fraction) were observed. Curcumin pretreatment prevented the ischemia-induced elevation in MDA contents and LDH release, but it did not affect the increase in MPO activity. Thus curcumin prevented ischemia-induced changes in the cat heart.

Nirmala and Puvanakrishnan [125] investigated the effect of curcumin on lysosomal hydrolases (β-glucuronidase, β-N-acetylglucosaminidase, cathepsin B, cathepsin D, and acid phosphatase) in serum and heart after isoproterenol (ISO)-induced MI. Rats treated with ISO (30 mg/100 g body weight) showed a significant increase in serum lysosomal hydrolase activities, which were found to decrease after curcumin treatment. ISO administration to rats resulted in decreased stability of the membranes, which was reflected by the lowered activity of cathepsin D in mitochondrial, lysosomal, and microsomal fractions. Curcumin treatment returned the activity levels almost to normal, showing that curcumin restored the normal function of the membrane. Histopathological studies of the infarcted rat heart also showed a decreased degree of necrosis after curcumin treatment. Nirmala and Puvanakrishnan [125] also examined the effect of curcumin on the biochemical changes induced by ISO administration in rats. ISO caused a decrease in body weight and an increase in heart weight, water content, and levels of serum marker enzymes, namely creatine kinase (CK), LDH, and LDH1 isozyme. It also produced electrocardiographic changes such as an increased heart rate, reduced R amplitude, and elevated ST. Curcumin at a concentration of 200 mg/kg, when administered orally, decreased serum enzyme levels, and the electrocardiographic changes were restored toward normalcy. MI was accompanied by the disintegration of membrane

polyunsaturated fatty acids expressed by an increase in TBARS, a measure of lipid peroxides, and by the impairment of natural scavenging, characterized by a decrease in the levels of SOD, catalase, glutathione peroxidase, ceruloplasmin, α-tocopherol, GSH, and ascorbic acid. Oral pretreatment with curcumin 2 days before and during ISO administration decreased the effect of lipid peroxidation. It has a membrane-stabilizing action by inhibiting the release of β-glucuronidase from nuclei, mitochondria, lysosomes, and microsomes. Curcumin given before and during treatment decreased the severity of pathological changes and thus could have a protective effect against the damage caused by MI.

Nirmala et al. [126] showed that curcumin treatment modulates collagen metabolism in ISO-induced myocardial necrosis in rats. This study evaluated whether curcumin had any specific role in the synthesis and degradation of collagen in rat heart with myocardial necrosis induced by ISO. The effect of curcumin (200 mg/kg) was examined on ISO-induced myocardial necrosis and collagen metabolism. The incorporation of [$^{14}$C] proline into collagen was studied as an index of collagen synthesis. The heart-weight/body-weight ratio, heart RNA/DNA ratio, and protein increased significantly in ISO-treated animals. Curcumin given before and during treatment with ISO reversed these changes and attenuated the development of cardiac hypertrophy 2 weeks after the second dose of ISO. Increased fractional synthesis rate and enhanced degradation of newly synthesized collagen were observed in ISO-treated animals. Curcumin before and during treatment with ISO decreased the degree of degradation of the existing collagen matrix and collagen synthesis 2 weeks after the second dose of ISO. The observed effects could have been due to free-radical scavenging capacity and inhibition of lysosomal enzyme release by curcumin.

Enzymes of the SOD family are key regulators of cellular oxidant stress caused by ischemia-reperfusion. In particular, the mitochondrial-associated MnSOD enzyme has been implicated in protection from ischemia-reperfusion injury. Shahed et al. [127] investigated the effect of curcumin compounds on expression of antioxidant enzymes mRNAs *in vivo* in rat kidney after ureteral obstruction or ischemia-reperfusion injury. Curcumin exhibited renoprotective properties by modulating the expression of MnSOD.

## 23.4 OTHER EFFECT OF CURCUMIN

### 23.4.1 Curcumin Suppresses Diabetes

Arun and Nalini [128] investigated the efficacy of turmeric and curcumin on blood sugar and polyol pathway in diabetic albino rats. Alloxan was used to induce diabetes. Administration of turmeric or curcumin reduced the blood sugar, hemoglobin, and glycosylated hemoglobin levels significantly [129]. Turmeric and curcumin supplementation also reduced the oxidative stress encountered by the diabetic rats, as demonstrated by lower levels of TBARS, which may have been due to the decreased influx of glucose into the polyol pathway, leading to an increased NADPH/NADP ratio and elevated activity of the potent antioxidant enzyme GPx. Moreover, the activity of sorbitol dehydrogenase, which catalyzes the conversion of sorbitol to fructose, was lowered significantly by treatment with turmeric or curcumin. These results also appeared to reveal that curcumin was more effective in attenuating diabetes mellitus-related changes than turmeric.

Babu et al. [130] also examined the influence of dietary curcumin on the progression of experimentally induced diabetes induced by cholesterol feeding in the albino rat. Albino rats fed 0.5% curcumin diet or 1% cholesterol diet were rendered diabetic with streptozotocin injection. Diabetic rats maintained on curcumin diet for 8 weeks excreted less albumin, urea, creatinine, and inorganic phosphorus. Urinary excretion of the electrolytes sodium and potassium were also significantly lowered under curcumin treatment. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creatine, and inorganic phosphorus in diabetic animals. On the other hand, glucose excretion or the fasting sugar level was unaffected by dietary curcumin, and so also the body weights were not improved to any significant extent. The curcumin diet

lowered liver weight and lowered lipid peroxidation in plasma and urine at the end of the study compared with controls. The extent of lipid peroxidation was still higher in cholesterol-fed diabetic groups compared with diabetic rats fed with control diet. Thus, the study reveals that curcumin feeding improves the metabolic status in diabetic conditions, despite no effect on hyperglycemic status or body weight. The mechanism by which curcumin improves this situation is probably by virtue of its hypocholesterolemic influence and its antioxidant and free-radical-scavenging properties.

In another study, Babu et al. [131] showed the hypolipidemic action of curcumin in rats with streptozotocin-induced diabetes. Rats were maintained on 0.5% curcumin-containing diet for 8 weeks. The diet lowered blood cholesterol significantly exclusively by decreasing the LDL-VLDL fraction. A significant decrease in blood triglyceride and phospholipids was also brought about by dietary curcumin. In a parallel study, wherein diabetic animals were maintained on a high-cholesterol diet, the extents of hypercholesterolemia and phospholipidemia were higher than those maintained on the control diet. Curcumin lowered cholesterol and phospholipid levels in these animals also. Liver cholesterol and triglyceride and phospholipid contents were elevated under diabetic conditions. Dietary curcumin showed a distinct tendency to counter these changes in lipid fractions of liver. This effect of curcumin was also seen in diabetic animals maintained on a high-cholesterol diet. Dietary curcumin significantly countered renal cholesterol and triglyceride elevation in diabetic rats. In order to understand the mechanism of hypocholesterolemic action of dietary curcumin, activities of hepatic cholesterol-7a-hydroxylase and HMG-CoA reductase were measured. Hepatic cholesterol-7$\alpha$-hydroxylase activity was markedly higher in curcumin-fed diabetic animals, suggesting a higher rate of cholesterol catabolism.

Suresh and Srinivasan [132] showed amelioration of renal lesions associated with diabetes by dietary curcumin in Wistar rats with streptozotocin-induced diabetes. For these studies, curcumin was fed at 0.5% in the diet for 8 weeks. Renal damage was assessed by the amount of proteins excreted in the urine and the extent of leaching of the renal tubular enzymes NAG, LDH, AsAT, AlAT, and alkaline and acid phosphatases. The integrity of the kidney was assessed by measuring the activities of several key enzymes of the renal tissue: glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, and LDH (carbohydrate metabolism); aldose reductase and sorbitol dehydrogenase (polyol pathway); and transaminases, ATPases, and membrane polyunsaturated/polysaturated fatty acid ratio (membrane integrity). Data on enzymuria, albuminuria, activity of kidney ATPases, and fatty acid composition of renal membranes suggested that dietary curcumin significantly inhibited the progression of renal lesions in diabetes. These findings were corroborated by histological examination of kidney sections. This beneficial influence was possibly mediated through curcumin's ability to lower blood cholesterol levels.

