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Inhibitory Effects of Curcumin on Tumorigenesis in Mice

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Abstract Curcumin (diferuloylmethane), the naturally occurring yellow pigment in turmeric and curry, is isolated from the rhizomes of the plant *Curcuma longa* Linn. Curcumin inhibits tumorigenesis during both initiation and promotion (post-initiation) periods in several experimental animal models. Topical application of curcumin inhibits benzo[*a*]pyrene (B[*a*]P)-mediated formation of DNA-B[*a*]P adducts in the epidermis. It also reduces 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced increases in skin inflammation, epidermal DNA synthesis, ornithine decarboxylase (ODC) mRNA level, ODC activity, hyperplasia, formation of c-Fos, and c-Jun proteins, hydrogen peroxide, and the oxidized DNA base 5-hydroxymethyl-2′-deoxyuridine (HmdU). Topical application of curcumin inhibits TPA-induced increases in the percent of epidermal cells in synthetic (S) phase of the cell cycle. Curcumin is a strong inhibitor of arachidonic acid-induced edema of mouse ears in vivo and epidermal cyclooxygenase and lipoxygenase activities in vitro. Commercial curcumin isolated from the rhizome of the plant *Curcuma longa* Linn contains 3 major curcuminoids (approximately 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin). Commercial curcumin, pure curcumin, and demethoxycurcumin are about equipotent as inhibitors of TPA-induced tumor promotion in mouse skin, whereas bisdemethoxycurcumin is somewhat less active. Topical application of curcumin inhibits tumor initiation by B[*a*]P and tumor promotion by TPA in mouse skin. Dietary curcumin (commercial grade) inhibits B[*a*]P-induced forestomach carcinogenesis, *N*-ethyl-*N′*-nitro-*N*-nitrosoguanidine (ENNG)-induced duodenal carcinogenesis, and azoxymethane (AOM)-induced colon carcinogenesis. Dietary curcumin had little or no effect on 4-(methylnitosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung carcinogenesis and 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced breast carcinogenesis in mice. Poor circulating bioavailability of curcumin may account for the lack of lung and breast carcinogenesis inhibition. J. Cell. Biochem. Suppl. 27:26–34.

Key words: anti-inflammatory agent; antioxidant; chemoprevention; Curcuminoid; cyclooxygenase inhibitor; food coloring agent; lipoxygenase inhibitor; plant phenol

The powdered dry rhizome of the plant *Curcuma longa* Linn, commonly called turmeric, has been used for centuries as a traditional medicine to treat inflammatory and other diseases [1,2]. Curcumin (diferuloylmethane; Fig. 1) is the major yellow pigment in turmeric, curry and mustard. Commercial curcumin isolated from the powdered dry rhizome of *Curcuma longa* Linn contains approximately 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin [3,4]. The antioxidant activity of the curcuminoids is in the order: curcumin > demethoxycurcumin > bisdemethoxycurcumin [5]. Turmeric and curcumin have high antioxidant and anti-inflammatory activity [5–7] and are widely used as a coloring agent in foods, drugs and cosmetics. Recent studies indicate that curcumin has a broad anti-carcinogenic activity [8–10]. In this manuscript, we briefly review the inhibitory effects of curcumin on tumorigenesis in mice and biochemical processes important to carcinogenesis.

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TOPICAL APPLICATION OF CURCUMIN ON DMBA/TPA-INDUCED SKIN CARCINOGENESIS

Topical application of curcumin to CD-1 mice inhibits the formation of [^{3}H]benzo[*a*]pyrene (B[a]P)-mediated DNA-[^{3}H]B[a]P adducts in epi-

