PERGAMON

Food and Chemical Toxicology 40 (2002) 1091–1097

Food and Chemical Toxicology

www.elsevier.com/locate/foodchemtox

Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: a short review

Young-Joon Surh*

Laboratory of Biochemistry and Molecular Toxicology, College of Pharmacy, Seoul National University, Seoul 151-742, South Korea

Abstract

A wide variety of phenolic substances derived from spice possess potent antimutagenic and anticarcinogenic activities. Examples are curcumin, a yellow colouring agent, contained in turmeric (*Curcuma longa* L., Zingiberaceae), [6]-gingerol, a pungent ingredient present in ginger (*Zingiber officinale* Roscoe, Zingiberaceae) and capsaicin, a principal pungent principle of hot chili pepper (*Capsicum annuum* L, Solanaceae). The chemopreventive effects exerted by these phytochemicals are often associated with their antioxidative and anti-inflammatory activities. Cyclo-oxygenase-2 (COX-2) has been recognized as a molecular target of many chemopreventive as well as anti-inflammatory agents. Recent studies have shown that COX-2 is regulated by the eukaryotic transcription factor NF-κB. This short review summarizes the molecular mechanisms underlying chemopreventive effects of the aforementioned spice ingredients in terms of their effects on intracellular signaling cascades, particularly those involving NF-κB and mitogen-activated protein kinases.

Keywords: Spice; Chemoprevention; Curcumin; Gingerol; Capsaicin; Intracellular signaling cascades

1. Introduction

Carcinogenesis is a multistage process that consists of at least three separate but closely linked processes: initiation, promotion and progression. Initiation is defined as irreversible modification of the target cell DNA whereas promotion represents the expansion of initially damaged or mutated cells to form a clone of an actively proliferating multicellular premalignant/benign tumor cell population, which eventually progresses to the malignant one characterized by increased invasiveness and metastatic potential. Of the multistage carcinogenesis, promotion is closely linked to oxidative and inflammatory tissue damage. Conversely, a substance with pronounced anti-oxidant and anti-inflammatory effects is anticipated to act as an anti-tumor promoter. A wide variety of phenolic substances derived from edible plants have been reported to retain marked anti-oxidant and anti-inflammatory activities, which contribute to their chemopreventive potential (Surh, 1999; Surh et al., 2001).

2. Role of oxidative and inflammatory tissue damage in tumor promotion

Hydrogen peroxide and certain organic hydroperoxides (e.g. benzoyl peroxide) promote transformation of chemically initiated mouse epidermal cells (reviewed by Cerutti, 1985). Oxidative stress induced by reactive oxygen intermediates (ROIs) has been linked to tumor promotion in mouse skin and other tissues (Cerutti, 1985; Kozumbo et al., 1985; Troll and Wiesner, 1985). When different types of tumor promoters were applied topically to mouse skin, there was a distinct increase in the production of hydrogen peroxide in the epidermis, which correlated with their promoting potential (Perchellet and Perchellet, 1989) Superoxide anion radicals were also formed in keratinocytes stimulated with the tumor promoter such as 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (Pence and Reiners, 1987). Further support for the association between pro-oxidant status and tumor promotion derives from the observation that many structurally unrelated antioxidants and radical scavengers exert anti-promotional activity (Cerutti, 1985; Kozumbo et al., 1985). Exogenous superoxide dismutase inhibited the promotion by TPA of JB6

Abbreviations: COX-2, cyclo-oxygenase-2; ERK, extracellular-regulated protein kinase; HL-60 cells, human promyelocytic leukemia cells; JNK, c-Jun NH_2-terminal kinase; MAP, mitogen-activated protein; ODC, ornithine decarboxylase; ROI, reactive oxygen intermediate; TPA, 12-*O*-tetradecanoylphorbol-13-acetate

* Tel.: +82-2-880-7845; fax: +82-2-874-9775.
E-mail address: surh@plaza.snu.ac.kr

0278-6915/02/$ - see front matter
PII: S0278-6915(02)00037-6

mouse epidermal cell transformation, providing additional evidence for a critical role of ROIs in tumor promotion (Srinivas et al., 1982). Similarly, the lipophilic biomimetic superoxide dismutase cupric 3,5-diidopropylsalicylic acid inhibited tumor promotion in mouse epidermis (Kensler et al., 1983). Ornithine decarboxylase (ODC), a rate-limiting enzyme in polyamine biosynthesis, has been utilized as a biochemical marker for tumor promotion. ODC induction was found to be suppressed by superoxide dismutase and catalase in murine mammary tumor cells and by butylated hydroxytoluene in mouse epidermal cells, suggesting the intermediacy of ROIs in the tumor promotion (Cerutti, 1985, and see references therein).