### 23.4.2 Curcumin Stimulates Muscle Regeneration

Skeletal muscle is often the site of tissue injury due to trauma, disease, developmental defects, or surgery. Yet to date no effective treatment is available to stimulate the repair of skeletal muscle. Thaloor et al. [133] investigated the kinetics and extent of muscle regeneration *in vivo* after trauma following systemic administration of curcumin to mice. Biochemical and histological analyses indicated faster restoration of normal tissue architecture in mice treated with curcumin after only 4 days of daily intraperitoneal injection, whereas controls required over 2 weeks to restore normal tissue architecture. Curcumin acted directly on cultured muscle precursor cells to stimulate both cell proliferation and differentiation under appropriate conditions. The authors suggested that this effect of curcumin was mediated through suppression of NF-$\kappa$B; inhibition of NF-$\kappa$B-mediated transcription was confirmed using reporter gene assays. They concluded that NF-$\kappa$B exerts a role in regulating myogenesis and that modulation of NF-$\kappa$B activity within muscle tissue is beneficial for muscle repair. The striking effects of curcumin on myogenesis suggest therapeutic applications for treating muscle injuries.

### 23.4.3 Curcumin Enhances Wound Healing

Tissue repair and wound healing are complex processes that involve inflammation, granulation, and remodeling of the tissue. Perhaps the earliest report that curcumin has wound-healing activity was reported by Gujral and coworkers [3]. Sidhu et al. [134] examined the wound-healing capacity of curcumin in rats and guinea pigs. Punch wounds in curcumin-treated animals closed faster in treated than in untreated animals. Biopsies of the wound showed reepithelialization of the epidermis and increased migration of various cells, including myofibroblasts, fibroblasts, and macrophages in the wound bed. Multiple areas within the dermis showed extensive neovascularization, and Masson's trichrome staining showed greater collagen deposition in curcumin-treated wounds. Immunohistochemical localization showed an increase of transforming growth factor beta 1 (TGF-β1) in curcumin-treated wounds as compared with untreated wounds. *In situ* hybridization and polymerase chain reaction analysis also showed an increase in the mRNA transcripts of TGF-β1 and fibronectin in curcumin-treated wounds. Because TGF-β1 is known to enhance wound healing, it possible that curcumin modulates TGF-β1 activity.

To further understand its therapeutic effect on wound healing, the antioxidant effects of curcumin on $H_2O_2$-induced and hypoxanthine-xanthine oxidase-induced damage to cultured human keratinocytes and fibroblasts were investigated by Phan et al. [135]. Cell viability was assessed by colorimetric assay and quantification of LDH release. Exposure of human keratinocytes to curcumin at 10 μg/ml significantly protected against the keratinocytes from $H_2O_2$-induced oxidative damage. Interestingly, exposure of human dermal fibroblasts to curcumin at 2.5 μg/ml showed significant protective effects against $H_2O_2$. No protective effects of curcumin on either fibroblasts or keratinocytes against hypoxanthine-xanthine oxidase-induced damage were found. These investigators thus concluded that curcumin indeed possessed powerful inhibitory capacity against $H_2O_2$-induced damage in human keratinocytes and fibroblasts and that this protection may contribute to wound healing.

Mani et al. [136] investigated the effect of curcumin treatment by topical application in dexamethasone-impaired cutaneous healing in a full-thickness punch-wound model in rats. They assessed healing in terms of histology, morphometry, and collagenization on the fourth and seventh days postwounding and analyzed the regulation of TGF-β1, its receptors type I (tIrc) and type II (tIIrc), and iNOS. Curcumin significantly accelerated healing of wounds with or without dexamethasone treatment, as revealed by a reduction in the wound width and gap length compared with controls. Curcumin treatment enhanced expression of TGF-β1 and TGF-β tIIrc in both normal and impaired healing wounds. Macrophages in the wound bed showed an enhanced expression of TGF-β1 mRNA in curcumin-treated wounds, as evidenced by *in situ* hybridization. iNOS levels were increased following curcumin treatment in unimpaired wounds, but not so in the dexamethasone-impaired wounds. Their study indicated an enhancement in dexamethasone-impaired wound repair by topical curcumin and its differential regulatory effect on TGF-β1, its receptors, and iNOS in this cutaneous wound-healing model.

### 23.4.4 Curcumin Suppresses Symptoms Associated with Arthritis

Deodhar et al. [137] were the first to report on the antirheumatic activity of curcumin in human subjects. They performed a short-term double-blind crossover study in 18 patients with "definite" rheumatoid arthritis to compare the antirheumatic activity of curcumin (1200 mg/day) with phenylbutazone (300 mg/day). Subjective and objective assessment in patients who were taking corticosteroids just prior to the study showed significant ($P < 0.05$) improvements in morning stiffness, walking time, and joint swelling following 2 weeks of curcumin therapy.

Liacini et al. [138] examined the effect of curcumin in articular chondrocytes. Interleukin-1 (IL-1), the main cytokine instigator of cartilage degeneration in arthritis, induces matrix metalloproteinase-3 (MMP3) and MMP13 RNA and protein in chondrocytes through activation of

mitogen-activated protein kinase (MAPK), AP-1, and NF-κB transcription factors. Curcumin achieved 48 to 99% suppression of MMP3 and 45 to 97% of MMP13 in human chondrocytes and 8 to 100% (MMP3) and 32 to 100% (MMP13) in bovine chondrocytes. Inhibition of IL-1 signal transduction by these agents could be useful for reducing cartilage resorption by MMPs in arthritis.

### 23.4.5 Curcumin Reduces the Incidence of Cholesterol Gallstone Formation

Hussain and Chandrasekhara [110] studied the efficacy of curcumin in reducing the incidence of cholesterol gallstones induced by feeding a lithogenic diet in young male mice. Feeding a lithogenic diet supplemented with 0.5% curcumin for 10 weeks reduced the incidence of gallstone formation to 26%, as compared with 100% incidence in the group fed with the lithogenic diet alone. Biliary cholesterol concentration was also significantly reduced by curcumin feeding. The lithogenic index, which was 1.09 in the cholesterol-fed group, was reduced to 0.43 in the 0.5% curcumin supplemented group. Further, the cholesterol:phospholipid ratio of bile was also reduced significantly when 0.5% curcumin-supplemented diet was fed. A dose-response study with 0.2, 0.5, and 1% curcumin-supplemented lithogenic diets showed that 0.5% curcumin was more effective than a diet with 0.2 or 1% curcumin. How curcumin mediates antilithogenic effects in mice was further investigated by this group [111]. For this purpose, the hepatic bile of rats was fractionated by gel filtration chromatography, and the low molecular weight (LMW) protein fractions were tested for their ability to influence cholesterol crystal growth in model bile. The LMW protein fraction from the lithogenic-agent-fed control group's bile shortened the nucleation time and increased the crystal growth rate and final crystal concentration. But with the LMW protein fractions from the bile of rats given curcumin, the nucleation times were prolonged, and the crystal growth rates and final crystal concentrations were decreased. The LMW fractions were further purified into three different sugar-specific proteins by affinity chromatography. A higher proportion of LMW proteins from the control group bile was bound to Con-A, whereas higher proportions of LMW proteins from the groups fed with curcumin were bound to wheat germ agglutinin (WGA) and helix pomatia lectin. The Con-A-bound fraction obtained from the control group showed a pronucleating effect. In contrast, the WGA-bound fraction obtained from the curcumin group showed a potent antinucleating activity.

