Review Article

THAI J GASTROENTEROL 2012
Vol. 13 No. 2
May - Aug. 2012

Protective Effects of Curcumin on Gastric Inflammation and Liver Diseases

Thong-Ngam D

Curcumin (diferuloylmethane), the natural yellow pigment in tumeric, 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 tumeric against biliary disorders, anorexia, coryza, cough, diabetic wounds, hepatic disorder, rheumatism, and sinusitis[2].

Active ingradients of tumeric

In the 19th century, there has been considerable interested in the active compounds in tumeric called curcuminoids. The major curcuminoid is called curcumin (diferuloylmethane), which makes up approximately 90% of the curcuminoid content in tumeric, 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. Administrating curcumin

Key words: curcumin, *Helicobacter pylori*, indomethacin-induced ulcer, paracetamol overdose, hepatotoxicity

Department of Physiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
Address for Correspondence: *Duangporn Thong-Ngam, MD, Department of Physiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. thongngam007@yahoo.com.*

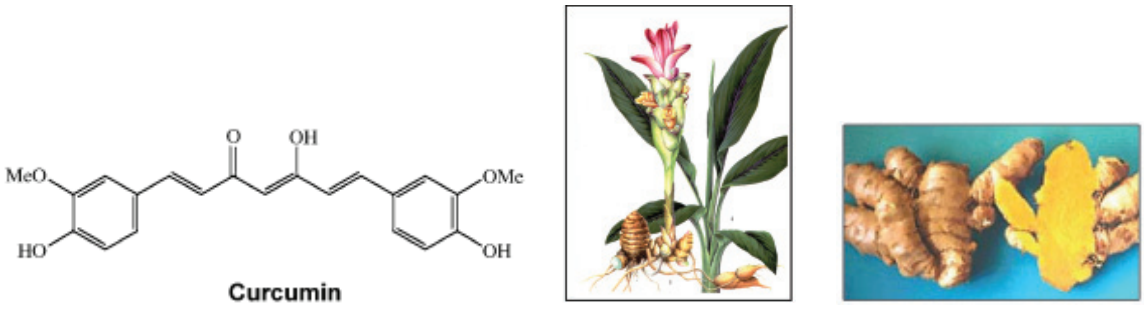

Figure 1. Chemical structure of curcumin (diferuloylmethane)

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 (cotton 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.

Mukophadhyay *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[16]. 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 IκB-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-E_2 (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 diethylnitrosamine-induced liver inflammation in rats. Other interesting action of curcumin was demonstrated by Park *et al*[33]. Curcumin inhibited liver injury in carbon tetrachloride (CCl_4) 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[35].

