PHARMACOKINETICS AND PHARMACODYNAMICS OF CURCUMIN

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Abstract: *Curcuma* spp. contain turmerin, essential oils, and curcuminoids, including curcumin. Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is regarded as the most biologically active constituent of the spice turmeric and it comprises 2–8% of most turmeric preparations. Preclinical data from animal models and phase I clinical studies performed with human volunteers and patients with cancer have demonstrated low systemic bioavailability following oral dosing. Efficient first-pass metabolism and some degree of intestinal metabolism, particularly glucuronidation and sulfation of curcumin, might explain its poor systemic availability when administered via the oral route. A daily oral dose of 3.6 g of curcumin is compatible with detectable levels of the parent compound in colorectal tissue from patients with cancer. The levels demonstrated might be sufficient to exert pharmacological activity. There appears to be negligible distribution of the parent drug to hepatic tissue or other tissues beyond the gastrointestinal tract. Curcumin possesses wide-ranging anti-inflammatory and anticancer properties. Many of these biological activities can be attributed to its potent antioxidant capacity at neutral and acidic pH, its inhibition of cell signaling pathways at multiple levels, its diverse effects on cellular enzymes, and its effects on cell adhesion and angiogenesis. In particular, curcumin’s ability to alter gene transcription and induce apoptosis in preclinical models advocates its potential utility in cancer chemoprevention and chemotherapy. With regard to considerable public and scientific interest in the use of phytochemicals derived from dietary components to combat or prevent human diseases, curcumin is currently a leading agent.

1. INTRODUCTION

There has been considerable public and scientific interest in the use of phytochemicals derived from dietary components to combat or prevent human diseases, especially the two commonest killers in the developed world: cardiovascular disease and cancer. The dried, ground rhizome of the perennial herb *Curcuma longa* Linn. has been used in Asian medicine since the second millennium BC. Its utility is referred to in the ancient Hindu scripture, the Ayurveda. In addition
to its aromatic, stimulant, and coloring properties in the diet, turmeric is mixed with other natural compounds such as slaked lime and has been used topically as a treatment for wounds, inflammation, and tumors. In contrast to the high dietary consumption (up to 1.5 g curcumin per person per day) in certain Southeast Asian communities, smaller quantities of turmeric tend to be used for medicinal purposes.2 The appeal of turmeric as a coloring, food preservative, and flavoring is global; according to the Food and Agriculture Organization of the United Nations, over 2400 metric tons of turmeric are imported annually into the United States for consumer use.

*Curcuma* spp. contain turmerin (a water-soluble peptide), essential oils (such as turmerones, atlantones, and zingiberene), and curcuminoids, including curcumin \([1,7\text{-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione}]\). Curcumin, which was first chemically characterized in 1910, is regarded as the most biologically active constituent of turmeric and comprises 2–8% of most turmeric preparations.3a,4 Curcumin has been the subject of hundreds of published articles over the past three decades, studying its antioxidant, anti-inflammatory, cancer chemopreventive, and potentially chemotherapeutic properties. The pharmacology and putative anticancer properties of curcumin have been the subject of several review articles,5–7 publication of which predates a number of clinical studies of curcumin that have been completed and reported within the last 2 years. The purpose of this chapter is to appraise the current level of knowledge of the fate of curcumin in mammalian organisms and its pharmacodynamic properties, with particular reference to its potential use in the chemoprevention of human cancer.

### 2. PHARMACOKINETICS AND METABOLISM

#### 2.1. Pharmacokinetics and Metabolism in Rodents

The absorption, distribution, metabolism, and excretion of curcumin in rodents have been described in at least 10 studies over the past three decades. Collectively, these studies support the notion that curcumin undergoes a rapid and efficient metabolism that severely curtails the availability of parent compound in the bio-phase. In an early study in rats, a dietary dose (1 g/kg) administered to rats resulted in about 75% of species related to curcumin being detected in feces, whereas negligible amounts appeared in the urine.8 In another early article, absorption of oral curcumin was 60%; urinary agent-derived species were characterized as glucuronide and sulfate conjugates.9 When curcumin bioavailability was investigated using a \(^{3}\text{H}\)-radiolabeled agent, the vast majority of the oral dose was excreted in the feces and one-third was excreted unchanged.10 Intravenous and intraperitoneal administration of curcumin in rats resulted in large quantities of curcumin and metabolites in bile.11,12 The metabolites were characterized mainly as glucuronides of tetrahydrocurcumin and hexahydrocurcumin. After intravenous dosing, more than
50% of the dose was excreted in the bile within 5 h. This finding was interpreted as evidence in support of the hypothesis that curcumin undergoes biotransformation during absorption in the intestinal tract and enterohepatic recirculation. More recently, curcumin (0.1 g/kg) administered intraperitoneally to the mouse was found to undergo metabolic reduction to dihydrocurcumin and tetrahydrocurcumin, which, in turn, were converted to monoglucuronide conjugates. High-pressure liquid chromatography (HPLC) analysis of plasma from rats that had received oral curcumin demonstrated substantial levels of curcumin glucuronide and curcumin sulfate, small quantities of hexahydrocurcumin, hexahydrocurcuminol, and hexahydrocurcumin glucuronide and negligible amounts of curcumin (see Figure 1). In suspensions of isolated human hepatocytes, or in microsomes derived from liver or gut tissues of rats and humans, curcumin was rapidly reduced to metabolites, as shown in Figure 1. In a separate study in rats, a high dose of curcumin mixed into the diet (2%, equating to approximately 1.2 g/kg) for 14 days yielded low-nanomolar levels of the parent compound in the plasma, with concentrations in the liver and colon mucosa ranging from 0.1 to 1.8 nmol/g tissue. It is also conceivable that other constituents of the dietary matrix might alter the
bioavailability of curcumin. When oral curcumin (2 g/kg) is coadministered to rats with l-piperoylpiperidine (piperine), a constituent of the fruit of the pepper vine (piper nigrum) that induces glucuronyl transferase enzymes, the systemic bioavailability of curcumin might be increased by as much as 154%.17