### 23.4.6 Curcumin Modulates Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that afflicts more than 1 million people worldwide. The destruction of oligodendrocytes and myelin sheath in the CNS is the pathological hallmark of MS. MS is an inflammatory autoimmune disease of the CNS resulting from myelin antigen-sensitized T cells in the CNS. Experimental allergic encephalomyelitis (EAE), a $CD4^+$ Th1 cell-mediated inflammatory demyelinating autoimmune disease of the CNS, serves as an animal model for MS. IL-12 plays a crucial proinflammatory role in the induction of neural antigen-specific Th1 differentiation and pathogenesis of CNS demyelination in EAE and MS.

Natarajan and Bright [61] investigated the effect of curcumin on the pathogenesis of CNS demyelination in EAE. *In vivo* treatment of SJL/J mice with curcumin significantly reduced the duration and clinical severity of active immunization and adoptive transfer of EAE [61]. Curcumin inhibited EAE in association with a decrease in IL-12 production from macrophage/microglial cells and differentiation of neural antigen-specific Th1 cells. *In vitro* treatment of activated T cells with curcumin inhibited IL-12-induced tyrosine phosphorylation of Janus kinase 2, tyrosine kinase 2, and STAT3 and STAT4 transcription factors. The inhibition of Janus kinase-STAT pathway by curcumin resulted in a decrease in IL-12-induced T-cell proliferation and Th1 differentiation. These findings show that curcumin inhibits EAE by blocking IL-12 signaling in T cells and suggest its use in the treatment of MS and other Th1-cell-mediated inflammatory diseases.

### 23.4.7 Curcumin Blocks the Replication of HIV

Transcription of type 1 human immunodeficiency virus (HIV-1) provirus is governed by the viral long-terminal repeat (LTR). Drugs can block HIV-1 replication by inhibiting the activity of its LTR. Li et al. [139] examined the effect of curcumin on HIV-1 LTR-directed gene expression and virus replication. Curcumin was found to be a potent and selective inhibitor of HIV-1 LTR-directed gene expression, at concentrations that have minor effects on cells. Curcumin inhibited p24 antigen production in cells either acutely or chronically infected with HIV-1 through transcriptional repression of the LTR. Sui et al. [140] examined the effect on the HIV-1 and HIV-2 proteases by curcumin and curcumin boron complexes. Curcumin was a modest inhibitor of HIV-1 ($IC_{50}$ = 100 μ*M*) and HIV-2 ($IC_{50}$ = 250 μ*M*) proteases. Simple modifications of the curcumin structure raised the $IC_{50}$ value, but complexes of the central dihydroxy groups of curcumin with boron lowered the $IC_{50}$ to a value as low as 6 μ*M*. The boron complexes were also time-dependent inactivators of the HIV proteases. The increased affinity of the boron complexes may reflect binding of the orthogonal domains of the inhibitor in intersecting sites within the substrate-binding cavity of the enzyme, while activation of the α, β-unsaturated carbonyl group of curcumin by chelation to boron probably accounts for time-dependent inhibition of the enzyme.

Mazumder et al. [141] examined the effect of curcumin analogs with altered potencies against HIV-1 integrase. They reported that curcumin inhibited HIV-1 integrase activity. They also synthesized and tested analogs of curcumin to explore the structure-activity relationships and mechanism of action of this family of compounds in more detail. They found that two curcumin analogs, dicaffeoylmethane and rosmarinic acid, inhibited both activities of integrase for $IC_{50}$ values below 10 μ*M*. They demonstrated that lysine 136 may play a role in viral DNA binding and that two curcumin analogs had equivalent potencies against both an integrase mutant and wild-type integrase, suggesting that the curcumin-binding site and the substrate-binding site may not overlap. Combining one curcumin analog with the recently described integrase inhibitor NSC 158393 resulted in integrase inhibition that was synergistic, again suggesting that drug-binding sites may not overlap. They also determined that these analogs could inhibit binding of the enzyme to the viral DNA, but that this inhibition is independent of divalent metal ion. Furthermore, kinetic studies of these analogs suggest that they bind to the enzyme at a slow rate. These studies can provide mechanistic and structural information to guide the future design of integrase inhibitors.

The transcription of HIV-1 provirus is regulated by both cellular and viral factors. Various pieces of evidence suggest that Tat protein secreted by HIV1-infected cells may have additional activity in the pathogenesis of AIDS because of its ability to also be taken up by noninfected cells. Barthelemy et al. [142] showed that curcumin used at 10 to 100 n*M* inhibited Tat transactivation of HIV1-LTR lacZ by 70 to 80% in HeLa cells. To develop more efficient curcumin derivatives, the researchers synthesized and tested in the same experimental system the inhibitory activity of reduced curcumin (C1), which lacks the spatial structure of curcumin; allyl-curcumin (C2), which possesses a condensed allyl derivative on curcumin that plays the role of metal chelator; and tocopheryl-curcumin (C3), whose structural alterations enhance the antioxidant activity of the molecule. Results obtained with the C1, C2, and C3 curcumin derivatives showed a significant inhibition (70 to 85%) of Tat transactivation. Despite the fact that tocopheryl-curcumin (C3) failed to scavenge $O^{2-}$, this curcumin derivative exhibited the most activity; 70% inhibition was obtained at 1 n*M*, while only 35% inhibition was obtained with the curcumin.

### 23.4.8 Curcumin Affects Alzheimer's Disease

Brain inflammation in Alzheimer's disease (AD) patients is characterized by increased cytokines and activated microglia. Epidemiological studies suggest reduced AD risk is associated with long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Whereas chronic ibuprofen suppressed inflammation and plaque-related pathology in an Alzheimer transgenic APPSw mouse model

(Tg2576), excessive use of NSAIDs targeting cyclooxygenase I can cause gastrointestinal, liver, and renal toxicity. One alternative NSAID is curcumin. Lim et al. [143] found that curcumin reduced oxidative damage and amyloid pathology in an Alzheimer transgenic mouse model. To evaluate whether it could affect Alzheimer-like pathology in the APPSw mice, they tested the effect of a low (160 ppm) and a high (5000 ppm) dose of dietary curcumin on inflammation, oxidative damage, and plaque pathology. Low and high doses significantly lowered oxidized proteins and IL-1β, a proinflammatory cytokine usually elevated in the brains of these mice. With low-dose, but not high-dose, curcumin treatment, the astrocytic marker glial fibrillary acidic protein was reduced, and insoluble beta-amyloid (Aβ), soluble Aβ, and plaque burden were significantly decreased, by 43 to 50%. However, levels of amyloid precursor in the membrane fraction were not reduced. Microgliosis was also suppressed in neuronal layers but not adjacent to plaques. In view of its efficacy and apparent low toxicity, this Indian spice component has promise for the prevention of Alzheimer's disease.

### 23.4.9 Curcumin Protects against Cataract Formation

Age-related cataractogenesis is a significant health problem worldwide. Oxidative stress has been suggested to be a common underlying mechanism of cataractogenesis, and augmentation of the antioxidant defenses of the ocular lens has been shown to prevent or delay cataractogenesis. Awasthi et al. [144] tested the efficacy of curcumin in preventing cataractogenesis in an *in vitro* rat model. Rats were maintained on an AIN-76 diet for 2 weeks, after which they were given a daily dose of corn oil alone or 75 mg curcumin/kg in corn oil for 14 days. Their lenses were removed and cultured for 72 h *in vitro* in the presence or absence of 100 μmol 4-hydroxy-2-nonenal (4-HNE)/L, a highly electrophilic product of lipid peroxidation. The results of these studies showed that 4-HNE led to opacification of cultured lenses, as indicated by the measurements of transmitted light intensity using digital image analysis. However, the lenses from curcumin-treated rats were resistant to 4-HNE-induced opacification. Curcumin treatment significantly induced the glutathione-*S*-transferase (GST) isozyme rGST8-8 in rat lens epithelium. Because rGST8-8 utilizes 4-HNE as a preferred substrate, we suggest that the protective effect of curcumin may be mediated through the induction of this GST isozyme. These studies suggest that curcumin may be an effective protective agent against cataractogenesis induced by lipid peroxidation.

