Mol. Nutr. Food Res. 2008, *52*, S103 – S127 DOI 10.1002/mnfr.200700238

Review

Anticancer and carcinogenic properties of curcumin: Considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent

Miguel López-Lázaro

Department of Pharmacology, Faculty of Pharmacy, University of Seville, Sevilla, Spain

A growing body of research suggests that curcumin, the major active constituent of the dietary spice turmeric, has potential for the prevention and therapy of cancer. Preclinical data have shown that curcumin can both inhibit the formation of tumors in animal models of carcinogenesis and act on a variety of molecular targets involved in cancer development. *In vitro* studies have demonstrated that curcumin is an efficient inducer of apoptosis and some degree of selectivity for cancer cells has been observed. Clinical trials have revealed that curcumin is well tolerated and may produce antitumor effects in people with precancerous lesions or who are at a high risk for developing cancer. This seems to indicate that curcumin is a pharmacologically safe agent that may be used in cancer chemoprevention and therapy. Both *in vitro* and *in vivo* studies have shown, however, that curcumin may produce toxic and carcinogenic effects under specific conditions. Curcumin may also alter the effectiveness of radiotherapy and chemotherapy. This review article analyzes the *in vitro* and *in vivo* cancer-related activities of curcumin and discusses that they are linked to its known antioxidant and prooxidant properties. Several considerations that may help develop curcumin as an anticancer agent are also discussed.

Keywords: Clinical trials / Oxidative stress / Reactive oxygen species / Safety / Toxicity

Received: June 27,2007; revised: January 22, 2008; accepted: January 24, 2008

1 Introduction

Curcumin (diferuloylmethane) is a yellow pigment derived from the rhizome of the plant *Curcuma longa* L. The powdered rhizome of this plant, called turmeric, is commonly used in the preparation of curries. In addition to its preservative, flavoring, or coloring properties in the diet, turmeric has been used in Asian medicine for generations for the treatment of many disorders including inflammation, skin wounds, hepatic and biliary disorders, cough, as well as certain tumors. Curcumin, a polyphenol with a diarylheptanoid structure that contains two α,β-unsaturated ketones, is considered to be the major active constituent of turmeric. The chemical properties and the historical background of curcumin have been reviewed elsewhere [1, 2].

Although curcumin has shown a wide range of pharmacological activities, its anticancer properties have attracted a great interest. The anticancer activity of curcumin has been the subject of hundreds of papers and has been reviewed in several recent articles [1 – 15]. These review articles have summarized preclinical data showing that curcumin can inhibit the formation of tumors in animal models of carcinogenesis, can induce apoptosis in cancer cells from different origin, and can act on a variety of signal transduction pathways and molecular targets involved in the development of cancer. Based on preclinical and clinical studies in which curcumin was administered orally to animals and humans, most of these articles consider that curcumin is a nontoxic or low-toxic agent. This seems to indicate that the putative anticancer activity of curcumin may be accompanied by a low toxicity. These articles also show that the systemic bioavailability of curcumin following oral dosing is

Correspondence: Dr. Miguel López-Lázaro, Department of Pharmacology, Faculty of Pharmacy, C/Profesor García González, 41012 Sevilla, Spain
E-mail: mlopezlazaro@us.es
Fax: +34-954-23-37-65

Abbreviations: GST, glutathione *S*-transferases; **HIF-1,** hypoxia-inducible factor 1; **i.v.,** intravenous; **MMP,** matrix metalloproteinase; **NF-κB,** nuclear factor kappa B; **ROS,** reactive oxygen species; **TNF-α**, tumor necrosis factor alpha; **TrxR,** thioredoxin reductase

Table 1. Cancer chemopreventive and chemotherapeutic effects of curcumin on different types of cancer

Cancer type	Chemopreventive effects	Chemotherapeutic effects
Lung	[124, 210–217]	[181, 218, 219]
Breast	[185, 186, 220–226]	[74, 78, 227–232]
Colon	[56, 82, 83, 217, 225, 233–241]	[4, 139–141, 209, 242–249]
Prostate	[250–252]	[172, 173, 178, 251, 253–264]
Stomach	[70, 210, 265–268]	[179, 246]
Liver	[39–44, 63, 130, 210, 216, 217, 269–284]	[75, 142, 285]
Pancreas	[286–288]	[157, 182, 208, 218, 289]
Kidney	[40, 40, 41, 45, 45, 135, 217, 290, 291]	[75, 143]
Bladder	[21, 292]	[176, 293, 294]
Blood/Lymph	[224]	[54, 77, 80, 160, 168, 295–303]
Skin	[223, 304–315]	[158, 316–319]
Esophagus	[320, 321]	
Brain/head and neck	[41, 46–49]	[322–329]
Uterus		[330, 331]
Ovary		[332–336]

low and that this agent is rapidly cleared from the body, therefore suggesting that the anticancer activity of oral curcumin may be limited to the gastrointestinal tract [1–15].

The present article compiles and analyzes the *in vitro* and *in vivo* cancer-related properties of curcumin. Since cancer chemopreventive and chemotherapeutic strategies are usually aimed at preventing or treating a specific type of cancer, the first aim of this work is to compile the most relevant cancer-related effects of curcumin on several common types of cancer. The limited bioavailability and extensive metabolism of curcumin suggest that many of its anticancer effects observed *in vitro* may not be attainable *in vivo*. This article analyzes which of these reported anticancer effects may be relevant *in vivo*. It is also discussed that, although relatively high concentrations of curcumin have not shown significant toxicity in short-term studies, these concentrations may lead to toxic and carcinogenic effects in the long term. In addition, this article provides evidence that suggests that the cancer-related activities of curcumin may be linked to its known antioxidant and pro-oxidant properties. After a critical analysis of the cancer-related properties of curcumin, several considerations that may help develop curcumin as a cancer chemopreventive and chemotherapeutic agent are discussed.

2 Anticancer activity of curcumin

The most relevant cancer chemopreventive and chemotherapeutic effects of curcumin on several common types of cancer are compiled in Table 1. This table gathers reports in which curcumin has shown cancer chemopreventive activity in animal models of carcinogenesis, as well as selected *in vitro* and *in vivo* studies that may have relevance to cancer chemoprevention. This table also compiles the most relevant reports in which curcumin has shown chemotherapeutic effects; it mainly includes selected studies in which this dietary agent induced apoptosis in cancer cells from different cancer types, as well as several works that studied the chemotherapeutic effects of curcumin *in vivo*. The chemopreventive and chemotherapeutic properties of curcumin are discussed in the following sections.

2.1 Cancer chemopreventive activity of curcumin. Possible *in vivo* mechanisms

The limited progress achieved by cancer therapy in the last three decades [16, 17] has increased the interest of researchers in cancer chemoprevention. It is becoming accepted that cancer chemoprevention (the use of chemicals to prevent, stop, or reverse the process of carcinogenesis) is an essential approach to controlling cancer. In addition, since the process of carcinogenesis can take several decades to complete, it makes more sense to prevent cancer at its earliest stages by using low-toxic chemicals (chemoprevention) than to wait until the disease has reached its final stages, where it becomes necessary to use more toxic chemicals (chemotherapy). Cancer chemoprevention can be aimed at healthy populations or at those with cancer predisposition (people with precancerous lesions or those who are at high risk for developing cancer). In the first case, chemopreventive interventions must be completely devoid of toxicity and chemicals should be supplemented orally. In the second case, some degree of toxicity is acceptable and the oral route is preferable [18–20].

Several lines of evidence suggest that curcumin may be used in cancer chemoprevention. Firstly, epidemiological data suggest that the incidence of several common cancers (*i.e.*, colon, breast, prostate, and lung cancer) is higher in Western countries than in countries such as India, where curcumin is highly consumed [1, 16]. Secondly, an elevated number of studies in rodents has shown that curcumin can prevent several types of cancer (*e.g.*, colon, lung, breast, liver, stomach, esophagus, skin, lymphomas, and leukemia)

Table 2. Recent selected reports showing possible molecular targets of curcumin

Molecular targets	References
Inhibition of NF-kappaB in cancer cells by curcumin. These recent reports, which are in agreement with previous results, suggest that this effect of curcumin might be exploited therapeutically	[176, 182, 335]
Inhibition of MDM2 oncogen through the transcription factor ETS2 by modulation of the PI3K/mTOR signaling pathway. This report also shows that curcumin sensitizes human cancer cells to chemotherapy and radiation through down-regulation of this oncogen	[173]
Induction of proteasome-mediated down-regulation of cyclin E and up-regulation of the CDK inhibitors p21 and p27 in several cancer cell lines; these effects may contribute to the antiproliferative effects of curcumin against various tumors	[337]
Inhibition of the Akt/mammalian target of rapamycin (mTOR)/p70S6K and the extracellular signal-regulated kinases 1/2 (ERK1/2) pathways. These effects resulted in the induction of authophagy (a response of cancer cells to various anticancer therapies, also designated as programmed cell death type II) and suppression of the growth of malignant gliomas	[322]
Inhibition of Akt and its key target Bad in B lymphoma *via* inhibition of spleen tyrosine kinase (Syk)	[299]
This report shows that c-Abl, a nonreceptor tyrosine kinase that regulates stress responses induced by oxidative agents such as ionizing radiation and H_2O_2, regulates curcumin-induced cell death through activation of c-Jun N-terminal kinase	[338]
Induction of an increase in the protein levels of the proapoptotic Bcl-2 family members Bax and Bak, which was essential for maximum apoptotic activity	[339]
Regulation of signal transducer and activator of transcription (STAT)	[297, 340, 341]
Inhibition of human colon cancer cell growth by suppressing gene expression of epidermal growth factor receptor (EGFR) through reduction of the activity of the transcription factor Egr-1	[249]
Inhibition of constitutively activated targets of PI3'-kinase (AKT, FOXO and GSK3) in T-cell acute lymphoblastic leukemia cells, leading to the inhibition of proliferation and induction of caspase-dependent apoptosis	[296]
Down-regulation of the Notch-1 signaling pathway	[289]

Table 3. Concentrations of curcumin in human plasma or tissues following oral administration

Oral dose	Plasma/tissue concentrations (μmol/L or μmol/kg)	Reference
2 g	< 0.03 in plasma	[342]
4, 6, and 8 g	0.51 ± 0.11, 0.63 ± 0.06, and 1.77 ± 1.87 in plasma	[21]
0.18 g/day/4 months	Not detectable in plasma or urine	[343]
3.6 g/day/4 months	0.01 in plasma, 0.1 – 1.3 in urine	[84]
3.6 g/day/7 days	Traces in peripheral circulation, 12.7 ± 5.7 in normal colorectal tissue, 7.7 ± 1.8 in malignant colorectal tissue	[81]
3.6 g/day/7 days	Low nM levels in the peripheral or portal circulation, not found in liver tissue	[71]

induced by different carcinogens (see Table 1). Thirdly, a Phase I clinical trial in participants with cancer predisposition taking curcumin orally for 3 months showed little toxicity and revealed histological improvement of precancerous lesions in 7 out of 25 patients [21]. Finally, hundreds of preclinical studies have reported that curcumin can act on a variety of pathways and molecular targets involved in cancer development (see ref. [5, 13, 15, 22] for reviews and Table 2 for recent selected reports). Most of these studies, however, have been conducted using high concentrations of curcumin, which cannot be achieved through the oral route. Several human studies have revealed that, after oral administration, the levels of curcumin in plasma are very low (generally in the nanomolar range); while they are higher in colorectal tissue (low micromolar) (see Table 3). This suggests that, outside of the gastrointestinal tract, most of the reported cancer-related effects of curcumin may not be achieved *in vivo*. In order to understand the possible mechanisms involved in the putative cancer preventive activity of curcumin, it is essential to analyze which of these numerous targets are really implicated *in vivo*. After reviewing the literature, the most relevant effects of curcumin *in vivo* have been compiled in Table 4.

Despite being challenged by some researchers [23 – 26], the most accepted theory of cancer ("somatic mutation theory of cancer") considers that this disease is caused by DNA alterations [27]. As shown in Table 4, several *in vivo* studies have revealed that curcumin can protect DNA from damage induced by different carcinogens. It is widely accepted, even by those who challenge the somatic mutation theory of cancer, that the formation of a malignant tumor requires that tumor cells acquire several capabilities (the so-called hallmarks of cancer), such as apoptosis resistance, increased angiogenesis, or capacity of invasion and metastasis [28]. The formation of a cancer requires that tumor cells develop apoptosis resistance, and it has been observed that curcumin can produce a mild but yet significant activation of apoptosis *in vivo* (see references in Table 4). Angiogenesis,

Table 4. Possible mechanisms involved in the cancer chemopreventive activity of curcumin *in vivo*

Mechanism	References
Inhibition/protection from DNA damage/alterations	[81, 183, 191, 240, 275, 313, 344–348]
Inhibition of angiogenesis	[208, 209, 259, 349–352]
Inhibition of invasion/metastasis	[215, 250, 353, 354]
Induction of apoptosis	[82, 83, 259]
Antioxidant activity	[39–49, 70, 135, 240, 281, 348, 355–375]
Inhibition of cytochromes P450	[210, 321, 376, 377]
Induction of GST	[40, 220, 240, 377–379]
Inhibition of NF-κB	[190, 271, 273, 276, 281, 310, 353, 371, 380–387]
Inhibition of AP-1	[381, 384, 387]
Inhibition of MMPs	[250, 266, 353, 384, 388]
Inhibition of COX-2	[273, 276, 310, 348, 353, 389–391]
Inhibition of TNF-α	[187, 206, 381, 392–394]
Inhibition of IL-6	[381, 392]
Inhibition of iNOS	[276, 389, 395]
Inhibition of IL-1β	[47, 381, 384]
Inhibition of oncogens ras/fos/jun/myc	[272, 306, 308, 396]
Inhibition of MAPK	[385, 389]
Activation of Nrf2	[130]
Induction of HO-1	[131]
Inhibition of ornithine decarboxylase	[45, 223, 239, 304, 305, 314, 315, 397]
Activation of PPAR-γ	[206, 375, 391]
Immunostimulant/immunorestorer	[59, 398–401]

the generation of new blood vessels, is necessary for the formation of solid tumors; without vascular growth, the tumor mass is restricted to a tissue-diffusion distance of approximately 0.2 mm. Malignant tumors are known to activate angiogenesis, and several reports have shown that curcumin can inhibit angiogenesis *in vivo*. It is recognized that the metastatic spread of primary tumors accounts for approximately 90% of all cancer deaths. The process by which cells from a localized tumor invade adjacent tissues and metastasize to distant organs can therefore be considered the most clinically relevant process involved in carcinogenesis [29, 30]. Experimental data support that curcumin can inhibit invasion and metastasis *in vivo* (Table 4).

Accumulating evidence suggests that reactive oxygen species (ROS) play a key role in carcinogenesis [31–33]. It has been demonstrated that the malignant phenotype of cancer cells can be reversed simply by reducing the cellular levels of ROS [34–38]. Antioxidant agents prevent or reduce excessive cellular levels of ROS and, therefore, play a protective role in cancer development. For instance, experimental data revealed that the expression of the antioxidant enzyme catalase in malignant cells decreased their cellular levels of hydrogen peroxide (H_2O_2); these cells reverted to a normal appearance, their growth rate normalized, and they were no longer capable of producing tumors in athymic mice [34]. These data suggest that the extensively reported antioxidant activity of curcumin may be a key mechanism by which this dietary phytochemical prevents cancer *in vivo*. As shown in Table 4, numerous studies have reported that curcumin exerts antioxidant effects *in vivo*. Interestingly, the antioxidant effects of curcumin following oral administration are not restricted to the gastrointestinal tract, as they have also been observed, for instance, in the liver [39–44], kidneys [40, 41, 45], or the brain [41, 46–49].

Inhibition of Phase I enzymes, such as cytochromes P450 (CYP), and activation of Phase II enzymes, such as glutathione *S*-transferases (GST), may participate in the cancer preventive activity of curcumin, as these enzymes play an important function in the activation and detoxification of carcinogens. As shown in Table 4, some studies indicate that curcumin can inhibit cytochromes P450 and activate GST *in vivo*.

Based on hundreds of preclinical reports, curcumin is regarded in the scientific literature as an anti-inflammatory agent. Several studies have reported beneficial effects when oral curcumin has been given to patients suffering from inflammatory disorders [50–52]. Recent research has established that the activation of the nuclear factor kappa B (NF-κB) is a crucial event both in inflammation and cancer [53]. Many recent reports have shown that curcumin is an efficient NF-κB inhibitor. For instance, Bharti *et al*. [54] observed that curcumin induced down-regulation of NF-κB in multiple myeloma cells in a time and dose-dependent manner. The efficient down-regulation of NF-κB in these cell lines required concentrations of curcumin in the 5–50 μM range and exposure times of approximately 2–4 h. As shown in Table 3 and observed in some animal studies, most data suggest that the plasma concentration of curcumin following oral dosing is low, and that this agent is rapidly cleared from the plasma and tissues [55–57]. This suggests that NF-κB inhibition by curcumin may not be relevant *in vivo*. Experimental data have demonstrated, however, that curcumin can

inhibit NF-κB activity *in vivo* (Table 4). It is well accepted that an increase in the cellular levels of ROS such as H_2O_2 results in the activation of NF-kB [58] and many reports have shown that curcumin can reduce the cellular levels of ROS *in vivo* (Table 4, antioxidant activity). This suggests that curcumin may prevent the activation of NF-κB *in vivo* by reducing the cellular levels of ROS.

Table 4 compiles references showing that, *in vivo*, curcumin can also modulate several other targets involved in carcinogenesis, including inhibition of activator protein 1 (AP-1), matrix metalloproteinases (MMPs), cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-α), IL-6, IL-1β, inducible nitric oxide synthase (iNOS), oncogens ras/fos/jun/myc, mitogen-activated protein kinases (MAPK), and ornithine decarboxylase; or induction/activation of nuclear factor E2-related factor 2 (Nrf2), heme oxygenase 1 (HO-1), and peroxisome proliferator-activated receptor-gamma (PPAR-γ). Curcumin has also been shown as an immunostimulant and immunorestorer *in vivo*; this mechanism may also participate in the cancer preventive activity of curcumin [59].

Recent data suggest that the hypoxia-inducible factor 1 (HIF-1) may be a key target for cancer chemoprevention [20]. In fact, the most important cancer gene pathways seem to culminate in the activation of this transcription factor [27]. HIF-1 activation is observed in most human cancers and has been associated with increased patient mortality. For instance, Zhong *et al*. [60] identified increased HIF-1 expression (relative to adjacent normal tissue) in 13 tumor types, including lung, prostate, breast, and colon carcinoma, which are the most common cancers in developed countries. In addition, HIF-1 activation seems to explain all the hallmarks of cancer [20, 61, 62]. These data suggest that HIF-1 activation is a key event in carcinogenesis and may therefore represent a key target for cancer chemoprevention. Recent *in vitro* studies have shown that curcumin can inhibit HIF-1 [63, 64]. Evidence suggests that curcumin might also inhibit HIF-1 activity *in vivo*. Indeed, it is now well established that HIF-1 can be activated by an increase in the cellular levels of ROS (*e. g*., H_2O_2) [65 – 68], and curcumin can reduce the cellular levels of ROS *in vivo* (see references in Table 4, antioxidant activity, *e. g*., [69, 70]).

Since curcumin is extensively metabolized in the body [55 – 57, 71 – 73], it is important to note that the *in vivo* anticancer properties of curcumin (Table 4) may be mediated, at least in part, by its metabolites. The evaluation of the anticancer properties of curcumin metabolites at relevant doses will probably help understand how curcumin works *in vivo*.

