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Comprehensive Invited Review

Curcumin: Preventive and Therapeutic Properties in Laboratory Studies and Clinical Trials

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ABSTRACT

Curcumin is a natural polyphenol used in ancient Asian medicine. Since the first article referring to the use of curcumin to treat human disease was published in *The Lancet* in 1937, >2,600 research studies using curcumin or turmeric have been published in English language journals. The mechanisms implicated in the inhibition of tumorigenesis by curcumin are diverse and appear to involve a combination of antiinflammatory, antioxidant, immunomodulatory, proapoptotic, and antiangiogenic properties *via* pleiotropic effects on genes and cell-signaling pathways at multiple levels. The potentially adverse sequelae of curcumin's effects on proapoptotic genes, particularly *p53*, represent a cause for current debate. When curcumin is combined with some cytotoxic drugs or certain other diet-derived polyphenols, synergistic effects have been demonstrated. Although curcumin's low systemic bioavailability after oral dosing may limit access of sufficient concentrations for pharmacologic effects in tissues outside the gastrointestinal tract, chemical analogues and novel delivery methods are in preclinical development to overcome this barrier. This article provides an overview of the extensive published literature on the use of curcumin as a therapy for malignant and inflammatory diseases and its potential use in the treatment of degenerative neurologic diseases, cystic fibrosis, and cardiovascular diseases. Despite the breadth of the coverage, particular emphasis is placed on the prevention and treatment of human cancers. *Antioxid. Redox Signal.* 10, 511–545.

1. INTRODUCTION

The importance of diet-derived agents in the maintenance of health should not be underestimated. The American Department of Health and Human Services (HHS), jointly with the Department of Agriculture (USDA), has been publishing dietary guidelines every 5 years since 1980. Based on published mortality data, the leading causes of death in the United States are cardiovascular diseases, malignant neoplasms, and cerebrovascular diseases, accounting for 55% of all deaths in 2003 (32). The HHS and USDA have suggested targets that aim for 16% and 9% reductions of mortality in men and women, respectively, by the adoption of desirable dietary behaviors (264).

Over the past decade, a significant increase has been noted in public and scientific interest in the beneficial effects of chemicals derived from plants, known as phytochemicals, and their role in the maintenance of health and prevention of disease. The term "nutraceutical" was coined in 1989 by Dr. Stephen DeFelice as a substance that either is a food or is a part of a food that provides medical or health benefits, including the prevention and treatment of disease.

Polyphenols are among the lead chemical substances that fulfill this definition. Consequently, their potential preventive and therapeutic properties have been studied extensively. Polyphenols are derived from many components of the human diet, including dark chocolate, peanuts, green and black tea, red wine, olive oil, and the spice, turmeric. Many of these natural substances, which were traditionally used in ancient medicines for their antiinflammatory and antioxidant actions, are now being investigated as cardioprotective, antiproliferative, preventive, or other biologic phytochemicals, either alone or as combinations of agents. In particular, traditional agents derived from ancient Hindu medicine, such as curcumin from turmeric or boswellic acid from gum resin, have been shown to have biologic activity at physiologically relevant concentrations in preclinical model systems (253). With regard to the chemoprevention and therapy of many diseases, particularly cancer, this article reviews the extensive published literature on the use of the natural polyphenol, curcumin, as a single agent and in combinatorial chemoprevention and treatment.

Curcumin is a component of turmeric, the yellow spice derived from the roots (rhizomes) of the plant *Curcuma longa*, the formal name in the Linnaeus system of classification. The *Curcuma* genus belongs to the division of Magnoliophyta, class of Liliopsyda, subclass of Zingiberidae, order Zingiberales, and family Zingiberaceae. Members of the same family include zingiber (ginger). *Curcuma longa* is a short-stemmed perennial, which grows to ~100 cm in height. It has curved leaves and oblong, ovate, or cylindrical rhizomes (see Fig. 1). *Curcuma longa* grows naturally throughout the Indian subcontinent and in tropical countries, particularly Southeast Asia.

The powdered colored extracts of dried roots, often called turmeric, ukon, or haldi, contain three principal curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Turmeric and curcumin have at least 76 synonyms, listed in WHO monograph 1999, the most common of which are *haldi*

FIG. 1. *Curcuma longa* plant showing rhizome and stem. Reproduction of original figure from Kings American Dispensatory, 1898, with permission.

(in Hindi), *haridra* or *gauri* (in Sanskrit), *chiang huang* (in Chinese), *ukon* (in Japanese), *kurkum* (in Arabic), Indian saffron, and yellow root (280). India produces most of the world's supply of turmeric, of which it consumes 90–95% and exports the remainder (10, 244). Turmeric and its chemical constituents have been used in Asian cookery and traditional medicine for thousands of years. More recently, they have been used by the food industry as additives (*e.g.*, in "curry" in the U.K.), flavorings, preservatives, and coloring agents (*e.g.*, in mustard, margarine, soft drinks, and beverages). As a safe coloring agent, curcumin is listed in the international numbering system for food additives with the code E100. Nonmedical applications of turmeric include cosmetic, particularly in Hindu rituals and ceremonies, and aromatic.

A. History

Curcumin was first extracted in impure form in 1815 by Vogel and Pelletier, but it was not until 1870 that it was prepared in pure and crystalline form by Daube, followed by Ivanov and Gajevsky almost three decades later (80). Roughley and Whiting determined its chemical structure in 1973 (39, 170). The first recorded article referring to *Curcuma* spp., "de curcuma officinarum," was published in 1748 by Loeber (185). The first pharmacologic review of curcumin was published 67 years later (267). Notably, the first article referring to the use of curcumin in human disease was published in *The Lancet* in 1937 (185). In this pioneering study, Oppenheimer and colleagues studied the effect of curcumin in patients with biliary diseases. They treated 67 patients with "curcunat dragées" containing 300–800 mg daily of curcumin for 3 weeks in divided escalating doses after meals. They reported symptomatic improvement in all cases and radiologic improvement by cholecystogram in 18 patients. Interestingly, this finding of curcumin's effect on gallbladder function was replicated by investigators in Indonesia more than half a century later by using contemporary ultrasonographic methods (204, 205).

B. At the crossroads of alternative and mainstream medicine

Turmeric has been used for thousand of years in Ayurvedic and traditional Chinese medicine. Its use was confined to the Asian continent until the 12th to 13th century AD, when it was introduced to western countries by Arab traders and Marco Polo, after they visited India. In modern times, curcumin continues to be used as an alternative medicinal agent in many parts of Southeast Asia for the treatment of common ailments such as stomach upset, flatulence, jaundice, arthritis, sprains, wounds, and skin infections, among many others.

Curcumin and turmeric products have been characterized as safe by health authorities such as the Food and Drug Administration (FDA) in United States of America, the Natural Health Products Directorate of Canada, and the Expert Joint Committee of the Food and Agriculture Organization/World Health Organization (FAO/WHO) on food additives (JECFA). Curcumin is available as an over-the-counter (OTC) supplement worldwide. Perhaps surprisingly, apart from the early study published in *The Lancet* in 1937 (185), curcumin has entered scientific clinical trials at the phase I and II clinical trial levels only in the last 10–15 years (see later).

A useful barometer of the potential that a drug or agent is generally regarded as having for future use is the level of clinical trial activity. At the time of writing this article, 17 clinical trials (nine phase II and eight phase I) have been published in the National Centre for Biotechnology Information (NCBI) website from the last decade, and only two trials before 1990 (61, 72, 85, 86, 106, 109, 117, 143, 145, 182, 194, 204, 205, 212, 218, 224, 229, 235, 236). In the United States, nine clinical trials are in progress involving curcumin, funded by the National Cancer Institute and individual medical centers. A phase III study of gemcitabine, curcumin, and celecoxib is due to open to recruitment at the Tel-Aviv Sourasky Medical Center for patients with metastatic colorectal cancer. As shown in Table 1, eight of the U.S. clinical trials are based on a phase II design, and one has a phase I design.

C. Recent publication trends

Basic searches of the most commonly internationally accessed scientific databases by using the key words "curcumin" and "turmeric" demonstrated that >2,600 articles have been published in English language journals since 1966. To demonstrate the publication trend over recent decades, searches were subdivided by year: Only 15 articles were published prior to 1979, 279 articles were recorded from 1980 to 1995, and 1875 from 1996 to 2005.

Eighteen review articles have been published over the past decade (3, 4, 9, 24, 40, 60, 77, 88, 91, 119, 127, 147, 164, 166, 212, 226, 240, 257). The reader should note that whereas these reviews have generally focused on the potential role of phytochemicals to treat or prevent particular diseases, the purpose of this comprehensive review is to offer a broader perspective on the potential for curcumin to prevent or treat diverse human disease pathologies, particularly cancer.

Table 1. Clinical Studies Currently in Progress Studying Curcumin or Curcuminoids in Selected Patient Groups in the USA*

Trial design phase	*Medical condition studied*	*Agent being used for intervention*	*Study sponsor*
II	Pancreatic cancer	Curcumin + gemcitabine	NCI/Rambam Health Care Campus
II	Advanced pancreatic cancer	Curcumin	MD Anderson Cancer Center/ Sabinsa Corp.*,†
II	Smokers with Aberrant Crypt Foci of the colon	Curcumin	NCI/Chao Family Comprehensive Cancer Center
II	Familial Adenomatous Polyposis	Curcumin	NCI/Johns Hopkins University
II	Subjects with Recently Resected Sporadic Adenomatous Polyps	Curcuminoids	NCI/University of Pennsylvania Robert Wood Johnson Foundation
II	Chronic Psoriasis Vulgaris	Curcuminoids "C3" complex (Sabinsa Corp., Piscataway, NJ)	NCI/University of Pennsylvania
I	Multiple Myeloma	Curcumin with or without Bioperine	M.D. Anderson Cancer Center
II	Oral Lichen Planus	Curcuminoids/placebo	University of California, San Francisco

Information sources; *http://clinicaltrials.gov/ct/search?term = curcumin; †http://www.mdanderson.org/patients_public/clinical_trials/; ‡http://www.cancer.gov/clinical trials.

II. CHEMISTRY

A. Turmeric preparations

Turmeric, the dried ground rhizome of the plant *Curcuma longa* L. is a spice and food coloring from which curcumin can be extracted. In addition to curcumin, commercially available preparations of turmeric may contain volatile (essential) and nonvolatile oils, protein, fat, minerals, carbohydrates, and moisture (39). As shown in Fig. 2, curcumin is one of turmeric's nonvolatile constituents (9, 39, 129, 146, 280). Whereas the aromatic properties of turmeric are thought to be attributable to its volatile oils, its coloring characteristics may be a largely due to its nonvolatile oils, particularly the curcuminoids, including curcumin (119). Different parts of the *Curcuma longa* plant contain different quantities of essential oils (146); the roots and rhizomes of *Curcuma longa* L. yield the highest concentration of volatile oils, 4.3% and 3.8% respectively, whereas the flowers of the plant contain the lowest (0.3%). In one study using gas chromatography–mass spectrometry (GC-MS) to analyze fractions, 24 compounds of volatile oils were separated and identified in oils extracted from *Curcuma longa* by hydrodistillation (146). Components identified included α-turmerone (3–70%), α-zingiberene,1-8 cineole, zerumbone, 1-(3-cyclopentylpropyl)-2,4-dimethylbenzene, β-sesquiphellandrene, and germacrone.

The curcuminoids, which constitute approximately 5% of most turmeric preparations, are a mixture of curcumin (sometimes referred to as curcumin I), desmethoxycurcumin (curcumin II), and bisdesmethoxycurcumin (curcumin III) (280). Recently, other

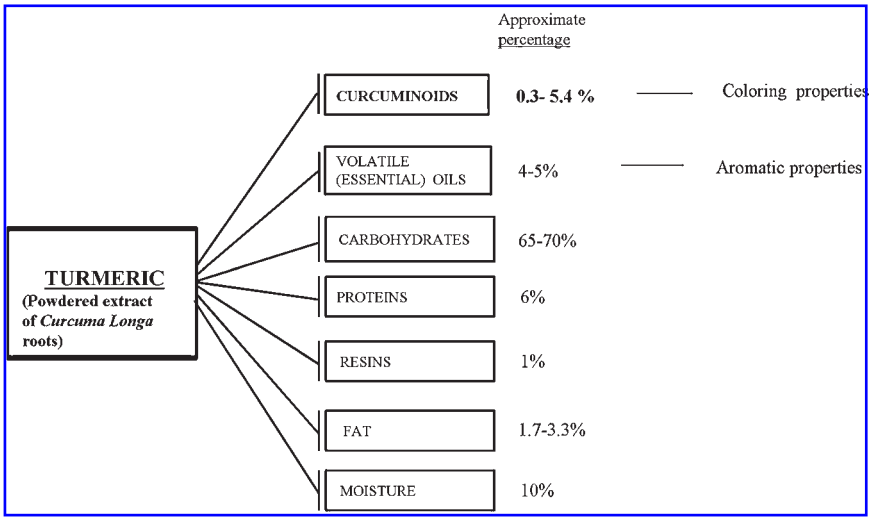

FIG. 2. Constituents of turmeric. Turmeric preparations vary in their constituent percentages. Approximate ranges are shown based on supporting references 9, 39, 181, and 280. Curcuminoids include curcumin, desmethoxycurcumin, bisdesmethoxycurcumin, and cyclocurcumin. The volatile oils include at least 45 different components, of which 24 have been identified by GC-MS (146).

curcuminoids have been isolated and identified from turmeric, such as cyclocurcumin (or curcumin IV) (134). It should be noted that most commercially available preparations of "curcumin" are not pure: They contain curcuminoids, most notably desmethoxycurcumin and bisdesmethoxycurcumin.

B. Chemistry of curcumin

Curcumin [chemical name: (*E*, *E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5 dione] is a bis-α,β-unsaturated β-diketone. It has a molecular weight (MW) of 368.38, a melting point of 179–183°C, and chemical formula $C_{21}H_{20}O_6$.

Under physiologic conditions, curcumin appears in both an enolate and a bis-keto form, which coexist in equilibrium (Fig. 3). In acidic and neutral conditions and in solid phase, the keto form predominates, and curcumin acts as a potent donor of H-atoms. In contrast, under alkaline conditions (pH >8), the enolic form predominates, and the phenolic part of the molecule plays the principal role as an electron donor (125).

Curcumin is more soluble in ethanol, dimethylsulfoxide, or acetone than it is in water. In solution, it has been demonstrated that curcumin is degraded to *trans*-6-(4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexanal, vanillin, feruloylmethane, and ferulic acid within 30 minutes (157). Similarly, at basic pH, curcumin is unstable. This degradation is blocked *in vitro* by the presence of fetal calf serum or human blood (273). Addition of antioxidants (ascorbic acid, *N*-acetylcysteine, or glutathione) to culture media or the use of phosphate buffer above pH 7 also block curcumin's degradation (273). Acidic conditions result in slower degradation of curcumin, with <20% of total curcumin decomposed at 1 h (273). Curcumin's photochemical instability is also worth noting by potential investigators. As a result of light sensitivity demonstrated by several researchers, biologic samples containing curcumin should be protected from light. In alkaline pH, curcumin's color appears less yellow and more red. Under physiologic conditions, maximal light absorption by curcumin occurs at 420 nm (260).

C. Curcumin analogues

As shown in Fig. 3, curcumin's chemical structure includes two methoxyl groups, two phenolic hydroxyl groups, and three double conjugated bonds. By modifying the chemical structure of curcumin, at least 60 compounds have been synthesized by investigators (213). Study of these analogues derived from curcumin has offered several interesting insights into structural–biologic relations. The hydroxyl groups of curcumin seem to play a significant role in curcumin's diverse antioxidant activity (252). In support of this theory, recent studies have shown that the ortho-dihydroxyl groups are responsible for the inhibitory effects of curcuminoids by creation of tighter binding affinity for two enzymes: aldose reductase, an enzyme present in many tissues that catalyzes the conversion of glucose to fructose; and α-glucosidase, an enzyme bound to the epithelium of the small bowel, involved in carbohydrate catabolism (71).

It is likely that more than one biochemical mechanism is involved in curcumin's antioxidant activity. According to some investigators, both hydroxyl and β-diketone groups exert antioxidant and antiinflammatory properties by induction of phase 2 detoxification enzymes (65). Others investigators have shown that selected curcumin analogues devoid of phenolic groups have antioxidant activity because of their ability to form stable carbon-centered radicals (274), thus supporting the finding that the keto form of curcumin can act as a potent donor of H-atoms under certain conditions (125). The range of chemical results demonstrates the multiple modes of antioxidant action of the parent compound.

Extensive research into the development of curcumin analogues continues in the hope of creating synthetic structures with better pharmacodynamic profiles than the parent curcumin, with particular reference to its antioxidant and cytotoxic properties. Although published data currently are lacking, it is also hoped that curcumin analogues may have more favorable pharmacokinetic profiles than the parent compound (see later), in particular, increased systemic bioavailability after oral dosing.

III. PHARMACOKINETIC PROPERTIES

A. Rodent models

The pharmacokinetic properties of curcumin have been studied in scientific rodent models since the 1970s. In the first published study, a dose of 1 g/kg was administered orally to rats, resulting in ~75% of the dose being excreted in the feces, and negligible amounts appearing in the urine (271). In a subse-

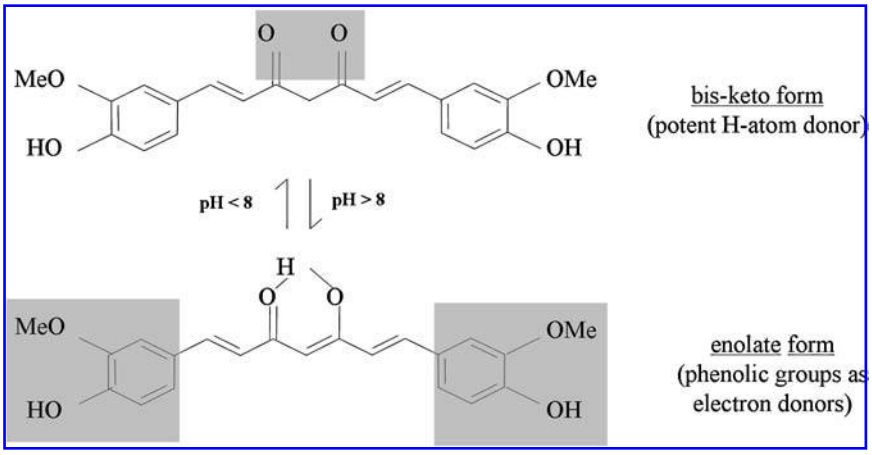

FIG. 3. Chemical structure of curcumin. The tautomerism of curcumin is demonstrated under different physiologic conditions. Under acidic and neutral conditions, the bis-keto form (*top*) is more predominant than the enolate form. For chemical details, see reference 125.

