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REVIEW

Curcumin: an orally bioavailable blocker of TNF and other pro-inflammatory biomarkers

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TNFs are major mediators of inflammation and inflammation-related diseases, hence, the United States Food and Drug Administration (FDA) has approved the use of blockers of the cytokine, TNF-α, for the treatment of osteoarthritis, inflammatory bowel disease, psoriasis and ankylosis. These drugs include the chimeric TNF antibody (infliximab), humanized TNF-α antibody (Humira) and soluble TNF receptor-II (Enbrel) and are associated with a total cumulative market value of more than $20 billion a year. As well as being expensive ($15 000–20 000 per person per year), these drugs have to be injected and have enough adverse effects to be given a black label warning by the FDA. In the current report, we describe an alternative, curcumin (diferuloylmethane), a component of turmeric (*Curcuma longa*) that is very inexpensive, orally bioavailable and highly safe in humans, yet can block TNF-α action and production in *in vitro* models, in animal models and in humans. In addition, we provide evidence for curcumin's activities against all of the diseases for which TNF blockers are currently being used. Mechanisms by which curcumin inhibits the production and the cell signalling pathways activated by this cytokine are also discussed. With health-care costs and safety being major issues today, this golden spice may help provide the solution.

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Abbreviations
ACR, American College of Rheumatology; AP-1, activator protein-1; ATF2, activating transcription factor 2; C/EBP, CCAAT/enhancer binding protein; CD, Crohn's disease; COPD, chronic obstructive pulmonary disease; CREB, cAMP response element binding protein; DAS, Disease Activity Score; DNBS, dinitrobenzene sulfonic acid; IBD, inflammatory bowel disease; LITAF, LPS-induced TNF-α factor; MCP-1, monocyte chemotactic protein-1; MD-2, myeloid differentiation protein-2; NFAT, nuclear factor of activated T-cell transcription factor; OA, osteoarthritis; PhK, phosphorylase kinase; RA, rheumatoid arthritis; SLCP, solid lipid curcumin particle; TLRs, toll-like receptors; TNBS, trinitrobenzene sulfonic acid; UC, ulcerative colitis

Introduction

Extensive research during the past century has revealed that inflammation plays a major role in most chronic diseases. It was Cornelius Celsus, a physician in first century Rome, who first attempted to describe inflammation as heat (calor), pain (dolor), redness (rubor) and swelling (tumour). Rudolf Virchow, a German scientist from Wurzburg, in 1850, was the first to observe a link between inflammation and various chronic diseases, which include cancer, atherosclerosis, arthritis, diabetes, asthma, multiple sclerosis and Alzheimer's disease (Heidland *et al*., 2006). More than 200 different types of inflammatory disease have been described. When the name of a disease ends with 'itis', this means inflammation of the affected organ. Thus, arthritis is inflammation of the joints, whereas bronchitis, sinusitis, gastritis, oesophagitis, pancreatitis, meningitis, rhinitis and gingivitis are, respectively, inflammation of the bronchi, sinuses, stomach, oesophagus, pancreas, brain, nose and gums. Acute inflammation is thought to be therapeutic as it helps an organism to heal. Chronic inflammation, however, can lead to a disease; inflammation of the colon (colitis), for example, when persistant, for as long as 30 years, can finally lead to colon cancer.

During the past three decades, molecular mechanisms that lead to inflammation have been extensively examined. Various enzymes, cytokines, chemokines and polypeptide hormones have been identified, which can mediate inflammation. These include COX-2, 5-lipooxygenase (LOX), TNF-α, IL-1, IL-6, IL-8, Il-17, IL-21, IL-23 and monocyte chemotactic protein-1 (MCP-1). Among these, TNF-α is a major mediator of inflammation, which is the primary focus of this review.

Discovery of TNFs

TNF has at various times been called *tumour necrosis serum*, *cachectin*, *lymphotoxin* or *monocyte cytotoxin* based on work from our laboratory and others. It is now clear that TNF is a 25 kDa transmembrane protein (17 kDa when secreted) produced primarily by activated macrophages. The ability of tumours to undergo haemorrhagic necrosis after injection of endotoxin was first shown by Shear and Perrault (1944). O'Malley *et al*. (1962) reported that endotoxin injection into normal mice resulted in the appearance of tumour necrotizing activity in the circulating blood. This activity was renamed *tumour necrosis factor* by Carswell *et al*. (1975). The true chemical identity of TNF, however, was unclear until our group isolated two different molecules: one from macrophages, which we named TNF-α (Aggarwal *et al*., 1985b), and the other from lymphocytes, which we named TNF-β (Aggarwal *et al*., 1984). The current review primarily deals with TNF-α.

Because of the amino acid sequence homology between human TNF-α and endotoxin-induced murine cachectin, a protein linked to endotoxin-mediated cachexia and shock (Beutler *et al*., 1985), it became clear that TNF-α and cachectin were identical. Soon thereafter, numerous groups independently identified the same molecule by using a variety of approaches (Haranaka *et al*., 1984; Old, 1985; Wang *et al*., 1985; Fiers *et al*., 1986; Wallach, 1986). TNF-α is now known to bind to two different receptors, TNFRSF1A and TNFRSF1B, and to activate caspase-mediated apoptosis, NF-κB, activator protein-1 (AP-1), JNK, p38 MAPK and ERK signalling (Figure 1). Our group demonstrated that both TNF-α and TNF-β bind to identical receptors and with similar affinities (Aggarwal *et al*., 1985a). Although much is known about TNF-α, very little is understood about TNF-β (Aggarwal, 2003; Aggarwal *et al*., 2012). Both overlapping and non-overlapping activities of the two molecules have been reviewed (Stone-Wolff *et al*., 1984; Kuprash *et al*., 2002; Liepinsh *et al*., 2006).

Aside from originating in monocytes, it is now clear that TNF-α is also produced by a variety of other cell types including Kupffer cells in the liver, astrocytes in the brain, T-cells and beta cells in the immune system, and ovarian cells. In general, under appropriate conditions, most cell types have the potential to produce TNF-α.

TNF-α and inflammation

It is only within the past few decades that the mechanisms by which inflammation is mediated at the molecular level have become apparent. Although the role of macrophages in inflammation has been known for quite some time, the first indication of the pro-inflammatory activity of TNF emerged in 1985 when it was found to stimulate collagenase and PGE_2 production by isolated human synovial cells and dermal fibroblasts (Dayer *et al*., 1985; Caput *et al*., 1986), thus sug-

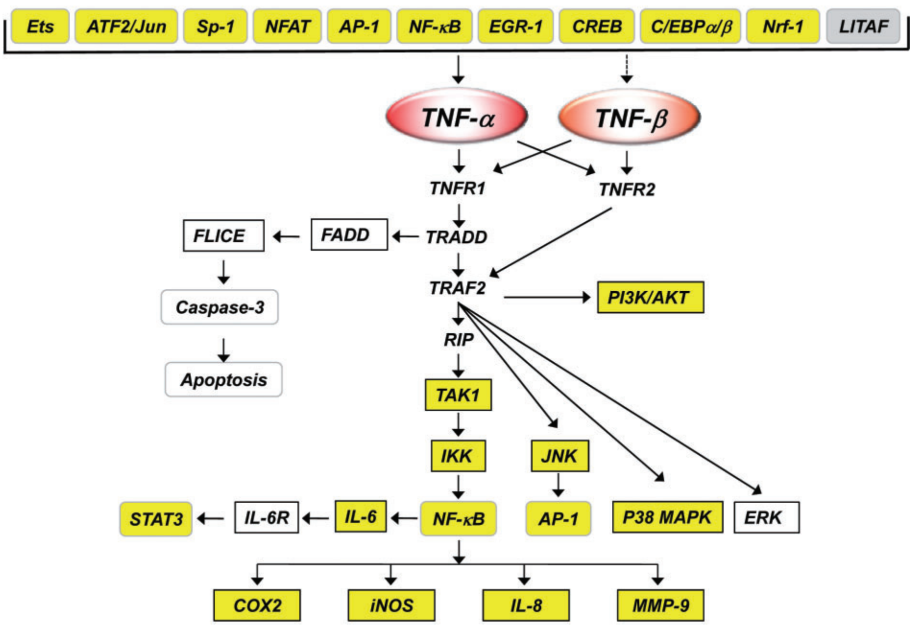

Figure 1

Regulation of the production and action of TNF by curcumin. TNFR1 and TNFR2 are TNF receptors TNFRSF1A and TNFRSF1B respectively. Targets highlighted as yellow are down modulated by curcumin.

gesting that TNF may play a role in the tissue destruction and remodelling associated with inflammatory diseases.

