

# Curcumin and Inflammatory Bowel Disease: Biological Mechanisms and Clinical Implication

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## Key Words

Curcumin · Turmeric · Inflammatory bowel disease · Herbal therapy

## Abstract

Increased recognition of the limits of conventional medicine has helped drive the growing interest in complementary and alternative medicine which is now being commonly used in patients with chronic diseases, including individuals with Crohn's disease and ulcerative colitis. Recently, scientific interest has unraveled the beneficial pharmacological effects of curcumin. We present an updated concise review of currently available in vitro, animal and clinical studies demonstrating the therapeutic effect of herbal medication in inflammatory bowel disease.

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## Introduction

Inflammatory bowel disease (IBD), which most commonly includes Crohn's disease (CD) and ulcerative colitis (UC), is believed to be due to the dysregulation of host immune responses leading to chronic intestinal inflammation in genetically susceptible populations. Therapeutic options for the management of IBD include amino-

salicylates, antibiotics, corticosteroids, antimetabolite immunomodulators (e.g., 6-mercaptopurine, azathioprine and methotrexate), and biologic therapies such as anti-tumor necrosis factor (anti-TNF) agents (e.g., infliximab, adalimumab, certolizumab pegol) and natalizumab [1–3]. However, clinical efficacy is limited because of the lower rate of sustained remission and the increased risks of serious infections and malignancies with certain agents such as anti-TNF agents [4–6]. Increased recognition of the limits of conventional medicine has helped drive the growing interest in complementary and alternative medicine (CAM) which is now being commonly used by the general public and patients with chronic diseases [7], including individuals with CD and UC [8].

The use of curcumin, a yellow pigment widely used as a coloring agent and spice in many foods, predates ancient times and remains a vital ingredient in Ayurvedic and Chinese medicine. Recently, scientific interest has unraveled its beneficial pharmacological effects; they include antioxidant, anti-inflammatory, anticarcinogenic [9–11], hypocholesterolemic [12], antibacterial [13], wound-healing, antispasmodic, anticoagulant, antitumor [14] and hepatoprotective [15] activities. However, clinical applications in certain inflammatory diseases including IBD remain largely limited to case studies and small clinical trials.

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## Methods

Literature searches were conducted in PubMed, Ovid, EM-BASE and Cochrane Library databases in accordance with published recommendations [16–18]. Databases were used to search English language literature using the search terms curcumin, turmeric, inflammatory bowel disease, Crohn's disease, and ulcerative colitis. Both human and animal studies were reviewed and data from these studies were either included or interpreted in the current review.

## Curcumin and Immune Function

Many studies have suggested beneficial effects of curcumin in vitro and in rodent models of chemically induced colitis [15, 19–31] (table 1). Curcumin significantly improves survival and colonic morphology, dampens local cytokine and chemokine production and reduces mucosal neutrophil infiltration. Curcumin modulates inflammation by downregulating genes involved in oxidative stress and fibrogenesis pathways. In the first study using genome-wide expression, *mdr1a*<sup>-/-</sup> mice fed a diet containing curcumin had lower colonic histologic injury scores than those fed a control diet [26]. The authors suggested that the favorable effect of curcumin on colonic inflammation likely resulted from upregulation of xenobiotic metabolism and a downregulation of proinflammatory pathways.

The anti-inflammatory properties of curcumin is attributed to its interference with the arachidonic acid cascade [32] and blocking nuclear factor (NF)- $\kappa$ B activity which is implicated in the regulation of proinflammatory enzymes, including cyclooxygenase 2, 5-lipoxygenase and inducible nitric oxide synthase. The inhibition of NF- $\kappa$ B is of particular importance and is considered a putative target for intervention in IBD [12, 33], since the induction of NF- $\kappa$ B by various signaling pathways is pivotal in the pathogenesis of IBD. One pathway through which NF- $\kappa$ B is induced in IBD is through the activation of Toll-like receptor 4 isoform [34]. Levels of Toll-like receptor 4 and NF- $\kappa$ B proteins in inflamed tissue are suppressed significantly by curcumin treatment in experimental colitis [25]. Although inhibition of downstream molecules such as cytokines, growth factors, interleukins and nitric oxide regulated by NF- $\kappa$ B has been extensively studied, identification of upstream signaling molecules remains poorly understood.