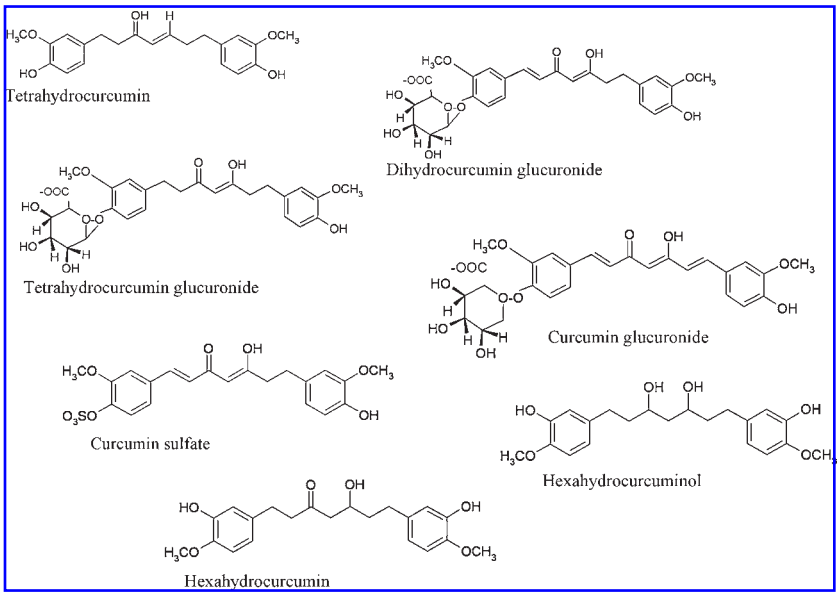

FIG. 4. Chemical structures of major metabolites of curcumin. Chemical structures shown refer to metabolites identified either in rodents or in humans.

quent study, oral curcumin administration to rats resulted in 60% absorption of curcumin and presentation of evidence for the presence of glucuronide and sulfate conjugates in the urine (208). The same investigators proceeded to study the bioavailability of curcumin by using ^{3}H-radiolabeling after oral administration. The majority of the oral dose was excreted in feces, and only ~35% was excreted unchanged, with the remaining 65% excreted as metabolites of curcumin (108, 207). After intravenous and intraperitoneal administration of curcumin in rodents, large quantities of this compound and its metabolites were excreted in the bile, mainly as tetrahydrocurcumin and hexahydrocurcumin glucuronides (Figs. 4 and 5) (206). These data offered evidence in favor of the hypotheses that curcumin undergoes transformation during absorption *via* the intestine and that it is possibly subject to enterohepatic recirculation (206). These data are in accordance with the original hypothesis proposed by the researchers who studied the fate of curcumin in rodents in 1978 (108).

Other investigators have studied the intraperitoneal administration of curcumin (0.1 g/kg) to mice, and they have suggested that curcumin is first biotransformed to dihydrocurcumin and tetrahydrocurcumin (THC), and that these compounds are subsequently converted to monoglucuronide conjugates (186). Ireson and colleagues (113) studied the oral dosing of curcumin in rats by using modern high-pressure liquid chromatography (HPLC) techniques. They showed that small quantities of curcumin, hexahydrocurcumin, hexahydrocurcuminol, and hexahydrocurcumin glucuronide were present in plasma with higher levels of curcumin glucuronide and curcumin sulfate. Interestingly, the transformation of curcumin to its metabolites occurred more extensively in rat hepatocytes grown *ex vivo* than in human hepatocytes. The same investigators extended their

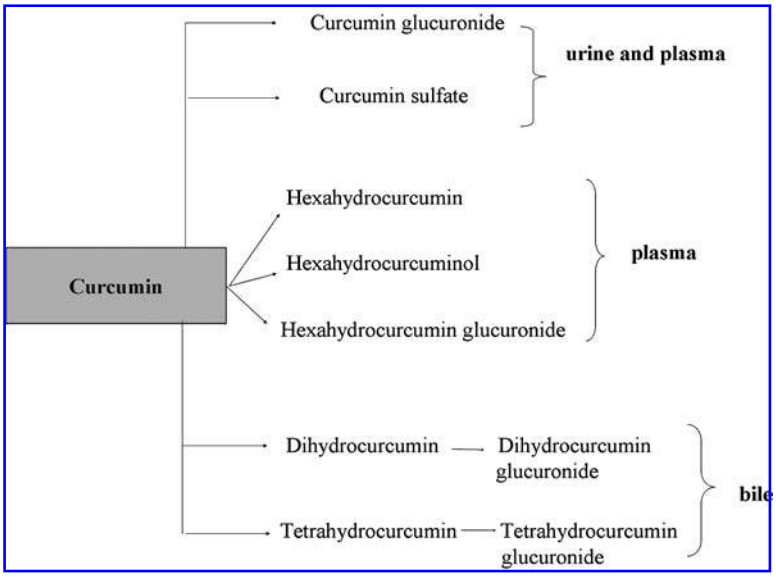

FIG. 5. Metabolic pathways of curcumin demonstrated in preclinical models. The metabolic pathways shown have been demonstrated in mice, *ex vivo* culture of rat hepatocytes, or *ex vivo* culture of human hepatocytes.

work by using suspensions of isolated human hepatocytes or liver or gut microsomes (114). The results suggested that the metabolic reduction occurred very rapidly (*i.e.*, within minutes).

A study of a high dose of oral curcumin (2% in the diet, or ~1.2 g curcumin per kilogram body weight) in F344 rats for 14 days showed that low nanomolar levels of parent compound are detectable in plasma, with concentrations in liver and colon mucosal tissue ranging from 0.1 to 1.8 nmol/g tissue (228). This study with modern HPLC techniques confirmed the findings of the pharmacokinetic studies performed more than two decades earlier (see earlier). Moreover, relevant to the translation of findings to clinical chemoprevention studies, these preclinical data represented the first published quantification of the levels measurable in colon mucosal tissue after oral dosing.

Because curcumin's poor systemic bioavailability after oral dosing compromises its potential therapeutic uses, many groups have focused on ways to improve its bioavailability. Coadministration of oral curcumin with piperine, an alkaloid found in plants of the Piperaceae family, which includes black pepper and long pepper, appeared to increase serum concentrations of curcumin in rodents. In a study using high doses of oral curcumin (2 g/kg) in rats, the investigators found that coadministration of piperine increased systemic bioavailability after oral dosing by as much as 154% (235). Although the mechanism of this effect has not been elucidated, one may speculate that it may involve the inhibition of hepatic and intestinal glucuronidation of curcumin.

In more recent studies, other researchers have tried to increase curcumin's systemic bioavailability by the application of novel delivery systems. In a study testing curcumin's uptake by spleen lymphocyte cells and EL4 lymphoma cell lines, it was found that the uptake of curcumin was higher when liposomal curcumin was applied rather than using human serum albumin or aqueous dimethyl sulfoxide as standard carriers (138). Furthermore, the effectiveness of liposomal curcumin as a delivery vehicle in inhibiting nuclear factor-κB (NF-κB) activation has been demonstrated in human pancreatic cancer cells grown *in vitro* and *in vivo* (151). Although systematic preclinical pharmacokinetic data are lacking, several research groups are currently studying liposomal formulations of curcumin in the hope that they may permit greater systemic biologic effectiveness than the parent compound. For example, researchers in Norway have studied the photosensitizing and photocytotoxic potential of natural and synthetic curcumin formulations on SM 10-12 salivary gland acinar cells (31). They used five different aqueous preparations of curcumin (5% DMSO, micelles, hydrophilic polymers, cyclodextrin, and liposomes), and their results suggested that the liposomal curcumin preparation was more photosensitizing and cytotoxic than the other preparations studied, an effect measured *via* generation of the photoreaction product, hydrogen peroxide (31).

In summary, the systemic bioavailability of curcumin after oral dosing in rodents is low. Curcumin may undergo intestinal metabolism, and it appears to undergo very rapid first-pass metabolism and excretion in bile. Coadministration with other agents or the use of different delivery vehicles such as liposomes may increase curcumin's systemic bioavailability.

B. Clinical pharmacokinetics

In contrast to the extensive preclinical evidence presented, fewer pharmacokinetic data are available from human studies. In addition to studying the fate of curcumin in rats (discussed earlier), Shoba and colleagues (235) administered 2 g of pure curcumin powder to fasting volunteers to demonstrate low curcumin concentrations in plasma (<10 ng/ml) 1 h after the dose. In the same study, concomitant administration of 20 mg of piperine appeared to increase curcumin's bioavailability in humans by 2,000%. In a study of higher doses of oral curcumin, clinical investigators in Taiwan administered up to 8 g of curcumin daily for 3 months to patients with preinvasive malignant or high-risk premalignant conditions. It was found that peak serum curcumin concentrations were achieved 1–2 h after oral intake and that levels gradually declined within 12 h. The highest (8 g/day) dose resulted in a peak serum concentration of 1.75 ± 0.80 μM (47). Doses >8 g/day were unacceptable to patients because of the bulky volume to be consumed. In a dose-escalation study performed in the United States, 50–200 mg of oral micronized curcumin, swallowed with orange juice, was administered to 18 healthy volunteers, resulting in no evidence for the presence of curcumin in the serum (215).

Two clinical phase I dose-escalation studies have been conducted in patients with advanced colorectal cancer in Leicester, England. In the pilot study of 15 patients, standardized oral *Curcuma* extract (doses up to 180 mg of curcumin) was administered in a formulation that also contained volatile oils derived from *Curcuma* spp. daily for up to 4 months. No evidence was detected of clinical toxicity definitely attributable to the experimental agent, nor evidence of detectable systemic bioavailability by using modern HPLC techniques (229). In a subsequent phase I study in 15 patients, a curcuminoid formulation was administered orally for up to 4 months, allowing rapid dose escalation and equating to curcumin doses between 0.45 and 3.6 g daily (224). By using multiple reaction-monitoring mass spectrometry and HPLC (Fig. 6), levels of curcumin and its metabolites in plasma, urine, and feces were analyzed.

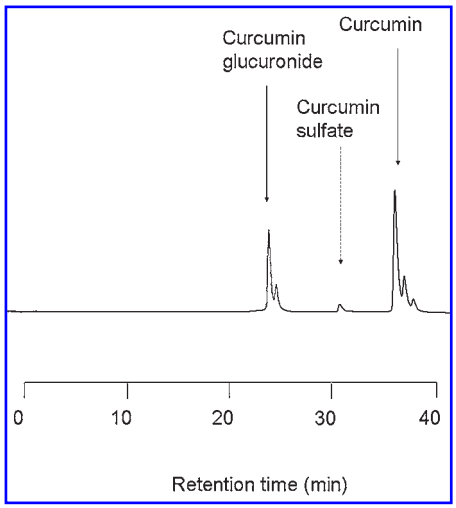

FIG. 6. Detection of curcumin and its metabolites by high-pressure liquid chromatography (HPLC). HPLC can be used to detect low levels of curcumin and its metabolites in biologic samples (113, 191, 224, 228, 229). Solutions of authentic curcumin, curcumin sulfate, and curcumin glucuronide are shown to demonstrate approximate differences in retention times observed.

Oral consumption of the highest dose of curcumin (3.6 g daily) resulted in detectable levels of drug and conjugates in plasma, just above the limit of detection of the assay (approximately 0.63 ng/ml). Surprisingly, analysis of urine from patients consuming the same dose suggested the presence of curcumin and its conjugates in samples from patients at the highest dose level (3.6 g curcumin/day). Lower doses of curcumin resulted in no detectable urinary levels of the drug. In the six patients consuming 3.6 g of curcumin daily, urinary levels varied between 0.1 and 1.3 μM (curcumin), 19 and 45 nM (curcumin sulfate), and 210 and 510 nM (curcumin glucuronide). The demonstration in this study of the consistent presence of curcumin and its metabolites in the urine of patients offers a reliable and convenient way of potentially testing the compliance of patients or volunteers consuming curcumin or *Curcuma* extract in clinical trials.

To determine levels of curcumin in gastrointestinal tissues, further studies were performed in Leicester in patients undergoing operations for colorectal cancer who offered voluntary consent to have their tissues used for research purposes (85, 86). Twelve patients with histologically confirmed colorectal cancer received oral curcumin (450, 1,800, or 3,600 mg daily) for 7 days before surgery. Levels of agent-derived species were determined in the peripheral circulation and in colorectal tissue obtained at the time of surgical resection. The concentrations of curcumin in normal and malignant colorectal tissue of patients consuming 3.6 g daily of curcumin were 12.7 ± 5.7 and 7.7 ± 1.8 nmol/g tissue, respectively. Curcumin sulfate and curcumin glucuronide were identified in the intestinal tissues of these patients. Trace levels of curcumin were found in the peripheral circulation. In accordance with the data from preclinical models discussed earlier, these clinical results in volunteers and patients suggest that curcumin has low systemic bioavailability in humans and that a dose of 3.6 g curcumin per day achieved measurable levels of the parent compound in colorectal tissue.

The same investigators examined the levels of curcumin in hepatic tissue after oral dosing in 12 patients with liver metastases from colorectal cancer who received 0.45–3.6 g of oral curcumin daily for 7 days before hepatic surgery (85). They measured the levels of curcumin and its metabolites with HPLC in portal and peripheral blood, bile, and liver tissue. Low nanomolar levels of curcumin and its glucuronide and sulfate conjugates were found in peripheral blood samples taken 1 h after dose seven of curcumin and in portal blood samples taken 6–7 h after dose seven of curcumin. In resected liver tissue, no parent drug was detected, but trace levels of its metabolic products were found. This pilot study showed that the doses of oral curcumin required to produce hepatic levels sufficient to exert pharmacologic activity are probably not feasible in humans with this pharmaceutical formulation.

In summary, the results from several pilot and phase I clinical studies in volunteers and patients are consistent with the findings performed with curcumin in preclinical models presented earlier. Collectively, they confirm that low systemic bioavailability is achieved after oral dosing, probably due to rapid first-pass metabolism and some degree of intestinal metabolism. A daily oral dose of 3.6 g of curcumin has been shown to be compatible with detectable levels of curcumin in colorectal tissue and in urine.

C. Safety and toxicity

Although curcumin and turmeric are natural products used in the diet, the doses administered in clinical trials exceed those normally consumed in the diet. This fact underlines the need for systematic safety and toxicity studies. Turmeric is Generally Recognized As Safe ("GRAS") by the U.S. FDA, and curcumin has been granted an acceptable daily intake (ADI) level of 0.1–3 mg/kg-BW by the Joint FAO/WHO Expert Committee on Food Additives, 1996 (181). In terms of dietary use in different countries, according to a study from Nepal, dietary consumption of turmeric up to 1.5 g per person per day, equivalent to ~50 mg/day of curcumin, does not appear to be associated with adverse effects in humans (77). In India, where the average intake of turmeric can be as high as 2.0–2.5 g per day (corresponding to ~60–100 mg of curcumin daily), no toxicities or adverse effects have been reported at the population level (33).

More valuable than such population dietary studies, which are potentially confounded by multiple variables and interactions, are the systematic preclinical studies funded by the Prevention Division of the U.S. National Cancer Institute. These studies did not demonstrate any adverse effects in rats, dogs, or monkeys at doses of curcumin up to 3.5 g/kg-body weight (BW) administered for up to 90 days (181). A single report of curcumin-induced gastric ulceration in albino rats was reported in 1980 (97), but this finding has not been replicated in subsequent studies. More recently, no toxicity has been observed in a preclinical study of the administration of 2% dietary curcumin (~1.2 g/kg BW) to rats for 14 days (228) or in a study of 0.2% dietary curcumin (~300 mg/kg BW) administered to mice for 14 weeks (191). Furthermore, a two-generation reproductive toxicity study in Wistar rats found no toxicity, reproductive or otherwise, related to oral curcumin administration (up to 1 g/kg-BW daily) in two successive generations of rats (83). Contrary to the lack of toxicity with studies of curcumin, a rarely cited carcinogenicity study of turmeric oleoresin reported: (a) hyperplasia of the mucosal epithelium in the cecum and colon of male and female rats; (b) an increased incidence of hepatocellular adenoma in male and female mice; (c) a significantly increased incidence of thyroid gland follicular cell hyperplasia in female mice; and (d) small but significant increases in sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells (1). Further studies with this preparation of turmeric oleoresin have not been performed.

Similar to the conclusions regarding the safety of curcumin in preclinical models, clinical trials have documented minimal toxicity from administration of curcumin or turmeric, although it has not been clearly stated by the reporters of most of these studies which methodologic criteria have been used to assess potential toxicity. In a study performed in India, administration of 1.2–2.1 g of oral curcumin to patients with rheumatoid arthritis daily for 2–6 weeks did not cause any toxicity (61). In another study of high-dose oral curcumin by Cheng and colleagues (47) in Taiwan, administration of up to 8 g daily of curcumin for 3 months to patients with preinvasive malignant or high-risk premalignant conditions had no adverse effects (47). In a phase I clinical trial of oral curcumin in patients with advanced colorectal cancer in which the U.S. National Cancer Institute

(NCI) criteria were used to assess potential toxicity, curcumin was well tolerated at all dose levels up to 3.6 g daily for up to 4 months (224). Adverse events probably related to curcumin consumption reported by patients in these studies were mainly gastrointestinal (nausea and diarrhea). Diarrhea (U.S. NCI toxicity grades 1 and 2, respectively) was experienced by one patient consuming 0.45 g curcumin daily and by another patient consuming 3.6 g daily, 1 and 4 months into treatment, respectively. A third patient, consuming 0.9 g of curcumin daily, reported nausea (NCI toxicity grade 2), which resolved spontaneously despite continuation of treatment. Two abnormalities were detected in blood tests in this trial, both possibly related to treatment: An increase in serum alkaline phosphatase level was observed in four patients (two were NCI grade 1, and two were grade 2); and three other patients had serum lactate dehydrogenase increases to >1.5 times the upper limit of normal. It is unclear whether these abnormal blood test results were related to the activity of the malignant disease in these patients or to treatment toxicity.

