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The Use of Curcumin in Ulcerative Colitis: Current Evidence and Practical Applications

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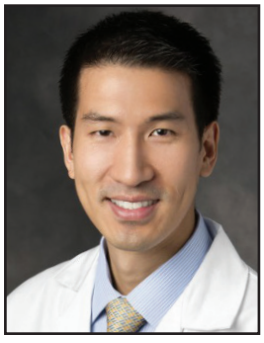

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Although pharmacologic agents (mesalamine, immunomodulators, biologics, and small molecule inhibitors) have been established as safe and effective treatments for inflammatory bowel disease (IBD), patients with IBD report using nutraceutical supplements despite limited evidence on their safety and efficacy. Curcumin, a polyphenol derivative of the *Curcuma longa* rhizome, has received increasing attention due to its proposed anti-inflammatory, antioxidant, anticarcinogenic, and microbiome altering effects. This review highlights the current evidence for the use of curcumin in ulcerative colitis, its mechanisms of action, bioavailability, and safety data, as well as recommendations for use in clinical practice. Evidence of curcumin's role in inducing clinical and endoscopic remission when used in combination with conventional treatment will be discussed, though larger scale and well-designed trials are still needed to fully establish its safety and efficacy.

INTRODUCTION

Ulcerative colitis (UC) is a relapsing and remitting immune-mediated chronic inflammatory bowel disease (IBD) with increasing global incidence and prevalence.[1,2] Patients often experience debilitating symptoms, including abdominal pain, diarrhea, rectal bleeding, and extraintestinal manifestations[2,3] as well as an increased risk of colorectal cancer.[4] The pathophysiology of IBD has been attributed to a complex interplay between genetic factors, diet and environmental factors, and the gut microbiome resulting in intestinal barrier dysfunction, immune system dysregulation, and chronic intestinal inflammation.[1,2,5]

Current pharmaceutical treatments target inflammation and include 5-aminosalicylic acid drugs, corticosteroids, immunomodulators,

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biologics, and novel small molecular inhibitors to improve clinical symptoms and induce remission.[2,3] However, these treatments carry an increased risk of serious adverse events (AEs) (e.g. infections, malignancy) and many patients relapse or require surgery despite treatment, highlighting the need for alternative therapeutic approaches.[2,6] Many patients with IBD turn to complementary and alternative medicine due to concerns about side effects and perceived lack of response to conventional treatment with up to 54% reporting nutraceutical use.[7,8]

Curcumin is an active polyphenol found in the *Curcuma longa* rhizome that has been used medicinally for thousands of years in Ayurveda and Traditional Chinese Medicine and as a dietary spice and dye in the food industry.[3,9] Several *in vitro* and mouse models have demonstrated the anti-inflammatory, antioxidant, anticarcinogenic, and microbiome altering effects of curcumin, and clinical studies in a variety of diseases have reported promising results.[10] In this review, we present the mechanisms of action, clinical evidence, and practical recommendations for curcumin use in UC.

Mechanism of Action

The primary mechanism by which curcumin ameliorates inflammation is through downregulation of inflammatory signaling pathways, which has been demonstrated *in vitro* and in dextran sodium sulfate (DSS)-induced colitis mouse models.[10–15] Curcumin also addresses immune system dysregulation by regulating Th1/Th2 expression,[15] follicular helper T cell (Tfh) differentiation via Tfh-related nuclear transcription factor expression,[16] toll-like receptor signaling,[17] and macrophage polarization[17] in colonic mucosa of DSS-induced colitis mice. Curcumin has demonstrated antioxidant effects by decreasing myeloperoxidase activity and inducible nitric oxide synthase expression in colonic mucosa of DSS-induced colitis mice,[11] increasing antioxidant enzyme levels *in vitro,*[15,18] and increasing serum total antioxidant capacity in human studies across a variety of diseases.[19] Curcumin has been found to strengthen intestinal barrier function and decrease inflammatory circulating lipopolysaccharide levels by normalizing tight junction protein expression in DSS-induced colitis mice.[11,20] Ingestion of curcumin can alter gut microbiome composition and biodiversity[20–22] with an increase in short-chain fatty acid producing bacteria, which may decrease intestinal inflammation and improve mucosal protection.[20,22] Curcumin can induce apoptosis and autophagy in colon cancer cells via endoplasmic reticulum stress-mediated and caspase-dependent mechanisms, which may be of particular importance given the increased risk of colon cancer in UC.[18,23]