Persistent, local inflammation has been considered to contribute to multistage carcinogenesis. ROIs produced during the inflammatory tissue damage can trigger a series of reactions which are responsible for malignant transformation, particularly in the stage of promotion (Cerutti, 1985). There is accumulating evidence that ROIs influence the intracellular signaling cascades mediating cell proliferation. Activity or expression of several protein kinases have been shown to be regulated by the pro-oxidant state of cells. ROIs are typical by-products of eicosanoid metabolism (Marnett, 1987). ROIs are released from the cells of the inflammatory skin infiltrate.

A correlation exists between the ability of a compound to induce prostaglandin release in vitro and its ability to promote papilloma formation in mouse skin in vivo. A previous study by Verma et al. (1980) suggests that prostaglandins play a crucial role in the induction of ODC activity and mouse skin tumor promotion by TPA. Both ROI generation by inflammatory cells and skin tumor promotion are efficiently inhibited by protease inhibitors, indicating an interrelationship between the two processes (Troll and Wiesner, 1985).

3. Cyclo-oxygenase-2 (COX-2) as a molecular target for cancer chemoprevention

COX-2 is a key enzyme catalyzing the production of prostaglandins in response to inflammatory stimuli. Multiple lines of evidence support the notion that COX-2 plays a role in the development of tumors (Prescott and Fitzpatrick, 2000). Conversely, selective COX-2 inhibitors (e.g., celecoxib) have chemopreventive potential. One nuclear target of the intracellular signaling pathways responsible for induction of COX-2 expression is the eukaryotic transcription factor NF-κB. Thus, NF-κB has been shown to be a positive regulator of COX-2 in diverse cell types (Surh et al., 2001). The 5′-promoter region of COX-2 contains two putative NF-κB binding sites. The functionally active NF-κB exists mainly as a heterodimer consisting of subunits of Rel family (e.g. p65/Rel A, p50, p52, c-Rel, v-Rel and Rel B), which is normally present in the cytoplasm as an inactive complex with the inhibitory protein, IκB. Exposure of cells to mitogens, inflammatory cytokines, UV, ionizing radiation, bacterial toxins, etc. causes rapid phosphorylation of IκB with subsequent degradation by proteosomes. Dissociation of IκB from NF-κB allows the activated free dimer to translocate to the nucleus, where it binds to the *cis*-acting κB element located in the promoter or enhancer regions of COX-2 and other genes, thereby regulating their expression. Activation of AP-1, another important eukaryotic transcription factor, is also implicated in the transcription of COX-2 (Adderley and Fitzgerald, 1999).

4. Intracellular signaling cascades regulating COX-2 induction

The molecular signaling mechanisms that lead to the induction of COX-2 as well as activation of NF-κB in response to various external stimuli have not been fully clarified (Surh et al., 2001). One of the most extensively investigated intracellular signaling cascades involved in pro-inflammatory responses is the mitogen-activated protein (MAP) kinase pathway. Three distinct groups of well characterized major MAP kinase subfamily members include extracellular-regulated protein kinase (ERK), c-Jun NH_2-terminal kinase (JNK)/stress-activated protein kinase and p38 MAP kinase which are serine/threonine protein kinases. The activated form of each of the above MAP kinases then phosphorylates and activates other kinases or transcription factors, thereby altering the expression of the target genes. The induction of COX-2 and/or resulting prostaglandin production were abolished by the pharmaceutical inhibition (Niiro et al., 1998; Jaffee et al., 2000; Wang et al., 2001) or by dominant-negative knockout of the corresponding MAP kinases (Xie and Herschman, 1995; Guan et al., 1998), suggesting that the MAP kinase cascades are responsible, at least in part, for up-regulation of COX-2. The proposed intracellular signaling cascades leading to COX-2 induction in response to external oxidative/inflammatory stimuli are schematically represented in Fig. 1.

5. Some examples of anti-oxidative and anti-inflammatory spice ingredients with chemopreventive potential

Because pro-inflammatory and pro-oxidant states are closely linked to tumor promotion, substances with potent anti-inflammatory and/or anti-oxidant activities are anticipated to exert chemopreventive effects on carcinogenesis, particularly in the stage of promotion.

