



Curcumin in Combination With Mesalamine Induces Remission in Patients With Mild-to-Moderate Ulcerative Colitis in a Randomized Controlled Trial

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BACKGROUND & AIMS: The phytochemical compound curcumin was reported to be effective in maintaining remission in patients with ulcerative colitis (UC). We investigated curcumin's efficacy in inducing remission in patients with active mild-to-moderate UC.

METHODS: We performed a multicenter randomized, placebo-controlled, double-blind study of 50 mesalamine-treated patients with active mild-to-moderate UC (defined by the Simple Clinical Colitis Activity Index [SCCAI]) who did not respond to an additional 2 weeks of the maximum dose of mesalamine oral and topical therapy. Patients were randomly assigned to groups who were given curcumin capsules (3 g/day, n = 26) or an identical placebo (n = 24) for 1 month, with continued mesalamine. The primary outcome was the rate of clinical remission (SCCAI ≤2) at week 4. Clinical and endoscopic responses were also recorded.

RESULTS: In the intention-to-treat analysis, 14 patients (53.8%) receiving curcumin achieved clinical remission at week 4, compared with none of the patients receiving placebo ($P = .01$; odds ratio [OR], 42; 95% confidence interval [CI], 2.3–760). Clinical response (reduction of ≥3 points in SCCAI) was achieved by 17 patients (65.3%) in the curcumin group vs 3 patients (12.5%) in the placebo group ($P < .001$; OR, 13.2; 95% CI, 3.1–56.6). Endoscopic remission (partial Mayo score ≤1) was observed in 8 of the 22 patients evaluated in the curcumin group (38%), compared with none of 16 patients evaluated in the placebo group ($P = .043$; OR, 20.7; 95% CI, 1.1–393). Adverse events were rare and comparable between the 2 groups.

CONCLUSIONS: Addition of curcumin to mesalamine therapy was superior to the combination of placebo and mesalamine in inducing clinical and endoscopic remission in patients with mild-to-moderate active UC, producing no apparent adverse effects. Curcumin may be a safe and promising agent for treatment of UC. Clinicaltrials.gov number: NCT01320436.

Keywords: IBD; Clinical Trial; Inflammatory Bowel Disease; Phytochemical.

See editorial on page 1450.

The mainstay of therapy for patients with mild-to-moderate ulcerative colitis (UC) is mesalamine agents, which can be given in oral or topical forms or a combination thereof.¹ Combining oral with topical mesalamine has been shown to be superior to oral treatment alone.² Nonetheless, in patients with mild-moderate active disease who have failed to respond to optimization of mesalamine drugs, escalation to corticosteroids and/or immunomodulators is often needed to control the disease. However, these drugs carry potential detrimental side effects.

Curcumin is a natural phytochemical derived from the Indian spice tumeric.³ It has been widely used for centuries in both ayurvedic and traditional Chinese medicine to treat a wide range of inflammatory diseases. In vitro experiments have demonstrated the anti-

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Abbreviations used in this paper: CI, confidence interval; OR, odds ratio; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis.

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inflammatory and antioxidative properties of curcumin in human lymphocytes and gut epithelial cell lines,^{4,5} and curcumin has also been shown to ameliorate murine experimental colitis.^{6,7} Recently, Hanai et al⁸ have demonstrated that curcumin was superior to placebo in maintaining remission in UC patients for up to 12 months. However, whether curcumin is also effective for the induction of remission of UC has hitherto not been investigated.

The aim of the present study was to investigate the efficacy of curcumin as an add-on therapy with optimized mesalamine treatment for the induction of remission in active mild-to-moderate UC patients.

Methods

Study Population

Patients with mild-to-moderate active UC were recruited between July 2011 and June 2014 from 3 medical centers in Israel, Hong Kong, and Cyprus. Active mild-to-moderate UC was clinically defined by a Simple Clinical Colitis Activity Index (SCCAI) score of ≥ 5 and < 12 .^{9,10} Patients aged 18–70 years who had a confirmed endoscopic and histologic diagnosis of UC were included. If patients were receiving immunomodulators (azathioprine or 6-mercaptopurine), stable dose had to be maintained for at least 12 weeks before inclusion.

