Curcumin for Inflammatory Bowel Disease: A Review of Human Studies

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Abstract
OBJECTIVE: To evaluate the use of curcumin in inflammatory bowel disease. DATA SOURCES: ALTMEDEX, Comprehensive Database of Natural Medicines, MEDLINE/PubMed were searched from January 1980 through May 2009 using the terms curcumin, turmeric, ulcerative colitis, Crohn's disease, *Curcuma longa, Curcuma domestica*, Indian saffron, inflammatory bowel disease. Data was limited to human trials. References of identified articles were reviewed. DATA SYNTHESIS: Data evaluating the use of curcumin in inflammatory bowel disease (including ulcerative colitis and Crohn's disease) is limited to two studies comprising data for only 99 patients. Curcumin in conjunction with mainstream therapy, consisting of sulfasalazine (SZ) or mesalamine (5-aminosalicylic acid [5-ASA] derivatives) or corticosteroids was shown to improve patient symptoms and allow for a decrease in the dosage of corticosteroids or 5-ASA derivatives. In one small study of 10 patients, some patients even stopped taking corticosteroids or 5-ASA. CONCLUSIONS: Although two small studies have shown promising results, all authors conclude that larger-scale, double-blind trials need to be conducted to establish a role for curcumin in the treatment of ulcerative colitis. In addition to improving results when used in conjunction with conventional medications for UC, curcumin may pose a less-expensive alternative.
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Background

Turmeric, used as a spice in curry powders and mustard, is known scientifically as *Curcuma longa* or *Curcuma domestica*. The perennial herb has multiple ingredients, including curcuminoids, the most active ingredients for medicinal use. These curcuminoids, comprising the yellow-pigmented fractions of turmeric, include diferuloylmethane (curcumin I), demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and the recently discovered cyclocurcumin.[1-3] The major components of commercial curcumin are curcumin I (77%), curcumin II (~17%), and curcumin III (~3%).[1] Curcumin is also known by many synonyms and translated into various languages around the world; in Tibetan language it is known as Gaser, in Swahili it is known as Manjano.[1]

Curcumin has well-documented historical use in Chinese, Hindu, and Ayurvedic medicine. Curcumin has been used for a variety of disorders, from respiratory conditions to dyspepsia to malignancy. To date, no studies in animals or humans have discovered significant toxicity related to curcumin, even at very high doses.[1,2]

Mechanisms of Action

Much is known about the molecular targets and interactions of curcumin with receptors, growth and transcription factors, cytokines, enzymes, and genes. Curcumin is often cited as pleiotropic, meaning it has the ability to interact with many cell targets.[1,3] For the purposes of this discussion, curcumin's molecular targets will be confined to those involved in gastrointestinal inflammation. Curcumin has been shown to inhibit the activity of lipoxygenase[4] or binding to phosphatidylcholine micelles, thereby inhibiting lipoxygenase I.[5] Of note in gastrointestinal disorders, curcumin has been found to inhibit the activation of various transcription factors that play a key role in inflammation, cell survival and proliferation, and angiogenesis. These include nuclear factor-kappaB (NF-κB), activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, peroxisome proliferator-activated receptor-gamma (PPAR-γ), and β-catenin.[6] Inflammatory stimuli activate one of three independent mitogen-activated protein kinase (MAPK) pathways leading to activation of the p44/42 MAPK, JNK, or p38 MAPK pathway.[6] Cyclooxygenase-2 (COX-2) proteins are crucial to

Key words: IBD, inflammatory bowel, inflammation, curcumin, turmeric, curcuma, Crohn's, colitis, ulcerative, UC, CD, proctitis, inflamed

the inflammation cascade and have been linked to certain cancers. There are several ways in which curcumin inhibits COX-2, both directly and indirectly. Curcumin downregulates the expression of COX-2, most likely through the downregulation of NF-κB that is required for COX-2 activation.[1] In cancer cells, curcumin exerts anti-inflammatory and growth-inhibition by inhibiting expression of interleukin-1beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).[7]