Although turmeric is often used to treat inflammatory skin conditions in traditional Southeast Asian medical systems, it should be noted by potential laboratory and clinical investigators that a few reports of allergic dermatitis after contact with curcumin have been published in the scientific literature (89, 154, 258). Allergic reaction to turmeric-related products also was described in one healthy volunteer enrolled in a phase 1 study testing the safety of turmeric oil and turmeric extract (124).

IV. SYNERGY AND ANTAGONISM WITH OTHER AGENTS

The field of phytochemical research has expanded rapidly over the past decade, resulting in the preclinical and early clinical development of many promising agents. Similarly, potentially beneficial interactions between diet-derived polyphenols and other drugs and between individual components of the human diet have been identified. Examples of this concept include the combination of curcumin with the green tea extract, epigallocatechin-3-gallate (EGCG) (130); curcumin combined with the flavonoid quercetin, found in apples, onions, and citrus fruits (56); and the synergy of indole-3-carbinol (I3C) combined with genistein (13). Interactions relevant to combinatorial treatment with curcumin are discussed in this section.

A. Synergy with diet-derived polyphenols

In addition to the potential interactions in pharmacokinetics discussed earlier, curcumin may also exhibit synergy in its pharmacodynamic effects with other diet-derived polyphenols. An example of this concept is the potential synergy with genistein, a natural product derived from soya beans. The combination of curcumin and genistein appears to inhibit growth of human breast MCF-7 cells synergistically compared with growth inhibition by each agent individually (266). Coadministration of curcumin with embelin, a natural product from the berries of *Embelia ribes*, has been shown to prevent oxidative damage and hepatocarcinogenesis in Wistar strain albino rats chemically induced by *N*-nitrosodiethylamine and phenobarbital (246).

Concomitant use of topical curcumin with oral administration of green tea has shown synergistic inhibition of chemical carcinogenesis, demonstrating the benefit that may be gained from a combination of chemopreventive agents derived from the diet. In particular, treatment of cell lines from normal oral epithelium, dysplastic leukoplakia, and squamous cell carcinoma with curcumin and EGCG alone or their combination demonstrated synergistic growth inhibition, probably because these two phytochemicals block different phases of the cell cycle (130, 152). Contrastingly, some researchers have demonstrated antagonistic effect of curcumin with EGCG on keratinocyte differentiation mediated by upregulation of involucrin gene expression. Involucrin gene expression is enhanced by EGCG, but it appears to be inhibited by curcumin (74). These findings have not been borne out by a study of the combination of curcumin with the prodifferentiation agent, all-*trans* retinoic acid human promyelocytic leukemia HL-60 cells. In this study, combination treatment resulted in synergistic inhibition of the proliferation of the cells studied, as well as improved induction of differentiation of these premalignant cells, both regarded as favorable effects (161). Synergistic effects of curcumin with other diet-derived polyphenols demonstrated in clinical trials is discussed later.

B. Synergy with cytotoxic drugs

Several investigators have studied the combination of curcumin with cytotoxic agents commonly used to treat cancer to look for additive or synergistic activity in cell kill. In a study in human colon cancer cell lines, curcumin was combined with 5-fluorouracil (5-FU) to demonstrate synergistic inhibitory effects on the growth of the cancer cells *in vitro*, associated with reduced expression of COX-2 protein (70). Such findings are compatible with curcumin's ability to inhibit the transcription of the COX-2 protein in colon cells grown *in vitro* (195). A study on human gastric adenocarcinoma (AGS) cells has replicated the synergistic effect of curcumin with 5-FU on growth inhibition, involving the induction of G_2/M phase cell cycle arrest (135).

In a recent study of human leukemia cells (HL-60) treated with a combination of curcumin (up to 20 μM) and trichostatin A, an antifungal agent known to inhibit histone deacetylase (44), an increased cytotoxic effect was demonstrated with the combination therapy. Interestingly, this effect was not seen with higher doses of curcumin (50–100 μM). This finding suggests the importance of adequate preclinical work *in vitro* and *in vivo* to determine the optimal ratios of agents to be used in pilot clinical trials of combinatorial therapy.

Curcumin has also been studied in combination with other cytotoxic agents widely used in the treatment of patients with cancer. Sen and colleagues (221) studied H520 squamous lung cancer cells sensitized initially with curcumin and then treated with the cytotoxic semisynthetic vinca alkaloid and antimitotic agent, vinorelbine. They demonstrated synergism between curcumin and vinorelbine, a cell cycle–specific cytotoxic agent that predominantly affects the G_1/S phase. They showed increased apoptosis in cells pretreated with curcumin and then exposed to vinorelbine compared with cells treated with vinorelbine alone or curcumin alone.

The combination of curcumin with anthracycline drugs has been studied *in vivo*. When rats were treated with curcumin 7 days before and 3 days after doxorubicin (Adriamycin)-induced cardiotoxicity (30 mg/kg Adriamycin given i.p.), Venkatesan *et al*. (265) demonstrated significantly fewer manifestations of cardiotoxicity, measured by less increase of creatine kinase and lactate dehydrogenase levels in serum, than in animals not receiving curcumin (265). The authors speculated that curcumin may therefore be of value to patients at risk of cardiotoxicity from high doses of anthracycline drugs (*e.g*., women with breast cancer).

To summarize these diverse reports of combinations with cytotoxic agents, curcumin may have a role in improving the therapeutic index of drugs used routinely in the chemotherapy of cancer, either by increasing cell kill in tumors or by protecting against oxidative damage induced in normal tissues.

C. Potential interactions with prescription drugs

More recently, scientific investigators have suggested that curcumin may potentiate the selective cyclooxygenase-2 (COX-2) inhibitory effect of celecoxib in pancreatic adenocarcinoma cells (150). Celecoxib is a selective COX-2 inhibitor in widespread use as an analgesic and in several clinical trials in the chemoprevention of cancer and coronary artery restenosis and cancer chemotherapy. COX-2 is a key enzyme in arachidonic acid metabolism, which is overexpressed in inflammatory processes and in several premalignant lesions and cancers, including colorectal adenomas and carcinomas (254). Synergistic growth-inhibitory and proapoptotic effects of the combination of celecoxib and curcumin have also been shown in colorectal cancer cells and in osteoarthritis synovial adherent cells (*i.e*., primary culture of cells prepared from human synovial tissue collected during knee replacement surgery), although one would predict that some of the cellular fates observed are likely to be attributable to the known COX-2–independent effects of both agents (149). In contrast to selective COX-2 inhibitors such as celecoxib, which competitively inhibit the catalytic activity of the isozyme, curcumin inhibits the transcription of COX-2 protein (195). Although the highly selective competitive inhibitor of the COX-2 isozyme, rofecoxib, was linked with an increased risk of cardiovascular disease in one study, which may or may not be related to its COX-2–inhibitory actions, it is not currently clear whether less-specific agents such as curcumin (which downregulates COX-1 and COX-2 mRNA levels, as discussed later) are associated with potentially adverse effects.

Apart from the synergy with these agents leading to an increasing cytotoxicity in the treatment of cancer, interactions of curcumin with drugs commonly prescribed to patients may result in various biologic effects relevant to the treatment of a variety of human diseases. Researchers in China tested the effect of curcumin combined with amiloride (a Na^+/H^+ exchange inhibitor) on the fibrosis of rat hepatic stellate cells (HSCs). They found that the combination of curcumin and amiloride had a superior antifibrotic effect to either curcumin or amiloride alone, potentially because of enhanced antioxidant activity (286). Such an effect is correctly described as additive rather than synergistic. In a further study, researchers tested the impact of the coadministration of curcumin with cyclosporine, an immunosuppressant used to prevent transplant rejection, on rat heterotopic heart-transplant models (50). They showed a synergy in immunosuppression when measured *via* attenuation of the expression of the cytokines, interleukin 2 (IL-2), and interferon gamma (IFN-γ). Synergy has also been suggested in the treatment of malaria from the combination of curcumin with artemisinin, an antimalarial drug extracted from the plant *Artemisia annua* (180). The antimicrobial efficacy of curcumin is discussed later.

Despite the lack of systematic testing of the interaction of curcumin with other commonly used drugs, the U.S. Department of Health and Human Services has recommended, based on published laboratory and animal studies, that coadministration of curcumin with nonsteroidal antiinflammatory drugs (NSAIDs) or anticoagulant drugs (heparin, clopidogrel, aspirin) may result in an increased risk of bleeding. They have also suggested that interference may be found with other drugs that affect or are metabolized by the cytochrome P450 (CYP) enzyme system, resulting in the potential for erratic drug levels in blood.

In addition to this advice, it has been speculated by certain researchers that *Curcuma* extract (rather than curcumin) may potentially interfere with histamine 2 (H^2)-receptors antagonists (*e.g*., ranitidine) and proton-pump inhibitors (*e.g*., omeprazole) *via* inhibitory effects on histamine receptors (132). Based on animal studies, other scientists have speculated that curcumin may enhance the hypoglycemic effect of antidiabetic medication or the efficacy of antilipemic drugs, *via* inhibition of the CYP enzyme system or reducing the low-density lipoprotein (LDL) fraction in the blood (18, 78). Anecdotal reports from animal studies suggest that concomitant use of herbal and dietary supplements, such as *Ginkgo biloba*, garlic extracts, and palmetto, may interfere with curcumin levels and may also increase the risk of bleeding (see: http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-turmeric.html), although published systematic data to confirm such speculation are currently lacking.

V. MOLECULAR MECHANISMS

Curcumin possesses a variety of potentially therapeutic properties, such as antiinflammatory, antioxidant, antineoplastic, pro- and antiapoptotic, antiangiogenic, cytotoxic, immunomodulatory, and antimicrobial actions. Compatible with this range of activity, curcumin has been shown to affect many cellular and molecular pathways. The complexity of the pleiotropic activity of curcumin may account for its efficacy in combating human diseases such as cancer, which are usually multifactorial in nature and usually involve cellular or molecular defects at more than one level. The cellular processes targeted by curcumin include gene expression, transcription factors, growth factors and their receptors, nuclear factors, hormones, and hormone receptors. In cancer, such targets have been implicated at all stages of carcinogenesis (initiation, promotion, and progression). In Fig. 7, some of the important biologic properties of curcumin are listed with regard to multiple human diseases. Figure 8 highlights some of the molecular targets of curcumin relevant to the therapy and prevention of cancer.

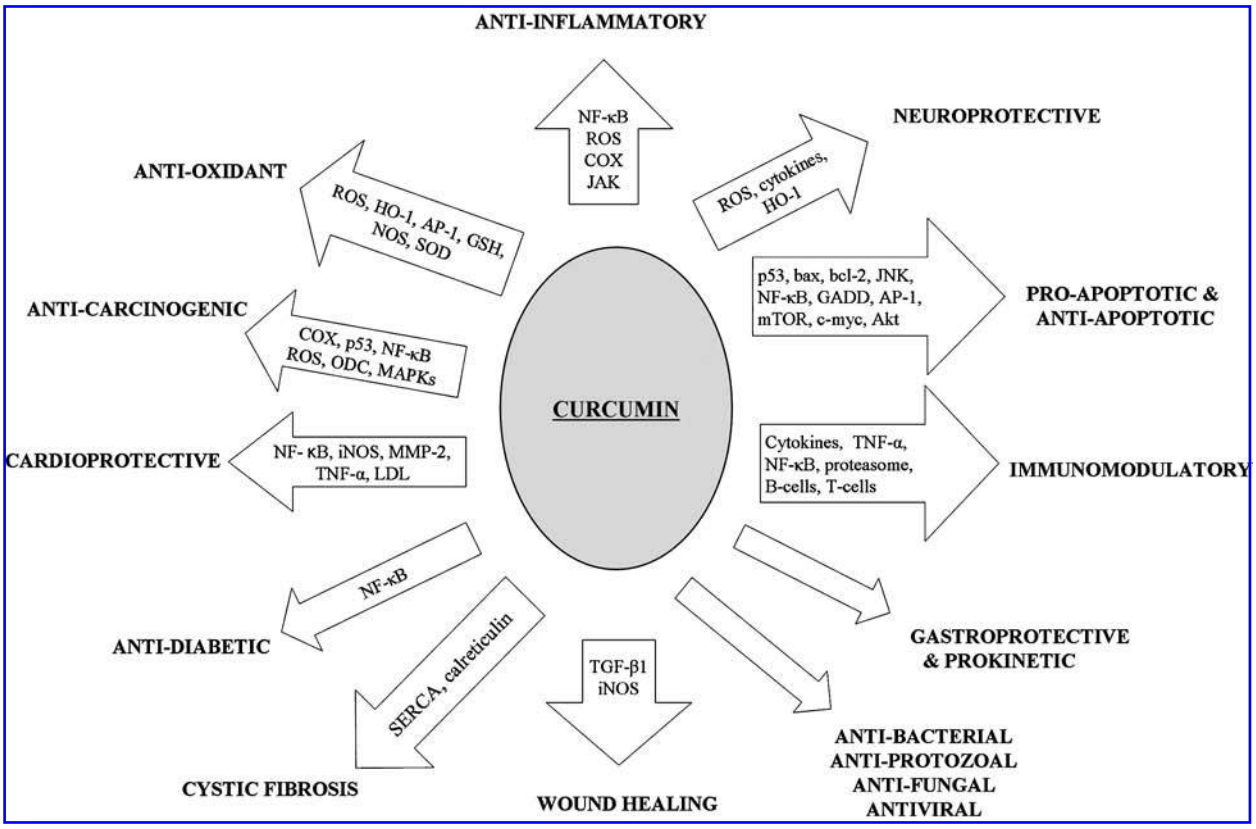

FIG. 7. Diverse biologic activities of curcumin. Diverse activities of biologic relevance demonstrated in preclinical models and in human studies are shown to illustrate the potential of curcumin to treat human diseases. Cellular mechanisms associated with the effects observed are shown inside the arrows. AP-1, activator protein-1; COX, cyclooxygenase; GADD, growth arrest and DNA damage; GSH, glutathione; HO-1, heme oxygenase-1; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK, janus kinase; JNK, c-Jun N-terminal kinase; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinases; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-kappa B; NO, nitric oxide; NOS, nitric oxide synthase; ODC, ornithine decarboxylase; ROS, reactive oxygen species; SERCA, sarco/endoplasmic reticulum calcium ATPase; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TNF, tumor necrosis factor.

A. Nuclear factors

An example of a cellular target with a central role in the pathogenesis of multiple pathogeneses, particularly cancer and inflammatory disease, is the cell survival–signaling transcription factor, nuclear factor κB (NF-κB). NF-κB is activated by various stimuli such as free radicals, inflammatory cytokines, endotoxins, ionizing radiation, ultraviolet (UV) light, carcinogens, and in general by any stimulus that can activate tumor necrosis factor (TNF). Under normal conditions, NF-κB is sequestered and bound in the cytoplasm by inhibitory proteins called IκBs. The IκBs activate IκB kinase (IKK), which mediates the phosphorylation and degradation of IκB so that NF-κB is released and may translocate to the nucleus, where it stimulates the transcription of many of the key genes responsible for inflammation, proliferation, invasion, metastasis, and inhibition of apoptosis. Activation of NF-κB results in upregulation of the molecules, cyclin D1, Bcl-2 (6), and Bcl-XL proteins, matrix metalloproteinases (MMPs), growth-factor receptors (GFRs) including vascular endothelial growth factor (VEGF) and the epidermal growth factor (EGF) family, survivin, inducible nitric oxide synthase (iNOS) (251), interleukin-6 (IL-6), IL-10, IL-18, activator protein-1(AP-1), HO-1, and many others (2). A common feature to all these cellular pathways is the involvement of NF-κB, potentially providing a link between the pathogenesis of many malignant, inflammatory and degenerative conditions.

In an early study, Singh *et al*. (238) showed that curcumin is a strong suppressor of NF-κB activation by inhibiting the activity of IKK and preventing the phosphorylation of IκB and the subsequent translocation of NF-κB to the nucleus. Subsequently, numerous studies by Aggarwal and other researchers confirmed the important role that curcumin can play in inhibiting the activation of NF-κB in cells (27, 234). Inhibition of NF-κB activation by curcumin is implicated as a mechanism by which curcumin suppresses the induction of *COX-2* gene expression, resulting in inhibition of the transcription of COX-2 protein (195).

