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Inhibitory Effects of Dietary Curcumin on Forestomach, Duodenal, and Colon Carcinogenesis in Mice[1]

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ABSTRACT

Curcumin (diferuloylmethane), a yellow pigment that is obtained from the rhizomes of *Curcuma longa* Linn., is a major component of turmeric and is commonly used as a spice and food-coloring agent. The inhibitory effects of feeding commercial grade curcumin (77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin) in AIN 76A diet on carcinogen-induced tumorigenesis in the forestomach, duodenum, and colon of mice were evaluated. Administration p.o. of commercial grade curcumin in the diet inhibited benzo(*a*)pyrene-induced forestomach tumorigenesis in A/J mice, *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine-induced duodenal tumorigenesis in C57BL/6 mice, and azoxymethane (AOM)-induced colon tumorigenesis in CF-1 mice. Dietary commercial grade curcumin was given to mice at: (*a*) 2 weeks before, during, and for 1 week after carcinogen administration (during the initiation period); (*b*) 1 week after carcinogen treatment until the end of the experiment (during the postinitiation period); or (*c*) during both the initiation and postinitiation periods. Feeding 0.5–2.0% commercial grade curcumin in the diet decreased the number of benzo(*a*)pyrene-induced forestomach tumors per mouse by 51–53% when administered during the initiation period and 47–67% when administered during the postinitiation period. Feeding 0.5–2.0% commercial grade curcumin in the diet decreased the number of *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine-induced duodenal tumors per mouse by 47–77% when administered during the postinitiation period. Administration of 0.5–4.0% commercial grade curcumin in the diet both during the initiation and postinitiation periods decreased the number of AOM-induced colon tumors per mouse by 51–62%. Administration of 2% commercial grade curcumin in the diet inhibited the number of AOM-induced colon tumors per mouse by 66% when fed during the initiation period and 25% when fed during the postinitiation period. The ability of commercial grade curcumin to inhibit AOM-induced colon tumorigenesis is comparable to that of pure curcumin (purity greater than 98%). Administration of pure or commercial grade curcumin in the diet to AOM-treated mice resulted in development of colon tumors which were generally smaller in number and size as compared to the control group of AOM-treated mice. These results indicate that not only did curcumin inhibit the number of tumors per mouse and the percentage of mice with tumors but it also reduced tumor size. Histopathological examination of the tumors showed that dietary curcumin inhibited the number of papillomas and squamous cell carcinomas of the forestomach as well as the number of adenomas and adenocarcinomas of the duodenum and colon.

INTRODUCTION

Epidemiology studies indicate that dietary habits play an important role in the development of many human cancers (1, 2). Large numbers of minor food components and chemically related compounds block different stages of the carcinogenic process in animal models (3) and some of these substances partially prevent or delay cancer formation in some high risk human populations (4–6).

The powdered dry rhizome of the plant *Curcuma longa* Linn. (turmeric) has long been used as a naturally occurring medicine for the treatment of inflammatory diseases (7). Curcumin (diferuloylmethane), the major yellow pigment in turmeric, curry, and mustard, is the major antioxidant and anti-inflammatory substance in turmeric (8). Turmeric and curcumin have been widely used as coloring agents and/or spices in foods as well as in cosmetics and drugs (8). The chemical, biological, and pharmacological properties of curcumin and turmeric have been reviewed elsewhere (7–10). Recently, we showed that application of curcumin to the skin of mice strongly inhibited TPA[3]-induced inflammation (mouse ear edema), epidermal ornithine decarboxylase activity, ornithine decarboxylase mRNA, hyperplasia, and formation of hydrogen peroxide (9, 11, 12). We also showed that curcumin inhibited TPA-induced progression of epidermal cells through the cell cycle (9). The anti-inflammatory and anti-tumor-promoting activities of curcumin could be explained by the potent inhibitory effects of curcumin on arachidonic acid-induced inflammation and on arachidonic acid metabolism through both the cyclooxygenase and lipoxygenase pathways in mouse epidermis (9, 13).

Additional studies by Flynn *et al.* (14) showed inhibitory effects of curcumin on 5-lipoxygenase activity in human neutrophils and on cyclooxygenase activity in bovine seminal vesicle. In other studies, it was found that topical application of curcumin inhibited the covalent binding of [^{3}H]B(*a*)P to epidermal DNA and inhibited the tumor-initiating activity of B(*a*)P and 7,12-dimethylbenz(*a*)anthracene in mouse skin (15). In an earlier study, we found that dietary curcumin inhibited AOM-induced dysplasia in mouse colon (16). In the present report, we describe inhibitory effects of dietary curcumin on B(*a*)P-induced forestomach carcinogenesis, ENNG-induced duodenal carcinogenesis, and AOM-induced colon carcinogenesis in mice.

MATERIALS AND METHODS

Chemicals and Reagents. TPA was obtained from the LS Services Corp. (Woburn, MA). Pure curcumin (purity, >98%) and commercial curcumin (turmeric type 97; containing 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin) were purchased from Kalsec, Inc. (Kalamazoo, MI). Commercial grade curcumin (curcumin) was used for all studies except when indicated that pure curcumin was used. Ten % buffered formalin-phosphate (10% formalin in neutral phosphate buffer) was purchased from Fisher Scientific (Springfield, NJ). B(*a*)P (purity, >98%) and AOM were obtained from the Sigma Chemical Co. (St. Louis, MO). ENNG (purity, >97%) was obtained from the Aldrich Chemical Company (Milwaukee, WI).

