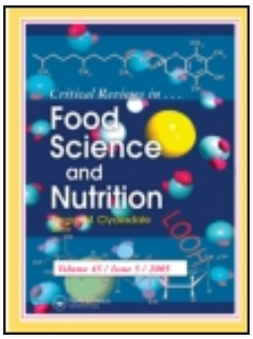

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Biological Properties of Curcumin-Cellular and Molecular Mechanisms of Action

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Curcuminoids, a group of phenolic compounds isolated from the roots of Curcuma longa *(Zingiberaceae), exhibit a variety of beneficial effects on health and on events that help in preventing certain diseases. A vast majority of these studies were carried out with curcumin (diferuloyl methane), which is a major curcuminoid. The most detailed studies using curcumin include anti-inflammatory, antioxidant, anticarcinogenic, antiviral, and antiinfectious activities. In addition, the wound healing and detoxifying properties of curcumin have also received considerable attention. As a result of extensive research on the therapeutic properties of curcumin, some understanding on the cellular, molecular, and biochemical mechanism of action of curcumin is emerging. These findings are summarized in this review.*

Keywords curcuminoid, spice, nutraceutical, food additive, inflammation, cancer

INTRODUCTION

Curcumin (diferuloyl methane), the natural yellow pigment in turmeric, is isolated from the rhizomes of the plant *Curcuma longa*. It constitutes about 3–4% of the composition of turmeric. In the south and southeast tropical Asian countries, turmeric has been used for centuries as a spice to give the specific flavor and yellow color to curry (Eigner and Scholz, 1999). Turmeric became a very important spice to mankind when it was observed that the addition of turmeric powder in food preparation preserved its freshness and nutritive value. Turmeric, as an additive, improved the palatability, aesthetic appeal, and shelf life of perishable food items. The use of turmeric became more popular when it was found to act as a therapeutic agent for various illnesses. In the Ayurvedic system of medicine, turmeric is used as a tonic and as a blood purifier. Its role in the treatment of skin diseases and its ability to soften rough skin resulted in the prolific use of turmeric in topical creams and bath soaps in India. Turmeric is also used in home remedies in the treatment of cuts, wounds, bruises, and sprains. Its use as an anti-inflammatory and antimicrobial agent has been recognized for more than a century.

The importance of turmeric in medicine took a new twist when it was discovered that the dried rhizome of *Curcuma longa* is very rich in phenolics, whose structures have been identified as curcuminoids (Figure 1). Phenolics are known to possess antioxidant properties. Free radical mediated damage to biological systems is recognized as the initiating agent for many diseases, such as cardiovascular diseases, cancer, and arthritis. Turmeric and its constituents show beneficial effects on these diseases and on other illnesses (Eigner and Scholz, 1999). For example, the low incidence of large bowel cancers in Indians could be attributed to a high intake of natural antioxidants, such as curcumin in the diet (Mohandas and Desai, 1999). The anti-mutagenic and anti-tumor effects of curcumin are most widely studied

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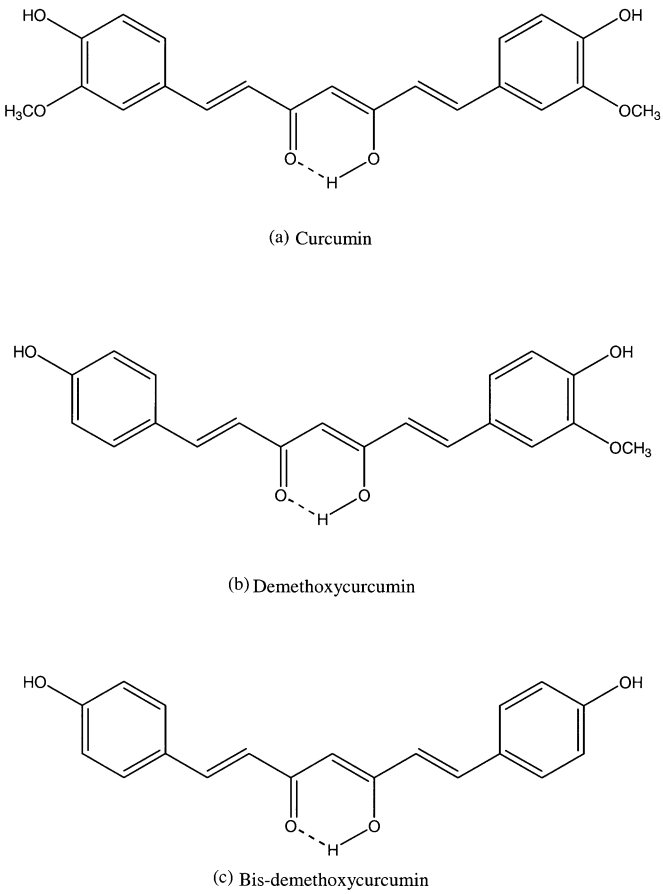

Figure 1 Molecular structures of curcuminoids: (a) Curcumin; (b) Demethoxycurcumin; (c) Bis-demethoxycurcumin.

(Anto et al., 1996; Surh, 1999). However, in recent years, it has been shown that the inhibition of arachidonic acid metabolism, modulation of cellular signal transduction pathways, inhibition of hormone, growth factor, and oncogene activity are some of the mechanisms by which curcumin causes tumor suppression (Gescher et al., 1998). Chemopreventive activity of curcumin is observed when administered prior to, during, and after carcinogen treatment as well as when it is given only during the promotion/progression phase (starting late in premalignant stage) of colon carcinogenesis in F344 rats (Kawamori et al., 1999). Curcumin is also a powerful inhibitor of the proliferation of several tumor cells (Chuang et al., 2000a, 2000b; Dorai et al., 2001), as well as an anti-inflammatory agent (Joe and Lokesh, 1994, 1997a, 2000; Joe et al., 1997). It exhibits anti-clastogenic (Antunes et al., 2000; Araujo and Leon, 2001; Mukhopadhyay et al., 1998), anti-fungal (Bartine and Tantaoui-Elaraki, 1997), and anti-viral properties (Barthelemy et al., 1998). However, the lack of information regarding the mechanisms of action of curcumin has precluded its clinical use in western countries. Several recent studies have given some insight into the molecular basis for the action of curcumin at the cellular level. This review looks at some of these insights into the cellular processes, molecular, and/or biochemical mechanisms that are influenced by curcumin.

THE BIOLOGICAL SOURCE OF CURCUMIN

Curcuma, a genus in the plant family of Zingiberacea, is the biological source for curcuminoids, including curcumin. *Curcuma longa*, the yellow tuberous root that is referred to as turmeric, was taken from India to Southeast Asia, China, North Australia, West Indies, and South America. Subsequently, its cultivation spread to many African countries. India, however, remains the largest producer of turmeric in the world, with a figure of 4,87,000 metric tonnes in production, of which 27,750 metric tonnes are exported. The yellow pigmented fraction of *Curcuma longa* contains curcuminoids, which are chemically related to its principal ingredient, curcumin. The three main curcuminoids isolated from turmeric are curcumin, demethoxy curcumin, and bisdemethoxy curcumin (Figure 1). Curcuminoids are present in 3–5% of turmeric. Curcumin is the important active ingredient responsible for the biological activity of turmeric. Curcumin, $C_2H_{20}O_6$ (m.p. 184°C), or diferuloyl methane was first isolated in 1815. The crystalline form of curcumin was obtained in 1910, and Lampe solved its structure in 1913. It is insoluble in water, but soluble in ethanol and acetone.