### 23.4.10 Curcumin Protects from Drug-Induced Myocardial Toxicity

Cardiotoxicity is one of the major problems associated with administration of many chemotherapeutic agents. Venkatesan [145] examined the protective effect of curcumin on acute adriamycin (ADR) myocardial toxicity in rats. ADR toxicity, induced by a single intraperitoneal injection (30 mg/kg), was revealed by elevated serum creatine kinase (CK) and LDH. The level of the lipid peroxidation products, conjugated dienes, and malondialdehyde were markedly elevated by ADR. ADR also caused a decrease in myocardial glutathione content and glutathione peroxidase activity and an increase in cardiac catalase activity. Curcumin treatment (200 mg/kg) 7 days before and 2 days following ADR significantly ameliorated the early manifestation of cardiotoxicity (ST segment elevation and an increase in heart rate) and prevented the rise in serum CK and LDH exerted by ADR. ADR-treated rats that received curcumin displayed a significant inhibition of lipid peroxidation and augmentation of endogenous antioxidants. These results suggest that curcumin inhibits ADR cardiotoxicity and might serve as a novel combination chemotherapeutic agent with ADR to limit free-radical-mediated organ injury.

### 23.4.11 Curcumin Protects from Alcohol-Induced Liver Injury

Because induction of NF-κB-mediated gene expression has been implicated in the pathogenesis of alcoholic liver disease (ALD) and curcumin inhibits the activation of NF-kappaB, Nanji et al. [146]

determined whether treatment with curcumin would prevent experimental ALD and elucidated the underlying mechanism. Four groups of rats (six rats/group) were treated by intragastric infusion for 4 weeks. One group received fish oil plus ethanol (FE); a second group received fish oil plus dextrose (FD). The third and fourth groups received FE or FD supplemented with 75 mg/kg/day of curcumin. Liver samples were analyzed for histopathology, lipid peroxidation, NF-κB binding, TNFα, IL-12, monocyte chemotactic protein-1, macrophage inflammatory protein-2, COX-2, iNOS, and nitrotyrosine. Rats fed FE developed fatty liver, necrosis, and inflammation, which was accompanied by activation of NF-kappaB and the induction of cytokines, chemokines, COX-2, iNOS, and nitrotyrosine formation. Treatment with curcumin prevented both the pathological and biochemical changes induced by alcohol. Because endotoxin and the Kupffer cell are implicated in the pathogenesis of ALD, they also investigated whether curcumin suppressed the stimulatory effects of endotoxin in isolated Kupffer cells. Curcumin blocked endotoxin-mediated activation of NF-κB and suppressed the expression of cytokines, chemokines, COX-2, and iNOS in Kupffer cells. Thus curcumin prevented experimental ALD, in part by suppressing induction of NF-κB-dependent genes.

Hepatic fibrogenesis occurs as a wound-healing process after many forms of chronic liver injury. Hepatic fibrosis ultimately leads to cirrhosis if not treated effectively. During liver injury, quiescent hepatic stellate cells (HSC), the most relevant cell type, become active and proliferative. Oxidative stress is a major and critical factor for HSC activation. Activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) inhibits the proliferation of nonadipocytes. The level of PPAR-γ is dramatically diminished along with activation of HSC during liver injury. Xu et al. [62] examined the effect of curcumin on HSC proliferation. They hypothesized that curcumin inhibits the proliferation of activated HSC by inducing PPAR-γ gene expression and reviving PPAR-γ activation. Their results indicated that curcumin significantly inhibited the proliferation of activated HSC and induced apoptosis *in vitro*. They also demonstrated, for the first time, that curcumin dramatically induced the expression of the PPAR-γ gene and activated PPAR-γ in activated HSC. Blocking its trans-activating activity by a PPAR-γ antagonist markedly abrogated the effects of curcumin on inhibition of cell proliferation. These results provided a novel insight into mechanisms underlying the inhibition of activated HSC growth by curcumin. The characteristics of curcumin, including antioxidant potential, reduction of activated HSC growth, and no adverse health effects, make it a potential candidate for prevention and treatment of hepatic fibrosis.

### 23.4.12 Curcumin Protects from Drug-Induced Lung Injury

Cyclophosphamide causes lung injury in rats through its ability to generate free radicals, with subsequent endothelial and epithelial cell damage. Venkatesan and Chandrakasan [147] examined the effect of curcumin on cyclophosphamide-induced early lung injury. In order to observe the protective effects of curcumin on cyclophosphamide-induced early lung injury, healthy, pathogen-free male Wistar rats were exposed to 20 mg/100 g body weight of cyclophosphamide, given intraperitoneally as a single injection. Prior to cyclophosphamide intoxication, curcumin was administered orally daily for 7 days. At various times (2, 3, 5, and 7 days after insult), serum and lung samples were analyzed for angiotensin-converting enzyme (ACE), lipid peroxidation, reduced glutathione, and ascorbic acid. Bronchoalveolar lavage fluid was analyzed for biochemical constituents. The lavage cells were examined for lipid peroxidation and glutathione content. Excised lungs were analyzed for antioxidant enzyme levels. Biochemical analyses revealed increased lavage fluid total protein, albumin, ACE, LDH, N-acetyl-beta-D-glucosaminidase, alkaline phosphatase, acid phosphatase, lipid peroxide, GSH, and ascorbic acid levels 2, 3, 5, and 7 days after cyclophosphamide intoxication. Increased levels of lipid peroxidation and decreased levels of GSH and ascorbic acid were seen in serum, lung tissue, and lavage cells of cyclophosphamide-treated groups. Serum ACE activity increased, which coincided with the decrease in lung tissue levels. Activities of antioxidant enzymes were reduced with time in the

lungs of cyclophosphamide-treated groups. A significant reduction in the lavage fluid biochemical constituents and in lipid peroxidation products in the serum, lung, and lavage cells occurred concomitantly with an increase in antioxidant defense mechanisms in curcumin-fed cyclophosphamide rats. Therefore, the study indicated that curcumin is effective in moderating the cyclophosphamide-induced early lung injury.

In another study, Venkatesan et al. [148] investigated the effect of curcumin on bleomycin (BLM)-induced lung injury. The data indicated that BLM-mediated lung injury resulted in increases in lung lavage fluid biomarkers such as total protein, ACE, LDH, N-acetyl-beta-D-glucosaminidase, lipid peroxidation (LPO) products, SOD, and catalase. BLM administration also increased the levels of malondialdehyde in bronchoalveolar lavage fluid and bronchoalveolar lavage (BAL) cells and led to greater amounts of alveolar macrophage (AM) SOD activity. In contrast, lower levels of reduced GSH were observed in lung lavage fluid, BAL cells, and AM. Stimulated superoxide anion and $H_2O_2$ release by AM from BLM-treated rats were higher. Curcumin treatment significantly reduced lavage fluid biomarkers. In addition, it restored the antioxidant status in BLM rats. These data suggested that curcumin treatment reduces the development of BLM-induced inflammatory and oxidant activity. Therefore, curcumin offers the potential for a novel pharmacological approach in the suppression of drug- or chemical-induced lung injury.