Animals. Female A/J mice (4–5 weeks old) were purchased from The Jackson Laboratory (Bar Harbor, ME). Male C57BL/6 mice (5 weeks old), female CD-1 mice (4–5 weeks old), and female CF-1 mice (4–5 weeks old) were purchased from the Charles River Laboratories (Kingston, NY). For female mice, 10 animals were placed in each plastic cage. Male mice were housed individually. The animals were maintained under the following standard conditions: 22 ± 2°C, 45 ± 10% relative humidity, and 12-h light/12-h dark cycles each day. All animals were fed AIN 76A diet (Research Diets, Inc., New Brunswick, NJ) and water *ad libitum*. All feeds were pelleted to avoid stratification and to assure uniform feed and curcumin intake in the treated animals.

B(*a*)P-induced Forestomach Tumorigenesis. B(*a*)P-induced forestomach tumorigenesis in A/J mice was performed according to the procedure described by Wattenberg (17) with slight modification. Female A/J mice (6 weeks old)

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[3] The abbreviations used are: TPA, 12-*O*-tetradecanoylphorbol-13-acetate; AOM, azoxymethane; B(*a*)P, benzo(*a*)pyrene; ENNG; *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine.

were treated with 100 μl of corn oil or 1.5 mg of B(*a*)P in 100 μl corn oil by p.o. gavage once weekly for 4 weeks. Twenty mice were used for group 1 (negative control), 41 mice were used for group 2 (B(*a*)P-treated positive control), and 30 mice were used for all other groups. In group 1, the mice were intubated with 100 μl corn oil once weekly for 4 weeks. In all other groups, the mice were intubated with 1.5 mg of B(*a*)P in 100 μl of corn oil once weekly for 4 weeks. Mice in groups 1 and 2 were given semisynthetic AIN 76A diet and water *ad libitum* from 2 weeks before administration of carcinogen until the end of the experiment. Mice in groups 3 and 4 were given 0.5% or 2.0% commercial grade curcumin, respectively, in AIN 76A diet and water *ad libitum* 2 weeks before, during, and 1 week after the last dose of B(*a*)P (initiation period). Mice in groups 5 and 6 were given 0.5 or 2.0% commercial grade curcumin, respectively, in AIN 76A diet and water *ad libitum* beginning 1 week after the last dose of B(*a*)P until the end of the experiment (postinitiation period). The mice were killed 24 weeks after the last dose of B(*a*)P. Ten % buffered formalin-phosphate was immediately injected into the stomach by intubation into the mouth, so that the stomach was distended and fixed. Each stomach was removed and placed on a plastic sheet, and the number of tumors in each forestomach was determined. The samples were stored in 10% buffered formalin-phosphate for histological examination.

ENNG-induced Duodenal Tumorigenesis. The experiments on ENNG-induced duodenal tumorigenesis in male C57BL/6 mice were performed according to the procedure described by Fujita *et al.* (18) with slight modification. The mice (6 weeks old) were given AIN 76A diet and ENNG (120 mg/liter) as the sole source of drinking water *ad libitum* for 4 weeks. One week later, all mice were shifted to water and fed AIN 76A diet or 0.5–2.0% commercial grade curcumin in AIN 76A diet for 16 weeks, and the mice were killed by cervical dislocation. Ten % buffered formalin-phosphate was immediately injected into the stomach by intubation into the mouth, so that the stomach and intestine were distended and fixed. The duodenum were removed and placed on a plastic sheet, and the number of tumors in each duodenum was determined. The duodenal tumors were counted using a magnifying lens, and the duodenal samples were stored in a 10% buffered formalin phosphate-buffer solution for histological examination.

AOM-induced Colon Tumorigenesis. AOM-induced colon tumorigenesis was performed according to the procedure of Deschner *et al.* (19) with slight modification. Female CF-1 mice (6 weeks old) were given s.c. injections of AOM (10 mg/kg body weight) in 100 μl of normal saline once weekly for 6 weeks. Mice in groups 1 and 2 were given AIN 76A diet. Mice in groups 3–5 were given 0.5, 2.0, or 4.0% commercial grade curcumin in AIN 76A diet and mice in group 6 were given 2.0% pure curcumin (purity, >98%) in AIN 76A diet. Mice in groups 3–6 received curcumin diets starting at 2 weeks before the first injection of AOM and continuing until the end of the experiment (during initiation and postinitiation periods). Mice in group 7 were given 2.0% commercial grade curcumin in AIN 76A diet 2 weeks before, during, and for 1 week after the last dose of AOM administration (during the initiation period). Mice in group 8 were given 2.0% commercial curcumin in AIN 76A diet at 1 week after the last dose of AOM injection until the end of the experiment (during the postinitiation period). The mice were killed by cervical dislocation at 27 weeks after the last dose of AOM. Ten % buffered formalin-phosphate was immediately injected into the colon by intubation into the anus, so that the colon and intestine were distended and fixed. The colons were removed and placed on a plastic sheet, and the number of tumors in each colon was determined. The size of the tumors and their locations were also determined, and the colon samples were stored in 10% buffered formalin-phosphate for histological examination.