Curcumin's effects on cellular signaling mechanisms relevant to the cellular response to oxidative stress may be even

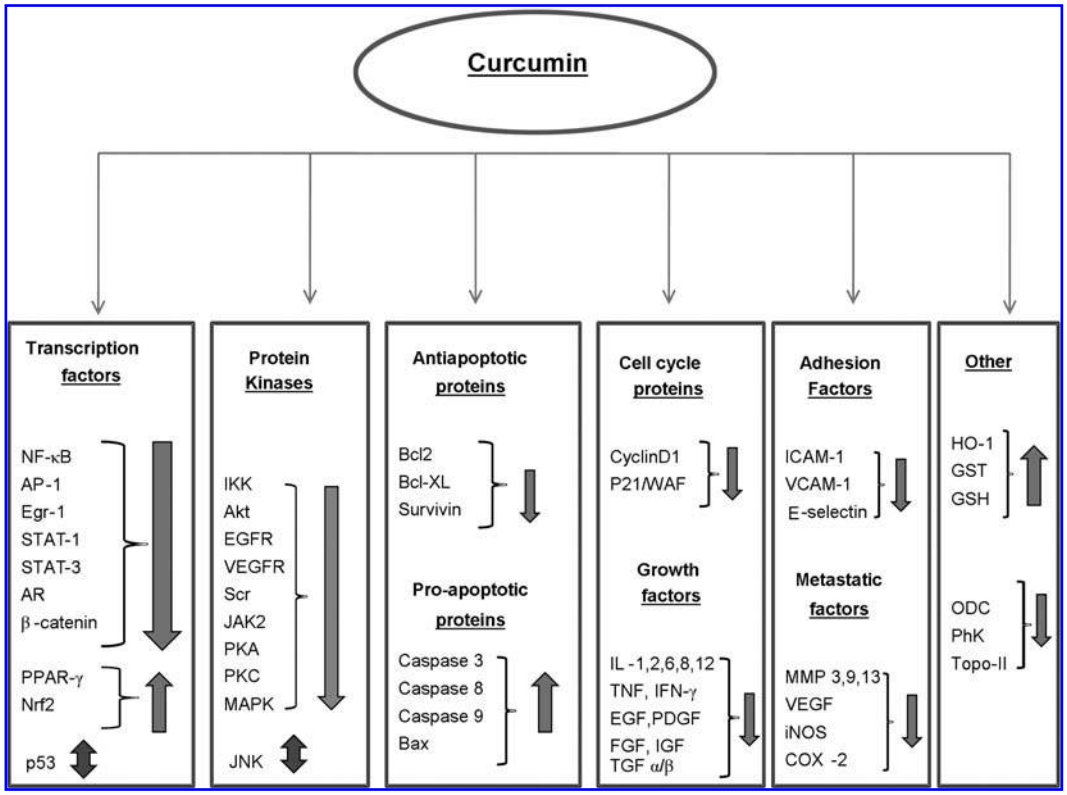

FIG. 8. Molecular targets of curcumin. Upward arrows, Increased activity; downward arrows, decreased activity of molecular targets as a result of curcumin treatment in preclinical studies performed *in vitro* and *in vivo*. Bilateral arrows, Discrepant results in independent studies (see text). AP-1, activator protein-1; AR, androgen receptor; COX, cyclooxygenase; EGFR, epidermal growth factor receptor; Egr-1, early growth response-1; FGF, fibroblast growth factor; GSH, glutathione; GST, glutathione-*S*-transferase; HO-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IGF, insulin-like growth factor; IκBα, inhibitory kappa B alpha; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK, janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; MMP, matrix metalloproteinase; NF-κB, nuclear factor-kappa B; Nrf-2, nuclear factor erythroid 2–related factor 2; ODC, ornithine decarboxylase; PDGF, platelet-derived growth factor; PhK, phosphorylase kinase; PKA, protein kinase A; PKC, protein kinase C; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TNF, tumor necrosis factor; Topo-II, topoisomerase II; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

more wide ranging than currently recognized. Recently, it was postulated that curcumin upregulates the nuclear factor erythroid 2-related factor 2 (Nfr-2). Nfr-2, a member of the cap'n'-collar family of transcription factors, is a key component of the antioxidant response elements (ARE)-mediated induction of phase 2 detoxifying and antioxidant enzymes, including glutathione-*S*-transferase (GST), NAD(P)H:quinone oxidoreductase (NQO1), and heme oxygenase-1 (HO-1). Nfr-2 is inactive in normal physiologic conditions because of its binding to the cytosolic protein Keap1. Redox stimulation causes activation of Nfr-2 and its consequent translocation to the nucleus, where it binds to ARE. Curcumin not only promotes inactivation of the Nrf2-Keap1 complex leading to increased Nrf2 binding to AREs, but it also stimulates *HO-1* gene activity (20). Providing interesting links to the biologic mechanisms discussed earlier, stimulation of Nfr-2 is regulated by other signaling pathways such as mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3 kinase (PI3K), and protein kinase C (PKC) (20, 120).

B. Growth-factor receptors and protein kinases

Curcumin also can interfere with the activation of other key cellular mediators involved in cancer and inflammation. An example is the activation of the peroxisome proliferator–activated receptor γ (PPAR-γ), which mediates the suppression of gene expression of cyclin D1 and the epidermal growth factor receptor (EGFR) and induces cell differentiation and cell-cycle arrest (41). Curcumin appeared to stimulate the activity of PPAR-γ in Moser human colon carcinoma cells (41). In a separate study, curcumin also appeared to inhibit the Akt/PI3K pathway, which transmits signals received by the EGFR tyrosine kinase. The mechanism appeared to involve inhibition of Akt phosphorylation (112, 278). A recent study in human colon cancer–derived cell lines has shown that curcumin inhibits cell growth by interference with the EGFR signaling pathway *via* downregulation of the early growth response-1 (*egr*-1) transcription factor (42). Curcumin has also been shown to suppress the mitogen-activating protein kinases (MAPKs) pathway,

which includes the c-Jun N-terminal kinases (JNKs), the extracellular signal-regulated kinases (ERKs), the p58 kinases, and the stress-activated protein kinases (SAPKs) (4, 45), although other studies have demonstrated that curcumin may facilitate apoptosis by inducing JNK and activating c-jun and c-abl (54, 126). The induced JNK proteins can activate c-jun, which, after phosphorylation, creates a homodimer or a heterodimer with c-fos. This homo/heterodimer attaches to the AP-1 response elements in the promoters of target genes such as *bax*, *bcl-2*, and *bcl-XL*, resulting in modification of their expression and eventually leading to cell death or apoptosis. Induction of JNK activity by curcumin was diminished when the colon cancer cells being studied *in vitro* were treated with the JNK-specific inhibitor, SP600125 (54).

Curcumin and some of its analogues cause direct suppression of the activator protein-1 (AP-1), a complex consisting of proteins belonging to the Jun and Fos family. AP-1 is a molecule that regulates genes responsible for cell apoptosis and proliferation, such *cyclin D1, p53, p21*, and *p16* genes (66, 75, 282). Contrastingly, other curcumin analogues seem to enhance activation of AP-1 in the presence of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in HEK293 cell lines (275). Activation of AP-1 by curcumin analogues is of uncertain significance at the cellular and molecular level, and it does not appear to be related to any of curcumin's known activities in cancer cells grown *in vitro*. Conversely, suppression of AP-1 has been linked with anticarcinogenesis and tumor antiangiogenesis and may be a valuable property of curcumin or certain analogues (4, 232).

Protein kinase C (PKC) belongs to the serine/threonine kinases family. It serves as an intracellular receptor for the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and as a cellular receptor for diacylglycerol (DAC). PKC activation by exogenous and endogenous oxidants influences tumor promotion, cellular growth, differentiation, and apoptosis. Tumor promoters and other oxidants activate PKC by reacting with zinc-thiolates found in its regulatory domain. In contrast, several chemopreventive agents, including curcumin and selenium compounds, inactivate PKC by reacting with the vicinal thiols of its catalytic domain. Inhibition of PKC function by curcumin has been documented in several independent studies (90, 156, 160, 279).

C. Oncogenes and tumor-suppressor genes

Curcumin can alter the expression of genes involved in tumor growth and apoptosis, evident by the downregulation of the survival genes, early growth response-1 (*egr-1*), *c-myc*, *bcl-X*, and *p53* in various cell lines *in vitro* (42, 100, 190). It is well known that *p53* is a key gene for tumor suppression and induction of apoptosis. Under normal conditions, p53 inhibits the proliferation and growth of cells with abnormal or damaged DNA, as seen in aging and cancer. Mutations of this gene can be found in many cancers (167, 220) and may lead to resistance to chemotherapy treatments because of impaired p53-induced apoptosis (250).

Curcumin has been shown to modulate p53 function in differing ways. For example, in an important study in normal thymocytes and myeloid leukemic cells grown *in vitro*, curcumin induced ubiquitin-independent degradation of wild-type (WT) p53 and inhibited p53-induced apoptosis. Like dicoumarol, curcumin inhibited the activity of recombinant NAD(P)H:quinine oxireductase 1(NQO1) activity *in vitro*, inhibited the activity of endogenous cellular NQO1 *in vivo*, and dissociated NQO1-WT p53 complexes (100, 262). These suggestions that curcumin may inhibit p53-induced apoptosis are consistent with another study showing that curcumin impairs the folding of p53 into the conformation required for its phosphorylation, its binding to DNA, and its transactivation of genes that execute its tumor-suppression function (173).

In contrast to these antiapoptotic results, curcumin has been found to increase *p53* gene expression in human HT-29 colon cancer cell lines and to regulate the levels of *p53*-related proapoptotic factors (*e.g.*, upregulation of *bax* and downregulation of *bcl-2* and caspases 3 and 9) (243). In a separate study of human mammary epithelial carcinoma cells, prostate cancer cells, and B-lymphoma cells grown *in vitro*, curcumin was found to induce apoptosis selectively in the malignant cell lines by increasing *p53* expression at the G_2 phase of the cell cycle and by releasing cytochrome *c* from mitochondria (49). An interesting finding in this study was that curcumin appeared to be sparing the normal epithelial cells by arresting them at the G_0 phase of the cell cycle by downregulation of cyclin D1 and its related protein kinases (Cdk4/Cdk6) or upregulation of the inhibitory protein p21*Waf-1*. In cancer cells in which cyclin D1 was overexpressed, curcumin did not influence the level of cyclin D1, and apoptosis was induced secondary to curcumin treatment during the G_2 phase of the cell cycle (49).

It is therefore apparent that the published studies of curcumin's effects on p53 regulation and activity are inconsistent. Indeed, current collective opinion states that the studies demonstrating the potential antiapoptotic effects of curcumin in cells grown *in vitro* promote a note of caution in curcumin's potential use in healthy individuals. Although extension of these studies in other preclinical model systems is ongoing, the limitations of such models in studying the effects of curcumin in normal or premalignant cells will not permit definite conclusions to be drawn until careful scrutiny of the effects of curcumin on p53 function is performed in early clinical studies.

Other potential targets of curcumin are oncoproteins implicated in carcinogenesis, such as β-catenin. Under normal conditions, β-catenin regulates the transcription of genes such as T-cell factor (TCF), lymphoid enhancer factor (LEF), and *c-myc* genes. In gastrointestinal and other cancers, this pathway is often dysregulated and associated with tumor invasion and poor prognosis (140, 153, 168, 171, 214). Curcumin is a potent inhibitor of β-catenin and can block its transcriptional activity, which is often overexpressed in cancers (116, 165, 189). In a recent study, it was demonstrated that curcumin may execute its anticancer activity by blocking the mammalian target of rapamycin (mTOR) and its related molecules (23). The mTOR complex is a serine/threonine kinase that is part of the cellular phosphatidylinositol 3-kinase (P13K) pathway that regulates translation and cell division and enhances growth by stimulating cells to pass from G_1 to S phase of the cell cycle (23). It is conceivable that curcumin exerts differential effects on cells dependent not only on their *p53* status but also on the phase of the cell cycle during which treatment occurs.

D. Angiogenesis and hypoxia

Curcumin also possesses antiangiogenic activity of potential importance in the treatment of inflammation (*e.g.*, wound heal-

ing) and cancer. Such effects may also be relevant to retinal diseases such as age-related macular degeneration. Angiogenesis is a physiologic process leading to the formation of new vessels and is necessary for tissue development and healing (82). In cancer, angiogenesis is generally considered to be a crucial step in tumor survival and growth beyond a certain size (~1–2 mm in diameter). Tumors produce growth factors that stimulate vasculature formation, such as vascular endothelial growth factor (VEGF), β fibroblast growth factor (bFGF), and endothelial growth factor (EGF). Antiangiogenic properties exhibited by curcumin include the downregulation of the production of VEGF, bFGF, EGF, and decreased expression of *angiopoietin 1* and *2* genes (98).

Although the multiple mechanisms of inhibition of processes implicated in cellular dysfunction by curcumin are complicated, it seems that many involve inhibition of NF-κB, interference with tyrosine kinases (such as Scr and focal adhesion kinase), and the downregulation of expression of COX-2, IL-8, and MMPs (particularly MMP-2, MMP-9, and aminopeptidase N) (11, 67, 98, 172, 233). A related and important recent finding is that curcumin inhibits hypoxia-inducible factor-1(HIF-1), which plays a pivotal role in hypoxia-stimulated angiogenesis and the expression of VEGF (19). Furthermore, HIF-1 influences the transcription of a wide array of genes such as *HO-1, iNOS*, the proapoptotic Bcl-2/adenovirus EIB 19-kDa–interacting protein 3 (*Bnip3*) gene, and glycolytic enzymes. Curcumin can thus interfere with tumor survival, metabolism, and progression. Data on curcumin's effects on cells under different oxygen tensions or degrees of hypoxia are currently lacking.

In summary, based on its influence on multiple cellular pathways, curcumin has diverse potential as a chemopreventive and therapeutic agent. It seems that a significant part of this potential can be attributed to the multiple ways in which curcumin can act at the molecular level, of which the pharmacology has been elucidated in some cases. Not only does curcumin upregulate or downregulate genes in pathways linked with carcinogenesis, but it also targets proteins and other molecules involved in chronic diseases (see later).

VI. BIOLOGIC DATA FROM PRECLINICAL MODELS

A. Antioxidant activity

Oxidative stress and oxidative damage are involved in the pathophysiology of many chronic inflammatory and degenerative disorders, particularly atherosclerosis, and the clinical complications of chronic diabetes mellitus, cardiomyopathy, ischemic heart disease, chronic obstructive lung disease (COPD), Alzheimer disease, and Parkinson disease. The generation of reactive oxygen species (ROS), particularly superoxide anions and hydroxyl radicals, lipid peroxidation of cellular membranes, altered balance of antioxidant enzymes, such as an increase in cellular glutathione levels (GSH) and stress-induced activation of AP-1, play pivotal roles in the development of these disorders (275). Consequently, "quenching" of activated oxygen species or preventing the cellular damage they cause to proteins and DNA is an important mechanism potentially to prevent chronic diseases such as cardiovascular disease.

An early study in rat peritoneal macrophages grown *in vitro* demonstrated impairment of ROS generation by 10 μM curcumin (122). Similar effects have been observed in red blood cells at comparable concentrations (259). Curcumin has also been shown to scavenge superoxide anion radicals and hydroxyl radicals (131, 136, 245). Similar to other dietary phytochemicals, such as resveratrol (found in grapes, wine, mulberries, and peanuts) and EGCG (found in green tea), curcumin may possess prooxidant activity or antioxidant effects, dependent on dose and the chemical environment (*e.g.*, availability of free Cu^{2+} ions) (7, 15, 21). The balance between antioxidant and prooxidant activity must be carefully considered when planning intervention trials in healthy volunteers, particularly if prooxidant activity results in potentially damaging effects, as suggested by biomarkers such as oxidative DNA adduct levels, shown in Fig. 9 (179).

Nitric oxide (NO) is a short-lived, lipophilic molecule generated from L-arginine by various NADPH-dependent enzymes called NO synthases (NOSs) (144). The physiologic functions of NO include vasodilatation, inhibition of platelet aggregation, neurotransmission, immune defense, and intracellular signaling. NO is classified as a free radical species because it contains an unpaired electron. Its bioactivity is related to the production of many reactive intermediates. Some of these nitrogen species intermediates can damage DNA directly or interfere with DNA repair *via* protein damage (62, 92). Preclinical studies have suggested that curcumin may inhibit induction of macrophage NOS activity at concentrations of 1–20 μM (30). In mice, it was shown that oral administration of an aqueous alkaline solution of curcumin, notably at a tiny dose of 92 ng/g BW, strongly inhibits murine hepatic lipopolysaccharide-induced *iNOS* gene expression (36). Whereas high doses of NO (millimolar) seem to be cytotoxic and induce apoptosis, lower doses of NO (micromolar) can protect malignant cells from apoptosis *in vitro* through upregulation of COX-2 (263, 268, 269). Because inhibition of *iNOS* activity may represent a mechanism of intervention during carcinogenesis, curcumin's apparent activity at low concentrations would have considerable implications for cancer chemoprevention if this effect is reproduced in subsequent preclinical studies.

Endothelial heme oxygenase-1 (*HO-1*) is a protein induced by cellular stress. Its main action is the degradation of heme to the antioxidant biliberdin and the vasoactive molecule carbon monoxide (CO). *In vitro* incubation of bovine aortic endothelial cells with curcumin (5–15 μM) resulted in a dose- and time-dependent increase of HO-1 mRNA, protein expression, and heme oxygenase enzymatic activity. Similar results were observed after incubation of human proximal renal tubular cells with curcumin (1–8 μM) (107). The postulated mechanism for these actions involves the NF-κB pathways and transcriptional mechanisms. Increased heme oxygenase activity also appears to play an important role in curcumin-mediated cytoprotection against oxidative stress and nitric oxide–induced toxicity or apoptosis (177).

B. Inhibition of arachidonic acid pathways

It has been known for well over a decade that curcumin can inhibit cyclooxygenase (COX) activity in rat peritoneal neutrophils and human platelets (8, 9). Arachidonic acid metabo-

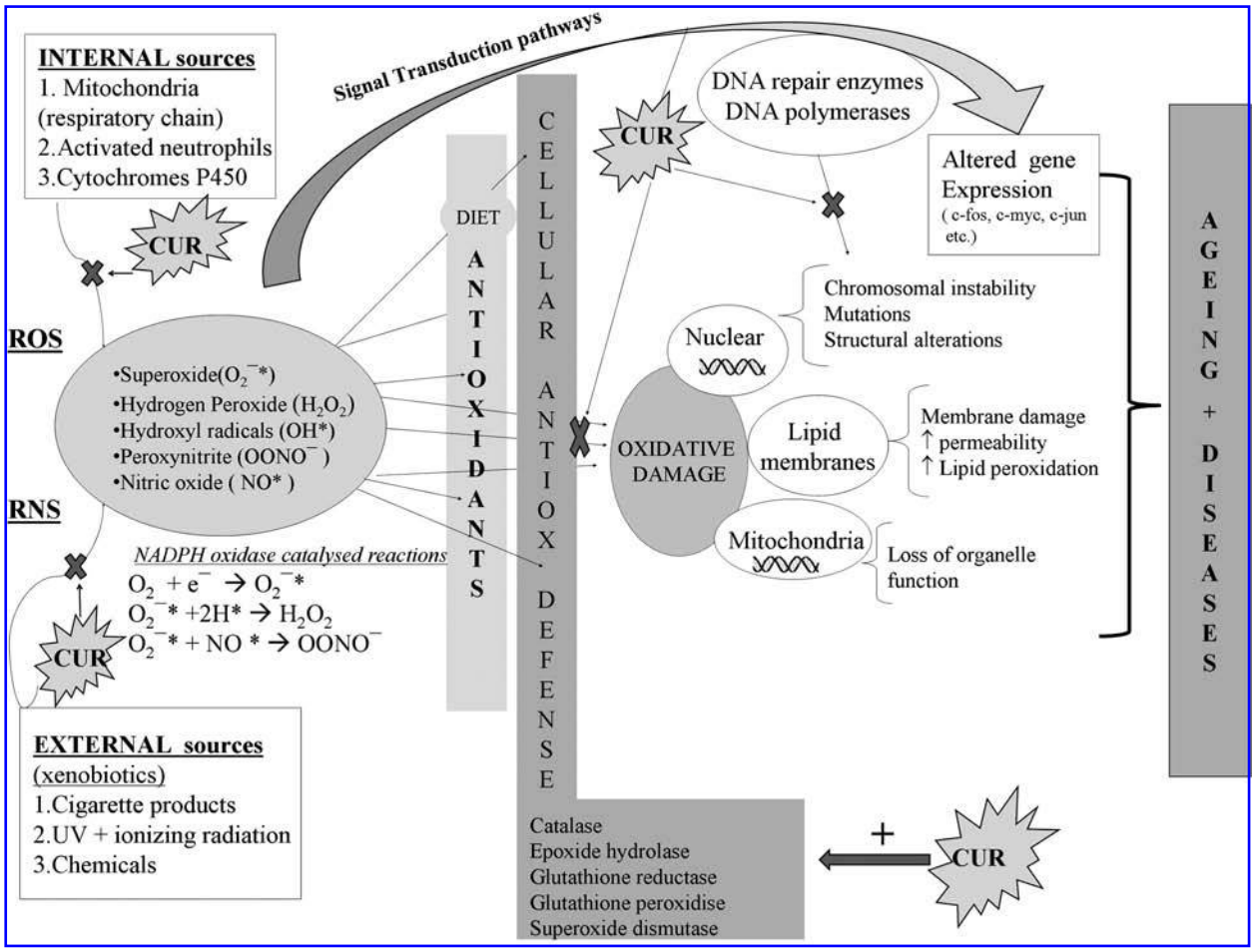

FIG. 9. Graphic representation of curcumin's activity on cellular redox events. Curcumin can prevent (dark crosses) or facilitate protection against (+) the generation of and cellular sequelae of RNS and ROS, dependent on cellular status (see text). For details of effects shown in preclinical models and clinical trials, see references 7, 30, 36, 93, 105, 125, 131, 136, 177, 262, 274, and 277. CUR, curcumin; RNS, reactive nitrogen species; ROS, reactive oxygen species; UV, ultraviolet light.

lism consists of two well-described pathways, the cyclooxygenase and the lipooxygenase pathways. COX is the key enzyme involved in the cyclooxygenase pathway, converting arachidonic acid to prostaglandins and thromboxanes (Fig. 10). COX exists in two isozymes, called COX-1 and COX-2. COX-1 is a constitutive isoform expressed in most tissues; its inhibition results in adverse effects such as gastrointestinal ulcers or impairment of renal blood flow. Conversely, COX-2 is inducible at sites of inflammation by cytokines and intracellular signals; it can also be induced in various normal tissues by the hormones of ovulation and pregnancy, growth factors, oncogenes, and tumor promoters (254). COX-2 is constitutively expressed only in brain and spinal cord tissue. COX-2 overexpression has been implicated in the carcinogenesis of many tumors such as in colon, rectum, breast, head and neck, lung, pancreas, stomach, and prostate (223).