2.2 Cancer chemotherapeutic properties of curcumin

Therapeutic selectivity, or preferential killing of cancer cells without significant toxicity to normal cells, is one of the most desirable properties of a cancer chemotherapeutic agent. It is worth mentioning that several reports have shown that curcumin can kill cancer cells selectively [74 – 78]. For instance, the percentage of apoptosis induced by curcumin (40 μM, 24 h) in three cancer cell lines (including HepG2 hepatocellular carcinoma cells) was approximately 90%, while it was lower than 3% in five different types of normal cells (including normal hepatocytes) [76]. Likewise, curcumin (48 h exposure) induced apoptosis in chronic lymphocytic leukemia (B-CLL) cells from 14 patients at lower concentrations (EC_{50} = 5.5 μM) than in whole mononuclear cells from healthy donors (EC_{50} = 21.8 μM) [77]. The percentage of apoptotic cells induced by curcumin (40 μM, 24 h) was also higher in the multidrug-resistant breast carcinoma cell line MCF-7/TH (46.65%) than in the human mammary epithelial cell line MCF-10A (1.80%) [74]. Gautam *et al*. [79] observed, however, that curcumin-induced inhibition of cell proliferation was not selective for cancer cells, although they also found that inhibition of cell proliferation by curcumin was not always associated with apoptosis.

Table 1 (chemotherapeutic effects) compiles experimental studies that have demonstrated that curcumin induces apoptosis in cancer cells from different origins. These reports show that curcumin induces apoptosis in a dose-dependent and time-dependent manner (see, for instance, ref. [76, 80]). Although the exposure times and doses required to induce apoptosis in cancer cells vary depending on the studied cell lines, most reports show that cancer cells exposed to curcumin 5 – 50 μM for 24 h or longer undergo apoptosis. At short exposure times, however, these concentrations of curcumin are not high enough to induce apoptosis efficiently. For instance, the percentage of apoptosis observed in MCF-7, MDAMB, and HepG2 cancer cells exposed to curcumin 50 μM for 2 h was 10% or lower [76]. As mentioned before, curcumin has low oral bioavailability (Table 3) and is rapidly cleared from the plasma and tissues [55 – 57]. This suggests that the oral administration of curcumin may not result in efficient induction of apoptosis *in vivo*.

The concentrations of curcumin observed in colon tissue following oral administration (approximately 10 μmol/kg) [81] suggest that oral curcumin can induce apoptosis in the gastrointestinal tract efficiently. This is supported by experimental data that have shown that curcumin can induce apoptosis in colon cells *in vivo* [82, 83]. On the other hand, it has been shown that curcumin undergoes extensive metabolic conjugation and reduction in the gastrointestinal tract [57]; this suggests that the high concentrations of curcumin achieved in the colon may not be held enough time to allow this agent to induce apoptosis efficiently. For instance, the apoptotic index in azoxymethane-induced colonic tumors in rats was 8.3% in the control group and 17.7% in a group that received 0.2% of curcumin in the diet [82]. Although this mild activation of apoptosis may be useful in cancer chemoprevention, it does not seem to be enough to be use-

ful in cancer chemotherapy. Accordingly, when 15 patients with advanced colorectal cancer refractory to standard chemotherapies were treated with curcumin at doses up to 3.6 g daily for up to 4 months, no partial responses to treatment or decreases in tumor markers were observed [84]. These data suggest that the therapeutic potential of oral curcumin is low and that alternative routes of administration or delivery systems should be explored. A different approach to overcome the "unfavorable" pharmacokinetics of curcumin would be the development of curcumin analogs with a better pharmacokinetic profile that retained curcumin anticancer properties. Several curcumin analogs have been synthesized and their anticancer activity has been evaluated [85–90].

3 Toxic and carcinogenic properties of curcumin

The toxic and carcinogenic properties of an extract of turmeric that is commonly added to food items and contains a high percentage of curcumin (79–85%) were evaluated in rats and mice by the National Toxicology Program, USA [91]. The percentage of curcumin of this extract is similar to that of commercial grade curcumin [2]. Animals were fed diets containing the turmeric extract at different concentrations for periods of 3 months (0.1, 0.5, 1, 2.5, and 5%) and 2 years (0.2, 1, and 5%). Hyperplasia of the mucosal epithelium was observed in the colon of rats that received 5% of turmeric extract for 3 months in the diet. Despite this unfavorable effect and a significant increase in liver weights in rats and mice fed with concentrations of 0.5% or higher, no signs of carcinogenic lesions were observed in these 3-month studies. However, toxic and carcinogenic effects were observed when animals were fed with the turmeric extract for a period of 2 years. Thus, male or female rats that received turmeric extract had ulcers, chronic active inflammation, hyperplasia of the cecum or forestomach, or increased incidences of clitoral gland adenomas; these effects were mainly observed in the group fed with a 5% of turmeric extract. Likewise, mice fed with different concentrations of the turmeric extract had increased incidence of hepatocellular adenoma (1% group) or carcinomas of the small intestine (0.2 and 1% groups). In the 2-year study of mice, a 0.2% of turmeric extract in the diet was estimated to deliver average daily doses of curcumin of approximately 200 mg/kg body weight [91].

Several mechanisms may account for the toxic and carcinogenic properties of curcumin. Although many studies have shown that curcumin can prevent DNA damage (see references in Table 4), it has also been demonstrated that curcumin can induce DNA damage/alterations *in vitro* [92–103] and *in vivo* [104, 105]. These studies revealed that copper facilitates curcumin-induced DNA damage and that ROS play an important role in this activity. DNA topoisomerase II (topo II) may also play a role in curcumin-induced DNA damage, as curcumin has been described *in vitro* as a topo II poison and as topo II poisons induce topo II-mediated DNA damage [106]. We have recently observed that curcumin induces high levels of topoisomerase I and II–DNA complexes in human leukemia cells; although the induction of cytotoxic levels of topo–DNA complexes may be exploited therapeutically, the induction of nonlethal levels of these complexes may lead to carcinogenic effects [107]. Other dietary agents such as flavonoids (*e.g.*, genistein) are known to induce topo II-mediated DNA damage, and a high consumption of these agents has already been associated with a higher risk of leukemia in humans [108, 109].

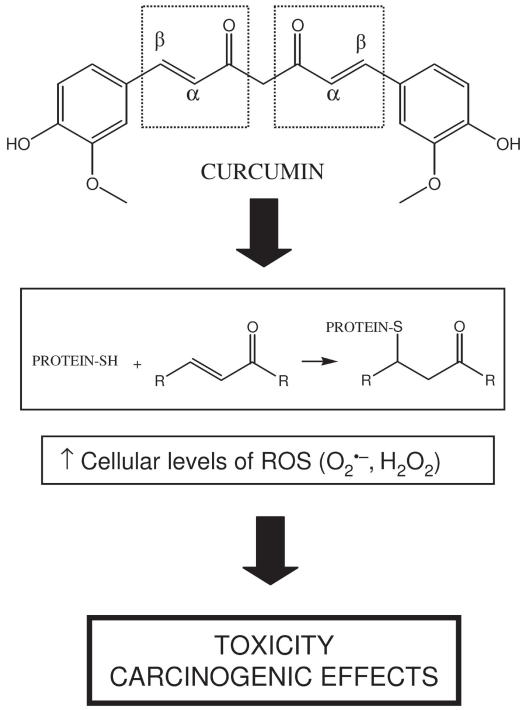

Figure 1. Possible mechanisms involved in the toxic and carcinogenic properties of curcumin. Curcumin possesses two electrophilic α,β-unsaturated ketones that can react with nucleophilic groups (*e.g.,* SH groups of proteins) through a reaction called Michael addition; this may produce toxic and carcinogenic effects. Specific concentrations of curcumin can also produce toxic and carcinogenic effects by increasing the cellular levels of ROS.

Curcumin possesses two electrophilic α,β-unsaturated ketones in its structure, which can react with nucleophilic groups through a reaction termed Michael addition. These α,β-unsaturated ketones can react covalently with the thiol (SH) groups of cysteine residues of different proteins; this may produce toxic effects (Fig. 1). For instance, Wang *et al.* [110] showed that thiol-reactive drugs containing an α,β-unsaturated ketone induced topo II–DNA complexes through thiol alkylation of topo II, and that these topo II–

DNA complexes were completely abolished in mutant yeast topo II with all cysteine residues replaced with alanine. They also showed that the potency of these drugs to stimulate topo II cleavable complexes correlated with their ability to undergo Michael addition [110]. This suggests that the formation of topo II – DNA complexes induced by curcumin [106] may be mediated by this reaction. Likewise, since drugs containing an electrophilic α,β-unsaturated ketone can produce inactivation of the tumor suppressor p53, Moos *et al*. evaluated the ability of curcumin to inactivate p53. They observed that curcumin disrupted the conformation of the p53 protein required for its serine phosphorylation, its binding to DNA, its transactivation of p53-responsive genes and p53-mediated cell cycle arrest [111]. These results are in agreement with another work that showed that curcumin can induce p53 degradation and inhibit p53-induced apoptosis [112]. Although these effects have not been observed *in vivo*, they support that curcumin may produce carcinogenic effects, as the inactivation of the tumor suppressor protein p53 is an important carcinogenic event.

Evidence indicates that an increase in the cellular levels of ROS (*e.g.*, superoxide anion ($O_2^{\bullet -}$), H_2O_2) plays a key role in carcinogenesis, and it is now well established that curcumin can increase the cellular levels of ROS (discussed in Section 4). Fang *et al*. [113] observed that curcumin increased the cellular levels of ROS by irreversibly modifying the antioxidant enzyme thioredoxin reductase (TrxR). In addition, the authors provided data supporting that this modification is caused by a reaction involving the α,β-unsaturated ketones of curcumin and the -SH and -SeH groups of the cysteine and selenocysteine residues of the active site of the enzyme.

Based on short-term studies conducted in animals and humans, it is generally considered that curcumin is a safe agent when administered orally (see [1, 2, 14] and references therein). No treatment-related toxicity was reported in 25 patients taking curcumin at concentrations up to 8000 mg/day (~115 mg/kg/day) for a period of 3 months [21]. As discussed above, no carcinogenic effects were observed in mice fed with turmeric extract for 3 months [91]. After 2 years, however, carcinogenic effects were observed in mice fed with concentrations of turmeric that delivered average doses of curcumin of approximately 200 mg/kg/day [91]. This suggests that we cannot conclude that oral consumption of curcumin is safe without conducting long-term studies in humans, as dietary supplements containing high concentrations of curcumin may produce carcinogenic effects when ingested chronically.

4 ROS, cancer, and curcumin

This section of the article discusses that many cancer-related activities of curcumin may be mediated by its ability to both reduce and increase the cellular levels of ROS, *i.e.*, by its antioxidant and pro-oxidant properties.

4.1 Key role of ROS in cancer development and cancer therapy

Most of the energy that aerobic cells need to live is obtained through oxidative phosphorylation. In this process, ATP generation is coupled with a reaction in which oxygen (O_2) is reduced to water (H_2O) by a mitochondrial protein complex called cytochrome oxidase. In this reaction, four electrons and four protons are added to O_2 to form two molecules of H_2O. However, when a molecule of O_2 gains only one electron to form $O_2^{\bullet -}$, this highly reactive species tends to gain three more electrons and four protons to form two molecules of H_2O; this process involves several reactions and generally results in the production of other ROS such as H_2O_2, hydroxyl radical ($OH^{\bullet}$) and peroxynitrite ($ONOO^-$).

It is now recognized that the controlled generation of ROS has an important physiological role [114]. An unrestrained production of ROS, however, seems to play a fundamental role in cancer development [31 – 33]. Thus, it has been shown that ROS, such as $O_2^{\bullet -}$ and H_2O_2, can cause and mediate cell malignant transformation [34, 115 – 118]. Overexpression of $O_2^{\bullet -}$ and H_2O_2-detoxifying enzymes (*e.g.*, superoxide dismutases or catalase) can reverse the malignant properties of different types of cancer cells [34 – 38]. In addition, recent data suggest that an increase in the cellular levels of $O_2^{\bullet -}$ and H_2O_2 may explain key aspects of the carcinogenesis process, including DNA alterations [119], increased cell proliferation [34], apoptosis resistance [120], angiogenesis [121], invasion/metastasis [122, 123], and HIF-1 activation [65, 66, 68].

Although an increase in the cellular levels of ROS seems crucial for cancer development, there is a threshold of ROS above which cells cannot survive. An adequate increase in the cellular levels of ROS can therefore induce cell death. It is recognized that H_2O_2 is an efficient inducer of apoptosis in cancer cells, and that the activity of several anticancer drugs commonly used in the clinic is mediated, at least in part, by H_2O_2. It has also been observed that specific concentrations of H_2O_2 can induce apoptosis in cancer cells without affecting nonmalignant cells. This suggests that any strategy capable of increasing the levels of this ROS adequately may produce selective killing of cancer cells and be useful in cancer therapy (see [33] and references therein).

4.2 Curcumin can both decrease and increase the cellular levels of ROS

The ability of curcumin to decrease the cellular levels of ROS has long been recognized and has been discussed in numerous reports. Basically, the antioxidant activity of curcumin seems to be mediated by its ability to both scavenge

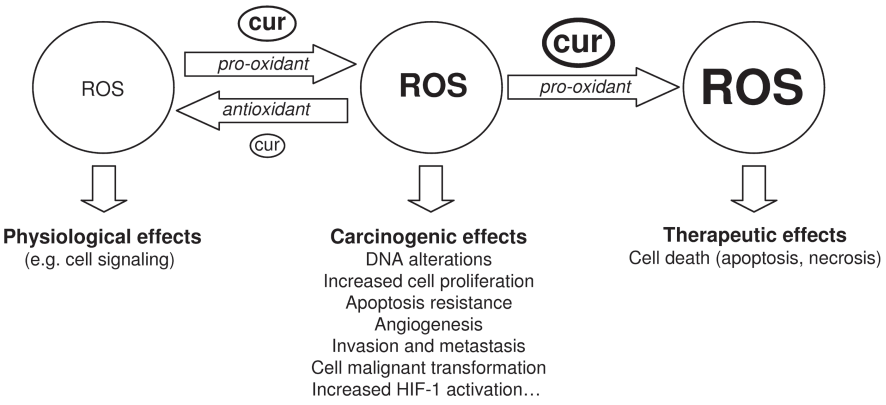

Figure 2. Possible involvement of the antioxidant and pro-oxidant activity of curcumin in its cancer chemopreventive, carcinogenic and therapeutic properties. Although low cellular levels of ROS play an important physiological role, an increase in their levels can produce carcinogenic effects. A sufficient increase in the levels of ROS can produce cell death and be exploited therapeutically. At low concentrations, curcumin can reduce the cellular levels of ROS (antioxidant activity) and prevent the process of carcinogenesis, therefore acting as a cancer chemopreventive agent. Concentrations of curcumin that result in an increase in the cellular levels of ROS (pro-oxidant activity) that is not sufficient to trigger cell death can produce carcinogenic effects. High concentrations of curcumin that increase the cellular levels of ROS (pro-oxidant activity) to cytotoxic levels can produce chemotherapeutic effects.

ROS [70, 124–129] and activate endogenous antioxidant mechanisms that reduce the cellular levels of ROS [40, 42, 130–135].

Although it is well known that curcumin possesses antioxidant activity, numerous reports have demonstrated that curcumin is also a pro-oxidant agent able to increase the cellular levels of ROS [92, 100, 113, 134, 136–144]. For instance, Kang *et al*. observed a significant decrease in the levels of ROS in human hepatoma Hep3B cells treated for 8 h with curcumin at concentrations of 10 and 20 μM. At 25, 50, and 100 μM, however, curcumin induced a significant increase in the cellular levels of ROS, which was dose and time-dependent [138]. A time-dependent induction of ROS was also observed when the human breast cancer cell lines MDAMB and MCF-7 and the human hepatocellular carcinoma cell line HepG2 were treated with curcumin 50 μM; this increase in the levels of ROS was not observed in rat hepatocytes under the same experimental conditions. A dose-dependent induction of ROS was also observed in human primary gingival fibroblasts and cancerous human submandibular adenocarcinoma cells treated for 1 h with curcumin in the 3–30 μM range; ROS production was higher in the cancer cells [145]. The lack of activity shown by tetrahydrocurcumin in this study suggests that the double bond of the two α,β-unsaturated ketones is important for the pro-oxidant activity of curcumin [145]. As mentioned before, Fang *et al.* [113] proposed a possible mechanism involved in the pro-oxidant activity of curcumin. They observed that curcumin irreversibly modified TrxR *in vitro* (IC_{50} 3.6 μM) and in HeLa cells (IC_{50} 15 μM), and proposed that this modification resulted in an increased production of ROS by a double mechanism. Whilst the inhibition of TrxR would impair the antioxidant thioredoxin system against oxidative stress, they observed that the curcumin-modified TrxR showed a strongly induced NADPH oxidase activity that resulted in an increased generation of ROS. Since the levels of TrxR seem higher in cancer cells than in nonmalignant cells [113], this effect may contribute to explain why curcumin induces higher ROS levels in cancer cells than in nonmalignant cells [138, 145]. In short, experimental data strongly support that, while low concentrations of curcumin exert an antioxidant activity, higher concentrations of this dietary agent produce pro-oxidant effects.

4.3 Link between the antioxidant/pro-oxidant effects of curcumin and its cancer-related activities

Figure 2 illustrates that the antioxidant and pro-oxidant activity of curcumin may play a key role in its chemopreventive, carcinogenic, and therapeutic properties. At low concentrations, the antioxidant activity of curcumin would reduce or keep the cellular levels of ROS within the physiological levels. This reduction in the levels of ROS may mediate the cancer chemopreventive properties of curcumin, as ROS are highly involved in carcinogenesis. At higher concentrations, the pro-oxidant activity of curcumin would increase the levels of ROS, which would produce carcinogenic effects. At concentrations that result in cytotoxic levels of ROS, curcumin would act as a chemotherapeutic agent.

In addition to the carcinogenic effects represented in Fig. 2, ROS are known to activate numerous cellular targets and pathways including, for instance, NF-κB [58], AP-1 [146], MMPs [122], TNF-α [65], Akt [147, 148], oncogen ras, src, and myc [149–154], and the ERK/MAPK, PI3K/

Akt, and JAK-signal transducer and activator of transcription (STAT) pathways [148, 155, 156]. Since curcumin can modulate the cellular levels of ROS, it is not surprising that it can interfere with these cellular targets and pathways (see [5, 13, 15, 22] and references in Tables 2 and 4).

Although numerous mechanisms have been proposed to be involved in curcumin-induced cell death, evidence suggests that this process may be governed by an increase in the cellular levels of ROS. For instance, it is acknowledged that the inhibition of NF-κB plays an important role in curcumin-induced apoptosis [54, 157 – 161]. However, evidence supports that high cellular levels of ROS (*e. g.*, H_2O_2) can inhibit this transcription factor [162 – 165]; this suggests that an increase in the cellular levels of ROS may precede curcumin-induced NF-κB inhibition and cell death. It is well known that curcumin can increase the cellular levels of ROS, and an increase in the levels of ROS has been observed in cells undergoing apoptosis during curcumin treatment. Numerous reports have demonstrated that curcumin-induced apoptosis is inhibited by antioxidants such as catalase or N-acetylcysteine [139, 140, 143 – 145, 166 – 168]. In addition, it is recognized that H_2O_2 is an efficient inducer of apoptosis in cancer cells and that several anticancer agents used in the clinic seem to exert their therapeutic effects by increasing the levels of this ROS [33, 169]. This suggests that the chemotherapeutic properties of curcumin may be mediated, at least in part, by an increase in the cellular levels of ROS.