Tumor Volume. Tumor volume was measured as described previously (20). Tumor volume was determined by measuring the three-dimensional size of all tumors using the average of the three measurements to calculate radius. Tumor volume was calculated as

$$\text{Volume} = \frac{4 \cdot \pi \cdot r^3}{3}$$

Histological Examination of Tumors. All tumors were examined with the aid of a magnifying lens, and tumor size was measured. Tumors found by visual examination were confirmed by histological examination. The forestomach, duodenal, and colonic samples were excised and fixed in 10% buffered formalin-phosphate. The tumor samples were embedded in paraffin and processed for histology with hematoxylin and eosin staining. Slides were read in blind fashion by two pathologists (Y-R. L. and K. R. R.), and the tumors were classified as described elsewhere (21, 22).

Statistical Analysis. The significance of our data was determined with the Student *t* test.

RESULTS

Inhibitory Effect of Dietary Curcumin on B(*a*)P-induced Forestomach Tumorigenesis. Treatment of A/J mice with 1.5 mg of B(*a*)P by gavage once a week for 4 weeks resulted in 4.9 forestomach

Table 1 *Inhibitory effect of dietary curcumin on B(a)P-induced forestomach tumorigenesis in A/J mice*

Female A/J mice (6 weeks old; 20 mice for group 1, 41 mice for group 2, and 30 mice for all other groups) were gavaged with 100 μl corn oil (group 1) or B(*a*)P (1.5 mg in 100 μl corn oil/mouse; groups 2–6) once weekly 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 postinitiation period (1 week after the last dose of B(*a*)P administration until the end of the experiment). The mice were killed at 24 weeks after the last dose of carcinogen. In group 2, one mouse died after the third dose of B(*a*)P, and one mouse died during the 10th week. One mouse was killed during the 19th week to determine the number of tumors and one mouse was killed during the 22nd week because it had a large skin tumor. In group 4, one mouse died after the first dose of carcinogen. In group 5, one mouse died after the first dose of carcinogen and one mouse was killed at 13 weeks and one at 22 weeks after carcinogen, because of the presence of a large skin tumor. In group 6, one mouse died during the 14th week and one mouse was killed during the 22nd week, since it had a large skin tumor. Each value represents the mean ±SE. Numbers in parentheses, percentage of inhibition.

			Papillomas		Squamous cell carcinomas		Total tumors	
Treatment	No. of mice/group	Body wt/ mouse (g)	Papillomas /mouse	% of mice with papillomas	Carcinomas/mouse	% of mice with carcinomas	Tumors/ mouse	% of mice with tumors
1. Vehicle + AIN 76A	20	26.9 ± 0.8	0[a]	0	0[a]	0	0[a]	0
2. B(*a*)P + AIN 76A	37	26.5 ± 0.7	4.4 ± 0.4	97	0.5 ± 0.1	41	4.9 ± 0.4	100
Curcumin administration during the initiation period								
3. B(*a*)P + 0.5% curcumin	30	26.3 ± 0.4	2.1 ± 0.3[b] (52)	87 (10)	0.2 ± 0.1[a] (60)	23 (44)	2.3 ± 0.3[b] (53)	90 (10)
4. B(*a*)P + 2.0% curcumin	29	25.9 ± 0.5	2.2 ± 0.3[b] (50)	83 (14)	0.1 ± 0.1[b] (80)	10 (76)	2.4 ± 0.3[b] (51)	86 (14)
Curcumin administration during the postinitiation period								
5. B(*a*)P + 0.5% curcumin	27	26.0 ± 0.6	2.2 ± 0.2[b] (50)	89 (8)	0.4 ± 0.1 (20)	30 (27)	2.6 ± 0.3[b] (47)	93 (7)
6. B(*a*)P + 2.0% curcumin	28	25.9 ± 0.5	1.5 ± 0.2[b] (66)	79 (19)	0.1 ± 0.1[b] (80)	14 (66)	1.6 ± 0.2[b] (67)	86 (14)

[a] Statistically different from group 2 [B(*a*)P-treated controls, $P < 0.01$], using Student's *t* test.
[b] Statistically different from group 2 [B(*a*)P-treated controls, $P < 0.001$], using Student's *t* test.

Table 2 *Inhibitory effect of dietary curcumin on the size of B(a)P-induced forestomach tumors in A/J mice*

The size of each forestomach tumor in animals described in Table 1 was determined. Each value represents the mean ±SE. Numbers in parentheses, percentage of inhibition.