Preclinical studies have shown that curcumin is able to inhibit induction of COX-2 gene expression in oral and colon epithelial cells (130, 291). At a concentration of 20 μM, curcumin showed a stronger inhibition of chemically induced PGE_2 production in colon cells than its metabolites, tetrahydrocurcumin, hexahydrocurcumin, curcumin sulfate, and hexahydrocurcuminol (113). In a recent study in human colon carcinoma cell lines, incubation of HT29 cells (constitutively expressing COX-2 protein) and SW480 cells (deficient in COX-2 expression) with different concentrations of curcumin (0–50 μM), resulted in inhibition of prostaglandin E_2 synthesis, downregulation of COX-2 protein levels, and increased apoptosis of those cells that constitutively express COX-2 protein (148). One of the implicated mechanisms for COX-2 downregulation is inhibition of the activity of the IKK signaling complex responsible for phosphorylation of IκB and subsequently the activation of the transcription factor NF-κB, discussed in more detail earlier in this article (195). This finding parallels studies of commonly used antiinflammatory drugs such as aspirin and salicylates, which inhibit the activity of IκB kinase-β and have also been linked with a decreased incidence of colorectal cancer (289).

In contrast to selective COX-2 inhibitors such as celecoxib, which inhibit the catalytic activity of the isozyme, it should be emphasized that curcumin inhibits the activity of the isozyme by inhibiting the transcription of COX-2 protein (195). Apart

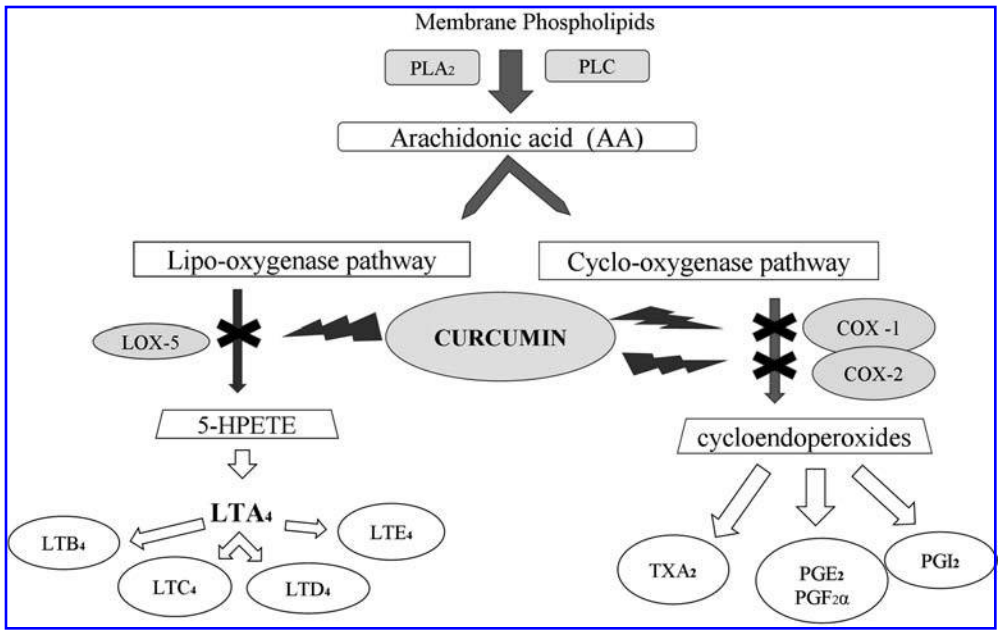

FIG. 10. Arachidonic acid pathway demonstrating catalysis by cyclooxygenase isozymes. Steps inhibited by curcumin are shown by black crosses. COX, cyclooxygenase; HPETE, hydroperoxyeicosatetraenoate; LOX, lipooxygenase; LT, leukotriene; PL, phospholipase; PG, prostaglandin; TX, thromboxane.

from the well-known roles of COX-2 (254), recent studies suggest that the COX-1 isoenzyme also plays a role in inflammation and carcinogenesis; indeed the balance between the metabolic products of COX1 and COX2 catalysis appears important in physiologic function and response to inflammation. Curcumin and some of its analogues do appear to inhibit COX-1 transcription (102, 195). Such inhibition is important because it has been linked to a potential influence on the local spread of malignancy and the communication between malignant cells and their neighboring stromal cells (247, 261).

From a philosophical standpoint, as cancer and most chronic diseases have a multifactorial etiology, natural diet-derived agents such as curcumin that act at multiple cellular levels may stand a better chance of improving the prevention or management of these diseases than agents that affect a single cellular target. A pleiotropic activity in the cell is provided by curcumin's ability to inhibit multiple levels of the NF-κB, AP-1, and JNK signaling pathways (2, 45, 111).

C. Influence on carcinogenesis

Carcinogenesis is the complex process by which normal cells develop into a malignant tumor. Some investigators describe it in three stages: *initiation*, during which normal cells becomes transformed; *promotion*, in which transformed cells become preneoplastic; and *progression*, which is the final irreversible step when the preneoplastic cell becomes neoplastic (29). Various stimuli can cause initiation of a cell, such as carcinogens, oxidative stress, chronic inflammation, UV radiation, and abnormal hormonal stimulation. Chemopreventive agents including curcumin can interfere in the described processes of carcinogenesis by inhibiting the initiation step or suppressing the promotion and progression stages. Curcumin has been shown to have effects relevant to all three stages of carcinogenesis.

Oral curcumin administration has been shown to prevent the development of cancers of the skin, soft palate, stomach, duodenum, colon, liver, lung, and breasts of rodents (181, 202). In particular, the effects of dietary curcumin at concentrations of 0.05–2.0% on colon carcinogenesis have been demonstrated in both chemical and genetic rodent models (128, 165, 216, 225).

Inhibition of initiation has been demonstrated in chemical models, incorporating the measurement of DNA adducts formed by benzo[a]pyrene or by aflatoxin B_1, which have been linked with this stage of carcinogenesis (128, 225). The multiple intestinal neoplasia (*e.g.*, APC^{Min} mouse) model is an example of a genetic model permitting study of the initiation and promotion phases of carcinogenesis (165, 191). Adenoma formation in the Apc^{Min} mouse is associated with a chemically induced mutation in the adenomatous polyposis coli (*APC*) gene. The Min mouse is therefore a model of the human disease, familial adenomatous polyposis (FAP) (162). Curcumin has been used in the prevention of adenoma formation in this model. Addition of curcumin in the diet for the animals' lifetimes at 0.1 and 0.2% showed significant reduction in adenoma number compared with that in control animals (165, 191). The dose of 0.2%, equating to ~300 mg/kg BW, resulted in levels of curcumin and metabolites in the plasma just above the limit of detection (~0.6 ng/ml) but below the limit of quantitation for the HPLC assay. Concentrations of curcumin in the gastrointestinal mucosa ranged from 40 to 240 nmol/g of tissue (191). Although the investigators correctly claimed that this result provides a likely "target concentration," reliable equations currently do not exist to permit estimation of how the results can be extrapo-

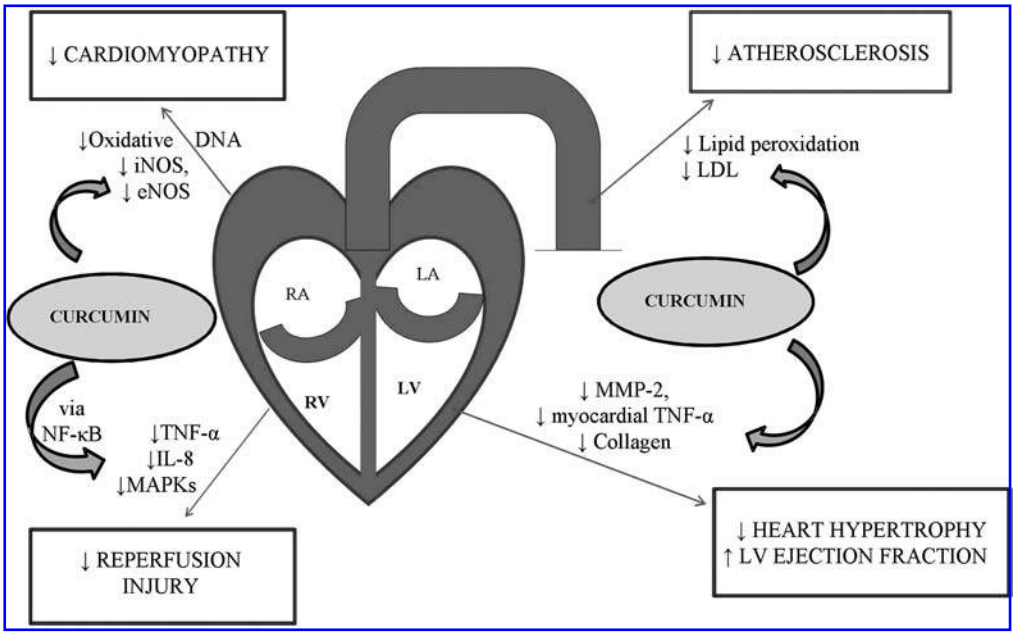

FIG. 11. Graphic representation of curcumin's potential for cardiovascular protection. Curved arrows, Curcumin's potential mechanisms of cardioprotection by inhibition of disease processes. RA, Right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; IL, interleukin; MAPK, mitogen-activated protein kinases; MMP, matrix metalloproteinase; LDL, low-density lipoprotein; NF-κB, nuclear factor-kappa B; NOS, nitric oxide synthase; TNF, tumor necrosis factor.

lated to studies of oral curcumin in human gastrointestinal mucosa.

Chemical models of the promotion and progression stages of colon cancer have also been used to study the effects of oral curcumin during carcinogenesis. In intestinal cancer in mice induced by azoxymethane (AOM), oral curcumin (2,000 parts per million) for 14 weeks produced a significant increase in the apoptotic histologic index when compared with controls (216). Similar results were demonstrated in a study in male F344 rats, when oral curcumin was administered for 2–3 weeks before and up to 52 weeks after subcutaneous injections of AOM. These findings are compatible with the hypothesis that curcumin inhibits colon tumorigenesis in the initiation and the promotion/progression stages (128). In another study in male Wistar rats, colon carcinogenesis induced by injection of 1,2-dimethylhydrazine (DMH), a toxin colon-specific carcinogen, was reduced significantly by intragastric curcumin or a bisdemethoxycurcumin analogue, bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione (BDMC-A) (63).

Topical application of curcumin has been also shown to inhibit the initiation and promotion stages of chemically induced skin cancer (55). In a series of studies, benzo[a]pyrene or 7,12-dimethylbenz[a]anthracene (DMBA) were used to induce tumor initiation, and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) was used for tumor promotion; all of which were inhibited by topical curcumin. The mechanisms for these effects were inhibition of inflammation and of arachidonic acid metabolism pathway (also discussed earlier and subsequently), inhibition of hydrogen peroxide formation, and inhibition of ornithine decarboxylase activity/transcription, the latter being the rate-limiting step in polyamine biosynthesis (55). In a subsequent study in Syrian golden hamsters, application of curcumin 3 times a week to the cheek pouch demonstrated inhibition of DMBA-induced oral carcinogenesis (152). Building on the studies of combinatorial chemoprevention by using curcumin and EGCG discussed earlier, concomitant use of topical curcumin with oral administration of green tea has been shown to have a synergistic effect on the inhibition of chemical carcinogenesis induced by topical application of 0.5% DBMA (9,10-dimethyl-1,2-benzanthracene) solution (130, 152).

In a study of curcumin's effect on tumor invasion and metastasis, androgen-resistant prostate cancer cells (DU-145) were studied *in vitro* and in a xenograft model (110). The investigators found that curcumin treatment significantly reduced the expression of the metalloproteinases (MMP) 2 and 9 and that the tumor volume was decreased *in vivo* (110). A further study of curcumin's activity against established prostate cancer has been performed in combination with the antimetabolite, gemcitabine. It was found that curcumin treatment could enhance the anticancer effects of gemcitabine measured by tumor size (137) and that the combination of these two agents could cause suppression of angiogenesis and of tumor proliferation. The mechanisms involved appeared to include the suppression of the NF-κB pathway and its related gene products (*i.e.*, c-myc, COX-2, cyclin D1, Bcl-2, Bcl-xL, cellular inhibitor of AP-1, MMP, and VEGF) (137).

To summarize the key findings in this subsection, oral and topical administration of curcumin has demonstrated significant properties in the attenuation of carcinogenesis and the behavior of established cancers in rodents. Its effects appear pertinent to the initiation and the more advanced stages of carcinogenesis. Curcumin's beneficial effects have been shown in both

chemical and genetic models, providing strong preclinical data for the justification of clinical studies in humans. The mechanisms implicated in the inhibition of tumorigenesis are diverse and appear to involve a combination of antiinflammatory, antioxidant, immunomodulatory, proapoptotic, and other properties of curcumin, as well as its effect on genes and molecular pathways. The combination of curcumin with other chemopreventing agents may improve the efficacy of antitumor effects, without any apparent compromise of favorable safety profiles.

D. Effects on metabolic enzyme systems

One of the body's cellular defense mechanisms against environmental toxicants, drugs, carcinogens, or xenobiotics occurs *via* metabolism of potentially toxic agents by metabolizing enzymes. The metabolizing enzyme systems can be classified as phase I and phase II, and in drug-metabolizing systems, some authors also include a phase III class of transporters (281). The phase I enzymes consist of cytochrome P450 (CYP) isoforms, the P450 reductase, the cytochrome *b5*, and the epoxide hydrolase. They catalyze reactions that modify the polar status of the substrate through aromatic hydroxylation, aliphatic hydroxylation, oxidative dealkylation, N- and S-oxidation, and deamination. The phase II enzymes include glutathione–S-transferase (GST), aryl sulfatase, UDP-glucuronic transferase, and NAD(P)H:quinone reductase (NQO1). Phase II enzymes facilitate the conjugation of the xenobiotics to another substance (*e.g.*, glutathione or glucuronic acid), thus rendering the xenobiotic more hydrophilic and enhancing its excretion in bile or urine (230). Phase III transporters include P-glycoprotein (P-gp), multidrug resistance–associated proteins (MRPs), and the organic anion transporting polypeptide 2 (OATP2). Their roles are drug absorption, distribution, and excretion (281).

Many compounds, such as tetrachloromethane and aflatoxin B_1, are metabolized and activated to toxic reactive metabolites by the cytochromes P450 (CYP) enzyme system. As a result, inhibition of this phase I enzymes system may protect organisms from the toxic effects of chemicals and carcinogens. Inhibition of CYP isoenzymes by curcumin has been demonstrated in cells cultured *in vitro* (81). In a mammary carcinoma cell line, curcumin's inhibition of CYP1A1-mediated activation of dimethylbenzanthracene (DMBA) resulted in diminished DNA adduct formation, providing an indication of its protective role against carcinogens (52). In this study, the authors also tested the interactions of curcumin with the carcinogen activation pathway mediated by aryl hydrocarbon receptor (AhR). AhR is a cytosolic protein that, after creating a complex with carcinogens or similar compounds, translocates to the nucleus, binds to the ARNT transcription-activating factor, and finally upregulates a group of AhR-regulated genes associated with carcinogen metabolism. The investigators of this study found that although curcumin could activate the AhR and increase the levels of CYP1A1 mRNA, curcumin administration resulted in a partial inhibition of both the activation of AhR and the activity of CYP1A1 in DMBA-treated cells. Therefore, the authors suggested that curcumin could possibly exert its chemopreventive properties by competing with the aryl hydrocarbons for both the AhR and the CYP1A1. The effects of curcumin on the AhR pathway were also shown in another study of oral squamous carcinoma cells (SCCs) and oral mucosal keratinocytes (211). Curcumin initiated the nuclear translocation of the AhR and the formation of the active AhR-ARNT compound. In this study, curcumin also caused an increase of CYP1A1 expression and function, but inhibition of CYP1A1-mediated benzo(a)-pyrene diol bioactivation (211). These discrepant findings emphasize the importance of detailed observation with relevant study end points.