Studies have demonstrated that curcumin can modulate both the proliferation and the activation of T cells. Curcumin inhibits the proliferation induced by concana-

valin A, phytohemagglutinin (PHA) and phorbol-12-myristate-13-acetate (PMA) of lymphocytes derived from fresh human spleen [35]. In addition, curcumin suppresses IL-2 synthesis and IL-2-induced proliferation of lymphocytes, suggesting that it exhibits immunosuppressive properties. In another study by the same authors, curcumin inhibits the proliferation induced by PMA and anti-CD28 antibody as well as the proliferation induced by PHA of T lymphocytes isolated from healthy donors [36]. In comparison, cyclosporine A suppresses PHA-induced T-cell proliferation but not that induced by PMA and anti-CD28 antibody. Thus, curcumin can overcome the resistance of PMA and CD28 pathway to cyclosporine A, highlighting its immunomodulating properties.

In addition to modulating T-cell activity, curcumin influences the proliferation of B cells and B-lymphocyte-mediated immune function. Of note, curcumin blocks Epstein-Barr virus-induced immortalization of human B cells [37]. Apart from affecting normal cells, curcumin can induce apoptosis to reduce the proliferation of immature B-cell lymphoma (BKS-2) cells by downregulating *egr-1*, *c-myc*, *bcl-XL*, the tumor suppressor gene *p53*, and by partial inhibition of NF- $\kappa$ B activity [33].

Furthermore, studies have shown that curcumin can modulate the activation of macrophages, dependent on its ability to downregulate Th1 and nitric oxide production [38]. Curcumin enhances the phagocytosis of peritoneal macrophages and differentially regulates the proliferation of splenocytes [39]. In addition, Joe and Lokesh [40] demonstrated that a daily diet of curcumin (30 mg/kg body weight/day) for 2 weeks in rats attenuates the ability of macrophages to generate reactive oxygen species and decreases the secretion of the lysosomal enzymes collagenase, elastase and hyaluronidase [41].

Neutrophils are important proinflammatory effector cells capable of associating with lymphocytes to foster epithelial dysfunction and injury associated with IBD. Impaired neutrophil recruitment has been implicated in the development of CD wherein neutrophil accumulation and associated bacterial clearance are impaired and favor the formation of granulomatous inflammation [42]. In a recent study, curcumin modulates neutrophil motility by inhibiting the expression and production of chemoattractant molecules, macrophage inflammatory protein 2, keratinocyte chemoattractant, macrophage inflammatory protein 1 $\alpha$  and IL-1 $\beta$  by peritoneal macrophages and colonic epithelial cells. Moreover, in addition to altering the chemoattractant gradient formation, curcumin directly affects neutrophil chemotaxis [23].