Exclusion criteria were recent (< 12 weeks) or current use of corticosteroids, current treatment with anti-tumor necrosis factor agents or cyclosporine, hemoglobin levels < 10 mg/dL, or other laboratory abnormalities including leukopenia, thrombocytopenia, or abnormal coagulation tests, significant comorbidities including renal or liver disease. Patients with positive stool culture for enteric pathogens or *Clostridium difficile* or with active infection in another organ as well as pregnant or nursing women were also excluded.

All patients signed an informed consent. The study was approved by the ethics committee of each center and was conducted in accord with the Declaration of Helsinki and registered in clinical trial registry (NCT01320436).

All authors had access to the study data and reviewed and approved the final manuscript.

Design and Procedures

This was a multicenter randomized, double-blind, placebo-controlled trial. Patients with active mild-to-moderate UC despite maximal mesalamine treatment (oral 4 g/day + topical enema/suppository) were enrolled. Patients taking suboptimal mesalamine dosing at screening (either because of < 4 g/day mesalamine and/or because of not receiving topical therapy) first underwent a run-in period of 2 weeks during which they received optimized oral + topical mesalamine treatment. Optimized mesalamine treatment was achieved in all patients

by 4 g/day oral mesalamine concurrently with topical mesalamine at 1 g/4 g enema or 1 g suppository per day, as indicated by disease extent and tolerated. Optimization used the same mesalamine formulation already taken by the patient. Patients who still had symptoms of active mild-to-moderate UC (≥ 5 SCCAI score) despite 2 weeks of optimized oral and topical mesalamine treatment were entered into the trial. On study entry, all patients were instructed to continue their optimized mesalamine medications unchanged and were randomly assigned in a 1:1 ratio to receive 1 month of add-on therapy of 3 g oral capsules of curcumin or an identical placebo in 2 divided doses daily (consisting of 3 capsules twice a day before meals). Curcumin (Cur-Cure, a 95% pure curcumin preparation) and identical placebo capsules were both purchased from Bara Herbs Inc (Yokneam, Israel). Sequential one-by-one blinded randomization was performed after stratification according to concomitant usage of immunomodulator therapy or not (Supplementary Figure 1). All other medications were continued throughout the trial period. All participating physicians were blinded to treatment assignment throughout the study except the clinician in charge of randomization, who did not participate in any assessment of the patients. After enrollment, patients underwent physical examination and laboratory blood tests including a complete blood count, liver function test, and C-reactive protein, which were performed at baseline and at the end of treatment protocol after 1 month. Clinical status was evaluated at entry and at study conclusion after 1 month by the SCCAI score. Consenting patients also underwent sigmoidoscopy at study entry and at the last visit after 1 month, and endoscopic activity was determined according to the endoscopic Mayo index sub-score.^{11,12}

Clinical Assessment and Trial End Points

The primary end point was the percentage of patients in clinical remission at the end of the 1-month treatment, defined as SCCAI score ≤ 2 . Secondary end points included the percentage of patients with clinical improvement (defined by a drop of ≥ 3 points of the SCCAI score), the rate of endoscopic remission (defined by an endoscopic Mayo score drop ≥ 1 to a score of 0 or 1), the mean change in the endoscopic activity score, and rate of endoscopic improvement defined by any ≥ 1 point drop in the Mayo endoscopic sub-score. Adverse events in both study arms were recorded. Participation in the trial was terminated for patients exhibiting disease complications during the study or disease worsening that required stepping up the therapy as determined by the investigator, as well as for patients withdrawing their consent.

Statistical Analysis

Comparisons between the 2 study groups were performed by Mann–Whitney *U* test for continuous variables

or by Fisher exact test for categorical variables. Odds ratios (ORs) and confidence intervals (CIs) were computed. Because of the lack of previous data regarding the anticipated effect size of mesalamine optimization, a formal power analysis calculation of sample size was not performed for this pilot trial. Therefore, 50 patients were planned to be enrolled for this pilot exploratory trial. All statistics were performed by using MedCalc software (Mariakerke, Belgium). $P < .05$ was considered significant.