Metabolism and Bioavailability

Although curcumin appears to have strong intrinsic activity, its oral bioavailability is limited by poor absorption, rapid metabolism, and low chemical stability[14] resulting in low serum levels.[24] However, murine studies have suggested that curcumin after oral administration may concentrate in the gastrointestinal tract.[22,25] A study of humans with colorectal cancer taking oral curcumin 3.6g/d for 7 days reported curcumin concentrations of 12.7 ± 5.7nmol/g and 7.7 ± 1.7nmol/g in normal and malignant colorectal cells, respectively, with trace levels in peripheral circulation.[26] Curcumin undergoes phase I biotransformation via reduction and phase II biotransformation via glucuronidation and sulfation to metabolites primarily in the liver and intestines.[22,27,28] Studies suggest that *Escherichia coli, Bifidobacteria longum,* and other intestinal microorganisms are capable of reducing or deconjugating curcumin and its metabolites, suggesting that an individual's intestinal microbiome can impact curcumin metabolism and its pharmacologic effects.[3,22,27] Given its low serum levels, curcumin's activity has been potentially attributed to its metabolites and degradation products[25,28] although this requires further elucidation.[3] Curcumin is rapidly eliminated from the body, primarily in feces.[3]

Studies have exhibited a wide range of serum curcumin concentrations after oral administration,[27] which may be due to variations in polyphenol concentration, intestinal microbiome, and diet. Dietary polyphenol concentration of curcumin can be influenced by seasonality, soil nutrients, plant stress, heating, drying, grinding, food storage, and food preparation.[22,27,29] Consumption with dietary lipids, such as lecithin-rich oil or eggs,

Table 1. Summary of Key Clinical Studies Investigating Curcumin in IBD

Author/Year	Population	Intervention	
Lang et al., 2016	50 adults with mild-moderate UC (SCCAI 5-12) taking stable concomitant immunomodulators (AZA, 6-MP)	1.5g curcumin capsules PO BID (Cur-Cure, 95% pure curcumin preparation from Bara Herbs Inc., Israel) with 4g/d PO and 1g/4g enema or 1g suppository mesalamine daily for 4 weeks	
Banerjee et al., 2021	69 adults with mild-moderate UC (partial Mayo score 2-6 with endoscopic score>1) who were biologic and immunomodulator naïve	50 mg bioenhanced curcumin PO BID (VALDONE Curcumin 50 mg Softgel; Cadila Pharmaceuticals Ltd, India) self-micro-emulsifying drug delivery system containing 70:30 ratio of curcumin mixture (curcumin dry crystals and oils) to turmeric extract) with 4.8g/d PO + 1g/d PR mesalamine for 6 weeks	
Sadeghi et al., 2020	70 adults with mild-moderate UC (SCCAI 5-12) taking concomitant salicylates, immunomodulators, or steroids; TNF-α inhibitors not permitted	500mg curcumin capsules PO TID with meals (Karen critical pharmaceutical and nutritional supplements company, Tehran, Iran) for 8 weeks	
Masoodi et al., 2018	56 adults with mild-moderate UC (SCCAI 5-11); concomitant use of prednisolone, AZA, TNF-α inhibitors permitted	80mg curcuminoids nanomicelles (Sinacurcumin; contains curcuminoids and a hydrophilic portion) PO TID with 3g/d PO mesalamine for 4 weeks	
Kedia et al., 2017	62 adults with mild-moderate UC (UCDAI 3-9); 6.5% taking AZA	150mg purified curcumin capsules PO TID (Himalaya Drug Company, Bangalore, India) with mesalamine 2.4g/d PO for 8 weeks	
Singla et al., 2014	45 adult subjects with mild to moderate distal UC (UCDAI 3-9); concomitant steroid, 5-ASA, and AZA use permitted	140mg NCB-02 enema QHS (Himalaya Drug Company, Bangalore, India) standardized extract with 72% curcumin, 18.08% dimethoxy curcumin, and 9.42% bis-dimethoxy curcumin) with 800mg mesalamine PO BID for 8 weeks	
Hanai et al., 2006	89 adult subjects with UC in remission only taking mesalamine or sulfasalazine	1g curcumin PO BID after breakfast and dinner (API Co, Ltd, Gifu, Japan containing 50% curcumin) with 1.5-3g mesalamine or 1-3g sulfasalazine daily for 6 months	
Suskind et al., 2013	6 CD and 5 UC pediatric (age 11-18) subjects in remission or with mildly active disease taking mesalamine or TNF-α inhibitors	500mg curcumin capsule PO BID (Vital Nutrients Inc, Middletown, CT, USA) for 3 weeks followed by 1g BID for 3 weeks followed by 2g BID for 3 weeks	