2.2. Clinical Pharmacokinetics and Metabolism

In comparison to the preclinical work summarized above, comprehensive pharmacokinetic data in humans do not exist. Healthy volunteers who ingested 2 g pure curcumin powder after fasting showed less than 10 ng/mL curcumin in their plasma 1 h postdose.17 In the same study, coingestion of curcumin with 20 mg of piperine appeared to increase the bioavailability of curcumin by 2000%. In a study of oral curcumin, patients with preinvasive malignant or high-risk premalignant conditions of the bladder, skin, cervix, stomach, or oral mucosa received 0.5–8 g curcumin by mouth daily for 3 months.18 Plasma curcumin concentrations were found to peak 1–2 h after intake and gradually declined within 12 hours. The 8-g/day dose resulted in a peak serum concentration of $1.75 \pm 0.80 \mu M$. When curcumin in micronized form was administered orally with orange juice at doses of 50–200 mg to 18 healthy volunteers, curcumin was not found in the plasma at or above the limit of quantitation (approximately 0.63 ng/mL).19

In a clinical phase I dose-escalation study using a standardized oral Curcuma extract comprised mainly of curcumin, doses up to 180 mg of curcumin per day were administered to patients with advanced colorectal cancer for up to 4 months without toxicity or detectable systemic bioavailability.20 In a follow-up study in 15 patients with advanced colorectal cancer refractory to standard chemotherapy, curcumin in the form of “Curcuminoids C3” (Sabinsa Corp., 90% curcumin) was consumed orally for up to 4 months at doses of curcumin between 0.45 and 3.6 g daily.21 Oral consumption of 3.6 g of curcumin per day resulted in levels of drug and glucuronide/sulfate conjugates in plasma near the limit of detection (5 pmol/mL). Curcumin and its conjugates were also detected in 24-h urine collections. In the six patients who had consumed 3.6 g curcumin, urinary levels (in \( \mu M \)) varied between 0.1 and 1.3 for curcumin, between 0.019 and 0.045 for curcumin sulfate, and between 0.21 and 0.51 for curcumin glucuronide. The presence of curcumin and its conjugates in the urine of patients taking 3.6 g of curcumin daily suggests that urinary curcumin/curcumin metabolites might serve as measures of compliance with treatment.

Exploratory studies have also been performed in patients undergoing operations for colorectal cancer who consented to have tissues analysed for research purposes.22,23 Twelve patients with confirmed colorectal cancer received oral curcumin at 0.45, 1.8, or 3.6 g/day for 7 days prior to surgery. Levels of agent-derived species were determined in blood and colorectal tissue obtained at the time of surgical resection. The mean concentrations of curcumin in normal and malignant colorectal tissue of patients who had ingested 3.6 g curcumin daily were 12.7 and 7.7 nmol/g tissue, respectively.22 Curcumin sulfate and curcumin glucuronide were also found in the intestinal tissue taken from these patients; trace levels of
curcumin were detected in peripheral blood samples. Compatible with the preclinical data presented earlier, these preliminary results in humans suggest that a daily dose of 3.6 g curcumin achieves measurable levels in colorectal tissue with negligible distribution of the parent drug outside of the gut. When 12 patients with liver metastases from colorectal cancer received oral curcumin (0–3.6 g) daily for 7 days prior to hepatic surgery, curcumin was not found in liver tissue resected 6–7 h after the last dose of curcumin, whereas trace levels of products of its metabolic reduction were detected. Levels of curcumin and glucuronide and sulfate conjugates in the low-nanomolar range were found in blood samples taken 1 h after the last dose. The results of this pilot study suggest that doses of oral curcumin required to produce hepatic levels sufficient to exert pharmacological activity are probably not feasible in humans.

To summarize the data from pilot and phase I clinical studies performed with curcumin, it appears that low systemic bioavailability following oral dosing is consistent with the findings in preclinical models presented earlier. Efficient first-pass and some degree of intestinal metabolism of curcumin, particularly glucuronidation and sulfation, might explain its poor systemic availability when administered via the oral route. A daily oral dose of 3.6 g of curcumin results in detectable levels in colorectal tissue, which might be sufficient to exert pharmacological activity, with negligible distribution of the parent drug in hepatic tissue or other tissues beyond the gastrointestinal tract.

3. PHARMACODYNAMICS AND SAFETY

3.1. Pharmacodynamics in Preclinical Models

Curcumin has been shown to exert a fascinating array of pharmacological effects in cells in vitro at physiologically attainable and supraphysiological concentrations (see Chapter 10). Table 1 lists some of these activities, many of which are highly relevant to the cancer chemopreventive activity and pharmacodynamic properties of curcumin. In the following subsections, evidence is reviewed pertaining to the ability of curcumin to interfere with carcinogenesis, drug- and carcinogen-metabolizing enzymes, and biological oxidative processes in rodents in vivo.

3.1.1. Inhibition of Carcinogenesis

Following oral administration, curcumin prevented cancer in the colon, skin, stomach, liver, lung, duodenum, soft palate, and breasts of rodents. In particular, the effects of dietary curcumin (0.05–2.0%) on colorectal carcinogenesis have been demonstrated in both carcinogen-induced and genetic rodent models. Curcumin inhibited carcinogenic initiation, as reflected by decreased levels of adducts induced by benzo[a]pyrene or by aflatoxin B1. In intestinal cancer induced in mice by azoxymethane, oral curcumin (2000 ppm) for 14 weeks produced a significant increase in the apoptotic histological index when compared to controls. In the azoxymethane-induced rat colon cancer model, dietary curcumin (0.8%)
Table 1. Molecular targets of curcumin in cells grown in vitro relevant to the chemoprevention of cancer.