Results

Patient Characteristics

Ninety-seven patients were screened for this trial between July 2011 and June 2014 from 3 medical centers in Israel, Hong Kong, and Cyprus. Of these, 47 failed to meet inclusion criteria: Thirty-one were excluded because of ineligible SCCAI score, 5 patients were excluded after sigmoidoscopy revealed a normal colonic mucosa (Mayo score of 0), 4 patients tested positive for *C difficile*, and 7 patients achieved clinical remission (SCCAI ≤ 2) after mesalamine optimization run-in period. Hence, 50 eligible patients were enrolled. Out of these, 34 patients were already receiving at screening an optimized oral + topical mesalamine treatment as defined above and were therefore enrolled directly. The remaining 16 patients were escalated to receive optimized oral mesalamine + topical therapy for a 2-week run-in period before being reassessed for inclusion in the trial (Table 1). From the 50 patients enrolled and randomized, 26 patients received add-on curcumin, and 24 received add-on placebo in addition to continued optimized oral and topical mesalamine in all patients. The flow chart of the patients enrolled in the trial is shown in Supplementary Figure 1. Patients' disposition at baseline is shown in Table 1 and was similar between the 2 groups with respect to age, gender, duration of disease, disease extent, immunomodulator use, SCCAI and endoscopic score, C-reactive protein levels, hemoglobin levels, smoking habits, and duration of oral and topical mesalamine use ($P = \text{NS}$ for all parameters, Table 1).

One patient from the placebo arm was lost to follow-up with no outcome available, 1 patient in the curcumin arm was hospitalized before initiation of study medication because of a peptic ulcer pain, and 1 patient in the placebo arm withdrew her consent after commencing the trial. These 3 patients were included in the intention-to-treat but not in the per-protocol analysis.

The trial was terminated in July 2014 after reaching its recruitment goal.

Main Outcomes

In the intention-to-treat analysis, clinical remission after 1-month treatment was achieved in 14 of 26

Table 1. Baseline Demographics and Clinical Characteristics of the Patients

	Curcumin (n = 26)	Placebo (n = 24)	P value
Mean age \pm SD (y)	40.4 \pm 12.7	41.4 \pm 13.9	NS
Sex (M/F)	17/9	16/8	NS
Smoking (%)	15	8	NS
Duration of disease \pm SD (y)	7.1 \pm 6	5.0 \pm 4.1	NS
Proctitis (%)	38	25	NS
Left-sided (%)	40	62	NS
Extensive (%)	16	13	NS
Mesalamine (%)	85	80	NS
Mesalamine + immunosuppressants	15	20	NS
Mean SCCAI \pm SD	6.5 \pm 1.5	7.0 \pm 1.8	NS
Mean partial Mayo score \pm SD	1.9 \pm 0.4	2.1 \pm 0.39	NS
Median duration of topical mesalamine use, y (IQR) ^a	1 (1–3)	1 (1–1.75)	NS
Median duration of oral mesalamine use, y (IQR) ^a	2 (2–4)	2 (2–3)	NS
Percentage of patients with elevated C-reactive protein, % (baseline)	16	12	NS
Percentage of patients with elevated C-reactive protein (4 wk)	12	12	NS
Percentage of patients with hemoglobin $<$ 12 g/dL (baseline)	12	4	NS
Percentage of patients with hemoglobin $<$ 12 g/dL (4 wk)	8	4	NS
Rectal suppositories, % (1 g) ^a	64	72	NS
Rectal enema, % (1 g) ^a	24	26	NS
Rectal enema, % (4 g) ^a	12	2	NS

IQR, interquartile range; SD, standard deviation.

^aContinuous use.

patients (53.8%) receiving curcumin and in 0 of 24 patients receiving placebo ($P = .01$; OR, 42.2; 95% CI, 2.3–760) (Figure 1).

Clinical improvement after 1 month of treatment was achieved in 17 of 26 patients (65.3%) receiving curcumin and in 3 of 24 patients (12.5%) receiving placebo ($P < .001$; OR, 13.2; 95% CI, 3.1–56.6) (Figure 1).

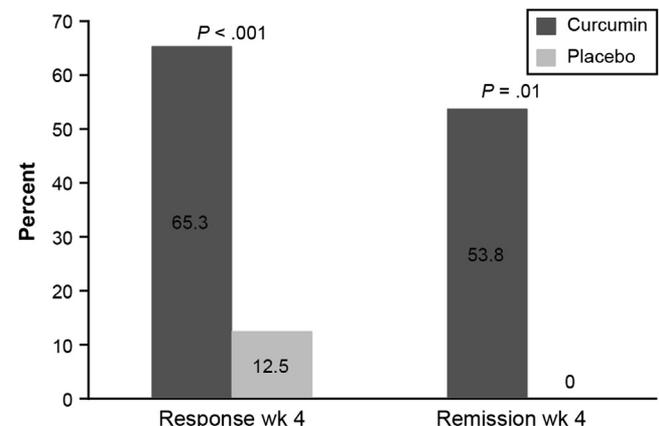


Figure 1. Clinical response and remission rate at study end point at week 4.