In a more recent study in F344 rats, it was found that curcumin (270 mg/kg) administered i.g. suppressed esophageal carcinogenesis induced by *N*-nitrosomethylbenzamine (NMBA), an effect associated with a decrease in the levels of esophageal and gastric CYP2B1 and CYP2E1 enzymes (174). No suppression occurred of the hepatic, lung or intestine CYP proteins studied, suggesting that the local effect seen in esophageal mucosa was dependent on the concentration achieved by the delivery method. The authors suggested that the effects observed were most relevant to the initiation stage of carcinogenesis (174). Based on such studies showing curcumin's effects on the metabolizing systems such as CYP isoenzymes, caution has been advised in clinical practice, and potential interactions with drugs, such as the antibiotic macrolides, warfarin, digoxin, and statins, were discussed earlier.

In contrast to the CYP family of isoenzymes, glutathione S-transferases (GSTs) and other phase II enzymes are thought to play a protective role by eliminating toxic substances and oxidants. Induction of these detoxifiers is believed to confer benefit in the prevention of the early stages of carcinogenesis. Epoxide hydrolase (EH) and various hepatic GST isoenzymes were significantly increased with curcumin feeding in mice (239). Induction of GST activity by dietary curcumin in both mice and rats has been replicated in other studies (65, 192, 228). The ability of curcumin's analogues to induce phase II enzymes appears to be associated with the presence of the hydroxyl groups at *ortho*-positions on the aromatic rings and the β-diketone functionality (65).

Although glutathione (GSH) plays a protective role against toxins, carcinogens, and reactive oxygen species, it may also be linked with multidrug resistance through its spontaneous reactions with drugs or as a cofactor for GST isoenzymes. Multiple GST isoenzymes are located either in the membrane or the cytoplasm of cells. In the GST superfamily, five families of cytosolic isoenzymes exist: classes α, μ, π, σ, and θ. In contrast to the early stages of carcinogenesis in advanced tumors, GST isoenzymes (mainly class π GSTs followed by class α and μ) may be aberrantly overexpressed and linked with resistance to chemotherapy (104). In contrast to its induction of total GST activity measured by certain chemical assays, curcumin appears to be capable of inhibiting specific GST isoenzymes (for example, *GSTP1* expression in leukemia cells grown *in vitro* as well as human recombinant *GST* α*1-1,* α*2-2,* μ*1-1,* μ*2-2* and π*1-1* in *Escherichia coli* cells) (73, 105). In the presence of conflicting results, it is important to define the cellular consequences that result from the effects observed. In the quoted studies of GST isoenzymes, a linear association was found between the level of inhibition by curcumin and the induction of apoptosis (73, 105).

E. Cytotoxicity and cell-cycle effects

Whereas curcumin may be relatively nontoxic to healthy cells, *in vitro* studies in various cell lines and particularly in

cancer cells suggest that curcumin is cytotoxic at low concentrations (*i.e*., low micromolar levels). Studies in colon adenocarcinoma cell lines demonstrated that curcumin inhibited cell proliferation, caused arrest of cells in the S phase and G_2/M interphase of the cell cycle, and induced apoptosis (248). Similar effects have been observed in breast, kidney, lung, pancreatic, gastric, ovarian, cervical, hepatocellular, lymphoid, myeloid, melanoma, oral epithelial, and prostatic cell lines derived from malignant tumors (16, 42, 66, 87, 100, 121, 231, 255, 284). Curcumin has also shown growth inhibitory effects *in vitro* in cancer cell lines derived from human prostate, breast, large intestine, bone, bladder, and leukemia (34, 41, 42, 68, 100, 139, 188, 237). In this diverse range of studies, curcumin has been shown to exert variable effects on the cell cycle, which may be dependent on the tissue type and cell origin.

Features of apoptosis such as cell shrinkage, increased membrane permeability, chromatin condensation, and DNA fragmentation have been observed in HT29 human colon carcinoma, human kidney carcinoma, mouse embryo fibroblast, mouse sarcoma, and human hepatocellular carcinoma cell lines grown *in vitro* after treatment with 30–90 μM curcumin (121). Curcumin caused cell-cycle arrest at the S and G_2/M phases in human colon cells (LoVo cells) cultured *in vitro* (43), and at G_2 or M phases in the MCF-7 human breast tumor cell line (237). The apoptotic effects described appear to require the presence of the diketone moiety of curcumin, which is not present in all curcuminoids (237). In a separate study in the human cancer cell lines, TK-10, MCF-7, and UACC-62, curcumin has been shown to cause DNA damage and induce apoptosis by interference with the activity of topoisomerase II, an enzyme that catalyzes the "unknotting" of DNA during mitosis (169). Compatible with this hypothesis, other investigators have shown that curcumin delays phosphorylation of histone H2AX (γH2AX), a marker of double-strand breaks, which can result in apoptotic DNA fragmentation (176). These preliminary findings are likely to be of great value in the future because the role of topoisomerases in replication fork collapse after single-strand breaks and the role of histone phosphorylation in the function and stability of proteins involved in DNA replication and repair are currently being elucidated.

The mechanisms implicated in curcumin-induced apoptosis appear to be multifactorial, including effects on the stability of p53, the release of cytochrome *c* from mitochondria, and the generation of ROS (3, 262). Activation of caspases-3 and -8, inhibition of telomerase, upregulation of *bax*, and downregulation of *bcl-2* gene appear relevant to the proapoptotic process initiated by curcumin (34, 203). Curcumin has also recently been found to inhibit the *survivin* and *aurora B* genes, members of the chromosomal passenger complex and important for several mitotic functions. Such inhibition leads to mitotic disturbances and potentially to apoptosis or mitotic catastrophe. The mTOR-mediated pathway has also been identified as a target of curcumin, which is important for the division and proliferation of cells (23, 277). Other mechanisms implicated in curcumin-mediated apoptosis involve inhibition of the molecules Akt, NF-κB, AP-1, or JNK, as discussed earlier (5, 45, 111, 112).

A critical determinant of whether an agent improves the therapeutic index in the treatment of cancer is the relative specificity of cell kill in tumor cells compared with normal cells. Although one study suggested that the inhibition of cell proliferation may be nonselective in transformed and nontransformed cell lines grown *in vitro* (87), one study published in abstract form of the SV40-virus transformed human colon epithelial cell line, HCEC, compared with the malignant colon adenocarcinoma cell line, HT29, suggested some degree of potential cancer specificity, with a 50% maximal inhibitory concentration (IC_{50}) for the malignant cells of $\sim$5 μM compared with 14 μM for the nonmalignant cells (193). On account of the limitations of *in vitro* models discussed earlier, further data from animal models are urgently required regarding the selectivity of cell kill by curcumin. Such data may be used in the prediction of curcumin's potential effects on the therapeutic index in humans (*i.e*., effects on malignant cells compared with effects on normal cells).

One factor that may confer potential tumor selectivity is p53 status. Studies in normal thymocytes, in colon carcinoma, and myeloid leukaemia cells *in vitro* have shown that curcumin induces degradation of the tumor-suppressor protein, p53, *via* inhibition of NAD(P)H:quinone oxidoreductase 1 (NQO1) activity (262). Contrary to this suggestion, in two human lung cancer cell lines, one p53 proficient and the other p53 null, apoptosis was achieved in a p53-independent fashion as curcumin induced cell death in both cell lines to the same extent (198). In a separate study, curcumin was found to enhance apoptosis in chemoresistant ovarian cancer cell lines pretreated with the tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) (270). Apoptosis induction has also been observed in cisplatin-resistant and cisplatin-sensitive ovarian cancer cells *in vitro* (276). Interestingly, this effect appeared to be achieved mainly by enhancement of p53 phosphorylation and caspase-3 activation. Current concerns regarding curcumin's effects on p53 activity were discussed earlier.

Curcumin has also been shown to induce apoptosis in the human leukemia cell line, K-562, by dose-dependent inhibition of telomerase (34). Telomerase is a reverse transcriptase enzyme that is frequently active in cancer cells to maintain telomere length. Telomeres are ribonucleoproteins located at the ends of the chromosomes, consisting of repetitive sequences of bases (*e.g*., TTAGGG in humans). Telomerase is inactive in normal cells, leading to progressive telomere shortening and subsequent apoptosis. Telomerase inhibition by curcumin (1–100 μM) has also been shown in other studies in cancer cell lines grown *in vitro* (58, 200).

G_2/M arrest renders cells more sensitive to the cytotoxic effects of radiation, suggesting that curcumin may be used as a radiosensitizer by interfering with the cell cycle. Radiosensitization by curcumin has been demonstrated in studies using prostate cancer and leukemia cell lines grown *in vitro* (17, 46). In the former study, prostatic cancer PC-3 cells were exposed to radiation. When these cell lines were treated concomitantly with curcumin (2–4 μM), downregulation of Bcl-2 was observed, which altered the Bcl2/bax2 ratio and was compatible with radiosensitization (17).

In contrast to these findings, other studies showed that curcumin may demonstrate antiapoptotic properties when apoptosis is induced by certain chemicals or mutagens. Curcumin prevented apoptosis induced by methylglyoxal (MG), an endogenous α-ketoaldehyde and dicarbonyl product of the cell metabolism and glycolytic cycle, in human hepatoma G_2 cells

and also reduced reactive oxygen species (ROS) and other apoptosis-related biochemical changes [*i.e*., cytochrome *c* release, caspase-3 activation, and poly-ADP ribose polymerase (PARP) cleavage (38)]. In a study of human epidermal cancer (A431) cells grown *in vitro*, curcumin inhibited the apoptotic process induced by photodynamic treatment (PDT) (37). Although the findings of these two studies may be relevant to the prevention of chronic sequelae of human diseases such as diabetes mellitus, they may also represent adverse results for the application of curcumin in the treatment of cancers, because curcumin may be preventing the killing of cancer cells induced by another treatment.

Some of these findings *in vitro* have been extended to studies in xenograft models. Dietary curcumin has been shown to inhibit chemotherapy-induced apoptosis in MCF-7, MDA-MB-231, and BT-474 human breast cancer cell lines grown *in vivo*. Exposure of these cells to 1 μM curcumin for ~3 h was found to antagonize the apoptotic effects of the drugs camptothecin, doxorubicin (Adriamycin), mechlorethamine, and cyclophosphamide in a time- and dose-dependent fashion (242). Based on these findings, the authors raised a note of caution regarding the concomitant use of curcumin in patients receiving chemotherapy for breast cancer.

Additionally, curcumin caused upregulation of growth arrest and DNA damage–inducible (*GADD)* genes and downregulation of the survival genes *egr-1*, *c-myc*, *bcl-X(L)*, IAP (inhibitor of apoptosis protein), and their related proteins, all of which have been associated with cancer cell proliferation and tumor survival (100, 278). In Moser cells grown *in vitro*, suppression of gene expression of cyclin D1 and the epidermal growth factor receptor (EGFR) by curcumin was achieved *via* activation of peroxisome proliferator–activated receptor γ (PPAR-γ), which affected the cell cycle and apoptosis (41). In a recent gene-expression profiling study aiming to identify novel molecular targets of curcumin, researchers used a 12,625-gene cDNA microarray approach to compare total RNA extracted from curcumin-treated and untreated MDA-1986 oral epithelial cancer cells (284). The researchers identified 202 upregulated mRNAs and 505 decreased transcripts with at least twofold differential expression, including the proapoptotic activating transcription factor 3 (ATF3), which was induced more than fourfold (284).

Cytotoxicity and inhibition of proliferation explain some of the antimicrobial, antiprotozoal, antiviral, and antifungal properties of curcumin. In the presence of oxygen, curcumin at micromolar concentrations caused photocytotoxicity to Gram-positive bacteria through hydrogen peroxide generation (59). Curcumin (6.25–50 μM) inhibited the growth *in vitro* of strains of *Helicobacter pylori* (163), suggesting potential anti-ulcerogenic efficacy in humans. Other preclinical studies have shown evidence of curcumin's activity against cultures of *Plasmodium falciparum* parasites *via* inhibition of histone acetyltransferase activity and generation of ROS (57). Previous studies demonstrated the antimalarial activity of curcumin in *P. falciparum* cultures *in vitro* and in Swiss mice infected by i.p. injection of *P. berghei*. In the latter *in vivo* experiment, oral curcumin resulted in a 90% reduction of parasitemia and a 29% overall survival benefit for the animals compared with the control group at day 21 after infection (209). Despite the initial enthusiasm about the effects of curcumin on the human immunodeficiency virus (HIV)-1 integrase, a systematic review published by The Cochrane Collaboration Library has found insufficient evidence of activity against HIV (159). It should be noted that antimicrobial activity of curcumin is potentially cancer chemopreventive because an increasing number of pathogens are linked with human cancers.

F. Effects on angiogenesis and cell adhesion

It has been well known for more than half a century that angiogenesis is linked to neoplasia (94). Angiogenesis, meaning the creation of new vessels, derived from the Greek words *angio* (vessel) and *genesis* (birth), is regarded as vital to the development of cancer from premalignant lesions as well as for tumor growth, survival, and metastasis (82). The density of the vasculature and the intensity of angiogenesis act as prognostic factors for many solid tumors, including breast, prostate, and ovarian cancers (82). This scientific association may also apply to early cancers of the endometrium and lung (227). Similarly, expression of angiogenic growth factors appears to correlate with prognosis for lung and other cancers (227).

Curcumin may inhibit angiogenesis directly and *via* regulation of the growth factors, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), endothelial growth factor (EGF), as well as the genes, *angiopoietin 1 & 2,HIF-1,HO-1*, and the transcriptional factors (*e.g*., NF-κB) discussed earlier. It is known that hypoxic stress and tissue growth factor β (TGF-β) activation induce VEGF expression in human HT-1080 fibrosarcoma cells through transcriptional activation of AP-1 and HIF-1 (232). Curcumin is a potent inhibitor of AP-1 activation, and recently, it also was found that curcumin is a direct inhibitor of the activity of the HIF-1 transcriptional factor (19, 48). HIF-1 is composed of two subunits, HIF-1alpha and the aryl hydrocarbon receptor nuclear translocator (ARNT). Curcumin promotes the proteasomal degradation and destabilization of the ARNT subunit and thus inactivates HIF-1 (48). The role of curcumin in preventing protein degradation (*e.g*., the ubiquitin-proteasome pathway) is an area of increasing research interest.

In an early study using a mouse corneal model, curcumin at concentrations of 10 μM and above demonstrated direct inhibition of angiogenesis *in vivo* (11). Inhibition of angiogenic growth factor production and metalloproteinase generation, both integral to the formation of new vasculature, has also been influenced by curcumin in nonmalignant and malignant cells grown *in vitro* (172, 256). *In vitro* and *in vivo* studies investigating the effect of curcumin on Ehrlich ascites tumor cells (EATs), human umbilical vein endothelial cells (HUVECs), and NIH3T3 cells showed that curcumin inhibits the growth of the EAT and HUVECs (98). In this study, curcumin's antiangiogenic properties were attributed to inhibition of the production of VEGF and *angiopoietin 1* and *2* (*Ang1* and *Ang2*) in EAT cells, VEGF and *Ang1* in NIH3T3 cells, and downregulation of expression of the *KDR* gene (*i.e*., an angiogenic receptor) in HUVECs.

Cancer progression, local invasion, and metastasis also require the involvement of molecules produced by the tumor or *via* its interaction with the surrounding matrix. These molecules influence cellular interaction and adhesion. Similar to the inhibition of angiogenic factors, curcumin has been shown to reg-

ulate proteins related to cell–cell adhesion, such as β-catenin, E-cadherin, and APC, and to inhibit the production of cytokines relevant to tumor growth [*e.g.*, tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1)] (116,189). Additionally, curcumin has been shown to reduce the expression of membrane surface molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin [also known as ELAM-1 (endothelial leukocyte adhesion molecule-1)] that play a role in cellular adhesion (35, 96, 116). This effect was achieved *via* inhibition of gene expression at a transcriptional level (96). Collectively, these results pertaining to direct and indirect inhibition of angiogenesis and attenuation of cell–cell adhesion necessary for malignant behavior render curcumin a promising agent for altering the invasive and metastatic behavior of established malignancy. The recent development of new preclinical models for studying tumor–stromal interactions provides an opportunity to study curcumin's effects on these interactions.

G. Immunologic modulation

The immune system in both prokaryotes and eukaryotes consists of a constellation of mechanisms protecting the host from infectious agents, tumors, and pathogens. These mechanisms include activation or suppression of various cell types, such as lymphocytes (*e.g.*, B cells, T cells, and natural killer cells) and leukocytes (*e.g.*, neutrophils, macrophages, and dendritic cells). In addition, effects exist at multiple levels of molecules excreted by these cells, for example, antibodies, enzymes, and cytokines. Many cellular and humoral factors are frequently involved in the pathophysiology, development, and progression of acute disorders (*e.g.*, infection, trauma, allergies) and chronic diseases (*e.g.*, autoimmune diseases and carcinogenesis).

Although curcumin has been found to exert differing and sometimes contradictory effects on cell-mediated immunity (reviewed in ref. 113 and represented in Table 2), its effect on humoral immunity appears consistent across studies performed in various preclinical model systems *in vitro*. These effects include inhibition of interleukin (IL)-2, -6, -8, and -12 production, inhibition of tumor necrosis factor (TNF)-α production, interference with the adhesion molecules, ICAM-1, VCAM-1, and E-selectin, and increases in the levels of TNF-related apoptosis-inducing ligand (TRAIL) (115). Curcumin, at a dose of 12.5–30 μM, caused irreversible inhibition of cytokine production *in vitro*, particularly IL-2 and IFN-γ by splenic T cells and TNF-α by peritoneal macrophages (84). The investigators of this study suggested that a key mechanism of the effect observed was inhibition of activation of NF-κB, a signaling pathway discussed earlier (84).

TNF is an important molecule in the pathogenesis of many inflammatory and autoimmune disorders; it is produced mainly by activated macrophages. Among its other properties, TNF also induces other cytokines, such as interleukins and adhesion molecules, as well as the transcriptional factor NF-κB. In a study of human monocyte–macrophage cells (Mono Mac 6) grown *in vitro*, treatment with 5 μM curcumin caused marked inhibition of lipopolysaccharide (LPS)-induced production of TNF-α and IL-1 (35).