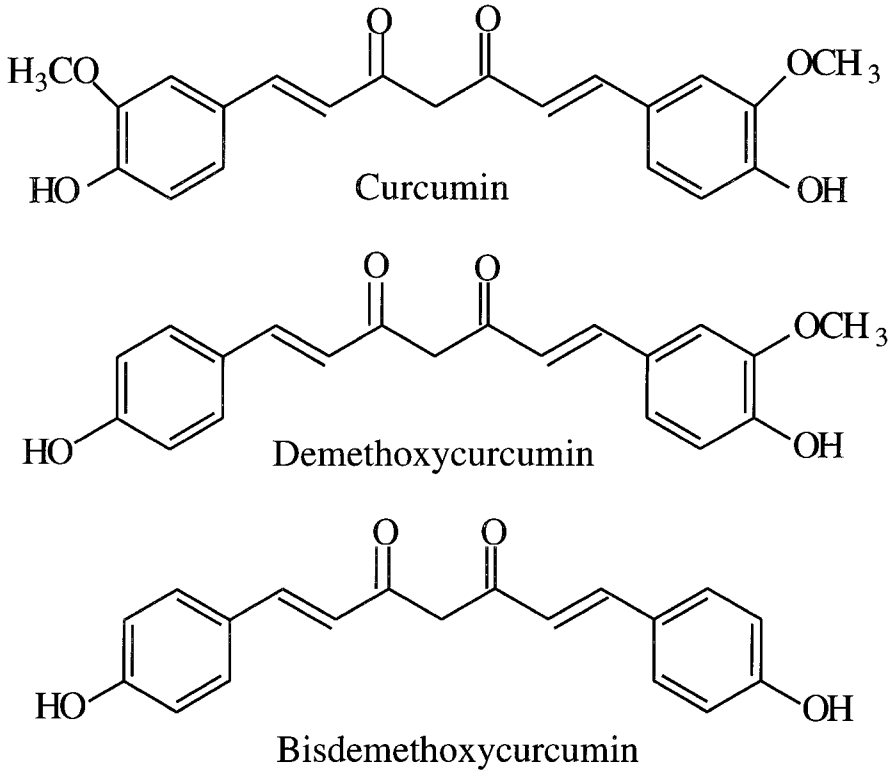

Fig. 1. Structures of curcumin, demethoxycurcumin, and bisdemethoxycurcumin.

dermis [11] and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ornithine decarboxylase (ODC) mRNA level, ODC activity, DNA synthesis, hyperplasia, and the formation of c-Fos and c-Jun proto-oncoproteins in the skin [12–14]. Topical application of curcumin inhibits skin tumor initiation by B[*a*]P and 7,12-dimethylbenz (*a*)anthracene (DMBA) as well as TPA-induced tumor promotion in CD-1 mice previously initiated with DMBA [11,12]. Recently, we studied the inhibitory effect of low-dose topical application of curcumin on TPA-induced tumor promotion and oxidized DNA base formation in mouse epidermis. Topical application of 10 or 100 nmol curcumin with 5 nmol TPA, to mice previously initiated with 200 nmol DMBA, inhibited TPA-induced tumor promotion by 15–59%, and TPA-induced formation of oxidized DNA base 5-hydroxymethyl-2'-deoxyuridine (HmdU) by 62–76% (see Fig. 2) [15].

EFFECT OF CURCUMIN ON TPA-INDUCED CHANGES IN CELL CYCLE OF MOUSE EPIDERMIS

A large percentage of cells exhibiting high proliferation rates are in the synthetic (S) phase. This is correlated with ODC activity and the incorporation of [^{3}H] thymidine into DNA. Epidermis or papillomas from mice initiated with DMBA and promoted with 5 nmol TPA twice weekly for 22 weeks had 34% of cells in the S-phase, whereas epidermis or papillomas from mice initiated with DMBA and promoted with TPA plus curcumin had 23% of cells in the S-phase [8,10].

INHIBITORY EFFECT OF TOPICAL APPLICATION OF CURCUMIN, DEMETHOXYCURCUMIN, AND BISDEMETHOXYCURCUMIN ON TUMOR PROMOTION IN DMBA-INITIATED MICE

Commercial curcumin, pure curcumin, and demethoxycurcumin had about equally potent inhibitory effect on TPA-induced ODC activity and TPA-induced tumor promotion in mice previously initiated with DMBA [4]. Bisdemethoxycurcumin was less active under the same conditions [4].