Pharmacokinetics

Curcumin studies in animals show it is rapidly metabolized, conjugated in the liver, and excreted in the feces with minimal amounts found in the urine.[8] A 40 mg/kg intravenous dose of curcumin given to rats resulted in complete plasma clearance at one hour post-dose, showing its rapid metabolism;[9] data in humans is inconclusive. A phase I clinical trial conducted on 25 patients with precancerous lesions showed oral doses of 4, 6, and 8 g curcumin daily for three months yielded serum curcumin concentrations of only 0.51 ± 0.11, 0.63 ± 0.06, and 1.77 ± 1.87 μM respectively, indicating poor absorption of straight curcumin. In this study serum levels peaked one and two hours post-dose and declined rapidly.[10]

Table 1. Differential Diagnosis of Ulcerative Colitis and Crohn's Disease

	Ulcerative Colitis (UC)	Crohn's Disease (CD)
Clinical		
Blood in stool	Yes	Occasionally
Mucus	Yes	Occasionally
Systemic symptoms	Occasionally	Frequently
Pain	Occasionally	Frequently
Significant perianal disease	No	Frequently
Fistulas	No	Yes
Small-intestinal obstruction	No	Frequently
Colonic obstruction	Rarely	Frequently
Response to antibiotics	No	Yes
Recurrence after surgery	No	Yes
Endoscopic		
Rectal sparing	Rarely	Frequently
Continuous disease	Yes	Occasionally
"Cobblestoning"	No	Yes
Granuloma on biopsy	No	Occasionally

Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease is a chronic immune disorder that involves an overactive immune component in the intestinal mucosa.[3] IBD is divided into two major categories, ulcerative colitis (UC) and Crohn's disease (CD). The two diseases have a fair amount of overlap, including presenting symptoms, quality of life issues, and treatments. Patients with IBD often have symptoms of abdominal pain, cramping, diarrhea, rectal bleeding, urgency, nausea, fever, and weight loss. Major differences of the two types of IBD are listed in Table 1.[11] Proctitis is ulcerative colitis confined to the rectal area.

Certain cytokines have been associated with IBD, including TNF-α, IL-1, IL-6, IL-8, and others.[12] Targeted drug therapies, specifically infliximab, have been successful in treating IBD. Infliximab is an anti-TNF-α monoclonal antibody that has been extensively studied in myriad inflammatory disorders, including CD and UC. Widespread use of infliximab is limited because of adverse effects, cost, and the emergence of antibodies that result after multiple administrations.[3]

Most recently, the role of NF-κB in IBD has been elucidated. Colon biopsies in IBD patients with active disease show increased levels of NF-κB p65 protein (a member of the NF-κB family of proteins).[13] The amount of NF-κB p65 in the tissue samples correlated with the severity of intestinal inflammation. This increased expression of NF-κB results in an increased ability to secrete inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12, and IL-23, the latter of which are directly responsible for mucosal damage in IBD.[13] TNF-α is also able to up-regulate the production of NF-κB, resulting in a cyclical feedback loop of inflammation.

Diagnosis and Staging of IBD in Clinical Studies

Ulcerative colitis is diagnosed through a colonoscopy, while the severity of symptoms can be rated on a number of severity index scales. Although several endoscopic indices are available to characterize the severity of ulcerative colitis, those currently used in clinical trials are not uniform. Hanai and colleagues, in the double-blind study discussed below, did not disclose their specific methodology for endoscopic index.[14] The Clinical Activity Index (CAI) was used to assess

UC severity in this same study. A CAI of ≤4 indicated remission, whereas a CAI ≥5 indicated relapse. A Crohn's disease activity index (CDAI) is often used to evaluate disease severity in CD – as was the case in the small pilot study discussed below.[15]

Clinical IBD Studies

Small Pilot Study

Holt and colleagues conducted a small, open-label, pilot study of curcumin in five patients with ulcerative colitis/proctitis and five patients with Crohn's disease.[15] Five patients with ulcerative proctitis, who were currently using 5-aminosalicylic acid (5-ASA) compounds and corticosteroids (four of five patients were on corticosteroids + 5-ASA compounds), were given 550 mg curcumin twice daily for one month, then 550 mg three times daily for the second month. The five patients with Crohn's disease received curcumin at a dose of 360 mg orally three times daily for one month and then 360 mg four times daily for an additional two months. Patient characteristics and demographics are reported in Table 2.