TNF-associated diseases

TNF dysregulation has been linked to a wide variety of diseases including cancer, obesity, cardiovascular diseases, pulmonary diseases, metabolic diseases, neurological diseases, psychological diseases, skin diseases and autoimmune diseases (Aggarwal, 2003; Aggarwal *et al.*, 2012). Thus, blockers of TNF have been approved for the treatment of various autoimmune disorders such as rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease (CD), psoriasis, hidradenitis suppurativa and refractory asthma. The inhibition of TNF can be achieved with monoclonal antibodies such as infliximab (Remicade; Janssen Biotech Inc., Horsham, PA, USA), adalimumab (Humira; Abbott Laboratories, North Chicago, IL, USA), certolizumab pegol (Cimzia; UCB, Brussels, Belgium) and golimumab (Simponi; Janssen Biotech) or with a circulating receptor fusion protein such as etanercept (Enbrel; Amgen, Thousand Oaks, CA, USA). Their potential use in other pro-inflammatory diseases is currently being explored. Some of the important adverse effects most extensively associated with TNF blockers include lymphoma, infections, congestive heart failure, demyelinating disease, a lupus-like syndrome, induction of auto-antibodies, injection site reactions and systemic adverse effects (Scheinfeld, 2004).

Suppression of TNF-α production by curcumin *in vitro*

Numerous reports have suggested that the production of TNF from macrophages activated by various stimuli can be suppressed by curcumin (Table 1). Studies have supported findings that LPS is one of the major inducers of TNF-α in macrophages and monocytes and that curcumin can down-regulate the expression of TNF-α (Chan, 1995; Abe *et al.*, 1999; Jang *et al.*, 2001; Gao *et al.*, 2004; Strasser *et al.*, 2005; Woo *et al.*, 2007; Liang *et al.*, 2008; 2009; Cheung *et al.*, 2009; Jain *et al.*, 2009; Nishida *et al.*, 2010; Zhao *et al.*, 2010). Besides being expressed by myeloid cells, TNF is also expressed by microglial cells, adipocytes and other cell types. Curcumin, however, has been shown to down-regulate TNF expression (Jin *et al.*, 2007; Lee *et al.*, 2007; Zhang *et al.*, 2008; 2010a). In addition to being induced by LPS, TNF is also upregulated by a variety of other stimuli including phorbol ester, palmitate and other inflammatory cytokines, and curcumin has been shown to block the expression of TNF induced by all of these stimuli (Abe *et al.*, 1999; Lee *et al.*, 2007; Jain *et al.*, 2009; Wang *et al.*, 2009).

How curcumin down-regulates TNF expression in different cell types and in response to a variety of stimuli has been examined extensively. TNF suppression primarily occurs at the transcriptional level. The factors known to be involved in TNF transcription include the transcription factor ETS (Kramer *et al.*, 1995), activating transcription factor 2 (ATF2)/Jun (Leitman *et al.*, 1991; Newell *et al.*, 1994; Tsai *et al.*, 1996a,b), Sp1 (Kramer *et al.*, 1994), nuclear factor of activated T-cell transcription factor (NFAT) (McCaffrey *et al.*, 1994; Tsai *et al.*, 1996a,b), NF-κB (Udalova *et al.*, 1998; Kuprash *et al.*, 1999), early growth response protein-1 (Kramer *et al.*, 1994), cAMP response element binding protein (CREB) (Geist *et al.*, 1997), CCAAT/enhancer binding protein β (C/EBPβ) (Pope *et al.*, 1994; Wedel *et al.*, 1996; Zagariya *et al.*, 1998), NF-E2-related factor 1 (Novotny *et al.*, 1998; Prieschl *et al.*, 1998) and LPS-induced TNF-α factor (LITAF) (Takashiba *et al.*, 1995; Myokai *et al.*, 1999) (Figure 1). Hence, different transcription factors appear to be involved in the stimulation of TNF expression by various stimuli and in different cell types. For instance, the transcription factor LITAF is involved in LPS-stimulated TNF expression. Whereas ATF2/Jun and NFATp are involved in TNF expression in activated beta and T-cells, C/EBPβ is involved in human monocytes. Several of these transcription factors have been shown to be modulated by curcumin.

Curcumin can mediate its effect on TNF expression by inhibiting p300/CREB-specific acetyl transferase, leading to repression of the acetylation of histone/non-histone proteins and histone acetyl transferase-dependent chromatin transcription (Balasubramanyam *et al.*, 2004). It is also well known that curcumin can down-modulate the activation of NF-κB by a variety of agents (Singh and Aggarwal, 1995) and this down-regulation of NF-κB by curcumin plays a major role in suppressing the expression of TNF. In addition, in a number of studies it has been shown that methylation of a TNF promoter may affect the promoter's function (Kochanek *et al.*, 1990; 1991; Muiznieks and Doerfler, 1994; Takei *et al.*, 1996). Thus, curcumin could affect TNF expression by affecting the methylation of a TNF promoter (Reuter *et al.*, 2011).

It is possible that the effects of curcumin on LPS-induced TNF production are mediated in part through its LPS signalling. Two of the toll-like receptors (TLRs), TLR2 and TLR4, mediate responsiveness to LPS. LPS-mediated TLR2 mRNA induction has been shown to be attenuated by pretreatment with curcumin (Matsuguchi *et al.*, 2000). In addition, there is biochemical evidence indicating that curcumin can inhibit both ligand-induced and ligand-independent dimerization of TLR4 (Youn *et al.*, 2006). The beneficial effect of curcumin is partly mediated by reducing the expression levels of TNF through inhibition of the expression of TLR2, TLR4 and TLR9 in mouse liver (Tu *et al.*, 2012). Curcumin also binds with sub-micromolar affinity to the myeloid differentiation protein-2 (MD-2), which is the LPS-binding component of the endotoxin surface receptor complex MD-2/TLR4 (Gradisar *et al.*, 2007). The binding site for curcumin overlaps with that of LPS; this results in the inhibition of MyD88-dependent and MyD88-independent signalling pathways of LPS signalling through TLR4, indicating that MD-2 is an important target of curcumin involved in its suppression of the innate immune response to bacterial infection.

Suppression of TNF-α-mediated signalling by curcumin in vitro

There are numerous reports suggesting that curcumin can not only block the production of TNF but also block the cell signalling mediated by TNF in a variety of cell types (Table 1). Our group was the first to show that curcumin can inhibit TNF-mediated NF-κB action in variety of cell types (Singh and Aggarwal, 1995). We also showed that TNF-mediated expression of various cell surface adhesion molecules in endothelial