BIOLOGICAL ACTIVITIES OF CURCUMIN

Anti-Inflammatory Properties

Inflammation is a necessary process for fighting infections. It results from a series of complex reactions, triggered by the host immunological response. Uncontrolled inflammatory responses may lead to undesirable effects, such as tissue damage. Many of the diseases, such as rheumatoid arthritis, are the result of sustained production of inflammatory mediators causing physical damage to joints. Many inflammatory mediators have been implicated in these complex reactions, some of which are modulated by curcumin (Srimal and Dhawan, 1973).

A. Effect on Cytokines

Macrophages and CD4+ cells, when activated, generate a number of proinflammatory cytokines. The pleiotropic cytokine, tumor, necrosis factor-alpha (TNF), induces the production of interleukin-1 β (IL-1), and together, they play significant roles in many acute and chronic inflammatory and autoimmune diseases. *In vitro* studies show that curcumin, at 5 μM, inhibited the lipopolysaccharide (LPS)-induced production of TNFα and IL-1 by a human monocytic macrophage cell line (Chan, 1995). As a consequence, downstream events involving TNFα and IL-1 are affected. For instance, TNFα induced expression of leukocyte adhesion proteins, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), E-selectin is lowered in curcumin treated cells (Gupta and Ghosh, 1999). Similarly, IL-1β-stimulated gene expression of a neutrophil chemotactic peptide, interleukin-8 (IL-8), is inhibited by curcumin (Chaudhary and Avioli, 1996). In addition,

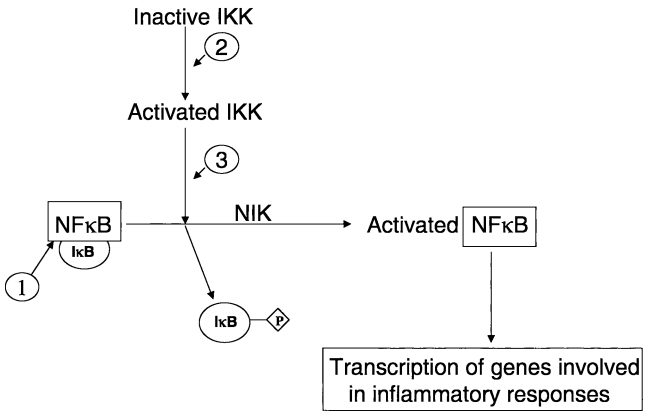

Figure 2 Curcumin interferes with inflammatory pathways by blocking the transcription factor NFκB. The numbers 1, 2, and 3 represent the pathways that are described to be affected by curcumin as detailed in Brennan et al., 1998, Jobin et al., 1999 and Plummer et al., 1999, respectively. NFκB: Nuclear transcription factor required for transcription of genes involved in the inflammatory responses; IκB: Cytosolic inhibitor of NFκB; NIK: NFκB inducing kinase; IKK: IκB kinases.

levels of certain other cytokines also are affected by curcumin. Curcumin-pretreated macrophages have a decreased ability to induce IFN-gamma and an increased ability to induce IL-4 in Ag-primed CD4+ T cells (Kang et al., 1999). This observation suggests that curcumin may inhibit the proinflammatory Th1 cytokine profile and therefore, may, be beneficial in the control of Th-1-mediated immune diseases (Kang et al., 1999).

Many genes that are implicated in the initiation of immune/inflammatory responses are regulated at the level of transcription by the transcription factor NF-κB. Cytoplasmic NF-κB is complexed with its inhibitor IκB and therefore, is, inactive. The cytokine mediated activation of NF-κB requires activation of various kinases, which ultimately lead to the phosphorylation and degradation of IκB (Figure 2). Several of the beneficial effects of curcumin are consistent with its ability to inhibit the activity of NF-κB (Bierhaus et al., 1997; Kuner et al., 1998; Pendurthi et al., 1997). Singh and Aggarwal (1995) observed that curcumin inhibits NF-κB activation pathway after the convergence of various stimuli mediated by protein tyrosine kinase, protein kinase, and ubiquitin conjugation enzymes, but before the phosphorylation and subsequent release of IκB complexed to NF-κB (Figure 2). Plummer et al. examined the modulatory potential of curcumin on NF-κB signalling pathways and observed that curcumin prevents phosphorylation of IκB by inhibiting the activity of IκB-kinases (IKKs) (Jobin et al., 1999; Plummer et al., 1999). Jobin et al. (1999) observed that curcumin inhibits IL-1β-induced serine 32 phosphorylation of IκB by interfering with IKK activation (Jobin et al., 1999). Brennan et al. (1998) found that curcumin inhibits NF-κB by interfering with IκBα degradation and reacts with p50 in the NF-κB complex (Brennan and O'Neill, 1998). Furthermore, it is reported that curcumin blocks gene expression in intestinal epithelial cells by inhibiting the signal leading to IKK activation without directly interfering with NF-κB inducing kinase (NIK) or IKK (Jobin et al., 1999). This inhibition of the yet unidentified activation signal going to the IKK complex by a signalling system upstream from NIK is in contrast with the recent description of the blockade of IKKβ activity by aspirin, the widely used anti-inflammatory compound (Yin et al., 1998). However, curcumin is not a specific inhibitor of the signalling kinases in the NF-κB pathway, since it also inhibits the c-Jun N-terminal kinase (JNK) signalling pathway (Chen and Tan, 1998) and is now routinely used as a standard inhibitor in some studies involving JNKs (Du et al., 2000; Henke et al., 1999).

B. Effect on Lipid Mediators and Eicosanoids

Eicosanoids play an important role in inflammation. Arachidonic acid is an important substrate for pro-inflammatory eicosanoids. The influence of curcumin on the formation and utilization of cellular arachidonic acid for the generation and release of pro-inflammatory eicosanoids, such as prostaglandins and leukotrienes, have been investigated (Joe and Lokesh, 1997a). Curcumin inhibits the cellular uptake of arachidonic acid, but not the release of arachidonic acid in response to phorbol ester treatment of rat peritoneal macrophage membranes (Joe and Lokesh, 1997a). Phospholipases are involved in the release of arachidonic acid from membranes. Curcumin inhibits several types of mammalian phospholipases, including phospholipases A2, C, and D (Yamamoto et al., 1997).

The noncompetitive inhibition of Δ^5 and Δ^6 desaturases by curcumin is observed in rat liver microsomes (Kawashima et al., 1996). The structural features of curcumin that are necessary for the inhibition of desaturases include the following: 1) the aromatic ring conjugated with the double bond between the 1 and 2 (or 6 and 7) positions; (2) both 4-hydroxy and 3-methoxy groups (for both desaturase inhibitions); (3) only a 4-hydroxy group (for delta 6 desaturase inhibition) (Kawashima et al., 1996).

Curcumin is an inhibitor of cyclo-oxygenases and lipoxygenases and inhibits the production of prostaglandin E2 and leukotrienes, B4 and C4 (Huang et al., 1997; Joe and Lokesh, 1997a; Rao et al., 1995a, 1995b). Molecular mechanisms for the inhibition of lipoxygenases are beginning to be understood. Two independent studies suggest that curcumin, or a degradation product of curcumin, may bind to the central cavity of the active site of lipoxygenases (Began et al., 1998; Skrzypczak-Jankun et al., 2000). Based on spectroscopic measurements, Began et al. concluded that the curcumin, after binding to phosphatidyl choline micelles, binds to iron, which is present in the active center of LOX1 and acts as a competitive inhibitor of lipoxygenase 1 (LOX1) (1998). On the other hand, using X-ray diffraction and mass spectrometry, Skrzypczak-Jankun et al. suggest that curcumin is a substrate for LOX1 (2000). They demonstrated that 4-hydroxyperoxy-2-methoxyphenol, a degradation product of curcumin, inhibits lipoxygenase by binding to the central cavity of its active site.