Tetrahydrocurcumin, a synthetic curcumin analogue, had higher antioxidant activity [16] than curcumin, but did not inhibit TPA-induced edema and tumor promotion in mouse skin to a similar degree [4]. Curcumin inhibits the metabolism of arachidonic acid to hydroxyeicosatet-

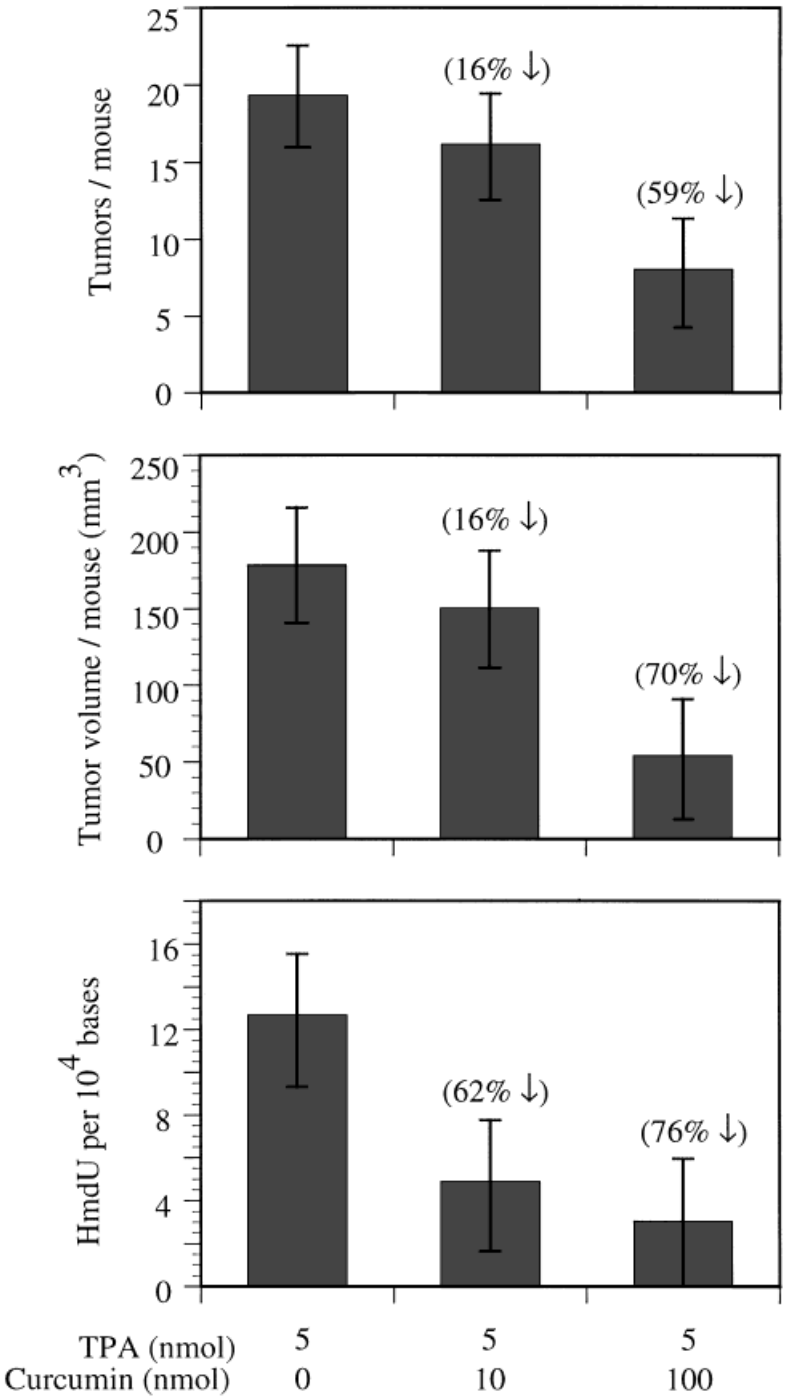

Fig. 2. Inhibitory effect of topical application of curcumin on TPA-induced skin tumor promotion and the formation of 5-hydroxymethyl-2'-deoxyuridine (HmdU) in DMBA-initiated CD-1 mice. Female CD-1 mice (30 per group) were initiated with 200 nmol of DMBA. One week later, the mice were treated with TPA (5 nmol), TPA (5 nmol) + curcumin (10 nmol), and TPA (5 nmol) + curcumin (100 nmol) twice weekly for 20 weeks. Each data represents the percent of control (TPA group). **Top:** Average number of tumors per mouse in TPA group is 19.2. **Middle:** Average tumor volume per mouse in TPA group is 178 mm^3. **Bottom:** Average number of HmdU bases in TPA group is 12.6 per 10^4 bases. Reproduced from Huang et al. [15] with permission of the publisher.