Table 1

Curcumin inhibits the production and action of TNF *in vitro*

Production of TNF
• Inhibited LPS-induced TNF and IL-1 release from macrophages (Chan, 1995). • Inhibited production of IL-8, MIP-1α, MCP-1, IL-1β and TNF-α by PMA- or LPS-stimulated human monocytes and alveolar macrophages (Abe *et al*., 1999). • Inhibited LPS-induced TNF-α release from macrophages (Jang *et al*., 2001). • Inhibited the expression/production of IL-12 and TNF-α by peritoneal macrophages (Gao *et al*., 2004). • Decreased NF-κB activation and TNF-α secretion after LPS exposure in U-937 cells (Strasser *et al*., 2005). • Inhibited the production of IL-1, IL-6 and TNF-α in LPS-stimulated BV2 microglia (Jin *et al*., 2007). • Exhibited neuroprotective effects through suppression of NO, TNF-α, IL-1α and IL-6 from Abeta (25–35)/IFN-γ- and LPS-stimulated microglia cells (Lee *et al*., 2007). • Inhibited inflammatory responses of adipose tissue in obesity by suppressing release of TNF-α, NO and MCP-1 from adipocytes (Woo *et al*., 2007). • Inhibited NO and TNF-α production in rat primary microglia induced by LPS (Zhang *et al*., 2008). • Inhibited LPS-induced TNF-α and IL-6 synthesis in macrophages (Liang *et al*., 2008). • Down-regulated TNF, IL-1, NO and PGE_2 in Raw 264.7 cells possibly through induction of phase II/antioxidant enzymes including HO-1 and NQO-1 (Cheung *et al*., 2009). • Reversed palmitate-induced insulin resistance through suppression of NF-κB, TNF-α and IL-6 in adipocytes (Wang *et al*., 2009). • Inhibited LPS-induced production of TNF-α, IL-1β, MCP-1, COX-2, iNOS and p65 NF-κB in the macrophages (Liang *et al*., 2009). • Inhibited the high glucose-induced secretion of IL-6, IL-8, MCP-1 and TNF-α in U937 monocytes (Jain *et al*., 2009). • Inhibited secretion of TNF-α and IL-6 *in vitro* (Tham *et al*., 2010). • Inhibited the release of TNF-α and IL-6 in LPS-stimulated RAW 264.7 macrophages (Zhao *et al*., 2010). • Inhibited IκB phosphorylation, NF-κB activation and TNF-α production induced by LPS in mouse macrophages (Nishida *et al*., 2010). • Decreased LPS-induced TNF-α and IL-1β expression at both transcriptional and protein level in microglial cells (Zhang *et al*., 2010a).
Action of TNF-α
• Inhibited TNF-induced NF-κB activation in human myeloid cells (Singh and Aggarwal, 1995). • Reduced TNF-induced endothelial tissue factor by inhibiting AP-1 and NF-κB in endothelial cells (Bierhaus *et al*., 1997). • Blocked the activation of AP-1 and NF-κB induced by IL-1α and TNF-α in stromal cells (Xu *et al*., 1997). • Inhibited TNF-α-induced expression of ICAM-1, VCAM-1 and E-selectin in HUVEC (Gupta and Ghosh, 1999; Kumar *et al*., 1998). • Suppressed TNF-α-induced VEGF secretion in U937 and Raji cells. Reduced the expression of VEGF165 and VEGF121 mRNA induced by TNF-α (Chen *et al*., 2005). • Inhibited TNF-mediated constitutive NF-κB activation linked to proliferation of mantle cell lymphoma cells (Shishodia *et al*., 2005). • Blocked TNF-α-induced endothelial dysfunction in HUVEC (Nan *et al*., 2005). • Down-regulated TNF-induced expression of cell proliferation and anti-apoptotic and metastatic gene products (Aggarwal *et al*., 2006). • Inhibited TNF-α-stimulated Gb3 synthase (GalT6) mRNA expression in intestinal epithelial cells (Moon *et al*., 2006). • Inhibited TNF-α-induced expression of IL-1β, IL-6, TNF-α and cyclin E, but not IL-8, in HaCaT cells (Cho *et al*., 2007). • Inhibited TNF-α-induced NF-κB activation in MCF-7 cells by inhibiting the proteasomal activities (Yoon and Liu, 2007). • Suppressed TNF-α-induced expression of ICAM-1 and VCAM-1, and secretion of IL-6, IL-8 and MCP-1 in HUVEC (Kim *et al*., 2007). • Inhibited TNF-α-induced NF-κB activation in chronic myeloid leukaemia cells through modulation of redox status of the cells (Sandur *et al*., 2007). • Down-regulated the expression of 29 out of 84 TNF-α-activated NF-κB-associated genes in leukaemia cells (Reuter *et al*., 2009). • Inhibited TNF-induced NF-κB activation in leukaemia cells (Yadav *et al*., 2010). • Inhibited TNF-α-induced cell migration, intracellular ROS generation, MMP-9 expression, MMP-9 activity and NF-κB in human aortic smooth muscle cells (Yu and Lin, 2010). • Attenuated TNF-α-induced enhancement of TRPC1 expression, and COX-2-dependent PGE_2 production in colonic myofibroblasts (Hai *et al*., 2011). • Inhibited NF-κB-mediated inflammation in human tenocytes through suppression of the PI3K/Akt pathway (Buhrmann *et al*., 2011).

AKT, AKT8 virus oncogene cellular homologue; AP-1, activator protein-1; HO-1, haeme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein-1α; MMP-9, matrix metallopeptidase-9; NQO1, NADH quinone oxidoreductase 1; TRPC1, transient receptor potential channel 1; VCAM-1, vascular cell adhesion molecule-1.

cells is down-regulated by curcumin (Kumar *et al*., 1998). Since then, a wide variety of cell signalling pathways activated by TNF have been shown to be down-regulated by curcumin; these include JNK, MAPK, PI3K/Akt.

In addition, curcumin has also been shown to modulate TNF-α function by directly binding to the ligand (Gupta *et al*., 2011). Wua *et al*. (2010) performed molecular docking studies with TNF-α and curcumin to predict and analyse the ability of curcumin to inhibit TNF-α by binding to it. The protein–ligand interactions were analysed by simulating the docking of the curcumin using Autodock 4.0. They identified three main binding regions for curcumin and found that curcumin is a potent inhibitor of TNF-α. They also observed that curcumin docked at the receptor-binding sites of TNF-α.

Covalent π-π aromatic interactions or π–cation interactions were found between curcumin and TNF-α. The authors predicted that curcumin is a strong inhibitor of TNF-α because of the covalent bonds it forms with Cys^{129} in TNF-α. In contrast to its interaction with TNF-α, it is unclear whether curcumin can interact or affect the expression of TNF-β or lymphotoxin.

Suppression of TNF by curcumin *in vivo*

The anti-inflammatory effect of curcumin was first demonstrated in acute and chronic models of inflammation in rats and mice (Srimal and Dhawan, 1973). The authors showed that curcumin (50–200 $mg\cdot kg^{-1}$) suppressed carrageenan-induced oedema in mice. Furthermore, curcumin was found to be as potent as phenylbutazone and exhibited minimal ulcerogenic activity. No mortality in mice was noted at doses as high as 2 $g\cdot kg^{-1}$ bodyweight (Srimal and Dhawan, 1973). In the same study, the authors showed that curcumin suppresses formaldehyde-induced arthritis in rats at a dose of 40 $mg\cdot kg^{-1}$ and inhibited granuloma formation at 80–160 $mg\cdot kg^{-1}$. However, the mechanism by which curcumin mediates these anti-inflammatory effects in animals was not revealed until several years later, when our group showed that curcumin can suppress TNF-induced NF-κB activation (Singh and Aggarwal, 1995) and other groups showed that curcumin blocked TNF production in cell culture (Chan, 1995) and the expression of pro-inflammatory genes (Jobin *et al.*, 1999). Since then, numerous mechanisms by which curcumin can exhibit anti-inflammatory activity have been proposed (Figures 1 and 2).

Numerous reports have been published suggesting that oral administration of curcumin down-regulates TNF-α expression both in the serum and in the tissue of animals (Nanji *et al.*, 2003; Yao *et al.*, 2004; Sharma *et al.*, 2007a; Billerey-Larmonier *et al.*, 2008; Larmonier *et al.*, 2008; Ung *et al.*, 2010; El-Moselhy *et al.*, 2011; Gutierres *et al.*, 2012) (Table 2). Attenuation of TNF-α levels by curcumin has been noted in mice (Leyon and Kuttan, 2003), rats (Siddiqui *et al.*, 2006) and rabbits (Yao *et al.*, 2004; Huang *et al.*, 2008). A dose of curcumin of 50–500 $mg\cdot kg^{-1}\cdot day^{-1}$ was used for most of these studies. Endotoxin has been shown to induce septic shock in animals, in part, through the production of TNF, and this condition has been shown to be reversed by curcumin (Siddiqui *et al.*, 2006; Chen *et al.*, 2007; 2008; Huang *et al.*, 2008; Nishida *et al.*, 2010). Decreased TNF-α levels have also been noted in tumour-bearing animals treated with this polyphenol (Leyon and Kuttan, 2003). In addition to cancer, down-regulation of TNF-α by curcumin has been associated with protection from various pro-inflammatory diseases, including sub-chronic inflammation (Nandal *et al.*, 2009; Nishida *et al.*, 2010), cardiovascular diseases (Yao *et al.*, 2004; 2005; Mito *et al.*, 2011; Avci *et al.*, 2012), diabetes (Jain *et al.*, 2009; El-Azab *et al.*, 2011; El-Moselhy *et al.*, 2011), acute pancreatitis (Gulcubuk *et al.*, 2006), enterocolitis (Jia *et al.*, 2010), enteritis (Song *et al.*, 2010), prostatitis (Zhang *et al.*, 2010b), diabetic neuropathy (Sharma *et al.*, 2007b), hepatic injury (Yun *et al.*, 2010), Th1-type ileitis (Bereswill *et al.*, 2010), hepatic fibrosis (Shu *et al.*, 2007; Zeng *et al.*, 2011), radiation-induced lung fibrosis (Lee *et al.*, 2010), asthma (Ammar el *et al.*, 2011), alcohol-induced liver disease (Nanji *et al.*, 2003), non-alcoholic steatohepatitis (Ramirez-Tortosa *et al.*, 2009), concanavalin A-induced liver injury (Tu *et al.*, 2012), renal injury (Hashem *et al.*, 2008; Pan *et al.*, 2012), infection (Allam, 2009), fatigue (Gupta *et al.*, 2009), bone turnover (Yang *et al.*, 2011) and high-fat diet-induced hyperglycaemia (El-Moselhy *et al.*, 2011). Curcumin has also been found to