C. Effects on Proteolytic Enzymes

Curcumin lowers the release of proteolytic enzymes, such as collagenase, elastase, and hyaluronidase from activated

macrophages (Joe and Lokesh, 1997b, 2000). Several matrix metalloproteinases are also inhibited by curcumin (Onodera et al., 2000; Thaloor et al., 1998). The macrophage migration inhibitory factor (MIF) plays an important role in the tissue destruction of rheumatoid joints via induction of the proteinases, MIF up-regulates matrix metalloproteinases -1(MMP-1; interstitial collagenase) and MMP-3 (stromelysin), via tyrosine kinase-, protein kinase C-, and AP-1- dependent pathways, bypassing IL-1β signal transduction. Curcumin inhibits the upregulation of MMPs, probably because of its inhibitory potential on protein kinase C (PKC) (Onodera et al., 2000).

ANTI-OXIDANT PROPERTIES

The discovery of the antioxidant properties of curcumin explains many of its wide ranging pharmacological activities. Curcumin is an effective antioxidant and scavenges superoxide radicals, hydrogen peroxide, and nitric oxide from activated macrophages (Joe and Lokesh, 1994). It inhibits the inducible nitric oxide synthase activity in macrophages (Brouet and Ohshima, 1995). Human keratinocytes are protected from Xanthinexanthine oxidase injury by virtue of the antioxidant property of curcumin (Bonte et al., 1997). Oral administration of 30mg/kg body weight of curcumin in rats for 10 days reduces the iron-induced hepatic damage by lowering lipid peroxidation (Reddy and Lokesh, 1996). Protection from radiation by dietary curcumin administered to mice is also attributed to the antioxidant property of curcumin. Curcumin protects renal cells and neural glial cells from oxidative stress (Cohly et al., 1998). Interestingly, curcumin not only exhibits antioxidative and free radical scavenging properties, but also enhances the activities of other antioxidants, such as superoxide dismutase, catalase, and glutathione peroxidase (Reddy and Lokesh, 1994). Lipid peroxidation is lower in liver, kidney, spleen, and brain microsomes from retinol deficient rats that are fed with 0.1% dietary curcumin for three weeks (Kaul and Krishnakantha, 1997). Another mechanism by which curcumin protects against oxidative stress in endothelial cells is by the induction of heme oxygenase-1 (Motterlini et al., 2000).

The phenolic and the methoxy groups on the benzene rings and the 1,3-diketone system are the two important structural features that contribute to its antioxidant properties (Sreejayan and Rao, 1996, 1997). The inhibitory action of 5′-n-alkylated curcumins on lipid peroxidation increases, as the length of hydrocarbon chains of 5′-n-alkylated curcumins is increased (Oyama et al., 1998). However, the most potent protective action was observed with 5′-n-C3H7-curcumin, because of its relatively higher permeability into cells (Oyama et al., 1998). Masuda et al. studied the oxidative coupling products of curcumin with a polyunsaturated fatty acid, linoleate, and concluded that the antioxidant property of curcumin is exhibited by the chain-breaking reaction at the 3′-position of the curcumin with the lipid, followed by a subsequent intramolecular Diels-Alder reaction (Masuda et al., 2001). In the presence of Cu(II) or chromium, however, curcumin turns into a pro-oxidant and damages DNA (Ahsan and Hadi, 1998; Ahsan et al., 1999). Curcumin also enhances chromosomal damage induced in Chinese hamster ovary cells (Antunes et al., 1999; Araujo et al., 1999). However, the relevance of the pro-oxidant nature of curcumin in an *in vivo* cellular scenario is not clearly determined. Notably, ascorbic acid similarly exhibits pro-as well as antioxidant properties, depending on its concentration and the presence of metal ions (Lee et al., 2001).

CURCUMIN AND MIGRATION OF CELLS

There is considerable evidence suggesting that curcumin interferes with the migration of cells. Curcumin inhibits leukocyte recruitment to sites of inflammation (Kumar et al., 1998). Cellular migration and invasion of SK-Hep-1, a highly invasive cell line from human hepatocellular carcinoma, is also inhibited by curcumin (Lin et al., 1998). Additionally, curcumin is observed to block transforming growth factor-beta 1 (TGF-beta 1) stimulated migration/invasion of mouse transformed keratinocytes (Santibanez et al., 2000). Intraperitoneal administration of 5 doses of curcumin encapsulated in liposomes increased total WBC counts and bone marrow cell numbers in Balb/c mice and increased the proliferation of haemopoietic stem cells (Antony et al., 1999). Heng et al. noted that curcumin is a specific inhibitor of Phosphorylase kinase (PhK), also known as adenosine triphosphate (ATP)-phosphorylase b phosphotransferase, which integrates multiple calcium/calmodulin-dependent signalling pathways, including those involved in cell migration and cell proliferation (Heng et al., 2000). Therefore, this may provide a biochemical basis for the involvement of curcumin in cell migration.

EFFECT OF CURCUMIN ON LYMPHOCYTES

Mucosal CD4 (+) T cells and B cells increase in animals treated with curcumin, suggesting that it modulates lymphocyte-mediated immune functions (Churchill et al., 2000). Dietary curcumin increases antibody response in rats *in vivo* (South et al., 1997). *In vitro*, curcumin enhances IgM production in rat spleen lymphocytes (Kuramoto et al., 1996). Han et al. studied the ability of curcumin to modulate proliferative responses of normal splenic and transformed B-lymphocytes (Han et al., 1999). These observations indicate that curcumin arrests growth and induced apoptosis of B cell lymphomas more effectively than normal B lymphocytes. In BKS-2 B lymphoma cells, the inhibitory effects of curcumin appear to be mediated by the down-regulation of survival genes (egr-1, c-myc, bcl-X_L and NF-κB), as well as the tumor suppressor gene p53. On the other hand, curcumin may be an effective adjunct in the prevention of post-transplant lymphoproliferative disorder in patients undergoing therapy with cyclosporine. A, because curcumin blocks the B-cell immortalization by EBV, which is promoted by oxidative stress induced by cyclosporin A (Ranjan et al., 1998).

EFFECT OF CURCUMIN ON PLATELET AGGREGATION

Curcumin inhibits platelet-activating factor (PAF), ADP, arachidonic acid (AA), epinephrine, and collagen mediated platelet aggregation (Shah et al., 1999; Srivastava et al., 1986, 1995). However, at lower doses (20–25μM), curcumin inhibits only PAF and AA mediated platelet aggregation and not those mediated by other agonists. Pretreatment of platelets with curcumin resulted in the inhibition of platelet aggregation induced by calcium ionophore A23187, but not by the PKC activator, PMA (Shah et al., 1999). Curcumin also inhibited thromboxane A2 (TXA2) formation by platelets. These observations suggest that curcumin-mediated preferential inhibition of PAF- and AA-induced platelet aggregation involves inhibitory effects on TXA2 synthesis and Ca^{2+} signaling.