Punithavathi et al. [149] also evaluated the ability of curcumin to suppress BLM-induced pulmonary fibrosis in rats. A single intratracheal instillation of BLM (0.75 U/100 g, sacrificed 3, 5, 7, 14, and 28 days post-BLM) resulted in significant increases in total cell numbers, total protein, and ACE and in alkaline phosphatase activities in bronchoalveolar lavage fluid. Animals with fibrosis had a significant increase in lung hydroxyproline content. AM from BLM-treated rats elaborated significant increases in TNF-$\alpha$ and in superoxide and nitric oxide production in culture medium. Interestingly, oral administration of curcumin (300 mg/kg) 10 days before and daily thereafter throughout the experimental time period inhibited BLM-induced increases in total cell counts and biomarkers of inflammatory responses in BALF. In addition, curcumin significantly reduced the total lung hydroxyproline in BLM-treated rats. Furthermore, curcumin remarkably suppressed the BLM-induced AM production of TNF-$\alpha$, SOD, and nitric oxide. These findings suggest that curcumin is a potent anti-inflammatory and antifibrotic agent against BLM-induced pulmonary fibrosis in rats. Punithavathi et al. [150] also examined whether curcumin prevented amiodarone-induced lung fibrosis in rats. They found that curcumin had a protective effect on amiodarone-induced pulmonary fibrosis. Curcumin inhibited the increases in lung myeloperoxidase activity, TGF-$\beta$1 expression, lung hydroxyproline content, and expression of type I collagen and c-Jun protein in amiodarone-treated rats.

Paraquat (PQ), a broad-spectrum herbicide, can cause lung injury in humans and animals. An early feature of PQ toxicity is the influx of inflammatory cells, releasing proteolytic enzymes and oxygen free radicals that can destroy the lung epithelium and cause pulmonary fibrosis. Suppressing early lung injury before the development of irreversible fibrosis is critical to effective therapy. Venkatesan [151] showed that curcumin confers remarkable protection against PQ-induced lung injury. A single intraperitoneal injection of PQ (50 mg/kg) significantly increased the levels of protein, angiotensin-converting enzyme (ACE), alkaline phosphatase, N-acetyl-beta-D-glucosaminidase (NAG), thiobarbituric acid reactive substances (TBARS), and neutrophils in the bronchoalveolar lavage fluid (BALF), while it decreased GSH levels. In PQ-treated rat BAL cells, TBARS concentration was increased at the same time as glutathione content was decreased. In addition, PQ caused a decrease in ACE and glutathione levels and an increase in levels of TBARS and myeloperoxidase activity in the lung. Interestingly, curcumin prevented the general toxicity and mortality induced by PQ and blocked the rise in BALF protein, ACE, alkaline phosphatase, NAG, TBARS, and neutrophils. Likewise, it prevented the rise in TBARS content in both BAL cell and lung tissue and MPO activity of the lung, reduced lung ACE, and abolished BAL cell and lung glutathione levels. These findings indicate that curcumin has important therapeutic potential in suppressing PQ lung injury.

### 23.4.13 Curcumin Prevents Adriamycin-Induced Nephrotoxicity

Nephrotoxicity is another problem observed in patients given chemotherapeutic agents. Venkatesan et al. [145, 152] showed that curcumin prevents adriamycin (ADR)-induced nephrotoxicity in rats. Treatment with curcumin markedly protected against ADR-induced proteinuria, albuminuria, hypoalbuminemia, and hyperlipidemia. Similarly, curcumin inhibited ADR-induced increase in urinary excretion of N-acetyl-β-D-glucosaminidase (a marker of renal tubular injury), fibronectin, glycosaminoglycan, and plasma cholesterol. It restored renal function in ADR-treated rats, as judged by the increase in glomerular filtration rate (GFR). The data also demonstrated that curcumin protected against ADR-induced renal injury by suppressing oxidative stress and increasing kidney glutathione content and glutathione peroxidase activity. In like manner, curcumin abolished ADR-stimulated kidney microsomal and mitochondrial lipid peroxidation. These data suggest that administration of curcumin is a promising approach in the treatment of nephrosis caused by ADR.

### 23.4.14 Curcumin Protects from Scarring

Keloid and hypertrophic scars commonly occur after injuries. Overproliferation of fibroblasts, overproduction of collagen, and contraction characterize these pathological scars. Current treatment of excessive scars with intralesional corticosteroid injections used individually or in combination with other methods often have unsatisfactory outcomes, frustrating both the patient and the clinician. Phan et al. [153] investigated the inhibitory effects of curcumin on keloid fibroblasts (KF) and hypertrophic scar-derived fibroblasts (HSF) by proliferation assays, fibroblast-populated collagen lattice contraction, and electron microscopy. Curcumin significantly inhibited KF and HSF proliferation in a dose- and time-dependent manner. Curcumin seemed to have potent effects in inhibiting proliferation and contraction of excessive scar-derived fibroblasts.

### 23.4.15 Curcumin Protects from Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by oxidative and nitrosative stress, leukocyte infiltration, and up-regulation of proinflammatory cytokines. Ukil et al. [154] recently investigated the protective effects of curcumin on 2,4,6-trinitrobenzene sulfonic acid-induced colitis in mice, a model for IBD. Intestinal lesions were associated with neutrophil infiltration, increased serine protease activity (may be involved in the degradation of colonic tissue), and high levels of malondialdehyde. Dose-response studies revealed that pretreatment of mice with curcumin at 50 mg/kg daily i.g. for 10 days significantly ameliorated diarrhea and the disruption of colonic architecture. Higher doses (100 and 300 mg/kg) had comparable effects. In curcumin-pretreated mice, there was a significant reduction in the degree of both neutrophil infiltration and lipid peroxidation in the inflamed colon as well as decreased serine protease activity. Curcumin also reduced the levels of NO and $O_2^-$ associated with the favorable expression of Th1 and Th2 cytokines and inducible NO synthase. Consistent with these observations, NF-κB activation in colonic mucosa was suppressed in the curcumin-treated mice. These findings suggested that curcumin exerts beneficial effects in experimental colitis and may, therefore, be useful in the treatment of IBD.

Salh et al. [155] also showed that curcumin is able to attenuate colitis in the dinitrobenzene (DNB) sulfonic acid-induced murine model of colitis. When given before the induction of colitis, it reduced macroscopic damage scores, NF-κB activation, and myeloperoxidase activity, and it attenuated the DNB-induced message for IL-1β. Western blotting analysis revealed a reproducible DNB-induced activation of p38 MAPK in intestinal lysates detected by a phosphospecific antibody. This signal was significantly attenuated by curcumin. Furthermore, Salh's group showed that the immunohistochemical signal is dramatically attenuated at the level of the mucosa by curcumin. Thus they concluded that curcumin attenuates experimental colitis through a mechanism that also inhibits the activation of NF-κB and effects a reduction in the activity of p38 MAPK. They proposed that this agent may have therapeutic implications for human IBD.

### 23.4.16 Curcumin Enhances the Immunosuppressive Activity of Cyclosporine

Chueh et al. [156] have demonstrated that curcumin enhances the immunosuppressive activity of cyclosporine in rat cardiac allografts and in mixed lymphocyte reactions. Their study demonstrated for the first time the effectiveness of curcumin as a novel adjuvant immunosuppressant with cyclosporine both *in vivo* and *in vitro*. The immunosuppressive effects of curcumin were studied in rat heterotrophic cardiac transplant models, using Brown-Norway hearts transplanted to WKY hosts. In the Brown-Norway-to-WKY model, curcumin alone significantly increased the mean survival time, to 20.5 to 24.5 days as compared with 9.1 days in nontreated controls. The combination of curcumin and subtherapeutic doses of cyclosporine further prolonged the mean survival time to 28.5 to 35.6 days, better than that of curcumin or cyclosporine alone. Cytokine analysis revealed significantly reduced expression of interleukin-2, IFN$\gamma$, and granzyme B in the day-3 specimens of the curcumin and curcumin plus cyclosporine-treated allografts compared with the nontreated allograft controls.

### 23.4.17 Curcumin Protects against Various Forms of Stress

Curcumin has been identified as a potent inducer of hemoxygenase-1 (HO-1), a redox-sensitive inducible protein that provides protection against various forms of stress. Curcumin stimulated the expression of Nrf2, an increase associated with a significant increase in HO-1 protein expression and HO-1 activity [157].