In the per-protocol analysis, 14 of 25 curcumin-treated patients (56%) experienced clinical remission compared with 0 of 22 (0%) in the placebo arm ($P < .01$). Clinical improvement was experienced by 17 of 25 patients (68%) on curcumin, compared with 3 of 22 (13.6%) receiving placebo ($P < .01$).

Endoscopic evaluation before and after study treatment was available for 38 patients who consented separately for endoscopy (22 in the curcumin arm and 16 in the placebo arm). Endoscopic remission was observed in 8 of 22 patients (36.3%) in the curcumin arm and in 0 of 16 patients (0%) receiving placebo ($P = .043$; OR, 20.7; 95% CI, 1.1–393) (Figure 2A).

Endoscopic improvement (defined as any drop of ≥ 1 in partial Mayo score) was observed in 10 of 22 patients (45.4%) in the curcumin arm and in 0 of 16 patients (0%) receiving placebo ($P < .01$; OR, 30.1; 95% CI, 1.6–567) (Figure 2A). The mean change in the endoscopic sub-score was $+0.15 \pm 0.49$ for the placebo arm, compared with -0.55 ± 0.79 in the curcumin arm ($P = .04$, Figure 2B).

In this sub-group of patients who underwent endoscopy, clinical remission was observed in 11 of 22 patients (50%) receiving curcumin and in 0 of 16 patients (0%) receiving placebo ($P = .02$; OR, 33; 95% CI, 1.8–618). Clinical improvement was observed in 16 of 22 patients (72.7%) receiving curcumin and in 3 of 16

patients (18.7%) receiving placebo ($P = .002$; OR, 11.5; 95% CI, 2.4–55.4).

Only 9 patients in the study were treated with immunomodulators concomitantly with mesalamine (4 in the curcumin group and 5 in the placebo group). This small sample of patients did not demonstrate any difference in outcomes, but statistical analysis is precluded by the small size of this subgroup.

Safety Evaluation

Three serious adverse events were observed and led to early withdrawal from the study. One event occurred in a patient in the active treatment arm who was hospitalized with abdominal pain caused by a peptic ulcer before initiation of the study medication. In addition, 2 patients had worsening UC symptoms necessitating early termination and the initiation of corticosteroids (1 from the active treatment arm and 1 from the placebo arm). The rate of severe adverse events was not different between the 2 groups. Mild adverse events were observed in 4 patients in this trial, which included mild nausea, transient increase in stool frequency, and abdominal bloating. The incidence of adverse effects was not significantly different between the 2 arms, and no patient discontinued the trial because of these mild adverse events. No new laboratory abnormalities were observed in either arm.

Discussion

The mainstay of therapy for the induction of remission in patients with mild-to-moderate active UC is a combination of oral and topical mesalamine.² Corticosteroid enemas and/or the probiotics VSL#3 may occasionally also prove to be useful for patients failing to respond to mesalamine.^{13,14} However, the therapeutic arsenal available for patients failing to respond to mesalamine compounds is limited, and such patients will often require the institution of systemic corticosteroids, immunomodulators, or biologics despite their potential serious side effects. Therefore, there is an unmet clinical need for new compounds that can induce remission in mild-to-moderate UC without reverting to systemic immunosuppression. In the present pilot study of UC patients who continued to have active symptoms despite optimized mesalamine treatment, 1 month of add-on oral curcumin at 3 g/day was superior to add-on placebo in inducing clinical remission, clinical response, and endoscopic remission. We deliberately elected to use curcumin as an add-on therapy with optimized oral and topical mesalamine treatment in all patients, because this is in keeping with current clinical guidelines that advocate optimized mesalamine as the first-line therapy of choice for these patients.¹ Moreover, mechanistically such an approach was driven by the rationale whereby combination of curcumin and