EFFECTS OF CURCUMIN ON DETOXIFICATION MECHANISMS

Curcumin, in a dose-dependent manner, inhibits the covalent adduct formation between aflatoxin B1 and DNA, as catalyzed by microsomes or reconstituted microsomal monooxygenase system (Firozi et al., 1996). The inhibition of aflatoxin B1-DNA adduct formation by curcumin in the reconstituted monooxygenase system could be reversed by increasing the amount of cytochrome P450, but not by that of NADPH-cytochrome P450 reductase (Firozi et al., 1996). Ciolino et al. (1998) examined the interaction of curcumin with the carcinogen activation pathway mediated by the aryl hydrocarbon receptor (AhR) in MCF-7 mammary epithelial carcinoma cells. Curcumin caused a rapid accumulation of cytochrome P450 1A1 (Cyp1a1) mRNA in a time- and concentration-dependent manner, and Cyp1a1 monooxygenase activity increased as measured by ethoxyresorufin-o-deethylation. Curcumin activated the DNA-binding capacity of the AhR for the xenobiotic responsive element of Cyp1a1. It was able to compete with the prototypical AhR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin for binding to the AhR in isolated MCF-7 cytosol, indicating that it interacts directly with the receptor (Ciolino et al., 1998). Although curcumin could activate the AhR on its own, it partially inhibited the activation of AhR and partially decreased the accumulation of Cyp1a1 mRNA caused by the mammary carcinogen dimethylbenzanthracene (DMBA) (Ciolino et al., 1998). Curcumin competitively inhibited Cyp1a1 activity in DMBA-treated cells and in microsomes isolated from DMBA-treated cells. Curcumin also inhibited the metabolic activation of DMBA, as measured by the formation of DMBA-DNA adducts, and decreased DMBA-induced cytotoxicity. These results demonstrate the ability of curcumin to compete with aryl hydrocarbons for both the AhR and Cyp1a1. Thus, curcumin may be a natural ligand and substrate of the AhR pathway (Ciolino et al., 1998). However, in another study, curcumin elevated the specific activity of quinone reductase in wild type, as well as in mutant cells defective in either the aryl hydrocarbon (Ah) receptor or cytochrome P4501a1 activity. This indicates that neither binding to this receptor, nor metabolic activation by P4501a1 is required for the signaling process, ultimately resulting in Phase 2-detoxification enzyme induction (Dinkova-Kostova and Talalay, 1999). Dinkova-Kostova and Talalay (1999), also used a series of compounds structurally related to curcumin and found that the presence of two structural elements are required for high inducer potency of phase 2 detoxifying enzymes: (1) hydroxyl groups at ortho-position on the aromatic rings and (2) the beta-diketone functionality.

Curcumin is an inhibitor of P-form phenolsulfotransferase (Eaton et al., 1996). Curcumin also modulates glutathione (GSH)-linked detoxification mechanisms *in vitro* in human leukemia cell (K562 cells), as well as *in vivo* in rats (Piper et al., 1998). When rats were fed curcumin at doses from 1 to 500 mg/kg body weight daily for 14 days, the induction of hepatic GST activity against a highly toxic product of lipid peroxidation, 4-hydroxynonenal (4-HNE), increased in a saturable dose dependent manner (Piper et al., 1998). Curcumin caused a dose dependent induction of rGST 8-8, an isozyme that is known to display the highest activity towards 4-HNE (Piper et al., 1998). Further, curcumin treatment caused a significant induction of the glutathione S-transferase (GST) isozyme rGST8-8 in rat lens epithelium, a property that could be useful for the management of cataractogenesis induced by lipid peroxidation (Awasthi et al., 1996). Because rGST8-8 utilizes 4-HNE as a preferred substrate, Awasthi et al. (1996) suggest that the protective effect of curcumin may be mediated through the induction of this GST isozyme. The induction of enzymes involved in the detoxification of the products of lipid peroxidation may also contribute to the anti-inflammatory and anti-cancer activities of curcumin.

CURCUMIN, CELL CYCLE, AND APOPTOSIS

Curcumin is an apoptotic agent (Kuo et al., 1996). While a low concentration of curcumin is known to arrest cell proliferation in the G0-G1/G2/S phase, a high concentration of curcumin induces apoptosis in rat A7r5 cells (Chen et al., 1999; Chen and Huang, 1998; Hanif et al., 1997). Several hallmarks of apoptosis, including DNA laddering, chromatin condensation and fragmentation, and an apoptosis specific cleavage of 28S and 18S ribosomal RNA were observed after treatment of immortalized mouse embryo fibroblast NIH 3T3, erb B2 oncogene-transformed NIH 3T3, mouse sarcoma S180, human colon cancer cell HT-29, human kidney cancer cell 293, and human hepatocellular carcinoma Hep G2 cells with curcumin (Jiang et al., 1996b). Curcumin-induced apoptosis in human basal cells was shown to be dependent on a p53-signaling pathway (Jee et al., 1998). Curcumin was shown to accumulate in plasma membrane, endoplasmic reticulum, and nuclear envelope and to produce apoptosis-like changes in plasma membranes in rat thymocytes (Jaruga et al., 1998a). Ramachandran and You (1999) demonstrated that apoptosis is involved in the differential curcumin-induced inhibition of mammary epithelial

and breast carcimona cell growth and suggested that genes associated with cell proliferation and apoptosis may be playing a role in the chemopreventive action of curcumin. The sequence and extent of primary events during apoptosis induced by curcumin have been compared with those occurring during dexamethasone-induced apoptosis in rat thymocytes (Jaruga et al., 1998a). Curcumin-treated cells exhibit typical features of apoptotic cell death, including shrinkage, transient phosphatidylserine exposure, increased membrane permeability, and decrease in mitochondrial membrane potential. The level of anti-apoptotic protein Bcl-2 was decreased in the presence of curcumin (Kuo et al., 1996).

Curcumin induces apoptosis of several, but not all, cancer cells. When COLO205 colorectal carcinoma cells were treated with curcumin (60 μM), the appearance of apoptotic DNA ladders was delayed, however, cell cycle arrest at G1 phase was detected (Chen et al., 1996). Further analysis of the endonuclease activities in these cells revealed that the activity of calcium dependent endonuclease in COLO205 cells was profoundly inhibited and that the extent of inhibition was dependent on the degree of calcium depletion (Chen et al., 1996). The reduction of p53 gene expression was accompanied by the induction of the heat shock protein, Hsp70, gene expression in the curcumin-treated cells. These findings suggest that curcumin may induce the expression of Hsp70 gene through the initial depletion of intracellular Ca^{2+}, followed by the suppression of p53 gene function in the target cells (Chen et al., 1996).

Many cancer cells protect themselves against apoptosis by activating NFκB/Rel, a transcription factor that helps in cell survival. Signal-induced activation of NFκB is inhibited by curcumin. The relA gene encodes the p65/RelA subunit of NF-κB (Anto et al., 2000). RelA-transfected cells were resistant to varying doses of curcumin, whereas the parental cells underwent apoptosis in a time and dose dependent manner. The relA-transfected cells showed constitutive NF-κB DNA binding activity that could not be inhibited by curcumin and did not show nuclear condensation and DNA fragmentation upon treatment with curcumin. When a super-repressor form of IκB-α was transfected transiently into relA-transfected cells, the cells were no longer resistant to curcumin, suggesting a critical anti-apoptotic role for NF-κB in curcumin-induced apoptosis (Anto et al., 2000).

Contrastingly, Sikora et al. (1997) observed that curcumin prevents apoptosis of dexamethasone-treated rat thymocytes and UV-irradiated Jurkat cells, as judged by DNA ladder formation, cellular morphological changes, and flow cytometry analysis. The inhibition of apoptosis by curcumin in rat thymocytes was accompanied by partial suppression of AP-1 activity (Sikora et al., 1997). Because cellular thiols seem to play a role in redox regulation of apoptosis, the mechanism of the anti-apoptotic effect of curcumin was studied by examining the levels of glutathione and acid-soluble sulfhydryl groups (Jaruga et al., 1998a). Curcumin was shown to prevent the glutathione loss occurring in dexamethasone-treated thymocytes, enhancing intracellular glutathione content at 8 hr to 192% and acid-soluble sulfhydryl groups to 60% to that of untreated cells. Redox signalling and caspase activation are also mechanisms responsible for the induction of curcumin mediated apoptosis in AK-5 tumor (rat histiocytoma) cells (Bhaumik et al., 1999). In fact, curcumin was used as an inhibitor of JNK activity, where it remarkably reduced methyl glyoxal-induced caspase-3 activation, poly (ADP-ribose) polymerase (PARP) cleavage, and apoptosis in mouse cells (Du et al., 2000).