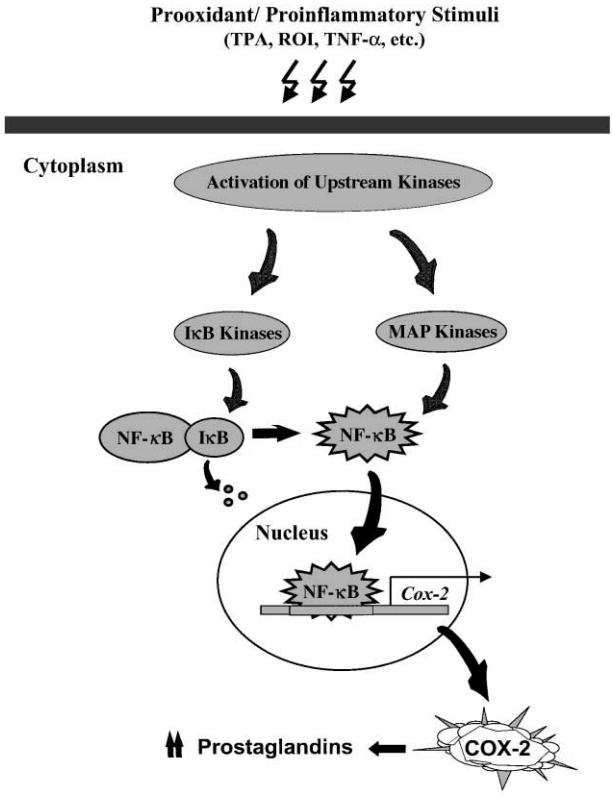

Fig. 1. Schematic representation of intracellular signalling cascades mediating oxidative and pro-inflammatory stimuli.

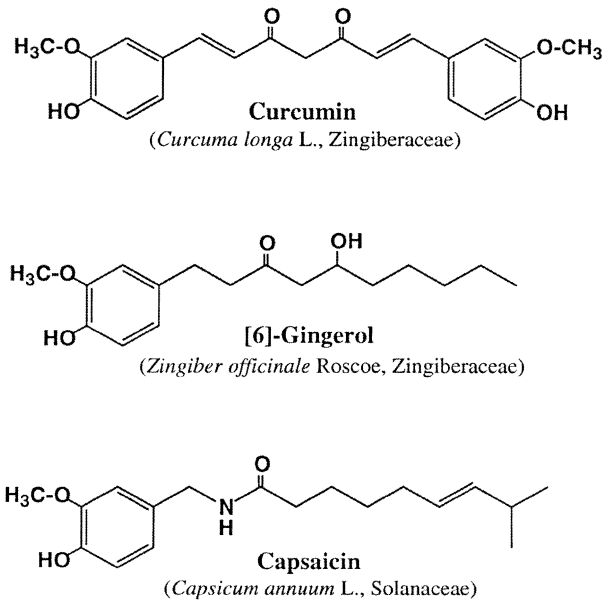

Fig. 2. Chemical structures of curcumin, [6]-gingerol and capsaicin.

Examples of some representative chemopreventive spice ingredients with substantial anti-oxidative and anti-inflammatory properties are listed below. These include, curcumin from turmeric (*Curcuma longa* L., Zingiberaceae), gingerol from ginger (*Zingiber officinale* Roscoe, Zingiberaceae) and capsaicin from hot chili pepper (*Capsicum annuum* L., Solanaceae). Their chemical structures are shown in Fig. 2.

5.1. Curcumin

Curcumin, a yellow pigment present in the rhizome of turmeric (*C. longa* Linn) and related species, has a wide array of pharmacological and biological activities (Ammon and Wahl, 1991). Anti-oxidant and anti-inflammatory effects of this compound have been assessed in various in vitro and in experimental animal systems (reviewed by Surh, 1999). Chemopreventive properties of curcumin have been extensively investigated and well documented (Nagabhushan and Bhide, 1992; Conney et al., 1997; Surh, 1999). One of the most plausible mechanisms underlying the chemopreventive effects of curcumin involves suppression of tumor promotion. Thus, topical application of curcumin strongly inhibited TPA-induced inflammation, hyperplasia, proliferation, ODC activity, ODC mRNA expression, generation of ROIs, oxidized DNA base modification and papilloma formation in mouse skin (Lu et al., 1993; Conney et al., 1997; Huang et al., 1997; Nakamura et al., 1998).