**Table 1.** Animal and in vitro studies on curcumin

Author/year	Animal model/qualification	Dose of curcumin	Duration	Markers studied	Findings
Sugimoto et al. [28], 2002, Japan	C57BL/6 and BALB/c mice, TNBS colitis	diet with 0.5, 2.0 and 5.0% (wt/wt)	7 days	CD4(+) T-cell infiltration and NF-κB	CD4+ T-cell infiltration and NF-κB activation suppressed
Ukil et al. [29], 2003, India	BALB/c mice, TNBS colitis	50, 100 and 300 mg/kg diet	10 days before treatment and 8 days after induction	MPO activity, protease activity, IFN-γ, IL-12, iNOS mRNA expression, NF-κB	significant reduction in inflammatory markers in the treatment group
Salh et al. [27], 2003, Canada	C3H mice, DNBS colitis	0.25% diet	5 days before treatment and 5 days after induction	MPO activity, IL-1β activity, NF-κB, p38 MAPK activity	reduced weight loss, histological severity and reduction in inflammatory markers
Jian et al. [56], 2005, China	SPF Wistar rats, TNBS colitis	2.0% diet	14 days	NF-κB, IκB, IL-1 and IL-10	improved histological score, suppression of NF-κB, blockage of IκB degradation, suppression of IL-1 and increase IL-10 expression
Jiang et al. [22], 2006, China	Sprague-Dawley rats, TNBS colitis	30 and 60 mg/kg day, intraperitoneal injection	14 days	MPO activity, COX-2, PGE <sub>2</sub> , IFN-γ, TNF-α and iNOS mRNA	reduced MPO activity, decreased COX-2, IFN-γ and TNF-α expression, and increased PGE <sub>2</sub> expression
Zhang et al. [31], 2006, China	Sprague-Dawley rats, TNBS colitis	30 mg/kg/day, intraperitoneal injection	15 days	MPO, mRNA, IFN-γ, IL-4	reduced MPO activity, suppression of Th1 cytokine activity, increase in Th2 activity, decreased production of IFN-γ and increased IL-4
Venkataramanna et al. [30], 2007, India	Wistar male rats, DNCB colitis	25, 50 and 100 mg/kg diet	10 days	MPO, LPO, ALP, NF-κB, iNOS	decrease in MPO, LPO, ALP activity, inhibition of iNOS and NF-κB
Camacho-Barquero et al. [20], 2007, Spain	TNBS colitis	50–100 mg/kg diet	14 days	MPO, COX-2, TNF-α, iNOS, p38 MAPK, JNK	reduced inflammatory markers, reduction in MAPK; reduced MAPK may lead to reduced COX-2 and iNOS immunosignals; no changes in JNK
Martelli et al. [57], 2007, Italy	BALB/c mice DNBS colitis	45 mg/kg diet; a separate group received capsazepine 30 mg/kg intraperitoneally, 30 min before each curcumin administration	7 days	MPO, TRPV1	reduced MPO; capsazepine (TRPV1 antagonist) abolished curcumin-mediated protective effects
Deguchi et al. [21], 2007, Japan	BALB/c mice DSS colitis	2.0% wt/wt diet	14 days	NF-κB, CD4 and CD8 cells	suppression of NF-κB and inhibitory effect on CD4 and CD8 cells
Billerey-Larmonier et al. [19], 2008, USA	BALB/c and SJL/J mice, TNBS colitis	2.0% wt/wt diet	9 days	TNF-α, IL-4 and IL-5	improves colonic histology in BALB/c but not in SJL/J mice; TNF-α, IL-4 and IL-5 reduced in BALB/c only
Larmonier et al. [24], 2008, USA	specific pathogen-free wild-type 129/SvEv mice and germ-free IL-10 <sup>-/-</sup> mice	diet with 0.1, 0.5 and 1% wt/wt	14 days	IFN-γ, NF-κB IL-12/23p40, IL-10	reduced IFN-γ and IL-12/23p40; curcumin and IL-10 act synergistically to inhibit NF-κB

**Table 1** (continued)

Author/year	Animal model/qualification	Dose of curcumin	Duration	Markers studied	Findings
Nones et al. [26], 2009, New Zealand	mdr1a <sup>-/-</sup> mice	0.2% curcumin diet	16–19 weeks	serum amyloid A, whole-genome microarrays	effect on colon inflammation via an upregulation of xenobiotic metabolism and downregulation of proinflammatory pathways
Lubbad et al. [25], 2009, Kuwait	Sprague-Dawley rats, TNBS colitis	oral 100 mg/kg	5 days	MPO, NF-κB TLR-4 protein expression	levels of TLR-4 and NF-κB proteins in inflamed tissue were suppressed
Larmonier et al. [23], 2010, USA	BALB/c mice, intra-peritoneal macrophage collection	100 µg/g	N/A	MIP, IL-1, KC	curcumin attenuated LPS-stimulated (MIP)-2, IL-1, KC, and MIP-1a in colonic epithelial cells and in macrophages
Midura-Kiela et al. [43], 2011, USA	T-84 cells and young adult mouse colonocyte cells	curcumin, 98.05% pure and free of contaminating curcuminoids	N/A	IFN-γ	curcumin inhibited IFN-γ-induced gene transcription, including CII-TA, MHC-II genes (HLA-DRα, HLA-DPα1, HLA-DRβ1), and T-cell chemokines (CXCL9, CXCL10 and CXCL11)

TNBS = Trinitrobenzene sulfonic acid; MPO = myeloperoxidase; IFN = interferon; iNOS = inducible nitric oxide synthase; DNBS = dinitrobenzene sulfonic acid; MAPK = mitogen-activated protein kinase; IκB = inhibitory κB; COX-2 = cyclooxygenase 2; PGE<sub>2</sub> = prostaglandin E<sub>2</sub>; DNCB = dinitrochlorobenzene; LPO = lipid peroxidase activity; ALP = alkaline phosphatase activity; JNK = c-Jun N-terminal kinase; TRPV1 = transient potential vanilloid receptor 1; DSS = dextran sulfate sodium; TLR = Toll-like receptor; MIP = macrophage inflammatory protein; KC = keratinocyte chemoattractant; LPS = lipopolysaccharide.