ANTI-CARCINOGENIC EFFECTS OF CURCUMIN

Anticarcinogenic effects of curcumin in animals, as indicated by its ability to inhibit both tumor initiation induced by benzo (a)pyrene and 7,12-dimethylbenz(a)anthracene and tumor promotion induced by phorbol esters (Deshpande and Maru, 1995; Huang et al., 1995), is possibly due to suppression of PKC activity and nuclear oncogene expression (Lin et al., 1997). Daily oral administration of curcumin (60, 120, and 240 mg/kg) for a week reduced the micronuclei formation induced by cyclophosphamide in mice (Li et al., 1998). Investigations on the inhibitory effect of curcumin on the formation of (3H)benzo(a)pyrene ({3H}B{a}P)-derived DNA adducts showed a dose-dependent decrease in cytochrome P450 and aryl hydrocarbon hydroxylase activity, resulting in relatively larger amounts of unmetabolized B(a)P in the presence of curcumin (Deshpande and Maru, 1995). Mutagenesis induced by UV irradiation is suppressed by the presence of curcumin (Oda, 1995). Comparison of structures of curcumins with their activity profiles suggested the importance of both parahydroxy (p-OH) and methoxy groups (-OCH3) for its biological activity (Deshpande and Maru, 1995). Studies also indicated that the presence of intact curcumin was essential for the inhibitory effect, as removal of curcumin resulted in restoration of cytochrome P450 activity and the levels of (3H)-B (a)P-DNA adducts to control values (Deshpande and Maru, 1995). Curcumin also has anti-tyrosine kinase activity and inhibits ligand-induced activation of the epidermal growth factor receptor tyrosine phosphorylation (Korutla et al., 1995). The erbB2/neu gene-coded $p185^{neu}$ tyrosine kinase is a potent oncoprotein, overexpressed in 30% of breast cancers. Hong et al. (1999) investigated the effect of curcumin on $p185^{neu}$ tyrosine kinase and on the growth of breast cancer cell lines. Curcumin dose-dependently inhibited $p185^{neu}$ tyrosine kinase phosphorylation and transphosphorylation *in vitro* and depleted $p185^{neu}$ protein *in vivo* by disrupting its binding with a molecular chaperone GRP94 (glucose regulated protein) (Hong et al., 1999). They have also demonstrated the ability of curcumin to inhibit the growth and colony formation of several breast cancer cell lines (Hong et al., 1999). Interestingly, the IC_{50} of curcumin on several breast cancer cell lines is close to that of chemotherapeutic agents, such as 5-flurouracil (Hong et al., 1999). Curcumin has a potent preventive activity during the diethylstilbestrol-dependent promotion stage of radiation-induced mammary tumorigenesis in pregnant rats (Inano et al., 1999). Contrastingly, female sencar mice fed with 7,12-dimethylbenz (a) anthracene

developed mammary tumors and lymphomas/leukemias and feeding 2% curcumin for 20 weeks had little or no effect on the incidence of mammary tumors. However, the incidence of lymphomas/leukemias was reduced by 53% (Huang et al., 1998). A therapeutic role of curcumin for mammary tumors and cancers could, therefore, depend on the inducing agent and warrants further study.

Ultraviolet A irradiation significantly enhances ornithine decarboxylase induction at an early stage (4–6 hr) and aggravates the dermatitis elicited by TPA (Ishizaki et al., 1996). Curcumin significantly inhibits these damaging effects in mouse skin and epidermal cell lines, which are essential for cellular proliferation (Lee and Pezzuto, 1999). The prognosis of cancer is mainly determined by the invasiveness of the tumor and its ability to metastasize. Proteolytic degradation of the basement membrane is a major step in the metastasis leading to invasion. Menon et al. have demonstrated that curcumin inhibits the invasion of B16F-10 melanoma cells that cause lung metastasis in mice by inhibition of metalloproteinases, such as collagenase (Menon et al., 1995; Menon et al., 1999).

An issue of concern stems from observations that curcumin inhibited the cellular growth of both transformed and nontransformed cells in clonogenic assays (Gautam et al., 1998). Without discriminating between transformed and nontransformed cells, the inhibition of cell proliferation by curcumin was not always associated with programmed cell death (Gautam et al., 1998). However, this observation remains to be confirmed and may have implications on the development of curcumin as an anti-cancer agent.

CLINICAL EVALUATION OF CURCUMIN AS AN ANTI-CANCER AGENT IN HUMANS

Because of their safety and the fact that they are not perceived as 'medicine,' food-derived products are of great interest in the development of chemopreventive agents, which may have a widespread long-term use in populations at normal risk. Curcumin is one such diet-derived agent that is being clinically evaluated as a chemopreventive agent for major cancer targets, including the breast, prostate, colon, and lung (Boone and Kelloff, 1997; Kelloff et al., 2000). For developing such agents, the National Cancer Institute (NCI) has advocated co-development of a single or a few putative active compounds (including curcumin) that are contained in the food-derived agent. The active compounds provide mechanistic and pharmacologic data that may be used to characterize the chemopreventive potential of the extract, and these compounds may be useful as chemopreventives in higher risk subjects (patients with precancers or previous cancers). Other critical aspects for developing the food-derived products are careful analysis and definition of the extract to ensure reproducibility (e.g., growth conditions, chromatographic characteristics, or composition) and basic science studies to confirm epidemiologic findings associating the food product with cancer prevention (Kelloff et al., 2000).

WOUND-HEALING PROPERTIES OF CURCUMIN

Tissue repair and wound healing are complex processes that involve inflammation, granulation, and tissue remodeling. Interactions of different cells, extracellular matrix proteins, and their receptors are involved in wound healing and are mediated by cytokines and growth factors. Curcumin enhances cutaneous wound healing in rats and guinea pigs by increasing the formation of granulation tissue, biosynthesis of extracellular matrix proteins, and TGF-β1 in wounds (Sidhu et al., 1998). Curcumin also accelerated wound healing in streptozotocin-induced diabetic swiss albino rats and genetically diabetic (C57/KsJ-db+/db+) mice by increasing the formation of granulation tissue, faster re-epitheliatization, and increased collagenization (Sidhu et al., 1999). Systemic treatment with curcumin after local muscle injury leads to faster restoration of normal tissue architecture, as well as an increased expression of biochemical markers associated with muscle regeneration (Thaloor et al., 1999).

