Protective Effects of Curcumin on Gastric Inflammation and Liver Diseases

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Curcumin (diferuloylmethane), the natural yellow pigment in turmeric, is isolated from the rhizomes of the plant *Curcuma longa* Linn. *C. longa* belongs to the Zingiberaceae family, a perennial herb that measures up to 1 meter high with a short stem, and is distributed throughout tropical and subtropical regions of the world. *C. longa* is widely cultivated in Asian countries, mainly in India and China. Its rhizomes are oblong, ovate, pyriform, and often short-branched. The rhizomes are a household remedy in Nepal(1). As a powder, called turmeric, it is bright yellow and has been used as a coloring agent in food in the United States. In India, it has been used for centuries as a spice and a food preservative, and also for its various medicinal properties. The current traditional Indian medicine claims the usage of turmeric against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism, and sinusitis(2).

**Active ingredients of turmeric**

In the 19th century, there has been considerable interested in the active compounds in turmeric called curcuminoids. The major curcuminoid is called curcumin (diferuloylmethane), which makes up approximately 90% of the curcuminoid content in turmeric, followed by demethoxycurcumin and bisdemethoxycurcumin(3). The chemical structure of curcumin was determined by Roughley and Whiting (Figure 1)(4).

**Pharmacokinetic study and safety**

Curcumin is dissolved in organic solvents such as Dimethylsulfoxide (DMSO), oil, alcohol, and petroleum agents. Interestingly, curcumin has been demonstrated the safety in human and animals. Human appeared to be able to tolerate high doses of curcumin without significant side-effects. A phase 1 study by Cheng et al.(5), found no adverse effects of curcumin ingestion for 3 months of doses up to 8000 mg/day. Other human studies of curcumin included the following: a double-blinded, crossover trial in 18 patients with rheumatoid arthritis(6), a randomized, placebo-controlled trial with 45 postsurgical patients(7). The doses of curcumin in these studies ranged from 1125 mg/day to 2500 mg/day. Only one postsurgical patient reported mild transient giddiness. No other adverse reactions were reported, including any changes in blood chemistry reports. Thus curcumin appears to be safe in human even using at high doses.

In animals, the previous study demonstrated that curcumin is rapidly metabolized and poorly absorbed in Sprague-Dawley rats. Administering curcumin

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orally were made by Wahlström and Blennow(8). They demonstrated that this compound in a dose of 1 to 5 g/kg BW given to rats apparently did not cause any adverse effects and it was excreted about 75% in the feces, while traces appeared in the urine. In addition, measurements of blood plasma levels and biliary excretion showed that curcumin was poorly absorbed by the gastrointestinal tract. Curcumin was disappeared within 30 min after adding to microsomes suspensions or hepatocyte suspensions. Furthermore, it was capable of disappearing from the blood after intravenous or after addition to the liver perfusion system. Moreover, oral LD50 was found to be 12.2 g/kg BW in rats(9).

In addition, a study in which rats were fed with curcumin 1.8 g/kg BW per day for 90 days and monkeys were fed with curcumin 0.8 mg/kg BW per day for 90 days showed no adverse effects(10).

Activities of curcumin

Hundreds of in vitro and animal studies have been published describing antioxidant, anti-inflammation, anti-protozoa, anti-bacteria, nematocidal activity, anti-venom, anti-HIV, and anti-tumor properties of curcumin(11).

Antibacterial activity

Bhavani Shankar and Murthy(12) investigated the activity of turmeric fractions against some intestinal bacteria in vitro. In this work, curcumin at the dose of 2.5-50 mg/mL inhibited Staphylococcus aureus. Mahady et al.(13) found that both of methanol extract of dried powder tumeric rhizome and curcumin inhibited H. pylori growth, with significantly activity against the CagA positive strains.

Anti-inflammatory activity

In previous studies, there are two models of inflammation to be studied. First, chronic models (cot- ton pellet and granuloma pouch), where the inflammation and granuloma development during a period of time (several days), indicating the proliferative phase of inflammation. Second, acute models, where acute effects of anti-inflammatory agents can be studied, testing their inhibitory action on the development of rat paw edema.

Mukophadhayay et al.(14) demonstrated the activity of curcumin and other semi-synthetic analogues in carrageenin-induced rat paw edema and cotton pellet granuloma models of inflammation in rats. In these experiments the authors used ferulic acid and phenylbutazone (reference drug) as a treatment. Curcumin and its analogues showed similar action to the reference drug, potent anti-inflammatory in the chronic model of inflammation and in carrageenin-induced paw edema in rats. Among the curcumin analogues, triethylcurcumin was the most, when compared with the others and with the drug reference, whereas tetrahydrocurcumin showed no activity in chronic model. In the acute inflammation condition, all the substances were more effective. The authors concluded that the activity of the compounds used in these experiments, would depend on the model of inflammation.

Moreover, Arora et al.(9) investigated the anti-inflammatory activity in different fractions of the petroleum ether extract of the rhizomes of turmeric (two constituents) in animals. They found that the extracts reduced the granuloma growth and no toxic effects were observed. Srimal and Dhawan(15) found that curcumin inhibited the carrageenan-induced edema in rats in dose range of 20-80 mg/kg BW and has a lower ulcerogenic index. Besides, Blood pressure and respiration of anaesthetized rats were not affected by curcumin.