raenoic acids (HETEs) by epidermal lipoxygenase and to prostaglandins (PGs) by epidermal cyclooxygenase in vitro in a dose-dependent manner [17,18]. The IC_{50} for curcumin's inhibitory effect on epidermal lipoxygenase, as well as cyclooxygenase activities, is about 5–10 μM [17].

SUPPRESSION OF B[A]P-INDUCED FORESTOMACH CARCINOGENESIS BY DIETARY CURCUMIN

Female A/J mice (6 weeks old) were intubated with 1.5 mg of B[*a*]P in 0.1 ml corn oil once weekly for 4 weeks. The mice were sacri-

ficed at 24 weeks after the last dose of B[*a*]P. In the control group, mice fed with AIN 76A diet developed 4.9 forestomach tumors per mouse (Fig. 3). Administration of 0.5% curcumin in the diet during the initiation period (starting at 2 weeks before the first dose of B[*a*]P, during and continuing for 1 week after the last dose of B[*a*]P) inhibited the B[*a*]P-induced number of forestomach tumors per mouse by 50% and tumor volume per mouse by 65%. Curcumin (0.5%) given in the diet during the post-initiation period (starting 1 week after the last dose of B[*a*]P and continuing until the end of the experiment) inhibited the number of B[*a*]P-induced forestomach tumors per mouse by 47% and tumor volume per mouse by 38% (Fig. 3). Increasing curcumin in the diet to 2% increased the inhibitory effects on both number of tumors per mouse and tumor volume per mouse [19].

INHIBITORY EFFECT OF DIETARY CURCUMIN ON N-ETHYL-N′-NITRO-N-NITROSOGUANIDINE-INDUCED DUODENAL CARCINOGENESIS

Male C57BL/6 mice were given N-ethyl-N′-nitro-N-nitrosoguanidine (ENNG) in water (120 mg per liter) as the sole source of drinking fluid for 4 weeks, resulting in formation of 1.1 duodenal tumors per mouse 16 weeks later. Administration of 0.5% curcumin in the diet during