In vitro studies indicate that curcumin can act directly on myoblasts to increase cell proliferation by inhibiting NF-κB (Thaloor et al., 1999). Therefore, the ability of curcumin to increase the rate and extent of muscle regeneration indicates that it may be administered systemically for treating muscle injuries. Nirmala et al. observed that curcumin decreased the degree of degradation of the existing collagen matrix and collagen synthesis in rat myocardial necrosis induced by isoproterenol. HCl (Nirmala et al., 1999). Curcumin prevented ischaemia-induced changes in the cat heart (Dikshit et al., 1995). These observed effects may be due to free radical scavenging activity and inhibition of lysosomal enzyme release by curcumin (Nirmala and Puvanakrishnan, 1996). Mechanical induction of epithelial cell mitogen heparin-binding epidermal growth factor-like growth factor (HB-EGF) by activator protein-1 (AP-1) in bladder smooth muscle cells may mediate adaptive responses of smooth muscle cells to increases in physical load (Park et al., 1999). Curcumin, by inhibiting AP-1 activation, not only suppressed the HB-EGF mRNA induction, but also the induction of matrix metalloproteinase-1 induction after mechanical stretch (Park et al., 1999), suggesting that curcumin could be beneficial in controlling compensatory bladder hypertrophy. Bladder hypertrophy arises in adult men, primarily from age-related growth of the prostate gland, and in children in association with several congenital uropathic syndromes.

CURCUMIN AND DIABETES

Feeding diabetic rats curcumin improved their metabolic status (Babu and Srinivasan, 1995, 1997). Diabetic rats maintained on a 0.5% curcumin diet for 8 weeks excreted comparatively lower amounts of albumin, urea, creatinine, inorganic phosphorus, sodium, and potassium. On the other hand, glucose excretion or the fasting sugar level was unaffected by dietary curcumin and also the body weights were not improved to any significant

extent. Diabetic rats fed a curcumin diet had a lower relative liver weight at the end of the study, compared to other diabetic groups. Diabetic rats fed a curcumin diet also showed lowered lipid peroxidation in plasma and urine. The extent of lipid peroxidation, however, was still higher in cholesterol fed diabetic groups, compared to diabetic rats fed with control diet. The mechanism by which curcumin improves this situation is probably by virtue of its hypocholesterolemic influence (Babu and Srinivasan, 1997), antioxidant nature, and free radical scavenging property (Babu and Srinivasan, 1995).

CURCUMIN AND STRESS RESPONSES

Curcumin is a potent stimulator of the stress-induced expression of Hsp27, αB crystallin, and Hsp70. When C6 rat glioma cells were exposed to arsenite (100 μM for 1 h), CdCl2 (100 μM for 1 h), or heat (42°C for 30 min) in the presence of 3–10 μM curcumin, induction of the synthesis of all three proteins was markedly stimulated (Kato et al., 1998). Curcumin prolonged the stress-induced activation of the heat shock element-binding (HSE-binding) activity of heat shock transcription factor (Hsf) in the cultured cells. The stimulatory effect of curcumin on the responses to stress was also observed in BRL-3A rat liver cells and Swiss 3T3-mouse fibroblasts (Kato et al., 1998). The induction of Hsp27, αB crystallin, and Hsp70 in the liver and adrenal glands of heat-stressed (42°C for 20 min) rats was also enhanced by prior injection of curcumin (20 mg/kg body weight). As curcumin is a potent inhibitor of arachidonic acid metabolism, it is suggested that the mechanism for the stimulation of stress responses by curcumin might be similar to that of salicylate, indomethacin, and nordihydroguaiaretic acid (Kato et al., 1998). In adjuvant induced arthritic rats, dietary curcumin decreases the levels of a number of serum proteins, including a 70kD acidic glycoprotein, which could be part of the biology of stress responses (Joe et al., 1997).

ANTIVIRAL PROPERTIES OF CURCUMIN

In vitro, curcumin (0.32 mg/ml) moderately inhibited the activity of human simplex virus-2 (Bourne et al., 1999). Curcumin provided significant protection in a mouse model of intravaginal human simplex virus-2 challenge (Bourne et al., 1999). Curcumin is also highly effective in inhibiting Type I Human Immunodeficiency Virus, (HIV) long terminal repeat directed gene expression, and viral replication (Jiang et al., 1996a; Li et al., 1993). Curcumin inhibited p24 antigen production in cells either acutely or chronically infected with HIV-1(Li et al., 1993). However, curcumin failed to inhibit the HIV-1 multiplication in acutely infected MT-4 cells (Artico et al., 1998). Nevertheless, curcumin specifically inhibited the enzymatic reactions associated with HIV-1 integrase but not other viral (HIV-1 reverse transcriptase) and cellular (RNA polymerase II) nucleic acid-processing enzymes (Artico et al., 1998; Burke et al., 1995). Mazumder et al. (1997) have synthesized and tested analogs of curcumin to explore the structure-activity relationships and mechanism of action of this family of compounds in more detail. Two curcumin analogs, dicaffeoylmethane and rosmarinic acid, inhibited integrase activity with IC50 values below 10 μM. The two curcumin analogs demonstrated equivalent potencies against integrase mutant at lysine 136 (which is required for viral DNA binding) and wild-type integrase, suggesting that the curcumin-binding site and the substrate-binding site may not overlap (Mazumder et al., 1997). Combining one curcumin analog with the recently described integrase inhibitor, NSC 158393, resulted in integrase inhibition that was synergistic or reflective of drug-binding sites that may not overlap. They have also determined that these analogs can inhibit binding of the enzyme to the viral DNA, but that this inhibition is independent of divalent metal ion. Furthermore, kinetic studies of these analogs suggest that they bind to the enzyme at a slow rate (Mazumder et al., 1997).

OTHER BIOLOGICAL EFFECTS OF CURCUMIN

Rats maintained on diets containing 0.5% curcumin had enhanced pancreatic lipase, pancreatic amylase, trypsin, and chymotrypsin activities (Platel and Srinivasan, 2000). Curcumin is also a stimulator of bile flow. Curcumin decreases cyclosporin-induced cholestasis by enhancement of bile acid independent bile flow (Deters et al., 2000). Curcumin is traditionally believed to have a positive contraction effect on the human gall bladder. Rasyid and Lelo (1999) studied the effect of 20 mg curcumin on the gall-bladder volume of healthy volunteers using ultrasonograpy and concluded that curcumin induces contraction of the human gall bladder. This may explain the reduced rate of gall stone formation in response to a lithogenic diet observed in mice fed with curcumin (Hussain and Chandrasekhara, 1992). Curcumin protected against ADR-induced renal injury by suppressing oxidative stress and increasing kidney glutathione content and glutathione peroxidase activity. In the same manner, curcumin abolished adriamycin-stimulated kidney microsomal and mitochondrial lipid peroxidation and nephrotoxicity (Venkatesan et al., 2000). The combination of mycophenolic acid with curcumin and quercetin reduced renal injury in rats (Jones and Shoskes, 2000). These data suggest that administration of curcumin is a promising approach in the treatment of renal disorders.

METABOLISM OF CURCUMIN

The studies reviewed provide strong evidence for curcumin to be a food additive with a variety of functional properties in biological systems. These numerous biological effects demonstrated by curcumin indicate that turmeric in the diet can be