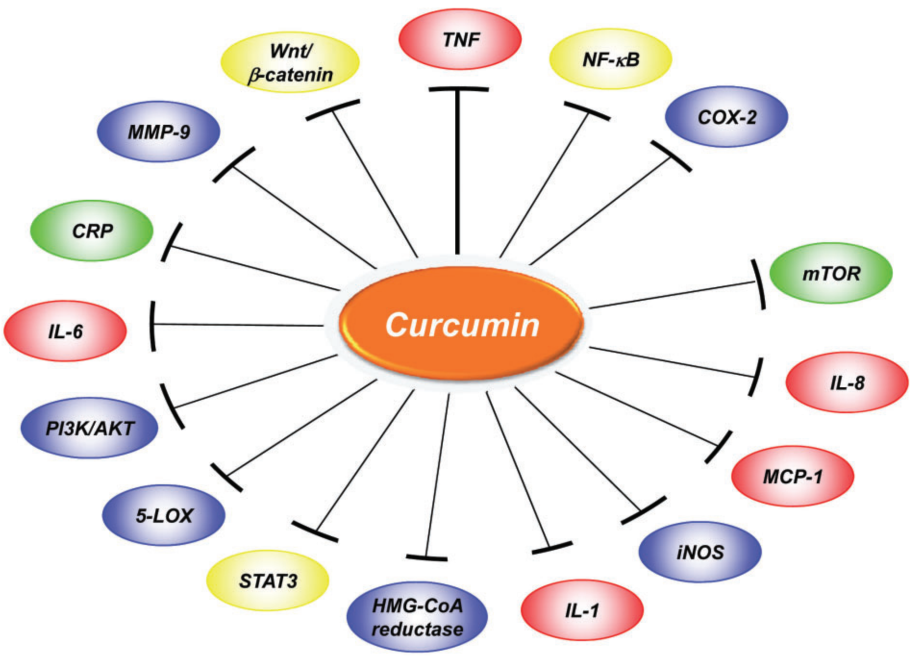

Figure 2
Inflammatory targets modulated by curcumin.

Table 2

Curcumin inhibits TNF production in animals

- Prevented alcohol-induced liver disease in rats by inhibiting the expression of NF-κB-dependent genes including TNF-α (Nanji *et al.*, 2003).
- Reduced the serum level of TNF-α and NO in B16F-10 melanoma cells bearing C57BL/6 mice (Leyon and Kuttan, 2003).
- Suppressed the myocardial TNF-α and MMP-2 expression and improved left ventricular function in pressure overloaded rabbits (Yao *et al.*, 2004).
- Decreased the elevations in plasma IL-8, IL-10 and TNF-α in rabbits after cardiopulmonary bypass and cardiac global ischaemia (Yeh *et al.*, 2005).
- Significantly lowered the serum TNF-α and IL-6 levels in rat model of acute pancreatitis (Gulcubuk *et al.*, 2006).
- Decreased the expression of TNF-α and reduced the mortality in rat model of sepsis (Siddiqui *et al.*, 2006).
- Reduced the mortality rate of LPS-infused rats by decreasing the circulating TNF-α levels and the consumption of peripheral platelets and plasma fibrinogen (Chen *et al.*, 2007).
- Significantly inhibited TNF-α and NO levels in rat model of diabetic neuropathy (Sharma *et al.*, 2007b).
- Down-regulated the expressions of TNF-α and IL-8 in the copper-overloaded rats (Wan *et al.*, 2007).
- Decreased the levels of NO, TGF-β1 and TNF-α in rat model of hepatic fibrosis (Shu *et al.*, 2007).
- Inhibited expression of TNF-α and IL-1β stimulated by LPS in murine macrophages through inhibition of NF-κB pathway (Chen *et al.*, 2008).
- Significantly reduced the LPS-induced overproduction of circulating TNF-α, IL-1β and IL-6, brain glutamate, PGE_2, and hydroxyl radicals in rabbit (Huang *et al.*, 2008).
- Significantly decreased TNF-α mRNA and caspase-8 that probably contributes to the protective role of the turmeric-based diet against renal injury in rat (Hashem *et al.*, 2008).
- Reduced TNF-α levels in a rabbit model of non-alcoholic steatohepatitis (Ramirez-Tortosa *et al.*, 2009).
- Decreased the levels of TNF-α in a rat model of subchronic inflammation (Nandal *et al.*, 2009).
- Exhibited anti-fibrosis activity by decreasing the levels of TNF-α and TGF-β1 in serum and lung tissue of SiO_2-induced fibrosis mice model (Jiang *et al.*, 2009).
- Prevented the injurious effects of DSS and ameliorated release of TNF-α and NO in a rat model (Arafa *et al.*, 2009).
- Decreased serum levels of IL-12 and TNF-α in mice infected with *Schistosoma mansoni cercariae* (Allam, 2009).
- Significantly attenuated oxidative stress and TNF-α levels in a mouse model of immunologically induced fatigue (Gupta *et al.*, 2009).
- Significantly decreased the blood levels of IL-6, MCP-1, TNF-α, glucose, HbA_1 and oxidative stress in streptozotocin-induced diabetic rat model (Jain *et al.*, 2009).
- Decreased LPS-induced TNF-α production in lungs of mice. At 5% concentration, curcumin significantly improved survival of mice and decreased radiation-induced lung fibrosis (Lee *et al.*, 2010).
- Exhibited protective effects against necrotizing enterocolitis in neonatal rats, possibly by inhibiting COX-2, reducing TNF-α and increasing IL-10 contents (Jia *et al.*, 2010).
- Significantly decreased the levels of TNF-α and IL-8 in the serum and prostate tissues in a rat model of prostatitis (Zhang *et al.*, 2010b).
- Significantly decreased the production of TNF-α in a mouse model of acute inflammation (Bansal and Chhibber, 2010).
- Protected mice from LPS/GalN-induced hepatic injury and inflammation by blocking TNF-α production (Yun *et al.*, 2010).
- Increased IFN-γ, IL-12 and IL-13 levels, but decreased TNF-α level in rats intoxicated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (Ciftci *et al.*, 2010).
- Lowered the production of IL-23p19, IFN-γ, TNF-α, IL-6 and MCP-1 in a murine model of hyperacute Th1-type ileitis (Bereswill *et al.*, 2010).
- Suppressed LPS stimulated TNF-α production in mice (Nishida *et al.*, 2010).
- Reduced the aluminum-induced inflammatory response as indicated by down-regulation of NF-κB and TNF-α in glial cells (Sood *et al.*, 2011).
- Improved the lipid metabolism and delayed the progression of hepatic fibrosis in rats with experimental steatohepatitis through suppression of TNF-α, NF-κB and HMG-CoA reductase (Zeng *et al.*, 2011).
- Inhibited mRNA expression of TNF-α in a murine model of asthma (Ammar el *et al.*, 2011).
- Suppressed inflammation by reducing levels of TNF-α, NF-κB and IL-6 in CCl_4-treated rats (Bassiouny *et al.*, 2011).
- Reduced cardiac inflammation through suppression of IL-1β, TNF-α, GATA-4 and NF-κB in a rat model of experimental autoimmune myocarditis (Mito *et al.*, 2011).
- Suppressed serum levels of TNF-α and IL-1β in a streptozotocin-induced diabetic mouse model (El-Azab *et al.*, 2011).
- Attenuated TNF-α levels and exhibited anti-hyperglycaemic effect and improved insulin sensitivity in high-fat diet-fed rats (El-Moselhy *et al.*, 2011).
- Prevented deterioration of the bone structure and produced beneficial effects in bone turnover in transgenic mice possibly through modulation of TNF-α and IL-6 (Yang *et al.*, 2011).
- Protected against ischaemia/reperfusion injury in rat skeletal muscle through inhibition of plasma TNF-α levels (Avci *et al.*, 2012).
- Inhibited the high glucose-induced plasma TNF-α production and macrophage infiltration and prevented renal injury in diabetic rats (Pan *et al.*, 2012).
- Attenuated concanavalin A-induced liver injury in mice by inhibition of TNF expression through TLR-2, TLR-4 and TLR-9 expression (Tu *et al.*, 2012).

CCl_4, carbon tetrachloride; DSS, dextran sulfate sodium; GalN, D-galactosamine; HbA1, haemoglobin α1; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; MCP-1, monocyte chemotactic protein-1; SiO_2, silicon dioxide.

down-regulate NF-κB-regulated gene products such as inducible NOS (iNOS), IL-1, IL-6, IL-8, MCP-1, MMP-2 and MMP-9 in animals (Yao *et al.*, 2004; Yeh *et al.*, 2005; Jain *et al.*, 2009). Curcumin also protects against the toxic effects of copper overload (Wan *et al.*, 2007), dextran sulfate sodium (Arafa *et al.*, 2009), *p*-dioxin (Ciftci *et al.*, 2010) and aluminum (Sood *et al.*, 2011) through down-modulation of TNF-α.