Patients were assessed at baseline and after two months of curcumin via hematological, biochemical, and inflammatory analysis (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) as well as sigmoidoscopy and biopsy. Subjective analysis was via a self-reported symptom diary. In the ulcerative proctitis group, all five patients had significant improvement. Two patients stopped taking 5-ASA compounds, two reduced 5-ASA dosages, and one stopped corticosteroids entirely. Although only four of five CD patients completed the study, they also experienced a reduction in CDAI scores, ESR, and CRP. The Crohn's disease group also reported symptomatic improvements of fewer bowel movements, less diarrhea, and less abdominal pain and cramping. In the absence of a clearly stated primary endpoint, it was considered to be the symptom diary. Based on the symptom diary ($p<0.02$), all patients improved from baseline after two months and inflammatory markers decreased to normal limits. The authors recommended larger scale, double-blinded, placebo-controlled trials in the future.

Table 2. Patient Characteristics and Medications at Study Entry

Patient Identifier	Age/ Gender	Extent of Disease	Length of Disease History (years)	Medications at Study Entry (frequencies not always noted)
Ulcerative Colitis Patients				
UC 1	52/F	Proctitis	32	5-ASA suppositories + SZ 2 g/day
UC 2	30/F	Proctitis	1	5-ASA enemas and suppositories
UC 3	28/M	Proctitis	5	5-ASA enemas
UC 4	29/M	Proctitis	7	SZ 2 g/day + 5-ASA suppositories
UC 5	54/F	Proctosigmoiditis	6	prednisone 10 mg + 5-ASA and enemas + azathioprine 100 mg
Crohn's Disease Patients				
CD 1	43/M	Ileocolitis	22	colestipol 3 g + 6-MP 75 mg
CD 2	47/M	Crohn's colitis	26	6-MP 75 mg
CD 3	65/F	Ileocolitis	11	6-MP 75 mg
CD 4	50/M	Ileojejunal colitis	23	metronidazole 500 mg + budesonide 9
CD 5	33/F	Ileitis	22	None

Adapted from: Holt PR, Katz S, Kirschoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. *Dig Dis Sci* 2005;50:2191-2193.

5-ASA = 5-aminosalicylic acid
SZ = sulfasalazine
6-MP = 6-mercaptopurine

Double-blind, Placebo-controlled Trial

Hanai and colleagues conducted a randomized, multicenter, double-blind, placebo-controlled trial of curcumin plus sulfasalazine (SZ) or mesalamine compared to placebo plus SZ or mesalamine in 89 patients with UC.[14] After a four-week washout period, subjects were randomly assigned to a six-month regimen of either placebo (n=44) or curcumin 1,000 mg after breakfast and 1,000 mg after dinner (n=45) in combination with SZ (1-3 g/day; median 2 g/day) or mesalamine (1.5-3 g/day; median 2.25 g/day). The inclusion and exclusion criteria were extensive (Table 3).