| TARGETS | EFFECTS | REFERENCES |
|---------|---------|------------|
| Protein kinases (MAPK, JNK, PKA, PKC, src tyrosine kinase, IkBα kinase, growth factor receptor protein tyrosine kinases) | Inhibition, downregulation | 67 |
| Antiapoptotic proteins | Induction of cytochrome-c release, Bax cleavage, activation of caspase-3 and caspase-9, downregulation of Bcl-2 and BclX2 | 68–71 |
| Proinflammatory proteins | Downregulation of COX-2, 5-LOX, and iNOS | |
| Cytokines/growth factors | Downregulation of TNF, IL-6, IL-8, IL-12, and fibroblast growth factor-2 | 72–74 |
| Transcription factors | Suppression of NF-κB, STAT3, Egr-1, AP-1, and PPAR-γ, activation of β-catenin | 59, 60, 75 |
| Oxidant systems | Upregulation of heme oxygenase, glutathione transferases, downregulation of xanthine oxidase, scavenging reactive oxygen/superoxide | 76, 77 |
| Phase I and Phase II drug/carcinogen-metabolizing enzymes | Inhibition of CYP1A1 | 78, 79 |
| MMP-9 expression | | 80 |

Abbreviations: AP, activator protein; JNK, c-Jun NH2-terminal kinases; PK, protein kinase; COX, cyclooxygenase; LOX, lipooxygenase; NOS, nitric oxide synthase; NF, nuclear factor; TNF, tumor necrosis factor; IL, interleukin; PPAR, peroxisome proliferators-activated factor; CYP, cytochromes p450; MMP, matrix metalloproteinase; STAT, signal transducer and activator of transcription; EGR, early growth response; CYP, cytochromes p450.

Table 1. Molecular targets of curcumin in cells grown in vitro relevant to the chemoprevention of cancer.

halved the number of aberrant crypt foci compared with control.29 Genetic models, such as the multiple intestinal neoplasia (e.g. ApcMin) mouse, permit the study of the inhibition of the promotion phase of carcinogenesis. Curcumin interfered with adenoma formation in the ApcMin mouse, which harbors an adenomatous polyposis coli (APC) gene mutation and is a model of the human disease familial adenomatous polyposis.30 When administered in the diet at 0.1% and 0.2% for the animals’ lifetimes, a significant decrease in adenoma number was observed compared to control animals.3,31 The decrease after the latter dose was accompanied by downregulation of the expression of the enzyme cyclooxygenase-2 (COX-2) and attenuation of tissue oxidative status, as reflected by levels of the oxidative DNA adduct pyrimido-[1,2α]purin-10(3H)-one-2′-deoxyguanosine (M1dG).32 The dietary dose of 0.2%, which equates to approximately 300 mg/kg per day, furnished
only trace levels of curcumin and metabolites in the plasma, but concentrations of curcumin in the 100-nmol/g tissue range in the gastrointestinal mucosa. This result might provide a tentative "target concentration," although reliable strategies to extrapolate these levels to the equivalent levels in human gastrointestinal mucosa do not currently exist.

Topical application of curcumin (3 or 10 μmol curcumin, 5min prior to the application of carcinogen) has been shown to inhibit chemical carcinogenesis of the skin. In this series of studies, tumor initiation was induced by benzo[a]pyrene or 7,12-dimethylbenz[a]anthracene (DMBA) and tumor promotion was induced by 12-O-tetradecanoylphorbol-13-acetate. Potential mechanisms of these effects were considered to involve inhibition of arachidonic acid-induced inflammation, inhibition of hydrogen peroxide formation, and inhibition of ornithine decarboxylase activity/transcription, which is a rate-limiting step in polyamine biosynthesis.

Topical application of curcumin (10 mmol) three times weekly to the buccal pouch of Syrian golden hamsters has also demonstrated inhibition of DMBA-induced oral carcinogenesis. In this early example of "combinatorial chemoprevention," the effect of topical curcumin appeared to be enhanced by the concomitant consumption of green tea (6 mg tea solids/mL) for 18 weeks. Subsequent studies combining curcumin with other chemopreventive agents have also shown augmented growth inhibitory effects. It should also be noted that studies have also been performed that have demonstrated no attenuation of chemically induced carcinogenesis by curcumin. For example, dietary curcumin (500 ppm) did not affect prostate carcinogenesis in rats exposed to 3,2′-dimethyl-4-aminobiphenol (DMAB)- or 2-amino-1-methylimidazo[4,5-b]pyridine (PhilP). Although there are numerous reports in the published literature to suggest that curcumin augments the cytotoxicity of anticancer drugs such as paclitaxel in cells in vitro, observations that confirm this notion in vivo are lacking at present. In a human breast cancer xenograft model, nude mice bearing the human-derived MDA-MB-435 breast tumor received dietary curcumin (2%) after excision of the primary tumor: Curcumin consumption decreased the load of breast cancer metastases and concomitantly suppressed the expression of nuclear factor (NF)-κB, COX-2, and matrix metalloproteinase-9 (MMP-9) in the lung metastases that did form. Interestingly, certain rodent studies have suggested a potential for curcumin to confound unwanted detrimental effects of cytotoxic anticancer drugs. For example, curcumin administered to rats by gavage (100 or 200 mg/kg daily for 7 days) ameliorated chromosomal mutations induced by cyclophosphamide in the bone marrow. The diversity of the biological actions of curcumin in mammalian species was recently emphasized by a noteworthy study demonstrating its beneficial effects in mice homozygous for a complete knockout of a gene linked with cystic fibrosis.

3.1.2. Effects on Carcinogen-Metabolizing Enzymes and Oxidant Systems

Phase II drug- and carcinogen metabolizing enzymes such as glutathione-S-transferases (GST) render xenobiotics more water soluble, thus facilitating their excretion. Because induction of phase II enzymes stimulates carcinogen excretion,
it is generally thought to confer a protective effect. Epoxide hydrolase and various hepatic GST isoenzymes were significantly increased upon curcumin feeding in mice; in other studies, total GST activity was induced by dietary curcumin in both mice and rats. A structure–activity study of the potency of curcumin analogues suggested that their ability to induce phase II enzymes might be linked to the presence of the phenolic hydroxy and β-diketone groups. Although induction of GST activity might be desirable in the prevention of the early stages of carcinogenesis, in patients with advanced malignancy GST isozymes might be aberrantly overexpressed and linked with resistance to chemotherapy. Paradoxically, curcumin also appears capable of inhibiting GST isoenzyme expression. An example is provided by a study of GSTP1 expression in leukemia cells, in which an association was observed between the level of inhibition by curcumin and the induction of apoptosis.