Curcumin down-regulates the NF-κB

In many studies showed that curcumin is an anti-inflammatory substance because it can inhibit the acti-
vation of the major transcription factor NF-κB. This transcription factors required for the expression of many genes linked with cell proliferation and host immune response(19). Duvoix et al.(17) described this effect in K562 leukemia cells in which curcumin strongly inhibits TNF-α-induced NF-κB and binding to the corresponding target sequences on glutathione S-transferase P1-1 (GSTP1-1) gene promoter or consensus binding sites. Bharti et al.(18) discovered that inhibition of IKK complex blocks both IkB-α phosphorylation as well as NF-κB p65 translocation and thus leads to NF-κB inhibition. Many reports confirmed these results and published that curcumin inhibits IL-1α, TNF-α, 12-O-tetradecanoylphorbol-13-acetate (TPA), lipopolysaccharide (LPS)- and thrombin-induced NF-κB activation(19).

NF-κB inhibition by curcumin is certainly an interesting strategy against diseases such as the pathogenesis of alcoholic liver disease, in which NF-κB is activated(20). In addition, NF-κB is an important transcription factor implicated in proangiogenic genes. Curcumin showed cancer chemoprevention by down regulation of proangiogenic genes, such as VEGF gene(21). In ovarian cancer study, NF-κB signaling blockade significantly inhibited in vitro and in vivo expression of two major proangiogenic molecules, VEGF and IL-8. The decreased expression of VEGF and IL-8 directly correlated with decreased tumorigenicity, decreased vascularization of lesions, decreased formation of malignant ascites, and prolonged survival of mice. These findings suggest that inhibition of NF-κB activity can suppress angiogenesis and progressive growth(22).

Interestingly, Foryst-Ludwig and co-workers(23) studied on H. pylori-infected gastric epithelial cells and suggested that curcumin, not a toxic agent on cell culture, can inhibit NF-κB activation and IL-8 production. In addition, curcumin inhibited H. pylori-induced scatter cells.

Curcumin down-regulates the enzymes involved in inflammation

Interestingly, it was published that curcumin inhibits cyclooxygenase 2 (COX-2) as well as lipoxygenase (LOX), two enzymes involved in inflammation(24). Indeed, cytokine-induced COX-2 transforms arachidonic acid in prostaglandins during acute inflammatory episodes. COX-2 is also the prevalent isoform during chronic inflammations. Curcumin at the doses of 100 and 200 mg/kg of body weight (BW) inhibited the granuloma formation. Moreover, treatment of the animals with 200 mg/kg BW of curcumin for 4 days reduced the prostaglandin-E2 (PGE-2) content(25). In addition, LOX transforms arachidonic acid in leukotrienes, which take part in leukocytes recruiting and play a role in inflammation(26). Besides, curcumin down-regulates leukocyte adhesion. Curcumin blocked the attachment of monocytes to endothelial cells by inhibiting the expression of endothelial cell adhesion molecules ICAM-1, VCAM-1, and ELAM-1(27). Furthermore, this yellow substance can suppress inflammatory cytokines TNF-α and IL-1 that disturb endothelial cell and induced expression of adhesion molecules(28).

The study of curcumin on gastric inflammation and liver diseases

Curcumin protects the gastrointestinal tract against irritants. Indomethacin-induced ulcer in rats were orally treated with tumeric suspended in 10% propylene glycol (0.25, 0.5, or 0.75 g/kg BW) for 3 days. Tumeric at dose 0.5 g/kg BW showed protecting and enhancing healing of gastric ulcer(29). Another study in 2010, 200 or 600 mg/kg curcumin once-a-day supplementation could attenuate nuclear factor-κB p65 expression and macromolecular leakage in the gastric mucosa of H. pylori-infected rats(30). The recent study, Thong-Ngam D et al. showed the protective effects of curcumin on gastric microcirculation and anti-inflammation action on rat with indomethacin induced gastric damage(31). Pretreatment with 200 mg/kg BW curcumin could reduced leukocyte adherence in postcapillary venule, decreased the elevation of ICAM-1 level and improved the stomach histopathology.

In 2000, Chuang et al.(32) showed that curcumin at concentrations of 200 mg/kg BW or 600 mg/kg BW could effectively inhibit diethylaminoethylamine-induced liver inflammation in rats. Other interesting action of curcumin was demonstrated by Park et al.(33). Curcumin inhibited liver injury in carbon tetrachloride (CCl₄) induced hepatotoxicity in rats. The recent study, Thong-Ngam D et al. showed curcumin can prevent most of the damage caused by paracetamol overdose by induction of hepatic GSH, reduction of oxidative stress, attenuation of liver inflammation, and the improvement of liver pathology. In addition, curcumin at the dose of 600 mg/kg tends to be more potent than 200 mg/kg(34). Another study showed Curcumin could
improve histopathology of liver in early stage of alcohol-induced liver injury by reduction of oxidative stress and inhibition the activation of NF-κB and it might have a trend of decreased hepatocyte apoptosis.

REFERENCES


