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# COMMENTARY

# Curcumin: potential for hepatic fibrosis therapy?

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The beneficial antioxidative, anti-inflammatory and antitumorigenic effects of curcumin have been well documented in relation to cancer and other chronic diseases. Recent evidence suggests that it may be of therapeutic interest in chronic liver disease. Hepatic fibrosis (scarring) occurs in advanced liver disease, where normal hepatic tissue is replaced with collagen-rich extracellular matrix and, if left untreated, results in cirrhosis. Curcumin inhibits liver cirrhosis in a rodent model and exerts multiple biological effects in hepatic stellate cells (HSCs), which play a central role in the pathogenesis of hepatic fibrosis. In response to liver injury, these cells proliferate producing pro-inflammatory mediators and extracellular matrix. Curcumin induces apoptosis and suppresses proliferation in HSCs. In addition, it inhibits extracellular matrix formation by enhancing HSC matrix metalloproteinase expression via PPARγ and suppressing connective tissue growth factor (CTGF) expression. In this issue, Chen and co-workers propose that curcumin suppresses CTGF expression in HSC by inhibiting ERK and NF-κB activation. These studies suggest that curcumin modulates several intracellular signalling pathways in HSC and may be of future interest in hepatic fibrosis therapy.
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**Keywords:** curcumin; ERK MAP kinase; NF-κB; PPAR-γ; anti-inflammatory; hepatic fibrosis; hepatic stellate cells

**Abbreviations:** CTGF, connective tissue growth factor; HSCs, hepatic stellate cells; Nrf2, nuclear factor-erythroid-2-related factor 2; PPAR-γ, peroxisome proliferator-activated receptor-γ

Turmeric, derived from the rhizome of the herb *Curcuma longa*, has been used for centuries in Asia as both a dietary spice and a treatment for inflammation, wounds and gastrointestinal, pulmonary and liver disorders. Curcumin (diferuloylmethane) is regarded as the most active constituent present in turmeric and exerts potent biological effects *in vitro* and *in vivo* (Sharma *et al*., 2005; Aggarwal *et al*., 2007). It possesses several functional groups that exhibit antioxidant activity (Weber *et al*., 2005) allowing it to modulate redox-signalling pathways in cells. It also activates an intracellular antioxidant defence system through its stimulation of nuclear factor-erythroid-2-related factor 2 (Nrf2), a transcription factor, which binds to the antioxidant response element in the regulatory region of several genes coding for intracellular antioxidants, cytoprotective and detoxification proteins (Chen and Kunsch, 2004). These include haem-oxygenase-1, NADPH–quinone oxidoreductase, ferritin and genes that regulate intracellular glutathione (Rushworth *et al*., 2006).

Curcumin also exerts potent anti-inflammatory effects in cells inhibiting pro-inflammatory cytokines and chemokines, adhesion molecules, cyclooxygenase-2, tissue factor and inducible nitric oxide synthase (Pendurthi *et al*., 1997; Sharma *et al*., 2005; Shishodia *et al*., 2007). These suppressive effects are due to the inhibition of the NF-κB pathway and other pro-inflammatory signalling pathways including AP-1, Egr-1, STAT members and MAP kinases (Pendurthi *et al*., 1997; Duvoix *et al*., 2005; Sharma *et al*., 2005; Shishodia *et al*., 2007). Chemopreventive and chemotherapeutic effects of curcumin have also been well documented. It inhibits cell proliferation, induces apoptosis and growth arrest in different phases of the cell cycle (depending on cell type) and inhibits angiogenesis (Shishodia *et al*., 2007). Several mechanisms are reported to regulate these effects including activation of peroxisome proliferator-activated receptor γ (PPAR-γ), degradation of p53, activation of pro-apoptotic genes (including caspases, Bax and Bak family members), downregulation of survival genes, for example Bcl2, and inhibition of NF-κB, AP-1, Akt, MAP kinases and other signalling pathways (Duvoix *et al*., 2005; Sharma *et al*., 2005; Bhattacharyya *et al*., 2007; Shankar and Srivastava, 2007; Shishodia *et al*., 2007).

Owing to these multiple biological effects, curcumin may be of therapeutic benefit in several diseases. In animal models, curcumin prevents development of several cancers (Sharma *et al*., 2005; Shishodia *et al*., 2007). Curcumin also reduces risk factors or symptoms associated with cardiovascular disease, type II diabetes, Alzheimer's disease, rheumatoid arthritis, multiple sclerosis, cataract formation, infection and pulmonary disease (Shishodia *et al*., 2007). In Phase-I clinical studies, oral administration of curcumin is generally well tolerated at pharmacological concentrations

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(3600–8000 mg day$^{-1}$ for 4 months). Preliminary Phase-I clinical trials in patients with cancer and various inflammatory disorders also support the use of curcumin in these diseases although these are small studies and warrant further investigation (reviewed in Sharma *et al.*, 2005; Hsu and Cheng, 2007).