A reduction in the production of iNOS mRNA was observed when BALB/c mouse peritoneal macrophages cultured *ex vivo* were treated with 1–20 μM curcumin (Chan *et al.*, 1998); *in vivo*, two oral treatments of 0.5 mL of a 10 μM solution of curcumin (92 $ng \cdot g^{-1}$ bodyweight) reduced iNOS mRNA expression in the livers of LPS-injected mice by 50–70% (Chan *et al.*, 1998). This suggests that curcumin is potent at nmol g^{-1} bodyweight. This efficacy was associated with two modifications of the schedule of dosing: firstly, an aqueous solution of curcumin was prepared by initially dissolving the compound in 0.5 N NaOH and then diluting it immediately with PBS; secondly, mice were fed curcumin at dusk after fasting. Inhibition of iNOS mRNA expression was not observed in the mice that were fed *ad libitum*, suggesting that food intake may interfere with the absorption of curcumin.

Oral bioavailability and safety of curcumin

Curcumin usually manifests its biological response when given orally to mice at about 50–500 $mg \cdot kg^{-1}$ bodyweight (Farombi and Ekor, 2006). These doses, however, are too low to detect significant levels of curcumin in the serum. The reason for this discrepancy is not clear; however, there are several possible explanations. Firstly, curcumin is known to bind to numerous proteins present in the serum including albumin (Gupta *et al.*, 2011; Kim *et al.*, 2012). Secondly, curcumin is rapidly transported across the cells and tissues (Anand *et al.*, 2007). Thirdly, tetrahydrocurcumin, a metabolite of curcumin, was found to be more active than curcumin for treating chloroquine-induced hepatotoxicity in rats (Pari and Amali, 2005). Fourthly, in another study it was shown that when curcumin was dissolved in 0.1 N NaOH it manifested its effects in animals in the $\mu g \cdot kg^{-1}$ range (Chan *et al.*, 1998).

In one recent study the potential of a novel solid lipid curcumin particle (SLCP) preparation to produce adverse effects in rats after acute and sub-chronic administration was investigated (Dadhaniya *et al.*, 2011). The oral LD_{50} of the preparation in rats as well as in mice was found to be greater than 2000 $mg \cdot kg^{-1}$ bodyweight. In the sub-chronic toxicity study, 180, 360 and 720 $mg \cdot kg^{-1}$ bodyweight day^{-1} of SLCP preparation was administered via oral gavage to Wistar rats (10 per sex per group) for 90 days. Administration of the curcumin preparation did not result in any toxicologically significant treatment-related changes in clinical (including behavioural) observations, ophthalmic examinations, bodyweights, bodyweight gains, food consumption and organ weights. No adverse effects of the curcumin preparation were noted on the haematology, serum chemistry parameters and urinalysis. Terminal necropsy did not reveal any treatment-related gross or histopathology findings. On the basis of these study results, the no observed-adverse-effect level for this standardized novel curcumin preparation was determined as 720 $mg \cdot kg^{-1}$ bodyweight day^{-1}.

In humans, as little as 150 mg of curcumin has been shown to be effective in reducing serum levels of pro-inflammatory cytokines (Usharani *et al.*, 2008) (Table 3). The effect of curcumin administration, 500 mg of curcumin day^{-1} for 7 days, on serum levels of cholesterol and lipid peroxides was studied in 10 healthy human volunteers (Soni and Kuttan, 1992). A significant decrease in the level of serum lipid peroxides was noted, along with an increase in high-density lipoprotein cholesterol and a decrease in total serum cholesterol. In another study, curcumin was given orally at up to 8000 $mg \cdot day^{-1}$ to 25 patients (Cheng *et al.*, 2001). The serum concentration of curcumin usually peaked at 1–2 h after oral intake of curcumin and gradually declined within 12 h. The average peak serum concentrations after oral intake of 4000, 6000 and 8000 mg of curcumin were 0.51 ± 0.11, 0.63 ± 0.06 and 1.77 ± 1.87 μM respectively. , However, urinary excretion of curcumin was undetectable.

Vareed *et al.* (2008) examined the pharmacokinetics of a curcumin preparation in healthy human volunteers at 0.25–72 h after a single oral dose. Curcumin was administered at doses of 10 g (n = 6 subjects) and 12 g (n = 6 subjects). Using HPLC with a limit of detection of 50 $ng \cdot mL^{-1}$, only one subject had detectable free curcumin at any of the 14 time points assayed, but curcumin glucuronides and sulfates were detected in all subjects. Based on the pharmacokinetic model, the area under the curve for the 10 and 12 g doses was 35.33 ± 3.78 and 26.57 ± 2.97 $\mu g \cdot mL^{-1} \times h$, respectively, whereas C_{max} was 2.30 ± 0.26 and 1.73 ± 0.19 $\mu g \cdot mL^{-1}$. The T_{max} and $t_{1/2}$ were estimated to be 3.29 ± 0.43 and 6.77 ± 0.83 h. The ratio of glucuronide to sulfate was 1.92:1. The curcumin conjugates were present as either glucuronide or sulfate, not as mixed conjugates. The group concluded that curcumin is absorbed after oral dosing in humans and can be detected as glucuronide and sulfate conjugates in plasma. Another study evaluated the efficacy of oral curcumin (4 $g \cdot day^{-1}$) in 26 patients with monoclonal gammopathy of undefined significance (Golombick *et al.*, 2009). They found that oral curcumin was bioavailable as it decreased paraprotein load. Thus, all of these studies clearly demonstrate that although serum levels of curcumin administered orally are very low, it can still manifest its effect *in vivo*.

Table 3

Curcumin inhibits TNF production in humans

- Improved endothelial function and reduced levels of malondialdehyde, IL-6, TNF-α and endothelin-1 in diabetic patients (Usharani *et al.*, 2008).
- Had non-significant effects on the production of IL-8, IL-1β, TNF-α and COX-2 in gastric mucosa from *Helicobacter pylori*-infected gastritis patients (Koosirirat *et al.*, 2010).
- Improved bodyweight, reduced serum TNF-α and induced p53 expression in patients with colorectal cancer (He *et al.*, 2011).

Suppression of TNF-α by curcumin in patients

At least two studies have suggested that orally administered curcumin can down-modulate the expression of TNF-α in patients (Usharani *et al.*, 2008; He *et al.*, 2011) (Table 3). In addition, several other pro-inflammatory biomarkers are decreased by curcumin in human subjects (Hanai and Sugimoto, 2009; Khajehdehi *et al.*, 2011; Koosirirat *et al.*, 2010). In most of these studies, 150–500 mg of curcumin was sufficient to manifest a response.

The interest in curcumin research in human participants has increased markedly over the years (Table 4). To date, over 60 clinical trials have evaluated the safety and efficacy of this polyphenol in humans, whereas another 35 clinical trials are further evaluating its efficacy. Curcumin was found to be effective in TNF-associated human diseases such as cancer, cardiovascular diseases, metabolic diseases, neurological diseases, skin diseases, RA, CD and psoriasis. However, whether curcumin exerts its effects through modulation of TNF in these patients is, at present, unclear. Given the fact that most of the currently available TNF blockers produce adverse effects in patients and are very expensive, this orally bioavailable polyphenol represents an important therapeutic for TNF-associated diseases.

In addition to its efficacy in TNF-associated human diseases, curcumin has been found to be effective in a number of other human diseases. Readers interested in such studies should refer to one of the recent reviews published from this laboratory (Gupta *et al.*, 2013).

Role of curcumin in TNF-related diseases

Rheumatoid arthritis

Numerous reports have suggested that TNF plays a major role in RA. Thus, TNF blockers have been found to be beneficial for patients with RA. Therefore, curcumin has been tested as a treatment for RA. One of the earliest indications of its potential efficacy was obtained in 1973, when curcumin was found to suppress formaldehyde-induced arthritis in rats at a dose of 40 $mg \cdot kg^{-1}$ and inhibit granuloma formation at 80–160 $mg \cdot kg^{-1}$ (Srimal and Dhawan, 1973). Later, Joe *et al.* (1997) showed that curcumin can lower the elevated serum acidic glycoprotein levels present in adjuvant-induced arthritis. Also, oral administration of curcumin has been shown to prevent streptococcal cell wall–induced arthritis in mice (Funk *et al.*, 2006) and to suppress MMP-1 and MMP-3 production and attenuate the inflammatory response in a collagen-induced arthritis model in mice (Moon *et al.*, 2010). In addition, curcumin has been found to down-regulate the expression of TNF-α and IL-1β in ankle joints and decrease NF-κB activity, PGE_2 production, COX-2 expression and MMP secretion in synoviocytes. Furthermore, curcumin has been shown to have a synergistic effect with methotrexate in decreasing adjuvant-induced arthritis in mice and in minimizing liver damage (Banji *et al.*, 2011).

Other *in vitro* findings indicate that the protective effects of curcumin against RA are mediated through inhibition of neutrophil activation, suppression of synoviocyte proliferation and inhibition of angiogenesis as suggested by curcumin's ability to inhibit collagenase and stromelysin in chondrocytes (Jackson *et al.*, 2006). Further, the suppression of NF-κB by curcumin has been found to be associated with its inhibition of the expression of COX-2, NO, PGE_2, IL-1β, IL-6, IL-8, MMP-3 and MMP-9 in human chondrocytes (Shakibaei *et al.*, 2007; Mathy-Hartert *et al.*, 2009). Curcumin has also been found to suppress IL-8 expression in human synovial fibroblasts (Tong *et al.*, 2008).