Nitric oxide (NO) is a short-lived, lipophilic molecule generated from l-arginine by various NADPH-dependent enzymes called NO synthases (NOS). NO is involved physiologically in vasorelaxation, neurotransmission, inhibition of platelet aggregation, immune defense, and intracellular signaling. NO has an unpaired electron and is therefore a free-radical species; its bioactivity is related to the production of many reactive intermediates and many of these reactive nitrogen species are capable of damaging DNA or hindering DNA repair. Peak inducible NOS (iNOS) activity might relate to the transition of colonic adenomas to carcinomas. Upregulation of COX-2 via NF-κB or activator protein (AP)-1 pathways, or increasing intracellular concentrations of reduced glutathione, appears to confer resistance to NO-induced apoptosis in malignant cells.

3.2. Clinical Pharmacodynamics

3.2.1. Dose–Effect Relationships

Substantial data supporting a dose–response relationship for any biomarker of the pharmacological efficacy of curcumin in humans are currently lacking. Nevertheless, several observations in volunteers and patients suggest that curcumin might possess systemic biological activity at low oral doses. A single oral dose of 20 mg of curcumin appeared to induce contraction of the gallbladder as adjudged by ultrasound scanning in human volunteers, compared to an amyllum placebo. Two potential surrogate biomarkers of the efficacy of curcumin were evaluated in the blood of patients with advanced colorectal cancer who received up to 180 mg
PHARMACOKINETICS AND PHARMACODYNAMICS 461

of curcumin per day for up to 4 months. In three patients on 36 mg of curcumin daily, lymphocytic activity of GST was decreased with time to reach 41% of control (untreated) on day 29 of treatment. This decline was not observed at the higher dose levels and was not reproduced in a subsequent study of higher doses in the patients with the same disease. Similarly, consumption of curcumin did not affect blood leukocyte levels of the oxidative DNA adduct, pyrimido-[1,2α]purin-10(3H)-one-2′-deoxyguanosine (M1dG), although interesting observations were made regarding GST isoenzyme genotypes and baseline leukocytic M1dG adduct levels.

In contrast to leukocyte M1dG and GST, the inducibility of prostaglandin (PG) E2 production in whole blood ex vivo might represent a surrogate biomarker for assessing the pharmacological activity of curcumin at a systemic level. COX-2 is an important target for chemoprevention, and its pharmacological modulation might hold implications for cancer treatment. At least part of the effect of curcumin on inducible PGE2 production in human blood can be attributed to inhibition of COX2 transcription, which might be due to the inhibition of the NF-κB-activating enzymes IKK-α/β. The effect of curcumin described in an ex vivo assay developed using blood from healthy volunteers was associated with a daily oral dose which furnished plasma levels in the 10−8 M range in patients with advanced colorectal cancer. This concentration of curcumin is less than a hundredth of that shown in vitro to elicit an effect in blood or colon cells. Blood was taken immediately predose or 1 h postdose on days 1, 2, 8, and 29 of treatment with 3.6 g of curcumin daily. Following the addition of acetylsalicylic acid (200 μM) to eliminate COX-1 activity, whole blood was incubated for 24 h in the presence of lipopolysaccharide (LPS, 10 μg/mL). In the same trial, oral administration of curcumin did not impact on nonstimulated PGE2 levels in leukocytes, nor did doses of 0.45–1.8 g daily alter LPS-induced PGE2. In contrast, consumption of 3.6 g of curcumin daily affected LPS-induced PGE2 levels. When values obtained immediately predose or 1 h postdose on days 1, 2, 8, and 29 were pooled for the six patients consuming this dose, PGE2 levels observed postdose were 46% lower than those measured immediately predosing. The difference reached significance on days 1 and 29 of treatment but not on day 2 or day 8; this discrepancy could not be explained scientifically by the study investigators. Although these results tentatively suggest that consumption of 3.6 g of curcumin daily was linked with inhibition of PGE2 induction in blood taken postdose compared to blood taken predose, overall time-dependent trends were not identified and dose–response was not demonstrated for this biomarker. Although the ex vivo assay described using human blood is limited in its clinical application by the high interindividual and high intra-individual variability, the results suggest the feasibility and potential utility of measurement of PGE2 levels in target tissue as a biomarker to reflect potential anticancer activity of curcumin. It should also be noted that curcumin sulfate and products of metabolic reduction of curcumin also inhibit PGE2 production in colon cells grown in vitro, although their inhibitory potency appeared lower than that of parent curcumin in colon cancer cells. Similarly, the activity of curcumin metabolites, relative to the parent compound, on levels of enzymes
involved in glucose and lipid metabolism has been demonstrated in other preclinical models.59

In parallel with studies in which potential changes in blood taken from patients with advanced colorectal cancer were analyzed, exploratory clinical investigations have also been performed in patients undergoing operations for resectable colorectal cancer in whom colorectal and hepatic tissues have been analyzed to study potential pharmacodynamic effects.22,23 Twelve patients with confirmed colorectal carcinoma received oral curcumin at 0.45, 1.8, or 3.6 g/day for 7 days prior to surgery. Whereas ingestion of 3.6 g of curcumin daily for 1 week affected M1dG levels in patients’ colorectal tissue, it did not decrease COX-2 protein expression in this tissue.22 Interestingly, M1dG adduct levels were 2.5-fold higher in malignant colorectal tissue than normal colorectal mucosa. Whereas administration of curcumin did not affect M1dG levels in normal colorectal mucosa, it caused a 58% decrease in adduct levels in malignant colorectal tissue. The effect was only observed at the highest dose level; it requires replication in a larger study before definite conclusions can be made. As in the above-presented results, a dose–response relationship was not established. A similar study of hepatic tissue with the same oral dosing regime suggested that the levels of curcumin attained in normal and malignant liver tissues were insufficient to exert biological activity.23