Curcumin is also emerging as a potential therapeutic compound in chronic liver disease, a major cause of morbidity and mortality worldwide. Curcumin exerts beneficial effects in animal models of liver injury and cirrhosis (Park *et al.*, 2000; Bruck *et al.*, 2007). Liver damage, caused by viruses, alcohol and other toxins, leads to a chronic inflammatory process with progressive hepatic fibrosis where normal hepatic tissue is replaced with collagen-rich extracellular matrix and eventually, if left untreated, results in cirrhosis. Hepatic stellate cells (HSCs) play a central role in the progression of fibrosis. Following liver injury, HSCs are activated and proliferate producing pro-inflammatory cytokines and chemokines, growth factors, pro-fibrogenic cytokines (including connective tissue growth factor CTGF) and metalloproteinase inhibitors resulting in a collagen-rich extracellular matrix that progresses to fibrosis. Several signalling pathways are involved in these processes (reviewed in Elsharkawy *et al.*, 2005). Emerging evidence suggests that fibrosis and cirrhosis are potentially reversible. Induction of HSC apoptosis is associated with reversal of fibrosis (Elsharkawy *et al.*, 2005) and therefore targeting HSC activation and proliferation may help to prevent or reverse fibrosis. In HSCs, curcumin exerts several antioxidative, anti-inflammatory, antifibrogenic and antiproliferative effects. Recently, Bruck *et al.* (2007) demonstrated that curcumin inhibited hepatic fibrosis in a rodent model by reducing oxidative stress and inhibiting HSC activation and collagen $\alpha$1(I) gene expression. *In vitro*, curcumin induces apoptosis and inhibits activation and proliferation of HSCs. In addition, it prevents formation and development of the extracellular matrix by inhibiting collagen $\alpha$1(I), fibronectin and $\alpha$-smooth muscle actin gene expression, by enhancing matrix metalloproteinase-2 and -9 expression and suppressing CTGF expression (Xu *et al.*, 2003; Zheng and Chen, 2006; Cheng *et al.*, 2007). Several intracellular signalling pathways are modulated by curcumin in HSCs including ERK, JNK, AP-1, PPAR-$\gamma$ and NF-$\kappa$B (Chen and Davis, 1999; Xu *et al.*, 2003; Cheng *et al.*, 2006; 2007). In addition, curcumin is most likely to activate Nrf2 in these cells since inhibition of HSC activation by curcumin requires *de novo* synthesis of the major cellular antioxidant glutathione and activation of glutathione-regulated gene expression (Zheng *et al.*, 2007), which requires this pathway. Chen, Xu and co-workers have previously demonstrated the importance of the PPAR-$\gamma$ pathway in curcumin's effects on HSC activation, proliferation and matrix-metalloproteinase expression (Xu *et al.*, 2003; Zheng and Chen, 2006; Cheng *et al.*, 2007). However, roles for NF-$\kappa$B and the ERK MAP kinase pathway are less clear although both ERK and NF-$\kappa$B activation are closely associated with HSC activation and NF-$\kappa$B is an important regulator of oxidative stress. In this issue of the *British Journal of Pharmacology*, Chen and co-workers confirm the previous work suggesting that curcumin activation of PPAR-$\gamma$ results in the inhibition of NF-$\kappa$B activation in HSCs (Xu *et al.*, 2003). In addition, they report that both NF-$\kappa$B and the ERK MAP kinase pathway are required for the expression of CTGF, a key fibrogenic growth factor produced by HSCs. The results suggest that ERK MAP kinase may act upstream of NF-$\kappa$B and that this kinase is also required for collagen $\alpha$1(I) expression. Furthermore, the results suggest that curcumin may suppress CTGF expression in HSCs by inhibiting the activation of NF-$\kappa$B and ERK MAP kinase. Although further work is required to confirm these observations, the results of this and the studies so far in HSCs suggest that curcumin can target several pro-inflammatory and fibrogenic pathways in these cells and therefore it may be a potential therapy in hepatic fibrosis in the future. Pharmacokinetic studies, however, suggest that oral administration results in low bioavailability. Pharmacologically active concentrations are achievable in tissues that are directly exposed to oral or topical curcumin including the colon, skin, eye and airways (Hsu and Cheng, 2007) and this suggests that alternative routes of administration are necessary for curcumin to be a successful therapy for hepatic fibrosis.

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