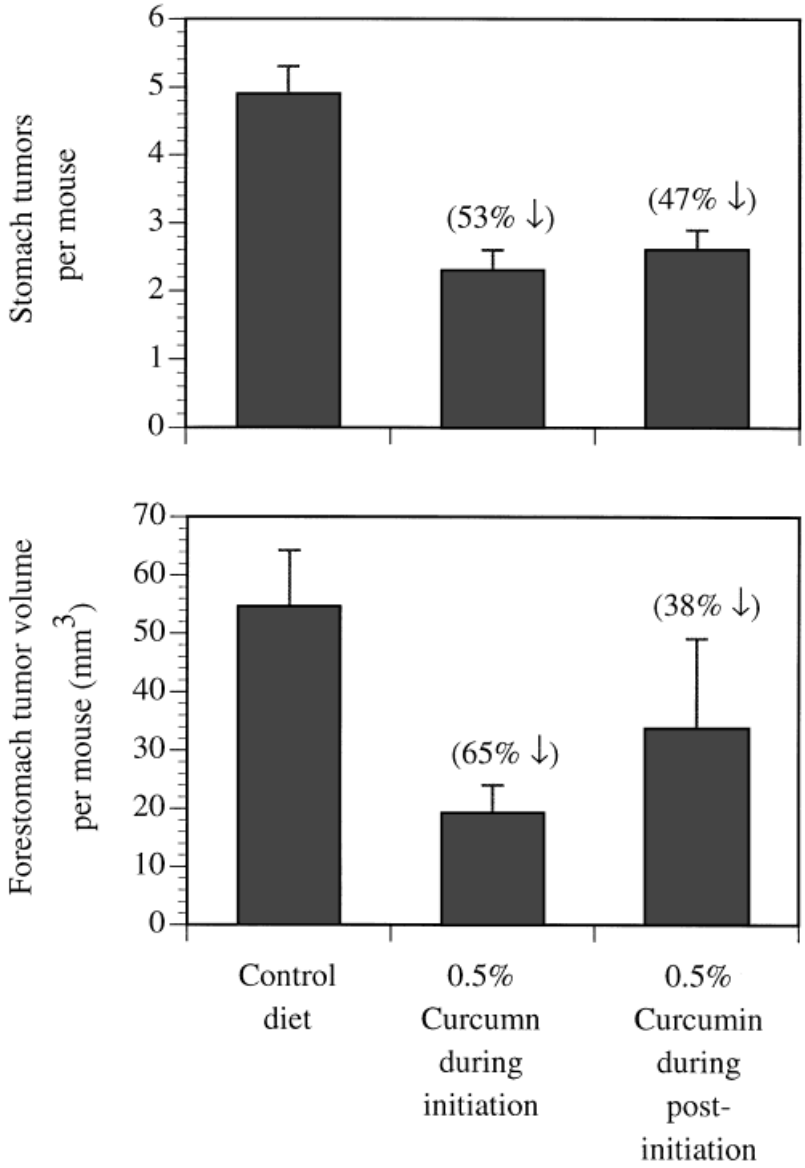

Fig. 3. Inhibitory effect of dietary curcumin on B[*a*]P-induced forestomach tumorigenesis in A/J mice. Female A/J mice (6 weeks old; 30–41 mice per group) were intubated with B[*a*]P (1.5 mg in 100 µl corn oil per mouse) once a week for 4 weeks. Curcumin (commercial grade) was given in AIN 76A diet during the initiation period (2 weeks before, during, and for 1 week after the last dose of B[*a*]P) or during the post-initiation period (1 week after the last dose of B[*a*]P administration until the end of the experiment). The mice were sacrificed 24 weeks after the last dose of B[*a*]P. Each value represents the mean ± SE. Reproduced from Huang et al. [19] with permission of the publisher.

post-initiation (starting 1 week after termination of ENNG treatment and continuing until the end of the experiment) decreased the number of duodenal tumors per mouse by 77%; percent of mice with duodenal tumors was reduced by 47% (Fig. 4) [19]. Increasing curcumin to 2% of diet did not show a dose-dependent increase of inhibition.

INHIBITORY EFFECT OF DIETARY CURCUMIN ON AZOXYMETHANE-INDUCED COLON CARCINOGENESIS

The subcutaneous injection of azoxymethane (AOM) (10 mg per kg body weight) to CF-1 mice once a week for 6 weeks resulted in the formation of 5.6 colon tumors per mouse at 27 weeks after the last dose of AOM (Fig. 5, the control diet group). Feeding 0.5% curcumin in the diet starting 2 weeks before the first dose of AOM and continuing until the end of the experiment (during initiation and post-initiation periods) inhibited the number of AOM-induced colon tumors per mouse by 50%, tumor volume per tumor by 43%, and tumor volume per mouse by 70% (Fig. 5) [19]. Curcumin (0.5%) in the diet given to the mice during either the initiation period only or the post-initiation period only had a similar inhibitory effect on AOM-induced colon carcinogenesis. Commercial curcumin and pure curcumin were equipotent inhibitors of AOM-induced colon carcinogenesis [19]. Feeding 0.2% curcumin in the diet of rats caused a similar inhibitory effect on AOM-induced colon carcinogenesis [18].

LACK OF EFFECT OF DIETARY CURCUMIN ON DMBA-INDUCED BREAST CARCINOGENESIS

Curcumin at 2% of the diet given to mice during the initiation and post-initiation periods had no effect on DMBA-induced breast tumorigenesis in Sencar mice when DMBA (1 mg per