Treatment	No. of mice/group	Papillomas		Squamous cell carcinomas		Total tumors	
		Papilloma vol/papilloma (mm^3)	Papilloma vol/mouse (mm^3)	Carcinoma vol/carcinoma (mm^3)	Carcinoma vol/mouse (mm^3)	Tumor vol/tumor (mm^3)	Tumor vol/mouse (mm^3)
1. Vehicle + AIN 76A	20	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]
2. B(*a*)P + AIN 76A	37	5.6 ± 0.8	24.9 ± 4.0	54.9 ± 12.3	29.7 ± 8.5	11.0 ± 1.9	54.6 ± 9.7
Curcumin administration during the initiation period							
3. B(*a*)P + 0.5% curcumin	30	6.3 ± 2.1 (0)	13.1 ± 4.2[a] (47)	26.5 ± 10.8 (52)	6.2 ± 3.2[a] (79)	8.4 ± 2.3 (24)	19.2 ± 4.8[a] (65)
4. B(*a*)P + 2.0% curcumin	29	2.1 ± 0.5[a] (63)	4.7 ± 1.1[a] (81)	29.6 ± 14.3 (46)	4.1 ± 2.7[a] (86)	3.7 ± 1.2[a] (66)	8.7 ± 2.9[a] (84)
Curcumin administration during the postinitiation period							
5. B(*a*)P + 0.5% curcumin	27	4.7 ± 1.2 (16)	10.5 ± 3.1[a] (58)	62.7 ± 40.2 (0)	23.2 ± 15.6 (22)	13.0 ± 6.1 (0)	33.7 ± 15.4 (38)
6. B(*a*)P + 2.0% curcumin	28	5.5 ± 1.5 (2)	8.3 ± 2.4[a] (67)	71.2 ± 29.7 (0)	10.2 ± 6.1 (66)	11.3 ± 3.8 (0)	18.5 ± 6.1[a] (66)

[a] Statistically different from the B(*a*)P control group (group 2), $P < 0.05$, using Student's *t* test.

tumors/mouse at 24 weeks after the last dose of carcinogen (Table 1, group 2). Administration of 0.5 or 2.0% curcumin in the diet for 2 weeks before, during, and for 1 week after the last dose of B(*a*)P (during the initiation period) inhibited the number of B(*a*)P-induced forestomach tumors per mouse by 51–53% (Table 1). Administration of 0.5 or 2.0% curcumin in the diet during the initiation period inhibited the number of B(*a*)P-induced forestomach papillomas per mouse by 52 and 50%, and the number of squamous cell carcinomas per mouse was inhibited by 60 and 80%, respectively (Table 1).

When 0.5 or 2.0% curcumin in AIN 76A diet was fed to the mice starting at 1 week after the last dose of B(*a*)P and continued until the end of the experiment (during the postinitiation period), the number of B(*a*)P-induced forestomach papillomas per mouse was inhibited by 50 and 66%, respectively, and the number of squamous cell carcinomas was inhibited by 20 and 80%, respectively (Table 1, group 2 *versus* groups 5 and 6).

Administration of curcumin in the diet reduced the size of B(*a*)P-induced forestomach tumors per mouse (Table 2). Administration of 0.5 or 2.0% curcumin in the diet during the initiation period decreased the papilloma volume per mouse by 47 and 81%, respectively, and the carcinoma volume per mouse was decreased by 79 and 86%, respectively (Table 2). Administration of 0.5 or 2.0% curcumin in the diet during the postinitiation period decreased papilloma volume per mouse by 58 and 67%, respectively, and carcinoma volume per mouse was decreased by 22 and 66%, respectively (Table 2).

Inhibitory Effect of Dietary Curcumin on ENNG-induced Duodenal Tumorigenesis. Administration of ENNG (120 mg/liter) in the drinking water to male C57BL/6 mice for 4 weeks resulted in formation of 0.97 duodenal adenoma and 0.09 duodenal adenocarcinoma per mouse 16 weeks later. Administration 0.5–2.0% curcumin in the diet during the postinitiation period decreased the number of ENNG-induced duodenal adenomas per mouse by 46–79%, the number of adenocarcinomas per mouse by 44–56%, and the total number of duodenal tumors per mouse by 47–77% (Table 3). The data indicated that administration of 0.5% curcumin in the diet was effective at inhibiting duodenal tumorigenesis. Administration of 1.0–2.0% curcumin in the diet also resulted in inhibition, but this was not statistically significant (Table 3). Administration of 2% dietary curcumin for 16 weeks to mice without ENNG pretreatment did not result in any duodenal tumors (data not shown). Administration of curcumin in the diet decreased the size of ENNG-induced duodenal adenomas per mouse, but there was no dose-response relationship (Table 4). This was not observed for ENNG-induced adenocarcinomas where there was a tendency for increased adenocarcinoma size in the curcumin-treated mice (Table 4).

Table 3 *Inhibitory effect of dietary curcumin on ENNG-induced duodenal tumorigenesis in C57BL/6 mice*

Male C57BL/6 mice (6 weeks old; 36 mice for group 2, and 25 mice for all other groups) were fed AIN 76A diet and given water or ENNG (120 mg/liter water) as the sole source of drinking water for 4 weeks. One week later, all mice were given water and AIN 76A diet or different doses of curcumin (commercial curcumin) in AIN 76A diet for 16 weeks. The mice were killed at 16 weeks after terminating ENNG administration. The number of duodenal tumors was determined. Numbers in parentheses, percentage of inhibition. In group 1, one mouse died during the 9th week. In group 2, one mouse was killed to examine the duodenal tumors during the 10th, 12th, and 14th weeks after termination of ENNG. In group 5, two mice died during the first week and one mouse died during the 3rd week after termination of ENNG. In group 6, one mouse died during the 10th week after ENNG. Each value represents the mean ±SE. Numbers in parentheses, percentage of inhibition.