With regard to cell-mediated immunity, curcumin has demonstrated various immunomodulatory effects, including activation of host macrophages and natural killer (NK) cells, inhibition of the proliferation of T cells by various stimuli, and IL-2

Table 2. Immunomodulatory Effects of Curcumin on Cellular and Humoral Immunity

	Effects	*References*
Immune cells		
T cells	Inhibition of proliferation/activity	35, 84, 283
	Inhibition of IL-2 expression in T cells	84, 283
B cells	↑ Production in intestinal mucosa	51, 241
	↓ EBV-driven proliferation of B cells	115
	Apoptosis, growth arrest	100
	Differential effects	
Dendritic cells	Suppressed activity	115
Natural killer cells	↑ Cytotoxicity	26, 283
Macrophages	Reduced ROS, RNS generation	26, 30, 122
	Differential effects	26
Peripheral blood cells	↑ White cell count	115
	↓ Neutrophil phagocytic functions	
	↑ increased serum antibody levels	
	Effects on function of spleen lymphocytes	
Humoral		
Interleukins (IL)	Inhibition/reduced production of IL -1, -2, -6, -8, -12, IFN-γ	35, 51, 84, 96, 283
TNF-α	Inhibition of expression	35, 84, 96
	↓ Levels	
TRAIL (TNF-related apoptosis inducing ligand)	↑ Activity → ↑ apoptosis	115
Adhesion molecules	Inhibition of VCAM-1, ICAM-1, and β-selectin	96
Histamine release	↓ Release from basophils	252

expression in T-cells, as well as suppression of dendritic cells and modulation of lymphocyte-mediated functions (26, 84). In a recently published study performed in RAW-264.7 mouse macrophage cells grown *in vitro*, the investigators suggested that curcumin inhibits phytohemagglutinin (PHA)-induced T-cell proliferation, interleukin-2 production, NO generation, and lipopolysaccharide-induced NF-κB activity, as well as stimulating NK cell cytotoxicity (283). In a study performed in Min (C57BL/6J-Min/+) mice, which bear a mutation of the *APC* gene and spontaneously develop intestinal adenomas, treatment with curcumin resulted in an increase of intestinal mucosal B cells and CD4(+) T cells, suggestive of curcumin's immunomodulatory functions (51). In a study of B cells and follicular lymphoma cells grown *in vitro*, treatment with curcumin resulted in inhibition of cellular growth and induction of apoptosis (241). This effect was associated with significant downregulation of the *bcl-2* gene (240). It is known that members of the *bcl-2* family are involved in mitochondrial membrane permeability (93), and therefore their downregulation may contribute, to some extent, to the increased mitochondrial permeability, edema, induction of apoptosis, and cell death observed *in vitro* (241).

Mitochondria play an important role in cell proliferation and apoptosis in both normal and malignant cells. Curcumin has been shown to increase mitochondrial membrane permeability in rat hepatocytes *via* opening of the permeability transition pore and by oxidation of the membrane protein thiols, resulting in edema, loss of membrane potential, and inhibition of ATP synthesis (175). Mitochondrial cell death may also be achieved by curcumin-induced dysregulation of the proteasome–ubiquitin pathway. Like general proteasome inhibitors currently used in clinical practice (*e.g.*, bortezomib), curcumin's effect on this pathway appears to target proliferating and malignant cells more efficiently than differentiated ones (118), although curcumin's specificity in inhibiting proteins in the pathway is not yet known. Because ligases in this pathway are responsible for the ubiquitination of several substrates from several pathways that are involved in roles as diverse as protein trafficking, DNA repair, protein refolding, and proteasome-dependent degradation, it is conceivable that curcumin's pleiotropic effects in cells may be attributable to effects on such ligases.

The breadth of curcumin's effects on the immune system are illustrated in Table 2. Because curcumin can affect multiple signaling pathways, enzymatic catalysis, RNA transcription, and protein translation, it is perhaps not surprising that the effects observed may depend on the cell type studied, the phase of the cell cycle, and how the model system is applied.

VII. PREVENTION AND TREATMENT OF NONMALIGNANT DISEASES

A. Effects on cardiovascular system

On account of its well-documented antioxidant properties, curcumin has been extensively investigated for its potential cardiovascular protection (summarized in Figs. 11 and 12). In a study performed on streptozocin-induced diabetic rats, the effect of curcumin, administered i.p. at doses of 150 mg/kg for 4 weeks, on rats' hearts was investigated (79). The researchers found that diabetic rats exhibited increased levels of eNOS and iNOS mRNA compared with control nondiabetic rats. They also found that curcumin prevented eNOS and iNOS mRNA upregulation in the diabetic rats. Curcumin also increased levels of endothelin-1 (ET-1) in the heart and the endothelial cells of the treated rats (79). ET-1 is a known vasoconstrictor, implicated as a contributory factor in atherosclerosis and hypertension. Other preclinical studies have shown that curcumin administered orally or intravenously in rats or rabbits can reduce cardiac hypertrophy *via* downregulation of MMP-2 and inhibition of collagen formation and remodeling (183, 287).

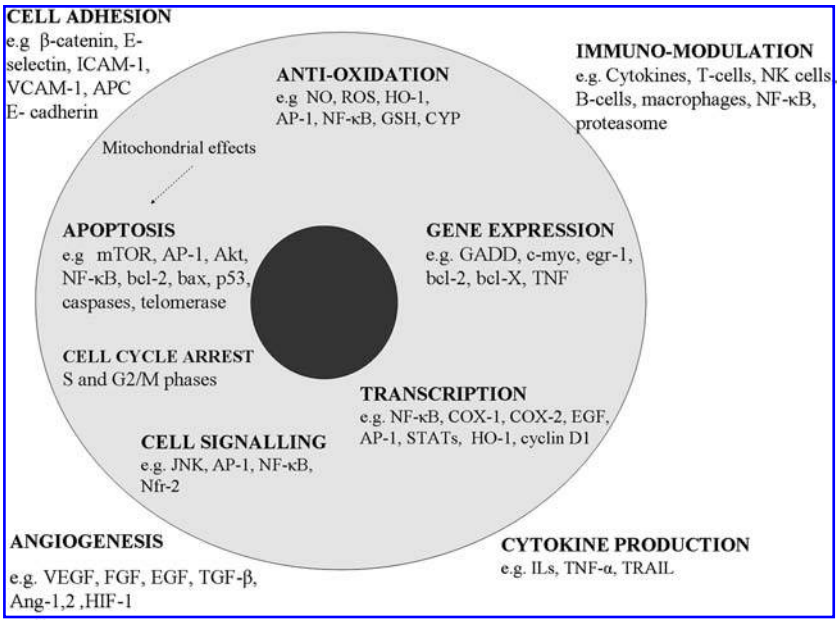

FIG. 12. Simplified representation of diverse cellular processes affected by curcumin in preclinical models, with selected examples of each process. AP-1, activator protein-1; APC, adenomatous polyposis coli; COX, cyclooxygenase; CYP, cytochrome P450; EGF, epidermal growth factor; Egr-1, early growth response-1; FGF, fibroblast growth factor; GADD, growth arrest and DNA damage; GSH, glutathione; HIF-1, hypoxia-inducible factor-1; HO-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IL, interleukin; JNK, c-Jun N-terminal kinase; mTOR, mammalian target of rapamycin; NO, nitric oxide; NF-κB, nuclear factor-kappa B; Nrf-2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

Curcumin has also been shown to ameliorate ischemia–reperfusion heart injury in preclinical models, both *in vivo* in rabbits during and after cardiopulmonary bypass and *ex vivo* in isolated rat hearts. Consistent with the data earlier, this effect was thought to involve inhibition of the NF-κB signal cascade and reductions of inflammatory cytokines (TNF-α and IL-8) (217, 288). In contrast to these potentially beneficial effects of curcumin, it was demonstrated in a single preclinical study that curcumin applied on heart tissues from infants with congenital cyanotic defects and on rabbit heart may abolish the cardioprotective role of chronic hypoxia through inactivation of p53, p38, and c-Jun kinase pathways (199).

Additional data on cardioprotection is provided by the antiatherosclerotic effects of curcumin. In an early study, 18 rabbits were fed, for 7 weeks, an atherosclerosis-inducing diet and were divided into three groups to receive oral turmeric extract at low dose (1.66 mg/kg BW), high dose (3.2 mg/kg BW), or no extract (201). The effects on LDL oxidation and plasma lipids were evaluated. It was found that treatment with turmeric extract resulted in reduced plasma lipid levels, and furthermore, the low-dose group had less LDL susceptibility to lipid peroxidation than did the other two groups (201). The same research team also studied the antiatherosclerotic effects of *Curcuma* extract in rabbits, with similar results (197). The reason for a lack of dose response is not clear, and further in vivo studies are required, incorporating three or more dose levels.

B. Effects on nervous system

Over the past decade, several interesting studies have used curcumin in neurodegenerative disorders, especially Alzheimer disease (AD) and Parkinson disease (PD). Based on the knowledge that oxidative damage and β-amyloid accumulation are involved in the pathogenesis of AD, researchers tested the effects of oral curcumin on the Tg2576 APPSw transgenic mouse, an animal model for AD (155). Mice were fed no curcumin, low-dose curcumin (160 ppm in the diet), or high-dose curcumin (5,000 ppm) for 6 months. The researchers found that curcumin at both low and high doses reduced oxidized proteins levels as well as levels of the inflammatory cytokine, IL-1β, in brain tissue. Notably, the low-dose curcumin group also showed a significant reduction of the astrocytic marker glial fibrillary acidic protein (GFAP), which is involved in brain injury and inflammation. Similar to the cardiovascular study discussed earlier, these effects were not observed with the high-dose curcumin group. The reason for this discrepancy is not known. However, it should be noted that the levels of amyloid precursor (APP) in the membrane fraction remained unaffected, underlining the need for further studies to scrutinize the mechanisms of curcumin's potential effects in AD (155).

Other studies using similar animal models have shown that curcumin effectively reduces amyloid formation, amyloid deposition, oxidative damage, and microglial activation, which have all been linked with neurodegenerative diseases (53, 285). In these studies, curcumin resulted in effects superior to those of nonsteroidal antiinflammatory drugs or other antioxidants. In a subsequent study of amyloid-β peptides (Abeta) performed in cells grown *in vitro*, curcumin (0.1–1 μM) inhibited the formation and the extension of β-amyloid fibrils (fAbeta) and promoted their destabilization (184). In a separate study, macrophages derived from patients with AD demonstrated increased Abeta uptake and clearance in response to curcumin, thus improving a deficit in amyloid phagocytosis seen in AD patients compared with controls (292). As discussed earlier, heme oxygenase-1 (HO-1) can play a cytoprotective role *via* generation of vasoactive carbon monoxide and the antioxidant bilirubin. In patients with AD, increased levels of Abeta bind with heme, forming a peroxidase complex, which causes depletion of functional regulatory heme and thus allows oxidative brain injury and neurotoxicity. Curcumin prevented this oxidative damage *in vitro* by stimulating HO-1 synthesis and inhibiting the heme–Abeta complex (12).

Oxidative stress and damage of the mitochondrial complex I have been implicated as mechanisms in the pathophysiology of PD. In brains of rats infused with 6-hydroxydopamine, a neurotoxin used as a model of PD, treatment with curcumin prevented loss of tyrosine hydroxylase (TH)-positive cells and sustained dopamine levels (290). Curcumin has also recently been shown to protect the brain mitochondrial complex I from oxidative damage caused by peroxynitrite, a potent free radical species (178).

In summary, curcumin exhibits the potential for neuroprotection against and reversal of degenerative diseases such as AD or PD in preclinical models, apparently and primarily because of its antioxidant properties. A double-blind, placebo-controlled phase II clinical study is currently in progress, studying the safety, tolerability, and efficacy of curcumin C3 complex in patients with AD (see Table 1).

C. Cystic fibrosis

Curcumin's potential activity in cystic fibrosis (CF) has received considerable media attention. CF is an autosomal recessive disease caused by a mutation of the gene, *cystic fibrosis transmembrane conductance regulator* (*CFTR*). Many mutations of this gene are known, but the most common one is the CF-ΔF508, which causes defective protein folding and results in CFTR being degraded by the endoplasmic reticulum (ER) rather than progressing to the cell membrane. Lack of CFTR results in reduced chloride (Cl) permeability and enhanced sodium absorption from the epithelial membrane; these events lead to mucosal dehydration and subsequently reduced resistance to bacteria and inflammation.

Curcumin is a low-affinity sarcoplasmic/endoplasmic reticulum calcium (SERCA) pump inhibitor, and as such, it has been suggested that it may prevent CFTR degradation and improve the manifestations of cystic fibrosis (28). Egan and colleagues (76) tested the effects of oral curcumin in mice with homologous ΔF508 CFTR mutation at doses similar to those used in human studies in other disease processes. They found that curcumin corrected the nasal potential difference (NPD) defect, which is characteristic of homozygous type CF. This effect was not observed in knockout mice that lack the CFTR gene and do not carry the ΔF508 mutation, suggesting that curcumin acts on the mutated ΔF508 CFTR gene (76). Although promising, these data have not been replicated in a preclinical study conducted by other investigators who tested the effect of curcumin on epithelial airway cells obtained from CF patients carrying the ΔF508 CFTR mutation and on baby hamster kidney (BHK-21) cells expressing the same mutation. They found no evidence

that curcumin restores the CFTR deficit associated with the ΔF508 CFTR mutation (69, 95). Further mechanistic studies are therefore warranted before clinical studies are planned in patients with CF.

Apart from the effect of curcumin as a SERCA inhibitor, other recent reports suggest that possible mechanisms for curcumin's enhancement of CFTR in ΔF508 CFTR cells may involve phosphorylation and activation of protein kinase alpha (PKA) (272), remodeling and activation of the keratin 18 (K18) network implicated in ΔF508 CFTR trafficking (158), and suppression of calreticulin, an ER protein that downregulates CFTR expression (103). The diverse mechanisms of curcumin's activity in CF being discovered demonstrate the current level of activity in this field of research and offer hope for cautious optimism for future translational clinical studies in patients with this chronic disease.

VIII. BIOLOGIC ACTIVITY IN HUMANS

A. Potential biomarkers of activity in patients with cancer

In a dose-escalation pilot study, patients with advanced colorectal cancer received an oral capsule of *Curcuma* extract at doses between 440 and 2,200 mg/day, containing 36–180 mg of curcumin, for up to 4 months (229). Two biomarkers of curcumin's potential systemic activity were evaluated, of which one showed a significant change. In patients who ingested 36 mg of curcumin daily, the investigators demonstrated reduced lymphocytic glutathione-S-transferase (GST) activity. The GST levels decreased gradually with time from a baseline value of 64 ± 19 to 26 ± 13 nmol/min/mg protein on day 29 of treatment (229). This effect was not observed at the higher dose levels of curcumin, nor was it reproduced in a subsequent study of higher doses of curcumin in patients with similar characteristics (224).

Another biomarker studied for curcumin's potential activity, measured for the first time in patients with colorectal cancer in the two aforementioned studies (224, 229), is the oxidative DNA adduct, pyrimido-[1,2α]purin-10(3H)-one-2′-deoxyguanosine (M_1dG). In both studies, patients who received curcumin did not demonstrate any significant change in blood leukocyte levels of M_1dG adducts (229).

In contrast to leukocyte M_1G and GST in blood cells, the inducibility of prostaglandin (PG) E_2 production in whole blood *ex vivo* may represent a biomarker of potential utility for assessing the pharmacologic activity of curcumin at a systemic level. As discussed earlier, enzymes of the arachidonic acid pathway, especially COX-2, are important targets for chemoprevention, and as such, their pharmacologic modulation may contribute to cancer treatment (195, 223, 254). The effect of curcumin, as described in an *ex vivo* assay with blood from healthy volunteers (194), was associated with plasma levels of the drug in the 10^{-8} *M* range in patients with advanced colorectal cancer (224). These drug concentrations were less than one hundredth of the concentrations of curcumin that have been shown *in vitro* to have an effect on this pathway in blood or colon cells (113, 195). It should be noted that *in vitro* studies on colon cells have shown that curcumin sulfate and products of metabolic reduction of curcumin may also inhibit PGE_2 production, although their inhibitory potency appeared lower than that of curcumin in the same cells (113, 187).

In the second phase I clinical study to use this biomarker in patients with advanced colon cancer, blood was taken immediately before the dose or 1 h after the dose on days 1, 2, 8, and 29 of treatment with 3.6 g of curcumin daily (224). In this study, oral administration of curcumin did not influence basal PGE_2 levels in leukocytes, nor did doses up to 1.8 g of curcumin daily alter LPS-induced PGE_2. Notably, consumption of 3.6 g of curcumin daily by patients with advanced colon cancer did affect LPS-induced PGE_2 levels (224); in the six patients who consumed this dose, a mean 46% reduction of the PGE_2 levels was observed after the dose compared with the predose levels. This difference was statistically significant on the first and the last days of treatment, but not on measurements taken on day 2 or day 8 (224). Other problems associated with this biomarker were the lack of a time-dependent trend and lack of a dose response. Therefore, despite the potential utility of measurement of levels in target tissue as a biomarker of potential anticancer activity of curcumin demonstrated in this translational study, practical constraints such as the high interindividual and high intraindividual variability may limit the applicability of this biomarker in larger-scale trials (194).

To augment these studies in which potential changes in the blood from patients with advanced colorectal cancer were analyzed, further studies have been performed in patients undergoing operations for resectable bowel cancer in whom colorectal and hepatic tissues have been analyzed to study potential pharmacodynamic effects of curcumin (85, 86). Twelve patients with confirmed colorectal cancer consumed oral curcumin at 0.45, 1.8, or 3.6 g daily for 7 days before surgery (85). In this study, patients who received 3.6 g of curcumin daily demonstrated reduced M_1dG levels in their colorectal tissue (85). No corresponding decrease of COX-2 protein expression was observed in this tissue (85). In the same study, it was also shown that administration of curcumin did not affect M_1dG levels in normal colorectal mucosa, whereas it caused a significant decrease in adduct levels in malignant colorectal tissue. Because the effect was observed only at the highest dose level (3.6 g of curcumin daily), a dose–response relation could not be established.

B. Potential biomarkers of antioxidant activity

A recent randomized controlled trial conducted in the United States provides a contemporary example of combinatorial therapy by using two diet-derived polyphenolic agents. In this study, the renoprotective and antioxidant properties of curcumin, in combination with the natural bioflavonoid, quecertin, were tested in dialysis-dependent patients with cadaveric renal transplants (236). It is known from previous published studies that the implicated mechanisms in renal graft rejection include alloimmune (T cell–mediated cytotoxicity) and nonimmune factors [*e.g.*, cytomegalovirus (CMV) infection, endothelial injury, and progressive atherosclerosis as a result of oxidative stress] (123, 222). Forty-three patients were recruited and randomized into three groups. Patients received oral Oxy-Q capsules, containing 480 mg of curcumin and 20 mg of quecertin.