3.2.2. Anti-inflammation

Data from preclinical models would suggest that suppression by curcumin of the inflammatory response might involve inhibition of the induction of COX-2 and iNOS and the production of cytokines such as interferon-γ, at least in part due to its suppression of the Janus kinase (JAK)–STAT signaling cascade via its effect on the Src homology 2 domain–containing protein tyrosine phosphatases (SHP)-2.59 Compatible with these immunological effects, data from an experiment involving chemical-induced inflammatory bowel disease in mice suggested that curcumin might be of value in the treatment of this disease.60

A number of studies have addressed the effect of oral curcumin on inflammatory diseases in humans. Curcumin at 400 mg three times daily for 5 days caused a significant anti-inflammatory effect measured objectively and subjectively in postoperative patients.61 In a double blind study, 300 mg curcumin was administered four times daily to 18 patients with rheumatoid arthritis for 2 weeks.62 The authors reported a significant improvement in their inflammatory symptoms without apparent toxicity.62 Ten patients with inflammatory bowel disease received pure curcumin at doses between 0.55 and 1.65 g daily for up to 2 months; all patients showed encouraging clinical improvement.63

One research team has studied the effects of oral curcumin on ophthalmological conditions. In their first study, 375 mg of curcumin was administered three times daily to patients with chronic anterior uveitis for 12 weeks, resulting in a suggestion of improvement in the condition.64 In their second study, the same dose of curcumin was administered to eight patients with idiopathic inflammatory orbital pseudotumors for 6–22 months.65 Complete responses were observed in half of
the patients up to 2 years of follow-up. Although histopathological details were not presented in this report, inflammatory orbital pseudotumor is currently regarded as low-grade non-Hodgkin's lymphoma in most cases; hence, this result hints at potential anticancer activity.

3.2.3. Anticarcinogenesis

Induction of apoptosis by curcumin in cancer cells is mediated via a variety of mechanisms (see Chapter 11). Such findings suggest that curcumin might have some potential for chemotherapeutic activity in the treatment of cancer. In this regard, there are published anecdotes of the activity of curcumin as a topical treatment for cancer. One example is the use of turmeric as a treatment for oral cancers and leukoplakia, in which the authors report a significant reduction in the size of the lesions in 10% of the 62 patients treated. Unfortunately, there was no control group, no assessment of anti-inflammatory activity and no chemical analysis of the preparation applied in this study.

In a pilot trial performed in the United Kingdom, low doses (36–180 mg) of curcumin were administered daily for up to 4 months to patients with progressive advanced colorectal cancer, refractory to standard chemotherapies. Five out of 15 patients treated in this study experienced radiologically stable disease for 3 months or longer. In one patient, venous levels of the tumor marker carcinoembryonic antigen (CEA) decreased during treatment. In a subsequent study in patients with progressive advanced colorectal cancer, doses of 0.45–3.6 g of curcumin were administered daily. Radiologically stable disease was observed in 2 out of 15 patients for up to 4 months of treatment.

Considering both of these studies together, although there were perhaps hints of cytostatic activity using macroscopic measures in these patients, the variable natural history of colorectal cancer renders the results difficult to interpret.

In a study performed in Taiwan, the potential anticancer activity of 1–8 g of curcumin (500 mg of curcumin per capsule, 99% pure) daily for 3 months was studied in patients with preinvasive malignant or high-risk premalignant conditions of the bladder, skin, cervix, stomach, or oral mucosa. Doses above 8 g per day were not tolerated by patients because of the excessive number of capsules that had to be consumed daily. Histological improvement was noted in one of two patients with presumed bladder carcinoma in situ, two of seven patients with oral leukoplakia, one of six patients with stomach metaplasia, one of four patients with cervical intraepithelial neoplasia (CIN), and two of six patients with Bowen’s disease of the skin. Conversely, in one of four patients with CIN and one of seven patients with oral leukoplakia, the treatment failed to prevent the development of invasive malignancy during the 3-month study period. The small numbers of patients with each condition, the variable natural history of premalignant lesions, and the lack of blinding of the interpreting pathologists make it difficult to draw definite conclusions. Nevertheless, the histological representations of treatment effects presented in this report reemphasise the biological activity that curcumin might possess in a range of human tissues.
3.3. Safety

Although the experience of using curcumin in the diet for many centuries inspires confidence in its safety, one cannot assume a priori that diet-derived agents are innocuous when administered as pharmaceutical formulations at doses that generally exceed those consumed in the dietary matrix. Anecdotal reports suggest that dietary consumption of turmeric up to 1.5 g per person per day, equating to a probable maximum of 150 mg of curcumin daily, are not associated with adverse effects in humans.2 Studies of curcumin in animals have confirmed a lack of significant toxicity. In an early investigation, doses up to 5 g/kg were administered orally to Sprague–Dawley rats, resulting in no demonstrable toxicity.8 Systematic preclinical safety studies orchestrated by the US National Cancer Institute (NCI) did not discover any adverse effects in rats, dogs, or monkeys at doses of up to 3.5 g/kg administered up to 3 months in duration.24 One early report suggested a potentially ulcerogenic effect of dietary curcumin in the stomach of the albino rat,67 but this finding has not been replicated in subsequent rodent studies. In more recent preclinical investigations of dietary curcumin, toxicity has not been observed at 2% of the diet in rats16 (approximately 1.2 g/kg) or at 0.2% of the diet in mice31 (approximately 300 mg/kg).

Only a few clinical studies of oral curcumin and curcuminoids have reported discernible adverse effects. Unfortunately, many investigators have not stated in their reports which methods or scales have been used to assess potential toxicity. Administration of 1.2–2.1 g of oral curcumin daily to patients with rheumatoid arthritis for 2–6 weeks did not result in any adverse effects.62 Similarly, 10 patients with inflammatory bowel disease received pure curcumin daily at between 0.55 and 1.65 g for up to 2 months without clinical manifestations of toxicity.63 No significant adverse events were observed in a study of up to 8 g of oral curcumin daily for 3 months in patients with preinvasive malignant or high-risk premalignant conditions.18 In patients with advanced colorectal cancer, curcumin was well tolerated at all dose levels up to 3.6 g daily for up to 4 months.21 Two types of gastrointestinal adverse event were reported by patients in this study, which were probably related to curcumin consumption: Two patients (on 0.45 and 3.6 g curcumin daily) developed diarrhea (NCI grades 1 and 2) 1 month and 4 months into treatment, respectively. One patient, who was receiving 0.9 g of curcumin daily, experienced nausea (NCI toxicity grade 2), which resolved spontaneously despite continuation of treatment. Two abnormalities were detected in blood tests, both of which might have been related either to curcumin treatment or malignant disease progression: Increases in serum alkaline phosphatase levels were observed in four patients and in serum lactate dehydrogenase in three patients.