Curcumin inhibited COX-2 and lipoxygenase activities in TPA-treated mouse epidermis (Huang et al., 1991a). Treatment of several human gastrointestinal cell lines with curcumin suppressed expression of COX-2 protein and mRNA, prostaglandin E_2 production, and AP-1 DNA binding induced by TPA or chenodeoxycholate (Zhang et al., 1999). Suppression of TPA-induced activation of c-Jun/AP-1 in cultured NIH3T3 cells has been proposed to be responsible for the anti-tumor promoting activity curcumin retains (Huang et al., 1991b). c-Fos is associated with c-Jun to form the AP-1 complex. Curcumin at a topical dose of 10 μmol almost completely inhibited TPA-induced expression of c-*fos* and c-*jun* mRNA in mouse skin (Kakar and Roy, 1994), which may account for its antitumor promoting activity in mouse skin carcinogenesis. Similarly, topical application of 10 μmol curcumin together with 5 nmol TPA once a day for 5 consecutive days strongly inhibited hyperplasia and reduced the levels of both c-Jun and c-Fos in CD-1 mouse skin (Lu et al., 1994). Quiescent JB6 cells treated with TPA exhibited morphological changes to form anchorage-independent colonies as determined by the soft-agar assay (Lu et al., 1994). Curcumin treatment reduced the TPA-induced foci formation and c-Jun expression in these cells (Lu et al., 1994). Besides AP-1, NF-κB appears to be a target for pleiotropic effects of curcumin. Thus, curcumin has been shown to reduce the TNF-α-induced expression of the tissue factor gene in bovine aortic endothelial cells by repressing activation of both AP-1 and NF-κB (Bierhous et al., 1997). In this study, curcumin blocked the degradation of IκBα and subsequent nuclear

translocation of NF-κB, while it interfered with AP-1 binding to DNA by directly interacting with the latter transcription factor (Bierhous et al., 1997). Transcriptional inhibition of the tissue factor gene activation by curcumin appeared to be mediated through suppression of activation of NF-κB and AP-1 (Pendurthi et al., 1997). Likewise, activation of NF-κB in cultured human myeloid monoblastic leukemia cell line (ML-1a) stimulated with TPA, TNF-α or hydrogen peroxide was suppressed by curcumin treatment (Singh and Aggarwal, 1995). In this study, curcumin not only abrogated TNF-α-induced phosphorylation and subsequent degradation of IκB, but also inhibited nuclear translocation of p65, the functionally active subunit of NF-κB. AP-1 binding was also down-modulated by curcumin (Singh and Aggarwal, 1995). Topical application of curcumin significantly attenuated the TPA-induced activation of NF-κB and AP-1 in mouse skin in vivo (Surh et al., 2000).

Curcumin inhibited TPA-induced activation of ERK and p38 MAP kinases, which are upstream of NF-κB, in mouse skin treated with TPA (Chun et al., 2001). Blockade of one or both of these key MAP kinases would result in inactivation of NF-κB and subsequent inhibition of COX-2.

5.2. Gingerol

The oleoresin from rhizomes of ginger contains [6]-gingerol (1-[4′-hydroxy-3′-methoxyphenyl]-5-hydroxy-3-decanone) and its homologs as pungent ingredients that have a wide array of pharmacological and physiological activities (Mustafa et al., 1993; Surh et al., 1998). Gingerol was reported to possess substantial antioxidant properties as determined by inhibition of phospholipid peroxidation induced by the $FeCl_3$-ascorbate system and also of the xanthine oxidase activity (Aeschbach et al., 1994). In addition, [6]-gingerol attenuated TPA-stimulated production of superoxide generation in differentiated human promyelocytic leukemia (HL-60) cells (Surh et al., 1999). Gingerol and structurally related pungent principles of ginger including shogaol exert inhibitory effects on biosynthesis of prostaglandins and leukotrienes through suppression of prostaglandin synthase or 5-lipoxygenase (Kiuchi et al., 1982, 1992; Flynn and Rafferty, 1986).

When topically applied prior to each TPA treatment during the entire period of tumor promotion after the initiation with 7,12-dimethylbenz[*a*]anthracene, gingerol strongly inhibited mouse skin tumor formation (Park et al., 1998a). [6]-Gingerol also suppressed TPA-induced epidermal ODC activity (Park et al., 1998a) and TNF-α production in mouse skin. Azoxymethane-induced intestinal tumorigenesis was ameliorated by dietary administration of gingerol (Yoshimi et al., 1992). Moreover, gingerol has been reported to abrogate the pulmonary metastasis in mice implanted with B16F10 melanoma cells (Suzuki et al., 1997). Gingerol induces apoptosis in cultured HL-60 cells (Lee and Surh, 1998). A recent study by Bode et al. (2001) has demonstrated that [6]-gingerol inhibits neoplastic transformation and activation of AP-1 in mouse epidermal JB6 cells treated with epidermal growth factor.