### 23.4.18 Curcumin Protects against Endotoxin Shock

Madan and Ghosh [158] have demonstrated that curcumin exerts protective effects in high-dose endotoxin shock by improving survival and reducing the severity of endotoxin shock symptoms such as lethargy, diarrhea, and watery eyes following a challenge with lipopolysaccharide. They demonstrated that curcumin inhibits the transmigration and infiltration of neutrophils from blood vessels to the underlying liver tissue and, hence, inhibits the damage to the tissue. Curcumin blocks the induced expression of ICAM-1 and VCAM-1 in liver and lungs.

### 23.4.19 Curcumin Protects against Pancreatitis

Gukovsky et al. [159] reported that curcumin ameliorates pancreatitis in two rat models. In both cerulein pancreatitis and pancreatitis induced by a combination of ethanol diet and low-dose curcumin, curcumin decreased the severity of the disease. Curcumin markedly inhibited NF-$\kappa$B and AP-1, IL-6, TNF$\alpha$, and iNOS in the pancreas. Based on these studies, Gukovsky et al. suggested that curcumin may be useful for treatment of pancreatitis.

### 23.4.20 Curcumin Inhibits Multidrug Resistance (MDR)

The effect of curcumin on apoptosis in multidrug-resistant cell lines has been reported. Piwocka et al. [160] demonstrated that curcumin induced cell death in multidrug-resistant CEM(P-gp4) and LoVo(P-gp4) cells in a caspase-3-independent manner. Mehta et al. [31] also examined the antiproliferative effects of curcumin against multidrug-resistant (MDR) lines, which were found to be highly sensitive to curcumin. The growth-inhibitory effect of curcumin was time- and dose-dependent and was correlated with its inhibition of ornithine decarboxylase activity. Curcumin preferentially arrested cells in the G2/S phase of the cell cycle.

## 23.5 CURCUMIN METABOLISM

Numerous studies have been performed on the biotransformation of curcumin. Lin et al. [161] showed that curcumin was first biotransformed to dihydrocurcumin and tetrahydrocurcumin and that these compounds subsequently were converted to monoglucuronide conjugates. Thus, curcumin-glucuronide, dihydro-curcumin-glucuronide, tetrahydrocurcumin-glucuronide, and tetrahydrocurcumin are major metabolites of curcumin in mice.

Since the systemic bioavailability of curcumin is low, its pharmacological activity may be mediated, in part, by its metabolites. To investigate this possibility, Iresson et al. [162] compared curcumin metabolism in human and rat hepatocytes in suspension with that in rats *in vivo*. Analysis by high-performance liquid chromatography with detection at 420 and 280 nm permitted characterization of metabolites with both intact diferoylmethane structure and increased saturation of the heptatrienone chain. Chromatographic inferences were corroborated by mass spectrometry. The major metabolites in suspensions of human or rat hepatocytes were identified as hexahydrocurcumin and hexahydrocurcuminol. In rats, *in vivo*, curcumin administered i.v. (40 mg/kg) disappeared from the plasma within 1 h of dosing. After p.o. administration (500 mg/kg), parent drug was present in plasma at levels near the detection limit. The major products of curcumin biotransformation identified in rat plasma were curcumin glucuronide and curcumin sulfate, whereas hexahydrocurcumin, hexahydrocurcuminol, and hexahydrocurcumin glucuronide were present in small amounts. To test the hypothesis that curcumin metabolites resemble their progenitor in that they can inhibit COX-2 expression, curcumin and four of its metabolites at a concentration of 20 $\mu M$ were compared in terms of their ability to inhibit phorbol ester-induced prostaglandin E2 (PGE2) production in human colonic epithelial cells. Curcumin reduced PGE2 levels to preinduction levels, whereas tetrahydrocurcumin, hexahydrocurcumin, and curcumin sulfate had only weak PGE2 inhibitory activity, and hexahydrocurcuminol was inactive. The results suggested that (a) the major products of curcumin biotransformation by hepatocytes occurred only at low abundance in rat plasma after curcumin administration and (b) metabolism of curcumin by reduction or conjugation generates species with reduced ability to inhibit COX-2 expression. Because the gastrointestinal tract seems to be exposed more prominently to unmetabolized curcumin than any other tissue, the results support the clinical evaluation of curcumin as a colorectal cancer chemopreventive agent.

Curcumin has very poor bioavailability. In Ayurveda, black pepper (*Piper nigrum*), long pepper (*Piper longum*), and ginger (*Zingiber officinalis*) are collectively termed Trikatu, and are essential ingredients of numerous prescriptions that are used for a wide range of disorders. Numerous studies suggest that Trikatu has a bioavailability-enhancing effect [163]. Since curcumin belong to the same family as ginger, it has similar enhancer activity [164].

Shoba et al. [164] found that curcumin has poor bioavailability due to its rapid metabolism in the liver and intestinal wall. In this study, the effect of combining piperine, a known inhibitor of hepatic and intestinal glucuronidation, was evaluated on the bioavailability of curcumin in rats and healthy human volunteers. When curcumin was given alone, in the dose 2 g/kg to rats, moderate serum concentrations were achieved over a period of 4 h. Concomitant administration of piperine at 20 mg/kg increased the serum concentration of curcumin for a short period of 1 to 2 h. Time to maximum was significantly increased, while elimination half-life and clearance significantly decreased, and the bioavailability was increased by 154%. On the other hand, after a dose of 2 g curcumin alone in humans, serum levels were either undetectable or very low. Concomitant administration of piperine at 20 mg/kg produced much higher concentrations from 15 min to 1 h later, and the increase in bioavailability was 2000%. The study shows that in the dosages used, piperine enhances the serum concentration, extent of absorption, and bioavailability of curcumin in both rats and humans, with no adverse effects.

In the studies by Kumar et al. [165], natural biodegradable polymers, namely bovine serum albumin and chitosan, were used to encapsulate curcumin to form a depot drug-delivery system. Microspheres were prepared by emulsion-solvent evaporation method coupled with chemical cross-linking of the

natural polymers. As much as 79.49 and 39.66% of curcumin could be encapsulated into the biodegradable carriers with albumin and chitosan respectively. *In vitro* release studies indicated a biphasic drug-release pattern, characterized by a typical burst-effect followed by a slow release that continued for several days. It was evident from Kumar's study that the curcumin-biodegradable microspheres could be successfully employed as a prolonged-release drug-delivery system for better therapeutic management of inflammation as compared with oral or subcutaneous administration of curcumin. Kumar et al. [166] synthesized bioconjugates of curcumin to improve its systemic delivery. Di-*O*-glycinoyl curcumin (I) and 2′-deoxy-2′-curcuminyl uridine (2′-cur-U) (IV) were quite potent against multiresistant microorganisms. These bioconjugates served the dual purpose of facilitating systemic delivery as well as providing therapeutic agents against viral diseases.

## 23.6 CLINICAL EXPERIENCE WITH CURCUMIN

Nine different studies of the safety and efficacy of curcumin in humans have been reported (Table 23.1). For example Deodar et al. [137] performed a short-term, double-blind, cross-over study in 18 patients (age 22 to 48 years) to compare the antirheumatic activity of curcumin and phenylbutazone. They administered 1200 mg curcumin/day or 300 mg phenylbutazone/day for 2 weeks. These investigators reported that curcumin was well tolerated, had no side effects, and showed comparable antirheumatic activity.