One of the earliest studies demonstrating that curcumin has anti-rheumatic activity in humans appeared almost three decades ago (Deodhar *et al.*, 1980). In a more recent, the efficacy of a proprietary complex of curcumin with soy phosphatidylcholine (Meriva®; Throne Research Inc., Dover, ID, USA) was investigated in 50 patients with osteoarthritis (OA) at a dosage of 200 mg of curcumin day^{-1} (Belcaro *et al.*, 2010b). OA symptoms were evaluated by the use of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. After 3 months of treatment with this complex, the global WOMAC score was found to be decreased by 58% ($P < 0.05$), walking distance in the treadmill test was prolonged from 76 to 332 m ($P < 0.05$) and C-reactive protein levels decreased from 168 ± 18 to 11.3 ± 4.1 $mg \cdot L^{-1}$ in the subpopulation with high C-reactive protein levels. In comparison, the control group experienced only a modest improvement in these parameters. These results show that curcumin is clinically effective in the management and treatment of OA. In another study, the same investigator examined the efficacy and safety of Meriva in 100 patients with OA after long-term administration (8 months) (Belcaro *et al.*, 2010a). The clinical end points were WOMAC score, Karnofsky performance scale index score and treadmill walking performance, and were complemented by the evaluation of a series of inflammatory markers including IL-1β, IL-6, sCD40L, soluble vascular cell adhesion molecule-1 and erythrocyte sedimentation rate. Significant improvements in both the clinical and the biochemical end points were observed for the Meriva group compared with the control group.

In another randomized pilot study, the efficacy of curcumin alone and in combination with diclofenac sodium was assessed in patients with active RA (Chandran and Goel, 2012). Forty-five patients diagnosed as having RA were randomized into three groups: patients receiving curcumin alone (500 mg), those receiving diclofenac sodium alone (50 mg) and those receiving combinations of curcumin and diclofenac sodium. The primary end points were reduction in Disease Activity Score (DAS) 28. The secondary end points included American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores. Patients in the curcumin group showed the highest percentage of improvement in overall DAS and ACR scores, which were significantly better than those of patients in the diclofenac sodium group. To our knowledge, this is the first evidence showing the potential of curcumin as a therapeutic for patients with active RA.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) consists of two separate diseases, CD and ulcerative colitis (UC); both characterized by chronic recurrent ulceration of the bowel (Kozuch and

Table 4

Chronological listing of curcumin studies in human participants

Year	Disease	Reference
1937	Cholecystitis	Oppenheimer, 1937
1972	Diabetes	Srinivasan, 1972
1980	Rheumatoid arthritis	Deodhar *et al.*, 1980
1986	Post-operative inflammation	Satoskar *et al.*, 1986
1987	Cancer lesions	Kuttan *et al.*, 1987
1992	Lung cancer	Polasa *et al.*, 1992
1992	Atherosclerosis	Soni and Kuttan, 1992
1993	Gastric ulcer	Kositchaiwat *et al.*, 1993
1996	Acquired immunodeficiency syndrome	James, 1996
1997	Cancer lesions	Hastak *et al.*, 1997
1999	Biliary dyskinesia	Niederau and Gopfert, 1999
	Gallbladder contraction	Rasyid and Lelo, 1999
	Chronic anterior uveitis	Lal *et al.*, 1999
2000	Idiopathic orbital inflammatory pseudotumour	Lal *et al.*, 2000
	Psoriasis	Heng *et al.*, 2000
2001	Cancer lesions	Cheng *et al.*, 2001
	Colorectal cancer	Sharma *et al.*, 2001
	Peptic ulcer	Prucksunand *et al.*, 2001
2004	Colorectal cancer	Sharma *et al.*, 2004
	Irritable bowel syndrome	Bundy *et al.*, 2004
2005	Colorectal cancer	Garcea *et al.*, 2005
	Pancreatic cancer	Durgaprasad *et al.*, 2005
	Crohn's disease	Holt *et al.*, 2005
	Ulcerative proctitis	Holt *et al.*, 2005
	Alzheimer's disease	Ringman *et al.*, 2005
	Renal transplantation	Shoskes *et al.*, 2005
2006	Colorectal cancer	Cruz-Correa *et al.*, 2006
	Ulcerative colitis	Hanai *et al.*, 2006
2007	Cancer lesions	Chainani-Wu *et al.*, 2007
	Multiple myeloma	Vadhan-Raj *et al.*, 2007
	Helicobacter pylori infection	Di Mario *et al.*, 2007
2008	Pancreatic cancer	Dhillon *et al.*, 2008
	Psoriasis	Kurd *et al.*, 2008
	Alzheimer disease	Baum *et al.*, 2008
	Acute coronary syndrome	Alwi *et al.*, 2008
	Diabetes	Usharani *et al.*, 2008
	Hepatoprotection	Adhvaryu *et al.*, 2008
2009	Multiple myeloma	Golombick *et al.*, 2009
	Irritable bowel syndrome	Shimouchi *et al.*, 2009
	Dejerine–Sottas disease	Burns *et al.*, 2009
	Recurrent respiratory tract infections	Zuccotti *et al.*, 2009
	Chronic bacterial prostatitis	Cai *et al.*, 2009
2010	Cancer lesions	Rai *et al.*, 2010
	Pancreatic cancer	Epelbaum *et al.*, 2010
	Breast cancer	Bayet-Robert *et al.*, 2010
	Prostate cancer	Ide *et al.*, 2010
	Inflammatory bowel disease	Epstein *et al.*, 2010
	Recurrent anterior uveitis	Allegri *et al.*, 2010
	Helicobacter pylori infection	Koosirirat *et al.*, 2010
	Osteoarthritis	Belcaro *et al.*, 2010a; Belcaro *et al.*, 2010b
	Diabetes	Wickenberg *et al.*, 2010
	Vitiligo	Asawanonda and Klahan, 2010
	β-Thalassaemia	Kalpravidh *et al.*, 2010
	Chronic arsenic exposure	Biswas *et al.*, 2010
	Osteosarcoma	Gota *et al.*, 2010
2011	Colorectal cancer	Carroll *et al.*, 2011; He *et al.*, 2011
	Pancreatic cancer	Kanai *et al.*, 2011
	Head and neck cancer	Kim *et al.*, 2011
	Ulcerative colitis	Lahiff and Moss, 2011
	Diabetic nephropathy	Khajehdehi *et al.*, 2011
	Diabetic microangiopathy	Appendino *et al.*, 2011
	Alcohol intoxication	Sasaki *et al.*, 2011
2012	Rheumatoid arthritis	Chandran and Goel, 2012
	Diabetes	Chuengsamarn *et al.*, 2012
	Lupus nephritis	Khajehdehi *et al.*, 2012

Hanauer, 2008). It is likely that the pathogenesis of these diseases involves genetic, environmental and immunological factors (Hanauer, 1996). The expression of several cytokines, including TNF-α, IL-1β, IL-6, IL-8 and chemokines, all regulated by NF-κB, is increased in IBD (Ferretti *et al*., 1994; Jijon *et al*., 2000; Yamamoto *et al*., 2000; Jobin, 2008). All of these critical proteins are up-regulated by NF-κB and suppression of NF-κB by anti-sense can attenuate experimental colitis in mice (Neurath *et al*., 1996). Among the various gut immune factors, TNF-α is a major pro-inflammatory cytokine in IBD (Brown and Mayer, 2007; Louis, 2001). Mucosal levels of TNF-α are elevated in patients with IBD (Murch *et al*., 1991; Braegger *et al*., 1992), and its inhibition (Papadakis and Targan, 2000) or neutralization can improve both UC (Jarnerot, 1989) and CD (Ardizzone and Bianchi Porro, 2005). Conventional therapies for UC include sulfasalazine, 5-aminosalicylic acid, salazosulfapyridine, azathioprine, mercaptopurines, cyclosporine, corticosteroids and TNF blockers (Kozuch and Hanauer, 2008; Ng and Kamm, 2009). All of these treatments have significant toxic side effects and are partly or completely ineffective in a significant number of patients.