5.3. Capsaicin

Hot red and chili peppers are among the most heavily and frequently consumed spices. Their principal pungent and irritating constituent is the phenolic substance named capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide). Capsaicin has been subjected to extensive experimental and clinical investigations, due to its prominent pharmacologic and toxicologic properties (reviewed by Surh and Lee, 1995; Szallasi and Blumberg, 1999). The role of this pungent vanilloid in multistage carcinogenesis, particularly in human cancer, is quite controversial (Surh and Lee, 1996). Although capsaicin has been suspected as a potential carcinogen or co-carcinogen, there has been a substantial body of data supporting that the compound has chemopreventive or chemoprotective effects (reviewed by Surh et al., 1998).

Capsaicin can act as an antioxidant, as revealed by attenuation of oxidative damage or lipid peroxidation in various organs of experimental animals (De and Ghosh, 1992; Toskulkao and Tekittipong, 1996). Anti-inflammatory properties of capsaicin have also been reported. Capsaicin was shown to antagonize the mouse ear edema induced by croton oil (Clementi et al., 1994). In another study, capsaicin ameliorated carrageenan-induced inflammation in rats (Pulla Reddy and Lokesh, 1994). Moreover, capsaicin has the ability to inhibit platelet aggregation possibly through blockade of phospholipase A_2 (Wang et al., 1984), a key enzyme responsible for formation of arachidonic acid from the membrane lipid. In addition, capsaicin repressed calcium-ionophore stimulated pro-inflammatory responses, such as generation of superoxide anion, phospholipase A_2 activity and membrane lipid peroxidation in macrophages (Savitha and Salimath, 1995). Capsaicin exerted protective effects against ethanol-induced gastric mucosal injury in rats (Kang et al., 1995). Ethanol-induced haemorrhagic erosion, lipid peroxidation and myeloperoxidase activity in rats were ameliorated by intragastric capsaicin treatment, which was associated with suppression of COX-2 (Park et al., 2000). In consideration of the association of tumor promotion with oxidative and inflammatory tissue damage, it would be worthwhile determining whether capsaicin that has antioxidant and anti-inflammatory activities could inhibit tumor promotion. While lacking an intrinsic tumor-promoting activity, capsaicin inhibited TPA-promoted mouse skin papillomagenesis (Park and Surh, 1997; Park et al., 1998b).

Constitutive activation of NF-κB has been associated with proliferation and survival of certain tumor cells (Bargou et al., 1997; Sovak et al., 1997), and also confers resistance to apoptosis (Giri and Aggarwal, 1998). Very recently, capsaicin has been reported to inhibit constitutive activation of NF-κB mediated by ROIs endogenously generated via the NAD(P)H:quinone oxidoreductase system in malignant melanoma cells (Brar et al., 2001). Topical application of capsaicin to dorsal skin of female ICR mice strongly suppressed TPA-stimulated activation of NF-κB by blocking degradation of the inhibitory protein IκBα and subsequent nuclear translocation of the free NF-κB dimer (Han et al., 2001). Capsaicin also inhibited epidermal activation of AP-1 in mice (Han et al., 2001). Similarly, TPA-stimulated activation of NF-κB and AP-1 in cultured HL-60 cells was suppressed by capsaicin (Surh et al., 2000).

6. Concluding remarks

The antipromotional effects of curcumin, gingerol and capsaicin appear to be associated with their anti-oxidant and/or anti-inflammatory activities. One of the most critical targets of these chemopreventive spice ingredients involves NF-κB that regulates expression of a whole variety of genes, including COX-2 responsible for inflammation and malignant transformation. The inhibition of NF-κB activation by curcumin, gingerol and capsaicin is thought to be mediated through multiple mechanisms, one of which involves the MAP kinase cascades. While data in cultured cells and in animal models confer enthusiasm over the aforementioned phytochemicals and related substances, clinical or epidemiological data supporting their chemopreventive potential in human populations are limited.

Acknowledgements

This work was supported by the grant (2002–2-20800–003–5) from the Basic Research Program of the Korea Science and Engineering Foundation (KOSEF).

References

Adderley, S.R., Fitzgerald, D.J., 1999. Oxidative damage of cardiomyocytes is limited by extracellular regulated kinases 1/2-mediated induction of cyclooxygease-2. Journal of Biological Chemistry 274, 5038–5046.

Aeschbach, R., Loliger, J., Scott, B.C., Murcia, A., Butler, B., Halliwell, B., Aruoma, O.I., 1994. Antioxidant actions of thymol, carbacrol, 6-gingerol, zingerone and hydroxytyrosol. Food and Chemical Toxicology 32, 31–36.

Ammon, H.P.T., Wahl, M.A., 1991. Pharmacology of *Curcuma longa*. Planta Medica 57, 1–7.