Treatment	No. of mice/group	Body wt (g)	Adenoma		Adenocarcinoma		Total tumors	
			Adenomas/mouse	% of mice with adenomas	Carcinomas/mouse	% of mice with carcinomas	Tumors/mouse	% of mice with tumors
1. Vehicle + AIN 76A	24	34.1 ± 1.1	0[a]	0	0[a]	0	0[a]	0
2. ENNG + AIN 76A	33	36.7 ± 1.0	0.97 ± 0.28	45	0.09 ± 0.07	6	1.06 ± 0.33	45
3. ENNG + 0.5% curcumin	25	34.6 ± 0.6	0.20 ± 0.08[a] (79)	20 (56)	0.04 ± 0.04 (56)	4 (33)	0.24 ± 0.09[a] (77)	24 (47)
4. ENNG + 1.0% curcumin	25	33.2 ± 0.9	0.52 ± 0.18 (46)	28 (38)	0.04 ± 0.04 (56)	4 (33)	0.56 ± 0.20 (47)	28 (38)
5. ENNG + 2.0% curcumin	22	34.4 ± 1.0	0.50 ± 0.19 (48)	27 (40)	0.05 ± 0.05 (44)	5 (17)	0.55 ± 0.23 (48)	27 (40)
6. Vehicle + 2.0% curcumin	24	34.4 ± 0.8	0[a]	0	0[a]	0	0[a]	0

[a] Statistically different from ENNG control group ($P < 0.05$), using Student's *t* test.

Table 4 *Inhibitory effect of dietary curcumin on ENNG-induced duodenal tumor size in C57BL/6 mice*

The size of each duodenal tumor in the animals described in Table 3 was determined. Each value represents the mean ±SE. Numbers in parentheses, percentage of inhibition.

		Adenomas		Adenocarcinomas		Total tumors	
Treatment	No. of mice/group	Adenoma vol/adenoma (mm^3)	Adenoma vol/mouse (mm^3)	Carcinoma vol/carcinoma (mm^3)	Carcinoma vol/mouse (mm^3)	Tumor vol/tumor (mm^3)	Tumor vol/mouse (mm^3)
1. Vehicle + AIN 76A	24	0[a]	0[a]	0	0	0[a]	0[a]
2. ENNG + AIN 76A	33	4.9 ± 1.6	7.5 ± 3.6	2.0 ± 1.3	2.0 ± 1.5	5.9 ± 1.7	9.5 ± 4.1
3. ENNG + 0.5% curcumin	25	0.8 ± 0.4[a] (84)	0.4 ± 0.4 (89)	3.1 ± 3.1 (0)	3.1 ± 3.1 (0)	3.9 ± 3.1 (34)	3.9 ± 3.1 (59)
4. ENNG + 1.0% curcumin	25	1.6 ± 0.4[a] (67)	2.0 ± 0.8 (73)	4.5 ± 4.5 (0)	4.5 ± 4.5 (0)	5.1 ± 3.5 (14)	6.5 ± 4.8 (32)
5. ENNG + 2.0% curcumin	22	1.4 ± 0.6[a] (71)	1.7 ± 1.2 (77)	5.1 ± 5.1 (0)	5.1 ± 5.1 (0)	0.6 ± 0.2[a] (90)	6.8 ± 6.2 (28)
6. Vehicle + 2.0% curcumin	24	0[a]	0[a]	0	0	0[a]	0[a]

[a] Statistically different from the ENNG control group (group 2; $P < 0.05$), using Student's t test.

Inhibitory Effect of Dietary Curcumin on AOM-induced Colon Tumorigenesis. Injections of AOM (10 mg/kg) were given s.c. to female CF-1 mice once a week for 6 weeks. The first dose of carcinogen unexpectedly killed 21% of the mice ingesting control AIN 76A diet (the animals died within 3 days). Subsequent weekly injections did not result in additional deaths. However, similar AOM injection into mice consuming 0.5–4% curcumin in AIN 76A diet for 2 weeks prior to the first AOM injection resulted in only 5–7.5% deaths indicating that administration of curcumin in the diet reduced the acute lethal effect of the first AOM dose by 63–76%. Administration of 2.0% pure curcumin in the diet had no significant inhibitory effect on azoxymethane-induced acute toxicity, possibly due to low solubility of pure curcumin resulting in less short term bioavailability.

The s.c. injection of AOM (10 mg/kg) once weekly for 6 weeks resulted in the formation of 4.91 colon adenomas/mouse and 0.72 colon adenocarcinoma/mouse (total of 5.63 colon tumors/mouse) at 27 weeks after the last dose of AOM (Table 5). Administration of 0.5–4.0% curcumin in AIN 76A diet 2 weeks before the first injection of AOM until the end of the experiment inhibited the number of AOM-induced colon tumors per mouse by 51–62% at 27 weeks after the last dose of AOM. The percentage of mice with colon tumors was inhibited by 16–37%. Treatment of the mice with 0.5–4.0% of curcumin in the diet starting at 2 weeks before the first injection until the end of the experiment inhibited the number of AOM-induced adenomas per mouse or adenocarcinomas per mouse by 50–62% or 57–100%, respectively (Table 5).

Administration of 2.0% curcumin in the diet for 2 weeks before, during, and for one week after the last dose of AOM (during the initiation period) inhibited the formation of colon adenomas per mouse by 64% and adenocarcinomas per mouse by 85% (Table 5). Administration of 2.0% curcumin in the diet during the postinitiation period (starting at 1 week after the last dose of AOM and until the end of the experiment) inhibited the number of colon adenomas per mouse by 19% and the number of adenocarcinomas per mouse by 67% (Table 5). Curcumin administration during the initiation period, during the postinitiation period, or during the initiation and the postinitiation periods decreased the size of AOM-induced adenomas and adenocarcinomas per tumor or per mouse by 43–100% (Table 6).