Overall, the comprehensive preclinical data and the phase I clinical data currently available inspire cautious confidence that curcumin possesses a safety spectrum suitable for a chemopreventive agent. In the planning of future studies using curcumin in any patient group, special attention must to be paid to the systematic documentation of potential toxicities that ultimately might influence the feasibility
4. CONCLUSIONS

Curcumin possesses anti-inflammatory and anticarcinogenic properties in rodent models and there are suggestions of related pharmacodynamic effects in a few clinical pilot studies. Many of these activities can be attributed to its potent antioxidant capacity, its inhibition of cell signaling pathways at multiple levels, and its diverse effects on cellular enzymes, angiogenesis, and cell adhesion. In particular, the ability of curcumin to affect gene transcription and induce apoptosis in malignant cells advocates its potential utility in cancer chemoprevention and perhaps chemotherapy. Phase I clinical data have confirmed that the low systemic bioavailability of curcumin following oral dosing limits the tissues that the parent compound can reach at efficacious concentrations to exert beneficial effects. Nevertheless, the attainment of physiologically active levels of curcumin in the gastrointestinal tract, particularly the colon and rectum, has been demonstrated in animals and humans. In view of the pharmacological properties of curcumin presented here, its phase II clinical evaluation in individuals at risk of developing cancers of the gastrointestinal tract appears opportune.

REFERENCES

1. B. Brouk, *Plants Consumed by Man*. New York: Academic Press, 1975, p. 331.
2. D. Eigner and D. Sholz, Ferula asa–foetida and curcuma longa in traditional medical treatment and diet in Nepal. *J Ethnopharmacol* 67, 1–6 (1999).
3. J. Milobedzka, V. Kostanec, and V. Lampe, Structure. *Chem Ber* 43, 2163 (1910).
4. D. D. Heath, F. Khwaja, and C. L. Rock, Curcumin content of turmeric and curry powders. *FASEB J* 18, A125 (2004).
5. H. P. Ammon and M. A. Wahl, Pharmacology of curcuma longa. *Planta Med* 57, 1–7 (1991).
6. B. B. Aggarwal, A. Kumar, and A. C. Bharti, Anticancer potential of curcumin: Preclinical and clinical studies. *Anticancer Res* 23, 363–398 (2003).
7. B. Joe, M. Vijaykumar, and B. R. Lokesh, Biological properties of curcumin: Cellular and molecular mechanisms of action. *Crit Rev Food Sci Nutr* 44, 97–111 (2004).
8. B. Wahlstrom and G. Blennow, A study on the fate of curcumin in the rat. *Acta Pharmacol Toxicol* 43, 86–92 (1978).
9. V. Ravindranath and N. Chandrasekhar, Absorption and tissue distribution of curcumin in rats. *Toxicology* 16, 259–265 (1980).
10. V. Ravindranath and N. Chandrasekhar, In vitro studies on the intestinal absorption of curcumin in rats. *Toxicology* 20, 251–257 (1981).
11. V. Ravindranath and N. Chandrasekhar, Metabolism of curcumin: Studies with [3H] curcumin. *Toxicology* 22, 337–344 (1981).
12. G. M. Holder, J. L. Plummer, and A. J. Ryan, The metabolism and excretion of curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] in the rat. *Xenobiotica* **8**, 761–768 (1978).

13. M. H. Pan, T. M. Huang, and J. K. Lin, Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab Dispos* **27**, 486–494 (1999).

14. C. Ireson, S. Orr, D. J. L. Jones, et al., Characterization of metabolites of the chemopreventive agent curcumin in humans and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Res* **61**, 1058–1064 (2001).

15. C. Ireson, D. J. L. Jones, S. Orr, M. W. H. Coughtrie, D. Boocock, M. L. Williams, P. B. Farmer, W. P. Steward, and A. J. Gescher, Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. *Cancer Epidemiol Biomarkers Prev* **11**, 97–104 (2002).

16. R. A. Sharma, C. R. Ireson, R. D. Verschoyle, 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* **7**, 1452–1458 (2001).

17. G. Shoba, D. Joy, T. Joseph, M. Majeed, R. Rajendran, and P. S. S. R. Srinivas, Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med* **64**, 353–356 (1998).

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

19. M. T. Ruffin, D. P. Normolle, D. D. Heath, J. M. Bailey, S. I. Murray, M. E. Boggs, J. A. Crowell, C. L. Rock, and D. E. Brenner, Dose escalation of curcumin in healthy adults. *Cancer Epidemiol Biomarkers Prev* **12**(Pt 2 Suppl S), 1324S–1324S (2003).

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

21. R. A. Sharma, S. A. Euden, S. L. Platton, et al., Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance. *Clin Cancer Res* **10**, 6847–6854 (2004).

22. G. Garcea, D. P. Berry, D. J. L. Jones, 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* **14**, 120–125 (2005).

23. G. Garcea, D. J. L. Jones, R. Singh, et al., Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. *Br J Cancer* **90**, 1011–1015 (2004).

24. NCI, DCP, Clinical development plan: Curcumin. *J Cell Biochem* **26S**, 72–85 (1996).

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

26. K. B. Soni, A. Rajan, and R. Kuttan, Reversal of aflatoxin induced liver damage by turmeric and curcumin. *Cancer Lett* **66**, 115–121 (1992).

27. T. Kawamori, R. Lubet, V. E. Steele, et al., Chemopreventative effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer. *Cancer Res* **59**, 597–601 (1999).
28. H. S. Samaha, G. J. Kelloff, V. Steele, C. V. Rao, and B. S. Reddy, 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* 57, 1301–1305 (1997).