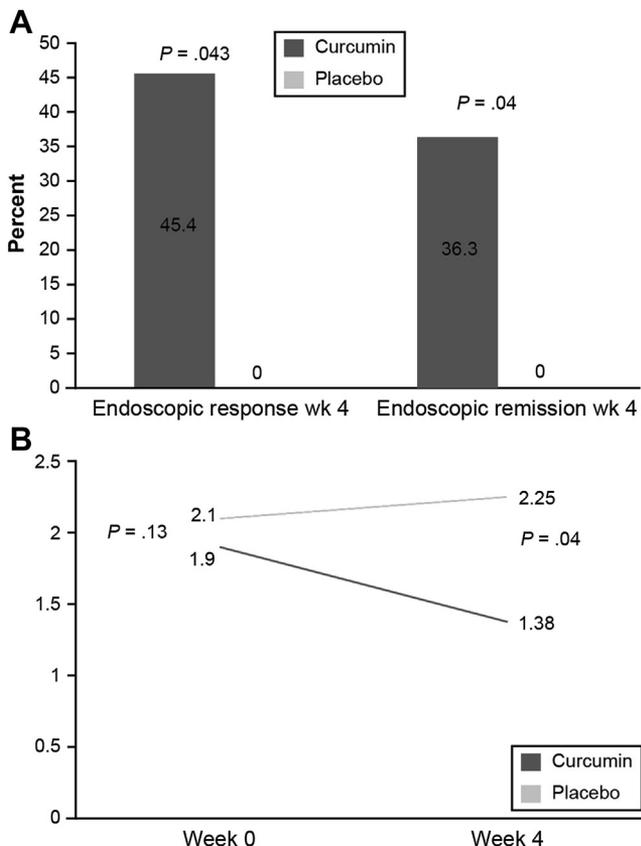


Figure 2. (A) Endoscopic response and remission rate at study end point at week 4. (B) Mean endoscopic rate at week 0 compared with week 4 in the 2 study groups.

mesalamine may have different but potentially synergistic mechanisms of action, hence producing a better outcome. Although only half of the patients (54%) receiving curcumin attained clinical remission, this remained significantly higher than the placebo arm, where no patient achieved clinical remission. Admittedly, such nil rate of remission in the placebo arm is much lower than that observed in trials of mesalamine therapy for this indication. However, in contrast with prior trials, all patients in the present study were already receiving and failing to respond to optimized oral and topical mesalamine treatment at screening. Those who were not required to fail a run-in period of optimized oral and topical mesalamine before being eligible to enter the study. Thus, it is likely that the zero remission rate and the low (12%) rate of clinical improvement in the placebo arm are a result of this design, which reduced the number of placebo responders and/or late responders to mesalamine. Another possible cause for the low remission rate in the present study is the use of SCCAI, which may not be entirely comparable with other clinical scores used by some other studies. Indeed, the SCCAI was recently suggested to be more reflective of actual disease activity¹⁵ compared with other clinical scores, and the strict definition of clinical remission requiring a SCCAI ≤ 2 was recently shown to correlate with patients' genuine sense of remission.¹⁶ Moreover, the results of the present study are in line with a previous study that found curcumin to be superior to placebo for maintaining remission for up to 12 months in 89 patients with mild-moderate UC,⁸ although its ability to induce remission was not explored in that study. A recent trial of curcumin enema for mild-moderate active distal UC did not show a significant benefit in the intention-to-treat analysis. However, significantly higher rates for clinical remission, clinical response, and endoscopic improvement were noted for the curcumin group compared with placebo in the per-protocol analysis,¹⁷ further supporting the possible beneficial effect of curcumin for mild-moderate active UC.

The mechanism of action of curcumin was not specifically investigated in the present work. Curcumin is a phytochemical derived from the Indian herb tumeric (*Curcuma longa*), which is a very popular food additive in Eastern cuisine. This plant has been used extensively in both Indian and Chinese herbal medicine for a wide variety of inflammatory diseases including gastrointestinal inflammation.³ Multiple studies have demonstrated different immunologic properties of curcumin, including the inhibition of nuclear factor kappa B pathway,^{6,18} tumor necrosis factor-alpha secretion,^{19,20} and CD4 T-cell proliferation.⁵ In animal models, curcumin has also been shown by several studies to ameliorate chemically induced murine experimental colitis.^{7,21,22} The exact mechanism by which curcumin may play a role in conferring the observed clinical effect in active UC still remains to be determined.