Bargou, R.C., Emmerich, F., Krappmann, D., Bommert, K., Mapara, M.Y., Arnold, W., Toyer, H.D., Grinstein, E., Greiner, A., Scheidereit, C., Dorken, B., 1997. Constitutive nuclear factor-κB-Rel activation is required for proliferation and survival of Hodgkin's disease tumor cells. Journal of Clinical Investigation 100, 2961–2969.

Bierhous, A., Zhang, Y., Quehenberger, P., Luther, T., Haase, M., Muller, M., Mackman, N., Ziegler, R., Nawroth, P.P., 1997. The dietary pigment curcumin reduces endothelial tissue factor gene expression by inhibiting binding of AP-1 to the DNA and activation of NF-κB. Thrombosis and Haematostasis 77, 772–782.

Bode, A.M., Ma, W.-Y., Surh, Y.-J., Dong, Z., 2001. Inhibition of epidermal growth factor-induced cell transformation and activator protein 1 activation by [6]-gingerol. Cancer Research 61, 850–853.

Brar, S., Kennedy, T.P., Whorton, A.R., Sturrock, A.B., Huecksteadt, T.P., Ghio, A.J., Hoidal, J.R., 2001. Reactive oxygen species from NAD(P)H:quinone oxidoreducase constitutively activate NF-κB in malignant melanoma cells. American Journal of Physiology and Cell Physiology 280, C659–676.

Cerutti, P.A., 1985. Prooxidant states and tumor promotion. Science 227, 375–381.

Chun, K.-S., Cha, H.-H., Han, S.-S., Lee, J.-Y., Surh, Y.-J., 2001. Curcumin down-regulates phorbol ester-induced cyclooxygenase-2 and inducible nitric oxide synthase in mouse skin by blocking activation of p38 MAPK and NF-κB. Proceedings of American Association for Cancer Research 42, 575.

Clementi, G., Amico-Rexas, M., Caruso, A., Cutuli, V.M.C., Prato, A., Maugeri, S., de Bernardis, E., Scapagnini, U., 1994. Effects of CGRP in different models of mouse ear inflammation. Life Sciences, 54, PL119–124.

Conney, A.A., Lou, Y.-R., Xie, J.-G., Osawa, T., Newmark, H.L., Liu, Y., Chang, R.L., Huang, M.-T., 1997. Some perspectives on dietary inhibitors of carcinogenesis; studies with curcumin and tea. Proceedings of the Society of Experimental Biology and Medicine 216, 234–245.

De, A.K., Ghosh, J.J., 1992. Studies on capsaicin inhibition of chemically-induced lipid peroxidation in the lung and liver tissues of rat. Phytotherapy Research 6, 34–37.

Flynn, D.L., Rafferty, M.F., 1986. Inhibition of 5-hydroxy-eicosatetraenoic acid (5-HETE) formation in intact human neutrophils by naturally occurring diarylheptanoids: inhibitory activities of curcuminoids and yakuchinones. Prostaglandins Leukotrienes and Medicine 22, 357–360.

Giri, D.K., Aggarwal, B.B., 1998. Constitutive activation of NF-κB causes resistance to apoptosis in human cutaneous T cell lymphoma HuT-78 cells. Journal of Biological Chemistry 273, 14008–14014.

Guan, Z., Buckman, S.Y., Miller, B.W., Springer, L.D., Morrison, A.R., 1998. Interleukin-1-β-induced cyclooxygenase-2 expression requires activation of both c-Jun NH_2-terminal kinase and p38 MAPK signal pathways in rat renal mesangial cells. Journal of Biological Chemistry 273, 28670–28676.

Han, S.S., Keum, Y.-S., Seo, H.-J., Chun, K.-S., Lee, S.S., Surh, Y.-J., 2001. Capsaicin suppresses phorbol ester-induced activation of NF-κB/Rel and AP-1 transcription factors in sedmis. Cancer Letters 164, 119–126.

Huang, M.-T., Lusz, T., Ferraro, T., Abidi, T.F., Laskin, J.D., Conney, A.H., 1991a. Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. Cancer Research 51, 813–819.

Huang, T.-S., Lee, S.-C., Lin, J.-K., 1991b. Suppression of c-Jun/AP-1 activation by an inhibitor of tumor promotion in mouse fibroblast cells. Proceedings of the National Academy of Sciences of the USA 88, 5292–5296.

Huang, M.-T., Ma, W., Yen, P., Xie, J.-G., Han, J., Frenkel, K., Grunberger, D., Conney, A.H., 1997. Inhibitory effects of topical application of low doses of curcumin on 12-*O*-tetra-

decanoylphorbol-13-acetate-induced tumor promotion and oxidized DNA bases in mouse epidermis. Carcinogenesis 18, 83–88.