Table 3. Inclusion and Exclusion Criteria in Hanai Study[14]

Inclusion Criteria	Exclusion Criteria Patients with or receiving:
Diagnosis of UC as confirmed by radiological, endoscopic, or histological criteria established by the Research Committee of Inflammatory Bowel Disease, the Japan Ministry of Health	An immunomodulator medication such as: azathioprine, 6-mercaptopurine, or cyclosporine
Age 13-65	Severe cardiovascular disease
Patient's UC CAI ≤ 4 & stable for the previous four weeks	Anemia (Hgb ≤ 9 g/dL), leukopenia, thrombocytopenia, or abnormal coagulation
Patient had achieved remission with corticosteroid dose ≥ 40 mg prednisone per day (or equivalent) and had successfully ceased therapy	Renal or hepatic disease, gallstones, pancreatitis, diabetes mellitus, sepsis, infection, or pneumonia
Hemoglobin (Hgb) ≥ 10 g/dL	Pregnant or nursing women were also excluded

Patients were followed during treatment and for six months after the treatment ended; patients received only SZ or mesalamine during the six-month follow-up. Seven patients requested to be excluded, leaving 82 evaluable patients. The relapse rate was significantly higher in the placebo group (20.5% [8/39]) than in the curcumin-treated group (4.7% [2/43]). Curcumin also suppressed disease-associated CAI and endoscopic index (EI) scores. The mean CAI in the curcumin group was improved from 1.3 to 1.0 at six months (p=0.38), while CAI in the placebo group increased from 1.0 to 2.2 (p=0.0003). Patients in the curcumin group also had significantly improved EI (1.3 to 0.8 [p=0.0001]), while EI values in the placebo group showed no significant improvement. The authors provided only before- and after-treatment data, despite assessments every two months. There was a statistically significant (p=0.049) difference between the percentage of patients with recurrence at six months in the curcumin (4.44 [95% confidence interval (CI) 0.54-15.15]) compared to the placebo (15.15 [CI 8.18-32.71]) group. This difference was not significant at 12 months.

Side effects reported by study subjects included abdominal bloating, nausea, hypertension (one patient), diarrhea, and elevated γ-guanosine triphosphate (GGTP) levels (one patient). This latter patient was a heavy drinker. With the exception of the patient that experienced hypertension, no patient discontinued curcumin therapy due to side effects.

Only two of 43 patients treated with curcumin in combination with SZ or mesalamine relapsed during six months of therapy; whereas, eight of 39 patients who received placebo with SZ or mesalamine relapsed during the same period. Although this difference was not statistically significant, the authors postulate curcumin may have an effect on suppressing relapse. The authors drew three major conclusions: (1) curcumin had better clinical

efficacy over placebo in the prevention of relapse, (2) curcumin significantly improved the CAI and EI, and (3) curcumin was well-tolerated. The authors, stating their results might have been better had they used a higher dose of curcumin, recommend that future studies use dosages greater than 2 g/day.

Precautions and Contraindications

Patients with gallstones or bile duct obstructions should use curcumin with caution, primarily due to curcumin's ability to cause gallbladder contractions. In a randomized, double-blind, crossover study involving 12 healthy volunteers, 20 mg curcumin produced as much as 29-percent reduction in gallbladder size, indicating gallbladder contraction (statistically different than placebo).[16] A subsequent study indicated that doses of 40 and 80 mg curcumin produced 50- and 72-percent decreases in gallbladder volume, respectively.[17]

Because curcumin inhibits platelet aggregation *in vitro* and in animal studies, it is theorized it could be additive in effect to antiplatelet medications such as aspirin, clopidogrel, and non-steroidal anti-inflammatories (NSAIDS).[18,19] In a mouse model, 100 mg/kg curcumin or 25 mg/kg aspirin resulted in 60- or 61.1-percent protection from thrombosis, respectively.[20] The concomitant use of curcumin and anticoagulant or antiplatelet medications should be approached with caution.

Conclusion

Although this review discusses just two clinical studies of inflammatory bowel disease, the uses of curcumin far exceed the scope of this article. Curcumin shows promise in treating myriad disorders. It has recently been studied, at wide-ranging daily dosages of as little as 20 mg and as much as 12 g, for ailments such as psoriasis, colorectal cancer, renal graft function, pancreatitis, dyspepsia, and chronic anterior uveitis, to name a few.[1] Larger-scale, prospective studies are needed to confirm its effect for IBD. Curcumin has an advantageous safety profile as well as low relative cost, making it an attractive option for IBD patients.

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