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

30. C. Luongo, A. R. Moser, S. Gledhill, and W. F Dove, Loss of Apc(+) in intestinal adenosas from Min mice. *Cancer Res* 54, 5947–5952 (1994).

31. S. Perkins, R. D. Verschoyle, K. A. Hill, I. Parveen, M. D. Threadgill, R. A. Sharma, M. L. Williams, W. P. Steward, and A. J. Gescher, Chemopreventive efficacy and pharmacokinetics of curcumin in the Min/+ mouse, a model of familial adenomatous polyposis. *Cancer Epidemiol Biomarkers Prev* 11, 535–540 (2002).

32. R. G. Tunstall, R. A. Sharma, S. Perkins, S. Sale, R. Singh, P. B. Farmer, W. P. Steward, and A. J. Gescher, Cyclooxygenase-2 expression and oxidative DNA adducts in murine intestinal adenomas: Modification by dietary curcumin and implications for clinical trials. *Eur J Cancer* 42, 415–421 (2006).

33. A. H. Conney, Enzyme induction and dietary chemicals as approaches to cancer chemoprevention: The seventh DeWitt S. Goodman Lecture. *Cancer Res* 63, 7005–7031 (2003).

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

35. K. Imaida, S. Tamano, K. Kato, Y. Ikeda, M. Asamoto, S. Takahashi, Z. Nir, M. Murakoshi, H. Nishino, and T. Shirai, Lack of chemopreventive effects of lycopene and curcumin on experimental rat prostate carcinogenesis. *Carcinogenesis* 22, 467–472 (2001).

36. B. B. Aggarwal, S. Shishodia, Y. Takada, S. Banerjee, R. A. Newman, C. E. Bueso-Ramos, and J. E. Price, Curcumin suppresses the paclitaxel-induced nuclear factor-kappa B pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice. *Clin Cancer Res* 11, 7490–7498 (2005).

37. S. V. Bava, V. T. Puliappadamba, A. Deepti, A. Nair, D. Karunagaran, and R. J. Anto, Sensitization of taxol-induced apoptosis by curcumin involves down-regulation of nuclear factor-kappa B and the serine/threonine kinase Akt and is independent of tubulin polymerization. *J Biol Chem* 280, 6301–6308 (2005).

38. Y. Shukla, A. Arora, and P. Taneja, Antimutagenic potential of curcumin on chromosomal aberrations in Wistar rats. *Mutat Res: Genet Toxicol Environ Mutag* 515, 197–202 (2002).

39. M. E. Egan, M. Pearson, S. A. Weiner, et al., Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. *Science* 304, 600–602 (2004).

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

41. M. Susan and M.A. Rao, Induction of glutathione S-transferase activity by curcumin in mice. *Drug Res* 42, 962–964 (1992).