Jaffee, B.D., Manos, E.J., Collins, R.J., Czerniak, P.M., Favata, M.F., Magolda, R.L., Scherle, P.A., Trzaskos, J.M., 2000. Inhibition of M.A.P. kinase kinase (MEK) results in an anti-inflammatory response in vivo. Biochemical and Biophysical Research Communications 268, 647–651.

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

Kang, J.Y., Teng, C.T., Wee, A., Chen, F.C., 1995. Effect of capsaicin and chilli on ethanol induced gastric mucosal injury in the rat. Gut 36, 664–669.

Kensler, T.W., Bush, D.M., Kozumbo, W.J., 1983. Inhibition of tumor promotion by a biomimetic superoxide dismutase. Science 221, 75–77.

Kiuchi, F., Shibuya, M., Sankawa, U., 1982. Inhibitors of prostaglandin biosynthesis from *Alpinia officinarum*. Chemical and Pharmaceutical Bulletin 30, 2279–2282.

Kiuchi, F., Iwakami, S., Shibuya, M., Hanaoka, F., Sankawa, U., 1992. Inhibition of prostagndin leukotriene biosynthesis by gingerols and diarylheptanoids. Chemical and Pharmaceutical Bulletin 40, 387–391.

Kozumbo, W.J., Trush, M.A., Kensler, T.W., 1985. Are free radicals invlolved in tumor promotion? Chemico–Biological Interactions 54, 199–207.

Lee, E., Surh, Y.-J., 1998. Induction of apoptosis in HL-60 cells by pungent vanilloids, [6]-gingerol and [6]-paradol. Cancer Letters 134, 163–168.

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

Lu, Y.P., Chang, R.L., Lou, Y.-R., Huang, M.-T., Conney, A.H., Newmark, H.L., 1994. Effect of curcumin on 12-*O*-tetradecanoylphorbol-13-acetate- and ultraviolet B light-induced expression of c-Jun and c-Fos in JB6 cells and in mouse epidermis. Carcinogenesis 15, 2363–2370.

Marnett, L.J., 1987. Peroxy free radicals: potential mediators of tumor initiation and promotion. Carcinogenesis 8, 1365–1373.

Mustafa, T., Srivastava, K.C., Jensen, K.B., 1993. Drug development report (9): pharmacology of ginger, *Zingiber officinale*. Journal of Drug Development 6, 25–39.

Nagabhushan, M., Bhide, S.V., 1992. Curcumin as an inhibitors of cancer. Journal of the American College of Nutrition 11, 192–198.

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

Niiro, H., Otsuka, T., Ogami, E., Yamaoka, K., Nagano, S., Akahoshi, M., Nakashima, H., Arinobu, Y., Izuhara, K., Niho, Y., 1998. MAP kinase pathways as a route for regulatory mechanisms of IL-10 and IL-4 which inhibit COX-2 expression in human monocytes. Biochemical and Biophysical Research Communications 250, 200–205.

Park, J.S., Choi, M.-A., Kim, B.-S., Han, I.-S., Kurata, T., Yu, R., 2000. Capsaicin protects against ethanol-induced oxidative injury in the gastrointestinal mucosa of rats. Life Sciences 67, 3087–3093.

Park, K.-K., Chun, K.-S., Lee, J.-M., Lee, S.S., Surh, Y.-J., 1998a. Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. Cancer Letters 129, 139–144.

Park, K.-K., Chun, K.-S., Yook, J.-I., Surh, Y.-J., 1998b. Lack of tumor promoting activity of capsaicin, a principal pungent ingredient of red pepper, in mouse skin carcinogenesis. Anticancer Research 18, 4201–4206.

Park, K.-K., Surh, Y.-J., 1997. Effects of capsaicin on chemically-induced two-stage mouse skin carcinogenesis. Cancer Letters 114, 183–184.

Pence, J.J., Reiners, J.J., 1987. Murine epidermal xanthine oxidase activity: correlation with degree of hyperplasia induced by tumor promoters. Cancer Research 47, 6388–6392.

Pendurthi, U.R., Williams, J.T., Rao, L.V.M., 1997. Inhibition of tissue factor gene activation in cultured endothelial cells by curcumin. Suppression of activation of transcription factor Egr-1, AP-1, and NF-κB. Thrombosis and Vascular Biology 17, 3406–3413.

Perchellet, E.M., Perchellet, J.P., 1989. Characterization of the hydroperoxide response observed in mouse skin treated with tumor promoters in vivo. Cancer Research 49, 6193–6201.

Prescott, S.M., Fitzpatrick, F.A., 2000. Cyclooxygenase-2 and carcinogenesis. Biochimica et Biophysica Acta 1470, M69–M78.