The reported selectivity of curcumin for cancer cells [74 – 78] might also be explained by its ability to increase the cellular levels of ROS. It has been observed that the ROS H_2O_2 can produce selective killing of cancer cells [33, 170]. Experimental data indicate that cancer cells produce higher levels of H_2O_2 than nonmalignant cells [171], and it is recognized that there is a threshold of H_2O_2 above which cells cannot survive. This suggests that specific concentrations of H_2O_2 can increase the amounts of H_2O_2 to cytotoxic levels in cancer cells but not in normal cells [33]. As mentioned previously, it has been observed that specific concentrations of curcumin can increase the cellular levels of this ROS [92, 139, 140, 143 – 145, 166 – 168]. Overall, this suggests that concentrations of curcumin that result in an adequate increase in the cellular levels of H_2O_2 would produce selective killing of cancer cells.

Experimental data have shown that the therapeutic effects of radiotherapy and some anticancer drugs are increased by curcumin; this suggests that curcumin might be used in the clinic to sensitize cancer cells to radiotherapy and chemotherapy [159, 172 – 182]. Conversely, other reports have shown that curcumin can reduce the activity (and toxicity) of radiations and several chemotherapeutic agents [183 – 191]. The antioxidant/pro-oxidant activity of curcumin may explain these apparently controversial data. It is well known that, in addition to inducing apoptosis in cancer cells, ROS can sensitize these cells to drug-induced apoptosis [33, 192 – 195]. It is also known that the therapeutic effect of radiation and some anticancer agents is mediated, at least in part, by an increase in the cellular levels of ROS. Therefore, concentrations of curcumin that induce an elevation in the cellular levels of ROS would facilitate the anticancer effects of radiotherapy and chemotherapy. For example, evidence suggests that ROS play an important role in paclitaxel (taxol)-induced cell death [169] and that curcumin sensitizes cancer cells to paclitaxel-induced cell death [159]. Conversely, concentrations of curcumin that produce antioxidant effects would reduce the levels of ROS induced by radiation and chemotherapeutic agents, therefore reducing their activity and toxicity. Accordingly, Somasundaram *et al*. [189] observed that curcumin decreased the activity of several anticancer agents by reducing the cellular levels of ROS. Figure 3 illustrates that, while pro-oxidant concentrations of curcumin may increase the effects of cancer therapy, antioxidant concentrations of curcumin may reduce its activity/toxicity.

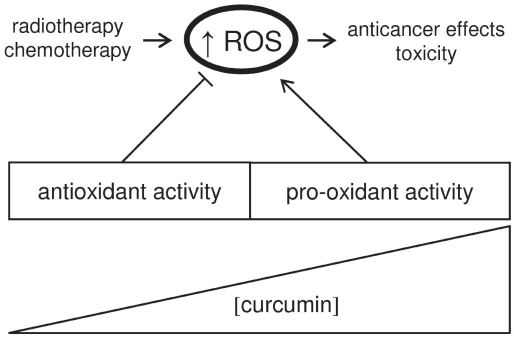

Figure 3. Curcumin can reduce or increase the activity/toxicity of radiotherapy and chemotherapy by reducing or increasing the cellular levels of ROS. Evidence supports that the activity and toxicity induced by radiotherapy and some chemotherapeutic agents is mediated, at least in part, by an increase in the cellular levels of ROS. Concentrations of curcumin that produce antioxidant effects would reduce the cellular levels of ROS and decrease the activity/toxicity of radiotherapy and chemotherapy. Conversely, concentrations of curcumin that produce pro-oxidant effects would elevate the cellular levels of ROS and increase the activity/toxicity of radiotherapy and chemotherapy.

5 Considerations for the clinical development of curcumin as an anticancer agent

Accumulating experimental data have revealed that curcumin possesses both cancer chemopreventive and chemotherapeutic properties. This section of the article discusses several aspects that may help develop curcumin as a clinically useful agent for the prevention and treatment of cancer.

5.1 Development of curcumin as a cancer chemopreventive agent

Epidemiological evidence indicates that people taking higher concentrations of curcumin in their diet have lower incidence of several common cancer types. Hundreds of preclinical reports have shown that curcumin has cancer chemopreventive properties. The last step before using curcumin in cancer chemoprevention is the confirmation of such preventive efficacy by using randomized controlled clinical trials, which are commonly regarded as the definitive study design for proving casualty. Three key aspects should be considered carefully in the design of cancer chemoprevention clinical trials: (i) the doses at which curcumin should be supplemented, (ii) the selection of the participants for the trials, and (iii) the duration of the trials and follow-ups.

Several short-term (3–4 months) human trials revealed that curcumin induced low levels of toxicity at concentrations of 3600 mg/day; these doses of curcumin have been considered safe and are recommended for future cancer chemoprevention clinical trials [14, 84, 196]. These doses, however, are around 20-times higher than the doses of curcumin estimated in people consuming high amounts of turmeric in their diet, which are approximately 150 mg/day [2, 197]. Although the use of chemicals at the maximum tolerated dose is a valid approach in cancer chemotherapy, this strategy may not be appropriate for cancer chemoprevention, as it may produce toxicity in the long term.

Beta-carotene is the classic example to show that supplementation of dietary agents at high doses may produce toxic and carcinogenic effects in the long term. Because the antioxidant agent β-carotene is found in vegetables and fruits and because eating vegetables and fruits is associated with a reduced risk of cancer, it seemed plausible that taking high doses of β-carotene supplements might reduce cancer risk. Preclinical studies also supported the potential cancer preventive activity of β-carotene. In three major clinical trials, people were given high doses of β-carotene (20–30 mg, which are approximately 10-times higher than those found in a diet rich in fruits and vegetables) in an attempt to prevent lung cancer and other cancers. These trials were stopped ahead of schedule because two of them found β-carotene supplements to be associated with a higher risk of lung cancer [198, 199]. The pro-oxidant activity of β-carotene may account for its carcinogenic properties observed in these trials. Like curcumin, β-carotene can behave as a pro-oxidant agent [200, 201], and pro-oxidant agents can increase the cellular level of ROS and produce toxic and carcinogenic effects. It is important to mention that, before the trials were stopped, β-carotene had not shown any apparent toxicity or carcinogenic activity during the 4–6 years of the studies. This lack of visible toxic and carcinogenic effects is understandable, as carcinogenesis is a long process that remains silent until its final stages. This example suggests that, although short-term studies can show that chemopreventive agents (*e.g.*, curcumin) do not produce apparent toxicity at doses that largely exceeded those taken in the diet, these doses may produce carcinogenic effects in the long term. Therefore, which doses of curcumin should be used for future cancer chemoprevention clinical trials? Since a diet rich in turmeric is considered safe and has been associated with a lower cancer risk, it seems appropriate to use doses of curcumin equivalent to those found in diets rich in turmeric. Although higher doses of curcumin may be more effective, it seems prudent to test the safety of such doses in long-term studies in humans before large cancer chemoprevention clinical trials are implemented.

Although cancer chemoprevention clinical trials can be aimed at healthy populations and at populations with cancer predisposition (people with precancerous lesions or who are at high risk for developing cancer), most cancer chemopreventive studies are implemented in those with cancer predisposition. In addition, the limited bioavailability of curcumin suggests that its cancer preventive activity may be limited to the gastrointestinal tract. Therefore, it is usually considered that the cancer chemopreventive activity of curcumin should be focused on people with colon cancer predisposition. Evidence suggests, however, that curcumin may also exert chemopreventive effects in healthy people on different organs and tissues. For instance, the antioxidant effects of curcumin following oral administration are not restricted to the gastrointestinal tract, as they have also been observed in other organs or tissues such as the liver [39–44], kidneys [40, 41, 45] or the brain [41, 46–49]. In addition, oxidative stress is known to play an important role not only in cancer progression, but also in cancer initiation. Overall, this suggests that the evaluation of the cancer chemopreventive activity of curcumin should not be restricted to people with colon cancer predisposition.

The duration of the trials and follow-ups is a crucial aspect to consider in the design of cancer chemoprevention clinical trials. A short trial or follow-up may hide the true effectiveness of a cancer chemopreventive agent. For example, a prospective epidemiological study assessed the influence of multivitamin use in colon cancer risk. Women who used multivitamins had no benefit with respect to colon cancer after 4 years of use (RR, 1.02) and had only non-significant risk reductions after 5–9 (RR, 0.83) or 10–14 (RR, 0.80) years of use. After 15 years of use, however, the risk was clearly lower (RR, 0.25 [CI, 0.13–0.51]) [202]. These data agree with the fact that cancer takes several years or decades to develop completely; for instance, it is estimated that 5–20 years are necessary for normal colon cells to form adenomas and that these adenomas require 5–15 additional years to become an invasive colon cancer [203]. In addition, the fact that cancer is not usually detected until it reaches its final stages suggests that we may need to wait several years after a trial finishes (follow-up) in order to observe a chemopreventive effect. Since the

most reliable endpoint for a cancer chemopreventive intervention is the presence or absence of cancer, we may need long follow-up periods. It should also be noted that the follow-ups of cancer chemoprevention clinical trials aimed at healthy populations should be longer than those conducted in people with premalignant lesions. Future validation of reliable surrogate endpoint biomarkers of carcinogenesis may reduce the duration of the follow-ups. In short, the duration and follow-up of any clinical trial evaluating the chemopreventive activity of curcumin should be designed long enough to let this dietary agent demonstrate its putative anticancer activity.

5.2 Development of curcumin as a cancer chemotherapeutic agent

Many *in vitro* studies have demonstrated that curcumin is an efficient inducer of apoptosis in different types of cancer cells. Some of these studies have shown that specific concentrations of curcumin can induce apoptosis in cancer cells without affecting nonmalignant cells. Several reports have also revealed that curcumin may sensitize cancer cells to the anticancer effects of radiotherapy and chemotherapy. These data indicate that curcumin has potential to be developed as a cancer chemotherapeutic agent.

In vitro studies have clearly established that curcumin-induced cancer cell death occurs in a dose and time-dependent manner. Cancer cells do not undergo apoptosis in the presence of curcumin unless this dietary agent is at concentrations of approximately 5 – 50 μM during several hours. These concentrations of curcumin are not achieved outside the gastrointestinal tract through the oral route. In the gastrointestinal tract, these concentrations cannot be kept during several hours, suggesting that the therapeutic effects of oral curcumin are limited. Indeed, when patients with advanced colorectal cancer were treated with curcumin at relatively high doses, no partial responses to treatment were observed [84]. High oral concentrations of curcumin may produce pro-oxidant effects that, although may not be high enough to exert a potent therapeutic effect, may sensitize cancer cells to the effects of radiotherapy and some anticancer drugs. It would be interesting to test whether the combinations of curcumin with radiation or these anticancer drugs can improve the efficiency of the standard therapies.

Intravenous (i. v.) infusion seems to be an appropriate route of administration to overcome the low oral bioavailability and extensive metabolism of curcumin in the human body. A continuous and prolonged administration of curcumin through the i. v. route would allow high concentrations of curcumin to be reached and maintained in plasma and tissues for longer periods of time. Curcumin has already been administered through the i.v. route to animals [55, 204 – 206], yet none of these experiments studied the safety and chemotherapeutic effect of curcumin under these conditions. It may be useful to evaluate the possible toxicity and therapeutic effectiveness of administering cytotoxic concentrations of curcumin through i.v. infusion to animals with cancer.

Although i.v. infusion seems to be the most straightforward route of administration to overcome the low oral bioavailability and extensive metabolism of curcumin, other delivery strategies are worth exploring [207 – 209]. For example, in order to overcome the low oral bioavailability of curcumin, Li *et al*. [208] encapsulated curcumin in a liposomal delivery system and tested its anticancer activity. *In vitro* studies revealed that liposomal curcumin inhibited the growth and induced apoptosis in pancreatic carcinoma cell lines. *In vivo*, lipomal curcumin (40 mg/kg, administered intravenously three times a week) suppressed *in vivo* growth of pancreatic tumor xenografts without showing significant toxicity to the host [208]. These encouraging results have also been observed by the same research group in colorectal cancer [209].

During the last decade, a high number of *in vitro* studies have clearly established that curcumin is an efficient inducer of apoptosis in cancer cells. In order to develop curcumin as a chemotherapeutic agent, now we need to evaluate its toxicity and therapeutic effectiveness in animals with cancer. In these studies, curcumin needs to be administered through the appropriate route or delivery system (*e. g*., i.v. infusion, liposomal or sustained release technologies) in order to achieve and maintain cytotoxic levels in the target tissues. The next step would be the evaluation of the possible toxicity and therapeutic activity of curcumin in a group of patients with cancer (Phase I/II clinical trial). Phase III clinical studies would be required to compare the anticancer efficiency of curcumin with that of standard anticancer therapies. These studies would reveal whether or not curcumin can be developed as a useful drug for the treatment of cancer.

6 Conclusions

Epidemiological studies suggest that populations that live on a diet rich in curcumin have a lower cancer risk. Accumulating preclinical studies have shown that curcumin can interfere with an increasing number of molecular targets, pathways and processes involved in cancer. Since a high consumption of curcumin in the diet is considered safe, it is commonly believed that the cancer chemopreventive and therapeutic properties of curcumin may be accompanied by a lack of toxicity. This belief is supported by short-term Phase I clinical studies that have shown that oral curcumin is well tolerated. This lack of toxicity is probably due to the low bioavailability of oral curcumin and to the extensive metabolism that this dietary agent undergoes in the human body. However, these pharmacokinetic parameters also suggest that many of the anticancer effects shown by curcumin

in vitro cannot be achieved *in vivo*. In addition, despite insufficient recognition, evidence strongly suggests that curcumin can exert toxic and carcinogenic effects under specific conditions. Although a high number of mechanisms have been proposed to participate in the anticancer and carcinogenic properties of curcumin, many of these properties seem to be mediated by the antioxidant and prooxidant activities of this dietary agent. After a critical analysis of the cancer-related properties of curcumin, several considerations that may help develop curcumin as an anticancer agent can be made. As far as cancer chemoprevention is concerned, evidence suggests that oral supplementation of curcumin at relatively high doses may produce carcinogenic effects in the long term, that the cancer chemopreventive potential of curcumin is not restricted to the gastrointestinal tract, and that future cancer chemoprevention clinical trials need to be designed long enough to let curcumin show its putative chemopreventive effects. Regarding cancer chemotherapy, evidence suggests that the therapeutic potential of oral curcumin is low even in cancers from the gastrointestinal tract, and that other routes of administration (*e.g.*, i.v. infusion) or other formulations (*e.g.*, liposomal or sustained release technologies) need to be considered to evaluate the potential of curcumin as a chemotherapeutic agent.

Experimental work carried out on curcumin in the author's laboratory is supported by the Spanish Ministry of Science and Technology (AGL2005-05132).

The author has declared no conflict of interest.

7 References

[1] Aggarwal, B. B., Kumar, A., Bharti, A. C., Anticancer potential of curcumin: Preclinical and clinical studies, *Anticancer Res*. 2003, *23*, 363 – 398.

[2] Sharma, R. A., Gescher, A. J., Steward, W. P., Curcumin: The story so far, *Eur. J. Cancer* 2005, *41*, 1955 – 1968.

[3] Leu, T. H., Maa, M. C., The molecular mechanisms for the antitumorigenic effect of curcumin, *Curr. Med. Chem. Anticancer Agents* 2002, *2*, 357 – 370.

[4] Chauhan, D. P., Chemotherapeutic potential of curcumin for colorectal cancer, *Curr. Pharm. Des*. 2002, *8*, 1695 – 1706.

[5] Surh, Y. J., Cancer chemoprevention with dietary phytochemicals, *Nat. Rev. Cancer* 2003, *3*, 768 – 780.

[6] Dorai, T., Aggarwal, B. B., Role of chemopreventive agents in cancer therapy, *Cancer Lett*. 2004, *215*, 129 – 140.

[7] Karunagaran, D., Rashmi, R., Kumar, T. R., Induction of apoptosis by curcumin and its implications for cancer therapy, *Curr. Cancer Drug Targets* 2005, *5*, 117 – 129.

[8] Duvoix, A., Blasius, R., Delhalle, S., Schnekenburger, M., *et al*., Chemopreventive and therapeutic effects of curcumin, *Cancer Lett*. 2005, *223*, 181 – 190.

[9] Maheshwari, R. K., Singh, A. K., Gaddipati, J., Srimal, R. C., Multiple biological activities of curcumin: A short review, *Life Sci*. 2006, *78*, 2081 – 2087.

[10] Thomasset, S. C., Berry, D. P., Garcea, G., Marczylo, T., *et al*., Dietary polyphenolic phytochemicals-promising cancer chemopreventive agents in humans? A review of their clinical properties, *Int. J. Cancer* 2007, *120*, 451 – 458.

[11] Thangapazham, R. L., Sharma, A., Maheshwari, R. K., Multiple molecular targets in cancer chemoprevention by curcumin, *AAPS J*. 2006, *8*, E443 – E449.

[12] Singh, S., Khar, A., Biological effects of curcumin and its role in cancer chemoprevention and therapy, *Anticancer Agents Med. Chem*. 2006, *6*, 259 – 270.

[13] Aggarwal, B. B., Shishodia, S., Molecular targets of dietary agents for prevention and therapy of cancer, *Biochem. Pharmacol*. 2006, *71*, 1397 – 1421.

[14] Johnson, J. J., Mukhtar, H., Curcumin for chemoprevention of colon cancer, *Cancer Lett*. 2007, *255*, 170 – 181.

[15] Shishodia, S., Chaturvedi, M. M., Aggarwal, B. B., Role of curcumin in cancer therapy, *Curr. Probl. Cancer* 2007, *31*, 243 – 305.

[16] Parkin, D. M., Bray, F., Ferlay, J., Pisani, P., Global cancer statistics 2002, *CA Cancer J. Clin*. 2005, *55*, 74 – 108.

[17] Jemal, A., Siegel, R., Ward, E., Murray, T., *et al*., Cancer statistics 2007, *CA Cancer J. Clin*. 2007, *57*, 43 – 66.

[18] Sporn, M. B., Suh, N., Chemoprevention: An essential approach to controlling cancer, *Nat. Rev. Cancer* 2002, *2*, 537 – 543.

[19] Sporn, M. B., Liby, K. T., Cancer chemoprevention: Scientific promise, clinical uncertainty, *Nat. Clin. Pract. Oncol*. 2005, *2*, 518 – 525.

[20] Lopez-Lazaro, M., Hypoxia-inducible factor 1 as a possible target for cancer chemoprevention, *Cancer Epidemiol. Biomarkers Prev.* 2006, *15*, 2332 – 2335.

[21] Cheng, A. L., Hsu, C. H., Lin, J. K., Hsu, M. M., *et al*., Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions, *Anticancer Res*. 2001, *21*, 2895 – 2900.

[22] Lin, J. K., Molecular targets of curcumin, *Adv. Exp. Med. Biol*. 2007, *59*, 227 – 243.

[23] Folkman, J., Hahnfeldt, P., Hlatky, L., Cancer: Looking outside the genome, *Nat. Rev. Mol. Cell Biol*. 2000, *1*, 76 – 79.

[24] Soto, A. M., Sonnenschein, C., The somatic mutation theory of cancer: Growing problems with the paradigm? *Bioessays* 2004, *26*, 1097 – 1107.