REFERENCES

1. Eigner D, Scholz D. Ferula asa-foetida and Curcuma longa in traditional medical treatment and diet in Nepal. J Ethnopharmacol 1999;67:1-6.
2. Ammon HPT, Anazodo MI, Safayhi H, *et al*. Curcumin: a potent inhibitor of leukotriene B4 formation in rat peritoneal polymorphonuclear neutrophils (PMNL). Planta Med 1992;58:26.
3. Ruby AJ, Kuttan G, Babu KD, *et al*. Antitumor and antioxidant activity of natural curcuminoids. Cancer Lett 1995;94:79-83.
4. Roughley PJ, Whiting DA. Experiments in the biosynthesis of curcumin. J Chem Soc 1973;20:2379-88.
5. Cheng AL, Hsu CH, Lin JK, *et al*. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 2001;21:2895-900.
6. Deodhar SD, Sethi R, Srimal RC. Preliminary studies on antirheumatic activity of curcumin. Indian J Med Res 1980;71: 632-4.
7. Satoskar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. Int J Clin Pharmacol Ther Toxicol 1986;24:651-4.
8. Wahltrom B, Blennow G. A study on the fate of curcumin in the rat. Pharmacol Toxicol 1978;43:86-92.
9. Arora R, Basu N, Kapoor V. Anti-inflammatory studies on Curcuma longa (tumeric). Indian J Med Res 1971;59:1289-95.
10. Majeed M, Badmaev V, Shivakumar U, *et al*. Curcuminoids; Antioxidant phytonutrients. Piscataway NJ: Nutriscience Publishers, Inc; 1995.
11. Roth G, Chandra A, Nair M. Novel bioactivities of Curcuma longa constituents. J Nat Prod 1998;61:542-5.
12. Bhavani Sankar TN, Murthy S. Effect of Turmeric (Curcuma longa) fractions on the growth of some intestinal and pathogenic bacteria in vitro. Indian J Exp Biol 1979;17:1363-6.
13. Mahady GB, Pendland SL, Yun G, *et al*. Tumeric (Curcuma longa) and curcumin inhibit the growth of *Helicobacter pylori*, a group 1 carcinogen. Anticancer Res 2002;22:4179-81.
14. Mukophadhyay A, Basu N, Ghatak N, *et al*. Anti-inflammatory and irritant activities of curcumin analogues in rats. Agents Actions 1982;12:508-15.
15. Srimal RC, Dhawan BN. Phamocology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. J Pharm Pharmacol 1973;25:447-452.
16. Pahl HL. Activators and target genes of Rel/NF-κB transcription factors. Oncogene 1999;18:6853-66.
17. Duvoix A, Morceau F, Delhalle S, *et al*. Induction of apoptosis by curcumin: mediation by glutathione S-transferase P1-1 inhibition. Biochem Pharmacol 2003;66:1475-83.
18. Bharti AC, Donato N, Singh S, *et al*. Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-kappa B and Ikappa Balpha kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. Blood 2003;101:1053-62.
19. Shishodia S, Potdar P, Gairola CG, *et al*. Curcumin (diferuloylmethane) down-regulates cigarette smoke-induced NF-kappaB activation through inhibition of IkappaBalpha kinase in human lung epithelial cells: correlation with suppression of COX-2, MMP-9 and cyclin D1. Carcinogenesis 2003;24:1269-79.
20. Nanji AA, Jokelainen K, Tipoe GL, *et al*. Curcumin prevents alcoholinduced liver disease in rats by inhibiting the expression of NF-kappa B-dependent genes. Am J Physiol Gastrointest Liver Physiol 2003;284:G321-G327.
21. Singh S, Khar A. Biological effects of curcumin and its role in cancer chemoprevention and therapy. Anticancer Agents Med Chem 2006;6:259-70.
22. Huang S, Robinson JB, DeGuzman A, *et al*. Blockade of nuclear factor-kB signaling inhibits angiogenesis and tumorigenicity of human ovarian cancer cells by suppressing expression of vascular endothelial growth factor and interleukin 8. Cancer Res 2000;60:5334-9.
23. Foryst-Ludwig A, Neumann M, Schneider-Brachert W, *et al*. Curcumin blocks NF-kB and the motogenic response in Helicobacter pylori-infected epithelial cells. BBRC 2004;316: 1065-72.
24. Huang MT, Lysz T, Ferraro T, *et al*. Inhibitory effects of curcumin on in vitro lipoxygenase and cyclooxygenase activities in mouse epidermis. Cancer Res 1991;51:813-9.
25. Ireson C, Orr S, Jones DJ, *et al*. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of theirability to inhibit phorbol ester-induced prostaglandin E2 production. Cancer Res 2001;61:1058-64.
26. Fiorucci S, Meli R, Bucci M, *et al*. Dual inhibitors of cyclooxygenase and 5-lipoxygenase. A new avenue in antiinflammatory therapy? Biochem Pharmacol 2001;62:1433-8.
27. Kumar A, Dhawan S, Hardegen NJ, *et al*. Curcumin (Diferuloylmethane) inhibition of tumor necrosis factor (TNF)-mediated adhesion of monocytes to endothelial cells by suppression of cell surface expression of adhesion molecules and of nuclear factor-κB activation. Biochem Pharmacol 1998;55: 775-83.
28. Li CJ, Zhang LJ, Dezube BJ, *et al*. Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. Proc Natl Acad Sci 1993;90:1839-42.
29. Wang, X., and R. Andersson. The role of endothelial cells in systemic inflammatory response syndrome and multiple system organ failure. Eur J Surg 1995;161:703-13.
30. Thong-Ngam D, Choochuay S, Patumraj S, *et al*. Curcumin prevents indomethacin-induced gastropathy in rats. World J Gastroenterol 2012;18:1479-84

31. Sintara K, Thong-Ngam D, Patumraj S, *et al*. Curcumin suppresses gastric NF-kappaB activation and macromolecular leakage in *Helicobacter pylori*-infected rats. World J Gastroenterol 2010;16:4039-46.
32. Chuang S, Cheng A, Lin J, *et al*. Inhibition by curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene products and cell-cycle-related proteins in rats. Food Chem Toxicol 2000;38:991-5.
33. Park EJ, Jeon CH, Ko G, *et al*. Protective effect of curcumin in rat liver injury induced by carbon tetrachloride. J Pharm Pharmacol 2000;52:437-40.
34. Somanawat K, Thong-Ngam D, Klaikeaw N. Effects of curcumin on hepatitis in mice with paracetamol overdose. Thai J Gastroenterol 2012;13:43-9.
35. Samuhasaneeto S, Thong-Ngam D, Kulaputana O, *et al*. Curcumin decreased oxidative stress, inhibited NF-kappaB activation, and improved liver pathology in ethanol-induced liver injury in rats. J Biomed Biotechnol 2009;981963. Epub 2009 Jul 6.