Abbreviations: 5-ASA (5-aminosalicylate), 6-MP (6-mercaptopurine), AE (adverse events), AZA (azathioprine), BID (twice daily), CAI (Clinical Activity Index), CD (Crohn's Disease), CRP (C-reactive protein), EI (endoscopic index), ESR (erythrocyte sedimentation rate), g/d (grams/day), ITT (intention to treat analysis), PCDAI (Pediatric Crohn's Disease Activity Index), PO (per oral), PR (per rectum), PUCAI (Pediatric Ulcerative Colitis Activity Index), QD (daily), QHS (at bedtime), SCCAI (Simple Clinical Colitis Activity Index), TID (three times daily), UC (ulcerative colitis), UCDAI (Ulcerative Colitis Disease Activity Index)

Table 1. Summary of Key Clinical Studies Investigating Curcumin in IBD (continued)

	Control	Key Findings (intervention vs. control)
	Placebo capsules PO BID with 4g/d PO and 1g/4g enema or 1g suppository mesalamine daily for 4 weeks	- Clinical response (SCCAI reduction ≥3 points): 65.3% vs. 12.5% (p<0.001) - Clinical remission (SCCAI ≤2): 53.8% vs. 0% (p=0.01) - Endoscopic response (≥1 point reduction in Mayo endoscopic subscore): 45.4% vs. 0% (p<0.01) - Endoscopic remission (Mayo endoscopic subscore 0-1): 38% vs. 0% (p=0.043) - No significant difference in AEs. Severe AEs included peptic ulcer and worsening UC.
	Placebo BID with PO 4.8g/d + PR 1g/d mesalamine for 6 weeks	- Clinical response (≥2 reduction in partial Mayo score): 52.9% vs. 14.3% (p=0.001) at 6 weeks; 58.8% vs. 28.6% at 3 months - Clinical remission (partial Mayo score ≤1): 44.1% vs. 0% (p<0.01) at 6 weeks; 55.9% vs. 5.7% at 3 months - Endoscopic remission (endoscopic Mayo score ≤1): 35.3% vs. 0% (p<0.01) at 6 weeks; 44% vs. 5.7% at 3 months - No significant difference in AEs. Severe AEs included worsening UC requiring study termination.
	Placebo capsules PO TID with meals for 8 weeks	- Clinical response (reduction in SCCAI ≥3): 93.5% vs. 59.4% (p<0.001) - Clinical remission (SCCAI ≤ 2): 83.9% vs. 43.8% (p=0.001) - No significant difference in AEs
	Placebo PO TID with 3g/d PO mesalamine for 4 weeks	- Significantly greater reduction in urgency of defecation score (p=0.041) in treatment vs. control, but not in daily bowel movement frequency (p=0.13) or blood in stool (p=0.781) at 4 weeks. - No significant difference in change in mean SCCAI between groups (p=0.05) - No significant difference in AEs.
	Placebo PO TID with mesalamine 2.4g/d PO for 8 weeks	- Clinical response (reduction of UCDAI ≥3): 20.7% vs. 36.4% (p=0.18) - Clinical remission (UCDAI ≤2): 31.3% vs. 27.3% (p=0.75) - Endoscopic response: 34.5% vs. 30.3% (p=0.72) - Mild AEs reported in control group
	Placebo enema QHS with 800mg mesalamine PO BID for 8 weeks	- Clinical response (reduction in UCDAI ≥3): 56.5% vs. 36.4% (p=0.175) - Clinical remission (UCDAI <3): 43.4% vs. 22.7% (p=0.14) - Endoscopic response (decrease in mucosal appearance score ≥1): 52.2% vs. 36.4% (p=0.29) - No significant difference in AEs. Severe AEs included worsening UC requiring study termination.
	Placebo PO BID with 1.5-3g mesalamine or 1-3g sulfasalazine daily for 6 months	- % recurrence at 6 months: 4.44% vs. 15.15% (p=0.049) - % recurrence at 12 months: 22.2% vs. 31.8% (p=0.4330) - Change in mean CAI: 1.3±1.1 to 1.0±2.0 (p=0.38) vs. 1.0±1.1 to 2.2±2.3 (p=0.003) at 6mo - Change in mean EI: 1.3±0.8 to 0.8±0.6 (p=0.0001) vs. 1.3±1.0 to 1.6±1.6 (p=0.0728) at 6mo - No serious AEs
	No control group	- 2 UC patients achieved clinical remission, 3 patients had lowering of PUCAI or PCDAI - No serious AEs reported - ESR, CRP, creatinine, alanine transaminase, and complete blood count remained stable