[25] Gibbs, W. W., Untangling the roots of cancer, *Sci. Am*. 2003, *289*, 56 – 65.

[26] Prehn, R. T., Cancers beget mutations versus mutations beget cancers, *Cancer Res*. 1994, *54*, 5296 – 5300.

[27] Vogelstein, B., Kinzler, K. W., Cancer genes and the pathways they control, *Nat. Med*. 2004, *10*, 789 – 799.

[28] Hanahan, D., Weinberg, R. A., The hallmarks of cancer, *Cell* 2000, *100*, 57 – 70.

[29] Gupta, G. P., Massague, J., Cancer metastasis: Building a framework, *Cell* 2006, *127*, 679 – 695.

[30] Lopez-Lazaro, M., Why do tumors metastasize? *Cancer Biol. Ther*. 2007, *6*, 141 – 144.

[31] Klaunig, J. E., Kamendulis, L. M., The role of oxidative stress in carcinogenesis, *Annu. Rev. Pharmacol. Toxicol*. 2004, *44*, *239* – 267.

[32] Lopez-Lazaro, M., Excessive superoxide anion generation plays a key role in carcinogenesis, *Int. J. Cancer* 2007, *120*, 1378 – 1380.

[33] Lopez-Lazaro, M., Dual role of hydrogen peroxide in cancer: Possible relevance to cancer chemoprevention and therapy, *Cancer Lett*. 2007, *252*, 1 – 8.

[34] Arnold, R. S., Shi, J., Murad, E., Whalen, A. M., *et al*., Hydrogen peroxide mediates the cell growth and transformation caused by the mitogenic oxidase Nox1, *Proc. Natl. Acad. Sci. USA* 2001, *98*, 5550 – 5555.

[35] Church, S. L., Grant, J. W., Ridnour, L. A., Oberley, L. W., *et al*., Increased manganese superoxide dismutase expression suppresses the malignant phenotype of human melanoma cells, *Proc. Natl. Acad. Sci. USA* 1993, *90*, 3113 – 3117.

[36] Safford, S. E., Oberley, T. D., Urano, M., St Clair, D. K., Suppression of fibrosarcoma metastasis by elevated expression of manganese superoxide dismutase, *Cancer Res*. 1994, *54*, 4261 – 4265.

[37] Yan, T., Oberley, L. W., Zhong, W., St Clair, D. K., Manganese-containing superoxide dismutase overexpression causes phenotypic reversion in SV40-transformed human lung fibroblasts, *Cancer Res*. 1996, *56*, 2864 – 2871.

[38] Zhang, Y., Zhao, W., Zhang, H. J., Domann, F. E., Oberley, L. W., Overexpression of copper zinc superoxide dismutase suppresses human glioma cell growth, *Cancer Res*. 2002, *62*, 1205 – 1212.

[39] Kaur, G., Tirkey, N., Bharrhan, S., Chanana, V., *et al*., Inhibition of oxidative stress and cytokine activity by curcumin in amelioration of endotoxin-induced experimental hepatoxicity in rodents, *Clin. Exp. Immunol*. 2006, *145*, 313 – 321.

[40] Iqbal, M., Sharma, S. D., Okazaki, Y., Fujisawa, M., Okada, S., Dietary supplementation of curcumin enhances antioxidant and Phase II metabolizing enzymes in ddY male mice: Possible role in protection against chemical carcinogenesis and toxicity, *Pharmacol. Toxicol*. 2003, *92*, 33 – 38.

[41] Kaul, S., Krishnakantha, T. P., Influence of retinol deficiency and curcumin/turmeric feeding on tissue microsomal membrane lipid peroxidation and fatty acids in rats, *Mol. Cell Biochem*. 1997, *175*, 43 – 48.

[42] Kempaiah, R. K., Srinivasan, K., Influence of dietary curcumin, capsaicin and garlic on the antioxidant status of red blood cells and the liver in high-fat-fed rats, *Ann. Nutr. Metab*. 2004, *48*, 314 – 320.

[43] Manjunatha, H., Srinivasan, K., Protective effect of dietary curcumin and capsaicin on induced oxidation of low-density lipoprotein, iron-induced hepatotoxicity and carrageenan-induced inflammation in experimental rats, *FEBS J.* 2006, *273*, 4528 – 4537.

[44] Reddy, A. C., Lokesh, B. R., Effect of curcumin and eugenol on iron-induced hepatic toxicity in rats, *Toxicology* 1996, *107*, 39 – 45.

[45] Okazaki, Y., Iqbal, M., Okada, S., Suppressive effects of dietary curcumin on the increased activity of renal ornithine decarboxylase in mice treated with a renal carcinogen, ferric nitrilotriacetate, *Biochim. Biophys. Acta* 2005, *1740*, 357 – 366.

[46] Bala, K., Tripathy, B. C., Sharma, D., Neuroprotective and anti-ageing effects of curcumin in aged rat brain regions, *Biogerontology* 2006, *7*, 81 – 89.

[47] Lim, G. P., Chu, T., Yang, F., Beech, W., *et al*., The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse, *J. Neurosci*. 2001, *21*, 8370 – 8377.

[48] Rajakrishnan, V., Viswanathan, P., Rajasekharan, K. N., Menon, V. P., Neuroprotective role of curcumin from curcuma longa on ethanol-induced brain damage, *Phytother. Res*. 1999, *13*, 571 – 574.

[49] Wu, A., Ying, Z., Gomez-Pinilla, F., Dietary curcumin counteracts the outcome of traumatic brain injury on oxidative stress, synaptic plasticity, and cognition, *Exp. Neurol*. 2006, *197*, 309 – 317.

[50] Satoskar, R. R., Shah, S. J., Shenoy, S. G., Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation, *Int. J. Clin. Pharmacol. Ther. Toxicol*. 1986, *24*, 651 – 654.

[51] Lal, B., Kapoor, A. K., Agrawal, P. K., Asthana, O. P., Srimal, R. C., Role of curcumin in idiopathic inflammatory orbital pseudotumours, *Phytother. Res*. 2000, *14*, 443 – 447.

[52] Lal, B., Kapoor, A. K., Asthana, O. P., Agrawal, P. K., *et al*., Efficacy of curcumin in the management of chronic anterior uveitis, *Phytother. Res*. 1999, *13*, 318 – 322.

[53] Karin, M., Nuclear factor-kappaB in cancer development and progression, *Nature* 2006, *441*, 431 – 436.

[54] Bharti, A. C., Donato, N., Singh, S., Aggarwal, B. B., Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and IkappaBalpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis, *Blood* 2003, *101*, 1053 – 1062.

[55] Ireson, C., Orr, S., Jones, D. J., Verschoyle, R., *et al*., Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat *in vivo*, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production, *Cancer Res*. 2001, *61*, 1058 – 1064.

[56] Perkins, S., Verschoyle, R. D., Hill, K., Parveen, I., *et al*., Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis, *Cancer Epidemiol. Biomarkers Prev.* 2002, *11*, 535 – 540.

[57] Ireson, C. R., Jones, D. J., Orr, S., Coughtrie, M. W., *et al*., Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine, *Cancer Epidemiol. Biomarkers Prev.* 2002, *11*, 105 – 111.

[58] Gloire, G., Legrand-Poels, S., Piette, J., NF-kappaB activation by reactive oxygen species: Fifteen years later, *Biochem. Pharmacol*. 2006, *72*, 1493 – 1505.

[59] Jagetia, G. C., Aggarwal, B. B., "Spicing up" of the immune system by curcumin, *J. Clin. Immunol*. 2007, *27*, 19 – 35.

[60] Zhong, H., De Marzo, A. M., Laughner, E., Lim, M., *et al*., Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases, *Cancer Res*. 1999, *59*, 5830 – 5835.

[61] Semenza, G. L., Targeting HIF-1 for cancer therapy, *Nat. Rev. Cancer* 2003, *3*, 721 – 732.

[62] Semenza, G. L., Development of novel therapeutic strategies that target HIF-1, *Expert. Opin. Ther. Targets* 2006, *10*, 267 – 280.

[63] Bae, M. K., Kim, S. H., Jeong, J. W., Lee, Y. M., *et al*., Curcumin inhibits hypoxia-induced angiogenesis via down-regulation of HIF-1, *Oncol. Rep*. 2006, *15*, 1557 – 1562.

[64] Choi, H., Chun, Y. S., Kim, S. W., Kim, M. S., Park, J. W., Curcumin inhibits hypoxia-inducible factor-1 by degrading aryl hydrocarbon receptor nuclear translocator: A mechanism of tumor growth inhibition, *Mol. Pharmacol*. 2006, *70*, 1664 – 1671.

[65] Haddad, J. J., Land, S. C., A non-hypoxic, ROS-sensitive pathway mediates TNF-alpha-dependent regulation of HIF-1alpha, *FEBS Lett*. 2001, *505*, 269 – 274.

[66] Chandel, N. S., McClintock, D. S., Feliciano, C. E., Wood, T. M. *et al*., Reactive oxygen species generated at mitochondrial complex III stabilize hypoxia-inducible factor-1alpha during hypoxia: A mechanism of O2 sensing, *J. Biol. Chem*. 2000, *275*, 25130 – 25138.

[67] Brunelle, J. K., Bell, E. L., Quesada, N. M., Vercauteren, K. *et al*., Oxygen sensing requires mitochondrial ROS but not oxidative phosphorylation, *Cell Metab.* 2005, *1*, 409 – 414.

[68] Lopez-Lazaro, M., HIF-1: Hypoxia-inducible factor or dysoxia-inducible Factor? *FASEB J.* 2006, *20*, 828 – 832.

[69] Nakamura, Y., Ohto, Y., Murakami, A., Osawa, T., Ohigashi, H., Inhibitory effects of curcumin and tetrahydrocurcuminoids on the tumor promoter-induced reactive oxygen species generation in leukocytes *in vitro* and *in vivo*, *Jpn. J. Cancer Res*. 1998, *89*, 361 – 370.

[70] Chattopadhyay, I., Bandyopadhyay, U., Biswas, K., Maity, P., Banerjee, R. K., Indomethacin inactivates gastric peroxidase to induce reactive-oxygen-mediated gastric mucosal injury and curcumin protects it by preventing peroxidase inactivation and scavenging reactive oxygen, *Free Radic. Biol. Med*. 2006, *40*, 1397 – 1408.

[71] Garcea, G., Jones, D. J., Singh, R., Dennison, A. R., *et al*., Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration, *Br. J. Cancer* 2004, *90*, 1011 – 1015.

[72] Pan, M. H., Lin-Shiau, S. Y., Lin, J. K., Comparative studies on the suppression of nitric oxide synthase by curcumin and its hydrogenated metabolites through down-regulation of IkappaB kinase and NFkappaB activation in macrophages, *Biochem. Pharmacol*. 2000, *60*, 1665 – 1676.

[73] Sharma, R. A., Steward, W. P., Gescher, A. J., Pharmacokinetics and pharmacodynamics of curcumin, *Adv. Exp. Med. Biol*. 2007, *595*, 453 – 470.

[74] Ramachandran, C., You, W., Differential sensitivity of human mammary epithelial and breast carcinoma cell lines to curcumin, *Breast Cancer Res. Treat*. 1999, *54*, 269 – 278.

[75] Jiang, M. C., Yang-Yen, H. F., Yen, J. J., Lin, J. K., Curcumin induces apoptosis in immortalized NIH 3T3 and malignant cancer cell lines, *Nutr. Cancer* 1996, *26*, 111 – 120.

[76] Syng-Ai, C., Kumari, A. L., Khar, A., Effect of curcumin on normal and tumor cells: Role of glutathione and bcl-2, *Mol. Cancer Ther.* 2004, *3*, 1101 – 1108.

[77] Everett, P. C., Meyers, J. A., Makkinje, A., Rabbi, M., Lerner, A., Preclinical assessment of curcumin as a potential therapy for B-CLL, *Am. J. Hematol*. 2007, *82*, 23 – 30.

[78] Choudhuri, T., Pal, S., Das, T., Sa, G., Curcumin selectively induces apoptosis in deregulated cyclin D1-expressed cells at G2 Phase of cell cycle in a p53-dependent manner, *J. Biol. Chem*. 2005, *280*, 20059 – 20068.

[79] Gautam, S. C., Xu, Y. X., Pindolia, K. R., Janakiraman, N., Chapman, R. A., Nonselective inhibition of proliferation of transformed and nontransformed cells by the anticancer agent curcumin (diferuloylmethane), *Biochem. Pharmacol*. 1998, *55*, 1333 – 1337.

[80] Duvoix, A., Morceau, F., Delhalle, S., Schmitz, M., *et al*., Induction of apoptosis by curcumin: Mediation by glutathione S-transferase P1 – 1 inhibition, *Biochem. Pharmacol*. 2003, *66*, 1475 – 1483.

[81] Garcea, G., Berry, D. P., Jones, D. J., Singh, R., *et al*., Consumption of the putative chemopreventive agent curcumin by cancer patients: Assessment of curcumin levels in the colorectum and their pharmacodynamic consequences, *Cancer Epidemiol. Biomarkers Prev.* 2005, *14*, 120 – 125.

[82] Samaha, H. S., Kelloff, G. J., Steele, V., Rao, C. V., Reddy, B. S., Modulation of apoptosis by sulindac, curcumin, phenylethyl-3-methylcaffeate, and 6-phenylhexyl isothiocyanate: Apoptotic index as a biomarker in colon cancer chemoprevention and promotion, *Cancer Res*. 1997, *57*, 1301 – 1305.

[83] Volate, S. R., Davenport, D. M., Muga, S. J., Wargovich, M. J., Modulation of aberrant crypt foci and apoptosis by dietary herbal supplements (quercetin, curcumin, silymarin, ginseng and rutin), *Carcinogenesis* 2005, *26*, 1450 – 1456.

[84] Sharma, R. A., Euden, S. A., Platton, S. L., Cooke, D. N., *et al*., Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance, *Clin. Cancer Res*. 2004, *10*, 6847 – 6854.

[85] Hahm, E. R., Gho, Y. S., Park, S., Park, C., *et al*., Synthetic curcumin analogs inhibit activator protein-1 transcription and tumor-induced angiogenesis, *Biochem. Biophys. Res. Commun*. 2004, *321*, 337 – 344.

[86] Jankun, J., Aleem, A. M., Malgorzewicz, S., Szkudlarek, M., *et al*., Synthetic curcuminoids modulate the arachidonic acid metabolism of human platelet 12-lipoxygenase and reduce sprout formation of human endothelial cells, *Mol. Cancer Ther.* 2006, *5*, 1371 – 1382.

[87] Leyon, P. V., Kuttan, G., Studies on the role of some synthetic curcuminoid derivatives in the inhibition of tumour specific angiogenesis, *J. Exp. Clin. Cancer Res*. 2003, *22*, 77 – 83.

[88] Mosley, C. A., Liotta, D. C., Snyder, J. P., Highly active anticancer curcumin analogues, *Adv. Exp. Med. Biol*. 2007, *595*, 77 – 103.

[89] Ohori, H., Yamakoshi, H., Tomizawa, M., Shibuya, M., *et al*., Synthesis and biological analysis of new curcumin analogues bearing an enhanced potential for the medicinal treatment of cancer, *Mol. Cancer Ther*. 2006, *5*, 2563 – 2571.

[90] Tamvakopoulos, C., Dimas, K., Sofianos, Z. D., Hatziantoniou, S., *et al*., Metabolism and anticancer activity of the curcumin analogue, dimethoxycurcumin, *Clin. Cancer Res*. 2007, *13*, 1269 – 1277.

[91] NTP Toxicology and Carcinogenesis Studies of Turmeric Oleoresin (CAS No. 8024-37-1) (Major Component 79 – 85% Curcumin, CAS No. 458-37-7) in F344/N Rats and B6C3F1 Mice (Feed Studies), *Natl. Toxicol. Program. Tech. Rep. Ser.* 1993, *427*, 1 – 275.

[92] Ahsan, H., Hadi, S. M., Strand scission in DNA induced by curcumin in the presence of Cu(II), *Cancer Lett*. 1998, *124*, 23 – 30.

[93] Blasiak, J., Trzeciak, A., Kowalik, J., Curcumin damages DNA in human gastric mucosa cells and lymphocytes, *J. Environ. Pathol. Toxicol. Oncol*. 1999, *18*, 271 – 276.

[94] Blasiak, J., Trzeciak, A., Malecka-Panas, E., Drzewoski, J., *et al*., DNA damage and repair in human lymphocytes and gastric mucosa cells exposed to chromium and curcumin, *Teratog. Carcinog. Mutagen*. 1999, *19*, 19 – 31.

[95] Cao, J., Jia, L., Zhou, H. M., Liu, Y., Zhong, L. F., Mitochondrial and nuclear DNA damage induced by curcumin in human hepatoma G2 cells, *Toxicol. Sci*. 2006, *91*, 476 – 483.

[96] Sahu, S. C., Washington, M. C., Effect of ascorbic acid and curcumin on quercetin-induced nuclear DNA damage, lipid peroxidation and protein degradation, *Cancer Lett*. 1992, *63*, 237 – 241.

[97] Sakano, K., Kawanishi, S., Metal-mediated DNA damage induced by curcumin in the presence of human cytochrome P450 isozymes, *Arch. Biochem. Biophys*. 2002, *405*, 223 – 230.

[98] Scott, D. W., Loo, G., Curcumin-induced GADD153 gene up-regulation in human colon cancer cells, *Carcinogenesis* 2004, *25*, 2155 – 2164.

[99] Urbina-Cano, P., Bobadilla-Morales, L., Ramirez-Herrera, M. A., Corona-Rivera, J. R., *et al*., DNA damage in mouse lymphocytes exposed to curcumin and copper, *J. Appl. Genet*. 2006, *47*, 377 – 382.

[100] Yoshino, M., Haneda, M., Naruse, M., Htay, H. H., *et al*., Prooxidant activity of curcumin: Copper-dependent formation of 8-hydroxy-2′-deoxyguanosine in DNA and induction of apoptotic cell death, *Toxicol. In vitro* 2004, *18*, 783 – 789.

[101] Antunes, L. M., Araujo, M. C., Dias, F. L., Takahashi, C. S., Modulatory effects of curcumin on the chromosomal damage induced by doxorubicin in Chinese hamster ovary cells, *Teratog. Carcinog. Mutagen*. 1999, *19*, 1 – 8.

[102] Araujo, M. C., Dias, F. L., Takahashi, C. S., Potentiation by turmeric and curcumin of gamma-radiation-induced chromosome aberrations in Chinese hamster ovary cells, *Teratog. Carcinog. Mutagen*. 1999, *19*, 9 – 18.

[103] Holy, J. M., Curcumin disrupts mitotic spindle structure and induces micronucleation in MCF-7 breast cancer cells, *Mutat. Res*. 2002, *518*, 71 – 84.

[104] Nair, J., Strand, S., Frank, N., Knauft, J., *et al*., Apoptosis and age-dependant induction of nuclear and mitochondrial etheno-DNA adducts in Long-Evans Cinnamon (LEC) rats: Enhanced DNA damage by dietary curcumin upon copper accumulation, *Carcinogenesis* 2005, *26*, 1307 – 1315.

[105] Giri, A. K., Das, S. K., Talukder, G., Sharma, A., Sister chromatid exchange and chromosome aberrations induced by curcumin and tartrazine on mammalian cells *in vivo*, *Cytobios* 1990, *62*, 111 – 117.