**Table 2.** Effects on cytokines by curcumin

Increased activity	Decreased activity
PGE <sub>2</sub> [22]	NF-κB [21, 22, 24, 30, 56]
IL-4 [31]	IFN-γ [22, 24, 31, 43]
IL-10 [56]	MAPK [20, 27]
	IL-1 [56], IL-4 [19], IL-5 [19] IL-12 [24, 29]
	TNF-α [19, 20, 22]
	MPO [20, 30, 31, 57]
	LPO [30]
	iNOS [20, 30]
	COX-2 [20, 22]
	TLR-4 [25]

PGE<sub>2</sub> = Prostaglandin E<sub>2</sub>; IFN-γ = interferon-γ; MAPK = mitogen-activated protein kinase; MPO = myeloperoxidase; LPO = lipid peroxidase activity; iNOS = inducible nitric oxide synthase; COX-2 = cyclooxygenase 2; TLR-4 = Toll-like receptor 4.

The intestinal epithelium, an essential component of the gut innate defense mechanisms, is profoundly affected by interferon-γ, which can disrupt the epithelial barrier function, prevent epithelial cell migration and wound healing, as well as prime epithelial cells to express major histocompatibility complex class II molecules and to serve as nonprofessional antigen-presenting cells [43]. Recently, curcumin has also been shown to act as an interferon-γ-signaling inhibitor in colonocytes [43].

The effects of curcumin on various cytokines are summarized in table 2.

### Human Studies with Curcumin

Curcumin has been used for centuries in Asia for many inflammatory disorders, infections and digestive diseases [44]. More recently, its use as a therapeutic agent has been suggested for atherosclerosis, hyperlipidemia, thromboembolism, myocardial infarction, rheumatoid arthritis, HIV and cancers [45]. A few single-arm phase I studies have shown beneficial effects of curcumin in various malignancies. Curcumin is well tolerated without any serious toxicity and side effects. Several clinical studies have confirmed the safety of curcumin in humans with no treatment-related toxicity up to 8,000 mg/day for 3 months [45, 46]. Minor gastrointestinal adverse events, including nausea and diarrhea, have been reported [47, 48].

The therapeutic effect of curcumin against a variety of chronic pathological conditions is likely driven by its an-

**Table 3.** Clinical studies on curcumin

Author/ year	Type of study/ patients	Disease	Dose of curcumin	Duration	Markers studied	Findings
Holt et al. [52], 2005	cohort/10	UC (proctitis-proctosigmoiditis) and CD	550 mg BID followed by 550 mg TID for UC and 360 mg TID followed by 360 mg QID for CD	2 months for UC 3 months for CD	global scale (UC) CDAI ESR (CD)	improved global scale ( $p < 0.02$ ; UC) 55-point decrease in CDAI and 10-mm/h drop in ESR (CD)
Hanai et al. [53], 2006	double-blind, placebo control/89	UC	1 g PO BID	6 months	CAI and EI	improved CAI ( $p < 0.038$ ) and EI ( $p < 0.0001$ )

BID = Two times a day; TID = three times a day; QID = four times a day; CDAI = Crohn's Disease Activity Index; ESR = erythrocyte sedimentation rate; PO = postoperatively; CAI = clinical activity index; EI = endoscopic index.

tioxidant and anti-inflammatory effect. The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit enzymes that mediate inflammatory processes, such as cyclooxygenase 2 and lipoxygenase [49], as well as inducible nitric oxide synthase [50]. Therefore, the potent anti-inflammatory property of curcumin is anticipated to exert chemopreventive effects on carcinogenesis given a complex inter-relationship between inflammation and tumorigenesis [51]. The oral application of curcumin for a variety of inflammatory diseases has been reported in several human studies. Because curcumin plays a key role in the inhibition of proinflammatory cytokines, it could be used as a novel therapeutic agent in several inflammatory diseases, such as IBD. However, to date, there have only been two human studies with curcumin and IBD that have achieved encouraging results (table 3).

In a pilot study, Holt et al. [52] reported its use in ulcerative proctosigmoiditis and CD. Five patients with ulcerative proctitis were treated with 550 mg curcumin twice daily for 1 month followed by 550 mg three times daily for another month. All 5 patients improved as judged by global score ( $p < 0.02$ ), with reductions in concomitant medications in 4 patients. The 5 patients with CD were treated with 360 mg curcumin three times daily for 1 month followed by 360 mg four times daily for another 2 months. Four out of 5 patients with CD improved, as evidenced by lowered Crohn's Disease Activity Index, with a mean reduction of 55 points and a sedimentation rate with a mean of 10 mm/h reduction.