Abbreviations: 5-ASA (5-aminosalicylate), 6-MP (6-mercaptopurine), AE (adverse events), AZA (azathioprine), BID (twice daily), CAI (Clinical Activity Index), CD (Crohn's Disease), CRP (C-reactive protein), EI (endoscopic index), ESR (erythrocyte sedimentation rate), g/d (grams/day), ITT (intention to treat analysis), PCDAI (Pediatric Crohn's Disease Activity Index), PO (per oral), PR (per rectum), PUCAI (Pediatric Ulcerative Colitis Activity Index), QD (daily), QHS (at bedtime), SCCAI (Simple Clinical Colitis Activity Index), TID (three times daily), UC (ulcerative colitis), UCDAI (Ulcerative Colitis Disease Activity Index)

can improve its absorption and solubility.[22,27] Piperine, an alkaloid found in black pepper, inhibits curcumin biotransformation and can increase its bioavailability by up to 2000%.[22,24,30] Bioenhanced delivery models, such as curcumin-piperine complexes, curcumin nanoparticles, and phospholipid complexes may improve bioavailability. NovaSol®, CurcuWin®, and LongVida® reportedly have 100-fold higher bioavailability compared to unformulated curcumin.[31]

Ulcerative Colitis

Key studies evaluating curcumin in UC are described in Table 1. A randomized controlled trial (RCT) by Lang et al. garnered significant attention for curcumin use in combination with mesalamine to induce remission in UC.[32] In this study, patients with active UC taking mesalamine and treated with 3g daily of curcumin had significantly higher rates of clinical response, clinical remission, endoscopic response, and endoscopic remission compared to placebo with mesalamine.[32] Since then, three additional RCTs by Banerjee et al., Sadeghi et al., and Masoodi et al. with varying curcumin doses and formulations have supported similar findings.[9,33,34] However, a study by Kedia et al. reported no significant difference in clinical response, clinical remission, or mucosal healing rates in patients with active UC treated with curcumin in addition to mesalamine.[35] This was potentially due to a lower dose of curcumin than used in the aforementioned studies, suggesting that doses of 1500mg-3g/d may have better efficacy.

Singla et al. investigated the use of daily curcumin enemas in active ulcerative proctitis/proctosigmoiditis.[36] Although there were promising results in the per-protocol analysis, there was no significant difference in clinical response, clinical remission, or mucosal healing between groups in the intention-to-treat analysis.[36] This discrepancy was attributed to a small sample size and high attrition rate, which limits reliability and interpretation of the data.