[106] Martin-Cordero, C., Lopez-Lazaro, M., Galvez, M., Ayuso, M. J., Curcumin as a DNA topoisomerase II poison, *J. Enzyme Inhib. Med. Chem*. 2003, *18*, 505 – 509.

[107] Lopez-Lazaro, M., Willmore, E., Jobson A., Gilroy, K. L., *et al*., Curcumin induces high levels of topoisomerase I- and II-DNA complexes in K562 leukemia cells, *J. Nat. Prod*. 2007, *70*, 1884 – 1888.

[108] Lopez-Lazaro, M., Willmore, E., Austin, C. A., Cells lacking DNA topoisomerase IIbeta are resistant to genistein, *J. Nat. Prod*. 2007, *70*, 763 – 767.

[109] Strick, R., Strissel, P. L., Borgers, S., Smith, S. L., Rowley, J. D., Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia, *Proc. Natl. Acad. Sci. USA* 2000, *97*, 4790 – 4795.

[110] Wang, H., Mao, Y., Chen, A. Y., Zhou, N., *et al*., Stimulation of topoisomerase II-mediated DNA damage via a mechanism involving protein thiolation, *Biochemistry* 2001, *40*, 3316 – 3323.

[111] Moos, P. J., Edes, K., Mullally, J. E., Fitzpatrick, F. A., Curcumin impairs tumor suppressor p53 function in colon cancer cells, *Carcinogenesis* 2004, *25*, 1611 – 1617.

[112] Tsvetkov, P., Asher, G., Reiss, V., Shaul, Y., *et al*., Inhibition of NAD(P)H:quinone oxidoreductase 1 activity and induction of p53 degradation by the natural phenolic compound curcumin, *Proc. Natl. Acad. Sci. USA* 2005, *102*, 5535 – 5540.

[113] Fang, J., Lu, J., Holmgren, A., Thioredoxin reductase is irreversibly modified by curcumin: A novel molecular mechanism for its anticancer activity, *J. Biol. Chem*. 2005, *280*, 25284 – 25290.

[114] Droge, W., Free radicals in the physiological control of cell function, *Physiol. Rev.* 2002, *82*, 47 – 95.

[115] Okamoto, M., Kawai, K., Reznikoff, C. A., Oyasu, R., Transformation *in vitro* of a nontumorigenic rat urothelial cell line by hydrogen peroxide, *Cancer Res*. 1996, *56*, 4649 – 4653.

[116] Okamoto, M., Reddy, J. K., Oyasu, R., Tumorigenic conversion of a non-tumorigenic rat urothelial cell line by overexpression of H2O2-generating peroxisomal fatty acyl-CoA oxidase, *Int. J. Cancer* 1997, *70*, 716 – 721.

[117] Suh, Y. A., Arnold, R. S., Lassegue, B., Shi, J., *et al*., Cell transformation by the superoxide-generating oxidase Mox1, *Nature* 1999, *401*, 79 – 82.

[118] Yang, J. Q., Buettner, G. R., Domann, F. E., Li, Q., *et al*., v-Ha-ras mitogenic signaling through superoxide and derived reactive oxygen species, *Mol. Carcinog*. 2002, *33*, 206 – 218.

[119] Park, S., You, X., Imlay, J. A., Substantial DNA damage from submicromolar intracellular hydrogen peroxide detected in Hpx- mutants of Escherichia coli, *Proc. Natl. Acad. Sci. USA* 2005, *102*, 9317 – 9322.

[120] del Bello, B., Paolicchi, A., Comporti, M., Pompella, A., Maellaro, E., Hydrogen peroxide produced during gamma-glutamyl transpeptidase activity is involved in prevention of apoptosis and maintainance of proliferation in U937 cells, *FASEB J*. 1999, *13*, 69 – 79.

[121] Arbiser, J. L., Petros, J., Klafter, R., Govindajaran, B., *et al*., Reactive oxygen generated by Nox1 triggers the angiogenic switch, *Proc. Natl. Acad. Sci. USA* 2002, *99*, 715 – 720.

[122] Nelson, K. K., Ranganathan, A. C., Mansouri, J., Rodriguez, A. M. *et al*., Elevated sod2 activity augments matrix metalloproteinase expression: Evidence for the involvement of endogenous hydrogen peroxide in regulating metastasis, *Clin. Cancer Res*. 2003, *9*, 424 – 432.

[123] Nishikawa, M., Hashida, M., Inhibition of tumour metastasis by targeted delivery of antioxidant enzymes, *Expert. Opin. Drug Deliv.* 2006, *3*, 355 – 369.

[124] Biswas, S. K., McClure, D., Jimenez, L. A., Megson, I. L., Rahman, I., Curcumin induces glutathione biosynthesis and inhibits NF-kappaB activation and interleukin-8 release in alveolar epithelial cells: Mechanism of free radical scavenging activity, *Antioxid. Redox. Signal*. 2005, *7*, 32 – 41.

[125] Das, K. C., Das, C. K., Curcumin (diferuloylmethane), a singlet oxygen ((1)O(2)) quencher, *Biochem. Biophys. Res. Commun*. 2002, *295*, 62 – 66.

[126] Khopde, M., Priyadarsini, K. I., Venkatesan, P., Rao, M. N., Free radical scavenging ability and antioxidant efficiency of curcumin and its substituted analogue, *Biophys. Chem*. 1999, *80*, 85 – 91.

[127] Manikandan, P., Sumitra, M., Aishwarya, S., Manohar, B. M., *et al*., Curcumin modulates free radical quenching in myocardial ischaemia in rats, *Int. J. Biochem. Cell Biol*. 2004, *36*, 1967 – 1980.

[128] Toniolo, R., Di Narda, F., Susmel, S., Martelli, M., *et al*., Quenching of superoxide ions by curcumin. A mechanistic study in acetonitrile, *Ann. Chim*. 2002, *92*, 281 – 288.

[129] Mishra, B., Priyadarsini, K. I., Bhide, M. K., Kadam, R. M., Mohan, H., Reactions of superoxide radicals with curcumin: Probable mechanisms by optical spectroscopy and EPR, *Free Radic. Res*. 2004, *38*, 355 – 362.

[130] Shen, G., Xu, C., Hu, R., Jain, M. R., *et al*., Modulation of nuclear factor E2-related factor 2-mediated gene expression in mice liver and small intestine by cancer chemopreventive agent curcumin, *Mol. Cancer Ther*. 2006, *5*, 39 – 51.

[131] Gaedeke, J., Noble, N. A., Border, W. A., Curcumin blocks fibrosis in anti-Thy 1 glomerulonephritis through up-regulation of heme oxygenase 1, *Kidney Int*. 2005, *68*, 2042 – 2049.

[132] Motterlini, R., Foresti, R., Bassi, R., Green, C. J., Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress, *Free Radic. Biol. Med*. 2000, *28*, 1303 – 1312.

[133] Balogun, E., Hoque, M., Gong, P., Killeen, E., *et al*., Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element, *Biochem. J.* 2003, *371*, 887 – 895.

[134] McNally, S. J., Harrison, E. M., Ross, J. A., Garden, O. J., Wigmore, S. J., Curcumin induces heme oxygenase 1 through generation of reactive oxygen species, p38 activation and phosphatase inhibition, *Int. J. Mol. Med*. 2007, *19*, 165 – 172.

[135] Farombi, E. O., Ekor, M., Curcumin attenuates gentamicin-induced renal oxidative damage in rats, *Food Chem. Toxicol*. 2006, *44*, 1443 – 1448.

[136] Bhaumik, S., Anjum, R., Rangaraj, N., Pardhasaradhi, B. V., Khar, A., Curcumin mediated apoptosis in AK-5 tumor cells involves the production of reactive oxygen intermediates, *FEBS Lett*. 1999, *456*, 311 – 314.

[137] Cao, J., Jia, L., Zhou, H. M., Liu, Y., Zhong, L. F., Mitochondrial and nuclear DNA damage induced by curcumin in human hepatoma G2 cells, *Toxicol. Sci*. 2006, *91*, 476 – 483.

[138] Kang, J., Chen, J., Shi, Y., Jia, J., Zhang, Y., Curcumin-induced histone hypoacetylation: The role of reactive oxygen species, *Biochem. Pharmacol*. 2005, *69*, 1205 – 1213.

[139] Moussavi, M., Assi, K., Gomez-Munoz, A., Salh, B., Curcumin mediates ceramide generation via the de novo pathway in colon cancer cells, *Carcinogenesis* 2006, *27*, 1636 – 1644.

[140] Scott, D. W., Loo, G., Curcumin-induced GADD153 gene up-regulation in human colon cancer cells, *Carcinogenesis* 2004, *25*, 2155 – 2164.

[141] Su, C. C., Lin, J. G., Li, T. M., Chung, J. G., *et al*., Curcumin-induced apoptosis of human colon cancer colo 205 cells through the production of ROS, Ca2+ and the activation of caspase-3, *Anticancer Res*. 2006, *26*, 4379 – 4389.

[142] Syng-Ai, C., Kumari, A. L., Khar, A., Effect of curcumin on normal and tumor cells: Role of glutathione and bcl-2, *Mol. Cancer Ther*. 2004, *3*, 1101 – 1108.

[143] Woo, J. H., Kim, Y. H., Choi, Y. J., Kim, D. G., *et al*., Molecular mechanisms of curcumin-induced cytotoxicity: Induction of apoptosis through generation of reactive oxygen species, down-regulation of Bcl-XL and IAP, the release of cytochrome c and inhibition of Akt, *Carcinogenesis* 2003, *24*, 1199 – 1208.

[144] Chan, W. H., Wu, H. Y., Chang, W. H., Dosage effects of curcumin on cell death types in a human osteoblast cell line, *Food Chem. Toxicol*. 2006, *44*, 1362 – 1371.

[145] Atsumi, T., Fujisawa, S., Tonosaki, K., Relationship between intracellular ROS production and membrane mobility in curcumin- and tetrahydrocurcumin-treated human gingival fibroblasts and human submandibular gland carcinoma cells, *Oral Dis*. 2005, *11*, 236 – 242.

[146] Wenk, J., Brenneisen, P., Wlaschek, M., Poswig, A., *et al*., Stable overexpression of manganese superoxide dismutase in mitochondria identifies hydrogen peroxide as a major oxidant in the AP-1-mediated induction of matrix-degrading metalloprotease-1, *J. Biol. Chem*. 1999, *274*, 25869 – 25876.

[147] Huang, C., Li, J., Ding, M., Leonard, S. S., *et al*., UV Induces phosphorylation of protein kinase B (Akt) at Ser-473 and Thr-308 in mouse epidermal Cl 41 cells through hydrogen peroxide, *J. Biol. Chem*. 2001, *276*, 40234 – 40240.

[148] Qin, S., Chock, P. B., Implication of phosphatidylinositol 3-kinase membrane recruitment in hydrogen peroxide-induced activation of PI3K and Akt, *Biochemistry* 2003, *42*, 2995 – 3003.

[149] Rao, G. N., Hydrogen peroxide induces complex formation of SHC-Grb2-SOS with receptor tyrosine kinase and activates Ras and extracellular signal-regulated protein kinases group of mitogen-activated protein kinases, *Oncogene* 1996, *13*, 713 – 719.

[150] Maki, A., Berezesky, I. K., Fargnoli, J., Holbrook, N. J., Trump, B. F., Role of [Ca2+]i in induction of c-fos, c-jun, and c-myc mRNA in rat PTE after oxidative stress, *FASEB J.* 1992, *6*, 919 – 924.

[151] Li, D. W., Spector, A., Hydrogen peroxide-induced expression of the proto-oncogenes, c-jun, c-fos and c-myc in rabbit lens epithelial cells, *Mol. Cell Biochem*. 1997, *173*, 59 – 69.

[152] Joseph, P., Muchnok, T. K., Klishis, M. L., Roberts, J. R., *et al*., Cadmium-induced cell transformation and tumorigenesis are associated with transcriptional activation of c-fos, c-jun, and c-myc proto-oncogenes: Role of cellular calcium and reactive oxygen species, *Toxicol. Sci*. 2001, *61*, 295 – 303.

[153] Chen, K., Vita, J. A., Berk, B. C., Keaney, J. F., Jr., c-Jun N-terminal kinase activation by hydrogen peroxide in endothelial cells involves SRC-dependent epidermal growth factor receptor transactivation, *J. Biol. Chem*. 2001, *276*, 16045 – 16050.

[154] Suzaki, Y., Yoshizumi, M., Kagami, S., Koyama, A. H., *et al*., Hydrogen peroxide stimulates c-Src-mediated big mitogen-activated protein kinase 1 (BMK1) and the MEF2C signaling pathway in PC12 cells: Potential role in cell survival following oxidative insults, *J. Biol. Chem*. 2002, *277*, 9614 – 9621.

[155] Cao, Q., Mak, K. M., Ren, C., Lieber, C. S., Leptin stimulates tissue inhibitor of metalloproteinase-1 in human hepatic stellate cells: Respective roles of the JAK/STAT and JAK-mediated H2O2-dependant MAPK pathways, *J. Biol. Chem*. 2004, *279*, 4292 – 4304.

[156] Simon, A. R., Rai, U., Fanburg, B. L., Cochran, B. H., Activation of the JAK-STAT pathway by reactive oxygen species, *Am. J. Physiol*. 1998, *275*, C1640 – C1652.

[157] Li, L., Aggarwal, B. B., Shishodia, S., Abbruzzese, J., Kurzrock, R., Nuclear factor-kappaB and IkappaB kinase are constitutively active in human pancreatic cells, and their down-regulation by curcumin (diferuloylmethane) is associated with the suppression of proliferation and the induction of apoptosis, *Cancer* 2004, *101*, 2351 – 2362.

[158] Siwak, D. R., Shishodia, S., Aggarwal, B. B., Kurzrock, R., Curcumin-induced antiproliferative and proapoptotic effects in melanoma cells are associated with suppression of Ikap-

paB kinase and nuclear factor kappaB activity and are independent of the B-Raf/mitogen-activated/extracellular signal-regulated protein kinase pathway and the Akt pathway, *Cancer* 2005, *104*, 879 – 890.

[159] Bava, S. V., Puliappadamba, V. T., Deepti, A., Nair, A., *et al*., Sensitization of taxol-induced apoptosis by curcumin involves down-regulation of nuclear factor-kappaB and the serine/threonine kinase Akt and is independent of tubulin polymerization, *J. Biol. Chem*. 2005, *280*, 6301 – 6308.

[160] Shishodia, S., Amin, H. M., Lai, R., Aggarwal, B. B., Curcumin (diferuloylmethane) inhibits constitutive NF-kappaB activation, induces G1/S arrest, suppresses proliferation, and induces apoptosis in mantle cell lymphoma, *Biochem. Pharmacol*. 2005, *70*, 700 – 713.

[161] Anto, R. J., Maliekal, T. T., Karunagaran, D., L-929 cells harboring ectopically expressed RelA resist curcumin-induced apoptosis, *J. Biol. Chem*. 2000, *275*, 15601 – 15604.

[162] Choi, J. J., Choi, J., Kang, C. D., Chen, X., *et al*., Hydrogen peroxide induces the death of astrocytes through the down-regulation of the constitutive nuclear factor-kappaB activity, *Free Radic. Res*. 2007, *41*, 555 – 562.

[163] Ginis, I., Hallenbeck, J. M., Liu, J., Spatz, M., *et al*., Tumor necrosis factor and reactive oxygen species cooperative cytotoxicity is mediated via inhibition of NF-kappaB, *Mol. Med*. 2000, *6*, 1028 – 1041.

[164] Ju, W., Wang, X., Shi, H., Chen, W., *et al*., A critical role of luteolin-induced reactive oxygen species in blockage of tumor necrosis factor-activated nuclear factor-kappaB pathway and sensitization of apoptosis in lung cancer cells, *Mol. Pharmacol*. 2007, *71*, 1381 – 1388.

[165] Jing, Y., Yang, J., Wang, Y., Li, H., *et al*., Alteration of subcellular redox equilibrium and the consequent oxidative modification of nuclear factor kappaB are critical for anticancer cytotoxicity by emodin, a reactive oxygen species-producing agent, *Free Radic. Biol. Med*. 2006, *40*, 2183 – 2197.

[166] Jung, E. M., Lim, J. H., Lee, T. J., Park, J. W., *et al*., Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through reactive oxygen species-mediated up-regulation of death receptor 5 (DR5), *Carcinogenesis* 2005, *26*, 1905 – 1913.

[167] Kim, M. S., Kang, H. J., Moon, A., Inhibition of invasion and induction of apoptosis by curcumin in H-ras-transformed MCF10A human breast epithelial cells, *Arch. Pharm. Res*. 2001, *24*, 349 – 354.

[168] Kuo, M. L., Huang, T. S., Lin, J. K., Curcumin, an antioxidant and anti-tumor promoter, induces apoptosis in human leukemia cells, *Biochim. Biophys. Acta* 1996, *1317*, 95 – 100.

[169] Alexandre, J., Batteux, F., Nicco, C., Chereau, C., *et al*., Accumulation of hydrogen peroxide is an early and crucial step for paclitaxel-induced cancer cell death both *in vitro* and *in vivo*, *Int. J. Cancer*. 2006, *119*, 41 – 48.

[170] Chen, Q., Espey, M. G., Krishna, M. C., Mitchell, J. B., *et al*., Pharmacologic ascorbic acid concentrations selectively kill cancer cells: Action as a pro-drug to deliver hydrogen peroxide to tissues, *Proc. Natl. Acad. Sci. USA* 2005, *102*, 13604 – 13609.

[171] Szatrowski, T. P., Nathan, C. F., Production of large amounts of hydrogen peroxide by human tumor cells, *Cancer Res*. 1991, *51*, 794 – 798.

[172] Chendil, D., Ranga, R. S., Meigooni, D., Sathishkumar, S., Ahmed, M. M., Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3, *Oncogene* 2004, *23*, 1599 – 1607.

[173] Li, M., Zhang, Z., Hill, D. L., Wang, H., Zhang, R., Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway, *Cancer Res*. 2007, *67*, 1988 – 1996.

[174] Khafif, A., Hurst, R., Kyker, K., Fliss, D. M., *et al*., Curcumin: A new radio-sensitizer of squamous cell carcinoma cells, *Otolaryngol. Head Neck Surg*. 2005, *132*, 317 – 321.

[175] Park, K., Lee, J. H., Photosensitizer effect of curcumin on UVB-irradiated HaCaT cells through activation of caspase pathways, *Oncol. Rep*. 2007, *17*, 537 – 540.

[176] Kamat, A. M., Sethi, G., Aggarwal, B. B., Curcumin potentiates the apoptotic effects of chemotherapeutic agents and cytokines through down-regulation of nuclear factor-kappaB and nuclear factor-kappaB-regulated gene products in IFN-alpha-sensitive and IFN-alpha-resistant human bladder cancer cells, *Mol. Cancer Ther.* 2007, *6*, 1022 – 1030.

[177] Du, B., Jiang, L., Xia, Q., Zhong, L., Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon cancer cell line HT-29, *Chemotherapy* 2006, *52*, 23 – 28.

[178] Hour, T. C., Chen, J., Huang, C. Y., Guan, J. Y., *et al*., Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21(WAF1/CIP1) and C/EBPbeta expressions and suppressing NF-kappaB activation, *Prostate* 2002, *51*, 211 – 218.

[179] Koo, J. Y., Kim, H. J., Jung, K. O., Park, K. Y., Curcumin inhibits the growth of AGS human gastric carcinoma cells *in vitro* and shows synergism with 5-fluorouracil, *J. Med. Food* 2004, *7*, 117 – 121.