Now there are numerous lines of evidence to suggest that curcumin has enormous potential against both CD and UC (Table 5). Firstly, epidemiological studies indicate that turmeric (which contains 2–8% curcuminoids) may contribute to the lower incidence of cancer, especially large-bowel cancers in Indians (Mohandas and Desai, 1999; Sinha *et al*., 2003). Secondly, curcumin, when administered orally in the diet, prevented trinitrobenzene sulfonic acid (TNBS)- or dinitrobenzene sulfonic acid (DNBS)-induced colitis in mice (Sugimoto *et al*., 2002; Salh *et al*., 2003; Venkataranganna *et al*., 2007; Ung *et al*., 2010). Thirdly, curcumin improves both the wasting and histopathological signs of colonic inflammation. Fourthly, curcumin inhibits $CD4^+$ T-cell infiltration and NF-κB activation in colonic mucosa. Fifthly, curcumin manifests its effects against colitis by suppressing the expression of inflammatory cytokines such as TNF-α (Camacho-Barquero *et al*., 2007; Mouzaoui *et al*., 2012), IFN-γ (Ung *et al*., 2010), IL-17 (Ung *et al*., 2010) and enzymes, such as p38 MAPK, iNOS, COX-2, myeloperoxidase and MMP-9, in the colonic mucosa (Camacho-Barquero *et al*., 2007). Sixthly, curcumin has a therapeutic effect on DNBS-induced colitis in mice induced by its agonistic action on the vanilloid receptor TRPV1 (Martelli *et al*., 2007). Seventhly, curcumin suppresses colonic inflammation induced by deletion of the *mdr1* gene in mice (Nones *et al*., 2009). The effects of curcumin in TNBS-induced colitis in mice were found to be strain-dependent: BALB/c mice were protected, whereas SJL/J mice were not protected (Billerey-Larmonier *et al*., 2008). The effect of curcumin against colitis was also limited in Th1-driven colitis in IL-10-deficient mice (Larmonier *et al*., 2008; Ung *et al*., 2010). Curcumin failed to inhibit NF-κB in these mice, but when combined with IL-10, curcumin inhibited NF-κB quite effectively. Eighthly, curcumin decreases TNF-α-induced oxidative stress and colitis in mice (Mouzaoui *et al*., 2012). Ninthly, curcumin combined with resveratrol and simvastatin decreases acute small intestinal inflammation in mice by down-regulating the Th1-type immune response (Bereswill *et al*., 2010). Tenthly, curcumin suppresses TNBS-induced colonic inflammation in mice by down-regulation of NF-κB, TLR4 and MyD88 (Lubbad *et al*., 2009a). Eleventhly, curcumin has been shown to inhibit colitis by inducing the production of tolerogenic dendritic cells that promote differentiation of T-cells into Treg, which include $CD4^+CD25^+Foxp3^+$Treg and IL-10-producing Tr1 cells, and by producing TGF-β (Cong *et al*., 2009). Twelfthly, curcumin can reverse TNF-α-mediated reduction in Phex protein in mice, which is responsible for the inhibition of osteoblast mineralization linked to the abnormal bone metabolism associated with IBD (Uno *et al*., 2006). For this, the authors examined calvaria of 6- to 7-week-old mice given TNBS with or without neutralizing TNF-α antibody, dietary curcumin or systemically with recombinant TNF-α. They found that compared to control animals, *Phex* mRNA expression decreased by 40–50% in both TNBS colitis and TNF-α-injected mice. Dietary curcumin and TNF-α antibody counteracted these detrimental effects of TNBS on *Phex* gene expression.

Thus, the above findings in animals clearly indicate that orally administered curcumin has the potential to protect from the development of IBD. Additional evidence suggests its potential in humans. Firstly, as little as 150 mg of curcumin twice daily can suppress the levels of expression of inflammatory cytokines TNF-α and IL-6 in serum (Usharani *et al*., 2008; He *et al*., 2011). Secondly, a dose of 2 $g{\cdot}day^{-1}$ of curcumin can suppress NF-κB activation in human peripheral blood mononuclear cells (Vadhan-Raj *et al*., 2007). Thirdly, curcumin was found to suppress p38 MAPK, reduce IL-1β and MMP-3, and enhance IL-10 in mucosa of children and adults with IBD (Epstein *et al*., 2010). Fourthly, more than 65 different trials have been conducted with orally administered curcumin in humans. Fifthly, promising results were obtained from a small open-label study examining the use of curcumin to treat IBD (Holt *et al*., 2005). A pure curcumin preparation was administered to five patients with ulcerative proctitis and to five patients with CD. All patients with proctitis improved, and four had their concomitant medications reduced; four of the five CD patients had lowered CDAI scores and sedimentation rates. Sixthly, in a randomized multicentre double-blind, placebo-controlled trial, curcumin was examined as a maintenance therapy for UC and found to produce favourable effects (Hanai *et al*., 2006). Of 89 patients with UC, 45 received 1 g of curcumin after breakfast and 1 g after their evening meal, plus sulfasalazine and mesalamine for 6 months. Of the 43 patients who received curcumin, 2 (4.65%) experienced relapse during the 6 months of therapy, whereas 8 (20.51%) of the 39 patients in the placebo group experienced relapse. Recurrence rates in the curcumin-treated and placebo groups were significantly different. Furthermore, curcumin use resulted in an improvement in both the clinical activity index and the endoscopic index and suppressed UC-associated morbidity. Thus, curcumin appears to be a promising and safe medication for maintaining remission in patients with quiescent UC. These two small studies have shown promising results for IBD. Seventhly, orally administered curcumin was found to have a therapeutic effect against colorectal cancer (He *et al*., 2011). In an open-label study in which 126 patients were treated with 360 mg, p.o., curcumin three times a day, curcumin's effects were noted within 10–30 days.

Table 5

Effect of curcumin on models of inflammatory bowel disease

- Prevented TNBS-induced colitis in mice; inhibited CD4+ T-cell infiltration and NF-κB activation, and expression of TNF-α, IFN-γ, IL-6 and IL-12 in colonic mucosa (Sugimoto *et al.*, 2002).
- Inhibited DNB-induced colitis in mice, prevented tissue damage, reduced MPO and IL-1β expression and inhibited NF-κB activation in the mucosal tissue (Salh *et al.*, 2003).
- Inhibited mucosal injury in TNBS-induced colitis in mice, reduced NO and ROS levels, inhibited neutrophil infiltration and inactivated NF-κB in colonic mucosa (Ukil *et al.*, 2003).
- Inhibited TNBS-induced colitis in rats, inhibited IL-1 expression, increased IL-10 expression in colonic mucosa and decreased NF-κB activation (Jian *et al.*, 2004).
- Attenuated TNBS-induced chronic colitis through inhibition of MPO and COX-2 in rats and improved survival (Jiang *et al.*, 2006).
- Prevented TNBS-induced chronic colitis, decreased Th1 (IL-12, IFN-γ/TNF-α, IL-1) and increased Th2 (IL-4 and IL-10) cytokines in colon mucosa; and increased IL-4 and IFN-γ in splenocytes and circulation (Zhang *et al.*, 2006).
- Reversed TNF-α-mediated reduction in Phex protein responsible for the inhibition of osteoblast mineralization linked abnormal bone metabolism in IBD (Uno *et al.*, 2006).
- Prevented the development of DSS-induced experimental colitis in BALB/c mice through inhibition of MPO and NF-κB (Deguchi *et al.*, 2007).
- Protected against DNCB-induced colitis through down-regulation of MPO, ALP, LPO, NF-κB and iNOS (Venkataranganna *et al.*, 2007).
- Prevented DNBS-induced colitis in mice by interaction with vanilloid receptor TRPV1 (Martelli *et al.*, 2007).
- Attenuated the TNBS-induced colitis in rats through inhibition of MPO, TNF-α, COX-2, iNOS, p38 MAPK in colonic mucosa (Camacho-Barquero *et al.*, 2007).
- Attenuated the TNBS-induced colitis in rats through inhibition of down-regulation of hepatic CYP3A2 (Masubuchi *et al.*, 2008).
- Inhibited the TNBS-induced colitis and splenocyte proliferation in BALB/c mice but not in NKT-deficient SJL/J mice (Billerey-Larmonier *et al.*, 2008).
- Exhibited protective effect on Th1-driven colitis in IL-10 deficient mice, with no effect on NF-κB (Larmonier *et al.*, 2008).
- Attenuated the TNBS-induced colitis in rats through reversal of carbachol-induced contraction of the colon and modulating NF-κB activation (Lubbad *et al.*, 2009b).
- Attenuated the TNBS-induced colitis in rats through suppression of expression in TLR-4, MyD88 and NF-κB proteins in inflamed tissue (Lubbad *et al.*, 2009a).
- Prevented the DSS-induced colitis in mice through suppression of serum TNF-α levels, NO and colonic MPO expression (Arafa *et al.*, 2009).
- Protected from IBD in mdr1a-KO mice through inhibition of TNF-α, IFN-γ, chemokine, p38, TLR2, CD14 and up-regulation of xenobiotic metabolism (Nones *et al.*, 2009).
- Protected from IBD by inducing the tolerogenic dendritic cell that promotes differentiation of intestine-protective regulatory T-cells *in vivo* (Cong *et al.*, 2009).
- Inhibited pro-inflammatory cytokine release in the IL-10-deficient mouse model of IBD (Ung *et al.*, 2010).
- Ameliorated small intestinal inflammation by down-regulating Th1 cell-associated cytokines (IFN-γ, TNF-α, IL-6, MCP-1) (Bereswill *et al.*, 2010).
- Protected intestinal mucosal barrier function of rat enteritis via activation of MKP-1 and attenuation of p38 and NF-κB activation (Song *et al.*, 2010).
- Inhibited DSS-induced colitis in mice via inhibition of beta catenin translocation, and down-regulation of TNF-α and IFN-γ levels (Villegas *et al.*, 2011).
- Attenuated TNF-α-induced oxidative stress, acute colitis and hepatotoxicity in mice (Mouzaoui *et al.*, 2012).
- Suppressed p38, reduced IL-1β and MMP-3, and enhanced IL-10 in mucosa of children and adults with IBD (Epstein *et al.*, 2010).