Lal et al. [167] administered curcumin orally to patients suffering from chronic anterior uveitis (CAU) at a dose of 375 mg three times per day for 12 weeks. Of 53 patients enrolled, 32 completed the 12-week study. They were divided into two groups: one group of 18 patients received curcumin alone, whereas the other group of 14 patients, who had a strong PPD reaction, in addition received antitubercular treatment. The patients in both the groups started improving after 2 weeks of treatment. All the patients who received curcumin alone improved, whereas the group receiving antitubercular therapy along with curcumin had a response rate of 86%. Follow-up of all the patients for the next 3 years indicated a recurrence rate of 55% in the first group and of 36% in the second

**TABLE 23.1**
**Clinical Studies with Curcumin in Human Subjects**

| Study | Patients | Dose | Comments | Ref. |
|---|---|---|---|---|
| Double blind, crossover study | 18 pts. (22–48 yrs) | 1200 mg/d ×2 wks | Anirheumatic | 137 |
| | 46 male pts. (15–68) | 400 mg; 3 × /d × 5 d | Inguinal hernia | 169 |
| | 111 pts (40–85 yrs) | Topical | HNSCC, breast, vulva, skin | 170 |
| | 10 volun. | 500 mg/d × 7 d | Serum cholesterol and LPO | 112 |
| | 40 pts. | 625 mg; 4 × /d × 8 wks | Well-tolerated | 171 |
| | 53 pts. | 375 mg; 3 × /d × 12 wks | Chronic anterior uveitis | 167 |
| | 8 pts. | 375 mg; 3 × /d 6–22 mo | Idiopathic inflammation, orbital pseudotumors | 168 |
| Prospective Phase I | 25 pts. | 500 mg–12,000 mg/d × 3 mo | H&N cancers | 7 |
| | 15 pts. | 36–180 mg 4 mo | Colorectal, serum GST-down | 172 |

group. Four of 18 (22%) patients in the first group and 3 of 14 patients (21%) in the second group lost their vision in the follow-up period because of various complications, e.g., vitritis, macular edema, central venous block, cataract formation, glaucomatous optic nerve damage, etc. None of the patients reported any side effects. The efficacy of curcumin and recurrences following treatment are comparable with corticosteroid therapy, which is at present considered the only available standard treatment for this disease. The lack of side effects with curcumin is its greatest advantage compared with corticosteroids. A double-blind multicenter clinical trial of this drug for CAU would be highly desirable to further validate the results of the study.

Satoskar et al. (1986) evaluated the anti-inflammatory properties of curcumin in patients with postoperative inflammation. They studied 46 male patients (between the ages of 15 and 68 years) having inguinal hernia and/or hydrocoele. After the hernia operation, spermatic cord edema, tenderness, and were evaluated. Either curcumin (400 mg) or placebo (250 mg lactose) or phenylbutazone (100 mg) was administered three times a day for a period of 5 days from the first postoperative day. Curcumin was found to be quite safe, and phenylbutazone and curcumin produced a better anti-inflammatory response than placebo [169].

Kuttan et al. [170] used an ethanol extract of turmeric as well as an ointment of curcumin and showed that it produces remarkable symptomatic relief in patients with external cancerous lesions. Reduction in smell were noted in 90% of the cases and reduction in itching in almost all cases. Dry lesions were observed in 70% of the cases, and a small number of patients (10%) had a reduction in lesion size and pain. In many patients, the effect continued for several months. An adverse reaction was noticed in only 1 of the 62 patients evaluated.

Soni et al. [109] examined the effect of curcumin on serum levels of cholesterol and lipid peroxides in 10 healthy human volunteers. A dose of 500 mg of curcumin per day for 7 days significantly decreased the level of serum lipid peroxides (33%), increased HDL cholesterol (29%), and decreased total serum cholesterol (11.63%). The results suggest curcumin as a chemopreventive substance against arterial diseases.

James [171] led a New England clinical trial of curcumin's effectiveness as an antiviral agent in 40 participants**.** Two dropped out; 23 were randomized to a high-dose group (four capsules, four times a day) and 15 to a low-dose group (three capsules, three times a day) for 8 weeks. Though it had no antiviral effects, curcumin was well tolerated, and most participants liked taking curcumin and felt better.

Lal et al. [168] described for the first time the clinical efficacy of curcumin in the treatment of patients suffering from idiopathic inflammatory orbital pseudotumors. Curcumin was administered orally at a dose of 375 mg, three times per day, for a period of 6 to 22 months in eight patients. They were followed up for a period of 2 years at 3-month intervals. Five patients completed the study, of which four recovered completely. In the remaining patient, the swelling regressed completely, but some limitation of movement persisted. No side effect was noted in any patient, and there was no recurrence. Thus curcumin could be used as a safe and effective drug in the treatment of idiopathic inflammatory orbital pseudotumors.

Cheng et al. [7] examined the toxicology, pharmacokinetics, and biologically effective dose of curcumin in humans. This prospective phase I study evaluated curcumin in patients with one of the following five high-risk conditions: (1) recently resected urinary bladder cancer; (2) arsenic Bowen's disease of the skin; (3) uterine cervical intraepithelial neoplasm (CIN); (4) oral leukoplakia; and (5) intestinal metaplasia of the stomach. Curcumin was taken orally for 3 months. Biopsy of the lesion sites was done immediately before and 3 months after starting curcumin treatment. The starting dose was 500 mg/day. If no toxicity of grade II or higher was noted in at least three successive patients, the dose was escalated to 1,000, 2,000, 4,000, 8,000, or 12,000 mg/day in order. The concentration of curcumin in serum and urine was determined by high-pressure liquid chromatography (HPLC). A total of 25 patients were enrolled in this study. There was no treatment-related toxicity for doses up to 8000 mg/day. Beyond 8000 mg/day, the bulky volume of the drug was unacceptable to the patients. The serum concentration of curcumin usually peaked at 1 to 2 h after oral intake of curcumin and

gradually declined within 12 h. The average peak serum concentrations after taking 4000 mg, 6000 mg, and 8000 mg of curcumin were 0.51 ± 0.11 μ*M*, 0.63 ± 0.06 μ*M*, and 1.77 ± 1.87 μ*M*, respectively. Urinary excretion of curcumin was undetectable. One of four patients with CIN and one of seven patients with oral leukoplakia developed frank malignancies in spite of curcumin treatment. In contrast, histological improvement of precancerous lesions was seen in one of two patients with recently resected bladder cancer, two of seven patients with oral leukoplakia, one of six patients with intestinal metaplasia of the stomach, one of four patients with CIN, and two of six patients with Bowen's disease. In conclusion, this study demonstrated that curcumin is not toxic to humans at doses up to 8000 mg/day when taken by mouth for 3 months. These results also suggested a biological effect of curcumin in the chemoprevention of cancer.

Sharma et al. [172] examined the pharmacodynamics and pharmacokinetics of curcumin in humans in a dose-escalation pilot study. A novel standardized Curcuma extract in proprietary capsule form was given at doses between 440 and 2200 mg/day, containing 36 to 180 mg of curcumin. Fifteen patients with advanced colorectal cancer refractory to standard chemotherapies received Curcuma extract daily for up to 4 months. The activity of glutathione-*S*-transferase and levels of a DNA adduct (M(1)G) formed by malondialdehyde, a product of lipid peroxidation and prostaglandin biosynthesis, were measured in patients' blood cells. 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. 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 to 4 months of treatment. The results suggested that (a) Curcuma extract can be administered safely to patients at doses of up to 2.2 g daily, equivalent to 180 mg of curcumin; (b) curcumin has low oral bioavailability in humans and may undergo intestinal metabolism; and (c) larger clinical trials of Curcuma extract are merited.

## 23.7 CURCUMIN ANALOGS

Commercial curcumin isolated from the rhizome of *Curcuma longa* Linn. contains three major curcuminoids (approximately 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin) (Figure 23.1). Commercial curcumin, pure curcumin, and demethoxycurcumin are approximately equipotent as inhibitors of TPA-induced tumor promotion in mouse skin, whereas bisdemethoxycurcumin is somewhat less active [15]**.** Besides natural curcumin, several analogs of curcumin have been synthesized and tested [173, 174]. Tetrahydrocurcumin, an antioxidative substance that is derived from curcumin by hydrogenation, has been shown to have a protective effect on oxidative stress in cholesterol-fed rabbits [175]. Kumar et al. [176] have developed an analog of curcumin, 4-hydroxy-3-methoxybenzoic acid methyl ester (HMBME), that targets the Akt/NF-κB signaling pathway. They demonstrated the ability of this novel compound to inhibit the proliferation of human and mouse PCA cells. Overexpression of constitutively active Akt reversed the HMBME-induced growth inhibition and apoptosis, illustrating the direct role of Akt signaling in HMBME-mediated growth inhibition and apoptosis. HMBME-mediated inhibition of Akt kinase activity may have a potential in suppressing/decreasing the activity of major survival/antiapoptotic pathways.