Histopathological examinations of AOM-induced colon adenomas and adenocarcinomas indicated that the colon adenomas in CF-1 mice could be classified into tubular adenomas, villous adenomas and tubovillous adenomas and that colon adenocarcinomas could be classified into tubular adenocarcinomas, papillary adenocarcinomas, tubopapillary adenocarcinomas, and mucin-secreting adenocarcinomas

Table 5 *Inhibitory effect of dietary curcumin on azoxymethane (AOM)-induced colon tumorigenesis in CF-1 mice*

Female CF-1 mice (6 weeks old; 15 mice for group 1, 72 mice for group 2, 38 mice for group 4, 48 mice for group 7, and 40 mice for all other groups) were given s.c. injections of vehicle or AOM (10 mg/kg body weight) once weekly for 6 weeks. Curcumin in AIN 76A diet was given during the initiation period (2 weeks before, during and for 1 week after the last dose of AOM administration), during the postinitiation period (1 week after the last dose of AOM administration until the end of the experiment), or during the initiation and the postinitiation periods. The mice were killed 27 weeks after the last dose of AOM. In group 1, 1 mouse died during the 16th week. In group 2, 16 mice died on the 2nd day after the first dose of AOM. In group 3, 3 mice died on the 2nd day after the first dose of AOM and 1 mouse died during the 22nd week after the last dose of AOM. In group 4, 2 mice died on the 2nd day after the first dose of AOM and 2 mice died during the 18th week after the last dose of AOM. In group 5, 2 mice died on the 2nd day after the first dose of AOM. In group 6, a total of 7 mice died between the 2nd and 3rd days after the first dose of AOM. In this group, 2 mice were killed during the 9th week and 2 mice were killed during the 14th week because of severe illness. In group 7, 2 mice died during the 2nd day after the 1st dose of AOM. In group 8, 7 mice died during the 2nd day after the first dose of AOM. Each value represents the mean ±SE. Numbers in parentheses, percentage of inhibition.

		Adenomas		Adenocarcinomas		Total tumors	
Treatment	No. of mice/group	Adenomas/mouse	% of mice with adenomas	Carcinomas/mouse	% of mice with carcinomas	Tumors/mouse	% of mice with tumors
1. Vehicle + AIN 76A	14	0[a]	0	0[a]	0	0[a]	0
2. AOM + AIN 76A	56	4.91 ± 0.56	93	0.72 ± 0.15	40	5.63 ± 0.64	93
Curcumin administration during the initiation and postinitiation periods							
3. AOM + 0.5% curcumin	36	2.47 ± 0.49[a] (50)	69 (26)	0.31 ± 0.11[a] (57)	22 (45)	2.78 ± 0.54[a] (51)	78 (16)
4. AOM + 2.0% curcumin	34	2.15 ± 0.48[a] (56)	68 (27)	0[a] (100)	0 (100)	2.15 ± 0.48[a] (62)	68 (27)
5. AOM + 4.0% curcumin	38	1.88 ± 0.38[a] (62)	56 (40)	0.17 ± 0.07[a] (76)	15 (63)	2.17 ± 0.43[a] (61)	59 (37)
6. AOM + 2.0% pure curcumin	29	2.07 ± 0.49[a] (58)	62 (33)	0.17 ± 0.09[a] (76)	14 (65)	2.24 ± 0.52[a] (60)	62 (33)
Curcumin administration during the initiation period							
7. AOM + 2.0% curcumin	46	1.78 ± 0.30[a] (64)	61 (34)	0.11 ± 0.06[a] (85)	9 (78)	1.89 ± 0.32[a] (66)	61 (34)
Curcumin administration during the postinitiation period							
8. AOM + 2.0% curcumin	33	3.97 ± 0.54 (19)	85 (9)	0.24 ± 0.08[a] (67)	24 (40)	4.21 ± 0.53[a] (25)	91 (2)

[a] Statistically different from the AOM-treated positive control group (group 2; $P < 0.05$), using Student's t test.

Table 6 *Inhibitory effect of dietary curcumin on the size of AOM-induced colon tumors in CF-1 mice*

The size of each colon tumor in the animals described in Table 5 was determined. Each value represents the mean ±SE. Numbers in parentheses, percentage of inhibition.