Subsequently, Hanai et al. [53] evaluated the use of curcumin in 89 patients with quiescent UC in a randomized, double-blind, multicenter trial. Forty-five patients received 1 g curcumin twice a day along with sulfasalazine or mesalamine, and 44 patients received placebo plus sulfasalazine or mesalamine for 6 months. Of 43 patients (2 patients violated the protocol) who received curcumin, 2 relapsed during 6 months of therapy (4.65%), whereas 8 of 39 patients (20.51%) in the placebo group relapsed ( $p = 0.040$ ). Recurrence rates evaluated on the basis of intention to treat showed a significant difference between curcumin and placebo ( $p = 0.049$ ). Furthermore, curcumin improved both the clinical activity index ( $p = 0.038$ ) and the endoscopic index ( $p = 0.0001$ ), measures used to evaluate the morbidity associated with UC. Based on these two studies, curcumin seems to be a promising and safe medication for maintaining remission in patients with quiescent UC as well as for improving symptoms in proctitis and CD. Further studies on curcumin and IBD are needed to strengthen these findings. The agent has the potential to be used as a steroid-sparing induction agent in mild to moderate colitis considering its effect on multiple inflammatory pathways. Alternatively, this agent can also be used as adjunct therapy in maintenance of remission in patients who encounter loss of response to an agent directed against a single cytokine such as anti-TNF agents.

**Limitations and Conclusion**

Despite the promising biological effects of curcumin, its poor oral bioavailability in both rodents and humans [54] has restricted its use in the management of human ailments. It is well known that many drugs have bioavailability problems due to their low water solubility, slow dissolution rate and instability in the gastrointestinal tract. Poor oral absorption due to its extremely low aque-

ous solubility or extensive presystemic metabolism may be responsible for the unfavorable pharmacokinetics of this molecule. In rodents, curcumin undergoes avid metabolism by conjugation and reduction, and its absorption after oral dosing is characterized by poor systemic bioavailability [55]. One study has used the cyclodextrin complex of curcumin to increase its solubility and dissolution that may overcome the pharmacokinetic problems [14]. New formulations are needed to increase the bioavailability of curcumin.

Furthermore, well-designed randomized clinical trials with large cohorts will be needed to validate the results of previous studies and evaluate the full clinical potential of curcumin in the treatment of human disease. Currently, several clinical trials are being conducted on the efficacy of curcumin in a variety of diseases, with two involving IBD. One is a recently completed phase I clinical trial seeking to determine the tolerability of curcumin in pediatric patients with IBD. However, results of this study are pending. Another trial aims to study the efficacy and tolerability of Colnect, which contains curcumin, green tea and selenium, as an add-on in patients with active UC. For details, please refer to [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

The key clinical question will be to define its role in the current therapeutic armamentarium of IBD. Studies to explore its role as a steroid-sparing induction agent in mild to moderate colitis or as an adjunct or rescue therapy to maintain remission in patients who are losing re-

sponse to agents such as immunomodulators or anti-TNF agents will be needed in near future.

In conclusion, the increase in patients' use of CAM has prompted substantial interest in CAM among gastroenterologists and other physicians who care for patients with IBD. Their side effect profiles, including serious infections and risk of lymphomas, have led to interest in natural anti-inflammatory compounds such as curcumin, derived from turmeric. The current medical therapy for IBD patients includes agents such as mesalamine, steroids and anti-TNF agents. These agents are associated with potential side effects including increased risk of serious infections and malignancies. The efficacy of these agents in inducing response and remission is also somewhat limited. One of the reasons to lose response to therapy such as anti-TNF therapy is a shift in the inflammatory pathway in which TNF may not be a major cytokine. That has led to some recent research exploring other cytokine pathways (e.g., IL-6) to control disease processes. Curcumin has been found to inhibit many of these cytokine pathways including IL-6, and thus, is an important natural compound that carries minimal toxicity with a favorable safety profile. Its anti-inflammatory and antioxidant effect have been shown in numerous animal models. However, lack of controlled human studies may limit its use in clinical practice. Further prospective trials of curcumin in the near future may help us determine its potential beneficial role in the management algorithm of the IBD patients.

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