Hanai et al. demonstrated a potential role for curcumin in maintenance of remission in UC, which showed that patients taking 2g oral curcumin daily had significantly lower rates of recurrence and clinical activity index scores compared to placebo.[37] There is limited data in pediatric patients with one small dose-escalation study reporting improvement in disease activity score in 5 patients with UC in remission.[38]

Safety

The U.S. Food and Drug Administration (FDA) classifies nutraceuticals as food supplements, which are not required to undergo rigorous drug approval like pharmaceutical drugs.[39] Current Good Manufacturing Practices (CGMP) implemented by the FDA are intentionally flexible and manufacturers are responsible for determining their procedures for testing for environmental contaminants and identity, purity, strength, and quality of ingredients.[40] Supplement brands may source their ingredients from potentially unregulated sources or from outside of the U.S. This results in significant variation in purity, potency, and potentially safety between brands.[39] Online resources, such as ConsumerLab.com[41] and Natural Medicines Comprehensive Database,[42] can help providers learn about ingredients, potential drug interactions, testing for potency, and contaminants of specific supplements.

Curcumin is Generally Regarded as Safe (GRAS) as a food additive by the FDA.[9] None of the aforementioned studies of curcumin in UC reported a significant difference in incidence of serious AEs, which were primarily disease flares, between treatment and control groups. This is supported by a review of 27 human studies using oral curcumin ranging from 150mg-4g/d to treat a variety of diseases for 4 weeks-6 months, which found no reports of major toxicity although headaches and mild gastrointestinal side effects (e.g. flatulence, diarrhea, nausea) were reported.[43]

Drug-induced liver injury (DILI) is a growing concern associated with nutraceuticals.[44] A review of 10 patients enrolled in the Drug-Induced Liver Injury Network reported that turmeric-related liver injury presented as self-limited hepatocellular injury within 1-4 months of use with rapid improvement after cessation and only rare cases of severe injury or death.[44] Doses were not reported. Piperine in curcumin products may also contribute to hepatotoxicity as 50% of the cases included products containing piperine, although there has not been evidence of piperine alone causing DILI.[44]

Table 2. Recommendations for Curcumin Use in Ulcerative Colitis

Patient population	• Patients with active mild-moderate UC who have not achieved clinical remission with 5-aminosalicylic acid compounds • Likely benefit in active UC or UC in remission taking other conventional therapies (e.g. azathioprine, steroids, biologics) • Avoid in children, pregnancy, and lactation given limited data • Monitor use in patients with history of bile duct obstruction and those susceptible to gallstones or nephrolithiasis
Dosing	• Start with low dose (i.e. 500mg/d) and increase weekly as tolerated with goal of 1.5-3g/day in 2-3 divided doses daily
Bioavailability	• Advise patients to take curcumin with black pepper and/or with a meal that has dietary fat (e.g., oil, avocado, nuts, dairy) • Products that contain black pepper, piperine, or BioPerine® or use a bioenhanced form of curcumin (e.g., NovaSOL®) can increase the bioavailability of curcumin, but there are limited studies in UC
Adverse effects	• Common: mild gastrointestinal side effects, yellow stool, and headaches • Rare cases of drug-induced liver injury • Theoretical risk of gallbladder contraction with curcumin and nephrolithiasis with turmeric • Products containing piperine may cause gastric mucosal irritation and bleeding[41]
Drug monitoring and safety	• May interact with amlodipine, anticoagulant/antiplatelet drugs, alkylating agents, diabetes medications, tacrolimus, sulfasalazine, tamoxifen, and topoisomerase inhibitors[53] • Theoretically may impact levels of drugs metabolized by cytochrome P450 1A1,1A2, and 3A4[53] • Products containing piperine may theoretically inhibit cytochrome P450 1A1, 2B1, 2D6, and 3A4 and interact with atorvastatin, lithium, phenytoin, carbamazepine, diclofenac, theophylline, and rifampin[41,53] • Monitor transaminase levels at 1 and 3 months after initiation

Sample brands*	• Puritan's Pride Curcuminoids from Turmeric
	  ○ 538mg turmeric extract (500mg curcuminoids) per capsule
	  ○ Start with 2 capsules once daily with meals and increase to 2 capsules 2-3 times daily with meals as tolerated
	• Pure Encapsulations Curcumin with Curcumin C3 Complex®
	  ○ 500mg turmeric extract (475mg curcuminoids) per capsule
	  ○ Start with 2 capsules once daily with meals and increase to 2 capsules 2-3 times daily with meals as tolerated

*Not a brand endorsement. Listing of brands are for educational purposes only.