considered as a nutraceutical or a functional food ingredient (Kottke, 1998). The development of new drugs requires pharmacokinetic and toxicity studies in conjuction with clinical verification of *in vivo* activity. The food additive, curcumin, has the advantage of being a non-toxic natural product (Commandeur and Vermeulen, 1996). The pharmacological safety of curcumin is shown by the non-toxic consumption of up to 100 mg/day in humans and up to 5 g/day in rats (Commandeur and Vermeulen, 1996). Pan et al. (1999) investigated the pharmacokinetic properties of curcumin in mice. After intraperitoneal administration of curcumin (0.1 g/kg) in mice, approximately 2.25 μg/ml of curcumin appeared in the plasma within the first 15 min. One hour after administration, the levels of curcumin in the intestines, spleen, liver, and kidneys were 177.04, 26.06, 26.90, and 7.51 μg/g, respectively. Only traces (0.41 μg/g) were observed in the brain at 1 hr. To clarify the nature of the metabolites of curcumin, the plasma was analyzed by reversed-phase HPLC, and two putative conjugates of curcumin were observed. Treatment of the plasma with beta-glucuronidase resulted in a decrease in the concentrations of these two putative conjugates and the concomitant appearance of tetrahydrocurcumin (THC) and curcumin, respectively. To investigate the nature of these glucuronide conjugates *in vivo*, the plasma was analyzed by electrospray. The chemical structures of these metabolites, determined by mass spectrometry/mass spectrometry analysis, suggested that curcumin was first biotransformed to dihydrocurcumin and THC, and that these compounds subsequently were converted to monoglucuronide conjugates. Because THC is one of the major metabolites of curcumin, its stability at different pH values was studied. THC was very stable in 0.1 M phosphate buffers of various pH values. Moreover, THC was more stable than curcumin in 0.1 M phosphate buffer, pH 7.2 (37°C). These results suggest that curcumin-glucuronoside, dihydrocurcumin-glucuronoside, THC-glucuronoside, and THC are major metabolites of curcumin *in vivo* (Figure 3) (Pan et al., 1999). Ireson et al. studied the biotransformation of curcumin by human and rat hepatocytes and identified hexahydrocurcumin and hexahydrocurcuminol as the major metabolites of curcumin. The chemical structures of dihyrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol are depicted in Figure 3. Ireson et al. also reported that none of the metabolites of curcumin, including THC, retained the inhibitory potential of curcumin on PGE2 levels (Ireson et al., 2001). Therefore, they suggest that the bioavailability of curcumin, for example, in the colon is greatest. Because the gastrointestinal tract seems to be exposed more prominently to unmetabolized curcumin than any other tissue, their results support the clinical evaluation of curcumin as a colorectal cancer chemopreventive agent.

The degradation kinetics of curcumin under various pH conditions and the stability of curcumin in physiological matrices are reported (Wang et al., 1997). When curcumin was incubated in 0.1 M phosphate buffer and serum-free medium, pH 7.2 at 37°C, approximately 90% decomposed within 30 min. A series of pH conditions ranging from 3 to 10 were tested, and the result showed that decomposition was pH-dependent and occurred faster at neutral-basic conditions. It is more stable in cell culture medium containing 10% fetal calf serum and in human blood; less than 20% of curcumin decomposed within 1 hr, and after incubation for 8 hrs, approximately 50% of curcumin is still intact. Trans-6- (4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexenal was predicted as a major degradation product and, vanillin, ferulic acid, and feruloyl methane were identified as minor degradation products (Wang et al., 1997). Curcumin may associate with serum albumin through hydrophobic interactions (Pulla Reddy et al., 1999) and may, thereby, be transported to appropriate target cells, where it elicits its pharmacological effects. Curcumin readily penetrates into the cytoplasm and is able to accumulate in membranous structures, such as plasma membrane, endoplasmic reticulum, and nuclear envelope (Jaruga et al., 1998a). Rat peritoneal macrophages pre-incubated with 10 μM curcumin for 1 hr resulted in the lowering of the uptake of arachidonic acid and subsequent release of pro-inflammatory mediators (Joe and Lokesh, 1997a).

In red blood cell membranes exposed to curcumin, changes in cell shape were accompanied by transient exposure of phosphatidylserine (Jaruga et al., 1998b). Membrane asymmetry was recovered by the action of aminophospholipid translocase, which remained active in the presence of curcumin. The lipids rearrangement caused changes of membrane fluidity (Jaruga et al., 1998b). Although many hold that curcumin needs to be given at dosages that are unattainable through diet to produce an *in vivo* effect, Chan et al. (1998) were able to observe the potency of curcumin at a nanomole level, which is easily attainable. This efficacy is associated with two modifications in their preparation and feeding regimen: (1) an aqueous solution of curcumin was prepared by initially dissolving the compound in 0.5 N NaOH and then immediately diluting it in PBS; (2) mice were fed curcumin at dusk after fasting (Chan et al., 1998). Therefore, there may be several environmental factors that interact and regulate the efficacy of curcumin.

The average daily intake of curcumin in France is 1 mg/day/kg body weight, and the theoretical maximum daily intake is 4.5 mg/day/kg body weight (Verger et al., 1998). According to Ammon and Wahl (1991), the bioavailability of curcumin *in vivo* is low after oral ingestion. However, it is interesting to note that the bioavailability of curcumin can be dramatically elevated by co-ingestion of piperine (a component of pepper) in both rats and humans (Shoba et al., 1998). Thus, the beneficial health effects of curcumin alone may be further magnified in the context of a mixture of dietary additives that are abundantly consumed as part of Asian diets (Bradlow et al., 1999). Interactions of curcumin with other food additives are being studied (Groten et al., 2000). For example, a synergestic effect on cellular differentiation was observed when curcumin was combined with all-*trans* retinoic acid or 1α, 25-dihydroxyvitamin D3 (Conney et al., 1997), and a chemopreventive synergism between epigallocatechin-3-gallate and curcumin was observed in normal, premalignant, and malignant human oral epithelial cells (Khafif et al., 1998). It is possible that many dietary chemicals in fruits, vegetables, and other edible plants can prevent cancer by synergizing with endogenously