The safety profile of curcumin was good, and it was generally well-tolerated and not associated with increased rate of adverse effects. However, the sample size of this pilot exploratory study may not be sufficient to preclude rare side effects that will require a large number of patients. Also, the short duration and the lack of post-study safety follow-up limit our ability to fully evaluate curcumin's safety profile. Nonetheless, clinical trials of curcumin for disorders such as diabetes mellitus, Alzheimer disease, and familial adenomatous polyposis have not demonstrated significant safety issues.²³⁻²⁵

Several limitations of our study need to be acknowledged. Curcumin was administered as a single dose of 3 g/day, and we did not incorporate a dose-finding study design. The particular dosing in the present trial was higher than that used in the Japanese maintenance trial of curcumin for UC,⁸ reasoning that higher doses of curcumin may be required for induction of remission as compared with maintenance of remission, as is true for mesalamine treatment. However, in the absence of a dose-finding strategy, it is difficult to know whether lower doses of curcumin may be as or even more effective in this setting. Second, this pilot exploratory trial consists of a relatively modest sample size. Although our results showed a marked superiority of curcumin over placebo, we did not perform formal power calculation because there were no previous data testing the efficacy of this drug in this particular setting. Therefore, further larger-size trials corroborating our findings are necessary before the widespread use of curcumin in routine clinical practice for this indication. A further limitation was that endoscopic evaluation was available for only 38 of the 50 patients (76%) included in the study (22 in the curcumin arm and 16 in the placebo arm). In addition, among patients who underwent baseline endoscopy we only excluded those with absolutely normal mucosa (Mayo 0). Although this could potentially create some overlap with the patients achieving remission during the study, endoscopic remission was defined as a partial Mayo score of ≤ 1 and endoscopic improvement with drop of >1 in this score. In actual terms, 3 patients who underwent endoscopy presented a partial Mayo score of 1 at baseline (2 in the curcumin arm and 1 in the placebo arm), and none of these 3 patients achieved endoscopic remission at the end of the study. A further limitation may be a possible unmasking because of changing of stool color to yellow in some patients taking curcumin, although this is not common in our clinical experience, and such unmasking is not expected to affect endoscopic outcome.

In conclusion, the findings of this trial suggest that curcumin as add-on therapy with optimized mesalamine is superior to optimized mesalamine alone in inducing clinical remission in patients with active mild-to-moderate UC. Further large clinical trials to evaluate curcumin for inflammatory bowel disease are warranted.

Supplementary Material

Note: To access the supplementary materials accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://dx.doi.org/10.1016/j.cgh.2015.02.019>.

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Reprint requests

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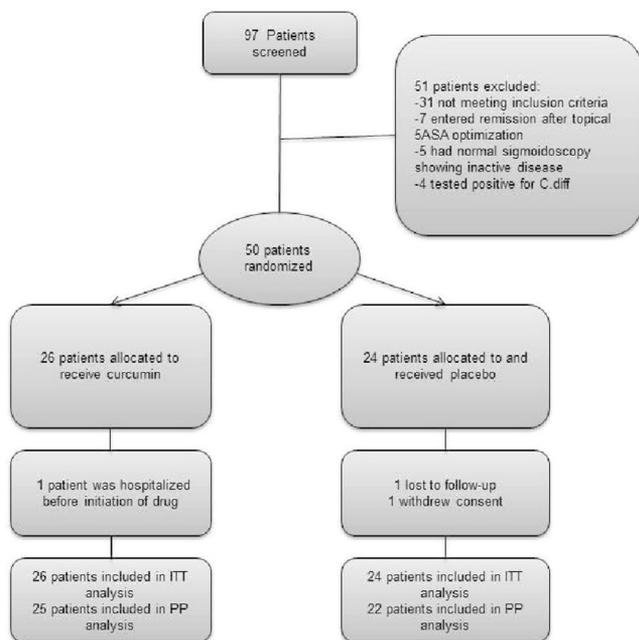
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Conflicts of interest

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Supplementary Figure 1. Flow chart of patient enrollment into the study and randomization scheme. 5ASA, mesal-amine; C.diff, *Clostridium difficile*; ITT, intention-to-treat; PP, per-protocol.