[180] Garg, A. K., Buchholz, T. A., Aggarwal, B. B., Chemosensitization and radiosensitization of tumors by plant polyphenols, *Antioxid. Redox. Signal*. 2005, *7*, 1630 – 1647.

[181] Sen, S., Sharma, H., Singh, N., Curcumin enhances Vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway, *Biochem. Biophys. Res. Commun*. 2005, *331*, 1245 – 1252.

[182] Kunnumakkara, A. B., Guha, S., Krishnan, S., Diagaradjane, P. *et al*., Curcumin Potentiates Antitumor Activity of Gemcitabine in an Orthotopic Model of Pancreatic Cancer through Suppression of Proliferation, Angiogenesis, and Inhibition of Nuclear Factor-{kappa}B-Regulated Gene Products, *Cancer Res*. 2007, *67*, 3853 – 3861.

[183] Abraham, S. K., Sarma, L., Kesavan, P. C., Protective effects of chlorogenic acid, curcumin and beta-carotene against gamma-radiation-induced *in vivo* chromosomal damage, *Mutat. Res*. 1993, *303*, 109 – 112.

[184] Chan, W. H., Wu, C. C., Yu, J. S., Curcumin inhibits UV irradiation-induced oxidative stress and apoptotic biochemical changes in human epidermoid carcinoma A431 cells, *J. Cell Biochem*. 2003, *90*, 327 – 338.

[185] Inano, H., Onoda, M., Inafuku, N., Kubota, M., *et al*., Potent preventive action of curcumin on radiation-induced initiation of mammary tumorigenesis in rats, *Carcinogenesis* 2000, *21*, 1835 – 1841.

[186] Inano, H., Onoda, M., Inafuku, N., Kubota, M., *et al*., Chemoprevention by curcumin during the promotion stage of tumorigenesis of mammary gland in rats irradiated with gamma-rays, *Carcinogenesis* 1999, *20*, 1011 – 1018.

[187] Okunieff, P., Xu, J., Hu, D., Liu, W., *et al*., Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines, *Int. J. Radiat. Oncol. Biol. Phys*. 2006, *65*, 890 – 898.

[188] Srinivasan, M., Rajendra, P. N., Menon, V. P., Protective effect of curcumin on gamma-radiation induced DNA damage and lipid peroxidation in cultured human lymphocytes, *Mutat. Res*. 2006, *611*, 96 – 103.

[189] Somasundaram, S., Edmund, N. A., Moore, D. T., Small, G. W., *et al*., Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer, *Cancer Res*. 2002, *62*, 3868 – 3875.

[190] van't Land, B., Blijlevens, N. M., Marteijn, J., Timal, S., *et al*., Role of curcumin and the inhibition of NF-kappaB in the onset of chemotherapy-induced mucosal barrier injury, *Leukemia* 2004, *18*, 276 – 284.

[191] Antunes, L. M., Araujo, M. C., Darin, J. D., Bianchi, M. L., Effects of the antioxidants curcumin and vitamin C on cisplatin-induced clastogenesis in Wistar rat bone marrow cells, *Mutat. Res*. 2000, *465*, 131 – 137.

[192] Hirpara, J. L., Clement, M. V., Pervaiz, S., Intracellular acidification triggered by mitochondrial-derived hydrogen peroxide is an effector mechanism for drug-induced apoptosis in tumor cells, *J. Biol. Chem*. 2001, *276*, 514 – 521.

[193] Ahmad, K. A., Iskandar, K. B., Hirpara, J. L., Clement, M. V., Pervaiz, S., Hydrogen peroxide-mediated cytosolic acidification is a signal for mitochondrial translocation of Bax during drug-induced apoptosis of tumor cells, *Cancer Res*. 2004, *64*, 7867 – 7878.

[194] Poh, T. W., Pervaiz, S., LY294002 and LY303511 sensitize tumor cells to drug-induced apoptosis via intracellular hydrogen peroxide production independent of the phosphoinositide 3-kinase-Akt pathway, *Cancer Res*. 2005, *65*, 6264 – 6274.

[195] Alexandre, J., Nicco, C., Chereau, C., Laurent, A., *et al*., Improvement of the therapeutic index of anticancer drugs by the superoxide dismutase mimic mangafodipir, *J. Natl. Cancer Inst*. 2006, *98*, 236 – 244.

[196] Hsu, C. H., Cheng, A. L., Clinical studies with curcumin, *Adv. Exp. Med. Biol*. 2007, *595*, 471 – 480.

[197] Eigner, D., Scholz, D., Ferula asa-foetida and Curcuma longa in traditional medical treatment and diet in Nepal, *J. Ethnopharmacol*. 1999, *67*, 1 – 6.

[198] Byers, T., What can randomized controlled trials tell us about nutrition and cancer prevention? *CA Cancer J. Clin*. 1999, *49*, 353 – 361.

[199] Goodman, G. E., Thornquist, M. D., Balmes, J., Cullen, M. R. *et al*., The beta-carotene and retinol efficacy trial: Incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements, *J. Natl. Cancer Inst*. 2004, *96*, 1743 – 1750.

[200] Palozza, P., Serini, S., Di Nicuolo, F., Piccioni, E., Calviello, G., Prooxidant effects of beta-carotene in cultured cells, *Mol. Aspects Med*. 2003, *24*, 353 – 362.

[201] Zhang, P., Omaye, S. T., Antioxidant and prooxidant roles for beta-carotene, alpha-tocopherol and ascorbic acid in human lung cells, *Toxicol. In vitro* 2001, *15*, 13 – 24.

[202] Giovannucci, E., Stampfer, M. J., Colditz, G. A., Hunter, D. J., *et al*., Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study, *Ann. Intern. Med*. 1998, *129*, 517 – 524.

[203] O'Shaughnessy, J. A., Kelloff, G. J., Gordon, G. B., Dannenberg, A. J. *et al*., Treatment and prevention of intraepithelial neoplasia: An important target for accelerated new agent development, *Clin. Cancer Res*. 2002, *8*, 314 – 346.

[204] Wahlstrom, B., Blennow, G., A study on the fate of curcumin in the rat, *Acta Pharmacol. Toxicol*. 1978, *43*, 86 – 92.

[205] Deters, M., Siegers, C., Hansel, W., Schneider, K. P., Hennighausen, G., Influence of curcumin on cyclosporin-induced reduction of biliary bilirubin and cholesterol excretion and on biliary excretion of cyclosporin and its metabolites, *Planta Med*. 2000, *66*, 429 – 434.

[206] Siddiqui, A. M., Cui, X., Wu, R., Dong, W., *et al*., The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-gamma, *Crit. Care Med*. 2006, *34*, 1874 – 1882.

[207] Bisht, S., Feldmann, G., Soni, S., Ravi, R., *et al*., Polymeric nanoparticle-encapsulated curcumin (nanocurcumin): A novel strategy for human cancer therapy, *J. Nanobiotechnol.* 2007, *5*, 3.

[208] Li, L., Braiteh, F. S., Kurzrock, R., Liposome-encapsulated curcumin: *In vitro* and *in vivo* effects on proliferation, apoptosis, signaling, and angiogenesis, *Cancer* 2005, *104*, 1322 – 1331.

[209] Li, L., Ahmed, B., Mehta, K., Kurzrock, R., Liposomal curcumin with and without oxaliplatin: Effects on cell growth, apoptosis, and angiogenesis in colorectal cancer, *Mol. Cancer Ther*. 2007, *6*, 1276 – 1282.

[210] Thapliyal, R., Maru, G. B., Inhibition of cytochrome P450 isozymes by curcumins *in vitro* and *in vivo*, *Food Chem. Toxicol*. 2001, *39*, 541 – 547.

[211] Chen, Y. S., Ho, C. C., Cheng, K. C., Tyan, Y. S., *et al*., Curcumin inhibited the arylamines N-acetyltransferase activity, gene expression and DNA adduct formation in human lung cancer cells (A549), *Toxicol. In Vitro* 2003, *17*, 323 – 333.

[212] Shishodia, S., Potdar, P., Gairola, C. G., Aggarwal, B. B., Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF-kappaB activation through inhibition of IkappaBalpha kinase in human lung epithelial cells: Correlation with suppression of COX-2, MMP-9 and cyclin D1, *Carcinogenesis* 2003, *24*, 1269 – 1279.

[213] Chen, H. W., Yu, S. L., Chen, J. J., Li, H. N., *et al*., Anti-invasive gene expression profile of curcumin in lung adenocarcinoma based on a high throughput microarray analysis, *Mol. Pharmacol*. 2004, *65*, 99 – 110.

[214] Lee, J., Im, Y. H., Jung, H. H., Kim, J. H., *et al*., Curcumin inhibits interferon-alpha induced NF-kappaB and COX-2 in human A549 non-small cell lung cancer cells, *Biochem. Biophys. Res. Commun*. 2005, *334*, 313 – 318.

[215] Menon, L. G., Kuttan, R., Kuttan, G., Anti-metastatic activity of curcumin and catechin, *Cancer Lett*. 1999, *141*, 159 – 165.

[216] Vanisree, A. J., Sudha, N., Curcumin combats against cigarette smoke and ethanol-induced lipid alterations in rat lung and liver, *Mol. Cell Biochem*. 2006, *288*, 115 – 123.

[217] Vietri, M., Pietrabissa, A., Mosca, F., Spisni, R., Pacifici, G. M., Curcumin is a potent inhibitor of phenol sulfotransferase (SULT1A1) in human liver and extrahepatic tissues, *Xenobiotica* 2003, *33*, 357 – 363.

[218] Lev-Ari, S., Starr, A., Vexler, A., Karaush, V., *et al*., Inhibition of pancreatic and lung adenocarcinoma cell survival by curcumin is associated with increased apoptosis, down-regulation of COX-2 and EGFR and inhibition of Erk1/2 activity, *Anticancer Res*. 2006, *26*, 4423 – 4430.

[219] Radhakrishna, P. G., Srivastava, A. S., Hassanein, T. I., Chauhan, D. P., Carrier, E., Induction of apoptosis in human lung cancer cells by curcumin, *Cancer Lett*. 2004, *208*, 163 – 170.

[220] Singletary, K., MacDonald, C., Wallig, M., Fisher, C., Inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumorigenesis and DMBA-DNA adduct formation by curcumin, *Cancer Lett*. 1996, *103*, 137 – 141.

[221] Lee, K. W., Kim, J. H., Lee, H. J., Surh, Y. J., Curcumin inhibits phorbol ester-induced up-regulation of cyclooxygenase-2 and matrix metalloproteinase-9 by blocking ERK1/2 phosphorylation and NF-kappaB transcriptional activity in MCF10A human breast epithelial cells, *Antioxid. Redox Signal*. 2005, *7*, 1612 – 1620.

[222] Deshpande, S. S., Ingle, A. D., Maru, G. B., Chemopreventive efficacy of curcumin-free aqueous turmeric extract in 7,12-dimethylbenz[a]anthracene-induced rat mammary tumorigenesis, *Cancer Lett*. 1998, *123*, 35 – 40.

[223] Gafner, S., Lee, S. K., Cuendet, M., Barthelemy, S., *et al*., Biologic evaluation of curcumin and structural derivatives in cancer chemoprevention model systems, *Phytochemistry* 2004, *65*, 2849 – 2859.

[224] Huang, M. T., Lou, Y. R., Xie, J. G., Ma, W., *et al*., Effect of dietary curcumin and dibenzoylmethane on formation of 7,12-dimethylbenz[a]anthracene-induced mammary tumors and lymphomas/leukemias in Sencar mice, *Carcinogenesis* 1998, *19*, 1697 – 1700.

[225] Pereira, M. A., Grubbs, C. J., Barnes, L. H., Li, H., *et al*., Effects of the phytochemicals, curcumin and quercetin, upon azoxymethane-induced colon cancer and 7,12-dimethylbenz[a]anthracene-induced mammary cancer in rats, *Carcinogenesis* 1996, *17*, 1305 – 1311.

[226] Singletary, K., MacDonald, C., Iovinelli, M., Fisher, C., Wallig, M., Effect of the beta-diketones diferuloylmethane (curcumin) and dibenzoylmethane on rat mammary DNA adducts and tumors induced by 7,12-dimethylbenz[a]anthracene, *Carcinogenesis* 1998, *19*, 1039 – 1043.

[227] Ramachandran, C., Rodriguez, S., Ramachandran, R., Raveendran Nair, P. K. *et al*., Expression profiles of apoptotic genes induced by curcumin in human breast cancer and mammary epithelial cell lines, *Anticancer Res*. 2005, *25*, 3293 – 3302.

[228] Squires, M. S., Hudson, E. A., Howells, L., Sale, S., *et al*., Relevance of mitogen activated protein kinase (MAPK) and phosphotidylinositol-3-kinase/protein kinase B (PI3K/PKB) pathways to induction of apoptosis by curcumin in breast cells, *Biochem. Pharmacol*. 2003, *65*, 361 – 376.

[229] Choudhuri, T., Pal, S., Agwarwal, M. L., Das, T., Sa, G., Curcumin induces apoptosis in human breast cancer cells through p53-dependent Bax induction, *FEBS Lett*. 2002, *512*, 334 – 340.

[230] Hong, R. L., Spohn, W. H., Hung, M. C., Curcumin inhibits tyrosine kinase activity of p185neu and also depletes p185neu, *Clin. Cancer Res*. 1999, *5*, 1884 – 1891.

[231] Mukhopadhyay, A., Banerjee, S., Stafford, L. J., Xia, C., *et al*., Curcumin-induced suppression of cell proliferation correlates with down-regulation of cyclin D1 expression and CDK4-mediated retinoblastoma protein phosphorylation, *Oncogene* 2002, *21*, 8852 – 8861.

[232] Shao, Z. M., Shen, Z. Z., Liu, C. H., Sartippour, M. R., *et al*., Curcumin exerts multiple suppressive effects on human breast carcinoma cells, *Int. J. Cancer* 2002, *98*, 234 – 240.

[233] Huang, M. T., Lou, Y. R., Ma, W., Newmark, H. L., *et al*., Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice, *Cancer Res*. 1994, *54*, 5841 – 5847.

[234] Kwon, Y., Malik, M., Magnuson, B. A., Inhibition of colonic aberrant crypt foci by curcumin in rats is affected by age, *Nutr. Cancer* 2004, *48*, 37 – 43.

[235] Rao, C. V., Rivenson, A., Simi, B., Reddy, B. S., Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound, *Cancer Res*. 1995, *55*, 259 – 266.

[236] Kawamori, T., Lubet, R., Steele, V. E., Kelloff, G. J., *et al*., Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer, *Cancer Res*. 1999, *59*, 597 – 601.

[237] Chen, J. C., Hwang, J. M., Chen, G. W., Tsou, M. F., *et al*., Curcumin decreases the DNA adduct formation, arylamines N-acetyltransferase activity and gene expression in human colon tumor cells (colo 205), *In Vivo* 2003, *17*, 301 – 309.

[238] Plummer, S. M., Holloway, K. A., Manson, M. M., Munks, R. J. *et al*., Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex, *Oncogene* 1999, *18*, 6013 – 6020.

[239] Rao, C. V., Simi, B., Reddy, B. S., Inhibition by dietary curcumin of azoxymethane-induced ornithine decarboxylase, tyrosine protein kinase, arachidonic acid metabolism and aberrant crypt foci formation in the rat colon, *Carcinogenesis* 1993, *14*, 2219 – 2225.

[240] Sharma, R. A., Ireson, C. R., Verschoyle, R. D., Hill, K. A., *et al*., Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: Relationship with drug levels, *Clin. Cancer Res*. 2001, *7*, 1452 – 1458.

[241] Wang, X., Wang, Q., Ives, K. L., Evers, B. M., Curcumin inhibits neurotensin-mediated interleukin-8 production and migration of HCT116 human colon cancer cells, *Clin. Cancer Res*. 2006, *12*, 5346 – 5355.

[242] Howells, L. M., Mitra, A., Manson, M. M., Comparison of oxaliplatin- and curcumin-mediated antiproliferative effects in colorectal cell lines, *Int. J. Cancer* 2007, *121*, 175 – 183.

[243] Collett, G. P., Campbell, F. C., Overexpression of p65/RelA potentiates curcumin-induced apoptosis in HCT116 human colon cancer cells, *Carcinogenesis* 2006, *27*, 1285 – 1291.

[244] Collett, G. P., Campbell, F. C., Curcumin induces c-jun N-terminal kinase-dependent apoptosis in HCT116 human colon cancer cells, *Carcinogenesis* 2004, *25*, 2183 – 2189.

[245] Jaiswal, A. S., Marlow, B. P., Gupta, N., Narayan, S., Beta-catenin-mediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells, *Oncogene* 2002, *21*, 8414 – 8427.

[246] Moragoda, L., Jaszewski, R., Majumdar, A. P., Curcumin induced modulation of cell cycle and apoptosis in gastric and colon cancer cells, *Anticancer Res*. 2001, *21*, 873 – 878.

[247] Rashmi, R., Kumar, S., Karunagaran, D., Human colon cancer cells lacking Bax resist curcumin-induced apoptosis and Bax requirement is dispensable with ectopic expression of Smac or downregulation of Bcl-XL, *Carcinogenesis* 2005, *26*, 713 – 723.

[248] Rashmi, R., Santhosh Kumar, T. R., Karunagaran, D., Human colon cancer cells differ in their sensitivity to curcumin-induced apoptosis and heat shock protects them by inhibiting the release of apoptosis-inducing factor and caspases, *FEBS Lett*. 2003, *538*, 19 – 24.

[249] Chen, A., Xu, J., Johnson, A. C., Curcumin inhibits human colon cancer cell growth by suppressing gene expression of epidermal growth factor receptor through reducing the activity of the transcription factor Egr-1, *Oncogene* 2006, *25*, 278 – 287.

[250] Hong, J. H., Ahn, K. S., Bae, E., Jeon, S. S., Choi, H. Y., The effects of curcumin on the invasiveness of prostate cancer *in vitro* and *in vivo*, *Prostate Cancer Prostatic. Dis*. 2006, *9*, 147 – 152.

[251] Khor, T. O., Keum, Y. S., Lin, W., Kim, J. H., *et al*., Combined inhibitory effects of curcumin and phenethyl isothiocyanate on the growth of human PC-3 prostate xenografts in immunodeficient mice, *Cancer Res*. 2006, *66*, 613 – 621.

[252] Nonn, L., Duong, D., Peehl, D. M., Chemopreventive anti-inflammatory activities of curcumin and other phytochemicals mediated by MAP kinase phosphatase-5 in prostate cells, *Carcinogenesis* 2007, *28*, 1188 – 1196.

[253] Chaudhary, L. R., Hruska, K. A., Inhibition of cell survival signal protein kinase B/Akt by curcumin in human prostate cancer cells, *J. Cell Biochem*. 2003, *89*, 1 – 5.

[254] Deeb, D., Jiang, H., Gao, X., Hafner, M. S., *et al*., Curcumin sensitizes prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L by inhibiting nuclear factor-kappaB through suppression of IkappaBalpha phosphorylation, *Mol. Cancer Ther*. 2004, *3*, 803 – 812.

[255] Deeb, D., Jiang, H., Gao, X., Al Holou, S., *et al*., Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1-6-heptadine-3,5-dione; C21H20O6]#sensitizes human prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand/Apo2L-induced apoptosis by suppressing nuclear factor-kappaB via inhibition of the prosurvival Akt signaling pathway, *J. Pharmacol. Exp. Ther*. 2007, *321*, 616 – 625.