Using an *in vitro* SVR assay, Robinson et al. [177] have demonstrated potent antiangiogenic properties in aromatic enone and dienone analogs of curcumin. Based on a simple pharmacophore model, the aromatic enone and aromatic dienone analogs of curcumin were prepared using standard drug design concepts.

Devasena et al. [178] examined the protective effect of a curcumin analog [bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione] on hepatic lipid peroxidation and antioxidant status during 1,2-dimethylhydrazine-induced colon carcinogenesis in male Wistar rats. They observed

that the curcumin analog exerted chemopreventive effects against cancer development at extrahepatic sites by modulating hepatic biotransformation enzymes and antioxidant status. The effect was comparable with that of curcumin. They proposed that the hydroxyl group in the aromatic ring is responsible for the protective effect rather than the methoxy group. Mishra et al. [179] synthesized a novel curcumin conjugate, namely 1,7-bis(4-O-glycinoyl-3-methoxyphenyl)-1,6-heptadiene-3,5,dione (I) that was attached to the deoxy-11 mer, 5′-GTT AGG GTT AG-3′, a complementary sequence of telomerase RNA template. This novel anticancer prodrug has the potential to target the telomerase sequence.

The antitumor properties of metal chelates of synthetic curcuminoids have also been investigated. John et al. [180] examined four synthetic curcuminoids, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione (curcumin 1); 1,7-bis(piperonyl)-1,6-heptadiene-3,5-dione (piperonyl curcumin); 1,7-bis(2-hydroxynaphthyl)-1,6-heptadiene-2,5-dione (2-hydroxynaphthyl curcumin); and 1,1-bis(phenyl)-1,3,8,10-undecatetraene-5,7-dione (cinnamyl curcumin) and their copper(II) complexes for their possible cytotoxic and antitumor activities. Copper chelates of synthetic curcuminoids showed enhanced antitumor activity. In addition to these, a novel curcumin derivative, hydrazinocurcumin (HC), was synthesized and examined for its biological activities by Shim et al. [181]. HC potently inhibited the proliferation of bovine aortic endothelial cells at nanomolar concentrations ($IC_{50}$ = 520 n*M*) without cytotoxicity. Snyder et al. [182] reported the synthesis of several different structural analogs of curcumin and examined their antitumor and antiangiogenic properties. They found analogs that are more potent than native curcumin.

## 23.8 SOURCES OF CURCUMIN

There are several good sources of curcumin with purity ranging from 60 to 98% (Table 23.2). Some companies supply curcumin in a powder form; other companies supply it in capsules. Curcumin supplied by Life Extension is in 900-mg capsules; turmeric curcumin is in 500-mg capsules. Likewise, Iherb, Club Natural, Immune Support, Nature's, Big Fitness, Powerhouse Gym, MMS

**TABLE 23.2**
**Sources of Curcumin**

| **Human use** |
|---|
| Sabinsa (www.sabinsa.com/products/circumin_book.htm), Piscataway, NJ |
| Kalsec (ww.kalsec.com/products/turmeric_over.cfm), Kalamazoo, MI |
| Life Extension (www.lef.org/hewshop/items/item00552.html?source=WebProtProd) |
| Turmeric Curcumin (www.turmeric-curcumin.com/) |
| Iherb (www.iherb.com/curcumin1.html) |
| Club Natural (www.clubnatural.com/curex9550180.html), Irvine, CA |
| American Nutrition (www.AmericanNutrition.com) |
| Amerifit (www.amerifit.geomerx.com/items/categories.cfm?category=2), Bloomfiled, CT |
| XKMS (www.xkms.org/WebVitamins-32/Curcumin-Power-60C.htm) |
| Immune Support (www.Immunesupport.com/shop/prodlisting.cfm?NOTE=NOC) |
| Nature's (ww.naturesnutrition.com/SKU/55114.htm) |
| Big Fitness (www.bfwse.com/jr-021.html) |
| Powerhoue Gym (store.yahoo.com/musclespot/curcumin95.html) |
| MMS Pro (www.mmspro.com) |
| Herbal Fields (www.herbalfields.com/curcumin.html) |
| **Research use** |
| Sigma Aldrich (www.sigmaaldrich.com/cgibin/hsrun/Distributed/HahtShop/HAHTpage/HS_CatalogSearch) |
| Calbiochem (www.calbiochem.com/Products/ProductDetail_CBCB.asp?catNO=239802) |
| LKT Laboratories (www.lktlabs.com) |

Pro, and American Nutrition supply 500-mg capsules; Amerifit supplies 1700-mg capsules; and XKMS supplies 300-mg capsules. Curcumin combined with piperine (also bioperine derived from black pepper), which has a higher bioavailability than curcumin alone, is available from Life Extension in a formulation referred to as "super curcumin" [164].

## 23.9 CONCLUSION

From all these studies, it is clear that curcumin exhibits activities against cancer, cardiovascular diseases, and diabetes, the major ailments in the U.S. This drug has also shown therapeutic effects against Alzheimer's disease, multiple sclerosis, cataract formation, HIV, and drug-induced nonspecific toxicity in the heart, lung, and kidney. Several of the studies establishing curcumin's potential were carried out in animals. Further testing of curcumin in humans is required to confirm these observations. A clinical development plan for using curcumin to treat cancer was recently described by the NCI. Studies also show that in countries such as India where curcumin is consumed, the profile of cancer incidence is very different than those that do not (such as the U.S.; see Table 23.3).

**TABLE 23.3**
**Comparison of Cancer Incidence in U.S. (Curcumin Non-Users) and India (Curcumin Users)**

| | U.S. | | India | |
|---|---|---|---|---|
| **Cancer** | **Cases** | **Deaths** | **Cases** | **Deaths** |
| Breast | 660 | 160 | 79 | 41 |
| Prostate | 690 | 130 | 20 | 9 |
| Colon/rectum | 530 | 220 | 30 | 18 |
| Lung | 660 | 580 | 38 | 37 |
| Head and neck SCC | 140 | 44 | 153 | 103 |
| Liver | 41 | 44 | 12 | 13 |
| Pancreas | 108 | 103 | 8 | 8 |
| Stomach | 81 | 50 | 33 | 30 |
| Melanoma | 145 | 27 | 1.8 | 1 |
| Testis | 21 | 1 | 3 | 1 |
| Bladder | 202 | 43 | 15 | 11 |
| Kidney | 115 | 44 | 6 | 4 |
| Brain, nervous system | 65 | 47 | 19 | 14 |
| Thyroid | 55 | 5 | 12 | 3 |
| Endometrial cancers | 163 | 41 | 132 | 72 |
| Ovary | 76 | 50 | 20 | 12 |
| Multiple myeloma | 50 | 40 | 6 | 5 |
| Leukemia | 100 | 70 | 19 | 17 |
| Non-Hodgkin's lymphoma | 180 | 90 | 17 | 15 |
| Hodgkin's disease | 20 | 5 | 7 | 4 |

Showing cases per 1 million persons calculated on the basis of current consensus: Endometrial cancers include Cervix uteri and Corpus uteri.

GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC Cancer Base No. 5. Lyon, IARC Press, 2001.

How curcumin produces its therapeutic effects is not fully understood, but they are probably mediated in part through the antioxidant and anti-inflammatory action of curcumin. It is quite likely that curcumin mediates its effects through other mechanisms as well. Over a dozen different cellular proteins and enzymes have been identified to which curcumin binds. High-throughput ligand-interacting technology can reveal more molecular targets of curcumin. Microarray gene chip technology may in the future indicate which genes are regulated by curcumin.

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