Treatment	No. of mice/group	Adenomas		Adenocarcinomas		Total tumors	
		Adenoma vol/adenoma (mm^3)	Adenoma vol/mouse (mm^3)	Carcinoma vol/carcinoma (mm^3)	Carcinoma vol/mouse (mm^3)	Tumor vol/tumor (mm^3)	Tumor vol/mouse (mm^3)
1. Vehicle + AIN 76A	14	0[a]	0[a]	0[a]	0[a]	0[a]	0[a]
2. AOM + AIN 76A	56	7.0 ± 1.1	34.6 ± 7.1	22.3 ± 6.1	29.3 ± 10.8	11.2 ± 1.7	64.0 ± 14
Curcumin administration during the initiation and postinitiation periods							
3. AOM + 0.5% curcumin	36	4.0 ± 0.1[a] (43)	11.1 ± 3.1[a] (68)	7.4 ± 2.7[a] (67)	8.1 ± 3.4 (72)	6.4 ± 1.1[a] (43)	19.1 ± 5.2[a] (70)
4. AOM + 2.0% curcumin	34	2.7 ± 0.6[a] (61)	6.7 ± 1.9[a] (81)	0[a] (100)	0[a] (100)	2.7 ± 0.6[a] (76)	6.7 ± 1.9[a] (89)
5. AOM + 4.0% curcumin	38	3.8 ± 0.9[a] (46)	9.2 ± 2.8[a] (73)	3.1 ± 1.9[a] (86)	3.1 ± 2.0[a] (89)	4.7 ± 1.1[a] (58)	12.3 ± 3.7[a] (81)
6. AOM + 2.0% pure curcumin	29	3.7 ± 1.2[a] (47)	9.0 ± 4.6[a] (74)	2.6 ± 1.8[a] (88)	2.7 ± 1.9[a] (91)	4.5 ± 1.3* (60)	11.7 ± 4.9[a] (82)
Curcumin administration during the initiation period							
7. AOM + 2.0% curcumin	46	2.9 ± 0.3[a] (59)	6.4 ± 1.3[a] (82)	2.4 ± 1.1[a] (89)	2.5 ± 1.2[a] (91)	4.0 ± 0.6[a] (64)	9.1 ± 2.2[a] (86)
Curcumin administration during the postinitiation period							
8. AOM + 2.0% curcumin	33	3.7 ± 0.6[a] (47)	15.7 ± 4.9[a] (55)	3.3 ± 1.7[a] (85)	3.3 ± 1.7[a] (89)	4.4 ± 0.7[a] (61)	18.6 ± 5.0[a] (71)

[a] Statistically different from the AOM control animals (group 2; $P < 0.05$), using Student's t test.

as described elsewhere (21, 22). In AOM-treated positive control animals (group 2), the colon adenomas were about 90% tubular adenomas, 5% villous adenomas, and 5% tubovillous adenomas. In the AOM-treated positive control group, the colon adenocarcinomas were 78% tubular adenocarcinomas, 2% papillary adenocarcinomas, 10% tubopapillary adenocarcinomas, and 10% mucin-secreting adenocarcinomas. Administration of dietary curcumin during both the initiation and the postinitiation periods, the initiation period, or the postinitiation period decreased the average number of all different types of colon adenomas or adenocarcinomas per mouse without altering the proportion of the different kinds of tumors. Examination of the location and distribution of total colon tumors, adenomas, or adenocarcinomas in the AOM-treated positive control group revealed that about 22% of the total number of colon tumors were localized from 0–10 mm from the anus, 60% were between 11 to 30 mm from the anus, and only about 3% of the colon tumors were localized more than 40 mm from the anus (*i.e.*, proximal colon). Dietary curcumin did not alter the location of the colon tumors.

Body weights, liver weights, and spleen weights were determined at the end of the AOM-induced carcinogenesis experiment and are shown in Table 7. No significant effects of AOM or curcumin on body weight were found. Treatment of mice with AOM increased the spleen weights by 176% and this increase was inhibited by administration of dietary curcumin during the initiation and postinitiation periods (Table 7). The results also indicate that administration of dietary curcumin during the initiation and postinitiation periods or during the postinitiation period increased liver weights (Table 7).

DISCUSSION

The results of the present study demonstrate that administration of dietary curcumin to mice inhibits B(*a*)P-induced forestomach tumorigenesis (when curcumin was given during the initiation or postinitiation period), ENNG-induced duodenal tumorigenesis (when curcumin was given during the postinitiation period), and AOM-induced colon tumorigenesis (when curcumin was given during the initiation

Table 7 *Effect of dietary curcumin on body weight, liver weight, and spleen weight*

Body weight, liver weight, and spleen weight of each mouse were determined at the end of the experiment described in Table 5. Each value represents the mean ±SE.

Treatment	No. of mice	Body wt (g)	Liver wt (g)	Spleen wt (mg)
1. Vehicle + AIN 76A	14	32.5 ± 1.3	1.52 ± 0.09	69 ± 7[a]
2. AOM + AIN 76A	56	34.9 ± 0.6	1.67 ± 0.04	190 ± 14
Curcumin administration during the initiation and postinitiation periods				
3. AOM + 0.5% curcumin	36	34.0 ± 1.8	2.13 ± 0.08[a]	129 ± 7[a]
4. AOM + 2.0% curcumin	34	34.9 ± 0.4	2.10 ± 0.05[a]	110 ± 6
5. AOM + 4.0% curcumin	38	33.7 ± 0.6	1.88 ± 0.07[a]	143 ± 20
6. AOM + 2.0% pure curcumin	29	33.8 ± 1.3	2.11 ± 0.07[a]	156 ± 17
Curcumin administration during the initiation period				
7. AOM + 2.0% curcumin	46	33.7 ± 0.6	1.63 ± 0.05	158 ± 18
Curcumin administration during the postinitiation period				
8. AOM + 2.0% curcumin	33	34.7 ± 0.6	1.94 ± 0.06[a]	151 ± 14[a]

[a] Statistically different from the AOM-treated positive control group (group 2; $P < 0.05$), using Student's t test.

period, the postinitiation period, or both the initiation and postinitiation periods).