[256] Deeb, D. D., Jiang, H., Gao, X., Divine, G., *et al*., Chemosensitization of hormone-refractory prostate cancer cells by curcumin to TRAIL-induced apoptosis, *J. Exp. Ther. Oncol*. 2005, *5*, 81 – 91.

[257] Dorai, T., Dutcher, J. P., Dempster, D. W., Wiernik, P. H., Therapeutic potential of curcumin in prostate cancer – V: Interference with the osteomimetic properties of hormone refractory C4-2B prostate cancer cells, *Prostate* 2004, *60*, 1 – 17.

[258] Dorai, T., Gehani, N., Katz, A., Therapeutic potential of curcumin in human prostate cancer-I. curcumin induces apoptosis in both androgen-dependent and androgen-independent prostate cancer cells, *Prostate Cancer Prostatic. Dis*. 2000, *3*, 84 – 93.

[259] Dorai, T., Cao, Y. C., Dorai, B., Buttyan, R., Katz, A. E., Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells *in vivo*, *Prostate* 2001, *47*, 293 – 303.

[260] Dorai, T., Gehani, N., Katz, A., Therapeutic potential of curcumin in human prostate cancer. II. Curcumin inhibits tyrosine kinase activity of epidermal growth factor receptor and depletes the protein, *Mol. Urol*. 2000, *4*, 1 – 6.

[261] Kim, J. H., Xu, C., Keum, Y. S., Reddy, B., *et al*., Inhibition of EGFR signaling in human prostate cancer PC-3 cells by combination treatment with beta-phenylethyl isothiocyanate and curcumin, *Carcinogenesis* 2006, *27*, 475 – 482.

[262] Mukhopadhyay, A., Bueso-Ramos, C., Chatterjee, D., Pantazis, P., Aggarwal, B. B., Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines, *Oncogene* 2001, *20*, 7597 – 7609.

[263] Nakamura, K., Yasunaga, Y., Segawa, T., Ko, D., *et al*., Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines, *Int. J. Oncol*. 2002, *21*, 825 – 830.

[264] Shankar, S., Srivastava, R. K., Involvement of Bcl-2 family members, phosphatidylinositol 3'-kinase/AKT and mitochondrial p53 in curcumin (diferulolylmethane)-induced apoptosis in prostate cancer, *Int. J. Oncol*. 2007, *30*, 905 – 918.

[265] Ikezaki, S., Nishikawa, A., Furukawa, F., Kudo, K., *et al*., Chemopreventive effects of curcumin on glandular stomach carcinogenesis induced by N-methyl-N′-nitro-N-nitrosoguanidine and sodium chloride in rats, *Anticancer Res*. 2001, *21*, 3407 – 3411.

[266] Swarnakar, S., Ganguly, K., Kundu, P., Banerjee, A., *et al*., Curcumin regulates expression and activity of matrix metalloproteinases 9 and 2 during prevention and healing of indomethacin-induced gastric ulcer, *J. Biol. Chem*. 2005, *280*, 9409 – 9415.

[267] Foryst-Ludwig, A., Neumann, M., Schneider-Brachert, W., Naumann, M., Curcumin blocks NF-kappaB and the motogenic response in Helicobacter pylori-infected epithelial cells, *Biochem. Biophys. Res. Commun*. 2004, *316*, 1065 – 1072.

[268] Zhang, F., Altorki, N. K., Mestre, J. R., Subbaramaiah, K., Dannenberg, A. J., Curcumin inhibits cyclooxygenase-2 transcription in bile acid- and phorbol ester-treated human gastrointestinal epithelial cells, *Carcinogenesis* 1999, *20*, 445 – 451.

[269] Bruck, R., Ashkenazi, M., Weiss, S., Goldiner, I., *et al*., Prevention of liver cirrhosis in rats by curcumin, *Liver Int*. 2007, *27*, 373 – 383.

[270] Busquets, S., Carbo, N., Almendro, V., Quiles, M. T., *et al*., Curcumin, a natural product present in turmeric, decreases tumor growth but does not behave as an anticachectic compound in a rat model, *Cancer Lett*. 2001, *167*, 33 – 38.

[271] Chuang, S. E., Cheng, A. L., Lin, J. K., Kuo, M. L., Inhibition by curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene products and cell-cycle-related proteins in rats, *Food Chem. Toxicol*. 2000, *38*, 991 – 995.

[272] Chuang, S. E., Kuo, M. L., Hsu, C. H., Chen, C. R., *et al*., Curcumin-containing diet inhibits diethylnitrosamine-induced murine hepatocarcinogenesis, *Carcinogenesis* 2000, *21*, 331 – 335.

[273] Leclercq, I. A., Farrell, G. C., Sempoux, C., dela, P. A., Horsmans, Y., Curcumin inhibits NF-kappaB activation and reduces the severity of experimental steatohepatitis in mice, *J. Hepatol*. 2004, *41*, 926 – 934.

[274] Lin, L. I., Ke, Y. F., Ko, Y. C., Lin, J. K., Curcumin inhibits SK-Hep-1 hepatocellular carcinoma cell invasion *in vitro* and suppresses matrix metalloproteinase-9 secretion, *Oncology* 1998, *55*, 349 – 353.

[275] Mukundan, M. A., Chacko, M. C., Annapurna, V. V., Krishnaswamy, K., Effect of turmeric and curcumin on BP-DNA adducts, *Carcinogenesis* 1993, *14*, 493 – 496.

[276] Nanji, A. A., Jokelainen, K., Tipoe, G. L., Rahemtulla, A., *et al*., Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-kappa B-dependent genes, *Am. J. Physiol. Gastrointest. Liver Physiol*. 2003, *284*, G321 – G327.

[277] Oetari, S., Sudibyo, M., Commandeur, J. N., Samhoedi, R., Vermeulen, N. P., Effects of curcumin on cytochrome P450 and glutathione S-transferase activities in rat liver, *Biochem. Pharmacol*. 1996, *51*, 39 – 45.

[278] Ohashi, Y., Tsuchiya, Y., Koizumi, K., Sakurai, H., Saiki, I., Prevention of intrahepatic metastasis by curcumin in an orthotopic implantation model, *Oncology* 2003, *65*, 250 – 258.

[279] Park, E. J., Jeon, C. H., Ko, G., Kim, J., Sohn, D. H., Protective effect of curcumin in rat liver injury induced by carbon tetrachloride, *J. Pharm. Pharmacol*. 2000, *52*, 437 – 440.

[280] Reyes-Gordillo, K., Segovia, J., Shibayama, M., Vergara, P., *et al*., Curcumin protects against acute liver damage in the rat by inhibiting NF-kappaB, proinflammatory cytokines production and oxidative stress, *Biochim. Biophys. Acta* 2007, *1770*, 989 – 996.

[281] Shapiro, H., Ashkenazi, M., Weizman, N., Shahmurov, M., *et al*., Curcumin ameliorates acute thioacetamide-induced hepatotoxicity, *J. Gastroenterol. Hepatol*. 2006, *21*, 358 – 366.

[282] Shukla, Y., Arora, A., Suppression of altered hepatic foci development by curcumin in wistar rats, *Nutr. Cancer* 2003, *45*, 53 – 59.

[283] Sreepriya, M., Bali, G., Chemopreventive effects of embelin and curcumin against N-nitrosodiethylamine/phenobarbital-induced hepatocarcinogenesis in Wistar rats, *Fitoterapia* 2005, *76*, 549 – 555.

[284] Sugiyama, T., Nagata, J., Yamagishi, A., Endoh, K., *et al*., Selective protection of curcumin against carbon tetrachloride-induced inactivation of hepatic cytochrome P450 isozymes in rats, *Life Sci*. 2006, *78*, 2188 – 2193.

[285] Notarbartolo, M., Poma, P., Perri, D., Dusonchet, L., *et al*., Antitumor effects of curcumin, alone or in combination with cisplatin or doxorubicin, on human hepatic cancer cells. Analysis of their possible relationship to changes in NF-κB activation levels and in IAP gene expression, *Cancer Lett*. 2005, *224*, 53 – 65.

[286] Gukovsky, I., Reyes, C. N., Vaquero, E. C., Gukovskaya, A. S., Pandol, S. J., Curcumin ameliorates ethanol and nonethanol experimental pancreatitis, *Am. J. Physiol. Gastrointest. Liver Physiol*. 2003, *284*, G85 – G95.

[287] Hidaka, H., Ishiko, T., Furuhashi, T., Kamohara, H., *et al*., Curcumin inhibits interleukin 8 production and enhances interleukin 8 receptor expression on the cell surface:impact on human pancreatic carcinoma cell growth by autocrine regulation, *Cancer* 2002, *95*, 1206 – 1214.

[288] Masamune, A., Suzuki, N., Kikuta, K., Satoh, M., *et al*., Curcumin blocks activation of pancreatic stellate cells, *J. Cell Biochem*. 2006, *97*, 1080 – 1093.

[289] Wang, Z., Zhang, Y., Banerjee, S., Li, Y., Sarkar, F. H., Notch-1 down-regulation by curcumin is associated with the inhibition of cell growth and the induction of apoptosis in pancreatic cancer cells, *Cancer* 2006, *106*, 2503 – 2513.

[290] Cohly, H. H., Taylor, A., Angel, M. F., Salahudeen, A. K., Effect of turmeric, turmerin and curcumin on H2O2-induced renal epithelial (LLC-PK1) cell injury, *Free Radic. Biol. Med*. 1998, *24*, 49 – 54.

[291] Okada, K., Wangpoengtrakul, C., Tanaka, T., Toyokuni, S., *et al*., Curcumin and especially tetrahydrocurcumin ameliorate oxidative stress-induced renal injury in mice, *J. Nutr.* 2001, *131*, 2090 – 2095.

[292] Sindhwani, P., Hampton, J. A., Baig, M. M., Keck, R., Selman, S. H., Curcumin prevents intravesical tumor implantation of the MBT-2 tumor cell line in C3H mice, *J. Urol*. 2001, *166*, 1498 – 1501.

[293] Tong, Q. S., Zheng, L. D., Lu, P., Jiang, F. C., *et al*., Apoptosis-inducing effects of curcumin derivatives in human bladder cancer cells, *Anticancer Drugs* 2006, *17*, 279 – 287.

[294] Park, C., Kim, G. Y., Kim, G. D., Choi, B. T., *et al*., Induction of G2/M arrest and inhibition of cyclooxygenase-2 activity by curcumin in human bladder cancer T24 cells, *Oncol. Rep*. 2006, *15*, 1225 – 1231.

[295] Chakraborty, S., Ghosh, U., Bhattacharyya, N. P., Bhattacharya, R. K., Roy, M., Inhibition of telomerase activity and induction of apoptosis by curcumin in K-562 cells, *Mutat. Res*. 2006, *596*, 81 – 90.

[296] Hussain, A. R., Al Rasheed, M., Manogaran, P. S., Al Hussein, K. A., *et al*., Curcumin induces apoptosis via inhibition of PI3'-kinase/AKT pathway in acute T cell leukemias, *Apoptosis* 2006, *11*, 245 – 254.

[297] Rajasingh, J., Raikwar, H. P., Muthian, G., Johnson, C., Bright, J. J., Curcumin induces growth-arrest and apoptosis in association with the inhibition of constitutively active JAK-STAT pathway in T cell leukemia, *Biochem. Biophys. Res. Commun*. 2006, *340*, 359 – 368.

[298] Tomita, M., Kawakami, H., Uchihara, J. N., Okudaira, T., *et al*., Curcumin (diferuloylmethane) inhibits constitutive active NF-kappaB, leading to suppression of cell growth of human T-cell leukemia virus type I-infected T-cell lines and primary adult T-cell leukemia cells, *Int. J. Cancer* 2006, *118*, 765 – 772.

[299] Gururajan, M., Dasu, T., Shahidain, S., Jennings, C. D., *et al*., Spleen tyrosine kinase (Syk), a novel target of curcumin, is required for B lymphoma growth, *J. Immunol*. 2007, *178*, 111 – 121.

[300] Han, S. S., Chung, S. T., Robertson, D. A., Ranjan, D., Bondada, S., Curcumin causes the growth arrest and apoptosis of B cell lymphoma by downregulation of egr-1, c-myc, bcl-XL, NF-kappa B, and p53, *Clin. Immunol*. 1999, *93*, 152 – 161.

[301] Skommer, J., Wlodkowic, D., Pelkonen, J., Cellular foundation of curcumin-induced apoptosis in follicular lymphoma cell lines, *Exp. Hematol*. 2006, *34*, 463 – 474.

[302] Uddin, S., Hussain, A. R., Manogaran, P. S., Al Hussein, K. *et al*., Curcumin suppresses growth and induces apoptosis in primary effusion lymphoma, *Oncogene* 2005, *24*, 7022 – 7030.

[303] Wolanin, K., Magalska, A., Mosieniak, G., Klinger, R., *et al*., Curcumin affects components of the chromosomal passenger complex and induces mitotic catastrophe in apoptosis-resistant Bcr-Abl-expressing cells, *Mol. Cancer Res*. 2006, *4*, 457 – 469.

[304] Huang, M. T., Newmark, H. L., Frenkel, K., Inhibitory effects of curcumin on tumorigenesis in mice, *J. Cell Biochem. Suppl*. 1997, *27*, 26 – 34.

[305] Huang, M. T., Ma, W., Lu, Y. P., Chang, R. L., *et al*., Effects of curcumin, demethoxycurcumin, bisdemethoxycurcumin and tetrahydrocurcumin on 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion, *Carcinogenesis* 1995, *16*, 2493 – 2497.

[306] Limtrakul, P., Anuchapreeda, S., Lipigorngoson, S., Dunn, F. W., Inhibition of carcinogen induced c-Ha-ras and c-fos proto-oncogenes expression by dietary curcumin, *BMC Cancer* 2001, *1*, 1.

[307] Limtrakul, P., Lipigorngoson, S., Namwong, O., Apisariyakul, A., Dunn, F. W., Inhibitory effect of dietary curcumin on skin carcinogenesis in mice, *Cancer Lett*. 1997, *116*, 197 – 203.

[308] Lu, Y. P., Chang, R. L., Lou, Y. R., Huang, M. T., *et al*., Effect of curcumin on 12-O-tetradecanoylphorbol-13-acetate- and UV B light-induced expression of c-Jun and c-Fos in JB6 cells and in mouse epidermis, *Carcinogenesis* 1994, *15*, 2363 – 2370.

[309] Philip, S., Kundu, G. C., Osteopontin induces nuclear factor kappa B-mediated promatrix metalloproteinase-2 activation through I kappa B alpha /IKK signaling pathways, and curcumin (diferulolylmethane) down-regulates these pathways, *J. Biol. Chem*. 2003, *278*, 14487 – 14497.

[310] Chun, K. S., Keum, Y. S., Han, S. S., Song, Y. S., *et al*., Curcumin inhibits phorbol ester-induced expression of cyclooxygenase-2 in mouse skin through suppression of extracellular signal-regulated kinase activity and NF-kappaB activation, *Carcinogenesis* 2003, *24*, 1515 – 1524.

[311] Balasubramanian, S., Eckert, R. L., Curcumin suppresses AP1 transcription factor-dependent differentiation and activates apoptosis in human epidermal keratinocytes, *J. Biol. Chem*. 2007, *282*, 6707 – 6715.

[312] Dujic, J., Kippenberger, S., Hoffmann, S., Ramirez-Bosca, A., *et al*., Low Concentrations of Curcumin Induce Growth Arrest and Apoptosis in Skin Keratinocytes Only in Combination with UVA or Visible Light, *J. Invest Dermatol*. 2007, *127*, 1992 – 2000.

[313] Huang, M. T., Ma, W., Yen, P., Xie, J. G., *et al*., Inhibitory effects of topical application of low doses of curcumin on 12-O-tetradecanoylphorbol-13-acetate-induced tumor promotion and oxidized DNA bases in mouse epidermis, *Carcinogenesis* 1997, *18*, 83 – 88.

[314] Huang, M. T., Smart, R. C., Wong, C. Q., Conney, A. H., Inhibitory effect of curcumin, chlorogenic acid, caffeic acid, and ferulic acid on tumor promotion in mouse skin by 12-O-tetradecanoylphorbol-13-acetate, *Cancer Res*. 1988, *48*, 5941 – 5946.

[315] Lu, Y. P., Chang, R. L., Huang, M. T., Conney, A. H., Inhibitory effect of curcumin on 12-O-tetradecanoylphorbol-13-acetate-induced increase in ornithine decarboxylase mRNA in mouse epidermis, *Carcinogenesis* 1993, *14*, 293 – 297.

[316] Odot, J., Albert, P., Carlier, A., Tarpin, M., *et al*., *In vitro* and *in vivo* anti-tumoral effect of curcumin against melanoma cells, *Int. J. Cancer* 2004, *111*, 381 – 387.

[317] Bush, J. A., Cheung, K. J., Jr., Li, G., Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53, *Exp. Cell Res*. 2001, *271*, 305 – 314.

[318] Zheng, M., Ekmekcioglu, S., Walch, E. T., Tang, C. H., Grimm, E. A., Inhibition of nuclear factor-kappaB and nitric oxide by curcumin induces G2/M cell cycle arrest and apoptosis in human melanoma cells, *Melanoma Res*. 2004, *14*, 165 – 171.

[319] Jee, S. H., Shen, S. C., Tseng, C. R., Chiu, H. C., Kuo, M. L., Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells, *J. Invest Dermatol*. 1998, *111*, 656 – 661.

[320] Ushida, J., Sugie, S., Kawabata, K., Pham, Q. V., *et al*., Chemopreventive effect of curcumin on N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats, *Jpn. J. Cancer Res*. 2000, *91*, 893 – 898.

[321] Mori, Y., Tatematsu, K., Koide, A., Sugie, S., *et al*., Modification by curcumin of mutagenic activation of carcinogenic N-nitrosamines by extrahepatic cytochromes P-450 2B1 and 2E1 in rats, *Cancer Sci*. 2006, *97*, 896 – 904.

[322] Aoki, H., Takada, Y., Kondo, S., Sawaya, R., *et al*., Evidence That Curcumin Suppresses the Growth of Malignant Gliomas *In vitro* and *in vivo* through induction of autophagy: Role of Akt and ERK signaling pathways, *Mol. Pharmacol*. 2007, *72*, 29 – 39.

[323] Belkaid, A., Copland, I. B., Massillon, D., Annabi, B., Silencing of the human microsomal glucose-6-phosphate translocase induces glioma cell death: Potential new anticancer target for curcumin, *FEBS Lett*. 2006, *580*, 3746 – 3752.

[324] Kim, S. Y., Jung, S. H., Kim, H. S., Curcumin is a potent broad spectrum inhibitor of matrix metalloproteinase gene expression in human astroglioma cells, *Biochem. Biophys. Res. Commun*. 2005, *337*, 510 – 516.

[325] Woo, M. S., Jung, S. H., Kim, S. Y., Hyun, J. W., *et al*., Curcumin suppresses phorbol ester-induced matrix metalloproteinase-9 expression by inhibiting the PKC to MAPK signaling pathways in human astroglioma cells, *Biochem. Biophys. Res. Commun*. 2005, *335*, 1017 – 1025.

[326] Karmakar, S., Banik, N. L., Patel, S. J., Ray, S. K., Curcumin activated both receptor-mediated and mitochondria-mediated proteolytic pathways for apoptosis in human glioblastoma T98G cells, *Neurosci. Lett*. 2006, *407*, 53 – 58.