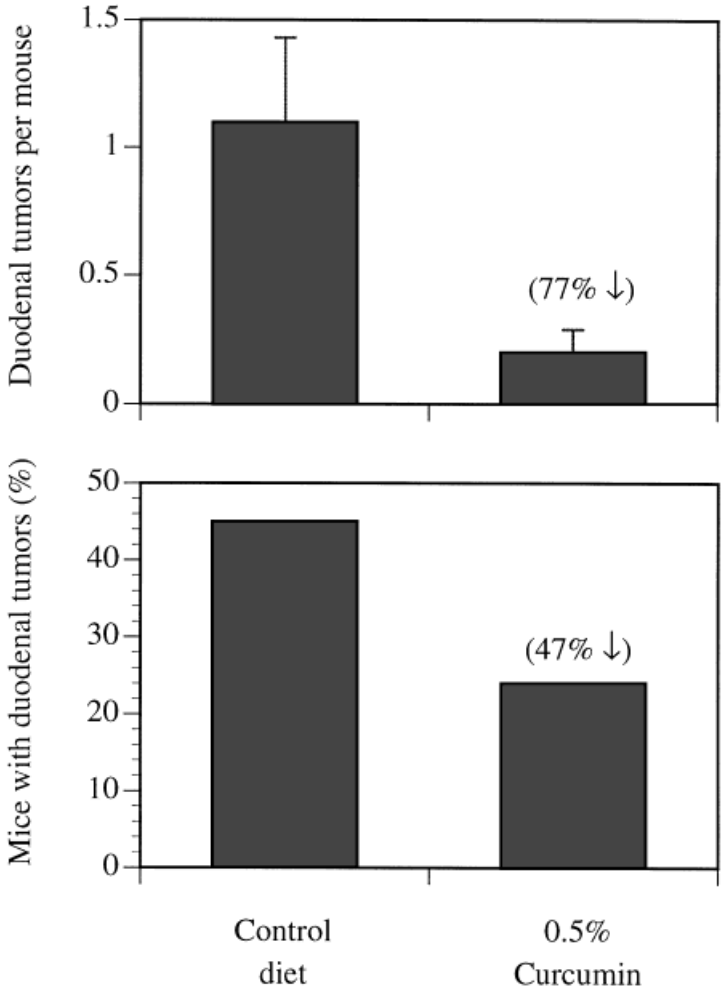

Fig. 4. Inhibitory effect of dietary curcumin on N-ethyl-N′-nitro-N-Nitrosoguanidine (ENNG)-induced duodenal tumorigenesis in C57BL/6 mice. Male C57BL/6 mice (6 weeks old; 25–36 per group) were fed AIN 76A diet and given water or ENNG (120 mg/liter water) as the sole source of drinking fluid for 4 weeks. One week later, all mice were given water and AIN 76A diet or 0.5% commercial grade curcumin in AIN 76A diet for 16 weeks. The mice were sacrificed at 16 weeks after terminating ENNG administration. The number of duodenal tumors was determined. Each value represents the mean ± SE. Reproduced from Huang et al. [19] with permission of the publisher.