42. J. T. Piper, S. S. Singhal, M. Salameh, R. T. Torman, Y. C. Awasthi, and S. Awasthi, Mechanisms of anticarcinogenic properties of curcumin: The effect of curcumin on glutathione linked detoxification enzymes in rat liver. *Int J Biochem Cell Biol* 30, 445–456 (1998).
43. W. A. Nijhoff, G. M. Groen, and W. H. M. Peters, Induction of rat hepatic and intestinal glutathione S-transferases and glutathione by dietary naturally occurring anticarcino-
gens. *Int J Oncol* 3, 1131–1139 (1993).
44. A. T. Dinkova-Kostova and P. Talalay, Relation of structure of curcumin analogs to
their potencies as inducers of Phase 2 detoxification enzymes. *Carcinogenesis* 20,
911–914 (1999).
45. J. D. Hayes and D. J. Pulford, The glutathione S-transferases supergene family. *Crit
Rev Biochem Mol Biol* 30, 445–600 (1995).
46. A. Duvoix, S. Delhalle, R. Blassius, et al., Effect of chemopreventive agents on glu-
tathione S-transferase P1-1 gene expression mechanisms via activating protein 1 and
nuclear factor kappaB inhibition. *Biochem Pharmacol* 68, 1101–1111 (2004).
47. P. K. Lala and C. Chakraborty, Role of nitric oxide in carcinogenesis and tumour
progression. *Lancet Oncol* 2, 149–156 (2001).
48. T. deRojas-Walker, S. Tamir, H. Ji, J. S. Wishnok, and S. R. Tannenbaum, Nitric oxide
induces oxidative damage in addition to deamination in macrophage DNA. *Chem Res
Toxicol* 8, 473–477 (1995).
49. M. Graziewicz, D. A. Wink, and F. Laval, Nitric oxide inhibits DNA ligase activity:
Potential mechanisms for NO-mediated DNA damage. *Carcinogenesis* 17, 2501–2505
(1996).
50. S. Ambs, W. P. Bennett, W. G. Merrium, et al., Relationship between p53 mutations
and inducible nitric oxide synthase expression in human colorectal cancer. *J Natl
Cancer Inst* 91, 86–88; reply 1510–1511 (1999).
51. A. Von Knethen and B. Brune B, Cyclooxygenase-2: An essential regulator of NO-
mediated apoptosis. *FASEB J* 11, 887–895 (1997).
52. A. Von Knethen, D. Callsen, and B. Brune, NF-κB and AP-1 activation by nitric oxide
attenuated apoptotic death in RAW 264.7 macrophages. *Mol Biol Cell* 10, 361–370
(1999).
53. I. Brouet and H. Ohshima, Curcumin, an anti-tumour promoter and anti-inflammatory
agent, inhibits induction of nitric oxide synthase in activated macrophages. *Biochem
Biophys Res Commun* 206, 533–540 (1995).
54. M. M. Chan, H. I. Huang, M. R. Fenton, and D. Fong, *In vivo* inhibition of nitric
oxide synthase gene expression by curcumin, a cancer preventive natural product with
anti-inflammatory properties. *Biochem Pharmacol* 55, 1955–1962 (1998).
55. A. Raysid and A. Lelo, The effect of curcumin and placebo on human gall-bladder
function: An ultrasound study. *Aliment Pharmacol Ther* 13, 245–249 (1999).
56. S. M. Plummer, K. A. Hill, M. F. W. Festing, W. P. Steward, A. J. Gescher, and R. A.
Sharma, Clinical development of leukocyte cyclooxygenase 2 activity as a systemic
biomarker for cancer chemopreventive agents. *Cancer Epidemiol Biomarkers Prev*
10, 1295–1299 (2001).
57. S. M. Plummer, K. A. Holloway, M. M. Manson, et al., Inhibition of cyclo-oxygenase
2 expression in colon cells by the chemopreventive agent curcumin involves inhibition
of NF-κB activation via the NIK/IKK signalling complex. *Oncogene* 18, 6013–6020
(1999).
58. F. Zhang, N. K. Altorki, J. R. Mestre, et al., Curcumin inhibits cyclooxygenase-2
transcription in bile acid- and phorbol ester-treated human gastrointestinal epithelial
cells. *Carcinogenesis* 20, 445–451 (1999).
59. A. C. Bharti, N. Donato, and B. B. Aggarwal, Curcumin (diferuloylmethane) inhibits
constitutive and IL-6-inducible STAT3 phosphorylation in human multiple myeloma
cells. *J Immunol* 171, 3863–3871 (2003).
60. K. Sugimoto, H. Hanai, K. Tozawa, et al., Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. *Gastroenterology* **123**, 1912–1922 (2002).
61. R. R. Satoskar, S. J. Shah, and S. G. Shenoy, Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with post-operative inflammation. *Int J Clin Pharmacol Ther Toxicol* **24**, 651–654 (1986).
62. S. D. Deodhar, R. Sethi, and R. C. Srimal, Preliminary study on antiinflammatory activity of curcumin (diferuloyl methane). *Indian J Med Res* **71**, 632–634 (1980).
63. P. R. Holt, S. Katz, and R. Kirshoff, Curcumin therapy in inflammatory bowel disease: A pilot study. *Dig Dis Sci* **11**, 2191–2193 (2005).
64. B. Lal, A. K. Kapoor, O. P. Asthana, et al., Efficacy of curcumin in the management of chronic anterior uveitis. *Phytother Res* **13**, 318–322 (1999).
65. B. Lal, A. K. Kapoor, P. K. Agrawal, et al., Role of curcumin in idiopathic inflammatory orbital pseudotumours. *Phytother Res* **14**, 443–447 (2000).
66. R. Kuttan, P. C. Sudheeran, and C. D. Josph, Turmeric and curcumin as topical agents in cancer therapy. *Tumori* **73**, 29–31 (1987).
67. W. H. Chan and H. Wu, Anti-apoptotic effects of curcumin on photosensitized human epidermal carcinoma A431 cells. *J Cell Biochem* **92**, 200–212 (2004).
68. M. C. Jiang, H. F. Yang Yen, J. J. Y. Yen, et al., Curcumin induces apoptosis in immortalized NIH 3T3 and malignant cancer cell lines. *Nutr Cancer* **26**, 111–120 (1996).
69. C. H. Yan, M. S. Jamaluddin, B. Aggarwal, J. Myers, and D. D. Boyd, Gene expression profiling identifies activating transcription factor 3 as a novel contributor to the proapoptotic effect of curcumin. *Mol Cancer Therapeut*. **4**, 233–241 (2005).
70. M. L. Kuo, T. S. Huang, and J. K. Lin, Curcumin, an antioxidant and anti-tumor promoter, induces apoptosis in human leukemia cells. *Biochim Biophys Acta* **1317**, 95–100 (1996).
71. G. P. Collett and F. C. Campbell, Curcumin induces c-jun N-terminal kinase-dependent apoptosis in HCT116 human colon cancer cells. *Carcinogenesis* **25**, 2183–2189 (2004).
72. M. M. Y. Chan, Inhibition of tumor necrosis factor by curcumin, a phytochemical. *Biochem Pharmacol* **49**, 1551–1556 (1995).
73. Y. Abe, S. Hashimoto, and T. Horie, Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. *Pharmacol Res* **39**, 41–47 (1999).
74. B. Gupta and B. Ghosh, Curcuma longa inhibits TNF-alpha induced expression of adhesion molecules on human umbilical vein endothelial cells. *Int J Immunopharmacol* **21**, 745–757 (1999).
75. Y. Moon, W. C. Glasgow, and T. E. Eling, Curcumin suppresses interleukin 1 beta-mediated microsomal prostaglandin E synthase 1 by altering early growth response gene 1 and other signaling pathways. *J Pharmacol Exp Ther* **315**, 788–795 (2005).
76. E. Balogun, M. Hoque, P. F. Gong, E. Killeen, C. J. Green, R. Foresti, J. Alam, and R. Motterlini, Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. *Biochem J* **371**, 887–895 (2003).
77. C. K. Andreadi, L. M. Howells, P. A. Atherfold, and M. M. Manson, Involvement of Nrf2, p38, B-Raf, and nuclear factor-kappa B, but not phosphatidylinositol 3-kinase, in induction of hemoxegenase-1 by dietary polyphenols. *Mol Pharmacol* **69**, 1033–1040 (2006).
78. P. F. Firozi, V. S. Aboobaker, and R. K. Bhattacharya, Action of curcumin on the cytochrome P450-system catalyzing the activation of aflatoxin B1. *Chem-Biol Interact* **100**, 41–51 (1996).

79. H. P. Ciolino, P. J. Daschner, T. T. Wang, and G. C. Yeh, Effect of curcumin on the aryl hydrocarbon receptor and cytochrome P450 1A1 in MCF-7 human breast carcinoma cells. *Biochem Pharmacol* **56**, 197–206 (1998).

80. M. S. Woo, S. H. Jung, S. Y. Kim, J. W. Hyun, K. H. Ko, W. K. Kim, and H. S. Kim, Curcumin suppresses phorbol ester-induced matrix metalloproteinase-9 expression by inhibiting the PKC to MAPK signaling pathways in human astrogloma cells. *Biochem Biophys Res Commun* **335**, 1017–1025 (2005).