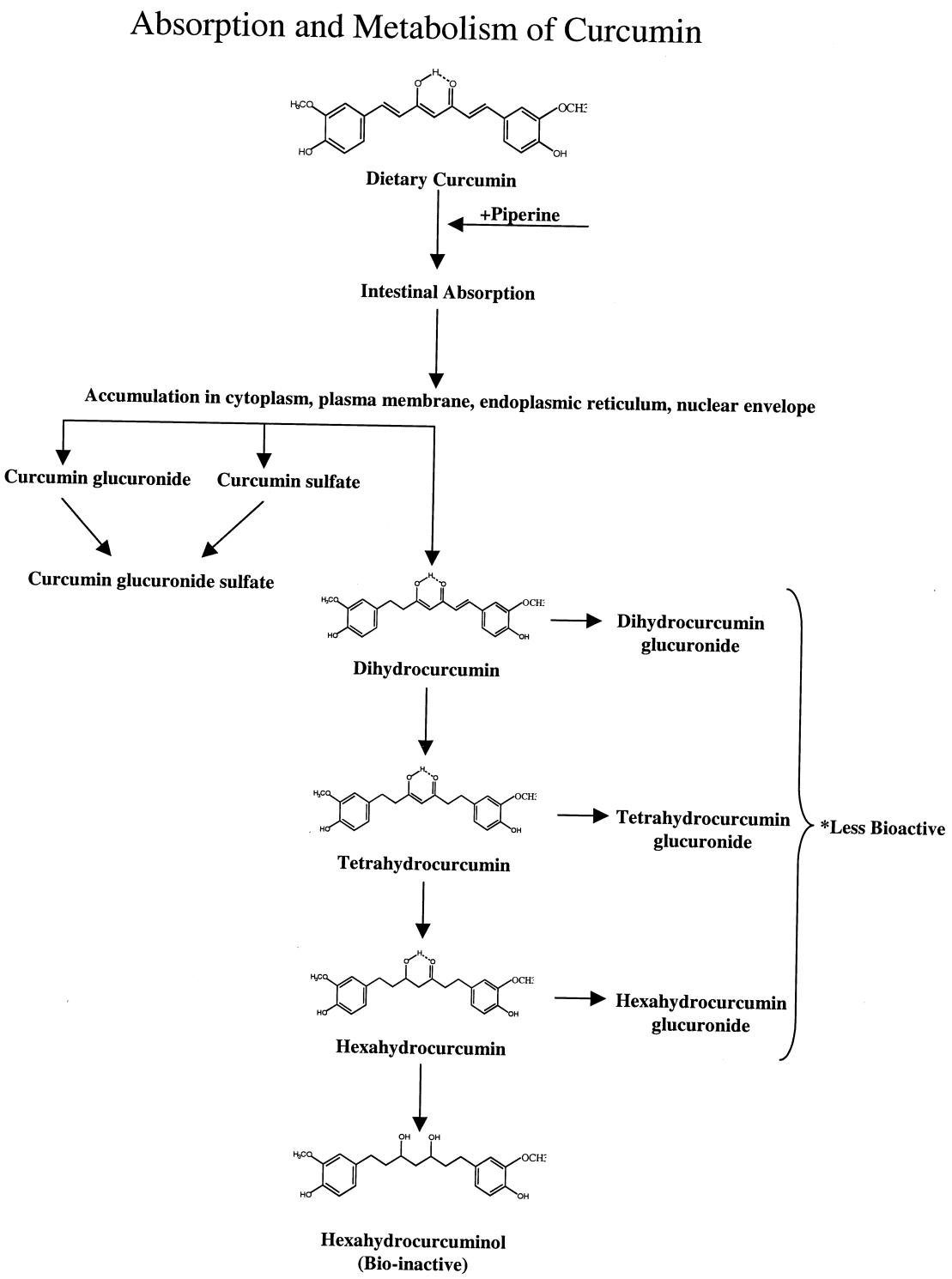

Figure 3 Absorption and metabolism of curcumin. Based on evidence from various isolated studies, the proposed fate of curcumin after oral administration in rodents and humans is depicted. *Less bioactive compared to curcumin in terms of the inhibitory effect on PGE2 formation (Ireson et al., 2001).

produced stimulators of differentiation, such as all-*trans* retinoic acid, 1α, 25-dihydroxyvitamin D3, and butyrate (Liu et al., 1997).

Combinatorial studies of curcumin with drugs also reveal synergistic actions. For example, curcumin enhances the antitumour effect of the widely used anticancer drug, cisplatin, when used in combination against fibrosarcoma (Navis et al., 1999). Therefore, efficacy and the synergistic effects of curcumin in combination with other dietary constituents warrants further study to exploit its full potential.

Table 1 Biological actions of curcumin

Protective biological effect observed	Cells/tissues/biological processes affected	Mediators	Mechanism(s)	Gene(s) identified to be influenced
Anti-inflammatory	Cells of the immune system	↓ TNFα, ↓ IL-1, ↓ IL-12, ↓ IFN-γ, ↓ ICAM-1, ↓ VCAM-1, ↓ E-Selectin	↓ Activation of IκB kinases, ↓ Dissociation of IκB complexed to NF-κB	↓ NF-κB expression
Anti-inflammatory	Cells of the immune system, endothelial cells	↓ TXA_2, ↓ PGE_2, ↓ LTB_4, ↓ LTC_4 ↓ Availability of precursor–arachidonic acid	↓ COX-2 ↓ LOX ↓ Phospholipases, ↓ Δ^5, Δ^6 desaturase	?
Anti-inflammatory	Cells of the immune system	↓ Degradation of Collagen ↓ Elastin ↓ Hyaluronic acid	↓ Collagenase ↓ Elastase ↓ Hyaluronidase ↓ Matrix metalloproteinase ↓ Macrophage migration inhibitory factor	↓ Protein kinase C
Antioxidant	Most eukaryotic tissues, Lipid peroxidation	↓ Superoxide anions ↓ Hydrogen peroxide ↓ Nitric oxide ↓ Oxidative stress	↑ SOD ↑ Catalase ↑ GSH Peroxidase ↓ Nitric oxide synthase ↑ Heme oxygenase-1	?
Immuno-stimulatory; Antithrombotic	Blood cells	?	↑ WBC count ↓ Platelet aggregation ↓ Platelet activating factor ↓ TXA_2	?
Anti-carcinogenic	Hepatic, renal cells	↓ Metabolic activation ↑ Detoxification	↓ Cytochrome P 450, ↓ Aryl hydrocarbon hydroxylase, Competes for AhR and CYP1A1 ↓ Phenolsulfotransferase ↑ GSH-S-transferase	?
Apoptotic agent Antimitotic agent	Cancer cells	↓ Cell proliferation	↑ DNA laddering ↑ Cleavage of 28S and 18S RNA ↑ Shrinkage, ↑ Phosphatidyl Serine exposure ↑ Calcium depletion ↑ Hsp 70 ↓ Membrane potential ↓ ATP synthesis	↓ NF-κB
Anti-apoptotic	Most eukaryotic cells, inhibition of induced apoptosis	↓ DNA laddering	↓ AP-1 activity ↓ Caspase ↓ Janus kinases ↓ PARP, ↑ Hsp 70 ↑ GSH, ↑ Thiols	?
Wound healing	Skin cells, tissue repair and remodeling	↓ Superoxide anions ↓ Lysosomal enzymes	↑ Granulation ↑ TGF-β 1 ↑ Extracellular matrix	↓ MMP-1 ↓ MMP-9 ↓ HGF ↓ NF-κB
Antidiabetogenic	Renal cells, diabetes	↓ Lipid peroxides ↓ Urinary excretion of albumin, urea, Na^+, K^+ and Pi ↓ Cholesterol	↓ Antioxidant enzymes	?
Anti-Stressor	Hepatic and adrenal cells, fibroblasts	↑ Hsp27, ↑ Hsp 70 ↑ Acute phase proteins	?	?
Antiviral; Antibacterial; Antifungal agent	Microbes	↓ P^{24} antigen production	↓ HIV-1 integrase	?
Anti-cancer	Cancer cells	↓ Metastasis ↓ Tyrosine phosphorylation ↓ DNA adducts ↓ Angiogenesis	↓ Collagenase ↓ Tyrosine kinase ↓ Protein kinase C ↓ VEGF, ↓ bFGF	?
Antilithogenic	Endocrine tissue	↑ Bile flow	↑ Gall bladder contraction	?

Note: ? = Unknown.

CONCLUSION

The turmeric spice has been used for many centuries mainly as a food additive, primarily because of its golden yellow color. The medicinal properties of this spice were recognized in Indian folklore medicine and in Ayurveda, which is an ancient Indian traditional system of medicine (Lad, 1995; Lodha and Bagga, 2000). It was used as a tonic for improving health and in various combinations for the treatment of diseases, such as the common cold. The major breakthrough in realizing the medicinal value of turmeric came with the isolation of phenolics called curcuminoids, of which curcumin is the major constituent. These phenolics are also responsible for the yellow pigmentation of turmeric, for which it was very highly valued. Even though a large number of studies unequivocally identified the numerous pharmaceutical actions of curcuminoids, its acceptance as a 'wonder compound' is slowly forthcoming. The reasons for this include non-physiological doses of curcumin used in many experiments, the lack of understanding about the mechanism of action of curcumin at the cellular and genetic levels, concerns regarding the safety of using high doses of curcumin, inappropriate vehicles used for delivering curcumin to target tissues, and the lack of adequate knowledge about enzymes involved in the degradation and metabolism of curcumin. These concerns need to be addressed for a wider acceptance of using curcumin for therapeutic purposes. However, recent studies have overwhelmingly thrown light on the efficacy and possible mechanism of action of curcumin regarding its various pharmaceutical properties (Table 1). Because curcumin is a constituent of the diet, it is non-toxic in nature. Curcumin has a plethora of beneficial effects and certainly qualifies for serious consideration as a pharmaceutical/nutraceutical/phytoceutical agent.

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