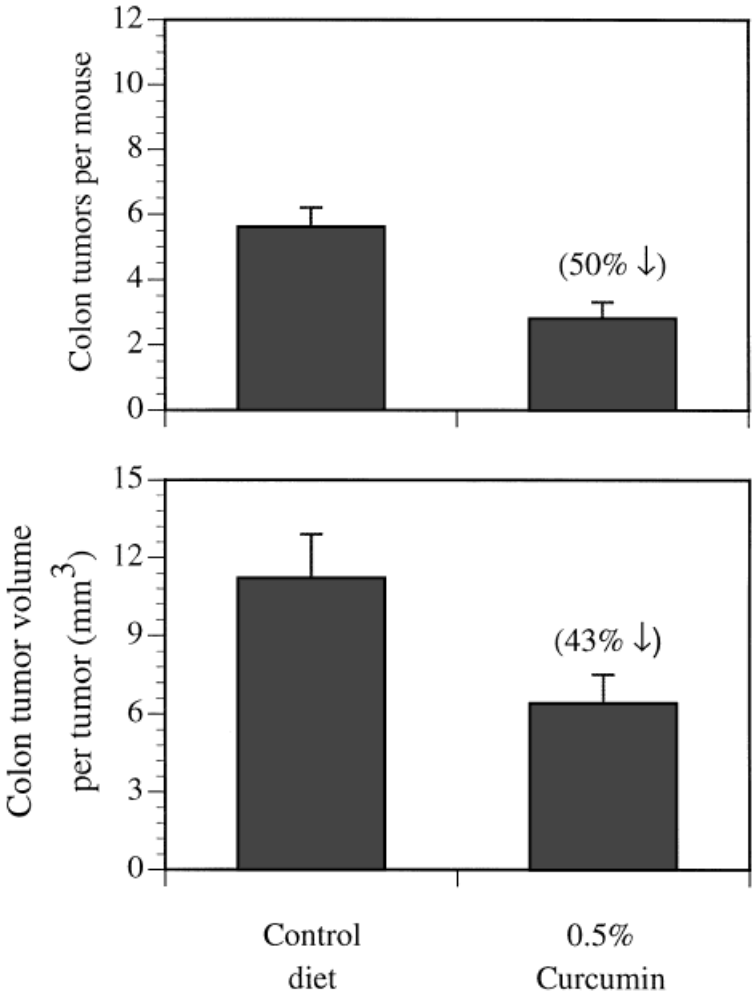

Fig. 5. Inhibitory effect of dietary curcumin on azoxymethane (AOM)-induced colon tumorigenesis in CF-1 mice. Female CF-1 mice (6 weeks old; 40–72 per group) were given s.c. injection of AOM (10 mg/kg body weight) once weekly for 6 weeks. Curcumin (commercial grade) in AIN 76A diet was given during the initiation and post-initiation periods (starting at 2 weeks before, during, and continuing until the end of the experiment). The mice were sacrificed 27 weeks after the last AOM dose administration. The number of colon tumors were determined. Each value represents the mean ± SE. Reproduced from Huang et al. [19] with permission of the publisher.

mouse) was given by gavage in corn oil once a week for 6 weeks (unpublished results). However, i.p. administration of curcumin at 100 mg/Kg or 200 mg per Kg once a day for 5 days before DMBA (30 mg per Kg) treatment significantly inhibited formation of [^{3}H]DMBA-mammary gland DNA adducts and number of DMBA-induced breast tumors per rat as well as breast tumor incidence in rats [20].

DIETARY CURCUMIN LACK OF EFFECT ON 4-(METHYLNITROSAMINO)-1-(3-PYRIDYL)-1-BUTANONE-INDUCED LUNG CARCINOGENESIS IN MICE

Feeding 2% curcumin in the diet to mice starting 2 weeks before 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) carcinogen treatment and continuing until the end of the experiment (16 weeks after NNK treatment) had no effect on NNK-induced lung tumorigenesis in A/J mice when NNK (2 mg/mouse) was administered once i.p. in saline (unpublished results).

DISCUSSION

The present results indicate that curcumin has broad anti-carcinogenic activity in several experimental animal models. Topical application of curcumin is believed to be the most efficient mode of treatment. Topical application of curcumin inhibited B[*a*]P-mediated formation of B[*a*]P-DNA adducts and the initiation of skin tumors in mice [11], and TPA-induced biochemical marker changes and tumor promotion in mice previously initiated with DMBA [12]. Dietary curcumin inhibited B[*a*]P-induced forestomach tumorigenesis, ENNG-induced duodenal tumorigenesis, and AOM-induced colon tumorigenesis in mice or rats when curcumin was given in the diet either during the initiation

period or during the post-initiation period. Feeding 0.2% curcumin in the diet also inhibits the initiation and post-initiation of tongue carcinogenesis [21]. However, there was little or no inhibitory effect of dietary curcumin on NNK-induced lung tumorigenesis or DMBA-induced mammary carcinogenesis in mice, when curcumin was given in the diet at 2 weeks before the carcinogen and continued until the end of the experiment (unpublished results). Feeding 0.1% curcumin (soluble in 1.25% Tween 80) also failed to inhibit DMBA-induced formation of mammary tumors in Sencar mice (unpublished). In the same experiment, feeding 0.75% butyl hydroxylanisole (BHA) in the diet inhibited DMBA-induced mammary tumors per mouse by 50% during initiation, and by 30% during post-initiation (unpublished results). In contrast, intraperitoneal administration of curcumin significantly inhibited DMBA-mediated formation of DMBA-DNA adducts in mammary gland, the number of mammary tumors per rat, and mammary tumor incidence [20].