ALP, alkaline phosphatase; DNBS, dinitrobenzene sulfonic acid; DNCB, 2,4-dinitrochlorobenzene; DSS, dextran sulfate sodium; IBD, inflammatory bowel disease; LPO, lipid peroxidation; MCP-1, monocyte chemotactic protein-1; MKP-1, mitogen-activated protein kinase phosphatase-1; MPO, myeloperoxidase; MyD88, myeloid differentiation primary response gene 88; NKT, natural killer T-cells; Phex, phosphate regulating gene with homologies to endopeptidases on the X chromosome; Th, T helper cell type; TLR, toll-like receptor; TNBS, trinitrobenzene sulfonic acid.

Psoriasis

Like IBD and RA, psoriasis is a common chronic inflammatory disease of the skin and joints that affects about 2% of the general population is another indication for which TNF blockers have been approved. Depending on the stage of disease, current treatment options include UVB, UVA plus psoralen, methotrexate, acitretin, cyclosporine, infliximab, etanercept, adalimumab, efalizumab and alefacept. Whereas infliximab, etanercept and adalimumab are specific TNF blockers, all of the others are immunosuppressive agents that could increase the risk of infections and malignancies, especially with long-term use (Greaves and Weinstein, 1995; Kurd *et al.*, 2007). Psoriasis is a chronic disease, which requires long-term treatment and 51% of patients with psoriasis use complementary and alternative therapies (Fleischer *et al.*, 1996). Thus, safe, affordable and effective agents are needed to treat this condition.

There are several reasons to believe that curcumin may have potential for treating psoriasis. Firstly, on irradiation with visible light, curcumin has been proven to be phototoxic for *Salmonella typhimurium* and *Escherichia coli*, even at very low concentrations (Tonnesen *et al.*, 1987). This observed phototoxicity makes curcumin a potential photosensitizing drug, which could be used in phototherapy of psoriasis. Secondly, when curcumin was tested as an anti-psoriatic drug in the modified mouse tail test, an animal model of psoriasis, it exhibited some activity (Bosman, 1994). Thirdly, curcumin has been shown to inhibit the proliferation of human keratinocytes through suppression of pro-inflammatory pathways (Pol *et al.*, 2003; Cho *et al.*, 2007). Curcumin inhibited the expression of TNF-α-induced IL-1β, IL-6, TNF-α, cyclin E, MAPKs (JNK, p38 MAPK and ERK) and NF-κB in HaCaT cells. Because curcumin can reverse the anti-apoptotic function of TNF-α in skin cells, it may have potential for the treatment of psoriasis (Sun *et al.*, 2012). Fourthly, as TNF blockers have been successfully used to treat psoriasis and since curcumin can block both the production and the action of TNF, curcumin may have potential as a treatment of psoriasis. Fifthly, our laboratory has shown that curcumin is a potent inhibitor of phosphorylase kinase (PhK) activity (Reddy and Lokesh, 1996), the elevation in which has been correlated with psoriatic activity (Heng *et al.*, 2000).

Heng *et al.* (2000) investigated whether the anti-psoriatic activity of curcumin in patients is due to suppression of PhK activity. In this study, PhK activity was assayed in four groups of 10 subjects each: (i) active untreated psoriasis; (ii) resolving psoriasis treated by calcipotriol, a vitamin D3 analogue and indirect inhibitor of PhK; (iii) curcumin treatment (1% in gel); and (iv) 10 normal non-psoriatic subjects. PhK activity, from highest to lowest, was as follows: the active untreated psoriasis group, the calcipotriol-treated group, the curcumin-treated group and the non-psoriatic subjects. The decrease in PhK activity in the curcumin-treated and calcipotriol-treated psoriasis groups was associated with a decrease in the expression of the keratinocyte transferrin receptor, a reduced severity of parakeratosis and a reduction in the density of epidermal $CD8^+$ T-cells. The authors of this study concluded that drug-induced suppression of PhK activity is associated with resolution of psoriatic activity and that the anti-psoriatic activity of curcumin may be achieved through its modulation of PhK.

The safety and efficacy of oral curcumin in patients with moderate to severe psoriasis has been investigated in a prospective phase II, open-label, Simon's two-stage clinical trial (Kurd *et al.*, 2008). Twelve patients with chronic plaque psoriasis were enrolled in this study and were given a 4.5 g curcumin capsule per day for 12 weeks; this was followed by a 4 week observation period. Curcumin was well tolerated and all participants completed the study. However, the response rate was low and possibly caused by a placebo effect or the natural history of psoriasis. Nevertheless, two patients who responded to the treatment showed 83–88% improvement at 12 weeks of treatment. There were no study-related adverse events that necessitated participant withdrawal. Small sample size and the lack of a control (placebo) group were the limitations of the study.

Refractory asthma

Patients' asthma is considered refractory when they experience persistent symptoms, frequent asthma attacks and/or low lung function despite taking asthma medications. Some patients with refractory asthma have to take oral steroids such as prednisone to manage their symptoms. TNF-α has been shown to have a pathobiological role in asthma, mainly in severe refractory asthma and in chronic obstructive pulmonary disease (COPD) (Matera *et al.*, 2010). Thus, TNF-α inhibitors (infliximab, golimumab and etanercept) are now regarded as potential new medications in asthma and COPD management.

Numerous rodent studies suggest that curcumin may also have potential for treatment of asthma. Firstly, curcumin (at 20 mg·kg^{-1} bodyweight) was reported to attenuate allergen-induced airway hyper-responsiveness in sensitized guinea pigs (Ram *et al.*, 2003). When administered to mice, it was found to prevent ovalbumin-induced airway inflammation by regulating NO (Moon *et al.*, 2008) and, in a more recent study, to diminish the development of allergic airway inflammation and hyper-responsiveness, possibly through inhibition of NF-κB activation in asthmatic lung tissue (Oh *et al.*, 2011). For these studies, BALB/c mice were sensitized to ovalbumin, allowing analysis of the effects of curcumin administration (200 mg·kg^{-1} bodyweight per day, i.p.) on airway hyper-responsiveness, inflammatory cell number and IgE levels in bronchoalveolar lavage fluid. Ammar el *et al.* (2011) also examined the anti-inflammatory activity of curcumin in a murine model of asthma and showed it down-modulated the serum levels of IgE, iNOS, transforming growth factor β1 and mRNA expression of TNF-α. Secondly, curcumin has been shown to have therapeutic potential for controlling allergic responses. Animals exposed to latex showed enhanced serum IgE; latex-specific IgG1, IL-4, IL-5 and IL-13; eosinophils; and inflammation in the lungs (Kurup *et al.*, 2007). Intragastric treatment of latex-sensitized mice with curcumin demonstrated a diminished Th2 response with a concurrent reduction in lung inflammation. Eosinophilia in the curcumin-treated mice was markedly reduced, as was the expression of the co-stimulatory molecules (CD80, CD86 and OX40L) on antigen-presenting cells, and expression of MMP-9, ornithine amino transferase and thymic stromal lymphopoietin genes was also attenuated. Thirdly, curcumin was found to reverse corticosteroid resistance in monocytes exposed to oxidants by maintaining histone deacetylase-2 activity (Meja *et al.*, 2008). Although no clinical data are available yet, all of these pre-clinical studies suggest that curcumin has potential as a therapeutic for asthma.

Conclusions

Overall, all these studies suggest that curcumin can suppress pro-inflammatory pathways linked with most chronic diseases. It can block both the production and the action of TNF. Curcumin also binds to TNF directly. Evidence for curcumin as a TNF blocker has been obtained in both *in vitro* and *in vivo* studies. However, only a few studies have demonstrated that curcumin is effective at inhibiting TNF production in humans. Unlike most other TNF blockers, curcumin can be given orally. In addition, it is quite safe and affordable. However, more studies are needed in humans to prove that curcumin has the ability to be an effective treatment of various pro-inflammatory conditions.

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Conflict of interest

The authors declare no conflicts of interest.

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