The treatment was commenced soon after the renal transplantation and continued for 1 month. The control group received placebo, the second group received low-dose treatment (one capsule and one placebo), and the third group received high-dose treatment with two capsules daily (236). The effects of treatment on early graft function (EF) compared with delayed graft function (DGF) were tested. In the control group, 14% of patients had DGF, but none in the two treatment groups. EF was observed in 43% of the control group, 71% in the low-dose group, and 93% in the high-dose group. The creatinine levels in a similar fashion were lower in the treatment groups, showing a dose-dependent relation. The investigators also reported that the incidence of acute rejection was 14.3% in the control and low-dose groups in contrast to zero in the high-dose group after 6 months of follow-up. Another interesting observation was that tremor and neurotoxicity appeared to be less common in the high-dose group than in the other groups. With regard to a potential biomarker of the effects observed in response to curcumin treatment, urinary heme oxygenase-1 (HO-1) levels were studied and found to be higher in the treatment groups. In acute renal allograft rejection, expression of *HO-1* is typically increased (14). The investigators suggested that HO-1 induction may play a role in the improved early outcomes of cadaveric renal recipients treated with curcumin and bioflavonoids (236).

The antioxidant properties of curcumin were demonstrated in a recent pilot study in patients with chronic, nonalcoholic, tropical pancreatitis. In this study, 20 patients were randomized to receive either 500 mg of oral curcumin in combination with 5 mg piperine or placebo for up to 6 weeks (72). The researchers evaluated the erythrocyte levels of malondialdehyde (MDA) and glutathione (GSH) as well as effects on clinical pain patterns by using the Visual Analogue Scale (VAS) for assessment of abdominal pain. Oxidative stress has been implicated in the pathogenesis of acute pancreatitis as well as in exacerbations of chronic pancreatitis (22, 99). MDA and GSH levels in the body are general indicators of lipid peroxidation and antioxidant potential, respectively. The results of this study showed that patients treated with curcumin and piperine had significantly lower levels of MDA compared with the placebo group. Conversely, erythrocyte GSH levels remained unaltered, analogous to studies that showed that high-dose curcumin did not result in GST levels reduction (see later). In this study, pain severity was unaffected by curcumin consumption. No side effects were reported by the patients, nor laboratory toxicities documented on blood tests done before and after the treatment course (72).

C. Anti-inflammatory activity

Curcumin's suppression of the inflammatory response, as shown in the preclinical studies *in vitro* and *in vivo* discussed previously, involves inhibition of the induction of COX-1, COX-2, iNOS, and production of cytokines such as interferon-γ (25, 102). It seems that many effects are achieved *via* suppression of the Janus kinase (JAK)-STAT signaling cascade *via* its effect on the Src homology 2 domain-containing protein tyrosine phosphatases (SHP)-2 (133). In human multiple myeloma cells, curcumin has been shown to inhibit STAT3 phosphorylation and therefore to downregulate IL-6 production (25). Similar immunologic effects were demonstrated in a chemical model of inflammatory bowel disease in mice, providing an early indication that curcumin may be of value in the treatment of this disease (249).

The effect of oral curcumin on inflammatory diseases has been investigated in a number of clinical studies in various patient groups. In a pilot open-label study conducted in New York, oral curcumin was given to five patients with ulcerative proctitis and five patients with Crohn disease (CD) (109). All the patients with proctitis noticed an improvement, and 80% of patients with CD showed better inflammatory profiles (109). Subsequently, a randomized double-blind, placebo-controlled study was performed in patients with ulcerative colitis (UC) (101). The objective of this study was to evaluate the efficacy of curcumin as maintenance therapy in patients with inactive UC. Of 89 patients enrolled, half received 1,000 mg of oral curcumin twice a day in combination with sulfasalazine or mesalazine, two aminosalicylates that are standard treatments for UC, and the other half of the patients recruited received an aminosalicylate plus placebo. The 6-month treatment schedule showed that patients in the curcumin group had a significantly reduced rate of relapse at 6 months (4.65% *vs*. 20.51% in the placebo group). Additionally, patients taking curcumin had an improved clinical activity index (CAI) and endoscopic index (EI), which were used to monitor disease activity objectively (101).

In a study of postoperative patients, a significant antiinflammatory effect was demonstrated from 400 mg of oral curcumin thrice daily for 5 days compared with placebo (218). Using similar methods, considerable improvements in the patients' symptoms were demonstrated in a double-blind study in India on patients with rheumatoid arthritis. In this study, 1,200 mg of curcumin was administered 4 times daily to 18 patients with rheumatoid arthritis for 2 weeks, resulting in symptomatic improvement without apparent toxicity (61). The antiinflammatory properties of curcumin were demonstrated in two further studies examining the effects of oral curcumin on ophthalmologic diseases. In one of those, 375 mg of curcumin was given orally thrice daily to patients with chronic anterior uveitis for 3 months, resulting in a suggestion of improvement in the condition with comparable efficacy to that of steroids, which are generally regarded as standard treatment (143). In a subsequent study by the same team, the same dose of curcumin (375 mg) was administered to eight patients with idiopathic inflammatory orbital pseudotumors for 6–22 months (142). Half of the patients showed complete responses up to 2 years of follow-up.

It is known that in patients with active psoriasis, increased activity of the enzyme phosphorylase kinase (PhK) mediates and triggers molecular mechanisms for continuous cell migration and proliferation. In an early preclinical study, Reddy and Aggarwal (210) demonstrated that curcumin is a selective inhibitor of PhK (210). More recently, PhK activity was assessed in 40 patients who were divided into four groups: a group of active untreated psoriasis, one of resolving psoriasis treated with calcipotriol (a vitamin D_3 analogue), a group of patients receiving curcumin, and a control group with healthy subjects (106). This study showed that PhK activity was much higher in untreated patients, lower in the groups treated with calcipotriol and curcumin, and even lower in the control group. The decrease in activity of PhK effected by curcumin and calcipotriol was associated with a suppression of keratinocyte transferrin receptor, the severity of parakeratosis, and the den-

sity of the epidermal cytotoxic $CD8^+$ T cells, all considered clinical hallmarks of psoriatic activity (106).

In contrast to the systemic antioxidant properties of oral curcumin, it has been suggested that topical application of curcumin may result in increased formation of ROS in the skin when used in combination with other therapies (219). Such potentially prooxidant effects may relate to dose or conditions, as discussed earlier. In a study performed in Bradford, England, 15 Asian patients with acute vitiligo consumed turmeric daily and were treated with topical application of low-dose UVB-activated pseudocatalase (PC-KUS) for 6 months (219). None of these patients showed any significant improvement of vitiligo. Eight patients were advised to stop turmeric consumption and continue with topical PC-KUS only twice daily. This led to a clinical improvement within 2 months and to an almost complete repigmentation at 6 months in six of the eight patients, leading the authors to suggest that turmeric was having an antagonistic effect on the treatment of the disease by PC-KUS. As in the studies of turmeric oleoresin discussed earlier, it is important to differentiate the potentially "adverse" effects of various turmeric preparations from the effects observed with curcumin. Chemical analysis of the turmeric preparations used in these studies would provide valuable additional information regarding potential toxicity of the multiple constituents of turmeric (see Fig. 2).

D. Anticancer effects

Curcumin can induce apoptosis in cancer cells by a variety of mechanisms described earlier, and it has demonstrated anticancer activity in animal models, discussed earlier. Similarly, its inhibition of DNA topoisomerase II at micromolar concentrations (169) indicates its potential for chemotherapeutic activity in the treatment of cancer in humans. Published anecdotes of curcumin's activity as a topical treatment for cancer can be found, most notably Kuttan's report of turmeric as a topical treatment for oral cancers and leukoplakia (141). This research group reported a reduction in the size of the lesions in 10% of the 62 patients treated, but there was no control group, no assessment of antiinflammatory activity, and no chemical analysis of the medicinal preparation.

A phase I clinical study performed in Taiwan investigated curcumin's potential anticarcinogenesis activity in patients with preinvasive malignant or high-risk premalignant conditions (47). Twenty-five patients with recently resected cancer of the bladder, Bowen disease of the skin, uterine cervical intraepithelial neoplasia, intestinal metaplasia of the stomach, or oral leukoplakia were administered doses of 1–8 g of curcumin (500 mg of curcumin per capsule, 99% pure) daily for 3 months. Although no toxicities were reported for doses up to 8 g per day, higher daily doses were not acceptable to patients on account of the bulky volume of the number of capsules that had to be ingested. Histologic improvement of the premalignant lesions 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 intestinal metaplasia, one of four patients with cervical intraepithelial neoplasia (CIN), and two of six patients with Bowen disease of the skin. On the contrary, one of four patients with CIN, and one of seven patients with oral leukoplakia developed malignancy despite the treatment. Limitations for drawing definite conclusions from this study are the small numbers of patients with each high-risk conditions studied and the possible bias from the interpreting pathologists, as the study was not blinded. Nevertheless, the results reported suggest biologic activity in the disease processes studied.

Further evidence to support the hypothesis that curcumin has activity against preneoplastic lesions is provided by a recent study performed at The Cleveland Clinic in Florida in patients with familial adenomatous polyposis (FAP) (56). FAP is an autosomal dominant condition characterized by the development of numerous bowel adenomas that can transform to adenocarcinoma. Curcumin (480 mg), in combination with quercetin (20 mg), was administered 3 times per day to five patients with FAP. Four patients had the rectum preserved, and one had an ileoanal pouch. All patients showed a decrease in the number and the size of polyps compared with baseline figures (56). These preliminary data strongly support the case for designing a randomized controlled trial of curcumin *versus* standard therapy for patients with FAP.

Preliminary results regarding curcumin's antitumor activity in patients with advanced pancreatic cancer enrolled in a phase II clinical trial have been published in abstract form (64). Doses of 8 mg of curcumin daily were given orally to patients for 2 months. Of the 17 patients enrolled at the time of abstract publication, four patients had stable disease for 2–7 months, and one achieved partial remission by radiologic criteria for 1 month. Collectively, these clinical trials highlight the level of current translational interest in studying the biologic potential of curcumin in the treatment of premalignant conditions and established malignancies.

E. Pharmacodynamic effects on gastrointestinal system

As mentioned earlier, the first report of curcumin's biologic activity in patients was published in 1937. The authors reported symptomatic improvement in patients with chronic cholecystitis when they were treated with oral curcumin preparations (185). The mechanism proposed for this improvement was the increased flow of bile and the rapid emptying of the gallbladder. Interestingly, data supportive of this hypothesis were published in 1999 in a pilot study in 76 patients with biliary dyskinesia. Three weeks of treatment with Cholagogum F, a combination of dried extracts from Schollkraut and *Curcuma*, resulted in a significant clinical improvement compared with placebo (182). In the same year, a randomized double-blind ultrasonography study in 12 healthy volunteers was published, in which administration of 20 mg of oral curcumin increased gallbladder contraction by up to 30% compared with the baseline volume (204). Despite the small sample size, the effect was statistically significant compared with the response to placebo. More recently, the same investigators have shown in a randomized single-blind study in 12 healthy volunteers that administration of 40 mg of oral curcumin produces significant gallbladder contraction (205).

Contrary to one early report of potential ulcerogenic activity of curcumin in the rat (97), curcumin appears to have mainly gastroprotective actions in humans. In a phase II clinical study in Thailand, 45 patients with peptic ulcer–like symptoms underwent upper GI endoscopy (196). Twenty-five patients were

found to have peptic ulcer disease. Subsequently, these patients started monotherapy treatment with oral curcumin at a dose of 600 mg, 5 times per day. After 4 weeks of treatment, 12 patients had no evidence of ulcers. This response increased to 72% of patients after 8 weeks of treatment, and up to 76% of patients at 12 weeks of treatment. The remaining 20 patients had gastritis, erosions, or dyspepsia rather than definite ulcers: They also reported symptomatic improvement within 2 weeks of the 4-week course of treatment with curcumin. No treatment-related toxicities were stated.

When combined with the data in earlier subsections, it is clear that curcumin's effects on the GI system are multiple and diverse. Evidence has been published in favor of curcumin's chemopreventive properties on bowel polyps, potential reduction of risk from premalignant conditions, improvement of inflammatory bowel disease, and treatment of dyspeptic and biliary-related symptoms. These data justify larger randomized studies in patients with GI disorders. As shown in Table 1, clinical studies are currently in progress studying curcumin in patients with colorectal and pancreatic cancer and esophageal Barrett disease.

IX. CONCLUSIONS

The powdered colored extracts of the dried rhizomes of the plant *Curcuma longa*, often called turmeric, ukon, or haldi, have been used in Asian cookery and traditional medicine for thousands of years. Curcumin is a polyphenolic component of turmeric, which possesses diverse antiinflammatory and anticancer properties. On account of the multiple constituents of different preparations (shown in Fig. 2), potentially adverse effects of turmeric in preclinical models and one clinical trial must be differentiated from preclinical and clinical studies using curcumin.

Oral or topical curcumin has demonstrated significant properties in the attenuation of carcinogenesis in rodents. Its effects appear pertinent to all stages of carcinogenesis, including the behavior of established malignancy. Curcumin's beneficial effects have been shown in both chemical and genetic models, providing strong preliminary data for the justification of clinical studies in humans. The mechanisms implicated in the inhibition of tumorigenesis are diverse and appear to involve a combination of antiinflammatory, antioxidant, immunomodulatory, proapoptotic, and other properties of curcumin, as well as its effect on genes and molecular pathways (see Figs. 8 and 12). The combination of curcumin with other chemopreventive agents may improve the efficacy of antitumor actions, without compromising safety profiles.

Curcumin has been shown to inhibit several cell signalling pathways at multiple levels, to affect the expression and activity of cellular enzymes such as cyclooxygenase and GSTs, and to influence immunomodulation, angiogenesis, and cell–cell adhesion. Curcumin's ability to affect gene transcription and to induce apoptosis is of particular relevance to cancer chemoprevention and chemotherapy, although its potentially contradictory effects on tumor-suppressor genes represent a cause for current debate. A particularly interesting area of current research, exemplified by recent high profile studies in preclinical models of cystic fibrosis, is the study of curcumin's role in protein degradation in cells by the endoplasmic reticulum and by the proteasome.

Although curcumin's low systemic bioavailability after oral dosing may limit access of sufficient concentrations for pharmacologic effect in certain tissues, chemical analogues and novel delivery methods are currently in preclinical development. Because an apparent paradox exists between the pharmacologic levels measurable in tissues by using liquid chromatography and mass spectrometry techniques and the effects observed in tissues in which the concentrations of parent drug are below the limit of detection, novel scientific studies should include measures of curcumin's ability to exert pharmacologic effects at nanomolar concentrations.

With regard to clinical research, the diverse and potent activity of curcumin demonstrated in a variety of GI disorders, particularly inflammatory and neoplastic, justifies randomized controlled studies in patients with diseases of the esophagus, stomach, biliary tract, and large intestine. The design of randomized clinical trials should also consider the likelihood of individuals in the non-curcumin arm of the trial consuming turmeric or curcumin of their own volition. Although such studies may choose to focus on patients with advanced cancer or patients receiving adjuvant therapy after resection of cancer, the design of such clinical studies should permit the advancement of curcumin in clinical chemoprevention and clinical chemotherapy for a variety of diseases, in particular by the incorporation and validation of biomarkers of curcumin's clinical activity. For an agent that exhibits such diverse activity at physiologically relevant concentrations in preclinical models, a wide and interesting choice exists of potential biomarkers of curcumin's clinical activity.

ABBREVIATIONS

AD, Alzheimer disease; ADI, acceptable daily intake; Ang, angiopoietin; AOM, azoxymethane; AP-1, activator protein-1; APC, adenomatous polyposis coli; ARE, antioxidant response element; ARNT, aryl hydrocarbon receptor nuclear translocator; ATF3, activating transcription factor 3; BDMC-A, bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione; Bnip3, Bcl-2/adenovirus EIB 19-kDa–interacting protein 3; BW, body weight; CAI, clinical activity index; CD, Crohn disease; Cdk, cyclin-dependent kinase; CEA, carcinoembryonic antigen; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CIN, cervical intraepithelial neoplasia; CO, carbon monoxide; COX, cyclooxygenase; CYP, cytochrome P450; DAC, diacylglycerol; DMBA, dimethyl-benz(*a*)anthracene; DMH, dimethylhydrazine; DMSO, dimethyl sulfoxide; EGCG, epigallocatechin-3-gallate; EGFR, epidermal growth factor receptor; *egr*-1, early growth response-1; EH, epoxide hydrolase; EI, endoscopic index; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; FAP, familial adenomatous polyposis; FGF, fibroblast growth factor; GADD, growth arrest and DNA damage; GC-MS, gas chromatography–mass spectrometry; GFAP, glial fibrillary acidic protein; GFR, growth factor receptor; GSH, glutathione; GST, glutathione-S-transferase; HIF-1, hypoxia inducible factor-1; HO-1, heme oxygenase-1;

HPLC, high-pressure liquid chromatography; I3C, indole-3-carbinol; IAP, inhibitor of apoptosis protein; ICAM-1, intercellular adhesion molecule-1; IFN-γ, interferon-γ; IκBα, inhibitory kappa B alpha; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK, janus kinase; JNK, c-Jun N-terminal kinase; LEF, lymphoid enhancer factor; LDL, low-density lipoprotein; LOX, lipooxygenase; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin, NF-κB, nuclear factor-kappa B; Nfr-2, nuclear factor erythroid 2-related factor 2; NK, natural killer; NMBA, *N*-nitrosomethylbenzamine; NO, nitric oxide; NQO1, NAD(P)H:quinone oxidoreductase; OATP2, organic anion-transporting polypeptide 2; ODC, ornithine decarboxylase; OTC, over the counter; PARP, poly adenosine-5′-diphosphate-ribose polymerase; PD, Parkinson disease; PDT, photodynamic treatment; PhK, phosphorylase kinase; PI3K, phosphatidylinositol 3 kinase; PKC, protein kinase C; PPAR-γ, peroxisome proliferator-activated receptor-γ; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; SERCA, sarco/endoplasmic reticulum calcium ATPase; SOD (superoxide dismutase); STAT, signal transducer and activator of transcription; TCF, T-cell factor; TGF, transforming growth factor; TH, tyrosine hydroxylase; THC, tetrahydrocurcumin; TNF, tumor necrosis factor; TPA, phorbol 12-*O*-tetradecanoate-13-acetate; TRAIL, TNF-related apoptosis-inducing ligand; UC, ulcerative colitis; VAS, visual analogue scale; VCAM-1, vascular cell-adhesion molecule-1; VEGF, vascular endothelial growth factor.

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