A possible reason for dietary curcumin's lack of an inhibitory effect on chemically-induced lung and breast tumors may be due to poor circulating bioavailability of curcumin in vivo. The pharmaceutics of curcumin remain unclear with contradictory data in rodent models to date. Several studies [22–24] have found that curcumin is poorly absorbed. However, Holder *et al.* found approximately 60–66% of the dose is absorbed after oral administration of 10, 80, or 400 mg to rats. Most of the compound is biotransformed in the intestinal epithelium and the liver to tetrahydro- and hexahydrocurcumin, which are then conjugated and excreted through the bile [25]. Dihydroferulic acid appears to be a minor metabolite. At low doses , no curcumin is detectable in plasma [25].

Anti-carcinogenic effects of curcumin appear to be based upon several different mechanisms. Curcumin modulates phase I and phase II metabolizing enzymes, thus inhibiting activation of carcinogens, enhancing detoxication carcinogens, or both [11,26,27]. Such activity may result in a decrease in carcinogen-DNA adduct formation and tumor initiation. Several investigators have found that curcumin inhibits cellular proliferation simulated by carcinogens or tumor promotors in intact animals and in cell culture systems. Some of these effects on biochemical, morphological, immunologic, and molecular surrogates of cellular transformation processes are summarized in Table I. While curcumin appears to inhibit many surrogate biomarkers of cellular carcinogenesis, the precise inhibitory effect of curcumin on specific target sites of cellular proliferation or tumor promotion remains unclear.

Data from studies by Reddy et al., 1995, 1993 [18,28], Kakar et al., 1994 [29], and our laboratory [4,8,10–15,17,19] suggest that inhibitory effects of curcumin on TPA- and arachidonic acid-induced inflammation, TPA-induced production of hydrogen peroxide, cyclooxygenase, lipoxygenase, phospholipase $A_{2,}$ and phospholipase Cg1 activities, as well as inhibitory effect of curcumin on TPA-induced formation of c-*jun* mRNA, c-Jun protein, c-*fos* mRNA, c-Fos protein, and c-*myc* mRNA, appear to play important roles in tumor promotion [12–15,27,28]. In these studies, the doses of curcumin used for biochemical marker change studies were essentially the same as doses used for tumor promotion inhibition studies in vivo. We believe that the ability of curcumin to inhibit phospholipase A_2, cyclooxygenase and lipoxygenase activities may be an important part of its inhibitory effect on tumor promotion. Inhibition of arachidonic acid metabolism by curcumin results in decreased formation of intermediate metabolites of leukotrienes and prostaglandins associated with tumor growth, as well as decreased formation of reactive oxygen sp formation of oxidized HmdU bases in epidermis [15]. Curcumin has been shown to inhibit induction of nitric oxide sythetase in mouse peritoneal cells [30–32] and to inhibit TPA-induced xanthine oxidase activity and production of superoxide in NIH 3T3 cells [33]. Curcumin at 5–10 μM is also able to inhibit TPA-induced formation of 8-hydroxydeoxyguanosine (8-OHdG) in NIH 3T3 cells [34], and at 10–20 μM inhibits TPA-induced protein kinase C activity [35] and TPA-induced activation of c-*jun*/AP-1 in NIH 3T3 cells [36]. Higher concentrations of curcumin (30–90 μM) induce apoptosis in several cancer cell lines [37]. It is possible that the strong inhibitory effects of curcumin on DNA synthesis may play a role in its inhibitory effects on carcinogenesis and on tumor growth. Recently, curcumin at very low concentrations has been shown to inhibit DNA synthesis in several cancer cell lines [15,38]. Inhibition of arachidonic acid metabolism may play an important role in its inhibitory effect on DNA synthesis. It was observed that inhibitors of 5-lipoxygenase in-

hibit DNA synthesis in several cancer cell lines [39–41], and conversely, metabolites of 5-lipoxygenase such as 5-HETE, leukotriene C_4 (LTC_4), and leukotriene D_4 (LTD_4) are able to stimulate DNA synthesis [41]. Further studies are needed to determine whether curcumin inhibits DNA synthesis and cellular proliferation by inhibiting the formation and/or action of mitogenic metabolites of the lipoxygenase pathway of arachidonic acid.

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