Pulla Reddy, A.Ch., Lokesh, B.R., 1994. Studies on anti-inflammatory activity of spice principles and dietary n-3 polyunsaturated fatty acids on carragenan-induced mouse ear edema. Inflammation Research 44, 470–474.

Savitha, G., Salimath, B.P., 1995. Effects of capsaicin on phospholipase A2 activity and superoxide generation in macrophages. Nutrition Research 15, 1417–1427.

Singh, S., Aggarwal, B.B., 1995. Activation of transcription factor NF-κB is suppressed by curcumin (diferuloylmethane). Journal of Biological Chemistry 270, 24995–25000.

Sovak, M.A., Bellas, R.E., Kim, D.W., Zanieski, G.J., Rogers, A.E., Traish, A.M., Sonnenshein, G.E., 1997. Aberrant NF-κB/Rel expression and the pathogenesis of breast cancer. Journal of Clinical Investigation 100, 2952–2960.

Srinivas, L., Gindhart, T., Colburn, N.H., 1982. Tumor-promoter-resistant cells lack trisialoganglioside response. Proceedings of the National Academy of Sciences of the USA 79, 4988–4991.

Surh, Y.-J., 1999. Molecular mechanisms of chemopreventive effects of selected dietary and medicinal phenolic substances. Mutation Research 428, 305–327.

Surh, Y.-J., Chun, K.-S., Cha, H.-H., Han, S.S., Keum, Y.-S., Park, K.-K., Lee, S.S., 2001. Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-κB activation. Mutation Research 480–481, 243–268.

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

Surh, Y.-J., Lee, E., Lee, J.-M., 1998. Chemoprotective properties of some pungent ingredients present in red pepper and ginger. Mutation Research 402, 259–267.

Surh, Y.-J., Lee, S.S., 1995. Capsaicin, a double-edged sword: toxicity, metabolism, and chemopreventive potential. Life Sciences 56, 1845–1855.

Surh, Y.-J., Lee, S.S., 1996. Capsaicin in hot chili pepper: carcinogen, co-carcinogen or anticarcinogen? Food and Chemical Toxicology 34, 313–316.

Surh, Y.-J., Park, K.-K., Chun, K.-S., Lee, J.-M., Lee, E., Lee, S.S., 1999. Anti-tumor promoting activities of selected pungent substances present in ginger. Journal of Environmental Toxicology, Pathology and Oncology 18, 131–139.

Suzuki, F., Kobayashi, M., Komatsu, Y., Kato, A., Pollard, R.B., 1997. Keishi-ka-kai-to, a traditional Chinese herbal medicine, inhibits pulmonary metastasis of B16 melanoma. Anticancer Research 17 (2A), 873–878.

Szallasi, A., Blumberg, P.M., 1999. Vanilloid (capsaicin) receptors and mechanisms. Pharmacological Reviews 51, 159–211.

Troll, W., Wiesner, R., 1985. The role of oxygen free radicals as a

possible mechanism of tumor promotion. Annual Review of Pharmacology and Toxicology 25, 509–528.

Toskulkao, C., Tekittipong, S., 1996. Capsaicin inhibits exercise-induced lipid peroxidation in cardiac and skeletal muscles of rat. Phytotherapy Research 6, 34–37.

Verma, A.K., Ashendel, C.L., Boutwell, R.K., 1980. Inhibition by prostaglandin synthesis inhibitors of the induction of epidermal ornithine decarboxylase activity, the accumulation of prostaglandins, and tumor promotion caused by 12-*O*-tetradecanoylphorbol-13-acetate. Cancer Research 40, 308–315.

Wang, J.-P., Hsu, M.-F., Teng, C.-M., 1984. Antiplatelet effect of capsaicin. Thrombosis Research 36, 497–507.

Wang, H.Q., Kim, M.P., Tiano, H.F., Langenbach, R., Smart, R.C., 2001. Protein kinase C-α coordinately regulates cytosolic phospholipase A2 activity and the expression of cyclooxygenase-2 through different mechanisms in mouse keratinocytes. Molecular Pharmacology 59, 86–866.

Xie, W., Herschman, H.R., 1995. v-*src* induces prostaglandin synthase 2 gene expression by activation of the c-Jun N-terminal kinase and the c-Jun transcription factor. Journal of Biological Chemistry 270, 27622–27628.

Yoshimi, N., Wang, A., Morishita, Y., Tanaka, T., Sugie, S., Kawai, K., Yamahara, J., Mori, H., 1992. Modifying effects of fungal and herb metabolites on azoxymethane-induced intestinal carcinogenesis in rats. Japanese Journal of Cancer Research 83, 1273–1278.

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