Kedia et al. did not report a significant change in laboratory parameters, including aspartate transaminase (AST), alanine transaminase (ALT), hemoglobin, or creatinine, with curcumin use[35] although this study used lower doses.

Two small studies with 12 subjects reported that curcumin can cause gallbladder contraction with potential concern for use in patients with gallstones or bile duct obstructions.[45,46] A study of 11 healthy subjects taking 2.8g turmeric daily for 4 weeks had increased urinary oxalate excretion, which may be of concern in patients susceptible to nephrolithiasis.[47] However, a murine study reported that curcumin may actually alleviate renal calcium oxalate crystal deposition.[48] This may be due to curcumin itself containing lower levels of oxalate as it is likely removed when isolated from turmeric.[41]

Evidence from animal and *in vitro* studies suggest that curcumin may have pharmacokinetic interactions, such as with anticoagulants, cardiovascular drugs, antidepressants, and antibiotics, through inhibition of some CYP450 subtypes and other drug metabolism pathways.[43,49] However, there is limited data in human studies, which may have different effects especially considering low serum levels of curcumin after oral administration of high doses.

Practical Applications

Based on the RCTs by Lang et al. and Sadeghi et al., 1.5-3g oral curcumin daily is likely a safe and effective dose in active UC.[32,33] Patients can be started on lower doses (e.g. 500mg/d) and increased weekly to a maximum of 3g/d as tolerated. Based on the evidence, a trial of 1-2 months is a reasonable treatment duration to observe for effect. Patients should be advised to use curcumin derived from the rhizome or extract of *Curcuma longa*[41] and manufactured by reliable supplement brands that are transparent about sourcing, testing for purity and contaminants, and adherence to CGMPs. To optimize bioavailability, patients should take curcumin in 2-3 divided doses per day with meals that contain black pepper and dietary fat (e.g., avocado, oil, nuts, eggs, dairy).[41] Patients may ask about using freshly grated or ground turmeric. However, 1g of ground turmeric only provides 33mg curcumin,[41] so it would be difficult to obtain an adequate dose.

Many commercially available curcumin supplements contain piperine or are bioenhanced to increase bioavailability. Although Banerjee et al. and Masoodi et al. reported efficacy in UC with lower doses of bioenhanced formulations, the specific formulations used in these studies are not available in the U.S. None of the studies advised subjects to take curcumin with fat or black pepper nor used formulations containing piperine, although this combination has been studied in other conditions.[50–52] It is reasonable to conclude that the increased bioavailability of these methods may result in a lower minimal effective dose, but this requires further investigation.

Patients should be counseled about common side effects, including gastrointestinal symptoms, headaches, and yellow stool.[49] Given the lack of clarity about potential drug-drug interactions, it would be reasonable to exercise caution when using curcumin with drugs that have a narrow therapeutic window or potential for significant AEs, such as anticoagulants. Monitoring of liver function in patients using high dose curcumin supplements should be considered especially when combined with other medications.

CONCLUSION

The evidence suggests that oral curcumin can be used as an adjuvant treatment with conventional therapy in patients with UC (Table 2). Given that curcumin has primarily been studied in patients with active mild-moderate UC taking concomitant mesalamine, this is likely the ideal population although it can be considered in patients taking immunomodulators or steroids. There is some evidence to suggest benefit in patients in remission or those taking other UC medications.

Small sample sizes and heterogeneity among studies with regard to formulations, dosages, duration, clinical scoring systems, and concomitant medications limit high quality pooled analyses. This underlies the need for larger and higher quality clinical trials to establish appropriate doses, potential drug-drug interactions, and the role of nanoparticle-based delivery systems (e.g., NovaSol®) and combination products with piperine. More stringent manufacturing practices and regulations in the nutraceutical industry are also needed. This is of particular importance given the prevalence of nutraceutical use and the strong potential for nutraceuticals, such as curcumin, in improving health outcomes in UC. ■

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