[327] Nagai, S., Kurimoto, M., Washiyama, K., Hirashima, Y., *et al*., Inhibition of cellular proliferation and induction of apoptosis by curcumin in human malignant astrocytoma cell lines, *J. Neurooncol*. 2005, *74*, 105 – 111.

[328] Aggarwal, S., Takada, Y., Singh, S., Myers, J. N., Aggarwal, B. B., Inhibition of growth and survival of human head and neck squamous cell carcinoma cells by curcumin via modulation of nuclear factor-kappaB signaling, *Int. J. Cancer* 2004, *111*, 679 – 692.

[329] LoTempio, M. M., Veena, M. S., Steele, H. L., Ramamurthy, B. *et al*., Curcumin suppresses growth of head and neck squamous cell carcinoma, *Clin. Cancer Res*. 2005, *11*, 6994 – 7002.

[330] Prusty, B. K., Das, B. C., Constitutive activation of transcription factor AP-1 in cervical cancer and suppression of human papillomavirus (HPV) transcription and AP-1 activity in HeLa cells by curcumin, *Int. J. Cancer* 2005, *113*, 951 – 960.

[331] Divya, C. S., Pillai, M. R., Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis, *Mol. Carcinog*. 2006, *45*, 320 – 332.

[332] Khar, A., Ali, A. M., Pardhasaradhi, B. V., Varalakshmi, C. H., *et al*., Induction of stress response renders human tumor cell lines resistant to curcumin-mediated apoptosis: Role of reactive oxygen intermediates, *Cell Stress. Chaperones* 2001, *6*, 368 – 376.

[333] Shi, M., Cai, Q., Yao, L., Mao, Y., *et al*., Antiproliferation and apoptosis induced by curcumin in human ovarian cancer cells, *Cell Biol. Int*. 2006, *30*, 221 – 226.

[334] Wahl, H., Tan, L., Griffith, K., Choi, M., Liu, J. R., Curcumin enhances Apo2L/TRAIL-induced apoptosis in chemoresistant ovarian cancer cells, *Gynecol. Oncol*. 2007, *105*, 104 – 112.

[335] Lin, Y. G., Kunnumakkara, A. B., Nair, A., Merritt, W. M., *et al*., Curcumin Inhibits Tumor Growth and Angiogenesis in Ovarian Carcinoma by Targeting the Nuclear Factor-{kappa}B Pathway, *Clin. Cancer Res*. 2007, *13*, 3423 – 3430.

[336] Weir, N. M., Selvendiran, K., Kutala, V. K., Tong, L., *et al*., Curcumin Induces G(2)/M Arrest and Apoptosis in Cisplatin-Resistant Human Ovarian Cancer Cells by Modulating Akt and p38 MAPK, *Cancer Biol. Ther*. 2007, *6*, 178 – 184.

[337] Aggarwal, B. B., Banerjee, S., Bharadwaj, U., Sung, B., *et al*., Curcumin induces the degradation of cyclin E expression through ubiquitin-dependent pathway and up-regulates cyclin-dependent kinase inhibitors p21 and p27 in multiple human tumor cell lines, *Biochem. Pharmacol*. 2007, *73*, 1024 – 1032.

[338] Kamath, R., Jiang, Z., Sun, G., Yalowich, J. C., Baskaran, R., c-Abl kinase regulates curcumin-induced cell death through activation of c-Jun N-terminal kinase, *Mol. Pharmacol*. 2007, *71*, 61 – 72.

[339] Shankar, S., Srivastava, R. K., Bax and Bak genes are essential for maximum apoptotic response by curcumin, a polyphenolic compound and cancer chemopreventive agent derived from turmeric, Curcuma longa, *Carcinogenesis* 2007, *28*, 1277 – 1286.

[340] Blasius, R., Reuter, S., Henry, E., Dicato, M., Diederich, M., Curcumin regulates signal transducer and activator of transcription (STAT) expression in K562 cells, *Biochem. Pharmacol*. 2006, *72*, 1547 – 1554.

[341] Chakravarti, N., Myers, J. N., Aggarwal, B. B., Targeting constitutive and interleukin-6-inducible signal transducers and activators of transcription 3 pathway in head and neck squamous cell carcinoma cells by curcumin (diferuloylmethane), *Int. J. Cancer* 2006, *119*, 1268 – 1275.

[342] Shoba, G., Joy, D., Joseph, T., Majeed, M., *et al*., Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers, *Planta Med*. 1998, *64*, 353 – 356.

[343] Sharma, R. A., McLelland, H. R., Hill, K. A., Ireson, C. R., *et al*., Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer, *Clin. Cancer Res*. 2001, *7*, 1894 – 1900.

[344] Huang, M. T., Wang, Z. Y., Georgiadis, C. A., Laskin, J. D., Conney, A. H., Inhibitory effects of curcumin on tumor initiation by benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene, *Carcinogenesis* 1992, *13*, 2183 – 2186.

[345] Krishnaswamy, K., Goud, V. K., Sesikeran, B., Mukundan, M. A., Krishna, T. P., Retardation of experimental tumorigenesis and reduction in DNA adducts by turmeric and curcumin, *Nutr. Cancer* 1998, *30*, 163 – 166.

[346] Shukla, Y., Arora, A., Taneja, P., Antimutagenic potential of curcumin on chromosomal aberrations in Wistar rats, *Mutat. Res*. 2002, *515*, 197 – 202.

[347] Thresiamma, K. C., George, J., Kuttan, R., Protective effect of curcumin, ellagic acid and bixin on radiation induced genotoxicity, *J. Exp. Clin. Cancer Res*. 1998, *17*, 431 – 434.

[348] Tunstall, R. G., Sharma, R. A., Perkins, S., Sale, S., *et al*., Cyclooxygenase-2 expression and oxidative DNA adducts in murine intestinal adenomas: Modification by dietary curcumin and implications for clinical trials, *Eur. J. Cancer* 2006, *42*, 415 – 421.

[349] Arbiser, J. L., Klauber, N., Rohan, R., van Leeuwen, R., *et al*., Curcumin is an *in vivo* inhibitor of angiogenesis, *Mol. Med*. 1998, *4*, 376 – 383.

[350] Mohan, R., Sivak, J., Ashton, P., Russo, L. A., *et al*., Curcuminoids inhibit the angiogenic response stimulated by fibroblast growth factor-2, including expression of matrix metalloproteinase gelatinase B, *J. Biol. Chem*. 2000, *275*, 10405 – 10412.

[351] Gururaj, A. E., Belakavadi, M., Venkatesh, D. A., Marme, D., Salimath, B. P., Molecular mechanisms of anti-angiogenic effect of curcumin, *Biochem. Biophys. Res. Commun*. 2002, *297*, 934 – 942.

[352] Li, N., Chen, X., Liao, J., Yang, G., *et al*., Inhibition of 7,12-dimethylbenz[a]anthracene (DMBA)-induced oral carcinogenesis in hamsters by tea and curcumin, *Carcinogenesis* 2002, *23*, 1307 – 1313.

[353] Aggarwal, B. B., Shishodia, S., Takada, Y., Banerjee, S. *et al*., Curcumin suppresses the paclitaxel-induced nuclear factor-kappaB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice, *Clin. Cancer Res*. 2005, *11*, 7490 – 7498.

[354] Bachmeier, B., Nerlich, A. G., Iancu, C. M., Cilli, M., *et al*., The chemopreventive polyphenol Curcumin prevents hematogenous breast cancer metastases in immunodeficient mice, *Cell Physiol. Biochem*. 2007, *19*, 137 – 152.

[355] Daniel, S., Limson, J. L., Dairam, A., Watkins, G. M., Daya, S., Through metal binding, curcumin protects against lead- and cadmium-induced lipid peroxidation in rat brain homogenates and against lead-induced tissue damage in rat brain, *J. Inorg. Biochem*. 2004, *98*, 266 – 275.

[356] Eybl, V., Kotyzova, D., Koutensky, J., Comparative study of natural antioxidants – curcumin, resveratrol and melatonin – in cadmium-induced oxidative damage in mice, *Toxicology* 2006, *225*, 150 – 156.

[357] Eybl, V., Kotyzova, D., Bludovska, M., The effect of curcumin on cadmium-induced oxidative damage and trace elements level in the liver of rats and mice, *Toxicol. Lett*. 2004, *151*, 79 – 85.

[358] Ghoneim, A. I., Abdel-Naim, A. B., Khalifa, A. E., El Denshary, E. S., Protective effects of curcumin against ischaemia/reperfusion insult in rat forebrain, *Pharmacol. Res*. 2002, *46*, 273 – 279.

[359] Inano, H., Onoda, M., Radioprotective action of curcumin extracted from Curcuma longa LINN: Inhibitory effect on formation of urinary 8-hydroxy-2'-deoxyguanosine, tumorigenesis, but not mortality, induced by gamma-ray irradiation, *Int. J. Radiat. Oncol. Biol. Phys*. 2002, *53*, 735 – 743.

[360] Joe, B., Lokesh, B. R., Role of capsaicin, curcumin and dietary n-3 fatty acids in lowering the generation of reactive oxygen species in rat peritoneal macrophages, *Biochim. Biophys. Acta* 1994, *1224*, 255 – 263.

[361] Nakamura, Y., Ohto, Y., Murakami, A., Osawa, T., Ohigashi, H., Inhibitory effects of curcumin and tetrahydrocurcuminoids on the tumor promoter-induced reactive oxygen species generation in leukocytes *in vitro* and *in vivo*, *Jpn. J. Cancer Res*. 1998, *89*, 361 – 370.

[362] Padmaja, S., Raju, T. N., Antioxidant effect of curcumin in selenium induced cataract of Wistar rats, *Indian J. Exp. Biol*. 2004, *42*, 601 – 603.

[363] Punithavathi, D., Venkatesan, N., Babu, M., Protective effects of curcumin against amiodarone-induced pulmonary fibrosis in rats, *Br. J. Pharmacol*. 2003, *139*, 1342 – 1350.

[364] Rajeswari, A., Curcumin protects mouse brain from oxidative stress caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *Eur. Rev. Med. Pharmacol. Sci*. 2006, *10*, 157 – 161.

[365] Rukkumani, R., Aruna, K., Varma, P. S., Rajasekaran, K. N., Menon, V. P., Comparative effects of curcumin and an analog of curcumin on alcohol and PUFA induced oxidative stress, *J. Pharm. Pharm. Sci*. 2004, *7*, 274 – 283.

[366] Sajithlal, G. B., Chithra, P., Chandrakasan, G., Effect of curcumin on the advanced glycation and cross-linking of collagen in diabetic rats, *Biochem. Pharmacol*. 1998, *56*, 1607 – 1614.

[367] Sharma, S., Kulkarni, S. K., Chopra, K., Curcumin, the active principle of turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats, *Clin. Exp. Pharmacol. Physiol*. 2006, *33*, 940 – 945.

[368] Shukla, P. K., Khanna, V. K., Khan, M. Y., Srimal, R. C., Protective effect of curcumin against lead neurotoxicity in rat, *Hum. Exp. Toxicol*. 2003, *22*, 653 – 658.

[369] Thiyagarajan, M., Sharma, S. S., Neuroprotective effect of curcumin in middle cerebral artery occlusion induced focal cerebral ischemia in rats, *Life Sci*. 2004, *74*, 969 – 985.

[370] Tirkey, N., Kaur, G., Vij, G., Chopra, K., Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys, *BMC. Pharmacol*. 2005, *5*, 15.

[371] Ukil, A., Maity, S., Karmakar, S., Datta, N., *et al*., Curcumin, the major component of food flavour turmeric, reduces mucosal injury in trinitrobenzene sulphonic acid-induced colitis, *Br. J. Pharmacol*. 2003, *139*, 209 – 218.

[372] Venkatesan, N., Punithavathi, D., Arumugam, V., Curcumin prevents adriamycin nephrotoxicity in rats, *Br. J. Pharmacol*. 2000, *129*, 231 – 234.

[373] Venkatesan, N., Punithavathi, V., Chandrakasan, G., Curcumin protects bleomycin-induced lung injury in rats, *Life Sci*. 1997, *61*, L51 – L58.

[374] Wang, Q., Sun, A. Y., Simonyi, A., Jensen, M. D., *et al*., Neuroprotective mechanisms of curcumin against cerebral ischemia-induced neuronal apoptosis and behavioral deficits, *J. Neurosci. Res*. 2005, *82*, 138 – 148.

[375] Watanabe, S., Fukui, T., Suppressive effect of curcumin on trichloroethylene-induced oxidative stress, *J. Nutr. Sci. Vitaminol*. 2000, *46*, 230 – 234.

[376] Cheng, P. Y., Wang, M., Morgan, E. T., Rapid transcriptional suppression of rat cytochrome P450 genes by endotoxin treatment and its inhibition by curcumin, *J. Pharmacol. Exp. Ther*. 2003, *307*, 1205 – 1212.

[377] Valentine, S. P., Le Nedelec, M. J., Menzies, A. R., Scandlyn, M. J., *et al*., Curcumin modulates drug metabolizing enzymes in the female Swiss Webster mouse, *Life Sci*. 2006, *78*, 2391 – 2398.

[378] Awasthi, S., Srivatava, S. K., Piper, J. T., Singhal, S. S., *et al*., Curcumin protects against 4-hydroxy-2-trans-nonenal-induced cataract formation in rat lenses, *Am. J. Clin. Nutr*. 1996, *64*, 761 – 766.

[379] Singh, S. V., Hu, X., Srivastava, S. K., Singh, M., *et al*., Mechanism of inhibition of benzo[a]pyrene-induced forestomach cancer in mice by dietary curcumin, *Carcinogenesis* 1998, *19*, 1357 – 1360.

[380] Belakavadi, M., Salimath, B. P., Mechanism of inhibition of ascites tumor growth in mice by curcumin is mediated by NF-κB and caspase activated DNase, *Mol. Cell Biochem*. 2005, *273*, 57 – 67.

[381] Gaddipati, J. P., Sundar, S. V., Calemine, J., Seth, P., *et al*., Differential regulation of cytokines and transcription factors in liver by curcumin following hemorrhage/resuscitation, *Shock* 2003, *19*, 150 – 156.

[382] Jian, Y. T., Mai, G. F., Wang, J. D., Zhang, Y. L., *et al*., Preventive and therapeutic effects of NF-kappaB inhibitor curcumin in rats colitis induced by trinitrobenzene sulfonic acid, *World J. Gastroenterol*. 2005, *11*, 1747 – 1752.

[383] Kuwabara, N., Tamada, S., Iwai, T., Teramoto, K., *et al*., Attenuation of renal fibrosis by curcumin in rat obstructive nephropathy, *Urology* 2006, *67*, 440 – 446.

[384] Parodi, F. E., Mao, D., Ennis, T. L., Pagano, M. B., Thompson, R. W., Oral administration of diferuloylmethane (curcumin) suppresses proinflammatory cytokines and destructive connective tissue remodeling in experimental abdominal aortic aneurysms, *Ann. Vasc. Surg*. 2006, *20*, 360 – 368.

[385] Salh, B., Assi, K., Templeman, V., Parhar, K., *et al*., Curcumin attenuates DNB-induced murine colitis, *Am. J. Physiol. Gastrointest. Liver Physiol*. 2003, *285*, G235 – G243.

[386] Sugimoto, K., Hanai, H., Tozawa, K., Aoshi, T., *et al*., Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice, *Gastroenterology* 2002, *123*, 1912 – 1922.

[387] Surh, Y. J., Han, S. S., Keum, Y. S., Seo, H. J., Lee, S. S., Inhibitory effects of curcumin and capsaicin on phorbol ester-induced activation of eukaryotic transcription factors, NF-kappaB and AP-1, *Biofactors* 2000, *12*, 107 – 112.

[388] Rukkumani, R., Aruna, K., Varma, P. S., Menon, V. P., Curcumin influences hepatic expression patterns of matrix metalloproteinases in liver toxicity, *Ital. J. Biochem*. 2004, *53*, 61 – 66.

[389] Camacho-Barquero, L., Villegas, I., Sanchez-Calvo, J. M., Talero, E. *et al*., Curcumin, a Curcuma longa constituent, acts on MAPK p38 pathway modulating COX-2 and iNOS expression in chronic experimental colitis, *Int. Immunopharmacol*. 2007, *7*, 333 – 342.

[390] Jiang, H., Deng, C. S., Zhang, M., Xia, J., Curcumin-attenuated trinitrobenzene sulphonic acid induces chronic colitis by inhibiting expression of cyclooxygenase-2, *World J. Gastroenterol*. 2006, *12*, 3848 – 3853.

[391] Zhang, M., Deng, C., Zheng, J., Xia, J., Sheng, D., Curcumin inhibits trinitrobenzene sulphonic acid-induced colitis in rats by activation of peroxisome proliferator-activated receptor gamma, *Int. Immunopharmacol*. 2006, *6*, 1233 – 1242.

[392] Gulcubuk, A., Altunatmaz, K., Sonmez, K., Haktanir-Yatkin, D. *et al*., Effects of curcumin on tumour necrosis factor-alpha and interleukin-6 in the late Phase of experimental acute pancreatitis, *J. Vet. Med. A Physiol Pathol. Clin. Med*. 2006, *53*, 49 – 54.

[393] Punithavathi, D., Venkatesan, N., Babu, M., Curcumin inhibition of bleomycin-induced pulmonary fibrosis in rats, *Br. J. Pharmacol*. 2000, *131*, 169 – 172.

[394] Sharma, S., Kulkarni, S. K., Agrewala, J. N., Chopra, K., Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain, *Eur. J. Pharmacol*. 2006, *536*, 256 – 261.

[395] Chan, M. M., Huang, H. I., Fenton, M. R., Fong, D., *In vivo* inhibition of nitric oxide synthase gene expression by curcumin, a cancer preventive natural product with anti-inflammatory properties, *Biochem. Pharmacol*. 1998, *55*, 1955 – 1962.

[396] Kakar, S. S., Roy, D., Curcumin inhibits TPA induced expression of c-fos, c-jun and c-myc proto-oncogenes messenger RNAs in mouse skin, *Cancer Lett*. 1994, *87*, 85 – 89.

[397] Ishizaki, C., Oguro, T., Yoshida, T., Wen, C. Q., *et al*., Enhancing effect of ultraviolet A on ornithine decarboxylase induction and dermatitis evoked by 12-o-tetradecanoylphorbol-13-acetate and its inhibition by curcumin in mouse skin, *Dermatology* 1996, *193*, 311 – 317.

[398] Churchill, M., Chadburn, A., Bilinski, R. T., Bertagnolli, M. M., Inhibition of intestinal tumors by curcumin is associated with changes in the intestinal immune cell profile, *J. Surg. Res*. 2000, *89*, 169 – 175.

[399] Bhattacharyya, S., Mandal, D., Sen, G. S., Pal, S., *et al*., Tumor-induced oxidative stress perturbs nuclear factor-kappaB activity-augmenting tumor necrosis factor-alpha-mediated T-cell death: Protection by curcumin, *Cancer Res*. 2007, *67*, 362 – 370.

[400] Bhattacharyya, S., Mandal, D., Saha, B., Sen, G. S., *et al*., Curcumin prevents tumor-induced T cell apoptosis through Stat-5a-mediated Bcl-2 induction, *J. Biol. Chem*. 2007, *282*, 15954 – 15964.

[401] Pal, S., Bhattacharyya, S., Choudhuri, T., Datta, G. K., *et al*., Amelioration of immune cell number depletion and potentiation of depressed detoxification system of tumor-bearing mice by curcumin, *Cancer Detect. Prev.* 2005, *29*, 470 – 478.