Although most of the studies described here were done with commercial food grade curcumin (77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin), pure curcumin had a similar inhibitory effect on AOM-induced colon tumorigenesis (Table 5). In other studies, topical application of pure curcumin had a similar inhibitory effect on TPA-induced tumor promotion as commercial grade curcumin (23). It is of interest that in most of our studies 0.5% dietary curcumin was as effective an inhibitor of gastrointestinal tumorigenesis as higher dose levels. Recent studies by Mukundan *et al.* (24) indicated that feeding 0.03% dietary curcumin or 0.5% dietary turmeric to rats for 4 weeks markedly decreased the level of B(*a*)P-DNA adducts in the liver at 24 h after the i.p. injection of B(*a*)P. Our results and those of Mukundan *et al.* suggest a need for additional studies to determine whether lower levels of dietary curcumin can inhibit chemically induced gastrointestinal tumorigenesis.

The mechanism(s) of the inhibitory effects of dietary curcumin on chemically induced gastrointestinal tumorigenesis in mice is unknown, but curcumin may influence the metabolic activation and detoxification of carcinogens as well as the postinitiation phase of carcinogenesis. Curcumin or turmeric has been reported to inhibit the metabolic activation of B(*a*)P to mutagens *in vitro*, the metabolic activation of B(*a*)P to B(*a*)P-DNA adducts in mouse skin *in vivo* (15, 24, 25), and the formation of B(*a*)P-DNA adducts or single strand breaks in DNA in the forestomach or liver of mice (26). In additional studies, dietary administration of curcumin or turmeric to mice or rats has been reported to increase the levels of hepatic phase I and phase II enzymes (25). Curcumin has also been reported to enhance the rate of DNA repair in yeast (27). Each of these effects may play a role in the inhibitory action of curcumin on the initiation of carcinogensis by B(*a*)P, AOM, or other chemicals. It would be of interest to determine whether or not curcumin administration inhibits the metabolic activation or enhances the detoxification of carcinogens. Topical application of curcumin has been shown to inhibit TPA-induced ornithine decarboxylase activity, cell proliferation, and tumor promotion in mouse epidermis (9, 11). Several compounds that possess antioxidant or anti-inflammatory activity have been shown to inhibit tumor promotion by TPA and to affect biochemical parameters associated with tumor promotion by TPA and the postinitiation phase of carcinogenesis (11, 19, 28–31). Curcumin has strong antioxidant and free radical-scavenging activity (32–34), inhibits epidermal arachidonic acid metabolism via the lipoxygenase and cyclooxygenase pathways (13), inhibits the inflammatory action of arachidonic acid (13), and inhibits TPA-induced inflammation, ornithine decarboxylase activity, and tumor promotion on mouse skin (11). Several studies suggest that anti-inflammatory inhibitors of arachidonic acid metabolism may inhibit colon carcinogenesis in animals and humans (35–46). Recent studies by Rao, Simi, and Reddy have indicated an inhibitory effect of administration of dietary curcumin to rats on AOM-induced increases in ornithine decarboxylase activity, tyrosine protein kinase activity, arachidonic acid metabolism, and the formation of aberrant crypt foci in the rat colon (47). Our studies in mice and those by Reddy *et al.* in rats indicate that dietary curcumin is a potent inhibitor of colon carcinogenesis in rodents.

Studies on the absorption and metabolism of curcumin indicated that it is absorbed after p.o. administration to rodents and that it is rapidly metabolized to glucuronide and sulfate conjugates that are excreted primarily in bile and to a lesser extent in urine (48–50). Low or undetectable blood levels of unchanged curcumin were observed after p.o. administration (49, 50). It is unclear if this is due to poor absorption or efficient first pass metabolism.

Toxicity studies with turmeric or curcumin in animals indicated no histopathological changes when these substances were fed to rats, dogs, guinea pigs, or monkeys (0.5 to 2 g/kg) for 8–60 weeks (51). In addition, studies with turmeric and curcumin in rats for three generations did not show any teratogenic or carcinogenic effects (49). However, feeding turmeric oleoresin to pigs at a dose of 296 to 1551 mg/kg for 16 weeks decreased body weight gain and concomitantly increased the weight of the liver and thyroid gland (51). Hyperplasia of the thyroid and epithelial changes in kidney, urinary bladder, and liver were also observed in the pigs fed turmeric oleoresin (51). Further studies are needed to determine whether these adverse effects were caused by curcumin *per se* or by other components in the turmeric oleoresin. Our findings that dietary curcumin can inhibit chemically induced carcinogenesis in the gastrointestinal tract (forestomach, duodenum, and colon) of rodents suggests a need for further pharmacological and toxicological studies to determine whether dietary curcumin may be a useful chemopreventive agent against gastrointestinal carcinogenesis. A major source of human consumption of curcumin is from turmeric which is used extensively in curry and mustard and as a coloring agent and spice in many foods. It has been estimated that some individuals ingest as much as 600 mg of dietary turmeric (10–30 mg of curcumin) in their diet daily (52). There is a need for carefully controlled epidemiology studies to determine whether individuals who ingest high levels of curcumin have a lower risk of gastrointestinal carcinogenesis than individuals who do not ingest curcumin.

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Inhibitory Effects of Dietary Curcumin on Forestomach, Duodenal, and Colon Carcinogenesis in Mice

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